WASHINGTON HEALTH CARE AUTHORITY

Peer Reviews, Public Comments & Responses

Health Technology Assessment

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CONTENTS

Note: *Spectrum is an independent vendor contracted to produce evidence assessment reports for WA HTA program. For transparency, all comments received during the comments process are included or otherwise made publically available. However, comments related to the key questions (and their formulation), context provided regarding the key questions, program decisions, process, policy decisions, or other matters not pertaining to the evidence presented in the report are acknowledged through inclusion, but are not within the scope of response for report accuracy and completeness.*

We thank all commenters for their time and attention to the report.

SPECTRUM RESEARCH RESPONSE TO FREQUENT COMMENTS

1. The HTA evidence report is intended to summarize and critically appraise available literature, based on a systematic search and review of the literature with a focus on the highest quality evidence available. RCTs provided information on efficacy while observational studies provided information on effectiveness. Critical appraisal and overall strength of evidence criteria are described in the Appendices.

Many commenters appear to have misunderstood overall strength of evidence (SoE). It does not state that a treatment is or is not efficacious. The overall SoE is a statement regarding the evidence available in specified literature sources, based on the systematic review to support the efficacy and effectiveness for a given topic. The overall strength of evidence evaluation used here incorporates the GRADE approach and is consistent with the AHRQ's concepts. It considers the study quality (which includes assessment of bias, confounding, variability, sample size, precision), and consistency of findings across different study populations (which includes constancy as well as magnitude and direction of effect). Consideration of whether an outcome is an intermediate or surrogate (i.e. "indirect") is part of specifying the outcomes and the quantity of evidence of primary outcomes of interest (usually more "direct" outcomes) is considered.

No policy or coverage recommendations are made in the document as this is the purview of the Health Technology Clinical Committee.

2. *Evidence and ethics of RCTs*. A number of comments related to the statements regarding the lack of RCTs to address the issue of efficacy. A certain clinical practice may be efficacious (and/or effective) but there may not be high quality literature to support or describe it. Statements regarding the overall strength or quality of evidence are based on the available literature.

We are fully aware of the ethical concerns, human subjects issues and regulations related use of children in research that many commenters cited. Nothing in the report states that such studies be done. The evidence that is available (based on the program's questions and context and the inclusion/exclusion criteria) is presented and includes RCTS (efficacy) ***as well as*** comparative observational studies (effectiveness) that met inclusion criteria.

2. *Glucose monitoring as part of a package of diabetes care*: The context provided by the State for this report can be found on the Health Technology Assessment Program's website. We recognize that glucose monitoring is an integral part of diabetes management and glycemic control that includes adjusting insulin dosage, diet, exercise, education, and clinical monitoring. We recognized that monitoring in and of itself does not improve glycemic control and is part of the management decision making related to these other factors. This is presented in several areas of the document background and elsewhere. Unfortunately, most studies did not include specific information regarding how (or if) data from monitoring were used to inform management decisions, thus the impact of monitoring (either SMBG or CGM) as an independent factor in management is not clear.

3. *Clinical guidelines*: Some commenters may have missed section 1.3 which summarizes pertinent recommendations from guidelines. It is recognized that different recommendations may have varying levels of literature support ranging from expert opinion to data from high quality studies, as described in the respective guidelines. The National Guideline Clearinghouse is the primary source for our search of evidence-based clinical guidelines. PubMed is also searched for guidelines. The 2010 Association of Clinical Endocrinologists (AACE) statement on CGM was published after the close of our literature search. DexCom also commented on guidelines from the Association of British Clinical Diabetologists (ABCD). This guideline has no recommendations specific to the pediatric age group.

4. *Safety:* Additional context and re-wording is reflected in the final report.

5. *Additional references:* Many commentators provided additional references. Most of these did not meet the inclusion criteria or met exclusion criteria for our HTA because of the subjects' age (subjects did not include those ≤ 18 years or results were not stratified to describe those ≤ 18 years); the topic (e.g., it did not address glucose monitoring or it did not relate glucose monitoring to health outcomes or it described insulin analogues); the setting; or the publication type (meeting abstract).

Commentators cited 131 distinct articles. All were reviewed at the title, abstract, or full-text level. Of these, 10 were already included in our HTA and 6 reports were added as primary evidence. (Two of these reports described follow-up to previously included studies and had been captured by our search; the other four added little substantive data). The other 115 did not meet inclusion criteria for this HTA. None of the additional references that met inclusion criteria added changed the overall strength of evidence or conclusions.

The following tables list articles and clinical guidelines suggested by commenters.

Study	Disposition/comment
Anderson 1997	This study is cited in our HTA (reference* 86).
Anderson 1999	This study does not relate glucose monitoring to a health outcome. It does not meet criteria for inclusion in our HTA.
Anderson 2002	This study is cited in our HTA (reference 87)
Arfken 1996	Less than 80% of the cohorts were < 18 years old, but this did not meet our age criteria for inclusion.
Ashville Project	The Ashville Project included employees, retirees, and their dependents. It did not meet age criteria for our HTA.
Beck 2009	This was included in our HTA (reference 115)
Bergenstal 2010	This was included in our HTA (reference 79)
Bjorn 2010	This observational study did not examine the effects of glucose monitoring. It does not meet criteria for inclusion in our HTA.
Butler 2008	This cross-sectional study is primarily about adherence. There is one sentence associating frequency of SMBG to A1c. *ADDED;*

	does not provide substantive data to answer key questions or change conclusions.
Cryer 2003	This nonsystematic review does not focus on the pediatric age group. Does not meet inclusion criteria.
DCCT 1993	Rather than cite this full report of the DCCT, we cited the secondary report limited to children and adolescents (reference 20)
DCCT 2000	This is a follow-up study of patient who were 13 to 39 years old when they entered the DCCT. Results for adolescents are not described separately. As it did not meet age criteria, this study was not included.
DCCT 2001 (White)	This is a follow-up (EDIC) study from the DCCT. ADDED to final together with White 2010.
DCCT JAMA 2002	This is a summary, not primary data, and does not reflect outcomes for the pediatric age group separately. Does not meet inclusion criteria.
Deiss 2006	Although this study included children, results are not stratified by age. Does not meet inclusion criteria.
Delamater 1999	This study does not address glucose monitoring. It does not meet criteria for inclusion in our HTA.
Egger 1997	This meta-analysis was published in 1997. It is not a primary study. Does not meet inclusion criteria.
Ellis 2008	This study does not address glucose monitoring. It does not meet criteria for inclusion in our HTA.
Franklin 2006	The intervention was a text-messaging system, not glucose monitoring. It does not meet criteria for inclusion in our HTA.
Gaudieri 2008	This meta-analysis does not relate glucose monitoring to cognitive function. It does not meet criteria for inclusion in HTA.
Gilmer	This study is based on adults and so was not included in our HTA
Haller 2004	This was not retrieved by our literature search. We can add it to those observational studies showing a correlation between frequency of SMBG and A1c. *ADDED* to final. It does not change our conclusions.
Hanauer 2009	The intervention in this study was a electronic reminders. It does not meet criteria for inclusion in our HTA.
Hanberger 2008	This registry study did not relate blood glucose monitoring to a health outcome. It does not meet criteria for inclusion in our HTA.
Hepburn 1990	Mean age of patients was 44 years. As it did not meet age criteria, this study was not included in our HTA.
Hood 2009	This meta-analysis is cited in our HTA (reference 61).
JDRF 2009 The effect of	This was included in our HTA (reference 77)
JDRF 2010 Effectiveness	This was *added* to our HTA in response to peer reviewers' comments.
Jiang	The analysis does not include glucose monitoring and so is not included in our HTA
Jungheim 2001	This is an abstract. Abstracts were not included in our HTA.
Karter 2001	This registry study addressed adults; it was not included in our HTA.
Khaw 2004	This study was in adults. As it did not meet age criteria, this study was not included in our HTA.
Karter 2001	This registry includes only adults and so was excluded from our HTA.
Kolb 2010	This nonsystematic review does not discuss SMBG specifically in children and so was not included in our HTA. We note its conclusions: that there is no formal evidence to support SMBG in patients with type 1 diabetes.
Kumar 2004	The intervention in this study was a motivational game. It does not meet criteria for inclusion in our HTA.
Laffel 2003	This cross-sectional study is primarily about adherence. There is one sentence associating frequency of SMBG to A1c. I put it in the drop box.
Levine 2001	This is cited in our HTA.
Mehta 2009	This was not retrieved by our literature search. We can add it to those observational studies showing a correlation between frequency of SMBG and A1c. It does not change our conclusions.
Moreland 2004	This is included in our HTA
Moreland 2006	This study was conducted in adults. It does not meet criteria for inclusion in our HTA.
Murata 2005	Study in veterans. As it did not meet age criteria, this study was not included in our HTA.
Naguib 2009	This meta-analysis does not relate glucose monitoring to cognitive function. It does not meet inclusion criteria..
Nathan 1996	While the regression model associating A1c to frequency of SMBG was adjusted for age, it was not stratified by age and does not report the association separately for the pediatric age group, and so was not included in our HTA.
Nguyen 2008	Although supervision of SMBG was part of this intervention, SMBG itself is not related to health outcomes. It does not meet criteria for inclusion in our HTA.
Northam 2009	This observational study does not describe glucose monitoring. It does not meet criteria for inclusion in our HTA.
Palmer 2006	This economic analysis was for adults with type 2 diabetes, and so was not included in our HTA
Paris 2009	This was cited in our HTA.
Pedersen-Bjergaard 2003	Mean age of subjects was 46 years. As it did not meet age criteria, this study was not included in our HTA.
Reichard 1990	Mean age of patients was 30.5 years. As it did not meet age criteria, this study was not included in our HTA.
Saleh 2001	This is a nonsystematic review that does not focus on the pediatric age group. It was not included in our HTA.
Sanchis S 2001	This is an abstract. Abstracts without an accompanying full length publication detailing methods and data in a peer-reviewed journal were not included in our HTA.
Saudek 2006	This systematic review is not limited to children and has no separate analysis for the pediatric age group. It was therefore not included in our HTA.
Schiffrin 1982	Patients in this study were age 15-36. It does not meet criteria for inclusion in our HTA.
Schutt M	This registry does not analyze the pediatric population separately, and so was excluded from our HTA. The same database, restricted to children and adolescents, was used in Ziegler 2010, which is included in our HTA.
Scottish Study 2001	This cross-sectional study did not relate blood glucose monitoring to a health outcome. It does not meet criteria for inclusion in our HTA.
Shichiri 2000	Patients' mean age was 47-53 years. As it did not meet age criteria, this study was not included in our HTA.
Springer 2006	This observational study did not examine glucose monitoring. It does not meet criteria for inclusion in our HTA.
Svoren 2003	This study did not relate blood glucose monitoring to a health outcome. It does not meet criteria for inclusion in our HTA.
Svoren 2007	This observational study does not examine the relationship between frequency of SMBG and health outcomes, and so was not included in our HTA.

Taplin 2010	This study took place in a clinical research center; the interventions were not related to glucose monitoring. It does not meet criteria for inclusion in our HTA.
Tsalikian 2005	This study took place in a clinical research center; the interventions were not related to glucose monitoring. It does not meet criteria for inclusion in our HTA.
Tunis 2008	This simulation economic model was for diabetics with a baseline age of 62.8 years treated with oral hypoglycemic agents, and so was not included in our HTA
Urbach 2005	This cross-sectional study did not examine associations between frequency of SMBG and A1c. It does not meet criteria for inclusion in our HTA.
Woerle 2004	This study was conducted among adults, and so was not included in our HTA
Ziegler 2010	This was retrieved through our literature search and is cited in our HTA (ref 91).
OTHER	66 Citations on insulin analogues were provided by Roche. These do not address the key questions and were therefore not included

Clinical Guidelines

ADA 2010	This was included in our HTA.
AACE 2002	This was included in our HTA.
AACE 2007	The 2007 guidelines were included in our HTA.
AACE 2010	Was published after close of our literature search
Association of British Clinical Diabetologists (ABCD	Does not provide specific recommendations to the pediatric age group for this report
Diabetes Coalition of California	This was included in our HTA.
International Diabetes Federation (2007)	This was included in our HTA.
International Diabetes Center (Bergenstal 2005)	This has no recommendations specific to the pediatric age group
National Institute for Clinical Excellence	This was included in our HTA.
ISPAD (Rewers 2009)	This was included in our HTA.
Silverstein 2005	This was included in our HTA.

SPECTRUM RESEARCH RESPONSE TO PEER REVIEW COMMENTS

Dace Trence, MD, FACE, Director, Diabetes Care Center, University of Washington

Dr. Dace Trence's comment in the Introduction (pg. 8), multiple paragraphs: The key questions in this HTA focus on outcomes specifically related to individuals 18 years old or under who require insulin. It is recognized that the care of children is complex and involves their relatives, caregivers or friends. Additional context acknowledging that complexity of care has been added to the introduction/background section. In-depth discussion of this is beyond the scope of this report. Information from the JDRF studies reporting quality of life were included in the report.

Response to Dr. Dace Trence's comment on Page 8. The sentence: "Several lines of evidence have suggested an association between glucose monitoring and increased discomfort, inconvenience and worsening of depression scores with regular self-monitoring…." comes directly from the HTA Program's introduction provided to the vendor and available publically prior to initiation of the report.

Dr. Dace Trence comment response: Page 10, Key Question 1.

We have now included information from EDIC studies that separately report outcomes for subjects who were adolescents at the start of the DCCT. Clarification regarding rates for ketoacidosis has been made.

Dr. Dace Trence comment response, Page 11: The ethical concerns with conducting trials are understood. Conducting such a trial has not been recommended in this document. None-the-less, we are required to state what types of evidence are and are not available to answer the questions posed.

Wording regarding the FDA recommendation that SMBG be used in conjunction with CGM has been modified. The use SMBG for verification of CGM readings is explained in detail in the Background section. The following is an example of what is stated on the FDA site (http://www.accessdata.fda.gov/cdrh_docs/pdf/P980022S015a.pdf) for the Paradigm systems from the approval order.

> The Paradigm® REAL-Time System is indicated for continuous or periodic monitoring ofglucose levels in the fluid under the skin, and possible low and high blood glucose episodes inadults, age 18 and over, and in children and adolescents, age 7 through 17. The system providesan alert if glucose levels fall below or rise above preset values. Glucose values provided by thesystem are not intended to be used directly for making therapy adjustments, but rather to providean indication of when a fingerstick may be required. All therapy adjustments should be based onmeasurements obtained using a home glucose monitor and not on sensor glucose readingsprovided by the Paradigm REAL-Time System.

Response to Dr Trence's comment on "Line section on results of CGM":
In the JDRF 2008 report on the main RCT, there was a non-significant difference between study groups in the rate of severe hypoglycemic events among 8 to 14 year olds. The sub analysis report and extension study (which are considered observational, non-randomized studies) included in this HTA in this age group describe consistency and frequency of GCM use and impact on outcomes was included in the section on effectiveness for Key Question 2. The significant changes in A1C for 8-14 years from the sub anlaysis (JDRF 2009"Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes." Diabetes Care**32**(11): 1947-1953.) are described as are the results for A1C change and proportion of individuals meeting A1C targets based on CGM use for the 8-17 year olds who were part of the extension study (Chase, H. P., R. W. Beck, et al. (2010). "Continuous glucose monitoring in youth with type 1 diabetes: 12-month follow-up of the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial " Diabetes Technology Therapeutics. 12(7): 507-15.). This later study states that the incidence of hypoglycemia was low during the 12 months irrespective of the amount of CGM use.

Information from the JDRF 2010 "Effectiveness" extension study has been added. For those 8-14 years old (n = 47) with A1c $\geq$ 7.0 when they started using a CGM, there was no significant change in A1c from beginning CGM use to 6 months (mean change in A1c +0.02; p = 0.85).No consistent pattern for improvement in A1C of $\geq$ 0.5% or achieving A1C <7% was seen. Among all 61 eight to 14 year olds, the incidence of severe hypoglycemic episodes trended higher during

the 6 months using SMBG than during the 6 months using CGM (26.4/100 person-years versus 13.0/100 person-years; p not reported for individual age group).

With respect to Dr. Trence's suggestion to include the reference on reported quality of life in CGM users (J. Halford, C. Harris. Diabetes Technology & Therapeutics. March 2010, 12(3): 210 – 205); this reference was reviewed for inclusion and was excluded because the study population was > 18 years of age

Response to Dr Trence's comment effectiveness of CGM.
This has been clarified in the report. We understand that the point of having data from CGM or SMBG is to make treatment and management decisions and that, taken together, the information and changes to management influence outcomes. Part of the point is indeed to indicate that they are integrated. It would be good to have information about how the data are acted upon, however. Specifics about how such data were used/what specific actions were taken for personal or clinical decision making were not provided in these studies. Thus the extent to which the data are used and how they are used is not reported so the independent effects of either method of monitoring on treatment or outcomes cannot be evaluated. Thus, there are questions that remain: To what extent were the data used or not (in either group)? Were patients with CGM more likely to use the data for decisions (assuming that SMBG was also done as part of the decision making) than those who used SMBG alone? If so, did it affect outcomes? Would this point to a benefit of one method over the other?

Response to Dr Trence's comment, page 12 Safety:
The comment correctly points out that issues of patient choice regarding device use (implementation and use of features) are different from specific safety issues related to device mechanics (e.g. subcutaneous insertion of sensors). While patient choice regarding use of the device are human/behavioral factors, they have the potential to lead to adverse events and therefore are considered in the context of safe device implementation and do relate to the design. The interaction between the device design and the human factors is considered in the broader scope of safety. The discussion of safety is intended to include CGM or SMBG device design and implementation as safe use is a function of both design and implementation. We are asked to provide detail on such issues as well as adverse events (major or not) that are reported.

We have included context with regard to the older studies and their applicability to modern devices and use.

Response to Dr Trence's comment on page 13: Since the publication of the DRAFT HTA results we contacted the authors to determine the age of the participant who died during this trial. The participant who died was over 18; therefore, we have changed the text to read, "No deaths among participants ≤ 18 years old were reported in any study."

Response to Dr Trence's comment on page 19, referring to "lines of evidence…".See above response to Dr. Dace Trence's comment on Page 8.

Response to Dr Trence'scomment on page 31. We appreciate Dr Trence's suggested phrasing, and have changed the wording about carbohydrate counting as suggested.

Response to Dr Trence's comment on page 34, third paragraph. We appreciate Dr Trence's suggested phrasing, and have changed the word "pain" to "discomfort," as suggested.

*Response to Dr Trence's comment on page 35, second paragraph.*We understand that the Medtronic Guardian Real-Time is a stand-alone CGM, whereas the Medtronic Paradigm Real-Time is meant to be used with and insulin pump. The FDA's approval letter for the devices listed them separately and Medtronic's website lists the devices separately. Therefore they are listed as two separate devices for purposes of this report.

Response to Dr Trence's comment on page 37. The AACE Consensus Statement was published in theSept/Oct issue of Endocrine Practice, and was published after the cut off for our literature search.

Response to Dr. Dace Trence's comment on Methods page 64, Treatment assignment paragraph. This criterion pertains to whether investigators took appropriate actions to conceal the intervention assignment prior to allocation, not whether the investigators, clinicians, or participants were blinded to the treatment assignment when assessing outcomes.There is a potential for bias in RCTs if allocation to the study groups is not concealed as investigators may tend to influence group assignment and undermine the purpose of random assignment. This is a standard criterion for critical appraisal of RCTs.

Response to Dr. Dace Trence comment on Results page 74, DCCT bullet points.
Information on neuropathy has been added.

Response to Dr. Dace Trence comment on Results page 77, Older studies paragraph: Context regarding older studies had been added.

Response to Dr. Dace Trence comment on Results page 78, section 3.2.2 last sentence.

We are aware that CGM use requires calibration against SMBG and have revised wording to reflect that the comparison is between CGM in conjunction with SMBG versus SMBG alone.

Response to Dr Trence's comment on page 94, hypoglycemia. Additional context on has been added. It is logical to assume that those who may be more at risk for hypoglycemia may monitor more frequently. However, data from these studies is cross-sectional and characteristics of how/why patients may monitor more frequently are not provided and finding of an association does not mean that it is causal.

Response to Dr Trence's comment on pages 94, 96 adverse events. See previous response. Wording has been revised.

Response to Dr Trence's comment on page 112, cost. Reference to these studies, which did not meet inclusion criteria, have been removed from this section.

Response to Dr Trence's comment on page 112, 113, 114 regarding summary: See previous response from pages 8-10.

Response to Dr Trence's comments on report. Responses above to the various sections appear to address these.

Angela Badaru, MD, Faculty, Division of Endocrinology and Diabetes, Seattle Children's Hospital

Response to Dr Badaru's comment on page 8 paragraph 4. We appreciate that in clinical experience there may be a clear correlation between SMBG and A1C. The task of the report is to summarize evidence from the literature related to this.

Response to Dr Badaru's comment on page 12 line 20. Both reviewers commented on this. Please see response above to Dr. Trence's comments. Wording has been revised.

Response to Dr Badaru's comment on page 12 line 31. (Both reviewers comment on this, also see response to Dr. Trence)
We appreciate Dr Badaru's interpretation. Additional context has been added. Our intent was to provide cautions about inferring causality from observational studies, especially since associations reported from 2 different studies were in the opposite direction. Context regarding children being unable to express symptoms of hypoglycemia is included in the background.

*Response to Dr Badaru's comment on page 13 line 24.*The publication by Paris, et.al, was included in the report (Table 16) together with similar studies. These studies did not specifically evaluate differential effectiveness by age. The statement regarding improvement in A1C for those 0-5 years old and 6-12 years old is from the Ziegler registry study (N = 26,723) and their conclusion regarding incremental benefit of additional tests per day. Per responses to other comments, these are all cross-sectional studies and while associations maybe seen (and statistically significant), they may not be causal. Statistically significant results may not correspond to clinically significant changes some studies.

Response to Dr Badaru's comment on pages 65, 66, and 67. The purpose of this section of the HTA is to review the quality of literature available to answer the HTA questions based on the critical appraisal methods described in appendix D, pages 12-21, of the Draft Appendices. Document. The degree of improvement in glycemic control associated with frequency of SMBG is appropriately detailed in the "Results" section, Table 16, page 92 for studies that provided this information. The majority of the studies looking at the associations between frequency of testing and A1C provided no data on either specific frequency or level of A1C associated with a specific frequency of testing.

Dr. Angela Badaru comment 6 response: Page 73, line 27. Please see responses to frequent comments regarding RCTs.

Response to Dr Badaru's comment on summary sections: Responses above and to other commenters appear to address these.

Response to Dr Badaru's comments on quality of report: The report does include the descriptions of data and relationships between monitoring and outcomes in the results section within the context of study quality. Section 1.3 summarizes clinical guidelines.

SPECTRUM RESEARCH RESPONSE TO PUBLIC COMMENTS

Please also refer to responses in the "SPECTRUM RESEARCH RESPONSE TO FREQUENT COMMENTS" section.

Clinician Professional Organizations

American Diabetes Association

The section on clinical guidelines includes guidelines cited in the ADA letter. The background and "Key considerations by clinical experts" provides includes context about the points raised in the letter regarding the individualization of care and SMBG as a fundamental component of care. Data from DCCT and other studies pertinent to the scope of the HTA are included.

The Endocrine Society

Data from DCCT and EDIC pertinent to scope of this HTA were included. We note that this organization will be putting forth a clinical guideline in 2011. It can be included in future updates.

Pediatric Endocrine Society

Please see comments "SPECTRUM RESEARCH RESPONSE TO FREQUENT COMMENTS" and other responses to comments regarding determination of overall strength of evidence, integration of monitoring as part of care, clinical guidelines, and additional study citations.

The report does not state that monitoring is ineffective but rather cites describe studies found and the overall strength of evidence supporting efficacy and effectiveness as discussed in responses to other commenters

Studies regarding morbidity and mortality of inadequate SMBG were not found. Information available on outcomes from included studies is reported provides evidence of the benefit of glycemic control, based on DCCT.

Comparative studies of SMBG and CGM, in the population specified by the State, are included in the report. Comparative studies using state of the art SMBG were not found to evaluate the "principal importance of SMBG per se". Data from DCCT and EDIC were found and included. Data from the JRDF studies included in the report appear to speak to the added benefit of CGM

since CGM use also includes SMBG for calibration and decision making, as pointed out by other commenters. The results details information on these studies, separated out by modality to the extent possible based on the literature found.

Peer review on the public draft was provided by individuals with expertise in diabetes management. Their comments and our responses/changes relative their comments are provided in this appendix.

Industry

Please also refer to responses in the "SPECTRUM RESEARCH RESPONSE TO FREQUENT COMMENTS" section.

Abbott Diabetes Care, Inc./UBC appendix

As stated previously, comments regarding formulation of and context around key questions, selections of topic for review, etc. will not be addressed as these we provided to us by the HTA program.

Please also refer to responses in the "SPECTRUM RESEARCH RESPONSE TO FREQUENT COMMENTS" section.

The report is intended to summarize and critically appraise available evidence. It is not within the scope of the report to suggest RCTS or offer alternatives to maintaining glycemic control without frequent self-monitoring.

Responses to comments not previously addressed in other portions of these appendices related to the UBC report commissioned by Abbot follow.

The authors of the UBC report cite studies among adults which did not meet inclusion criteria (those 18 year or younger). (See list of studies presented earlier).

Search: We are aware of the issues raised regarding use of MeSH terms and indexing and disagree that the strategy was "very likely" to miss any pertinent major studies, particularly those more than a year old. It is reassuring to note that with few exceptions, the citations suggested by various commenters, (listed previously in the response document), were indeed caught by our search through the dates indicated and most did not meet the inclusion criteria. The few that were not captured but included in the final report for completeness added almost no substantive data or substantive impact on the final synthesis or conclusions. In addition to hand searches of bibliographies and use of "related articles" links, selected key word searches were conducted to facilitate inclusion of relevant literature. Extensive, unstructured key word searches typically bring up a large percentage of citations that are not relevant. The strategy used is consistent with what has been used in technology assessments elsewhere.

Grey literature: The author apparently missed the listing of clinical guidelines, HTAs and systematic reviews that are listed in the initial sections of the report, based on grey literature

searches of the National Guideline Clearinghouse, INAHTA (via CDR) and others. Abstracts from meetings and meeting proceedings are not included for several reasons: Meeting abstracts do not generally contain sufficient information for critical appraisal, may represent preliminary or limited findings and the peer review process is not rigorous compared with full length research reports published in indexed journals. It is not possible to effectively, systematically search and evaluate potential sources, leading to potential bias in selection.

Relevant clinical guidelines were cited. As stated in the report, the focus of the report is on those 18 years old or under, the majority of whom will have type 1 diabetes. Self-monitoring is considered an essential part of management in these individual thus, guidelines relevant to children with are included and specify type 1. No studies on individuals 18 years old or under who are type 2 and require insulin, or had gestational diabetes were found to address the questions posed. We do not consider it necessary to include recommendations for type 2 diabetes in this report given the focus and studies found to answer the questions posed.

Use of nonrandomized, observational studies: Information from numerous observational studies meeting inclusion criteria was presented in the report in sections related to effectiveness primarily. RCTs have the potential for the least biased information on efficacy. We recognize that methodologically rigorous, comparative observational studies that are of high quality may add important evidence with regard to effectiveness and safety. The provide information on the "real world" use of devices. Lower quality comparative studies (e.g. retrospective cohort studies which don't control for confounding, cross-sectional studies which do not provide sufficient information for determining causality) may, however, have conflicting results versus RCTs and/or other high quality observational studies that may be attributable more to bias than to at true effect. Because case series lack a valid comparison group, when comparative studies are available, case series may add little high quality information on a topic. So an evidence based synthesis would logically include and focus on the highest quality studies. Critical appraisal provides important context around the findings and potential biases of a study (or studies) so as to help one put the results of a study in perspective and allow the astute reader to assess the extent to which such biases may influence the results. All of these are important when considering the extent to which the results of a study are valid and believable. Unfortunately, the largest percentage of observational studies found were not of high quality and/or did not provide sufficient data relevant to the key questions. They were included if they met the inclusion criteria. A primary concept of evidence-based practice indicates that the focus be on the highest quality of evidence, not necessarily an extensive list of studies that have been done on a given topic. Focus on the highest quality of evidence available is consistent with processes reported across numerous health technology assessment bodies.

Long term outcomes and safety related to risks and consequences of poor control: Included studies of CGM did not address the long-term outcomes and no additional relevant studies were found which met inclusion criteria. Data from the 10 year EDIC follow-up to DCCT are included in the final report. As noted previously no studies on morbidity and mortality of inadequate SMBG were found in the population specified.

Bayer HealthCare

The clinical guidelines cited are included in the report. Context related to the use of SMBG for self-care and decision making leading to glycemic control is provided in the early sections of the document. It is recognized (and reported) that the guidelines suggest multiple tests per day be used to determine patterns of hypoglycemia and hypoglycemia and make appropriate insulin does adjustments. Data from DCCT and the EDIC follow-up in the relevant population are included.

Dexcom

The commenter points out that the success of monitoring depends on the training, knowledge, skills and motivations of patients, parents and providers relative to the use of devices as well as how to use and act upon the data they provide. We recognize this (together with adherence) and there is some context to this effect is in the background. Most studies only provided general information regarding the instructions provided to study participants and few provided information on consistent use of devices. Specifics of how data are used to make decisions are also not delineated in these studies.

We recognize that technology changes and that reports such as this are snapshots of what is available in the literature. The HTA program has provisions for periodic review and update of topics to reflect new studies.

Medtronic

As previously stated, comments on key questions, context, process and rationale for the topic etc. are not included in the scope of these responses. The focus of the report was not intended to be on the benefits of intensive insulin management. Additional studies cited in these comments were either already included in the report or did not meet inclusion criteria.

Health plan coverage: We are required to provide information on the CMS NCDs and information from at minimum of two bell-weather payers. These are included in the report. It is not intended to be a comprehensive or selective list.

CGM use: The included comparative studies include rt-CGM used in conjunction with insulin pump or MDI, based on the stated inclusion criteria for these studies. We recognize that technology changes and that reports such as this are snapshots of what is available in the literature. The HTA program has provisions for periodic review and update of topics to reflect new studies.

*Hypoglycemia:*The report does include the outcomes mentioned to the extent that they are reported in the included studies. The importance of avoiding hypoglycemia while maintaing good metabolic control is described in several places in the document. No studies meeting inclusion criteria discussed the impact of monitoring in patients with hypoglycemic unawareness and no additional comparative studies meeting the inclusion criteria were found.

*Safety:*We are expected to list all potentially relevant adverse events. Sections of this section have been revised.

CGM studies on frequency of device use: The studies cited were included in the report.

Star 3 Study: Information from this study reported by Bergenstal, et. al is presented in the results section of the report. This compared two different sets of treatment interventions; use of an integrated CGM and insulin pump system in one group versus multiple daily injections with SMBG in the comparison group. This design addresses the question of whether an integrated CGM and pump lead to better outcomes than MDI with SBMG. This design does not allow for assessment of the separate effects of CGM and SMBG. Thus, it was not appropriate to include the findings as part of the summary of the overall body of evidence on the questions we were asked to address.

Roche

Comments made appear to have been addressed in responses elsewhere in this appendix.

The citations provided on insulin do not meet the inclusion criteria and an in depth discussion of this topic is not within the scope of the report.

Individual clinicians and members of the public

The following is a list of individuals (clinicians and/or members of the public) who provided comments. Comments from listed individuals are included in this appendix following those from industry (in the order listed below). Substantially similar comments from individuals are not included in full in this section. An overview of the primary comments from clinicians and members of the public is provided below.

Spectrum Response: Comments that relate to the report have been addressed via the above responses in the peer review and public comments section. Comments that relate to key questions are not timely as the report already included a draft key question comment period and key questions guide the report development. Comments that related to program decisions, program process, committee policy decisions, and/or other matters not pertaining to the report, are acknowledged here, but are not within the scope of the commissioned evidence report and response for report accuracy and completeness.

Comments from Medical Professionals

Individual	*Profession and Professional Relationship*
Eric Adman, Paramedic	Paramedic Shoreline Fire Department
C. Childs, PT	Physical therapist; Did not cite a professional relationship
Dawn Corl, Diabetes CNS	Harborview Medical Center
Louise Suhr, Glycemic Team ARNP	
Dawn Giberson, RN, BSN, CDE, CPH	Did not cite a professional relationship
Carla Greenbaum, MD	Director, Diabetes Program, Did not write on behalf of the Benaroya Research institute, the University of Washington, or the ADA
Irl Hirsch, MD	Specialist in endocrinology and diabetes, University of Washington Medical Center
DoriKhakpour, RD, CD, CDE	Diabetes Research Nutrition Coordinator, University of Washington Medical Center
Virginia O'Kelly RD, CDE	Make a DIF (Diabetes Intervention & Follow-up)
Alyssa Olsen	American Diabetes Association

Megan O'Neill	Physician Assistant and CDE working in endocrinology and diabetes, Did not cite a professional relationship
Kim Schrier, MD	Pediatrician, Did not cite a professional relationship
Jody Stanislaw, ND	Naturopathic Doctor, Did not cite a professional relationship
Andy Swanson, BAH, BSN, RN	VA Hospital

Overview of individual medical professional comments: The most common comment from medical professionals related to concerns regarding policy and coverage for SMBG and/or CGM. Two state that there would be ethical concerns regarding conducting RCTs of self-monitoring. (Hirsch, Greenbaum) All but two (Giberson, O'Kellly) commenters provided description of experience in caring for patients with diabetes and/or personal experiences as individuals with diabetes, speaking from their experience and perspective to stress the importance of home glucose monitoring for achieving control while avoiding hypoglycemic events and providing assurance regarding blood sugar levels. Dr. Hirsch describes the trends from the past 3 decades toward improved glycemic control while reducing rates of hypoglycemia, data and figure from the full DCCT (all age groups) and information on unpublished data on the negative correlation between SMBG and A1C. One clinician (Giberson) provides an opinion on the expense (of CGM) and suggests use of funds to provide hbg machines to poor people. One clinician (O'Kelly) states that CGM saves health provider time in assessing insulin dosing/self-management. One clinician group (Corl and Suhr) find professional CGM extremely valuable for medication adjustment and patient education.

Commentsfrom Individuals

Writer	*Relationship to Person with Diabetes*
Brant Baetz	Adult with type 1 diabetes diagnosed in adulthood
Ted C. Bearor	Person with type 1 diabetes for 10 years who uses CGM
Rob Berg	Two children have type 1 diabetes
Tiffany Butler	Adult with type 1 diabetes for 20 years
Will Butler	Wife has type 1 diabetes
Samantha Corbin	Adult with type 1 diabetes who uses CGM
E. B. "Van" Corley	Adult with diabetes for 70 years
Thierry Douet	Adult with type 1 diabetes who uses CGM
Stephen A. Douglass, PhD	Adult with type 1 diabetes for 30 years diagnosed in adulthood
Adam Erickson	Friends have diabetes
Steve Fuchs	Adult diagnosed with type 1 diabetes at age 11,Participant in DCCT: randomized to intensive treatment
Anne Gimotea	Has type 1 diabetes
Jo Hansen	Grand-nephew has type 1 diabetes
Nancy Hansen	Grandson has type 1 diabetes
Tanya Hansen	Nephew and/or son has type 1 diabetes
Jeremy Johnston	Has type 1 diabetes for 35 years; 5-year-old son also has type 1 diabetes
Brad Joss	37 year old with type 1 diabetes for 36 years
Sondra Kornblatt	Type 1 diabetes in her family
Kristen and Jeff Kuhns	Daughter has type 1 diabetes diagnosed at age 3
Cheryl Laurenzo	Adult with type 1 diabetes who uses CGM
Suzanne Leamer	Ten-year-old son has type 1 diabetes, diagnosed at age 3 ½
Nancy Lewis-Williams	
Lucia Linn	The writer, her brother, mother, and nephew have diabetes
LieschanLopuszynski	Son has type 1 diabetes
Kathryn Mack	Writer has diabetes
Karyn Martin	Friend would be affected by limits
Rebecca McFarland	Child has type 1 diabetes
Dorota McHenry and family	Nephew has type 1 diabetes
Meryl C. Mims	
Jami Pratt	Writer and sister are adults with type 1 diabetes
Danielle S. Regan	Friends have type 1 diabetes
Ann Ripley	Has type 1 diabetes

Jessica Royce	Daughter has juvenile onset diabetes; brother also has diabetes
Shannon Scott	Daughter and brother-in-law have juvenile onset type 1 diabetes
Stephanie Scott	Sister and uncle have juvenile onset type 1 diabetes
JoAnn Silkes	Daughter has type 1 diabetes
Tony and Laurel Smith	Son has type 1 diabetes, diagnosed at age 14
Wendy Smith	Adult with type 1 diabetes diagnosed in adulthood who uses CGM
Emily Sproule	
John Sullivan	
Liz Taylor	
Chris Warner	Daughter has type 1 diabetes
Christine Webber	Brother and son have diabetes (childhood onset and type 1, respectively)
Clark Webber	21 year old with type 1 diabetes for 9 years
Melinda Woods	Mother of 13-year-old son with type 1 diabetes
Beth Woolford	Performs SMBG

(All comments provided in full in this appendix following those made by individual providers in the order listed in the above table).

Overview of individual comments: Almost all described their personal experiences and struggles with managing diabetes or that of someone they care for or know who has diabetes. Almost all comments focus on questions of coverage for testing strips and/or continuous glucose monitoring devices and the importance of monitoring to managing diabetes. Several mention the DCCT and EDIC, which are described in the report. A number of commenters express concern that the HTA report recommends specific limits for SMBG and that the limit is once per day. Some commenters provided information on the pathology of diabetes. Some expressed concern that the report does not describe aspects of hypoglycemia and quality of life issues.
One individual (Douglas) comment on specific study content: "Results showing comparisons between groups with so called tight control versus non tight control to be flawed. There is no mention about the willingness and ability of the participants to very carefully control what they eat, and how much exercise they get". Commenter also states that studies of intensive monitoring related to quality of life are not considered. Response to both of these is found in responses to peer reviewers.

Below is a summary of the primary comments made across the letters received.

- Importance of control and importance of testing in maintaining control
- Monitoring is essential/requirement, not an option; monitoring is the compass/informs self-management decisions by diabetic patients/their care givers
- Without constant testing, cannot make informed decisions
- Cannot imagine managing diabetes with only one test/day
- Upset that need for monitoring is questioned or is topic of policy change/decision
- Urge continuation of coverage of glucose test strips and to encourage patients with the disease to follow aggressive testing regimens and encourage patients with the disease to follow aggressive testing regimens, as said regimens are recognized as the best option for monitoring glucose levels to maintain good health (multiple letters with same wording)
- Concerns raised that severe limitations would be placed on testing supplies for juvenile type1 diabetics in need of State aid and that these are the most vulnerable diabetic patients (multiple letters with the similar/same wording)
- Limiting coverage endangers children's lives

- Cost savings you achieve from denying BG tests will pale compared to the costs of unmanaged diabetes. Providing the support and reimbursement necessary for people to manage their disease should be the desirable outcome.
- Many describe personal routine for testing, insulin use and A1C values as well as diet and exercise or such routines for family members/children.
- Several individuals suggest the prices for strips are too high and should be reduced (by manufacturers and insurance companies) or regulated
- Many point out the financial and societal costs of not caring for diabetes and that short-term savings on strips would result in greater long-term cost.
- Limiting coverage/number of strips reduces quality of life for children and their families.
- Those who use CGM cite its benefit in warning them of hypoglycemia and/or hyperglycemia; benefit as a teaching tool for how their body responds to changes.
- Some commenters urge support for advances in glucose monitoring as it is both an definite increase in the quality of life of those with diabetes, and is also a wise investment in helping to avoid of delay the extremely high costs associated with the complications of the disease
- One individual (Corley) commenting on monitoring stated: I do not attach any significance to blood glucose tests. I have been diabetic almost 70 years. I had one 16 year stretch in which I did not check myself in any way. I just regulated my diabetes by how much exercise I did, how much I ate, and how much insulin needed. I took two shots a day for over 66 years; if I could still get beef pork insulin, I am sure I would never have to use the BG tests.

PEER REVIEW COMMENTS

Dace Trence, MD

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for ***Glucose Monitoring in those under 18 years old.*** Your contribution and time are greatly appreciated.

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to Andrea C. Skelly, PhD, andrea@specri.com by November 28, 2010 (or earlier if possible).

If you have questions or concerns please contact Andrea Skelly: andrea@specri.com
Thanks so much!

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INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate?
- Topic of assessment is important to address?
- Public policy and clinical relevance are well defined?

Page 8	Line multiple paragraphs

There is frequent commentary pertaining to patients under 18 monitoring their glucose. In this age range, often the monitoring is not done by the patient and certainly is not done solely by the patient. It is really a family affair, yet there is no mention of the effects that self-monitoring can have on family/ parental well-being in knowing what the blood sugar is at any particular time. Also, no mention of patient friends or sibling sense of safety in having self-blood glucose monitoring readily available, as a concern beyond just efficacy/ effectiveness of individual monitoring. These are critical considerations and should be mentioned on page one of the introduction.

Page 8	Line paragraph 4

There is reference to " several lines of evidence" suggesting discomfort, etc. Need to be clear that you are referring to these "lines of evidence" as specific to those under 18 y/o, and that these "lines of evidence" are not from reports in older age populations, particularly as relates to depression. I strongly suspect your comment refers to published reports in adults, as am not aware of these in the under 18 y/o. If you do not have any data in those under 18 y/o, this comment should be removed from this paper.

Page 10	Line Key question 1 response

There is reference to the DCCT, but the EDIC trial continues, as an observational study extension of a considerable majority of DCCT participants and their development of diabetes associated complications. To really use the DCCT data fully, the original study participants should be reviewed in the light of their follow-up, specific to macrovascular disease (this data has been published in the New England Journal of Medicine) , as well as additional published data referencing other end organ complication rate being impacted over time with the positive legacy effect of better glycemic control. Also at bottom of page 10, unclear comment about "significant differences in nephropathy of rates of ketoacidosis" – please clarify.

P11- first paragraph

In reference to "no RCTs" for efficacy of SMBG testing- this is a comment of concern, as no Institutional Review Board would approve in this day and age, a study in which no testing against testing, as ethical.

Second paragraph:

There is commentary referring to fingerstick glucoses being used concomitantly with CGM as part of "FDA requirement". CGM must be calibrated against fingerstick glucoses, this is not an FDA requirement, but a requirement to be able to initiate CGM as well as maintain quality control. Additionally, as CGM technology uses interstitial fluid rather than capillary, there is a well recognized lag in glucose levels reflected by CGM as reflected in fingerstick glucose determinations. Therefore, as part of the education in

use of CGM, patients are specifically instructed to rely not on CGM, but instead to use fingerstick approach if glucose trends are rapidly changing- either decreasing or increasing.

Line section on results of CGM:

The analysis is missing several important points brought out by the referenced studies. First that there was a very specific correlation in A1c decrease with more time spent using CGM- specifically that the more time off CGM, the less the impact on A1c. Also, there was less hypoglycemia in those using CGM most consistently- this is a critical piece of information- glucoses improved with less hypoglycemia. Even in follow-up, the same improvement in A1c was noted with significantly less hypoglycemia in the control group for the 6 month JDRF study mentioned. (Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. Diabetes Care. 2010 Jan;33(1):17-22. Epub 2009 Oct 16.) Also, QOL in CGM users has been reported as very positive, specific to a sense of control, decreased hypoglycemia- this has been published (Jean Halford, Claudia Harris. Diabetes Technology & Therapeutics. March 2010, 12(3): 201-205.).

P12- Effectiveness paragraph

There is much attention placed to attempts to separate out use of CGM or SMBG reflecting overall better outcomes versus acting on the information. This makes no sense- the point of obtaining data is to act on the information- not just obtaining a numerical value. So to suggest that " changes in treatment regimen and management may have impacted on the results" rather then use of CGM seems ridiculous- the point of CGM as well as SBGM is to use the data to indeed make treatment and management changes. The reasoning noted here seems rather bizarre.

Page 12: Safety of devices.

Mention made of "false positive results" as a concern. More concerning is when patients do not pay attention to their device and specifically chose to ignore visualized glucose trends or put their CGM on vibrate and then do not check the CGM screen, or walk away from the device rather than carry with them. These issues are not device safety issues but patient choice- very different issues. The purpose is to alert the patient of glucose trend changes, so equally noted concerns regarding "irritated by alarms" seems similar to saying deliveries in those pregnant should be all under general anesthesia, as the pain is "irritating".

Page 13: 3rd bullet point

Need to clarify your comment about cardiac arrest- in whom did this occur? If not clear whether child or adult, this point should be removed as non-contributory and highly misleading (falls outside your own insistence in the document that you reviewed only literature pertanent to those under 18 years of age).

Page 19- last paragraph

Reference to "lines of evidence" should be deleted if these are not specific to those under 18 years of age, your paper's focus.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient?

Page 31 ,
MDI
paragraph

Sentence that "Patients must know how to do carbohydrate counting" should be changes to "Patients benefit from knowing how to do carbohydrate counting, which typically requires an approximation of planned carbohydrate intake" Absolute precision is not required of this skill for the ability to match food to insulin.

Page 34: Third paragraph

"…major barrier to testing…pain" would suggest changing to "discomfort"

Page 35: second paragraph

Misleading to state that there are four CGM systems- really only 3. The Medtronic CGM is really the same system, whether Paradign-REAL, Guardian REAL, Paradigm Guardian.

Page 37:

AACE has published a concensus paper with recommendations re CGM:

AACE Consensus Statement: Continuous Glucose Monitoring *Endocr Pract* 2010 (16): sept-oct, that includes recommendations for use of CGM in childern

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue?
- Key questions clearly defined and adequate for achieving aims?

Page Line

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METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate?
- Criteria for the inclusion and exclusion of studies is appropriate?
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?
- Data abstraction and analysis/review are adequate?

Page page 64	Line "Treatment assignment"

Concerns regarding the applicability of requiring blinding from study staff as whether pump vs multiple daily injections were used with CGM or SMBG. Discussion regarding management of diabetes issues, specific to insulin dosing would inherently be different if pump vs injections were used, so blinding would be impossible as data with study participant reviewed. Also, data appearance would be considerably different from a CGM versus glucose meter download or even self-record. To state that the evidence level is therefore 2 for these studies, does not have real world significance.

Page	Line

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RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate?
- Key questions are answered?
- Figures, tables and appendices clear and easy to read?
- Implications of the major findings clearly stated?
- Have gaps in the literature been dealt with adequately?
- Recommendations address limitations of literature?

Page 94 top bullet points	Line

The comments pertaining to no nephropathy impact in DCCT study seems misleading as there was an impact on decreased development of both de novo microalbuminuria and well as a decrease in macroalbuminuria. Also, no mention of impact on neuropathy development- was this an omission? There is reference to both later, on page 77.

Page 77 “older studies” paragraph

The data presented would be in direct contrast to information that SMBG gave children a sense of more control than urine testing. This important sense of control should be mentioned in your introductory comments, not “line of evidence” that pain, depression, associated with SMBG, for which you have no data in children.

Page 78:

There is again reference to SMBG not being distinct from CGM. This would be impossible, as initialization process of the CGM device, as well as continued use of CGM, requires minimally calibration against SMBG, so it would be impossible to construct a study that separates the two. These comments strongly suggest a lack of familiarity with CGM use requirements.

Page	Line

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CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid?

Page p 94	Line hypoglycemia

It is recognized that more hypoglycemia is associated with more frequent SMBG as patients check more often if they feel possible symptoms of hypoglycemia. Am concerned that to interpret this as possibly

more frequent monitoring is directly related to more hypoglycemia, as incorrect cause and effect.

Page	Line
page 94	Comment on CGM users associated with death

Where is your evidence based data supporting the statement that patients using CGM are at risk of death as opposed to those not using CGM? Page 96, where death is listed under sensor side-effects is very misleading and should be removed- you have extremely limited details on this individual's medical history, age, events, so linking this to CGM is extremely misleading

Page 96 review of SMBG adverse effects

Although you note the age of the studies referred to, in earlier portions of this paper, there is reference to older studies lacking applicability as to analysis. Why include at this point information that pertains to older devices- reports pertaining to close to 30 years ago- as now pertaining to your review? Do not understand applicability.

Page 112 cost burden

Cited are 2 reports- a German report and a Mexican report. Question of what value these reports are, given a very different structure of health care cost coverage in these different countries, and certainly not comparable to the Washington state system.

Page	Line

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OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?
- Are the main points clearly presented?
- Is it relevant to clinical medicine?
- Is it important for public policy or public health?

Page	Line
Page113	Summary key q #1

Neuropathy was lessened by intensive glycemic control, this should be mentioned. Also, the issue regarding nephropathy needs clarification, as the included reference to nephropathy development not being different between standard versus intensive control is also misleading. Additionally, no information on EDIC included, which is the extension study of DCCT.

Page 113 Key q #2

CGM cannot be used without SMBG as noted earlier, this is impossible, so to state that studies reviewed are inadequate as they do not strictly separate out these two modalities, makes no sense. Also there is reference to CGM studies showing better A1c goal attainment with CGM, but then note made of no changes in hypoglycemia- the issue is specifically that lower glucose control was achieved *without more* hypoglycemia, exactly the opposite of would be expected, as you note in the review of the hypoglycemia rate seen in the DCCT with glycemic improvement.

Page 114

Cannot separate CGM or SMBG associated benefits from treatment regimen changes or management. In real world medicine, why would these be divorced? Glucose checks are done to act on, to make management decisions.

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QUALITY OF REPORT

Quality Of the Report
(Click in the gray box to make your selection)

Superior ☐

Good ☐

Fair x☐

Poor ☐

Enter Comments Here

We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

Although the literature search and consequent bibliography is extensive, there is a considerable mix of reported data- very dated (1980's) that does not reflect current technology, mix of ages in studies (although some effort is made to separate out data, the mixed age data is still frequently referred to), and have significant concerns as to whether the technology, specifically CGM, is understood, when reference is made that CGM studies are always confounded by SMBG, when SMBG is requisite to operating CGM. Data pertinent to increased SMBG frequency associated with better glycemic control is noted, but reference to possible side-effects is confounded by published data in older aged individuals is cited

frequently, and yet an old study suggesting benefit in sense of control over diabetes in young performing SMBG, seems mentioned only once. And the ability to manage diabetes and make treatment changes is exactly the reason that SMBG is recommended as a standard of care for those with diabetes, specifically those on medication, such as insulin, the majority of individuals below the age of 18. CGM is noted as being an evolving technology and indeed we are still learning in which patients it is most effective, but achieving better glycemic control with less hypoglycemia is a critical finding in the Hirsch CGM studies. There is an increased burden of diabetes incidence, both Type 1 and Type 2, rapidly evolving- how without the access to frequent SMBG and/or CGM, will there be ability to decrease the costly onslaught of diabetes associated complications?

Finally a key question not brought up and yet very important to this issue is the quality of life of those caring for the person under 18 years of age, and even more specifically the infant or toddler that cannot report symptoms of change in well being, or hypoglycemia unawareness that requires frequent SMBG.

Angela Badaru, MD

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for ***Glucose Monitoring in those under 18 years old.*** Your contribution and time are greatly appreciated.

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to Andrea C. Skelly, PhD, andrea@specri.com by November 28, 2010 (or earlier if possible).

If you have questions or concerns please contact Andrea Skelly: andrea@specri.com
Thanks so much!

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INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate? yes
- Topic of assessment is important to address? yes
- Public policy and clinical relevance are well defined? Yes in some respects, but it appears to attend to only short-term cost effectiveness

Page 8	Line paragraph 4

In everyday clinical practice there is clear correlation between frequency of SMBG and glycemic control. Poor self monitoring is associated with unacceptably high A1C levels.

Page 12	Line 20

This is an irrelevant comment as the same can be said about other group who wore for less than 6 days and did not show improvement in A1C.

Page 12	Line 31

This is because those who test most frequently are generally on an intensive insulin regimen run lower glucose readings in general and hence have better glycemic control and lower A1C. The downside may be higher risk for hypoglycemic episodes. Children are particularly prone to hypoglycemia, with younger children unable to express symptoms of hypoglycemia; thus frequent monitoring is essential.

Page 13 Line 24

I disagree with this conclusion. Children less than 5 yrs especially benefit from frequent monitoring with regards to improved glycemic control and fewer episodes of severe hypoglycemia. There are recent publications that support this (Paris et al J Pediatrics 2009).

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient? Yes

Page 46 table 7

Even though specific reference to the pediatric population in the St John study is not made, it would be informative to summarize and at least comment on the effectiveness and benefits of SGM in the adult population here.

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REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue? Yes
- Key questions clearly defined and adequate for achieving aims? NO

Page 65 66 67 Line

In this section (Observational studies of effectiveness: SMBG frequency), it would be informative to highlight not only what the studies did not accomplish but also the degree of improvement (if any) in glycemic control associated with frequency of SMBG.)

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METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate? yes
- Criteria for the inclusion and exclusion of studies is appropriate? yes
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained? no
- Data abstraction and analysis/review are adequate? yes

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RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate? No; incomplete presentation of data (skewed presentation to de-emphasize benefits of intensive monitoring)
- Key questions are answered? Disagree with some conclusions
- Figures, tables and appendices clear and easy to read? Yes
- Implications of the major findings clearly stated? No; incomplete presentation of data and disagree with interpretation/conclusions
- Have gaps in the literature been dealt with adequately? no
- Recommendations address limitations of literature? No.

Page 73 Line 27

The DCCT trial clearly established that intensive insulin therapy improves glycemic control and reduces long-term complication rates. Intensive insulin therapy in the pediatric population is currently accepted as standard of care and endorsed by the ADA, JDRF and ISPAD. Without frequent SMBG, optimal diabetes care in the pediatric population would not be achievable. Given that intensive insulin therapy is advocated in the pediatric population, it would be unethical in current practice to design a RCT where a subgroup of children would be assigned to a sub-standard (less frequent) monitoring schedule.

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CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid? no

Page 114 Line 41

This is an irrelevant comment as the same can be said about other group who wore for less than 6 days and did not show improvement in A1C.

Page 115 line 6- 10

This is because those who test most frequently are generally on an intensive insulin regimen run lower glucose readings in general and hence have better glycemic control and lower A1C. The downside may be higher risk for hypoglycemic episodes. Children are particularly prone to hypoglycemia, with younger children unable to express symptoms of hypoglycemia; thus frequent monitoring is essential.

Page 116 line 8

I disagree with this conclusion. Children less than 5 yrs especially benefit from frequent monitoring with regards to improved glycemic control and fewer episodes of severe hypoglycemia. There are recent publications that support this (Paris et al J Pediatrics 2009).).

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OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized? yes
- Are the main points clearly presented? yes
- Is it relevant to clinical medicine? Yes—very relevant
- Is it important for public policy or public health? yes

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QUALITY OF REPORT

Quality Of the Report
(Click in the gray box to make your selection)

Superior

Good

Fair

Poor x

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While the content of this report is robust and literature discussion extensive, the conclusions reached are biased. Emphasis has been placed on various study omissions/weaknesses while positive outcome associations between frequent SMBG and improved glycemic control have not been highlighted or have been down played.

Page	Line

Glucose monitoring remains the cornerstone of optimal diabetes management. The need for liberal and flexible access to its use is particularly true for children with their inability to recognize and/or verbalize symptoms and the frequent variability of their daily routine, some of which are unpredictable (e.g. illness). This view has been supported by national and international organizations, including the American Diabetes Association (ADA, 2008) and the International Society for Pediatric and Adolescent Diabetes (Rewers et al, 2007, 2009). Multiple studies have clearly stated the importance of frequent blood glucose monitoring in the pediatric population (Rewers et al, 2007, 2009; Paris et al, 2009).

Page	Line

Enter Comments Here

We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

Enter Form Comments Here

PUBLIC COMMENTS

The following pages contain comments from clinical/professional organizations and industry that were received. Comments from individuals listed in the section titled "Individual clinicians and members of the public" are included in this appendix following those from industry in the alphabetical order listed on pages 15 and 17.

Clinician professional organizations

American Diabetes Association (ADA)
The Endocrine Society
Pediatric Endocrine Society

Industry

Abbott Diabetes Care (with appendix from UBC)
Bayer HealthCare
DexCom
Medtronic Diabetes
Roche Diagnostics

Comments from Individual Medical Professionals (see page 15 for alphabetical listing)

Comments from Individuals (see page 16 for alphabetical listing)

December 10, 2010

Leah Hole-Curry
Director
Health Technology Assessment Program
676 Woodland Square Loop SE
Lacey, WA 98503

RE: Glucose Monitoring: Self-monitoring in patients under 18 years old

Dear Ms. Hole-Curry:

We support the Washington Health Technology Assessment (HTA) Program's mission to assure that individuals covered by state health plans receive the most effective diagnoses and treatments. With this goal in mind, we write to express our concern that children with diabetes have access to the tools they need to effectively manage their disease. We are particularly concerned that blood glucose monitoring may be restricted in ways that are harmful to the health and safety of children with diabetes and counter to nationally and internationally recognized guidelines.

As you review technologies and the available evidence related to glucose monitoring in children with diabetes, we urge the HTA Program to recognize the current standards of clinical care for pediatric diabetes patients. For care of patients with diabetes, treatment must be comprehensive and individualized. To effectively manage the disease, a person with type 1 diabetes needs to balance food, physical activity and insulin by utilizing self-monitoring of blood glucose (SMBG). Successfully monitoring blood glucose levels is essential for children with diabetes to avoid dangerous – and potentially deadly – acute complications caused by extremely high and low blood glucose levels. In the long term, monitoring is key to avoiding or delaying painful, debilitating, and costly complications of diabetes including heart disease, stroke, amputation, blindness and end-stage kidney disease. SMBG became a fundamental component of care following the irrefutable evidence published in 1993 in the Diabetes Control and Complications Trial (DCCT) that intensive therapy improves glycemic control and delays the onset and progression of diabetes complications. SMBG is the widely accepted cornerstone enabling patients to achieve control of blood glucose levels and Continuous Glucose Monitoring (CGM) is the added tool necessary in appropriate cases.

Each year, the American Diabetes Association publishes clinical practice recommendations[1] based on a complete review of the relevant literature by a diverse group of highly trained medical experts utilizing evidence from rigorous double-blind

[1] American Diabetes Association. *Standards of Medical Care in Diabetes – 2010*. Available at: http://care.diabetesjournals.org/content/33/Supplement_1

clinical trials to expert opinion. The American Diabetes Association has also published a statement on the "Care of Children and Adolescents with Type 1 Diabetes."[2] These documents provide expert guidance on current standards of care for children with diabetes and call for checking blood glucose levels before eating and when there are symptoms of high and low blood glucose levels as well as periodically after meals, before and after exercise, and at night. To be clear, all experts in pediatric diabetes agree that checking blood glucose multiple times per day is absolutely essential to the health and safety of children with type 1 diabetes. Further, recently published and ongoing clinical trials in pediatric diabetes include SMBG as intrinsic components of family-focused, school-based, and community clinical interventions. There will not be randomized clinical trials to establish something that is so well-established within diabetes care and indeed such a study would be unethical.

Children with diabetes face special challenges including the inability of younger children to self identify the warning signs of dangerous blood glucose levels, the hormone changes in older children, and growing bodies for all. Consider the irate three year-old at risk for dangerously low blood glucose levels (hypoglycemia) because he decides not to eat his entire meal after receiving a dose of insulin meant to cover more food; the fourteen-year old who just finished a particularly grueling football practice and is at risk for hypoglycemia over the next twelve or more hours; and the sixteen year-old at home with the flu who needs to test frequently because infection can cause severe high blood glucose levels (hyperglycemia) or diabetic ketoacidosis. All of these situations, and more, are common in the lives of children and can require additional blood glucose checking. The danger is real: not only can severe hypoglycemia and diabetes ketoacidosis be life-threatening, recent evidence reinforces previous findings that recurrent, severe low blood glucose levels, such as may occur in young children without the advantages of consistent and frequent blood glucose monitoring, may yield permanent neurologic damage. Against this great need stands the current standard in Washington's Medicaid program of three glucose testing strips per day, an allotment that does not meet the needs of a child with diabetes in even the most uncomplicated case.

CGM has greatly evolved over the past decade and is now recognized as an important tool for pediatric endocrinologists to utilize for appropriate patients. In 2010, the American Association of Clinical Endocrinologists issued a report from its Consensus Panel on Continuous Glucose Monitoring. The report recommended CGM for certain patients, including children and adolescents with type 1 diabetes who have achieved hemoglobin A1C levels less than 7.0% (these patients and their families are typically highly motivated) and youth with type 1 diabetes who have hemoglobin A1c levels of 7.0% or higher and use the device on a near-daily basis.

[2] A statement of the American Diabetes Association. *Care of Children and Adolescents With Type 1 Diabetes*. 2005. Available at: http://care.diabetesjournals.org/content/28/1/186.full

Diabetes is a complex disease to manage and can lead to costly complications. According to the 2006 Washington State Diabetes Disparities Report, it was estimated a person with uncomplicated diabetes incurs $1,600 in medical costs per year. Washington diabetes-related hospitalizations charges in 2003 averaged $23,600 for one admission of coronary heart disease, $20,400 for an amputation, and $7,300 for diabetic ketoacidosis. The total charges for diabetes-related hospitalizations in Washington amounted to more than $1.27 billion dollars in 2003. The goal of diabetes care is to avoid the painful and costly complications of this terrible disease. If access to the tools necessary to perform SMBG is further limited, Washington will instead pay for avoidable, and expensive, hospitalizations due to hypoglycemia, diabetic ketoacidosis, and other complications.

The individualized needs of the child with diabetes as well as current accepted standards of medical practice established by experts in pediatric endocrinology must be kept in the forefront of the HTA Program's process as payment policies are considered. Accordingly, we strongly urge the HTA Program to refrain from establishing a standard limit for SMBG in children with diabetes, particularly one as low as testing three times a day, and from enacting a blanket denial of CGM for children. Such limits will be costly both for the state's budget and for our children and their future.

Sincerely,

David M. Kendall, M.D.
Chief Scientific and Medical Officer
American Diabetes Association

Lori M. Laffel, MD, MPH
Chair, Youth Strategies Committee
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Chief, Pediatric, Adolescent & Young Adult Section
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Chief Scientific Officer
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Daniel Einhorn, MD, FACP, FACE
President,
American Association of Clinical Endocrinologists

President,
The Endocrine Society

Catherine Pihoker, MD
Division Head, Pediatric Endocrinology and Diabetes
Seattle Children's Hospital

Paul J. Turek, MD
President,
American Society of Andrology

December 10, 2010

Leah Hole-Curry, JD Director,
Health Technology Assessment
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RE: DRAFT Report: Glucose Monitoring: Self Monitoring In Patients Under 18 years Old (November 12, 2010)

Dear Ms. Hole-Curry:

The Endocrine Society, the world's oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology, appreciates the opportunity to comment on the Washington State Health Care Authority's (the Authority) report, "Glucose Monitoring: Self-monitoring in Patients under 18 Years Old."

While we support the Washington Health Technology Assessment Program's mission to assure that individuals covered by state health plans receive the most effective diagnoses and treatments, we are concerned that the report ignores the long-established standard of care for self-monitoring of blood glucose (SMBG) of capillary blood obtained by fingerstick and read on a point-of-care meter. Although there may be disagreement about whether or not SMBG is useful in patients with type 2 diabetes on oral agents, there is little controversy among endocrinologists about the effectiveness of its use in pediatric, adolescent and adult patients on multiple daily insulin (MDI) regimens.

As the report indicates, the Diabetes Complications and Control Trial (DCCT) study indirectly provided the most compelling evidence that intensive diabetes management reduces complications of diabetes. This was truly a landmark study that settled the question of whether or not tight glycemic control was beneficial. That it was so not only in the medium term (7 years) but in the long-term (20+ years) (according to the EDIC study[1]) has influenced subsequent management of diabetes. The study was also shown to be cost-effective and has saved both lives and money in the ensuing decades. The tight and highly beneficial glucose control achieved in this study could not have been accomplished without SMBG. Furthermore, to conduct a randomized controlled trial at this point would be considered unethical since SMBG-based MDI or insulin pump therapy is the standard of care in the United States.

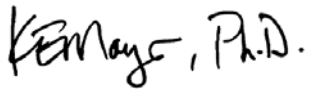
Continuous glucose monitoring (CGM) is a relatively new technology that has quickly been adopted by endocrinologists because of its clear benefits. The Endocrine Society has developed a clinical practice guideline (estimated to be published in late 2011) that makes several recommendations on the use of real-time CGM (RT-CGM) in children and adolescents. This Endocrine Society Council approved, evidence-based clinical practice guideline used the GRADE system[2] to evaluate the strength of the recommendations and the quality of the evidence. Based on the GRADE system the guideline strongly recommended that RT-CGM be used in the following circumstances:

- In those who have achieved HbA1c levels <7.0% because it will assist in maintaining target HbA1c levels while limiting the risk of hypoglycemia;
- In those who have HbA1c levels ≥7.0% who are able to use these devices on a nearly daily basis; and
- In combination with insulin pump therapy in those who cannot achieve glycemic control on MDI treatment aided by standard glucose self-monitoring.

The guideline also suggested that RT-CGM be used by selected children with type 1 diabetes who are younger than 8 years old; and CGM systems be intermittently used in short-term retrospective analysis of pediatric patients with diabetes in whom clinicians worry about nocturnal hypoglycemia, dawn phenomenon, and postprandial hyperglycemia; in patients with hypoglycemic unawareness; and in patients experimenting with important changes in their diabetes regimen (instituting new insulin or switching from MDI to pump therapy).

We urge the Authority to recommend that SMBG and CGM be available to patients based on the best clinical judgment of their health care providers. To do otherwise puts a vulnerable population at short-, intermediate-, and long-term risk that is greater than existed prior to 1993.

Sincerely,



Kelly E. Mayo, PhD
President
The Endocrine Society

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PEDIATRIC ENDOCRINE SOCIETY
Formerly named in honor of Lawson Wilkins

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Leah Hole-Curry, Director
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December 09, 2010

Dear Ms. Hole-Curry and Health Technology Assessment Program members:

The Pediatric Endocrine Society (PES) is the largest U.S. professional organization dedicated to advancing the care of children and adolescents with endocrine disorders – including diabetes. As concerned members of PES, we are writing to provide comments on the posted report entitled "Glucose Monitoring: Self Monitoring in Patients Under 18 Years Old HTA" compiled by Spectrum Research, Inc which aims to assess the efficacy, safety and cost effectiveness of glucose testing in the pediatric population. While several conclusions of the HTA report are problematic in our view, this letter focuses on the following HTA report conclusions, with which the PES has major concerns:

1) That there is low standard of evidence to support the value of intensive diabetes care management (self-monitoring of blood glucose [SMBG] several times per day, education on how adjust insulin, diet and exercise) compared to standard care (urine or SMBG up to X times per day, no daily changes in insulin or diet)
2) That there is low standard of evidence to support the value of higher SMBG frequency compared to lower SMBG frequency
3) That there is only moderate standard of evidence to support the safety of SMBG

The Pediatric Endocrine Society applauds the efforts of the Washington State Health Care Authority (WSHCA) and the Health Technology Assessment (HTA) Program to assess the role of diabetes-related technology, including SBGM and continuous glucose monitors (CGM), in improving the health of children with diabetes. The PES welcomes initiatives to analyze the efficacy, safety, and cost-effectiveness of medical interventions, and approaches to enhancing translation of those deemed beneficial. We appreciate the extensive work conducted by Spectrum Research, Inc in compiling the report. However, there are several methodological and conceptual problems with the analysis that significantly detract from the results and are likely to invalidate the report's conclusions. We outline the report's challenges along with the provision of substantial contrary evidence in order to help that WSHCA and HTA

Program to derive informed conclusions regarding the use of SMBG in the pediatric population with diabetes. The problems include:

1. The report seeks to identify recent randomized controlled studies on the use of SMBG as a basis for its conclusions. However, the landmark Diabetes Control and Complications results unequivocally proved the importance of tight diabetes control and lowering hemoglobin A1C to prevent diabetes complications (Diabetes Control and Complications Trial. *Pediatr.*1994; 125(2):177-188); in this pivotal study, tight control was achieved by intensive insulin management using the results of frequent SMBG. The DCCT had to be discontinued in 1993 when an interim analysis revealed that the benefits of intensive management of diabetes were so great and unequivocal that it was no longer ethical to continue to conventionally managed patients with diabetes. Since then, it has been justifiably considered unethical to deny any group of children frequent SMBG as to do so would preclude intensive insulin management. Therefore, it is not reasonable or ethical to assume that a dearth of randomized studies of SMBG indicates such monitoring to be ineffective; in fact, the dearth of studies actually results from the fact that intensive insulin management based on frequent SMBG *is* effective. Most of the randomized trials cited in the Report predated the DCCT and were using insulin regimens that are no longer considered state-of-the-art. Current regimens most commonly require knowledge of pre-prandial BG values to determine the amount of insulin to be given before meals. A list of more recent clinical trials assessing SMBG as an intrinsic and fundamental component of improving glycemic control in pediatric patients with diabetes is included below.
2. SMBG is not by itself a method to improve glycemic control – it is instead a *necessary* means for adjusting insulin doses and the other important modalities (diet and exercise) involved in managing diabetes to achieve target glycemic control. Simply attempting to examine the relationship of SMBG and glycemic control may miss the fundamental intermediary, i.e., insulin dosing. In fact, the critical role of SMBG in enabling rational insulin dosing and thereby achieving improved glycemic control is underscored by the fact that many successful interventions use increase in the frequency of SMBG as a means to improve insulin dosing. Furthermore, studies in children have demonstrated that frequency of SMBG is a potent predictor (and sometimes the only predictor of hemoglobin A1C (Haller MJ et al. *J. Pediatr*, 144(5):660-661, 2004. Levine BS et al. J Pediatr 2001;139:197-203).
3. It is not possible to separate the effects of SMBG from the effects of other diabetes self-management components (e.g., insulin regimen, diet, exercise etc). In this review, the lack of separation is cited as a weakness of many studies, whereas it is actually a reflection of the fact that these components are integrated in self-care. For example, studies of approaches to avoiding excessive glycemic excursions with exercise for youth with diabetes highlight the fundamental importance of blood glucose monitoring (Taplin CE et al, J Pediatr. 2010;157(5):784-8. Tsalikian E, et al. J Pediatr 2005;147(4):528-34.).
4. Children are often unable to express symptoms of hypoglycemia and have less predictable food intake and activity than adults; furthermore, children are susceptible to long-term sequelae from hypoglycemia (Bjørn O, et al. Diabetes Care 2010 33:1945-1947) There are also growing concerns about the potential for hyperglycemia to impact cognitive function (Gaudieri PA, et al. Diabetes Care

2008;31(9):1892-7. Naguib JM, et al. J Pediatr Psychol 2009;34(3):271-82. Northam EA, et al. Diabetes Care 2009;32(3):445-50) Therefore, it is particularly inappropriate to place a limit on SMBG in children.

5. Regarding safety, the report does not address morbidity and mortality with inadequate SMBG. Proper insulin dosing cannot be safely given without the knowledge gained from SMBG. Further, many costly hospitalizations for diabetic ketoacidosis in pediatric patients can be prevented by frequent and timely SMBG.
6. The report does not distinguish between discrete SMBG and continuous glucose monitors (CGM). This is a major flaw as it does not distinguish between the principal importance of SMBG per se and the potential added value of newer technology. It is imperative that these two management tools, SMBG and CGM, should be analyzed separately with regard to efficacy, safety, and cost-effectiveness.
7. The report lacks the perspective and input from appropriate content experts in the field of pediatric diabetes management.

The limitations of the report are underscored by the fact that its conclusions differ from other well-respected technology assessments, including:

- National Collaborating Centre for Women's and Children's Health commissioned by the National Institute for Health Excellence. Type 1 diabetes: diagnosis and management of type 1 diabetes in children and young people. London (UK): Royal College of Obstetricians and Gynecologists; 2004, update June 2009, 217p.

Recommendations:

1. "Children and young people with type 1 diabetes should be encouraged to use blood glucose measurements for short-term monitoring of glycaemic control because this is associated with reduced levels of glycated haemoglobin. Urine glucose monitoring is not recommended because it is less effective and is associated with lower patient satisfaction."
2. "Children and young people with type 1 diabetes and their families should be encouraged to perform frequent blood glucose monitoring as part of a continuing package of care that includes dietary management, continued education and regular contact with their diabetes care teams."
3. "Children and young people using multiple daily injection regimens should be encouraged to adjust their insulin dose if appropriate after each preprandial, bedtimeand occasional night-time blood glucose measurement."
4. "Children and young people using twice-daily injection regimens should be encouraged to adjust their insulin dose according to the general trend in preprandial, bedtime and occasional night-time blood glucose measurements."
5. "Children and young people with type 1 diabetes who are trying to optimise their glycaemic control and/or have intercurrent illness should be encouraged to measure their blood glucose levels more than four times per day."

http://www.nice.org.uk/nicemedia/live/10944/29394/29394.pdf

- Canadian Optimal Medication Prescribing and Utilization Service (Compus). Optimal therapy recommendations for the prescribing and use of blood glucose test strips.

Ottawa (ON): Canadian Agency for Drugs and Therapeutics in Health (CADTH); 2009 Jul. 50 p.

Recommendation: "The optimal daily frequency of SMBG (self-monitoring blood glucose) should be individualized for children with type 1 diabetes."
http://www.cadth.ca/media/pdf/compus_BGTS_OT_Rec_e.pdf

Further, multiple national organizations around the world that endorse SMBG frequency in the care of youth with diabetes (e.g. American Diabetes Association, the German Diabetes Association) based upon the literature and consensus among experts in the field. Therefore, the combined evidence derived from the historical context of SMBG, numerous scientific reports, and critical reviews by other respected health technology assessors strongly support that *frequent blood glucose testing in some form is critical for the intensive management of diabetes mellitus and is appropriately considered standard of care nationally and internationally.* If accepted and implemented, the HTA conclusions that there is low standard of evidence supporting for the efficacy of frequent blood glucose testing would set back diabetes mellitus management 17 years, and could be misused by those with financial motivation to limit the capacity of children and adolescents to achieve glycemic control, maintain normal growth and development, and avoid the debilitating acute and chronic complications of diabetes.

The Pediatric Endocrine Society therefore strongly urges re-evaluation and revision of this report so that it is fully evidence –based and does not harm children. We respectfully suggest that a revised assessment by the HTA will be strengthened by the addition, if not already done, to the assessment team of at least two board-certified pediatric endocrinologists currently involved with the care of pediatric patients with diabetes, 1-2 diabetes educators, and parents of children with diabetes. We are confident that such a re-examination will support frequent blood glucose testing in children.

On behalf of the PES, we thank you for your attention. Please feel free to contact us with any questions or concerns or requests for assistance.

Sincerely,

David B. Allen, M.D, President, Pediatric Endocrine Society
Janet Silverstein, MD, President-Elect, Pediatric Endocrine Society
Dorothy Becker, MD, Past-President, Pediatric Endocrine Society
Alan Rice, MD, Co-Chair, PES Public Policy Council
Leona Cuttler, MD, Co-Chair, PES Public Policy Council
Sara Divall, MD, Co-Chair, PES Drug and Therapeutics Committee
Mark Parker, MD, Chair, PES Practice Management Council
Lori Laffel, MD, MPH, Chief, Adolescent and Young Adult Section, Joslin Diabetes Center, Boston
Richard Mauseth, MD, Pediatric Diabetologist, Woodinville, WA
Catherine Pihoker, MD, Head of Endocrinology and Diabetes, Seattle Children's Hospital

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Richton S. Risk for metabolic control problems in minority youth with diabetes. Diabetes Care 1999 May;22(5):700-5

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Honorable Leah Hole-Curry, JD
Program Director
Washington State Health Care Authority
Health Technology Assessment Program
P.O. Box 42712
Olympia, WA 98504-2712

Dear Ms. Hole-Curry:

We would like to acknowledge the effort that the Washington State Health Care Authority has expended undertaking a health technology assessment (HTA) of blood glucose monitoring among persons age 18 and under who suffer from insulin-dependent diabetes mellitus. We share the State of Washington's goal of ensuring that children who are covered by state health insurance programs receive appropriate evidence-based medical care while making best use of public financial resources. We appreciate the opportunity to review the draft health technology assessment report and offer our comments in the spirit of achieving that goal. However, the appropriateness of this HTA with regards to the questions posed, in particular, with a focus on children under the age of 18 should be undertaken with considerable care to ensure safety of this population. The HTA asserts that this topic lacks support from randomized controlled trials (RCTs), which are considered to be one of the highest levels of evidence available. Due to the lack of RCTs, the HTA draws conclusions that there is little support for testing more than once per day for children under 12 years of age. We believe this conclusion to be misguided. Therefore, we commissioned a report by United BioSource Corporation to review and provide comment on your draft report (attached).

According to the "Final Key Questions" document (6/21/2010), the topic was chosen because, "*...there is currently several well conducted and recent publications to help*

glucose monitoring policies for adults with non-insulin requiring diabetes, but not for youth with insulin requiring diabetes." Results of the technology assessment bear this out. However, the draft document misplaced emphasis on the lack of RCTs that evaluated the efficacy of frequent SMBG in diabetic patients under 18 years old. The lack of RCTs is not surprising, because it is unethical to conduct trials that would prevent children who require insulin treatment from receiving the frequent SMBG they need (fully explained in attached UBC report). By definition, children with insulin-dependent diabetes mellitus require frequent administration of insulin along with frequent SMBG.

Federal regulations as well as ethical conduct require that RCTs demonstrate clinical equipoise. In other words, one arm of the trial must not be seen *a priori* as potentially more harmful to participants. Given the state of knowledge, a trial comparing glucose testing versus no glucose testing would undoubtedly be seen as unethical in any insulin dependent diabetic population. Additionally, federal regulations also require special protection for children who are enrolled in clinical trials. For this reason RCTs where insulin dependent participants are age 18 or below, who do not have access to SMBG, are not done for patient safety reasons.

In addition to the points mentioned previously, the lack of more recent randomized clinical trials evaluating the efficacy, effectiveness, and safety of SMBG is likely not due to the lack of importance; but instead, the fact of allowing a group of children to be assigned to not monitor their glucose levels and administer insulin would increase the risk of hypoglycemia and other safety events related to poor glycemic control (which could result in death). Dosing must be adjusted according to blood glucose measurements and must be individualized. There is a general consensus and absence of controversy with respect to frequency of testing as exemplified by numerous clinical practice guidelines. For example, the American Diabetes Association (ADA) recommends that self monitoring of blood glucose be carried out at least four times daily

for children and adolescents with type 1 diabetes and that more frequent SMBG may be necessary to achieve postprandial glucose targets.[1]

Although the report asserts that there is lack of evidence to make a causal claim for the impact of self-monitoring on HbA1c levels, this is still the best established standard of care of insulin dependent children. The report offers no alternative for maintaining glycemic control without frequent self-monitoring.

Clinical guidelines and well established clinical practice support the frequent monitoring of blood glucose for children (under age 18) who are insulin dependent to maintain glycemic control. The alterative of not monitoring would result in a larger proportion of children with poor glycemic control likely resulting in a lifetime of diabetes-related adverse events and significant mounting associated medical costs. Although this condition is uncommon, with an estimated incidence of 1.7 cases per 1000 persons age ≤19, it is the most prevalent chronic condition among children. Careful management of blood glucose is critical to avoiding episodes of hypoglycemia or hyperglycemia that can have devastating short-term as well as long-term consequences

The State of Washington Health Care Authority seeks to establish payment policies that are aligned to support appropriate utilization of diabetes management technologies. With respect to the care of young people with insulin-dependent diabetes mellitus, it is essential that coverage is available for glucose monitoring in accordance with widely accepted clinical practice guidelines.

Abbott Diabetes Care understands the importance of and respects the need to conduct health technology assessments. Although this effort is important, it is also crucial that a critical eye is applied in deciding the topics and the usefulness of these reviews. Given

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[1] American Diabetes Association (ADA). Care of Children and adolescents with type 1 diabetes. A statement of the American Diabetes Association. *Diabetes Care* 2005;28:186-212.

the federal regulations and clinical practices already in place on the topic of glucose monitoring, the application of this HTA could cause immediate negative impacts on the health of children with diabetes. It is a goal of Abbott Diabetes Care to help ensure high quality care for people with diabetes, in particular, children, so if the State of Washington chooses to pursue other topics within this area, Abbott is happy and ready to assist in these endeavors.

Sincerely,

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United BioSource Corporation
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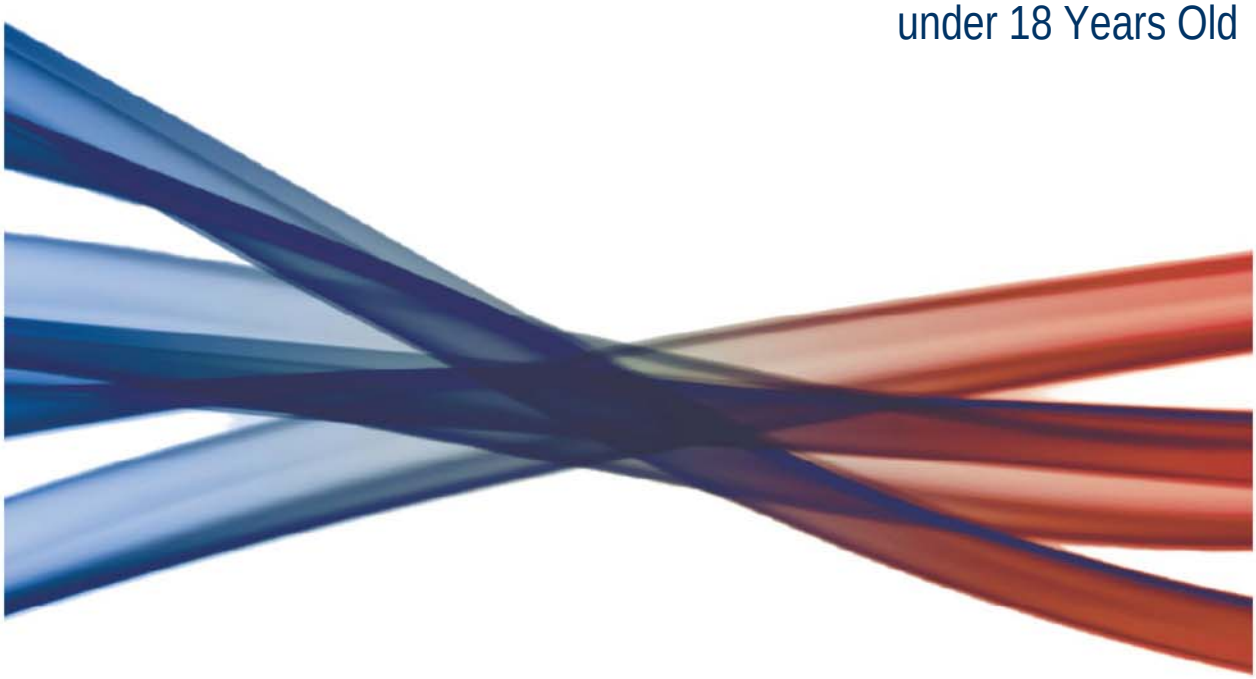
Report prepared for:

Abbott Diabetes Care

Abbott Diabetes Care

Review of the State of Washington Health Technology Assessment: Glucose Monitoring: Self-monitoring in Patients under 18 Years Old



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EXECUTIVE SUMMARY

The Washington State Health Care Authority Health Technology Assessment Program has issued a draft report entitled, "Glucose Monitoring: Self-monitoring in Patients under 18 Years Old." The report addressed 5 key questions:

1. What is the evidence of efficacy and effectiveness of glucose monitoring?
2. What is the evidence on optimal or improved efficacy or effectiveness of glucose monitoring based on frequency or mode (continuous versus self monitoring) of testing?
3. What is the evidence of the safety of glucose monitoring?
4. What is the evidence that glucose monitoring has differential efficacy or safety issues in sub populations?
5. What is the evidence of cost implications and cost-effectiveness of glucose monitoring?

- Federal regulations as well as ethical conduct require that randomized control trials (RCTs) demonstrate clinical equipoise. In other words one arm of the trial must not be seen *a priori* as potentially more harmful to participants. Given the state of knowledge, a trial comparing glucose testing versus no glucose testing would undoubtedly be seen as unethical in any insulin-dependent diabetic population.
- Federal regulations also require special protection for children who are enrolled in clinical trials. For this reason published RCTs where participants are age 18 or below are generally not done for SMBG testing for safety reasons.
- The stated focus of the HTA report is on the efficacy, safety and cost effectiveness related to SMBG, however, the report neglects to address the indirect long-term impact of not maintaining glycemic control. Overwhelming evidence and an established standard of care in support of glucose monitoring to maintain glycemic control has been widely accepted and practiced for at least several decades. In accordance with regulatory guidelines and as evidenced in the existing published literature, it is critical to monitor blood glucose levels to determine the effectiveness of the management plan as quickly and conveniently as possible, and thus help to

prevent hypoglycemia and extreme hyperglycemia and to avoid complications of diabetes.

- In addition to the points mentioned previously, the lack of more recent randomized clinical trials evaluating the efficacy, effectiveness, and safety of SMBG is likely not due to the lack of importance, but instead the fact that the standard of care is well established and the guidelines for treatment of human subjects, in particular, children are quite strict with regards to guidelines for randomization. Given these guidelines, it would be highly unlikely a study would be conducted that would allow a group of children to be assigned to not monitor their glucose levels, therefore, increasing the risk of hypoglycemia and other safety events related to poor glycemic control. Further, it would seem unnecessary to study an area of care and treatment which is considered well-accepted.

- While the report asserts that there is lack of evidence to make a causal claim for the impact of self-monitoring on HbA1c levels, this is still the best established standard of care of insulin dependent children. The report offers no alternative for maintaining glycemic control without frequent self-monitoring.

- Clinical guidelines and well established clinical practice support the frequent monitoring of blood glucose for children (under age 18) who are insulin dependent to maintain glycemic control. The alterative of not monitoring would result in a larger proportion of children with poor glycemic control likely resulting in a lifetime of diabetes-related adverse events and significant mounting associated medical costs.

BACKGROUND

Project Objectives

The Washington State Health Care Authority Health Technology Assessment Program issued a report entitled "Glucose Monitoring: Self-monitoring in Patients under 18 Years Old." Public comments on the draft report will be received until December 10, 2010. Abbott Diabetes Care (Abbott) has engaged United BioSource Corporation (UBC) to perform a rapid review and critique of the report. The UBC review examines:

- Study questions
- Literature review methodology
- Findings with respect to study questions
- Overall conclusions

Organization of This Report

We begin by presenting a brief summary of the glucose monitoring technology assessment report ("Glucose Monitoring HTA"). We review the study questions that were addressed in the technology assessment, and the main conclusions with respect to each question.

We then describe our assessment of the literature review and synthesis: the methodology for identifying potentially relevant publications, the process for selecting articles that were reviewed, and the review process itself, including the overall appropriateness of the key questions given the complete lack of clinical community doubt of the critical nature of self-monitoring of blood glucose in patients under 18 years old.

Following this section, we offer our own commentary on published evidence for self-monitoring of blood glucose (SMBG). As previously stated, due to limited time allowed, we could not perform an independent literature review as a component of this project. Our commentary is based on our technical knowledge and experience in evaluating technology assessments combined with the knowledge and experience in the diabetes therapeutic area.

Next, we examine the key study questions with respect to principal findings of the technology assessment as well additional focused literature review. Here the central issue is the overall appropriateness of the questions whether findings are firmly grounded and consonant with the evidence that was identified and synthesized.

Finally, we present a summary assessment and critique of the Glucose Monitoring HTA.

SUMMARY OF THE WASHINGTON STATE HTA REPORT

The State of Washington Glucose Monitoring HTA report focused on self-monitoring methods used by insulin-dependent children and adolescents under the age of 18 to assess glucose levels

at home for daily decision making regarding self-care. Key questions addressed in the study include:

1. What is the evidence of efficacy and effectiveness of glucose monitoring? Including consideration of:
    a. Achieving target A1c levels
    b. Maintaining target A1c levels
    c. In conjunction with provider specific report cards for target (e.g. under 7/over 9)
    d. Reduce hospitalizations or acute episodes of diabetic ketoacidosis, hyperglycemia and hypoglycemia
    e. Reduce microvascular complications (retinopathy, nephropathy, neuropathy)
    f. Reduce mortality
    g. Effect on medication or nutritional management
    h. Quality of life
2. What is the evidence on optimal or improved efficacy or effectiveness of glucose monitoring based on frequency or mode (continuous versus self monitoring) of testing?
3. What is the evidence of the safety of glucose monitoring? Including consideration of:
    a. Adverse event type and frequency (mortality, major morbidity, other)
4. What is the evidence that glucose monitoring has differential efficacy or safety issues in sub populations? Including consideration of:
    a. Gender
    b. Age (differential within the 18 and under population)
    c. Psychological or psychosocial co-morbidities
    d. Other patient characteristics or evidence based patient selection criteria
    e. Provider type, setting or other provider characteristics
    f. Health care system type, including worker's compensation, Medicaid, state employees
5. What is the evidence of cost implications and cost-effectiveness of glucose monitoring? Including consideration of:

a. Costs (direct and indirect) in short term and over expected duration of use

b. Estimates of costs saved by preventing morbid events

Based upon the studies identified, selected, and reviewed in the HTA report, the authors conclude that there is conflicting evidence regarding whether more frequent SMBG results in lower rates of hypoglycemia. Furthermore, the overall strength of the evidence is low. Published reports indicate that performing SMBG 4 to 5 times per day was associated with lower glycosylated hemoglobin (HbA1c) levels. However, because these findings were primarily based on observational study designs, it was not possible to establish a causal relationship between HbA1c levels and frequency of SMBG.

CRITIQUE OF THE LITERATURE REVIEW AND SYNTHESIS

In this section of the report we offer a review and critique of the methods underlying the literature review that forms the basis of the technology assessment. In particular, the HTA methodology was reviewed for overall organizing framework, definition of the study questions and objectives, thoroughness and clarity of search algorithms, criteria used for article selection, and rules for data abstraction.

The State of Washington described the methodology used to identify, screen and examine information from the resulting group of studies; however, there are several gaps within the described methodology, including a narrow definition of search strategy, that may account for partial findings and conclusions within the assessment that require further attention.

Study Key Questions

The individual research questions outlined within the report address the areas of efficacy, effectiveness, and safety in self-glucose monitoring; however, there are fundamental issues with the questions in terms of their appropriateness for the topics covered in the HTA. The standard practice for glucose monitoring to maintain good glycemic control is well established and documented therefore, to assess the efficacy of this not necessary. Additionally, there are few safety concerns with the monitoring practices themselves and instead far greater concern with the impact the lack of monitoring can have on glycemic control. Furthermore, the appropriateness of the questions in the context of a HTA may be problematic given the disease state that is being addressed. As discussed in greater detail in subsequent sections of this report, current federal

regulations as well as ethical conduct require that randomized control trials (RCTs) demonstrate clinical equipoise and also require special protection for children who are enrolled in clinical trials. For this reason published RCTs in insulin requiring diabetics in children and adolescents are generally not done for SMBG testing for safety reasons.

Furthermore, the study questions themselves are somewhat repetitive and overlapping. According to the Study Rationale, the "core" of the glucose monitoring concerns addressed by the Health Technology Assessment Program is reflected in key question #2 "What is the evidence on optimal or improved efficacy or effectiveness of glucose monitoring based on frequency or mode (continuous versus self monitoring) of testing"? Yet key question #1, which addresses long term outcomes of self-glucose monitoring, appears equally important and is clearly related to key question #2.

Search Algorithm

The search algorithms used to conduct this review are made up of several different independent search strings that were combined to target articles most relevant to this assessment. The initial disease string used to define the diabetic population(s) of interest was limited to only terms indexed through Medline (MeSH terms). A substantial concern with relying on only index terms is that technique used to classify each article, human review of the citation, may mean a particular article could be indexed incorrectly. Likewise, another key area of concern is that many of the limits available to hone in on the target population (such as age limiters, which is key to this evaluation) can also prove to be incomplete in selecting the population of interest. Moreover, as the index process is done manually rather than through an automatic algorithm for assigning MeSH terms, there is a lag time between when a citation first appears in Medline and when it is indexed within the MeSH database. This lag can be as substantial as six months, and therefore to ensure that the most relevant articles are captured, a supplemental keywords search with no limits should be run for the most recent six month period. In the case of this review, this supplemental search was not included.

Also, the search string developed to focus on studies in which self or continuous monitoring practices for measuring glycemic control was limited to the MeSH term for self monitoring and a series of keywords for continuous monitoring. To ensure that this search was thorough, keywords for self monitoring, such as self monitoring blood glucose and SMBG, should have

been used to make sure all relevant citations were caught. Finally, the searches used to focus on different areas of interest, such as safety and study design, were incomplete with regards to the terms used and therefore it is highly likely pertinent articles were omitted.

Article Selection

Although the report details the search strategies used and the resulting attrition diagram, it is unclear whether citations from the overall search (Glucose Monitoring HTA report 2010) were reviewed or just those from the sub-searches. Based on the documentation, it appears that only the sub-searches were reviewed, and thus, as referenced above, relevant citations were most likely excluded from the review. For example, articles by Haller et al. (2004) and Levine et al. (2001), are identified through the broader search, but are excluded from all of the sub-search strings. Given the research questions examined within the HTA, it would be imperative and crucial for a complete review to make certain all relevant articles were captured, such as the two listed above

With regards to the selection criteria, the authors do not describe the underlying reasons and justification for their choice of inclusion/exclusion criteria used to establish which publications would be summarized within the HTA report. The report is clear in identifying the criteria for inclusion in the systematic review, but it is not clear how these criteria were determined. Specifically, by including all types of diabetes – Type 1, Type 2, and gestational, the review combines diagnoses driven by different underlying factors (e.g., insulin requiring diabetes, non-insulin requiring diabetes, pharmacologically treated diabetes) and typically with different treatment regimens. Historically, in the juvenile population, the presence of diabetes was almost exclusively limited to Type 1, however, with the increase in childhood obesity, the incidence of Type 2 is on the rise. The selection criteria also references including only studies with a high level of evidence, however, the search used to identify these types of studies does not include terms for cohorts or cross-sectional studies that may be of interest.

Data Abstraction

The report and data tables also reference each publication separately even in cases where the same study population is reported. To avoid inflating the findings from these studies, it is standard practice that each study should be counted a single time and all information should be pooled under the most comprehensive publication.

CRITIQUE OF EVIDENCE BASE

There are additional factors that may impact the overall quality of the findings and conclusions of the HTA.

Protection of Human Research Subjects

Considered the "gold standard" of human research, randomized controlled trials (RCTs), which are becoming increasingly more common, often drive medical advancement; however, they should only be conducted when they are ethically and practically feasible. Equipoise, genuine uncertainty regarding the comparative therapeutic benefits on the part of the investigator or medical experts regarding the preferred treatment, is often considered a necessary criterion for human subjects in randomized trials (Freedman 1987).

In general, an RCT is considered to be in equipoise when there is honest scientific uncertainty about the expected health outcome of each group. Importantly, although equipoise may be difficult to maintain during a trial, all research involving human subjects requires approval by an Institutional Review Board (IRB), prior to study initiation. As mentioned in section 46.111 CFR, the IRB is responsible for determining whether the study requirements are acceptable. In making this determination, the IRB evaluates the risks and associated benefits to ensure that any risks to subjects are minimized "which are consistent with sound research design and which do not unnecessarily expose subjects to risk." Moreover, the regulations also mention that the "adequate provision" for the safety of subjects must be considered in the research plan.

This is a highly important issue, because although the use of randomized trials has become a standard method of evaluating therapies, experimental research involving any type of treatment or intervention requires safeguards to protect the rights and welfare of humans participating as subjects in research. Randomly assigning subjects to no or limited daily glucose monitoring would be an obvious ethical dilemma with adverse consequences and resulting safety concerns. As such, the authors of the HTA report should more readily consider **the value of non-randomized studies and clinical guidelines** in this therapeutic area. Currently, the importance of non-randomized trials **has been greatly underestimated and because of the ethical issues with the SMBG in insulin requiring diabetics, more attention to examining alternatives to randomized trials should be considered.**

Special Protections for Children as Research Subjects

Several sections within the findings of the report note that no randomized controlled trials (RCTs) were found on the topic of self-glucose monitoring. Because of the ethical standards in place for the treatment of human subjects in RCTs, it is not surprising that very few trials have been conducted in the pediatric population. SMBG is an integral component of disease management for patients with type 1 diabetes. However, there is a paucity of well-designed clinical trials in children and adolescents with type 1 diabetes. Although a well-designed large RCT would be an ideal study to determine the effectiveness for frequency of monitoring, such trials may no longer be feasible in the given population, due to the ethical principles and guidelines for the protection of children in research. The Belmont Report (1979), a key reference document influencing federal regulations and guidelines for research using human subjects, details the special consideration for and protection of potentially vulnerable subject populations, including children. Moreover, the Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP) has specific provisions supported by the federal government when a proposed research study involves children. For instance, the research institution's Institutional Review Board (IRB) must take into consideration the additional protection for the children who would be involved in the research. As stated in 45 CFR 46.405, when research involves greater than minimal risk in children, "the risk must be justified by the anticipated benefits to the subjects and the relation of the anticipated benefit to the risk presented by the study is at least as favorable to the subjects as that provided by available alternative approaches".

CRITIQUE OF RESEARCH QUESTIONS

Research Question Conclusions

1. **What is the evidence of efficacy and effectiveness of glucose monitoring?**

   The main finding for key question 1 is that, "*No randomized controlled trials or observational studies which directly evaluated current methods of SMBG testing were found*." Although in accordance with the search criteria, this conclusion misses a fundamental issue: daily glucose monitoring is critical for achieving glycemic control in persons with insulin-dependent diabetes. In a crossover study published nearly 30 years ago, the findings demonstrated the benefit on glycemic control of frequent daily self-monitoring

of glucose among young adults (Schiffrin & Belmonte 1982). Thus, the fact that there are no recent studies is likely due to the fact that the importance of glycemic control is so well established and the inappropriateness of conducting randomized trials in these patients as previously described.

The HTA report references the Diabetes and Complications and Control Trial (DCCT) as indirect evidence for the efficacy of SMBG for diabetes management. The major conclusions of this study are widely regarded and not viewed as indirect evidence. The results of this trial clearly showed significantly lower HbA1c levels by 6-12 months and lower average daily blood glucose concentrations ($p<0.001$) in children 13 to 17 years of age, thus providing evidence for the effectiveness of glucose monitoring. The majority of evidence in the literature and clinical practice guidelines emphasize the importance of SMBG in the management of diabetes as a critical component for long-term maintenance of glycemic control (ADA 2010; AACE 2002; Schiffri & Belmonte 1982). Furthermore, monitoring glucose as directed by healthcare providers will allow patients to recognize the effects that medications, diet, stress, and exercise have on their blood glucose levels, which will allow patients to become more easily achieve specific glycemic goals (AACE 2002).

2. What is the evidence on optimal or improved efficacy or effectiveness of glucose monitoring based on frequency or mode (continuous versus self monitoring) of testing?

No randomized clinical trials were identified that evaluated efficacy of SMBG frequency. However, the report briefly acknowledges the findings from the recent study by Ziegler et al. (2010). The aim of the study by Ziegler and colleagues (2010) was to correlate the frequency of SMBG to the quality of long-term metabolic control as measured by HbA1c in 26,723 children and adolescents. Study findings showed that more frequent SMBG was significantly associated with better long-term metabolic control. Furthermore, HbA1c decreased by 0.20% with each additional SMBG per day ($p<0.001$) up to five SMBG per day. Interestingly, in children 0–5 years and 6–12 years, an increase in SMBG frequency beyond one SMBG per day showed less improvement in HbA1c compared to adolescents older than 12 years; however, in all age groups increased frequency of SMBG was statistically significant (all

p<0.05). The authors conclude that higher frequency of SMBG measurements were related to better metabolic control, especially in adolescents 12 years of age and older.

While the finding of lack of strong evidence for frequency of SMBG is correct based on the narrow search criteria, the methodology fails to capture the fact that there appears to be very wide consensus in the clinical community. All of the major and respected organizations in diabetes (for example, the American Diabetes Association) have issued clinical practice guidelines and recommendations for glucose monitoring in children and insulin requiring diabetics; the practice guidelines are discussed in detail later in this report). The findings of this draft technology assessment are inconsistent with the standard of practice in the US. The clinical practice recommendations across the organizations are in major agreement regarding SMBG. Overall, it is typically recommended that blood glucose be tested a minimum of 3 to 4 times daily. Depending on the management plan, it may also be important to test pre- and postprandial blood glucose to achieve patient glucose targets. For instance, postprandial testing is important to reduce the risk for cardiovascular disease associated with postprandial hyperglycemia (Woerle et al. 2004); whereas pre-prandial testing may provide valuable information regarding glucose control and potential risk of hypoglycemia.

The HTA report concludes that the overall strength of evidence regarding the efficacy or effectiveness of CGM relative to SMBG is inconclusive. Differences in achieved HbA1c levels in the cited trials were not statistically significant. Frequencies of hypoglycemia or hyperglycemia episodes were not different. Quality of life, that might be associated with the discomfort of SMBG, did not differ at 26 weeks in one study. Association of monitoring technology with long-term outcomes was not reported.

3. What is the evidence of the safety of glucose monitoring? Including consideration of: Adverse events and frequency (mortality, major morbidity, other)

For this key question, relevant evidence from clinical trials and observational studies was identified. Some safety issues have been reported for CGM but "…suggest that major adverse events are uncommon." It is well recognized that there are few (if any) safety issues related to conventional self glucose monitoring, mainly due to improved blood drawing technology.

Safety is certainly an important issue for any diagnostic technology, and particularly in the case of the newer and more complex continuous glucose monitoring technology. However, key question 3 fails to address what seems to be a critical safety issue, the risks and health consequences of related to poor glycemic control due to inadequate blood glucose monitoring. SMBG is essential for the prevention of hypoglycemia and additional long-term complications of unregulated diabetes, including heart disease, stroke, kidney failure, and nerve damage.

4. **What is the evidence that glucose monitoring has differential efficacy or safety issues in sub populations? Including consideration of: Gender, Age (differential within the 18 and under population), Psychological or psychosocial co-morbidities, Other patient characteristics or evidence based patient selection criteria, Provider type, setting or other provider characteristics, Health care system type, including worker's compensation, Medicaid, state employees**

While there may be little evidence in the literature regarding differences in efficacy and safety issues in sub-population, as noted in the HTA report, as discussed in detail above, Ziegler et al. (2010) reported an association between higher frequency of SMBG measurements and better metabolic control, especially in adolescents 12 years of age and older. It is also important to consider the purpose of SMBG and that it is primarily used to determine the efficacy or effectiveness of the management plan, providing both the clinician and the patient with critical information on glycemic control that will allow for informed decisions regarding care. SMBG also helps to prevent dangerous fluctuations in hypoglycemia and hyperglycemia, which will help to prevent both acute and long-term complications of unregulated diabetes. Furthermore, to our knowledge, no gender differences in the efficacy and safety of SMBG have been published in the literature. With respect to the other issues included in the HTA report, it is unclear how such issues (worker's compensation, state employees, etc.) are relevant in children and adolescents.

5. **What is the evidence of cost implications and cost effectiveness of self-glucose monitoring?**

The report indicates that there is no evidence available to assess the cost-effectiveness of SMBG or CMG in children under the age of 18 who require insulin to treat diabetes.

No studies evaluating the costs of diabetes in a pediatric population in the US were located – only two studies were referenced (one from Germany and one from Mexico). Although the findings of these papers show that glucose testing constitutes the bulk of costs associated with type 1 diabetes in children, there were no assessments to determine the cost-effectiveness of glucose monitoring in children. One reason for this could be, as described below, that there are ethical issues associated with randomized controlled trials in this therapeutic area for all patients, adults and children, in relation to equipoise. Furthermore, the rules are even more stringent for children in particular, as they are a protected class. Another reason is that all major treatment guidelines suggest that patients who require insulin to treat their diabetes should test their glucose levels several times a day. Thus, it would be very difficult to establish a comparison group using data from observational or retrospective studies of persons who do not test their glucose daily. In terms of cost-effectiveness, it is most likely that costs associated with unregulated diabetes and resulting poor glycemic control would be much higher than the cost of continuously testing and maintaining target glucose levels. Studies which examine the cost-effectiveness of SMBG in adults compared with no SMBG indicate that glucose monitoring is cost effective and offsets human and financial costs of complications (Tunis and Minshall 2008; Palmer et al. 2006).

UBC COMMENTARY: EVIDENCE ON GLUCOSE MONITORING IN INSULIN-REQUIRING DIABETES

Published Studies of SBMG in Children

There were several randomized and non-randomized trials included in the technology assessment that provided details on the efficacy of SMBG with respect to frequency. For instance findings from the Diabetes and Control Complications Trial (DCCT), a randomized study in children 13-17 years of age, showed that SMBG at least four times per day in conjunction with an education program (intensive therapy) resulted in significantly lower HbA1c levels by 6-12 months and for the remainder of the study duration, in addition to significantly lower average daily glucose concentrations compared with the conventional therapy group (testing once per day) (DCCT, 1994). Additionally, children and adolescents with poorer glycemic control had more frequent short-term adverse outcomes when compared to adults.

Using multivariate analysis, evidence across several non-randomized observational studies suggests an association with SMBG frequency and HbA1c levels. For instance, when compared to children who tested 1-2 times per day or less, children who performed SMBG 4-5 times daily had lower HbA1c levels (Anderson et al. 1997 and 2002; Levine et al. 2001; Moreland et al. 2004; Paris et al. 2009). Moreover, in the study by Levine and colleagues (2001), frequency of blood glucose monitoring was the single modifiable predictor of HbA1c.

There is additional published evidence available in the literature on the effectiveness of glucose monitoring in patients with diabetes requiring insulin therapy not included in the WA Health Technology Assessment report (Saudek et al. 2006; Karter et al. 2001; Haller et al. 2004; Mehta et al. 2009; Nathan et al. 1996). All of these sources included patients treated with insulin. In the Florida Camp for Children and Youth with Diabetes (FCCYD) study, the frequency of SMBG was correlated with lower HbA1c, consistent with other findings in the literature (Levine et al. 2001; Karter et al. 2001). In a study by Karter et al. (2001), SMBG of three of more times per day among patients with type 1 diabetes was associated with lower HbA1c levels. Interestingly, more frequent SMBG was also clinically and statistically associated with improved glycemic control, regardless of diabetes type (type 1 or 2) or therapy (i.e., pharmacologically or diet-controlled). Furthermore, in another study by Nathan et al. (1996), a significant association between frequency of self-monitoring of glucose and lower HbA1c levels in adults with type 1 diabetes was reported. The omission of these sources draws into question the thoroughness of the review and completeness of the HTA findings and conclusions. Overall, findings published in the literature indicate that frequent blood glucose monitoring may promote better metabolic control, potentially reducing the risk of diabetic complications.

Clinical Practice Guidelines on Frequency of SMBG

Many respected organizations have issued clinical practice guidelines and recommendations for glucose monitoring in children and insulin requiring diabetics. These guidelines were also presented in the WA Health Technology Assessment report. The American Diabetes Association (ADA) Clinical Practice Recommendations (2010) provides evidence from published studies when possible, and expert opinion or consensus when necessary. Additionally, the guidelines also recommend more frequent self monitoring of blood glucose (SMBG) to achieve postprandial glucose targets. Although the most recent report does not specifically refer to the

pediatric population, it is recommended that SMBG be performed three or more times daily for patients requiring insulin therapy and this most certainly applies to children. Moreover in an earlier statement published by the ADA (Silverstein et al. 2005), it is recommended that the SMBG be carried out at least four times daily for children and adolescents with type 1 diabetes.

Guidelines published by the Diabetes Coalition of California (California Diabetes Program 2008), recommend SMBG testing in children and adolescents with type 1 diabetes a minimum of four times daily, consistent with recommendations published by the ADA. In addition, the International Society for Pediatric and Adolescent Diabetes (Rewers et al. 2009), states that "SMBG is an essential tool in the optimal management of childhood and adolescent diabetes" and as such, recommends SMBG should be performed at a frequency of 4-6 times daily to optimize diabetes control in children. The International Diabetes Federation (IDF 2007) recommends SMBG a minimum of three times per day in insulin requiring diabetics. Although more general guidelines are offered by the National Institute for Clinical Excellence (NICE 2009), recent recommendations of this report state that children with type 1 diabetes should monitor their blood glucose frequently as part of their management plan to optimize glycemic control.

More recently, a global consensus conference by the International Diabetes Center (IDC), a World Health Organization (WHO) Collaborating Center for Diabetes Education and Translation, published recommendations for the frequency and timing of SMBG (Bergenstal et al. 2005). As recommended by the consensus panel, frequencies for SMBG for patients receiving multiple daily insulin injections is three to four times daily, with many patients requiring more frequent monitoring to prevent hypoglycemia. Furthermore, recommendations also included profiling of blood glucose through self monitoring various times of the day, including fasting, preprandial, and postproandial glucose to provide an overview of glycemic control.

In addition, the HTA states that the "primary focus is on evaluation of self-monitoring methods used to assess glucose levels at home for daily decision making regarding self-care", which is suggestive of inclusion of both type 1 and 2 diabetes in children and adolescents; however, the guidelines included in Section 1.3 only cover Type 1 diabetes. To adequately cover the recommendations for self-glucose monitoring, if all populations are to be covered within the

report, supporting guidelines should be presented for Type 2 and possibly gestational diabetes as well.

SUMMARY AND CONCLUSIONS

The stated focus of the HTA report is on the efficacy, safety and cost effectiveness related to SMBG, however, the report neglects to address the indirect long-term impact of not maintaining glycemic control. Overwhelming evidence and an established standard of care in support of glucose monitoring to maintain glycemic control has been widely accepted and practiced for at least several decades. In accordance with regulatory guidelines and as evidenced in the existing published literature, it is critical to monitor blood glucose levels to determine the effectiveness of the management plan as quickly and conveniently as possible, and thus help to prevent hypoglycemia and extreme hyperglycemia and to avoid complications of diabetes.

The lack of more recent randomized clinical trials evaluating the efficacy, effectiveness, and safety of SMBG is likely not due to the lack of importance, but instead the fact that the standard of care is well established and the guidelines for treatment of human subjects, in particular, children are quite strict with regards to guidelines for randomization. Given these guidelines, it would be highly unlikely a study would be conducted that would allow a group of children to be assigned to not monitor their glucose levels, therefore, increasing the risk of hypoglycemia and other safety events related to poor glycemic control. Further, it would seem unnecessary to study an area of care and treatment which is considered well-accepted.

Furthermore, the study questions and execution bring several factors into question. First and foremost, the defined research questions neglect to address some of the key factors related to SMBG such as long-term impact of poor glycemic control with regards to patient safety and associated cost. There are far more potential safety concerns related to poor glycemic control than concerns over the safety of performing SMBG which are addressed in this report. Also, while efficacy and effectiveness are evaluated for SMBG, there is substantial evidence to support the importance of frequent glucose monitoring which is established to be the best way to self-monitor.

The search and screening process used to assess the available evidence also allowed for gaps in the collection of evidence. Reliance on indexing terms, in particular, creates a scenario where

mis-indexed or newly published articles would not be captured. Additionally, the exclusion of grey literature such as conference proceedings and HTA assessments may suggest that the latest and greatest with regards to this topic are not covered within this HTA report.

While the report asserts that there is lack of evidence to make a causal claim for the impact of self-monitoring on HbA1c levels, this is still the best established standard of care of insulin dependent children. The report offers no alternative for maintaining glycemic control without frequent self-monitoring.

Clinical guidelines and well established clinical practice support the frequent monitoring of blood glucose for children (under age 18) who are insulin dependent to maintain glycemic control. The alterative of not monitoring would result in a larger proportion of children with poor glycemic control likely resulting in a lifetime of diabetes-related adverse events and significant mounting associated medical costs.

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APPENDIX A:

THE BELMONT REPORT

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection Of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

Ethical Principles and Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often

occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethic of research involving human subjects: the principles of respect for persons, beneficence and justice.

1. Respect for Persons. Respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give

weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense. as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process

of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to give forethought the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical. psychotherapeutic. and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children - even when individual research subjects are not direct beneficiaries. Research also makes is possible to avoid the harm that may result from the appli-cation of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A diffi-cult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according

to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conflict of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied. While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative

procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal. and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the preservation of the information to the subject's capabilities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to

ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited --- for example, by conditions of immaturity or mental disability. each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails pro-providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence --- especially where possible sanctions are involved - urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for

determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk / benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons.

The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/ benefit assessments are concerned with the probabilities and magnitudes of possible harms and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider

alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject - or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. --- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/ benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects. even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social. racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution. unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting. They can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

APPENDIX B:

SCHIFFRIN & BELMONTE, *DIABETES CARE*, 1982

Multiple Daily Self-Glucose Monitoring: Its Essential Role in Long-Term Glucose Control in Insulin-dependent Diabetic Patients Treated with Pump and Multiple Subcutaneous Injections

ALICIA SCHIFFRIN AND MIMI BELMONTE

Twenty-one insulin-dependent diabetic patients, previously treated with continuous subcutaneous insulin infusion (CSII), multiple subcutaneous insulin injections (MSI), and a combination of CSII and MSI (combined CSII-MSI) all supported by frequent capillary self-blood glucose (CBG) determinations (5–7 times daily) participated in a program to assess the importance of frequent CBG monitoring. We used a crossover design where diabetic control as measured by mean blood glucose and glycosylated hemoglobin were compared during periods of frequent and infrequent capillary blood glucose monitoring. Diabetic control was significantly better during periods of frequent self-glucose monitoring. We conclude that in compliant, motivated young adults with insulin-dependent diabetes, frequent self-glucose monitoring is critical for the long-term maintenance of glycemic control. DIABETES CARE 5: 479–484, SEPTEMBER–OCTOBER 1982.

The goal of achieving long-term normoglycemia continues to stimulate the search for optimized methods of management of insulin-dependent diabetes. Recent studies indicate that glucose control may be improved in these diabetic patients with continuous subcutaneous insulin infusion (CSII)[1–6] or conventional treatment with home glucose monitoring.[7–11] Previous reports by our group have shown achievement of long-term glucose control with CSII,[12] multiple subcutaneous injections (MSI),[13] and overnight continuous insulin infusion with MSI during the day (combined CSII-MSI),[14] all supported by self-glucose monitoring 5–7 times daily. The purpose of the present study was to evaluate the need of frequent capillary blood glucose (CBG) determinations once an established pattern of insulin requirements and stabilization of metabolic control had been obtained for 1 yr. With this aim, we undertook a prospective crossover study in which patients under CSII, MSI, and combined CSII-MSI treatment alternated periods of frequent and infrequent CBG monitoring.

METHODS

Subjects. Twenty-one insulin-dependent diabetics aged 15–36 yr participated in the study. All patients had fasting C-peptide levels below 0.08 pmol/ml and responded to i.v. glucagon with C-peptide levels below 0.2 pmol/ml. Patients followed a diet which consisted of 30–40% fat, 15–20% protein, and 40–45% carbohydrate given as three meals and a bedtime snack.

Fourteen patients had been previously treated with CSII and MSI for 6 mo each, in a random order, supported by self-glucose monitoring 5–7 times daily. At the end of the crossover trial, the results of which have been published elsewhere,[13] seven patients elected to remain on CSII and seven patients remained on MSI. The remaining seven patients were treated with combined CSII-MSI for 1 yr.[14]

Protocol. At the end of the crossover study, the patients on MSI and CSII were allowed to monitor their CBG as often as they considered necessary. During phase 1 (months 12–18) group A was the group of patients on CSII who monitored their CBG at least 4 times daily, group B was the group on CSII who monitored their CBG twice daily, group C was the group of patients on MSI who monitored their CBG 4 times daily, and group D was one patient on MSI who elected to monitor twice daily. During phase 2 (months 18–21), the groups were crossed over, so that groups A and C, who monitored their CBG 4 times daily during phase 1, were asked to monitor twice daily while the patients in groups B and D, who monitored twice daily during phase 1, were asked to monitor their CBG 4 times daily. Finally, during phase 3

(months 21–24), all groups were asked to monitor their CBG at least 4 times daily. The seven patients on combined CSII-MSI who monitored their CBG 5–7 times daily for one year were asked to monitor their CBG twice daily for 3 mo (phase 1) and to restrict CBG monitoring at least before each meal and at bedtime for a similar period (phase 2) thereafter.

For patients on CSII, insulin was delivered using a portable battery-driven infusion pump (Mill Hill infuser, model 1001-GM, Muirhead Ltd, Beckman, Kent, England). Regular insulin Connaught (Connaught Laboratories Ltd, Ontario) or Lilly (Eli Lilly and Company, Indianapolis) diluted in physiologic saline was infused at a basal rate of 33 μl/L via a 27-gauge butterfly needle (The Deseret Company, Sandy, Utah) which was inserted subcutaneously in the anterior abdominal wall. The basal infusion rate varied between 0.6 and 1.2 U/h while each set of premeal or presnack "clicks" provided a total of 2–10 U of insulin. Patients were instructed to adjust their premeal dose according to an individualized sliding scale. Details were reported elsewhere.[13,14] For the patients on MSI, insulin was administered 4 times a day, given as regular insulin before breakfast, lunch, and supper and NPH at bedtime. Insulin was adjusted according to a sliding scale similarly to the patients on CSII. For the patients on combined CSII-MSI, overnight continuous subcutaneous infusion was delivered using the Mill Hill infuser. Twenty to twenty-five percent of the total insulin dose was used for the basal rate (0.8–1.2 U/h) from bedtime until the following morning. The pump was used to administer the prebreakfast dose and the butterfly needle was left in place, covered with its sterile cap and secured in place with tape. The syringe with its solution was taken out of the pump, the tip sealed with a similar cap, and the whole carried in a protective casing to be used as needed for premeal boluses. At bedtime, the pump was reconnected. Premeal boluses represented 76–80% of the total insulin dose and were given 30 min before meals manually with the pump syringe through the indwelling catheter.

Capillary blood glucose monitoring was performed (by groups A and C during phase 1, B and D during phase 2, all four groups during phase 3 and the patients on combined CSII-MSI during phase 2) at fasting, just before administering the premeal boluses and at bedtime. During the periods of infrequent monitoring, CBG was determined twice daily in early morning and at bedtime. CBG was obtained by finger prick using disposable lancets (Monolet, Monojet, Sherwood Medical, Brunswick Co., St. Louis, Missouri) and a small portable trigger device that rendered bloodletting virtually painless (Autolet, Ulster Scientific, Inc., New York). Capillary blood glucose was measured by the patients with reagent strips alone (Chemstrip bG, Boehringer-Mannheim, Canada) or with a reflectance meter Reflomat (Boehringer-Mannheim). At the end of each study period, the patients came to the hospital, and capillary blood glucose was measured at 0730, 0930, 1200, 1330, 1700, and 1930 h for 2 consecutive days. Concentrations of $HgbA_1$ were estimated at the beginning and at the end of each study period as well.

TABLE 1
Mean blood glucose (mg/dl) and mean $HgbA_1$ concentration (%) for each of the patients under CSII treatment, at initiation of phase 1

	CSII	
Patient	MBG (mg/dl)	$HgbA_1$ (N = 6.5–8.5%)
1	122 ± 26	8.3
2	121 ± 30	8.2
3	106 ± 27	7.6
4	110 ± 35	8.5
5	104 ± 29	8.3
6	125 ± 42	8.8
7	108 ± 36	7.8
Mean	116	8.2
SD	36	0.4

Laboratory procedures. Capillary blood glucose was measured in hospital by an automated glucose-oxidase method (Beckman glucose analyzer, Beckman Instruments, Inc., Fullerton, California). Glycosylated hemoglobin ($HgbA_1$) concentrations were estimated using pre-packed microcolumns (Hemoglobin Quick Columns, Helena Laboratories, Beaumont, Texas). The normal range obtained in our laboratory was 6.5–8.5%. C-peptide concentrations were determined by radioimmunoassay using a commercial kit (Novo Research Lab., Copenhagen, Denmark) following polyethylene extraction of serum[15,16] obtained at fasting and after 2,4,6,8, and 20 min after the i.v. injection of 1 mg of glucagon.[17] Values obtained in our laboratory in normal controls showed a range of fasting C-peptide concentration of 0.28–0.60 pmol/ml and a range of peak post-glucagon C-peptide concentration of 0.96–1.60 pmol/L.

Statistical analysis. Results were assessed by calculation of mean plasma glucose, M-value,[18] and glycosylated hemoglobin concentration. Because of the small number of patients in groups B and D, patients were segregated in two groups

TABLE 2
Mean blood glucose (mg/dl) and mean $HgbA_1$ concentration (%) for each of the patients under MSI treatment, at initiation of phase 1

	MSI	
Patient	MBG (mg/dl)	$HgbA_1$ (N = 6.5–8.5%)
1	128 ± 30	8.2
2	113 ± 39	8.3
3	112 ± 37	8.5
4	114 ± 28	8.2
5	108 ± 28	7.9
6	130 ± 36	9.0
7	120 ± 31	7.6
Mean	120	8.3
SD	37	0.4

TABLE 3
Mean blood glucose (MBG) and $HgbA_1$ concentrations in each of the groups at initiation and at the end of phases 1, 2, and 3

	Initiation		Phase 1		Phase 2		Phase 3	
Group	MBG (mg/dl)	$HgbA_1$ (%)	MBG (mg/dl)	$HgbA_1$ (%)	MBG (mg/dl)	$HgbA_1$ (%)	MBG (mg/dl)	$HgbA_1$ (%)
A	112 ± 35	8.1 ± 0.5	114 ± 29	7.9 ± 0.4	156 ± 50	10.3 ± 0.5	119 ± 30	8.0 ± 0.1
B	116 ± 31	7.9 ± 0.4	165 ± 42	10.2 ± 0.5	115 ± 35	8.2 ± 0.4	120 ± 29	8.1 ± 0.2
C	117 ± 36	8.3 ± 0.6	116 ± 37	8.1 ± 0.4	165 ± 52	10.0 ± 0.9	115 ± 24	8.0 ± 0.6
D	108 ± 28	8.2	158 ± 48	10	119 ± 32	8.6	113 ± 30	8.7

TABLE 4
Mean ± SD fasting, preprandial, and postprandial CBG, mean M-values and $HgbA_1$(%) for groups A and C (pooled) and groups B and D (pooled) obtained in hospital at 18, 21, and 24 mo

	Groups A + C					Groups B + D				
Month	Fasting	Pre-prandial*	Post-prandial†	M-value	$HgbA_1$ (N = 6.5–8.5%)	Fasting	Pre-prandial*	Post-prandial†	M-value	$HgbA_1$ (N = 6.5–8.5%)
6	90 ± 29	93 ± 23	137 ± 41§	8.5 ± 5‡	8.0 ± 0.5‡	126 ± 34	124 ± 38	191 ± 50§	25 ± 7‡	10.3 ± 0.4‡
9	128 ± 43	131 ± 46	188 ± 45§	28 ± 10‡	10.1 ± 1.2‡	107 ± 36	89 ± 25	139 ± 30§	8.0 ± 5‡	8.5 ± 0.3‡
12	99 ± 28	91 ± 28	125 ± 32	9.0 ± 6	8.0 ± 0.6	83 ± 19	94 ± 25	135 ± 37	8.5 ± 4	8.4 ± 0.7

* Mean of prelunch and presupper CBG.
† Mean of postbreakfast, postlunch, and postsupper CBG.
‡ $P < 0.01$.
§ $P < 0.05$.

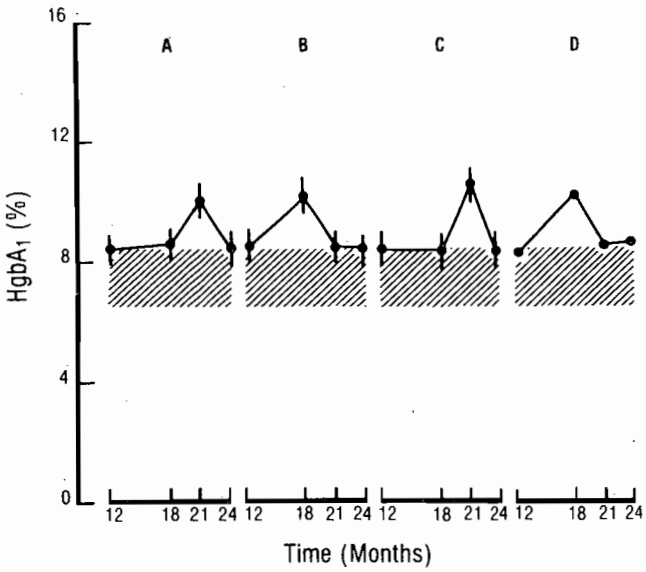

FIG. 1. Mean $HgbA_1$ concentrations (%) obtained in patients of groups A, B, C, and D at initiation (month 12) and at 18, 21, and 24 mo of the study. The shaded area represents the normal $HgbA_1$ range obtained in our laboratory.

according to whether they monitored or did not monitor blood glucose frequently (four times daily or more). Thus the data of groups A and C and B and D were pooled together. Statistical analysis was made by two-way analysis of variance and the Newman Keuls A Posteriori test.[19]

RESULTS

Patients under CSII and MSI. Before initiation of the study, while patients were monitoring their CBG at least 4 times daily, the mean blood glucose (MBG) was 116 ± 36 mg/dl and mean $HgbA_1$ was 8.2 ± 0.4% for the patients under CSII (Table 1). Mean blood glucose was 120 ± 37 mg/dl and mean $HgbA_1$ was 8.3 ± 0.4% for the patients under MSI (Table 2).

Results of the mean blood glucose and $HgbA_1$ concentrations at initiation and at the end of each phase, for each of the groups, are shown in Table 3.

Phase 1: Mean CBG increased from 116 ± 31 mg/dl to 165 ± 42 mg/dl in group B (N = 2) and from 108 ± 28 mg/dl to 158 ± 58 mg/dl in group D (N = 1), that is, the patients under CSII and MSI who reduced the number of CBG determinations to twice daily. Mean hemoglobin A_1 levels increased from 7.9 ± 0.4% to 10.2 ± 0.5% in group B

TABLE 5
Mean blood glucose and $HgbA_1$ levels at initiation of the study and at the end of phase 1 and phase 2 in the patients under combined CSII-MSI

	Initiation		Phase 1		Phase 2	
Patient	MBG (mg/dl)	$HgbA_1$ (N = 6.5–8.5%)	MBG (mg/dl)	$HgbA_1$ (N = 6.5–8.5%)	MBG (mg/dl)	$HgbA_1$ (N = 6.5–8.5%)
1	114 ± 27	7.8	166 ± 50	11.2	123 ± 28	8.7
2	121 ± 32	8.3	163 ± 47	10.5	118 ± 29	8.2
3	110 ± 27	8.0	154 ± 39	9.8	106 ± 32	7.8
4	108 ± 31	7.9	162 ± 58	10.7	118 ± 36	8.3
5	122 ± 25	8.7	153 ± 42	9.3	115 ± 35	7.7
6	114 ± 23	7.6	159 ± 43	9.9	120 ± 29	8.8
7	117 ± 32	8.6	170 ± 50	11.1	118 ± 33	7.9
Mean	115	8.6	161	10.3	116	8.2
SD	29	0.4	51	0.7	30	0.3
		($P < 0.05$)		($P < 0.05$)		

and from 8.2% to 10% in group D. In contrast, MBG did not change in group A (N = 5): 112 ± 35 mg/dl versus 114 ± 29 mg/dl, and group C (N = 6): 117 ± 36 mg/dl versus 116 ± 37 mg/dl, who continued to monitor their CBG at least 4 times daily. Levels of $HgbA_1$ remained unchanged in both groups as well: 8.1 ± 0.5 versus 7.9 ± 0.4 (group A) and 8.3 ± 0.6 versus 8.1 ± 0.4% (group C).

Phase 2: During this phase, mean CBG and $HgbA_1$ increased in group A: 156 ± 50 mg/dl and 10.3 ± 0.5%, respectively, and in group C: 165 ± 52 mg/dl and 10 ± 0.9%, respectively. Groups B and D, who resumed monitoring their CBG at least 4 times/day, showed a decrease in MBG to 115 ± 35 mg/dl (group B) and 119 ± 32 mg/dl (group D). Levels of glycosylated hemoglobin decreased towards normal in both groups as well: 8.2 ± 0.4% and 8.6%, respectively.

Phase 3: Mean CBG and $HgbA_1$ levels were comparable to those levels achieved at the beginning of the second year of the study in all patients: 119 ± 30 mg/dl and 8 ± 0.1% (group A), 120 ± 29 mg/dl and 8.1 ± 0.2% (group B), 115 ± 24 mg/dl and 8 ± 0.6% (group C), and 113 ± 30 mg/dl and 8.7% (group D).

Results of the mean fasting, preprandial, and postprandial CBG, M-value, and $HgbA_1$ for groups A and C (pooled) and groups B and D (pooled) are shown in Table 4. Figure 1 shows the mean $HgbA_1$ concentration in groups A, B, C, and D, obtained at initiation and at months 18, 21, and 24.

Combined CSII-MSI. Phase 1: Blood glucose profiles obtained at the beginning of phase 1 showed a mean blood glucose of 115 ± 29 mg/dl and a mean $HgbA_1$ of 8.6 ± 0.7%. Blood glucose profiles obtained at the end of this period showed a mean blood glucose of 161 ± 50 mg/dl and a mean $HgbA_1$ of 10.3 ± 0.7%.

Phase 2: The return to multiple daily CBG determinations decreased the MBG in these patients to 116 ± 30 mg/dl. Also, $HgbA_1$ decreased from 10.3 ± 0.7% to 8.2 ± 0.3%. Table 5 shows the MBG and $HgbA_1$ for each of the patients at the beginning of the study and at the end of phases 1 and 2. Figure 2 shows the blood glucose range (mg/dl) and the

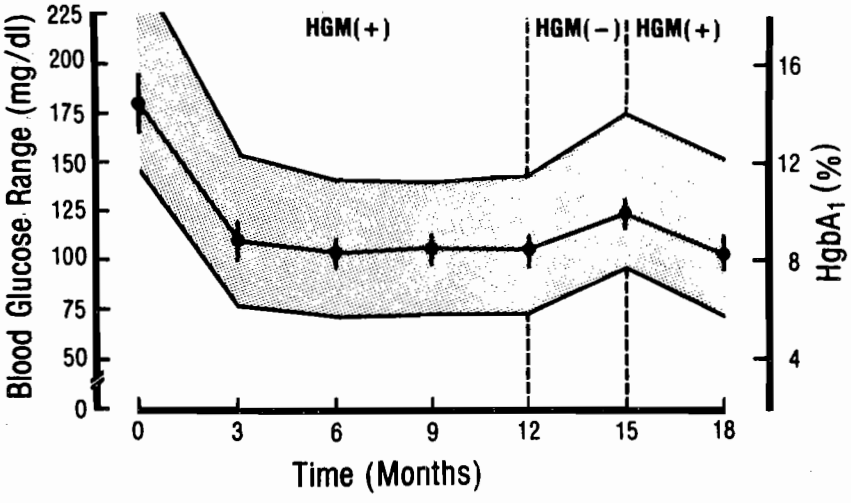

FIG. 2. Blood glucose range (mg/dl) and mean $HbgA_1$ (%) obtained in the patients under combined CSII-MSI treatment during the study. HGM+ depicts frequent monitoring and HGM− depicts infrequent monitoring (see text).

mean $HgbA_1$ concentration obtained during the first year of the study (HGM+), and at 15 (HGM−) and 18 mo (HGM+).

DISCUSSION

Research on management of the insulin-dependent diabetic patient has shifted towards the development of newer forms of insulin delivery capable of achieving normoglycemia. Many groups using closed-loop[20–24] and open-loop devices[1–6] for the treatment of type I diabetic patients have reported improvement of metabolic control.[7,25–27]

We have previously shown in a 1-yr prospective randomized crossover study that CSII and MSI provide comparable glycemic control when supported by CBG determinations 5–7 times daily.[13] Patient self-glucose monitoring is generally accepted as a useful technique to monitor and improve glycemic control.[7–11] It was hoped that with long-term glucose control and establishment of a stable pattern with the use of open-loop systems and intensive conventional therapy, frequent determinations of CBG would not be required.

The present study extended our previous findings by showing that optimized glucose control cannot be maintained over long periods in insulin-dependent diabetic patients when frequent self-glucose monitoring is interrupted. In our experience, the pattern of insulin requirements varied so often in the same individual that adjustments of the insulin dose according to CBG determinations in addition to diet and activity, were essential to maintain strict control.

Our study design with the crossover of patients with frequent and infrequent CBG determinations permitted us to establish the relevance of self-glucose monitoring. With both CSII and MSI treatments, the discontinuation of frequent CBG monitoring and, as a consequence, the inability to appropriately use the algorithms for insulin-dose adjustments resulted in the deterioration of glycemic control. This was seen with groups B and D during phase 1 and groups A and C during phase 2. The return to frequent CBG determinations during phase 3 resulted in an improvement of glucose control in all patients. With combined CSII-MSI treatment, the interruption of multiple daily CBG determinations also resulted in deterioration of glucose control.

The large-scale application of pump treatment in clinical practice seems premature, since the experience is still too limited. The liability of these devices to mechanical failure, the lack of an adequate alarm system with the potential danger of under or over insulinization (which in fact has occurred), the individual characteristics of some insulin-dependent diabetic patients with regard to instability, and inadequate counterregulatory mechanisms in response to hypoglycemia demand frequent self-glucose determination. Self-monitoring thus serves a dual purpose, that of monitoring the device and adjusting the insulin dose, to avoid lapses of control. These potential complications demand extreme motivation and compliance on the part of the patient as well as constant supervision from the health-care team.

Subcutaneous injections of insulin with self-glucose monitoring will likely remain the main tool for achieving good diabetic control for years to come in the great majority of insulin-dependent diabetic patients. Since, at present, it appears to produce similar control to CSII, it seems more appropriate to individualize the best mode of therapy for each patient. The interruption of home glucose monitoring that closes the loop results in deterioration of diabetic control even when such intensive forms of insulin administration are employed. More and longer controlled clinical trials are needed to determine which methodology of insulin delivery is more advantageous in the long term. In short, our results suggest that the adjustment of insulin doses based on frequent CBG determinations is indispensable to maintain improved glucose control in patients treated with CSII and MSI.

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APPENDIX C:

CODE OF FEDERAL REGULATIONS – PART 46: PROTECTION OF HUMAN SUBJECTS

Code of Federal Regulations

TITLE 45
PUBLIC WELFARE

Department of Health and Human Services

PART 46
PROTECTION OF HUMAN SUBJECTS

* * *

Revised January 15, 2009
Effective July 14, 2009

SUBPART A—
Basic HHS Policy for Protection of Human Research Subjects

Sec.

SUBPART B—
Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Sec.

SUBPART C— Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Sec.

SUBPART D— Additional Protections for Children Involved as Subjects in Research

Sec.

Authority: 5 U.S.C. 301; 42 U.S.C. 289 (a).

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SUBPART E — Registration of Institutional Review Boards

Sec.

Editorial Note: The Department of Health and Human Services issued a notice of waiver regarding the requirements set forth in part 46, relating to protection of human subjects, as they pertain to demonstration projects, approved under section 1115 of the Social Security Act, which test the use of cost-sharing, such as deductibles, copayment and coinsurance, in the Medicaid program. For further information see 47 FR 9208, Mar. 4, 1982.

SUBPART A
Basic HHS Policy for Protection of Human Research Subjects

Authority: 5 U.S.C. 301; 42 U.S.C. 289; 42 U.S.C. 300v-1(b).

Source: 56 FR 28012, 28022, June 18, 1991, unless otherwise noted.

§46.101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in §46.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in §46.102(e) must be reviewed and approved, in compliance with §46.101, §46.102, and §46.107 through §46.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:(i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Human Research Protections, Department of Health and Human Services (HHS), or any successor office, and shall also publish them in the FEDERAL REGISTER or in such other manner as provided in department or agency procedures.[1]

[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.102 Definitions.

(a) *Department or agency head* means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.

(b) *Institution* means any public or private entity or agency (including federal, state, and other agencies).

(c) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

(e) *Research subject to regulation*, and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(f) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context

in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) *IRB* means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) *IRB approval* means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

(i) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.

[1]Institutions with HHS-approved assurances on file will abide by provisions of Title 45 CFR part 46 subparts A-D. Some of the other departments and agencies have incorporated all provisions of Title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, subpart C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

§46.103 Assuring compliance with this policy -- research conducted or supported by any Federal Department or Agency.

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Human Research Protections, HHS, or any successor office, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Human Research Protections, HHS, or any successor office.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(1)A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to Federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under §46.101(b) or (i).

(2)Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3)A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the department or agency head, unless in accord with §46.103(a) of this policy, the existence of an HHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Human Research Protections, HHS, or any successor office.

(4)Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(5)Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.

(d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the department or agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The department or agency head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under §46.101(b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by §46.103 of this Policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by §46.103 of the Policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

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[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991, as amended at 70 FR 36328, June 23, 2005]

§§46.104--46.106 [Reserved]

§46.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB

§46.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:

(a) Follow written procedures in the same detail as described in §46.103(b)(4) and, to the extent required by, §46.103(b)(5).

(b) Except when an expedited review procedure is used (see §46.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

§46.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with §46.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

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[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, HHS, has established, and published as a Notice in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the FEDERAL REGISTER. A copy of the list is available from the Office for Human Research Protections, HHS, or any successor office.

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited procedure set forth in §46.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§46.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§46.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

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[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

§46.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described in §46.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in §46.103(b)(4) and §46.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by §46.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

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[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

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[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by §46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

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[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under §46.101(b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the department or agency.

§46.119 Research undertaken without the intention of involving human subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the department or agency, and final approval given to the proposed change by the department or agency.

§46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the department or agency through such officers and employees of the department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§46.121 [Reserved]

§46.122 Use of Federal funds.

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§46.123 Early termination of research support: Evaluation of applications and proposals.

(a) The department or agency head may require that department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

§46.124 Conditions.

With respect to any research project or any class of research projects the department or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

Subpart B

Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Source: 66 FR 56778, Nov. 13, 2001, unless otherwise noted.

§46.201 To what do these regulations apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates conducted or supported by the Department of Health and Human Services (DHHS). This includes all research conducted in DHHS facilities by any person and all research conducted in any facility by DHHS employees.

(b) The exemptions at §46.101(b)(1) through (6) are applicable to this subpart.

(c) The provisions of §46.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in §46.101(f) is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.

(d) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.202 Definitions.

The definitions in §46.102 shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

(b) Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.

(c) Fetus means the product of conception from implantation until delivery.

(d) Neonate means a newborn.

(e) Nonviable neonate means a neonate after delivery that, although living, is not viable.

(f) Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

(g) Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(h) Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a neonate is viable for purposes of this subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D of this part.

§46.203 Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart and the other subparts of this part.

§46.204 Research involving pregnant women or fetuses.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

§46.205 Research involving neonates.

(a) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

(1) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

(2) Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

(3) Individuals engaged in the research will have no part in determining the viability of a neonate.

(4) The requirements of paragraph (b) or (c) of this section have been met as applicable.

(b) Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:

(1) The IRB determines that:

(i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

(ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

(2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(c) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

(1) Vital functions of the neonate will not be artificially maintained;

(2) The research will not terminate the heartbeat or respiration of the neonate;

(3) There will be no added risk to the neonate resulting from the research;

(4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

(5) The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

(d) Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

§46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.

(a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

(b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable.

§46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

The Secretary will conduct or fund research that the IRB does not believe meets the requirements of §46.204 or §46.205 only if:

(a) The IRB finds that the research presents

a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the FEDERAL REGISTER, has determined either:

(1) That the research in fact satisfies the conditions of §46.204, as applicable; or

(2) The following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;

(ii) The research will be conducted in accord with sound ethical principles; and

(iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

Subpart C

Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Source: 43 FR 53655, Nov. 16, 1978, unless otherwise noted.

§46.301 Applicability.

(a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.302 Purpose.

Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

§46.303 Definitions.

As used in this subpart:

(a) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(b) *DHHS* means the Department of Health and Human Services.

(c) *Prisoner* means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

(d) *Minimal risk* is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

§46.304 Composition of Institutional Review Boards where prisoners are involved.

In addition to satisfying the requirements in §46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

(a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.

(b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

[43 FR 53655, Nov. 16, 1978, as amended at 46 FR 8366, Jan. 26, 1981]

§46.305 Additional duties of the Institutional Review Boards where prisoners are involved.

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:

(1) The research under review represents one of the categories of research permissible under §46.306(a)(2);

(2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

(3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

(5) The information is presented in language which is understandable to the subject population;

(6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

(7) Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

(b) The Board shall carry out such other duties as may be assigned by the Secretary.

(c) The institution shall certify to the Secre-

tary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

§46.306 Permitted research involving prisoners.

(a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:

(1) The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under §46.305 of this subpart; and

(2) In the judgment of the Secretary the proposed research involves solely the following:

(i) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(ii) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(iii) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or

(iv) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of the intent to approve such research.

(b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

Subpart D

Additional Protections for Children Involved as Subjects in Research

Source: 48 FR 9818, March 8, 1983, unless otherwise noted.

§46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (i) of §46.101 of subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §46.101 (b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101 of subpart A are applicable to this subpart.

[48 FR 9818, Mar.8, 1983; 56 FR 28032, June 18, 1991; 56 FR 29757, June 28, 1991.]

§46.402 Definitions.

The definitions in §46.102 of subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) *Children* are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

(b) *Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) *Permission* means the agreement of parent (s) or guardian to the participation of their child or ward in research.

(d) *Parent* means a child's biological or adoptive parent.

(e) *Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

§46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§46.404 Research not involving greater than minimal risk.

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:

(a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1) that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or (2) the following:

(i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) the research will be conducted in accordance with sound ethical principles;

(iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

§46.408 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A.

(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by §46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §§46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in §46.116 of subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by §46.117 of subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

§46.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

Subpart E

Registration of Institutional Review Boards

Source: 74 FR 2399, January 15, 2009, unless otherwise noted.

§46.501 What IRBs must be registered?

Each IRB that is designated by an institution under an assurance of compliance approved for federalwide use by the Office for Human Research Protections (OHRP) under §46.103(a) and that reviews research involving human subjects conducted or supported by the Department of Health and Human Services (HHS) must be registered with HHS. An individual authorized to act on behalf of the institution or organization operating the IRB must submit the registration information.

§46.502 What information must be provided when registering an IRB?

The following information must be provided to HHS when registering an IRB:

(a) The name, mailing address, and street address (if different from the mailing address) of the institution or organization operating the IRB(s); and the name, mailing address, phone number, facsimile number, and electronic mail address of the senior officer or head official of that institution or organization who is responsible for overseeing activities performed by the IRB.

(b) The name, mailing address, phone number, facsimile number, and electronic mail address of the contact person providing the registration information.

(c) The name, if any, assigned to the IRB by the institution or organization, and the IRB's mailing address, street address (if different from the mailing address), phone number, facsimile number, and electronic mail address.

(d) The name, phone number, and electronic mail address of the IRB chairperson.

(e)(1) The approximate numbers of:

(i) All active protocols; and

(ii) Active protocols conducted or supported by HHS.

(2) For purpose of this regulation, an ``active protocol'' is any protocol for which the IRB conducted an initial review or a continuing review at a convened meeting or under an expedited review procedure during the preceding twelve months.

(f) The approximate number of full-time equivalent positions devoted to the IRB's administrative activities.

§46.503 When must an IRB be registered?

An IRB must be registered before it can be designated under an assurance approved for federalwide use by OHRP under §46.103(a).

IRB registration becomes effective when reviewed and accepted by OHRP.

The registration will be effective for 3 years.

§46.504 How must an IRB be registered?

Each IRB must be registered electronically through http://ohrp.cit.nih.gov/efile unless an institution or organization lacks the ability to register its IRB(s) electronically. If an institution or organization lacks the ability to register an IRB electronically, it must send its IRB registration information in writing to OHRP.

§46.505 When must IRB registration information be renewed or updated?

(a) Each IRB must renew its registration every 3 years.

(b) The registration information for an IRB must be updated within 90 days after changes occur regarding the contact person who provided the IRB registration information or the IRB chairperson. The updated registration information must be submitted in accordance with §46.504.

(c) Any renewal or update that is submitted to, and accepted by, OHRP begins a new 3-year effective period.

(d) An institution's or organization's decision to disband a registered IRB which it is operating also must be reported to OHRP in writing within 30 days after permanent cessation of the IRB's review of HHS-conducted or -supported research.

Bayer HealthCare

December 9, 2010

Ms. Denise C. Santoyo
Health Technology Assessment
Program Coordinator
Washington State Health Care Authority
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PO Box 42712
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Re: Washington State Health Care Authority, Health Technology Assessment Program, Glucose Monitoring

Dear Ms. Santoyo:

Bayer HealthCare LLC

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VP of Public Policy &
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Bayer is a leader in the blood glucose monitoring field and has been providing high quality diabetes-related products and services to generations of beneficiaries. Bayer's commitment to providing beneficiaries with diabetes with the necessary blood glucose monitoring equipment, supplies and services to manage their disease has played a role in fighting the growing diabetes epidemic.

As a leader in the efforts to combat the explosive growth of diabetes, Bayer HealthCare LLC ("Bayer") wishes to thank the Washington State Health Care Authority ("HCA") for this opportunity to offer additional comments on the recently released draft evidence report regarding glucose monitoring in patients with diabetes under 18 years old. These comments build upon earlier evidence Bayer submitted to the Authority (see attached), which supports the importance of glucose monitoring for children, the most vulnerable diabetes patient population. Please refer to Bayer's previous comments in response to questions II and III.

I. What is the evidence of efficacy and effectiveness of glucose monitoring?

The International Society for Pediatric and Adolescent Diabetes (ISPAD) has clearly stated in their Clinical Practice Consensus Guidelines 2009 Compendium (Assessment and monitoring of glycemic control in children and adolescents with diabetes) that measurement of immediate glycemic control is best determined by self-monitoring of blood glucose (SMBG) as this provides immediate documentation of hyperglycemia and hypoglycemia,

allowing implementation of strategies to optimally treat, as well as to avoid, out of range glucose values.[1]

Self monitoring of blood glucose helps to monitor immediate and daily levels of control, helps to determine immediate and daily insulin requirements, helps guide insulin adjustments to decrease fluctuations in blood glucose levels, detects hypoglycemia and assists in its management and assists in safe management of hyperglycemia.[1] Additionally, Continuous Glucose Monitoring (CGM) has been "…helpful in adjusting management following initiation of insulin infusion pumps and identification of asymptomatic hypoglycemia and unrecognized postprandial hyperglycemia."[1]

Additionally, HCA references the 2010 American Diabetes Position statement[2] which is a general position statement on glucose monitoring for all age groups, but primarily focused on the adult population as well as a 2005 article from Diabetes Care entitled "Care for Children and Adolescents with Type I Diabetes"[3] in their draft evidence report. Unfortunately, the report put forth by HCA does not fully take into consideration additional evidence as presented in the article which clearly states that self-management of diabetes is the ultimate goal for all patients with diabetes, with insulin dosing decisions based on interpretation of blood glucose results. Self-monitoring of blood glucose (SMBG) allows people with diabetes and their families to measure blood glucose levels rapidly and accurately. All basal/bolus diabetes management regimens and all self-management skills rely on frequent SMBG. Additionally, the author states that SMBG is necessary for individuals to achieve optimal glycemic control. Multiple blood glucose measurements are recommended each day to determine patterns of hypoglycemia and hyperglycemia and to provide data for insulin dose adjustments. Pre-prandial blood glucose levels are important, but postprandial and overnight levels are also valuable in determining insulin dose adjustments. Finally, the recommendation for children and adolescents is that testing should occur at least 4 times a day.

[1] Rewers M, Pihoker C, Donaghue K, Hanas R, Swift P, Klingensmith GJ.Assessment and monitoring of glycemic control in children and adolescents with diabetes. Pediatric Diabetes 2009: 10 (Suppl. 12): 71–81.

[2] American Diabetes Association. Standards of medical care in diabetes--2010. *Diabetes Care.* Jan 2010;33 Suppl 1:S11-61.

[3] Silverstein J, Klingensmith G, Copeland K, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care.* Jan 2005;28(1):186-212.

We would also like to reiterate the findings of the Diabetes Control and Complications Trial (DCCT), which contained a cohort of adolescents >13 years of age, and showed a significant link between blood glucose control and later development of diabetes complications, with improved glycemic control decreasing the risk of these complications.[4] HCA challenged the strength of the data presented in this study in their draft evidence report. The DCCT is one of the largest studies of its kind which addresses diabetic control in a younger population. This is significant. Additionally, it is not clear from the evidence report the type of study HCA would propose to assess this population since it would be deemed unethical to conduct a clinical trial in a group of children <18 and on insulin without self monitoring of their blood glucose.

Additionally, the long-term follow up of the DCCT participants has been reassuring that there was no evidence for permanent neurocognitive changes related to hypoglycemia in adolescent and young adult individuals, suggesting that the effect of severe hypoglycemia on long term neuropsychological functioning may be age dependent.[1]

Experts agree that at present, safest recommendation for improving glycemic control generally in all children is to achieve the lowest HbA1c that can be sustained without disabling or severe hypoglycemia while avoiding prolonged periods of significant hyperglycemia and episodes of diabetic ketoacidosis and that these goals can only be achieved by some form of frequent glucose monitoring.[1]

V. What is the evidence of cost implications and cost effectiveness of glucose monitoring?

Elevated A1C levels are associated with a greater risk of diabetes complications and higher costs.[5] Acute complications in children with type 1 diabetes carry the risk of high cost and heavy resource utilization.[6]

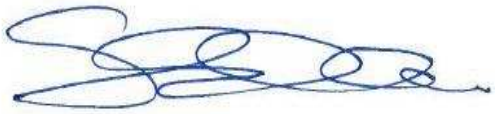
Other studies, like The Asheville Project demonstrate that diabetic patients that received pharmaceutical care services which included home glucose meters maintained improvement in A1C over time. The Asheville Project

[4] Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Journal of Pediatrics, Volume 139, No. 6.
[5] Gilmer,TP, O'Connor, PJ,Rush W., Crain, AL., Whitebird, R., Hanson, A., and Solberg, L. Predictors of Healthcare Costs in Adults with Diabetes. Diabetes Care, Volume 28, Number 1, January 2005.
[6] Jiang HJ, Stryer D, Friedman B, Andrews R. Multiple hospitalizations for patients with diabetes. *Diabetes Care*. 2003;26(5):1421-1426.

was started by the City of Asheville, North Carolina, a self-insured employer, to provide education and personal oversight for employees with chronic health problems such as diabetes, asthma, hypertension, and high cholesterol. Through the Asheville Project, employees with these conditions were provided with intensive education through the Mission-St. Joseph's Diabetes and Health Education Center. Patients were then teamed with community pharmacists who made sure they were using their medications correctly. Studies have also demonstrated that "to develop a successful value-based benefit design, stakeholders cannot simply cut costs or cut copays"[7].

We trust that this additional information will be helpful to you as you continue to thoroughly evaluate the link between diabetes monitoring and improved health outcomes in children and young adults with diabetes.

Sincerely,



Sandra S. Oliver
Vice President, Public Policy &
Government Affairs

Attachments:

Bayer letter to Washington State Health Care Authority May 7, 2010
ISPAD Clinical Practice Consensus Guidelines 2009 Compendium

[7] http://www.theashevilleproject.net/

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Dec 10, 2010

Washington State Health Care Authority
Health Technology Assessment
sent electronically to shtap@hca.wa.gov

Dear HTA Review:

Thank you for the opportunity to comment on the recent Washington State HTA draft questions on Glucose Monitoring. As stated in the letter from Claudia Graham on March 7th, DexCom is a medical device company dedicated solely to continuous glucose sensing. We design, develop and commercialize continuous glucose monitoring (CGM) systems for ambulatory use by people with diabetes. Our device is not approved in children and I am providing my comments as a diabetologist that has spent my career taking care of children with diabetes in private practice, as medical director at Lifescan, and currently as medical director at Dexcom. I will focus my discussion to key question #1- the efficacy and effectiveness of monitoring in improving glycemic, health, and economic endpoints.

1) Monitoring is not therapy and has no DIRECT benefit on glycemic, health, and economic endpoints. The question would have been better phrased: How effective are patients, parents, and health care professionals in utilizing the monitoring data to adjust lifestyle and/ or insulin? If the question was phrased in this manner, it would become apparent that the success of monitoring in improving outcomes is highly dependent on the training, knowledge, skills, and motivation of the patients, parents and providers. The literature review that was performed for this health technology assessment needs to consider and discuss these factors. An example: Active monitoring with CGM requires looking at a receiver screen. CGM is dynamic. The arrows on the receiver instantly report if the glucose is rising and falling and the rate of change and the glucose trend graph informs if the rate of change is constant or changing. In a review of the benefit of CGM, it is important to understand how often subjects were instructed to engage and actually engaged with the device, and how they were taught to use the information (such as the rate of change arrows and trend graphs) and their compliance in following the instructions. Failure to see a benefit in the population at large in a randomized control trial does not mean that other patients with different motivation and training may not have significant benefit.

2) Using a device through enrollment in a clinical trial likely result in different motivation than using a device because your physician prescribed it, often because of a problem. Once again, as monitoring is not a direct therapy, this difference in motivation may impact how subjects or patients use the device or the information from the device. Observational studies are of high importance in understanding how monitoring impacts outcomes when monitoring is prescribed by a treating physician.

3) There are significant differences not only between CGM and SMBG but also between CGM systems. For SMBG to help patients detect or prevent hypoglycemia, it requires them to actively monitor by lancing their fingertips and placing a blood drop on a test strip. CGM can passively monitor as it can alarm when glucoses are dropping or when glucose is low. However, the alarms on different CGM devices are different. The alarm volume varies and some CGM systems have predictive alarms, others alarm based on glucose thresholds. The

performance of different CGM systems at the hypoglycemic range differs considerably. These differences impact whether the CGM monitor awakens a sleeping patient and whether the alarm is ignored or acted upon. Unlike pharmaceuticals, the life cycles of devices are short, and therefore can pose confusion when conducting health technology assessments. As a case in point, Dexcom recently submitted a forth generation system to the FDA. However, most of the published data is from first or second generation devices. As technologies evolve, the performance and usability incrementally improve, thus affecting their ability to impact outcomes. Accordingly, in the literature review, the specific systems used in the studies need to be called out. All CGM are not created equal and failure to see benefits or the demonstration of benefits with a particular system should not be extrapolated to CGM in general.

From a clinician perspective, as recommended in global Standards of Care, there is little doubt patients and families that are knowledgeable, well trained in self-management, and motivated get significant benefit from monitoring. Since Washington State Health Care Authority has performed this review, there are new consensus recommendations from The American Association of Clinical Endocrinologists[i] and the Association of British Clinical Diabetologists that need consideration[ii].

Once again, thank you for the opportunity to respond to these draft questions. We recognize the need to conduct technology assessments with new technology. However, as CGM is a relatively new, the scientific evidence is limited but continuing to evolve and grow. While DexCom is committed to the development of evidence based medicine and the appropriate use of health technology assessments, we believe that with emerging technologies such as CGM, these tools are best used in combination with emerging clinical guidance and sound medical judgment by the treating clinicians.

Sincerely,

David A Price, MD
Executive Director, Clinical Affairs

[i] Blevins T, Bode B, Garg S, Grunberger G, Hirsch I, et al for the AACE Continuous Glucose Monitoring Task Force. Statement by the American Association of Clinical Endocrinologists Consensus Panel on Continuous Glucose Monitoring. *Endocrine Practice* Sept/Oct 2010; 730-745.

[ii] Hammond PJ, Amiel SA, Dayan CM, Kerr D, Pickup JC, Shaw JA, Campbell FM, Greene SA, Hindmarsh PC;on behalf of the Association of British Clinical Diabetologists (ABCD). ABCD position statement on continuous glucose monitoring: use of glucose sensing in outpatient clinical diabetes care. *Pract Diab Int* 2010 March; 66-68

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December 7, 2010

Washington State Health Care Authority
Health Technology Assessment Program
P.O. Box 42712
Olympia, WA 98504-2712
Attn: Leah Hole-Curry, JD, Program Coordinator

VIA EMAIL: shtap@hca.wa.gov

Subject: Draft Evidence Report - Glucose Monitoring

Dear Ms. Hole-Curry,

This letter constitutes Medtronic, Inc.'s response to the public request for comments issued by the Washington State Health Care Authority (HCA) regarding the **Draft Evidence Report - Glucose Monitoring**. Medtronic Diabetes is the world leader in integrated diabetes management solutions, including insulin pump therapy, continuous glucose monitoring, algorithm development and therapy management software. Our vision is to provide access and exceptional solutions to create a world where everyone living with diabetes can lead a fuller, healthier life.

We respectfully submit the following comments on the draft Health Technology Assessment (HTA), *Glucose Monitoring: Self-monitoring in patients under 18 years old*. Our comments address several components of the draft HTA and its conclusions:

- In its current form, the HTA is not relevant to actual clinical practice (all Key Questions).
- In evaluating the relative efficacy and effectiveness of CGM (Key Question 2), the HTA should evaluate differences in time spent hypoglycemic in addition to the number of hypoglycemic events.
- The outcomes used to measure efficacy and effectiveness of CGM (Key Question 2) should be consistent with the age of the technology being evaluated.
- The HTA should evaluate the growing body of evidence that demonstrates which patients benefit most from CGM (Key Question 4).

- Studies evaluating CGM in conjunction with CSII and/or MDI should be included in the HTA (Key Questions 2, 3 and 4).

We hope that you find this information useful in evaluating the role of real-time continuous glucose monitoring technology (rt-CGM) in the optimal management of diabetes for patients under 18 years of age. If you have any questions regarding this information, please contact me at 818-576-5331, or fran.kaufman@medtronic.com.

Sincerely,

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COMMENTS

We respectfully submit comments focusing on the following six issues:

1. In its current form, the HTA is not relevant to actual clinical practice (all Key Questions).
2. The outcomes used to measure efficacy and effectiveness of CGM (Key question 2) should be consistent with the age of the technology being evaluated and appropriate to the patient population under consideration.
3. In evaluating the relative efficacy and effectiveness of CGM (Key question 2), the HTA should evaluate differences in time spent hypoglycemic in addition to the number of hypoglycemic events.
4. Clinically relevant measures of safety should be used to evaluate CGM and SMBG (Key Question 3).
5. The HTA should evaluate the growing body of evidence that demonstrates which patients benefit most from CGM (Key question 4).
6. Studies evaluating CGM in conjunction with CSII and/or MDI should be included in the HTA (Key questions 2, 3 and 4).

These issues are addressed in order below.

1. Lack of Relevance to Current Clinical Practice (All Key Questions)

We are concerned that as currently structured, the HTA lacks relevance regarding standard clinical practice for the treatment of patients with diabetes under the age of 18. As currently structured, the HTA is not relevant to patients or clinicians and thus cannot serve its stated purpose, "*The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care service."*

In the remainder of this section we highlight the following three key areas where we believe the HTA diverges from standard clinical practice and provide specific recommendations for modifications to the HTA in order to ensure it is clinically relevant:

A. The value of intensive management for patients under age 18 has been clearly proven.
B. CGM should be evaluated according to its current use in clinical practice.
C. Health plan coverage of SMBG and CGM provide additional insight regarding current practice and the evidence supporting frequent SMBG and CGM for certain patients under the age of 18.

A. The Value of Intensive Management

Intensive glycemic control has demonstrated clinical and economic benefits for patients with diabetes.

In terms of clinical benefits, the risk of vascular complications has been clearly associated with elevated blood glucose levels in both Type 1 and Type 2 diabetes. Limiting hyperglycemia remains the most crucial factor for reducing the risk of diabetes-related complications. The

landmark 1993 DCCT in Type 1 diabetes[1,2,3,4] conclusively demonstrated both that intensive therapy substantially improves glycemic control and that glycemic control substantially lowers diabetes-related complications (both microvascular and macrovascular) and extends life expectancy. The DCCT cohort included participants 13 years of age and older. Other randomized prospective studies have confirmed these findings.[5,6]

The findings summarized above highlight the critical importance of intensive glycemic control in patients with diabetes. The benefits of intensive management have been confirmed over time and are reflected in all major guidelines for the treatment of diabetes as well as standard clinical practice. The American Diabetes Association's (ADA) Standards for Medical Care in Diabetes 2010, among others, recommend self-monitoring of glucose levels for patients of all ages with Type 1 diabetes.[7] Specifically, the ADA Standards state the following, "SMBG should be carried out three or more times daily for patients using multiple insulin injections or insulin pump therapy." This recommendation is supported with the highest evidence ranking of "A". [8]

Similarly, the American Association of Clinical Endocrinologists (AACE) Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007) recommend self-monitoring of glucose levels for insulin taking patients (of all ages), "Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump (grade B)."[9]

Per Medtronic's previously submitted comments, given the long-standing clinical evidence and clear recommendations regarding the importance of glucose monitoring in the clinical guidelines for insulin-taking patients with diabetes of all ages, it is unclear why the HCA is raising questions regarding the value of glucose monitoring for insulin-taking diabetes patients 18 years of age or under. It is even more puzzling how a credible technology assessment could have classified the evidence supporting the benefits of intensive insulin management as "Low".

As the HTA notes, the landmark studies do not use the most current technology. However, while substantial improvements in areas such as patient convenience, comfort, data transmittal and the like have occurred over time, the evidence from DCCT and other studies remains relevant to the existing SMBG technology. Furthermore, the evidence that reduced A1C results

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[1] The Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 2002;287(19):2563-9.

[2] White NH, Cleary PA, Dahms W, Goldstein D, Malone J, Tamborlane WV. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). J Pediatr 2001;139(6):804-12.

[3] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329(14):977-86.

[4] The Diabetes Control and Complications Trial Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. N Engl J Med 2000;342(6):381-9.

[5] Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care 2000;23 Suppl 2:B21-9.

[6] Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann Intern Med 2004;141(6):413-20.

[7] By definition, individuals with Type 1 diabetes are insulin-taking.

[8] Evidence Grade of "A" means the following:
"Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered, including: (1) Evidence from a well-conducted multicenter trial, (2) Evidence from a meta-analysis that incorporated quality ratings in the analysis, (3) Compelling nonexperimental evidence, i.e., "all or none" rule developed by Center for Evidence Based Medicine at Oxford, and (4) Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including: (a) Evidence from a well-conducted trial at one or more institutions and (b) Evidence from a meta-analysis that incorporated quality ratings in the analysis.

[9] American Association of Clinical Endocrinologists. Medical guidelines for clinical practice for the management of diabetes mellitus. Endocrine Practice 2007; 13(Supp 1).

in fewer complications for insulin-taking patients with diabetes under age 18 remains entirely relevant, regardless of the technologies used to achieve this objective. Moreover, contrary to the statement in the HTA that, "The effectiveness and optimal frequency of self-monitoring of blood glucose in patients is controversial," there is absolutely no controversy regarding the value of frequent testing for patients with diabetes under the age of 18. Some questions have been raised recently regarding the value of intensive management for older, sicker patients with Type 2 diabetes (which ultimately resulted in a reaffirmation of existing clinical guideline recommendations), but there is no disagreement regarding the value of intensive management for younger patients.[10]

In light of this evidence and the strong recommendations in widely accepted clinical guidelines, it is not surprising that studies comparing frequent SMBG to other options (e.g., no or infrequent testing or urine testing) have not been conducted since the DCCT results were released. Such studies would be, at best, ethically questionable and would be highly unlikely to receive approval from Institutional Review Boards.

Thus, we believe that the analysis of Key Question 1 and the conclusions are seriously flawed and should be reconsidered in their entirety.

B. CGM Should be Evaluated Consistent with its Use in Clinical Practice

As discussed in detail in Issue 6 below, the HTA should evaluate CGM in the context of current clinical practice. Because rt-CGM is used almost exclusively in conjunction with either an insulin pump or MDI, studies evaluating CGM in conjunction with these insulin regimens should be included in the analysis. Such studies are the most relevant and applicable to actual clinical use of rt-CGM, and they build on the body of evidence that evaluates these treatments separately. See Issue 6 for additional discussion.

C. Health Plan Coverage of Frequent SMBG and CGM Further Supports the Value of These Technologies

The draft HTA provides incomplete and in some cases inaccurate and irrelevant information regarding health plan coverage of SMBG and CGM. Almost all patients under 18 years of age with diabetes who self-monitor their glucose are covered by private insurers or Medicaid, rather than Medicare.[11]

It is therefore important for the HTA to include the leading national private payers in the overview of the payer assessments and policies for SMBG and CGM. The HTA appropriately recognizes the coverage of glucose self-monitoring by Aetna and Cigna, two of the four largest nationwide plans based on covered lives. Policies from the two largest US plans, UnitedHealth and WellPoint, should also be included.

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[10] Questions have been raised about intensive management for older patients with Type 2 diabetes, due to results from recent studies including ACCORD, ADVANCE, and VADT. These results are not relevant for patients under the age of 18. Moreover, upon detailed analysis of the study results, the professional organizations focused on diabetes and cardiovascular disease have confirmed the importance of tight glycemic control in all patients with diabetes.

[11] We also note that, under Medicare, coverage of SMBG is required by law and is covered under the DME benefit. All of the DME Medicare Administrative Contractors (MACs) have policies covering SMBG, and all cover frequent (at least 4 times per day) testing for patients on MDI or insulin pump therapy. In fact, the DME MACs have proposed a revision to their SMBG local coverage policies increasing coverage to 600 strips every 3 months for patients on MDI or insulin pump therapy.

- UnitedHealth: Blood glucose monitors and long-term CGM use are covered for patients with Type 1 diabetes who either have been unable to obtain glycemic control as defined by the ADA or have experienced hypoglycemic unawareness. (https://www.unitedhealthcareonline.com/b2c/CmaAction.do?channelId=016228193392b010VgnVCM100000c520720a____).

- WellPoint: Blood glucose monitors, long-term CGM use, and associated supplies are covered for patients with Type 1 diabetes who meet certain criteria (http://www.anthem.com/medicalpolicies/policies/mp_pw_a049550.htm). Specifically related to younger persons, long-term CGM use is covered for those < 25 years of age with recurring episodes of severe hypoglycemia, inadequate glycemic control despite self-monitoring at least four times per day, and insulin injections of three or more times per day.

In addition to the four largest plans, the HTA includes information on Harvard Pilgrim, a recognized thought leader among health plans, and BlueCross/BlueShield. Because each individual BlueCross/BlueShield plan develops its own coverage policies, we assume the BlueCross/BlueShield policy noted in the HTA is the model policy of the BlueCross BlueShield Association. However, many BlueCross/BlueShield plans, such as the two largest (Wellpoint and HealthCare Services Corporation), as well as Premera Blue Cross and Regence Blue Cross Blue Shield in the state of Washington, have expanded their coverage beyond this recommendation and cover both frequent SMBG and rt-CGM use for a wide range of patients under age 18.

The widespread private payer coverage of SMBG and rt-CGM for patients with diabetes under age 18, particularly those with Type 1 diabetes, reinforces the inconsistency of the draft HTA's findings with current clinical practice. Private health plans have strong financial incentives to cover and pay only for medical services with proven scientific results from credible studies. Even with these incentives, Medical Directors at the major private health plans cover SMBG and rt-CGM use for patients with Type 1 diabetes who meet certain criteria. Many coverage policies reference both the DCCT and JDRF CGM study, as well as guidelines from the ADA and other organizations as rationale for their coverage policies (e.g., United's policy: https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Medical%20Policies/Cont_Glucose_Monitor_and_Insulin_Pumps.pdf).

The recognition of these studies as a rationale for coverage policies demonstrates their credibility as valid studies. In addition, insurer coverage policies are indicative of the standard of care for patients. Therefore, the Low SoE assigned to both the DCCT and the body of evidence on CGM in the HTA does not accurately reflect the strength and credibility of the findings from these studies.

2. Outcomes Measures Should be Consistent with the Age of the Technology and Appropriate to the Patient Population under Consideration (Key Question 2)

Long-term outcomes that cannot be reasonably expected to occur over a five-year time period should not be considered as direct outcomes for rt-CGM, given the fact that rt-CGM has been on the market for only five years. Instead, Washington State HCA should focus on shorter term

outcomes such as hypoglycemia (see discussion above) and hyperglycemia, as well as the well-validated and widely accepted surrogate measure for long-term diabetes outcomes, A1C. The use of A1C as a valid marker for long-term diabetes outcomes is well documented in the literature and reflected in recognized clinical guidelines, including the ADA's Standards of Medical Care in Diabetes, the AACE Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus, among others.

In addition to taking into account the age of the technology in question, it is critically important to look at the patient population that this assessment is focusing on and determine the applicability of outcomes. Specifically, microvascular and macrovascular complications of diabetes are long-term results of poor glycemic control. The likelihood of these complications appearing in patients with diabetes who are under 18 years old is extremely low given the relatively short duration of disease present in this population (maximum 18 years if diagnosed at or near birth). Including long-term complications of diabetes as key direct outcomes in assessing the evidence for SMBG and rt-CGM in pediatric and adolescent patients indicates a strong disconnect between the design of this technology assessment and the clinical realities of diabetes and the patient sub-population of interest.

3. Definition of Hypoglycemia (Key Question 2)

The HTA does not clearly define the definition used for the hypoglycemia outcome in Key Question 2. However, it would appear that the analysis included only the frequency of episodes of severe hypoglycemia. This definition does not adequately address the importance of time spent in the hypoglycemic range as a primary outcome measure for all patients with diabetes, particularly young children, who may be less likely to recognize or alert caregivers of symptoms of hypoglycemia. As evidenced in the published literature, there are three ways that hypoglycemia is typically measured: (1) frequency of hypoglycemia events, (2) time spent hypoglycemic and (3) frequency of severe hypoglycemia events. All three are clinically meaningful for patients with diabetes, particularly insulin taking patients. Given the importance of hypoglycemia as a clinical outcome for patients with diabetes, it is important that WA State's HTA include the various clinically meaningful measures of hypoglycemia in the assessment. Therefore, we strongly recommend the inclusion of all three definitions (time spent hypoglycemic, and frequency of hypoglycemia and severe hypoglycemia events) as clinically relevant outcome measures for Key Question 2. Below we provide additional information on the importance of hypoglycemia, whether measured as time spent hypoglycemia or by frequency of events, as a clinical outcome for patients with diabetes.

Hypoglycemia is a critical clinical outcome presenting real safety issues for intensively managed patients with diabetes and is a significant barrier to achieving target levels of glucose control.[12] Hypoglycemia induces two types of physical symptoms: autonomic symptoms (e.g., sweating, tremor, palpitations) resulting from stimulation of the sympatho-adrenal system and neuroglycogenic symptoms (e.g., confusion, drowsiness, seizure) resulting from the direct effect of glycopenia on cerebral function.[13] Typically, the mild-to-moderate autonomic symptoms serve as early warning signs of hypoglycemia, which is treated to prevent the potentially severe neuroglycogenic symptoms from occurring. A prospective study of adults with insulin-dependent Type 2 diabetes found that over half developed hypoglycemia (blood glucose ≤ 60 mg/dL) with a

[12] Saleh M, Grunberger G. Hypoglycemia: an excuse for poor glucose control? Clin Diabetes 2001;19(4):161-67.
[13] Hepburn DA, Patrick AW, Eadington DW, Ewing DJ, Frier BM. Unawareness of hypoglycaemia in insulin-treated diabetic patients: prevalence and relationship to autonomic neuropathy. Diabet Med 1990;7(8):711-7.

median frequency of 6 episodes per year.[14] About 20% of hypoglycemic episodes were asymptomatic, 77% were mild to moderate, and 3% were severe. Unrecognized and untreated hypoglycemia can result in coma or death; an estimated 2-4% of deaths in people with Type 1 diabetes have been attributed to hypoglycemia.[15] Clearly, achieving tighter glucose control without increases in hypoglycemia offers direct clinical benefit.

Hypoglycemia is a major barrier to attaining glycemic control targets that are essential for the prevention of diabetes-related complications. Studies have shown that intensive glycemic control increases the risk for severe hypoglycemia. In the DCCT, patients receiving intensive glycemic control had a threefold higher rate of severe hypoglycemia compared with patients on conventional therapy.[16] More than half of all hypoglycemic episodes in the DCCT occurred during sleeping hours. In the Stockholm Diabetes Intervention Study, a 5-year randomized trial comparing outcomes in 97 insulin-dependent patients randomized to intensive diabetes therapy or conventional treatment, the rate of serious hypoglycemia was 2.5 times higher in the intensive therapy group.[17] A meta-analysis of 14 randomized, controlled trials found that the likelihood of at least one severe hypoglycemic event was about 3 times greater in patients receiving intensive therapy than in those receiving conventional therapy (odds ratio 2.99; 95% CI, 2.45 to 3.64, $p<0.0001$).[18]

Frequent episodes of hypoglycemia can cause a condition called hypoglycemia unawareness, in which individuals lose their ability to detect the autonomic symptoms of developing hypoglycemia.[19] Because they do not react to early signs of hypoglycemia, individuals with hypoglycemia unawareness are more likely to experience severe episodes of hypoglycemia.[20] Studies indicate that 50 to 60% of insulin-dependent diabetes patients have impaired hypoglycemia awareness.[21,22] In the most recent study, 13% of Type 1 diabetes patients had hypoglycemia unawareness (defined as total absence of symptoms) and another 47% had an impaired awareness of hypoglycemic symptoms.[23] Patients with partial or complete hypoglycemia unawareness have 5.1 and 9.6 times higher rates of severe hypoglycemia, respectively, than those with normal hypoglycemia awareness ($p<0.001$).[24] Type 1 diabetes patients with presumed hypoglycemia unawareness fail to recognize 40-60% of hypoglycemic episodes even when performing 4 to 7 fingerstick blood glucose measurements each day.[25,26]

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[14] Murata GH, Duckworth WC, Shah JH, Wendel CS, Moher MJ, Hoffman RM. Hypoglycemia in stable, insulin-treated veterans with type 2 diabetes: a prospective study of 1662 episodes. J Diabetes Complications 2005;19:10-7.
[15] Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care 2003;26(6):1902-12.
[16] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329(14):977-86.
[17] Reichard P, Britz A, Carlsson P, et al. Metabolic control and complications over 3 years in patients with insulin dependent diabetes (IDDM): the Stockholm Diabetes Intervention Study (SDIS). J Intern Med 1990;228(5):511-7.
[18] Egger M, Davey Smith G, Stettler C, Diem P. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. Diabet Med 1997;14(11):919-28.
[19] Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care 2003;26(6):1902-12.
[20] IBID.
[21] Hepburn DA, Patrick AW, Eadington DW, Ewing DJ, Frier BM. Unawareness of hypoglycaemia in insulin-treated diabetic patients: prevalence and relationship to autonomic neuropathy. Diabet Med 1990;7(8):711-7.
[22] Pedersen-Bjergaard U, Pramming S, Thorsteinsson B. Recall of severe hypoglycaemia and self-estimated state of awareness in type 1 diabetes. Diabetes Metab Res Rev 2003; 19(3):232-40.
[23] IBID
[24] IBID
[25] Sanchis S, Jeandidier N, Meyer L, Busch M, Ott F, Pinget M. Use of continuous monitoring system in 23 insulin treated diabetic patients: feasibility, reliability, and efficacy for diagnosis of undiagnosed hypoglycemia (Abstract). Diabetes 2001; 50(Suppl 2):A447.
[26] Jungheim K, Wientjes K, Volker LK, T., Schoonen A. Glucose Monitor Group: Frequent glucose spot measurements miss half of all hypoglycemia episodes in insulin treated diabetes patients (Abstract). Diabetes 2001; 50(Suppl 2):A448.

4. Clinically Relevant Safety Measures Should be Used to Evaluate CGM and SMBG (Key Question 3)

The HTA rightly concludes that device-specific safety issues related to SMBG, namely sore fingers and difficulty drawing blood, are based on outdated technologies and studies and therefore are not relevant. In light of the decrease in lancet size, the decrease in the amount of blood required, and ability to test in alternate sites mean that sore fingers or difficulty drawing blood are no longer major concerns. It is also important to note that none of the device related safety issues raised in the HTA are significant adverse events and do not pose a threat of serious morbidity or mortality.

The discussion of adverse events attributed to rt-CGM in the HTA is also deficient. First, the adverse events listed related to skin irritation appear to be minor at best, and in no way life-threatening to patients. Further, the HTA includes reports of dissatisfaction with the devices (e.g., sensor is too bulky) that in no way relate to patient safety. The crux of the analysis of rt-CGM safety centers on missed or ignored alerts, leading a patient to fail to take action to treat an impending hyper- or hypoglycemic excursion. The assessment fails to note that the rt-CGM technology itself does not cause the glycemic excursion which would rightly be considered an adverse event for diabetes patients. In addition, the assessment that risk of patients treating a glycemic excursion based on a false positive rt-CGM alarm would require patients to not follow the FDA-labeled use of rt-CGM, which stipulates that all treatment decisions must be made based on a confirmatory SMBG reading. As such, the adverse event would be due to improper self-management by the patient, not caused by the device itself.

Conversely, the assessment of rt-CGM safety does not address at all the utility of these technologies to help patients prevent both hyper- and hypoglycemic excursions and thereby prevent adverse events. In addition, rt-CGM detects hypoglycemia in patients who suffer from hypoglycemia unawareness or when patients are sleeping, excursions that would go undetected in the absence of rt-CGM and potentially result in severe adverse events. Failing to acknowledge this potential of rt-CGM in children and adolescents with Type 1 diabetes results in an incomplete assessment of the true safety profile of these devices.

5. The HTA Should Include an Evaluation of Patients Who Benefit Most from CGM (Key Question 4)

For Key Question 4, the only sub-population analysis mentioned for CGM is the comparison of patients 8-14 years old and those 15-24 years old in the JDRF study. The study found no differential by age.

The HTA does not discuss the most relevant sub-population analysis from a clinical perspective; i.e., analyses that demonstrate which patients under age 18 are most likely to benefit from rt-CGM. There is a growing body of evidence demonstrating the characteristics of patients under age 18 who benefit most from rt-CGM. In particular, two large RCTs have shown that children and adolescents who use rt-CGM frequently achieve statistically significant improvements in A1C compared to SMBG alone. Specifically, an analysis of data from the JDRF study on rt-CGM showed that patients, including teens and young adults, who used the device at least six days per week had substantially lower HbA1c levels after six months compared with patients who used rt-CGM less than six days a week. Analysis further determined that frequency of

SMBG and initial rt-CGM use may be predictive of patients likely to benefit from rt-CGM in the long-term.[27]

In the STAR3 study, statistically significant reductions in A1C were observed for all patients, including children and adolescents. However, analysis showed that a frequency of sensor use of 41 to 60% was associated with a reduction of 0.64 percentage points in glycated hemoglobin levels, and sensor use of greater than 80% doubled the effect.[28] These sub-population findings should be acknowledged in the HTA, since they directly inform decisions about which patients under age 18 would most benefit from access to rt-CGM.

6. Studies Evaluating CGM in Conjunction with CSII and/or MDI Should be Included (Key Questions 2, 3, and 4)

As noted previously, the HTA should evaluate rt-CGM in the context of current clinical practice. Because rt-CGM is used almost exclusively in conjunction with either an insulin pump or MDI, studies evaluating rt-CGM in conjunction with these insulin regimens should be included in the analysis. Such studies are the most relevant and applicable to actual clinical use of rt-CGM, and they build on the body of evidence that evaluates these treatments separately.

Therefore, we recommend that the inclusion/exclusion criteria for the HTA be revised to include clinically relevant studies comparing CGM in combination with the insulin delivery methods routinely used in clinical practice (including sensor-augmented pump therapy). This revision would add several important studies to the HTA, including the STAR 3 study, which demonstrates that people with diabetes, including those under age 18, using an insulin pump with integrated CGM can achieve better glucose control while avoiding increased adverse events such as hypoglycemia, diabetes ketoacidosis and weight gain, relative to multiple daily injection therapy (MDI) with Self-monitored Blood Glucose (SMBG).[29] Further details of the STAR 3 Study are provided in the Appendix at the end of this document.

Several other studies, randomized and non-randomized included pediatric patients (under 18 years of age), though results were not reported separately for this age group. In two randomized trials, a greater proportion of patients in the CGM arm had statistically or clinically meaningful A1C reductions relative to the SMBG arm.[30,31] In a third study, a six month continuation of patients from a randomized trial, results for patients under 18 were also aggregated with adults and reported.[32] In this study, control patients with continuation phase baseline A1C > 7% were switched to CGM. CGM use was associated with A1C reduction after 6 months (p = 0.02 with age-group adjustment).Severe hypoglycemia decreased from 27.7 events per 100 person-years in the 6-month RCT Study phase for patients not on CGM, to 15.0 events per 100 person-years in the 6-month CGM follow-up phase (p= 0.08).

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[27] Beck RW et al. Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. Diabetes Care 2009; 32: 1947-1953.
[28] Bergenstal RM et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. N Engl J Med, 2010; 363(4): 311-320.
[29] IBID.
[30] Deiss D, Bolinder J, Riveline JP, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes Care. 2006;29:27302732.
[31] Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care. 2009;32(8):1378-1383.
[32] Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the JDRF-CGM trial. Diabetes Care. 2010;33:17-22.

Appendix: The STAR 3 Study

STAR 3 highlights include:

- People with diabetes using an insulin pump with *integrated CGM* can achieve better glucose control while avoiding increased adverse events such as hypoglycemia, diabetes ketoacidosis and weight gain, relative to multiple daily injection therapy (MDI) with Self-monitored Blood Glucose (SMBG).
- The study demonstrated *a statistically significant reduction in A1C* for *patients 18 and younger* as well as adults, for CGM enabled pump therapy, compared to multiple daily injections (MDI) therapy with SMBG.
- Among patients 18 and younger, the CGM arm achieved glycemic improvements rapidly (within the first 3 months of therapy), relative to MDI, and sustained the improvement over the long term (12 months).

As the longest and largest study of its kind, STAR 3 outcomes could redefine the standard of care for diabetes management. CGM integrated insulin pump therapy (the MiniMed Paradigm REAL-Time System ®) provides optimal glucose control that allows people with diabetes to improve their A1C and ultimately reduce the risk for long-term complications of diabetes, as described in the Diabetes Complications and Control Study.[33]

We provide a detailed Study synopsis below.

STAR 3 Study synopsis

Purpose:
To evaluate improvements in metabolic control in subjects with type 1 diabetes placed on sensor-augmented insulin pump therapy (SAP). SAP refers to the feature of an insulin pump that integrates CGM data from a continuous glucose monitoring sensor. In the remainder of this synopsis, we refer to the SAP arm, as CGM. The CGM patients had previously failed to meet glycemic targets with multiple daily injection (MDI) therapy and conventional self-monitoring of blood glucose.

Endpoints:
- Change in glycated hemoglobin (A1C) from baseline to 1 year between the two study groups: CGM and MDI.
- Rate of severe hypoglycemia (defined as an episode requiring assistance).

Methods:
- This was an unmasked, randomized, controlled trial conducted at 30 sites in the United States and Canada. The sites represent a wide variety of academic and private-practice diabetes centers.
- Subject eligibility criteria: Use of MDI for 3 months, documented self-monitoring of blood glucose (SMBG) 4 times/day for the prior 30 days, 7-70 years of age, type 1 diabetes, and a baseline A1C of ≥7.4% to ≤9.5%. Subjects were required to have access to a computer.

[33] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329(14):977-86.

- Subject exclusion criteria: Use of an insulin pump within the previous 3 years, ≥2 severe hypoglycemic events in the year prior to enrollment, use of oral anti-diabetes agents in the previous 3 months, and pregnancy or intent to become pregnant.
- 495 subjects were randomized to CGM or MDI via a block design, stratified by center and age group:
    - Adult group: 19-70 years of age
    - Pediatric group: 7-18 years of age
- Prior to randomization, all study subjects received training in insulin diabetes management, carbohydrate counting and correction insulin bolusing. Training for MDI and CGM subjects included use of diabetes management software (CareLink® Therapy Management System for Diabetes-Clinical).
- The pump therapy group used a device that integrates an insulin pump with CGM, the MiniMed Paradigm® REAL-Time System (Medtronic), with insulin aspart for 2 weeks before initiating continuous glucose sensor therapy.
- The MDI subjects used both insulin glargine and insulin aspart.
- In the first 5 weeks after randomization, there was a difference in the visit schedules between the 2 groups, in order to provide the technical training required for the CGM arm. For the remaining 47 weeks of the study phase, the visit schedule was identical between the CGM and MDI groups, with routine clinic visits at 3, 6, 9, and 12 months to reflect standard diabetes care.
- Sensor glucose values were collected for 1 week periods at baseline, 6 months and 1 year in both groups. The MDI group used a device that collected, but did not display data (Guardian REAL-Time Clinical ®, Medtronic).

Results:

- 10 subjects lacked follow-up A1C values and were not included in this final analysis of results. There were 485 patients included in the intent-to-treat group and reported on in these results.
- There were no significant differences in baseline characteristics between the two study groups except for weight among adults.
- The change in A1C between study groups favored the CGM group and was statistically and clinically significant in both adult and pediatric subjects.
- In the pediatric group at one year follow-up, the change in A1C from baseline favored the CGM group: -0.5, 95% confidence interval [–0.80, –0.22], ($p < 0.001$).
- For adults, the change from baseline A1C also favored the CGM group: –0.6, 95% confidence interval (–0.76, –0.45) ($p<0.001$).
- In the CGM group, A1C values fell rapidly from baseline to 3 months and remained lower than levels in the MDI group for the rest of the study *for both the adult and pediatric sub-groups.*
- In a post-hoc analysis, nearly half (44%) of the pediatric sub-group in the CGM arm achieved the American Diabetes Association's age-specific A1C targets, compared to only 20% in the multiple daily injection arm ($p=0.005$).
- For all subjects in the CGM arm, 27% reached the A1C target of less than or equal to 7%, while only 10% achieved this target for the MDI group ($p < 0.001$).
- An increased frequency of use of CGM was associated with a greater reduction in A1C values from baseline to 1 year ($p=0.003$).
- There was no difference in weight gain between the CGM and MDI groups.

Adverse Events:

- There were no clinical or statistically significant differences in the rates of severe hypoglycemia or diabetic ketoacidosis between study groups and for the adult and pediatric age groups.

Conclusion:

- The decrease in A1C levels in the CGM group was achieved at 3 months and sustained throughout the 1 year study for adults and pediatric patients.
- The improvement in A1C levels was achieved without an increase in the rate of severe hypoglycemia events and without an increase in the time spent in the hypoglycemic range.
- A significantly greater number of adults and pediatric patients in the CGM group were able to reach ADA age-specific A1C targets relative to MDI.

December 10, 2010

Washington State Health Care Authority
Health Technology Assessment Program
676 Woodland Square Loop SE
Olympia, Washington 98504-2712
shtap@hca.wa.gov

RE: Comments on Health Technology Assessment for Glucose Monitoring: Self Monitoring in patients under 18 years old.

To Whom It May Concern:

On behalf of Roche Diagnostics Diabetes Care, a global leader in diabetes self-monitoring systems, insulin delivery and diabetes management solutions, we welcome the opportunity to submit comments concerning this Health Technology Assessment.

The current impact of diabetes on the quality of life, productivity and healthcare costs are staggering. The ever growing prevalence of the condition, the demographic shifting of minority populations where the incidence is greater and our aging society are clear reasons to evaluate healthcare for patients with diabetes.

Glycemic control as demonstrated in a number of clinical trials shows a reduction of co-morbid and costly complications of diabetes.

Self Monitoring of Blood Glucose (SMBG) is the use of a blood glucose meter in combination with a test strip to accurately identify the patients' metabolic state (in regards to his/her blood glucose level). These systems have been validated and tested for accuracy, reliability and other common interferences to ensure meaningful and reliable results, on which both the provider as well as the patient may make a decision in regards to medication titration, dietary intake or exercise as means to control blood glucose levels. Additionally SMBG is a diagnostic support to behavioural decision making.

The clinical guidelines for medication, dietary decisions and exercise regimens and the patient adherence to them is the foundation toward positive clinical outcomes. The diagnostic delivery of information provides the start of the decision process on how to implement the clinical guidelines established for the patient. In contrast to medications, a diagnostic test in and of itself does not produce a pharmacologic effect, only drugs produce this. The purpose of the use of SMBG is to assist in the safe and effective use of diabetes medications, included but not limited to insulin, and to achieve the optimal desired clinical outcomes.

Clinical guideline recommendations from the America Diabetes Association, International Diabetes Federation, and The International Society for Pediatric and Adolescent Diabetes all provide clinical guidelines as to the use and frequency of SMBG. They also do this in regards

to the use of insulin in combination with SMBG.

The following recommendations for SMBG are as follows: (Both ADA and ISPAD)*

- Helps to monitor immediate and daily levels of control;
- Helps to determine immediate and daily insulin requirements;
- Helps guide insulin adjustments to decrease fluctuations in BG levels;
- Detects hypoglycemia and assists in its management; and
- Assists in the safe management of hyperglycemia.

The consensus from all the clinical guidelines is that SMBG and the use of insulin are ultimately linked together for the safe and effective use of insulin therapy and that SMBG is key and necessary to safely treat patients, respectably of any age, and to prevent them from both short term complications (i.e. hypoglycemia) as well as long term complications (i.e. long term diabetes complications like nerve, kidney or eye damages.)

* Standards of Medical Care in Diabetes—2010, DIABETES CARE, VOLUME 33, SUPPLEMENT 1, JANUARY 2010 and ISPAD Clinical Practice Consensus Guidelines 2009 Compendium, Insulin treatment in children and adolescents with diabetes Pediatric Diabetes 2009: 10(Suppl. 12): 82–99 and Assessment and monitoring of glycemic control in children and adolescents with diabetes, Pediatric Diabetes 2009: 10(Suppl. 12): 71–81

Policy context

Individualized Diabetes Medical Management Plans and clinical guidance has been developed according to ADA Standards of Medical Care in Diabetes, ISPAD and the American College of Clinical Endocrinologists (ACCE) including specific instructions for each child and adolescent recommendations concerning the frequency and circumstances of blood glucose monitoring[1].
Contents of guidelines especially by ADA, ISPAD, and ACCE need to be incorporated into the summary/appraisal of the HTA. FDA approved product labelling for insulin also recommends the specific use of SMBG for the safe and effective use of insulin therapy.

The Juvenile Diabetes Research Foundation International states: People with type 1 diabetes must check their blood sugar (glucose) levels throughout the day using a blood glucose meter. The meter tells them how much glucose is in their blood at that particular moment. Based upon that reading, they take insulin, eat, or modify activity to keep blood sugars within the target range. Regularly checking blood sugar levels is an essential part of type 1 diabetes care.

Clinical context

Self Monitoring of Blood Glucose (SMBG) is the use of a blood glucose meter in combination with a test strip to accurately identify the patients' metabolic state (with regards to his/her blood glucose level). These systems have been validated and tested for accuracy, reliability and other common interferences to ensure meaningful and reliable results, on which both the provider as well as the patient may make a decision with regards to medication titration, dietary intake or exercise as means to control blood glucose levels. Additionally SMBG is a diagnostic support to behavioural decision making. Thus, SMBG is

[1] AMERICAN DIABETES ASSOCIATION: Diabetes care in the school and day care setting, DIABETES CARE, VOLUME 33, SUPPLEMENT 1, JANUARY 2010

an important part of type 1 management and can not be separated from other disease management components.
SMBG is a prerequisite for CGM as ADA phrases it: "CGM through the measurement of interstitial glucose (which correlates well with PG) is available. These sensors require calibration with SMBG, and the latter are still recommended for making acute treatment decisions."[2]
Guiding questions for an appropriate description of technologies in HTA are provided in Chapter 3.1 of this document.
A clinical relevance frontier of 0.5% reduction Haemoglobin A1c (HbA1c) is not based upon scientific consensus. The HTA lines out: "Similarly, there is no consensus on what constitutes a clinically meaningful change in A1C. A value of 0.5% was used. "[3]
Such a use of a clinical relevance frontier would need to be based on a sound and widely accepted publication.

The Role of Insulin

In the HTA by the Washington State Health Care Authority self-monitoring of blood glucose (SMBG) is considered as an independent diagnostic test and not as an essential part of care in patients with diabetes who are using insulin. Haemoglobin A1c (HbA1c) is the gold standard for monitoring glycemic control and serves as a surrogate for diabetes-related complications. HbA1c does not provide information about day-to-day changes in glucose levels. Patients with normal or near-normal HbA1c levels may still display postprandial hyperglycemia, putting them at risk for long-term adverse outcomes[4]. "Self-monitoring of blood glucose represents an important adjunct to HbA1c because it can distinguish among fasting, pre-prandial, and postprandial hyperglycemia; detect glycemic excursions; identify hypoglycemia; and provide immediate feedback to patients about the effect of food choices, activity, and medication on glycemic control"[5]. This feedback is very important in self-management of diabetes leading to adjustment of insulin dosage and/ or nutritional changes. The measuring of the blood glucose levels pre- and postprandial as well as before, during and after sport activities is particularly relevant for children and adolescents. Nutrition intake in children is often difficult to plan and control[6]. Thus, SMBG is very helpful for avoiding hypoglycemia and achieving target blood glucose levels.

The clinical guidelines for medication, dietary decisions and exercise regimens and the patient adherence to them is the foundation toward positive clinical outcomes. The diagnostic delivery of information provides the start of the decision process on how to implement the clinical guidelines established for the patient. In contrast to medications, a diagnostic test in and of itself does not produce a pharmacologic effect, only a drug produces this. In this context, the purpose of the use of SMBG is to assist in the safe and effective use of diabetes medications, included but not limited to insulin, and to achieve the optimal desired clinical outcomes also via dietary changes and exercise.

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[2] AMERICAN DIABETES ASSOCIATION: Standards of Medical Care in Diabetes—2010, DIABETES CARE, VOLUME 33, SUPPLEMENT 1, JANUARY 2010
[3] WASHINGTON STATE HEALTH CARE AUTHORITY: Glucose Monitoring: Selfmonitoring in patients under 18 years old, Health Technology Assessment: http://www.hta.hca.wa.gov/glucose.html
[4] Fava, S: Role of postprandial hyperglycemia in cardiovascular disease. In: Expert.Rev.Cardiovasc.Ther. 6 (2008) Nr. 6, S. 859-872
[5] Danne, T: Self-monitoring of Blood Clucose (SMBG): From Theory to Clinical Practice. In: Medscape CME Diabetes & Endocrinology(2009)
[6] Powers, SW; Byars, KC; Mitchell, MJ; Patton, SR; Standiford, DA; Dolan, LM: Parent report of mealtime behavior and parenting stress in young children with type 1 diabetes and in healthy control subjects. In: Diabetes Care 25 (2002) Nr. 2, S. 313-318

The consensus from all the clinical guidelines is that SMBG and the use of insulin are ultimately linked together for the safe and effective use of insulin therapy and that SMBG is key and necessary to safely treat patients, respectably of any age, and to prevent them from both short term complications (i.e. hypoglycemia) as well as long term complications (i.e. long term diabetes complications like nerve, kidney or eye damages.)
"Major clinical trials of insulin-treated patients that demonstrated the benefits of intensive glycemic control on diabetes complications have included SMBG as part of multifactor interventions, suggesting that SMBG is a component of effective therapy. SMBG allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being achieved. Results of SMBG can be useful in preventing hypoglycaemia and adjusting medications (particularly prandial insulin doses), MNT, and physical activity."[7]

"Since the time of the DCCT, a number of rapid-acting and long-acting insulin analogs have been developed. These analogs are associated with less hypoglycemia with equal A1C lowering in type 1 diabetes[8,9]. Recommended therapy for type 1 diabetes therefore consists of the following components: 1) use of multiple dose insulin injections (3–4 injections per day of basal and prandial insulin) or CSII therapy;
2) matching of prandial insulin to carbohydrate intake, premeal blood glucose, and anticipated activity; and 3) for many patients (especially if hypoglycemia is a problem), use of insulin analogs. There are excellent reviews available that guide the initiation and management of insulin therapy to achieve desired glycemic goals[10,11, 12,,13].

The Washington State HTA clearly explains the benefits of insulin analogs: "The older insulins Regular and NPH didn't mimic the normal insulin release profile very well and were absorbed unreliably. Analog insulins now provide more reliable options for insulin therapy with shorter or longer action to better mimic a natural insulin curve. Routine dietary intake and exercise make it easier to match insulin, but routine is difficult for children."[14] Or in a guide for patients: "With frequent testing, you do not have to wait for the A1c test results and you have a better guide to making insulin dose adjustments each day"[15].

Recommendations for additional Literature Search Criteria

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[7] AMERICAN DIABETES ASSOCIATION: Standards of Medical Care in Diabetes—2010, DIABETES CARE, VOLUME 33, SUPPLEMENT 1, JANUARY 2010

[8] DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA 2003; 289:2254–226

[9] Rosenstock J, Dailey G, Massi-Benedetti, M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. Diabetes Care 2005; 28:950–955

[10] American Diabetes Association. Intensive Diabetes Management. Alexandria, VA, American Diabetes Association, 2009

[11] DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA 2003; 289:2254–226

[12] Mooradian AD, Bernbaum M, Albert SG. Narrative review: a rational approach to starting insulin therapy. Ann Intern Med 2006;145:125–134

[13] American Diabetes Association. Intensive Diabetes Management. Alexandria, VA, American Diabetes Association, 2009; Mooradian AD, Bernbaum M, Albert SG. Narrative review: a rational approach to starting insulin therapy. Ann Intern Med 2006;145:125–134

[14] WASHINGTON STATE HEALTH CARE AUTHORITY: Glucose Monitoring: Selfmonitoring in patients under 18 years old, Health Technology Assessment: http://www.hta.hca.wa.gov/glucose.html

[15] J Walsh et al. Using insulin, Torrey Pines Press 2003

The additional evidence if considering short- and rapid-acting insulin analogues is considerable and can be estimated by a quick search in PubMed database using the search strings below

- Combining “type 1 diabetes” with “insulin analogues” with “short acting” or “rapid acting “ and “efficacy” or “Ab1c” or “blood glucose” or “treatment outcome ”a total of 71 respectively 66 publications were found
- Adding the MeSH terms “children” and “adolescents” leads to 19 hits.
- Looking for economic studies we found one, restricting to young none.

Search History

Search	Most Recent Queries	Time	Result
#16	Search **#15 AND (#11 OR #12)**	13:18:30	0
#15	Search **#1 AND (#5 OR #6) AND #14 AND #7**	13:17:40	1
#14	Search **cost effectiveness**	12:38:36	67951
#13	Search **#10 AND (#11 OR #12)**	12:35:43	19
#12	Search **adolescent [MeSH Terms]**	12:33:06	1362871
#11	Search **child [MeSH Terms]**	12:32:32	1347164
#10	Search **#1 AND (#9 OR #3 OR #4) AND (#5 OR #6) AND #7**	12:29:09	66
#9	Search **treatment outcomes [MeSH Terms]**	12:27:45	456874
#8	Search **#1 AND (#2 OR #3 OR #4) AND (#5 OR #6) AND #7**	12:26:56	71
#7	Search **diabetes mellitus type 1**	12:20:49	53267
#6	Search **rapid acting**	12:20:18	4711
#5	Search **short acting**	12:20:06	9163
#4	Search **blood glucose**	12:19:43	176961
#3	Search **ab1c**	12:19:22	1
#2	Search **efficacy**	12:19:01	371699
#1	Search **insulin analogue**	12:18:23	2369

This means that within the search of insulin analogues restricting to young patients significantly diminishes the evidence base.
The search strategy determines the studies included in the HTA and thus the results of the HTA. The literature search in the HTA could be enhanced to be more comprehensive: Only the search strategies for PubMed and EMBASE are shown.. The vast majority of the Medline search is built by MeSH terms. However, more free-text terms should be used[16] e.g. for the MeSH term ‘blood glucose self monitoring’ the following free-text terms could be used to enhance the full data available: intermittent blood glucose monitoring, self-monitoring of blood glucose, SMBG.

Key questions

Efficacy and effectiveness of monitoring

Any advisory committee would rate unethical to conduct a RCT of SMBG versus no SMBG in insulin-treated type 1 diabetes. It is a conceptual error to equate SMBG with a medication or intervention and to compare groups treated in a similar manner except for the use of SMBG in one arm of the trial. SMBG is not an intervention per se. Stand-alone it can not improve glucose control just as measuring blood pressure does not improve hypertension. SMBG is only as good as the actions taken in response to measured glucose levels. In order to respond the glucose levels measured, fairly common disease management rules and insulin dose adjustments exist in type 1 diabetes[17] .
SMBG is an important and integrated component of type 1 diabetes management. Several studies evaluated special training programs that led to a sustained improvement of glycaemic

[16] Higgins et al. Cochrane Handbook for systematic reviews of interventions, Wiley-Blackwell 2009 chapter 6.4.5 ‘In order to identify as many relevant records as possible searches should comprise a combination of subject terms selected from the controlled vocabulary or thesaurus (‘exploded' where appropriate) with a wide range of free-text terms’.

[17] Kolb H, Kempf K, Martin S, Stumvoll M, Landgraf R: On what evidence-base do we recommend self-monitoring of blood glucose?, Diabetes Res Clin Pract. 2010 Feb;87(2):150-6

control[18,19,20]. None of those were designed to assess the benefit of SMBG separate from the other components of self-management. In other words, they did not prove the effectiveness of SMBG, but the integrated SMBG supported approach [4].
Not only in the DCCT but also in the Stockholm Diabetes Intervention Study[21] SMBG was part of the protocol for intensive insulin treatment that led to better clinical outcome, in the case of the Stockholm Diabetes Intervention Study less microvascular complications. The scheme of insulin dosing needs to be tailored to the needs of the day. Therefore, the course of blood glucose levels should be followed by SMBG. Urine glucose testing can not substitute SMBG due to its limited accuracy and applicability. Possible liability in case of avoidable hypoglycaemia, can be avoided by the determination of blood glucose levels before the injection of rapid or intermediate acting insulin[22]. Self-monitoring among patients with type 1 diabetes (>= 3 times daily) was associated with 1% lower HbA1c levels than was with less frequent monitoring[23] . Algorithms developed on the basis of SMBG levels to adopt intensive insulin therapy are useful in determining the optimal dose of insulin and can improve glycemic control (difference = 1.77%; p = 0.01) and lipid metabolism.[24] As previously mentioned SMBG is an important component of diabetes management. And as evidence upon adults can only be excluded with compelling reasons, the role of SMBG in glycaemic control has to be acknowledged. Guided self-determination in persistent poor glycaemic control (HbA1c > 7.9%) enabled Danish adult participants in a randomized trial to improve their life skills over 1 year as measured by:
(a) increased autonomy support perceived from health professionals ($p < 0.01$);
(b) higher frequency of self-monitored blood glucoses ($p < 0.001$);
(c) increased perceived competence in managing diabetes ($p < 0.01$);
(d) fewer diabetes-related problems ($p < 0.05$); and
(e) improved glycaemic control (mean difference = 0.41%; $p < 0.0099$)[25]
As previously discussed, evidence of short and rapid acting insulin analogues needs to be considered in appropriately assessing SMBG. Within our search we found 29 studies to be incorporated (numbers of the abstract in the attached search results file: 1, 2, 5,7, 13, 16, 19, 20, 22, 23, 24, 28, 29, 30, 31, 42, 46, 47, 48, 50, 52, 53, 55, 56, 58, 59, 60, 61, 64) We did not count medical review papers.
A summary of those studies is beyond the scope of this statement.

Efficacy and effectiveness by frequency or mode of testing

[18] I. Muhlhauser, I. Bruckner, M. Berger, D. Cheta, V. Jorgens, C. Ionescu-Tirgoviste, et al., Evaluation of an intensified insulin treatment and teaching programme as routine management of type 1 (insulin-dependent) diabetes. The Bucharest–Dusseldorf Study, Diabetologia 30 (1987) 681– 690
[19] T.R. Pieber, G.A. Brunner, W.J. Schnedl, S. Schattenberg, P. Kaufmann, G.J. Krejs, Evaluation of a structured outpatient group education program for intensive insulin therapy, Diabetes Care 18 (1995) 625–630
[20] DAFNE Study Group, Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial, Br. Med. J. 325 (2002) 746.
[21] Reichard P, Nilsson BY, Rosenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus; N Engl J Med. 1993 Jul 29;329(5):304-9
[22] Kolb H, Kempf K, Martin S, Stumvoll M, Landgraf R: On what evidence-base do we recommend self-monitoring of blood glucose?, Diabetes Res Clin Pract. 2010 Feb;87(2):150-6
[23] Karter AJ et al: Self-monitoring of Blood Glucose Levels and Glycemic Control: the Northern California Kaiser Permanente Diabetes Registry.; Am J Med. 2001;111:1–9
[24] K Miyako, R Kuromaru, H Kohno and T Hara: Improved diabetes control by using ‘close adjustment algorithms’, Pediatrics International 2004; 46:678–684
[25] V Zoffmann and T Lauritzen Guided self-determination improves life skills with Type 1 diabetes and A1C in randomized controlled trial,. Patient Education and Counseling 2006; 64:78–86

The paper published by Schütt et al.[26]is not included. As this is a large study addressing the efficacy of SMBG under real-life conditions and including 24,500 patients, it should be considered in the HTA. N=19,491 were patients with type 1 diabetes, there are no data regarding age in the abstract. Still, with one additional daily BG measurement improved the HbA1c-level by 0.26%, while this relationship is present for pediatric and adult patients. More frequent SMBG effected HbA1c reductions by 0.32% per one additional measurement/day when intensified conventional (>= 4 daily injections) or continuous subcutaneous insulin infusion therapy were applied.

The Washington HTA states: "SMBG in general has been extensively reviewed by the ADA and is recommended for patients of all ages with type 1 diabetes. The 2010 report did not specifically address frequency for children, however, in a statement published in 2005 by the ADA entitled Care of Children and Adolescents with Type 1 Diabetes[26] it is recommended that SMBG be performed at least four times daily."[27]

"The frequency and timing of SMBG should be dictated by the particular needs and goals of the patient. SMBG is especially important for patients treated with insulin in order to monitor for and prevent asymptomatic hypoglycemia and hyperglycemia. For most patients with type 1 diabetes and pregnant women taking insulin, SMBG is recommended three or more times daily. For these populations, significantly more frequent testing may be required to reach A1C targets safely without hypoglycemia."[28] Most patients include children and adolescents. In case of restricting SMBG for them needs to provide compelling reasons why SMBG is less necessary.

ISPAD: "SMBG should be prescribed at a frequency to optimize each child's diabetes control, usually 4–6 times a day, because frequency of SMBG correlates with glycemic control."[29]

Furthermore, Nathan et al.[30] demonstrated a significant association between increased frequency of self-monitoring and lower HbA1c levels in two large cohorts of adults with type 1 diabetes who were followed up during an 8-year interval.

"All basal/bolus diabetes management regimes and all self-management skills rely on frequent SMBG"[31].

"SMBG should be carried out three or more times daily for patients using multiple insulin injections or insulin pump therapy. For patients using less frequent insulin injections, noninsulin therapies, or medical nutrition therapy (MNT) alone, SMBG may be useful as a guide to the success of therapy. To achieve postprandial glucose targets, postprandial SMBG may be appropriate."[32]

"Note: successful application of intensified diabetes management with multiple injection therapy or insulin infusion therapy requires frequent SMBG (four to six times per day) and

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[26] Schütt, M; Kern, W; Krause, U; Busch, P; Dapp, A; Grziwotz, R; Mayer, I; Rosenbauer, J; Wagner, C; Zimmermann, A; Kerner, W; Holl, RW: Is the frequency of self-monitoring of blood glucose related to long-term metabolic control? Multicenter analysis including 24,500 patients from 191 centers in Germany and Austria. In: Exp Clin.Endocrinol.Diabetes 114 (2006) Nr. 7, S. 384-388.

[27] WASHINGTON STATE HEALTH CARE AUTHORITY: Glucose Monitoring: Selfmonitoring in patients under 18 years old, Health Technology Assessment: http://www.hta.hca.wa.gov/glucose.html

[28] AMERICAN DIABETES ASSOCIATION: Diabetes care in the school and day care setting, DIABETES CARE, VOLUME 33, SUPPLEMENT 1, JANUARY 2010

[29] Rewers M. et al. : ISPAD Clinical Practice Consensus Guidelines 2006–2007: Assessment and monitoring of glycemic control in children and adolescents with diabetes, Pediatric Diabetes 2007: 8: 408–418

[30] Nathan DM, McKitrick C, Larkin M, Schaffran R, Singer DE: Glycemic control in diabetes mellitus: have changes in therapy made a difference? Am J Med 1996;100:157-63

[31] Silverstein et al.: Care of Children and Adolescents With Type 1 Diabetes- A statement of the American Diabetes Association, diabetes Care, Vol. 28, No. 1 2005

[32] AMERICAN DIABETES ASSOCIATION: Standards of Medical Care in Diabetes—2010, DIABETES CARE, VOLUME 33, SUPPLEMENT 1, JANUARY 2010

regular, frequent review of the results to identify patterns requiring adjustment to the diabetes treatment plan."[33]

Safety

From an analysis of an American clinical database from 1993 through 1998, it can be seen that HbA1c levels declined in the age-groups <5, 5-12, 13-17, <18 years after the DCCT. Unfortunately, in concurrence with the findings of the DCCT, the number of severe hypoglycemic episodes increased. However, a second significant decline in HbA1c values occurred with the introduction of Humalog insulin. Fortunately, the incidence of severe hypoglycemic episodes did not increase after Humalog therapy[34] .

The intensified insulin therapy is recommended in type 1 diabetes. The risk of hypoglycemia increases with the treatment intensity (DCCT 1994). The increasing occurrence of hypoglycemic episodes can be reduced by means of blood glucose measurements[35,36].

The safety of self monitoring in itself is very safe and a proven methodology for patients to self manage their medications, diet and exercise programs to achieve clinical targets and improved outcomes.

What is the evidence that glucose monitoring has differential efficacy or safety issues in sub populations?

The literature search demonstrates significant populations of patients regardless of gender, age and ethnicity with no specific reports of any sub populations concerning clinical issues in regards to efficacy with SMBG

What is the evidence of cost implications and cost-effectiveness of self-glucose monitoring?

A cost-efficient use of insulin analogues relies on dose adjustments based on SMBG. Therefore, SMBG has to be understood as an value component in the therapy of type 1 diabetes: "For type 1 diabetes, insulin aspart was more effective and less costly than regular human insulin. Insulin lispro was associated with an incremental cost of Can$28 996 per quality-adjusted life-year."[37] The fully burdened cost of diabetes shows that over 50% of the costs are related to hospitalization expenses due to consequences of poor glycemic control. Milliman and Associates have demonstrated that from an actuarial perspective that for very 1 point of HBA1c change annualized health care costs are impacted by 5.4%. The costs associated with patients and practices that foster strong self management behaviours have better clinical and economic outcomes. SMBG is the foundation of diabetes self management.

Roche Diagnostics Diabetes Care again thanks the Health Care Authority for this opportunity to submit comments and additional information for their consideration for their final report. In summary, the use of SMBG in patients 18 years of age or under with diabetes requiring

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[33] Rewers M. et al. : ISPAD Clinical Practice Consensus Guidelines 2006–2007: Assessment and monitoring of glycemic control in children and adolescents with diabetes, Pediatric Diabetes 2007: 8: 408–418

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[36] Svoren et al.: Temporal trends in the treatment of pediatric Type 1 Diabetes and impact on acute outcomes, The Journal of Pediatrics 2007

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insulin therapy is based upon the Standards of Care for the safe and effective use of insulin. SMBG is also the foundation to any rational self management protocol recommended by a physician and then executed by the patient.

If we can be of any assistance in the review please contact myself or my colleagues, Bruce Taylor, bruce-t.taylor@roche.com or Joyce Irwin, Joyce.Irwin@roche.com .

Respectfully,

Andreas Stuhr, MD, MBA
Medical Director, North America
Roche Diagnostics

Appendix: Literature search results

- Combining “type 1 diabetes” with “insulin analogues” with “short acting” or “rapid acting “ and “efficacy” or “Ab1c” or “blood glucose” or “treatment outcome” a total of 71 respectively 66 publications were found:

Results: 66

1. Drugs. 2009 May 29;69(8):1035-57. doi: 10.2165/00003495-200969080-00006.

Insulin glulisine: a review of its use in the management of diabetes mellitus.
Garnock-Jones KP, Plosker GL.

Wolters Kluwer Health/Adis, 41 Centorian Drive, Mairangi Bay, North Shore 0754, Auckland, New Zealand. demail@adis.co.nz

Abstract
Insulin glulisine (Apidra) is a human insulin analogue approved for the improvement of glycaemic control in adults, adolescents and children with diabetes mellitus. It has similar binding properties, and is associated with a faster onset but similar level of glucose disposal, to regular human insulin (RHI). Insulin glulisine and insulin lispro have similar effects on glucose levels. Insulin glulisine is effective when compared to other short- and rapid-acting insulins, demonstrating either no inferiority, no significant difference, or superiority in primary endpoints in studies involving patients with type 1 and type 2 diabetes. It is more effective and has a faster onset and shorter duration of activity than RHI. Insulin glulisine is as effective as insulin lispro in patients with type 1 diabetes; however, there is a need for further, well designed head-to-head comparisons with insulin lispro in patients with type 2 diabetes and with insulin aspart in patients with type 1 or type 2 diabetes to fully establish the place of insulin glulisine in the management of diabetes. Insulin glulisine has a flexible administration period, as it can be administered immediately before or after meals. Hypoglycemia, a common risk with insulins, occurs at a similar rate among recipients of insulin glulisine to that seen with other insulins. Thus, insulin glulisine is an effective and well tolerated option for the treatment of patients with type 1 and type 2 diabetes.

PMID: 19496630 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Adolescent
Adult
Blood Glucose/drug effects
Child
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/drug therapy*
Humans
Hypoglycemia/chemically induced
Hypoglycemic Agents/adverse effects
Hypoglycemic Agents/pharmacokinetics
Hypoglycemic Agents/pharmacology*
Insulin/adverse effects

Insulin/analogs & derivatives*
Insulin/pharmacokinetics
Insulin/pharmacology
Substances:
Blood Glucose
Hypoglycemic Agents
Insulin
insulin glulisine
2.Diabet Med. 2008 Sep;25(9):1030-5.

Effects of fat supplementation on glycaemic response and gastric emptying in adolescents with Type 1 diabetes.
Lodefalk M, Aman J, Bang P.

Pediatric Endocrinology and Diabetes Unit, Department of Woman and Child Health, Karolinska Institute, Stockholm, Sweden. mskorre@hem.utfors.se

Abstract
AIMS: To compare the glycaemic response to meals with different fat content in adolescents with Type 1 diabetes mellitus (T1DM) and to investigate associations with gastric emptying.

METHODS: In this randomized, cross-over study, paired results were obtained from seven adolescents with T1DM who ingested on different days two meals with the same carbohydrate and protein content, but different fat and energy content (2 and 38 g fat, 320 and 640 kcal, respectively). Paracetamol was mixed into the meals and gastric emptying was estimated by the paracetamol absorption method. All subjects were normoglycaemic and given 7 IU insulin aspart at commencement of ingestion. Postprandial blood samples were taken during 4 h.

RESULTS: The areas under the curves for plasma glucose and serum paracetamol concentrations were larger after the low-fat than after the high-fat meal during the first 2 h ($P = 0.047$ and $P = 0.041$, respectively). The difference between meals in time-to-peak in glucose and paracetamol concentrations did not reach statistical significance (high-fat vs. low-fat meal: 210 min (120-240) vs. 120 min (50-240), $P = 0.080$ and 120 min (75-180) vs. 60 min (60-120), $P = 0.051$, respectively). Changes in glucose concentrations correlated with simultaneous changes in paracetamol concentrations ($P < 0.001$).

CONCLUSIONS: For the first time, we have shown that the initial glycaemic response is reduced after a meal with higher compared with a meal with lower fat content in adolescents with T1DM given a rapid-acting insulin analogue pre-prandial. The type and dose of pre-prandial insulin may need adjustment to the fat content of the meal to reach postprandial normoglycaemia.

PMID: 19183308 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:

Acetaminophen/pharmacokinetics
Adolescent
Area Under Curve
Blood Glucose/metabolism*
Cross-Over Studies
Diabetes Mellitus, Type 1/metabolism*
Dietary Fats/administration & dosage*
Female
Gastric Emptying/physiology
Humans
Hypoglycemic Agents/pharmacology*
Insulin/pharmacology*
Intestinal Absorption
Lipid Metabolism/physiology
Male
Postprandial Period
Substances:
Blood Glucose
Dietary Fats
Hypoglycemic Agents
Acetaminophen
Insulin
3.Clin Pharmacokinet. 2008;47(9):595-610.

New insulin analogues and routes of delivery: pharmacodynamic and clinical considerations.
Roach P.

Division of Endocrinology and Metabolism, Indiana University School of Medicine, Indianapolis, Indiana 46202, USA. paroach@iupui.edu

Abstract
Analogues of human insulin have been developed to more closely replicate the physiology of meal-related and basal insulin secretion. Three rapid-acting analogues and two basal analogues are available for clinical use. Insulin aspart and insulin lispro have nearly identical pharmacokinetic and pharmacodynamic profiles and provide better postprandial glucose control and less hypoglycemia (primarily nocturnal and severe hypoglycemia in type 1 diabetes mellitus) than regular insulin. Insulin glulisine is a new rapid-acting analogue and has characteristics nearly identical to those of its predecessors. Insulin glargine was the first basal analogue approved for clinical use and has shown better fasting glucose control and less risk of ,hypoglycemia than conventional human neutral protamine Hagedorn (NPH) insulin. More recent studies have indicated that insulin glargine may not be truly 'peakless' at higher doses and that the adjustment of dose timing and frequency may have favorable effects on the risk of hypoglycemia and the duration of the effect. Insulin detemir is a new basal insulin analogue with superiority to NPH insulin similar to that demonstrated by insulin glargine, though its duration of action appears to be shorter. The intraindividual variability in the response to a given dose is lower for insulin detemir than for both NPH insulin and insulin glargine. The clinical significance of this finding is not clear, though it may contribute to the lower rate of hypoglycemia seen with insulin detemir. A number of 'alternative routes' of insulin administration have been studied, the most promising of which has been the pulmonary route. The time-action profile of inhaled insulins is generally characterized by a rapid onset of action similar to those of rapid-acting analogues and a slightly protracted duration of action similar to that of regular insulin. Inhaled insulin is similar to regular insulin

with respect to efficacy and safety, though small reversible changes in pulmonary function have been noted. For technical and practical reasons, other alternative routes have generally not met with clinical success.

PMID: 18698880 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Blood Glucose/drug effects
Clinical Trials as Topic
Diabetes Mellitus/drug therapy*
Drug Administration Routes
Humans
Hypoglycemic Agents/administration & dosage
Hypoglycemic Agents/pharmacology*
Insulin/administration & dosage
Insulin/analogs & derivatives*
Insulin/pharmacology
Substances:
Blood Glucose
Hypoglycemic Agents
glargine
insulin detemir
Insulin
insulin glulisine
4.Med Hypotheses. 2008 Nov;71(5):706-8. Epub 2008 Aug 9.

People with type 1 diabetes using short acting analogue insulins are less dehydrated than those with using human soluble insulin prior to onset of diabetic ketoacidosis.
Dhatariya K.

Elsie Bertram Diabetes Centre, Norfolk and Norwich University Hospital NHS Foundation Trust, Colney Lane, Norwich, Norfolk NR4 7UY, UK. ketan.dhatariya@nnuh.nhs.uk

Abstract
Diabetic ketoacidosis (DKA) is associated with disturbances of acid base, fluid balance and electrolytes. Much of the established literature states that the fluid deficit in someone presenting with DKA is in the region of 6-8 l of fluid (about 100 ml/Kg), and this needs to be the fluid volume that is replaced in the first 24 h following admission to hospital. The physiology of fluid loss in DKA is complex. In summary, however, as blood glucose levels rise, the renal threshold for active glucose reabsorb ion is exceeded leading to glucose loss in the urine. This leads to an osmotic diuresis, and thus dehydration if oral intake is insufficient. Further losses are accounted for by hyperventilation, sweating and vomiting. With the older insulins--such as soluble human insulins, the duration of action was 8-10 h, with a peak of action at approximately 2-4 h after subcutaneous injection. Because very low insulin concentrations are sufficient to prevent ketone production, and because insulin concentrations would stay sufficiently high enough to do this, ketones would not be formed for up to 10 h after the last injection. Furthermore, concentrations of ketones sufficiently high enough to

make a person unwell may take several more hours to develop. However, during this time, as insulin concentrations declined, blood glucose levels would increase, eventually overcoming the renal threshold, causing the renal diuresis and subsequent dehydration. Thus, on human soluble insulin, there is the opportunity to become profoundly dehydrated prior to the onset of significant ketoacidosis. The new rapid acting analogue insulins have durations of action of between 4 and 6 h. Thus the individual would become absolutely insulin deficient relatively quicker than with human soluble insulin. In this circumstance, the blood glucose would not have time to rise as high as with human soluble insulin deficiency before significant ketosis develops, thus leading to a lesser degree of dehydration. New rapid acting insulin analogues are becoming more widely used. This suggests that the volumes needed to replace those lost prior to the onset of significant DKA may be lower.

PMID: 18694627 [PubMed - indexed for MEDLINE]

Related citations

MeSH Terms, SubstancesMeSH Terms:
Administration, Oral
Animals
Blood Glucose/metabolism
Dehydration/etiology*
Diabetes Mellitus, Type 1/drug therapy*
Diabetic Ketoacidosis/etiology*
Diabetic Ketoacidosis/prevention & control
Glucose/analysis
Humans
Insulin/analogs & derivatives
Insulin/therapeutic use*
Models, Biological
Models, Theoretical
Solubility
Substances:
Blood Glucose
Insulin
Glucose

5.J Matern Fetal Neonatal Med. 2008 May;21(5):309-13.

A comparison of lispro and regular insulin for the management of type 1 and type 2 diabetes in pregnancy.

Durnwald CP, Landon MB.

Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, The Ohio State University, Columbus, Ohio 43210, USA.

Abstract
OBJECTIVE: To describe perinatal outcomes of women with pregestational diabetes treated with short-acting, regular insulin and the short-acting insulin analogue, lispro.

STUDY DESIGN: This was a prospective observational study of women with pregestational diabetes maintained on short-acting insulin regimens over a 3-year period. Clinical characteristics, aspects of diabetic therapy, and perinatal/neonatal outcomes were collected.

RESULTS: Of 107 women, 49 were maintained on regular insulin and 58 utilized the insulin analogue, lispro. Frequency of type 1 diabetes, maternal age, overweight/obese pregravid body mass index (> or =25 kg/m2), preexisting hypertension, and presence of vascular disease were similar between groups. Women treated with lispro had a longer duration of diabetes (11.4 vs. 8.3 years, p = 0.04). Glycemic control was improved in women managed with lispro compared to regular insulin (HgbA1c 5.9 vs. 6.7, p = 0.009). Total insulin requirements were lower in the lispro group in the first (0.58 vs. 0.79 units/kg, p = 0.02), second (0.75 vs. 1.10 units/kg, p = 0.002), and third (0.98 vs. 1.25 units/kg, p = 0.03) trimesters of pregnancy. Mean infant birth weight was greater in the lispro group, whereas the rate of large for gestational age infants and ponderal indices were similar between groups. Malformation rate, gestational age at delivery, neonatal intensive care unit admission, neonatal length of stay, rates of respiratory distress syndrome, and hypoglycemia were similar.

CONCLUSIONS: Women treated with lispro demonstrated improved glycemic control and lower total insulin requirements during pregnancy compared to those receiving regular insulin. Perinatal outcomes were similar between women treated with both types of insulin.

PMID: 18446657 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Comparative Study
MeSH Terms:
Adult
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/drug therapy*
Female
Humans
Hypoglycemic Agents/therapeutic use*
Infant, Newborn
Insulin/analogs & derivatives*
Insulin/therapeutic use
Pregnancy
Pregnancy Outcome
Pregnancy in Diabetics/drug therapy*
Prospective Studies
Treatment Outcome
Substances:
Hypoglycemic Agents
Insulin
insulin LISPRO
6.Curr Med Res Opin. 2007 Dec;23(12):3131-6.

Long-term efficacy of insulin glargine therapy with an educational programme in type 1 diabetes patients in clinical practice.
Schreiber SA, Russmann A.

Diabetes Practice, Quickborn, Germany. stephan.schreiber@diabetes-hamburg.de

Abstract
OBJECTIVE: To investigate the effect of initiating insulin glargine (glargine: LANTUS), a once-daily basal insulin analogue, plus an educational programme, on glycaemic control and body weight in patients with type 1 diabetes in clinical practice.

RESEARCH DESIGN AND METHODS: A retrospective analysis of the medical records of 65 patients (mean age: 40.7 +/- 13.3 years) with type 1 diabetes was performed. Patients had previously been treated with NPH insulin (NPH; n = 54) or NPH insulin + lente insulin (NPH + lente; n = 11) and then received glargine once daily (bedtime), plus short-acting prandial insulin, for 30 months. Before initiation of glargine, patients participated in a diabetes educational programme and then received physician consultations throughout the study. Metabolic control, body weight and severe hypoglycemia data were analysed at 9 and 30 months.

RESULTS: Following initiation of glargine, patients showed a decrease in HbA(1c) from 7.29 +/- 1.1% to 7.06 +/- 1.0%; $p < 0.01$ at 30 months. When the results were analysed by pre-treatment, both NPH-pre-treated and NPH+lente-pre-treated patients showed a significant reduction in HbA(1c) of 0.14% and 0.82%, respectively, at 30 months (7.27 +/- 1.2% to 7.13 +/- 1.1% and 7.42 +/- 1.2 to 6.60 +/- 0.3%, respectively; $p < 0.01$). No change in body weight was observed in the overall group. No episodes of severe hypoglycemia (blood glucose < 40 mg/dL [< 2.2 mmol/L] occurred.

CONCLUSIONS: In this retrospective study of medical records, patients with type 1 diabetes treated with insulin glargine over 30 months in combination with educational support and close clinical supervision decreased their HbA(1c) levels without weight gain versus previous treatment with NPH insulin or insulin lente. Further studies in a larger cohort of patients would help to confirm these results.

PMID: 17988433 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
MeSH Terms:
Adult
Diabetes Mellitus, Type 1/drug therapy*
Female
Hemoglobin A, Glycosylated/analysis
Humans
Hypoglycemic Agents/therapeutic use*
Insulin/analogs & derivatives*
Insulin/therapeutic use
Male
Middle Aged
Patient Education as Topic*
Retrospective Studies
Treatment Outcome
Weight Gain
Substances:

Hemoglobin A, Glycosylated
Hypoglycemic Agents
glargine
hemoglobin A1c protein, human
Insulin
7.Chin Med J (Engl). 2007 Oct 5;120(19):1700-3.

A 2-way cross-over, open-labeled trial to compare efficacy and safety of insulin Aspart and Novolin R delivered with CSII in 21 Chinese diabetic patients.

Bi YF, Zhao LB, Li XY, Wang WQ, Sun SY, Chen YH, Hong J, Su TW, Liu JM, Ning G.

Shanghai Clinical Center for Endocrine and Metabolic Diseases, Shanghai Institute of Endocrinology and Metabolism, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025, China.

Abstract
BACKGROUND: Subcutaneous absorption is accelerated by the monomeric conformation of insulin Aspart, which provides good glycemic control with a lower risk of hypoglycemia and less body weight increase. In the present study we investigated the efficacy and safety of a rapid-acting human insulin analogue (insulin Aspart) delivered with continuous subcutaneous insulin infusion (CSII) into Chinese diabetic patients.

METHODS: A total of 21 patients with type 1 or type 2 diabetes were recruited for the 2-way cross-over, open-labeled trial, and then randomized to Group A (n = 10, treated with insulin Aspart) or Group B (n = 11, treated with Novolin R). Insulin Aspart and Novolin R were administered by CSII. Capillary glucose concentrations were measured at 8 time points, pre-prandial and postprandial, bedtime (10 pm), midnight (2 am) every day during the treatment.

RESULTS: The average capillary glucose profiles for the day were much better controlled in Group A than in Group B ($P < 0.01$). The blood glucose levels were particularly better controlled in Group A than in Group B at pre-breakfast ((6.72 +/- 1.24) mmol/L vs (7.84 +/- 1.58) mmol/L, $P = 0.014$), post-breakfast ((8.96 +/- 2.41) mmol/L vs (11.70 +/- 3.11) mmol/L, $P = 0.0028$), post-supper ((8.15 +/- 2.10) mmol/L vs (10.07 +/- 2.36) mmol/L, $P = 0.008$), bed time ((7.73 +/- 1.72) mmol/L vs (9.39 +/- 2.05) mmol/L, $P = 0.007$) and midnight ((6.32 +/- 1.16) mmol/L vs (7.48 +/- 1.36) mmol/L, $P = 0.0049$). There was no significant difference in the frequency of hypoglycemic episodes between the two groups.

CONCLUSION: Insulin Aspart results in better control of blood glucose levels than regular human insulin (Novolin R) in diabetic patients during delivery by CSII.

PMID: 17935674 [PubMed - indexed for MEDLINE]Free Article

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adult
Aged
Blood Glucose/analysis

Cross-Over Studies
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/drug therapy*
Female
Humans
Hypoglycemic Agents/administration & dosage*
Insulin/administration & dosage
Insulin/analogs & derivatives*
Insulin Infusion Systems*
Male
Middle Aged
Substances:
Blood Glucose
Hypoglycemic Agents
insulin aspart
Insulin
8.Vasc Health Risk Manag. 2007;3(3):245-54.

Combining insulins for optimal blood glucose control in type I and 2 diabetes: focus on insulin glulisine.
Ulrich H, Snyder B, Garg SK.

Barbara Davis Center for Childhood Diabetes, University of Colorado at Denver and Health Sciences Center, Denver, CO 80232, USA. heather.ulrich@uchsc.edu

Abstract
Normalization of blood glucose is essential for the prevention of diabetes mellitus (DM)-related microvascular and macrovascular complications. Despite substantial literature to support the benefits of glucose lowering and clear treatment targets, glycemic control remains suboptimal for most people with DM in the United States. Pharmacokinetic limitations of conventional insulins have been a barrier to achieving treatment targets secondary to adverse effects such as hypoglycemia and weight gain. Recombinant DNA technology has allowed modification of the insulin molecule to produce insulin analogues that overcome these pharmacokinetic limitations. With time action profiles that more closely mimic physiologic insulin secretion, rapid acting insulin analogues (RAAs) reduce post-prandial glucose excursions and hypoglycemia when compared to regular human insulin (RHI). Insulin glulisine (Apidra) is a rapid-acting insulin analogue created by substituting lysine for asparagine at position B3 and glutamic acid for lysine at position B29 on the B chain of human insulin. The quick absorption of insulin glulisine more closely reproduces physiologic first-phase insulin secretion and its rapid acting profile is maintained across patient subtypes. Clinical trials have demonstrated comparable or greater efficacy of insulin glulisine versus insulin lispro or RHI, respectively. Efficacy is maintained even when insulin glulisine is administered post-meal. In addition, glulisine appears to have a more rapid time action profile compared with insulin lispro across various body mass indexes (BMIs). The safety and tolerability profile of insulin glulisine is also comparable to that of insulin lispro or RHI in type 1 or 2 DM and it has been shown to be as safe and effective when used in a continuous subcutaneous insulin infusion (CSII). In summary, insulin glulisine is a safe, effective, and well tolerated rapid-acting insulin analogue across all BMIs and a worthy option for prandial glucose control in type 1 or 2 DM.

PMID: 17703632 [PubMed - indexed for MEDLINE]PMCID: PMC2293970Free PMC Article

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Blood Glucose/drug effects
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/blood
Diabetes Mellitus, Type 2/drug therapy*
Humans
Hypoglycemic Agents/pharmacokinetics*
Hypoglycemic Agents/therapeutic use
Insulin/analogs & derivatives*
Insulin/pharmacokinetics
Insulin/therapeutic use
Randomized Controlled Trials as Topic
Substances:
Blood Glucose
Hypoglycemic Agents
Insulin
insulin glulisine
9.Mymensingh Med J. 2007 Jan;16(1):117-21.

Insulin analogues: new dimension of management of diabetes mellitus.
Siddiqui NI.

Mymensingh Medical College, Mymensingh, Bangladesh. nisendo@yahoo.com

Abstract
Insulin is one of the fundamental tools for the management of diabetes mellitus. All type 1 diabetic patients and most of the type 2 require the appropriate support of insulin for good glycemic control, long term healthy outcome and also to overcome the acute crisis. It is almost impossible to mimic the endogenous physiological insulin secretion curve by external administration of short acting human insulin and conventional intermediate acting insulin, neutral protamin Hagedorn (NPH), the so called basal insulin. Short acting human insulin has got a delayed onset of action, late peak and a long tail leading to postprandial hyperglycemia and late hypoglycemia. The so called basal insulin (NPH) is not truly a basal or peakless insulin. Its onset of action takes about 2 - 4 hours with a peak action and a tail. It can not maintain a constant basal level leading to premeal and fasting hyperglycemia and chance of hypoglycemia during peak action, particularly after night injection. To overcome the limitations of human insulin, during the last decade, three ultrashort acting and two long acting basal analogues have been developed by modifications of primary molecule of human insulin. The ultrashort acting analogue insulins are insulin lispro, insulin aspart and insulin glulisine. The basal analogues are insulin glargin and insulin detemir. The pharmacokinetic profiles of novel analogue molecules provide a better opportunity to mimic a physiological pattern of insulin administration, better glycemic control, less chance of hypoglycemia, greater flexibility and a healthy longterm outcome.

PMID: 17344794 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Blood Glucose/drug effects
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/drug therapy*
Humans
Hypoglycemic Agents/pharmacology
Hypoglycemic Agents/therapeutic use*
Insulin/analogs & derivatives
Insulin/therapeutic use*
Substances:
Blood Glucose
Hypoglycemic Agents
glargine
insulin detemir
Insulin
insulin LISPRO
10.Prescrire Int. 2006 Oct;15(85):163-7.

Insulin detemir: new drug. A second long-acting insulin analogue: many uncertainties, few advantages.
[No authors listed]

Abstract
(1) The standard treatment for type 1 diabetes is intensive insulin therapy, consisting of at least 3 daily injections of different insulins, one of which is a long-acting insulin. (2) Insulin detemir is the second long-acting human insulin analogue to be marketed in Europe (after insulin glargine) for the treatment of diabetes in adults and children over 6 years of age. Its action lasts about 12 hours. (3) Insulin detemir was evaluated in around 10 comparative trials, all unblinded, examining the effect of insulin detemir in terms of global glycaemic control (HbA1c level). None of these trials examined whether insulin detemir prevented complications of diabetes. (4) About 10 trials, involving more than 3000 patients, showed that insulin detemir, insulin isophane and insulin glargine have similar efficacy in treating both type 1 and type 2 diabetes. (5) The short-term adverse effect profile of insulin detemir is similar to that of isophane insulin. There is slightly less weight gain with insulin detemir, but injection site reactions occur more frequently. The long-term adverse effects of insulin detemir are not known. (6) Insulin detemir is a clear solution, leading to a risk of confusion with ordinary human insulin or a fast-acting insulin analogue. (7) In practice, isophane insulin remains the first choice long-acting insulin for patients with type 1 or type 2 diabetes.

PMID: 17121210 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Comparative Study
MeSH Terms:
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/drug therapy*
Drug Approval
Europe
Humans
Insulin/administration & dosage
Insulin/adverse effects
Insulin/analogs & derivatives*
Insulin/therapeutic use
Insulin, Long-Acting/administration & dosage
Insulin, Long-Acting/adverse effects
Insulin, Long-Acting/therapeutic use*
Randomized Controlled Trials as Topic
Treatment Outcome
Substances:
Insulin, Long-Acting
Insulin
11.Diabetes Res Clin Pract. 2007 Jul;77(1):1-15. Epub 2006 Nov 16.

A review of human and analogue insulin trials.

Gough SC.

Institute of Biomedical Research, The Medical School, University of Birmingham, Birmingham, UK. s.c.gough@bham.ac.uk

Abstract
A recent meta-analysis evaluated trials of the rapid-acting analogues insulin lispro and insulin aspart, performed before the introduction of the basal analogues, insulin glargine and insulin detemir. This article reviews the effect of rapid-acting and basal insulin analogues separately and in combination, relative to human insulin. Outcomes evaluated include HbA(1c), hypoglycemia, postprandial glucose (PPG), and weight changes. Results from trials that matched defined criteria are presented in tables. In type 1 diabetes, compared with human insulin, the rapid-acting analogues generally reduced hypoglycemia and postprandial glucose, whereas the basal analogues tended to reduce hypoglycemia -- particularly nocturnal hypoglycemia. Weight gain may also be reduced with basal analogues, compared with human basal insulin. In type 2 diabetes, premix rapid-acting analogues controlled postprandial glucose better than human insulin mixes; basal analogues used as basal-only therapy reduced hypoglycemia compared with NPH insulin; and some advantages were apparent with analogues in basal-bolus therapy. Whilst the benefits on individual metabolic and clinical outcomes appear modest, almost all studies report some advantage when using insulin analogues in type 1 and type 2 diabetes. Significant benefits, including PPG lowering with the rapid-acting analogues and the potential for reduction in cardiovascular risk, should be investigated further.

PMID: 17112621 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Blood Glucose/drug effects
Blood Glucose/metabolism
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/drug therapy*
Drug Administration Schedule
Hemoglobin A, Glycosylated/analysis
Humans
Hypoglycemia/prevention & control
Insulin/administration & dosage
Insulin/analogs & derivatives*
Insulin/therapeutic use*
Insulin, NPH/therapeutic use
Postprandial Period
Randomized Controlled Trials as Topic
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
glargine
hemoglobin A1c protein, human
insulin aspart
insulin detemir
Insulin
insulin LISPRO
insulin glulisine
Insulin, NPH
12.Arch Pediatr. 2006 Sep;13(9):1275-82. Epub 2006 Aug 22.

[Rational use of insulin analogues in the treatment of type 1 diabetic children and adolescents: personal experience]
[Article in French]

Dorchy H.

Clinique de diabétologie, hôpital universitaire des enfants Reine Fabiola, 15, avenue J.-J.-Crocq, 1020 Bruxelles, Belgique. hdorchy@ulb.ac.be

Abstract
In the last decade, four fast- and long-acting insulin analogues have been created. Due to the pharmacokinetic characteristics of insulin analogues, they provide an insulin profile closer to normal physiology than can be achieved with human insulins. However, they do not necessarily improve glycated haemoglobin, but they allow better quality of life. In the two daily insulin injection regime, fast-acting analogues are very useful to rapidly correct hyperglycaemia, to allow sleeping in and eating something sweet. In the basal-bolus regime (> or =4 insulin injections), long-acting analogues reduce nocturnal hypoglycaemias and improve fasting blood glucose. In the two insulin regime (2 or > or =4 injections), rapid-acting human insulin must not be systematically replaced by a fast-acting analogue. On the other hand, insulin dose alteration must be triple: retrospective, according to numerous previous experiments, in order to enjoy more freedom for meals, sports, etc.; prospective

according to programmed changes in meals and sports; with only a "touch" of compensatory adaptation according to actual glycaemia.

PMID: 16920339 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
English Abstract
Review
MeSH Terms:
Adolescent
Child
Delayed-Action Preparations
Diabetes Mellitus, Type 1/drug therapy*
Hemoglobin A, Glycosylated/analysis
Humans
Hypoglycemic Agents/therapeutic use*
Insulin/analogs & derivatives*
Insulin/therapeutic use*
Substances:
Delayed-Action Preparations
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Insulin
13.Diabet Med. 2006 Aug;23(8):879-86.

Twice-daily compared with once-daily insulin glargine in people with Type 1 diabetes using meal-time insulin aspart.
Ashwell SG, Gebbie J, Home PD.

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Abstract
AIM: To compare blood glucose control when using insulin glargine twice daily at breakfast- and dinner-times with insulin glargine once daily at dinner time, in unselected people with Type 1 diabetes using insulin aspart at meal-times.

METHODS: In this 8-week, two-way, cross-over study, 20 people with Type 1 diabetes were randomized to insulin glargine injection once daily at dinner-time or twice daily at breakfast- and dinner-times, both plus meal-time insulin aspart. Each 4-week treatment period concluded with a 24-h inpatient metabolic profile.

RESULTS: Insulin doses, HbA1c, fructosamine concentration and pre-breakfast self-monitored blood glucose (SMBG) concentration did not differ between treatment periods. SMBG concentrations after breakfast, after lunch and before dinner were lower with twice-daily compared with once-daily dinner-time glargine [9.3 +/- 0.5 (+/- se) vs. 6.7 +/- 0.5 mmol/l, P = 0.003; 10.2 +/- 0.9 vs. 7.0 +/- 0.9 mmol/l, P = 0.024; 9.6 +/- 0.5 vs. 6.6 +/- 0.5 mmol/l, P = 0.001]. Mean 24-h SMBG concentration was lower with twice-daily glargine (7.1 +/- 0.5 vs. 8.8 +/- 0.5 mmol/l, P = 0.031). Within-day variability of SMBG concentration was lower with twice-daily glargine (sd 3.2 +/- 0.2 vs. 4.0 +/- 0.3 mmol/l, P = 0.044). Plasma

free insulin concentration was higher in the afternoon with twice-daily glargine (21.9 +/- 1.4 vs. 16.1 +/- 1.3 mU/l, P = 0.009), but lower overnight (12.1 +/- 1.7 vs. 17.8 +/- 1.7 mU/l, P = 0.030), compared with once-daily injection. Plasma glucose concentration overnight was higher with twice-daily compared with once-daily glargine (mean 9.0 +/- 0.4 vs. 6.6 +/- 0.4 mmol/l, P = 0.001).

CONCLUSIONS: Blood glucose concentration rises in the late afternoon in association with falling plasma insulin levels towards the end of the 24-h period after insulin glargine injection in some people with Type 1 diabetes using once-daily glargine at dinner-time plus a rapid-acting insulin analogue at meal-times. This is prevented by twice-daily injection of insulin glargine.

PMID: 16911626 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Comparative Study
Randomized Controlled Trial
MeSH Terms:
Adolescent
Adult
Aged
Blood Glucose/metabolism
Cross-Over Studies
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Drug Administration Schedule
Female
Humans
Hypoglycemic Agents/administration & dosage*
Hypoglycemic Agents/blood
Insulin/administration & dosage
Insulin/analogs & derivatives*
Insulin/blood
Male
Middle Aged
Treatment Outcome
Substances:
Blood Glucose
Hypoglycemic Agents
glargine
Insulin
14.Expert Opin Pharmacother. 2006 Jul;7(10):1357-71.

Insulin glargine and its place in the treatment of Types 1 and 2 diabetes mellitus.
Chatterjee S, Tringham JR, Davies MJ.

Diabetes Research Unit, University Hospitals of Leicester, UK.

Abstract

Insulin treatment in Type 1 and Type 2 diabetes has come a long way since its discovery by Banting and Best in 1922. Early insulin therapy was life-saving, but was associated with practical problems and had side effects such as lipoatrophy. Initial modifications of insulin structure produced several classes of insulins with varying pharmacokinetics, but did not sufficiently mimic physiological insulin release. Novel long- and short-acting insulin analogues, the so-called 'designer insulins', developed through genetic engineering in the 1990s, paved the way for more physiological insulin therapy, which was theoretically less problematic in terms of hypoglycemia and patient satisfaction. Insulin glargine (glargine) was the first DNA-recombinant long-acting insulin analogue. The replacement of asparagine with glycine and the addition of two arginine molecules in the molecular structure results in modified pharmacokinetics. Consequently, glargine has a longer, often 24-h profile, which is described as 'peakless' compared with other insulins such as neutral protamine Hagedorn insulin (NPH) and insulin ultralente. Since its launch, the use of glargine in Type 1 and Type 2 diabetes has been extensively reviewed to determine its place in the current insulin market. A potential advantage of glargine seems to be a lower risk of hypoglycemia, particularly at night. The UK National Institute of Clinical Excellence has recommended that glargine is a treatment option for people with Type 1 diabetes. In Type 2 diabetes, it has been advised that glargine only be considered for: those who require assistance to administer insulin injections; those whose lifestyle is restricted significantly by recurrent symptomatic hypoglycaemic episodes; or those who would otherwise need twice-daily basal insulin injections in combination with oral glucose-lowering drugs.

PMID: 16805721 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Amino Acid Sequence
Animals
Blood Glucose/metabolism
Delayed-Action Preparations
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/blood
Diabetes Mellitus, Type 2/drug therapy*
Humans
Hypoglycemic Agents/administration & dosage
Hypoglycemic Agents/pharmacokinetics
Hypoglycemic Agents/therapeutic use*
Injections, Subcutaneous
Insulin/administration & dosage
Insulin/analogs & derivatives*
Insulin/pharmacokinetics
Insulin/therapeutic use
Molecular Sequence Data
Patient Satisfaction
Randomized Controlled Trials as Topic
Substances:
Blood Glucose

Delayed-Action Preparations
Hypoglycemic Agents
glargine
Insulin
15.Drugs. 2006;66(6):861-9.

Insulin glulisine.
Robinson DM, Wellington K.

Adis International Limited, 41 Centorian Drive, Mairangi Bay, Auckland 1311, New Zealand. demail@adis.co.nz

Comment in:

Drugs. 2006;66(6):870-2.

Abstract
Insulin glulisine is a rapid-acting human insulin analogue that has a faster onset of action and shorter duration of action than regular human insulin (RHI) in patients with type 1 or 2 diabetes mellitus and is efficacious in controlling prandial blood glucose levels in these patients. In large, well designed trials in patients with type 1 diabetes, insulin glulisine demonstrated a similar degree of glycaemic control, as measured by glycosylated haemoglobin (HbA(1c)) levels, to RHI after 12 weeks and insulin lispro after 26 weeks. Pre-meal insulin glulisine was also more effective than RHI at controlling 2-hour post-prandial glucose excursions in patients with type 1 or 2 diabetes over a period of 12 weeks. In patients with type 2 diabetes, insulin glulisine induced significantly greater reductions in HbA(1c) levels and 2-hour post-breakfast and post-dinner blood glucose levels than RHI over a period of 26 weeks. Insulin glulisine was generally well tolerated by patients with type 1 or 2 diabetes and had a similar safety profile to insulin lispro or RHI. Severe hypoglycemia was experienced by similar proportions of insulin glulisine or comparator insulin (insulin lispro or RHI) recipients with type 1 or type 2 diabetes.

PMID: 16706558 [PubMed - indexed for MEDLINE]

Related citations

MeSH Terms, SubstancesMeSH Terms:
Adult
Area Under Curve
Clinical Trials as Topic
Diabetes Mellitus/drug therapy*
Diabetes Mellitus, Type 1/drug therapy
Diabetes Mellitus, Type 2/drug therapy
Humans
Hypoglycemic Agents/chemistry
Hypoglycemic Agents/pharmacokinetics
Hypoglycemic Agents/therapeutic use
Insulin/analogs & derivatives*
Insulin/pharmacokinetics
Insulin/therapeutic use
Middle Aged

Molecular Sequence Data
Recombinant Proteins/pharmacokinetics
Recombinant Proteins/therapeutic use
Treatment Outcome
Substances:
Hypoglycemic Agents
Recombinant Proteins
Insulin
insulin glulisine
16.J Pediatr. 2006 Apr;148(4):481-4.

Mixing rapid-acting insulin analogues with insulin glargine in children with type 1 diabetes mellitus.
Fiallo-Scharer R, Horner B, McFann K, Walravens P, Chase HP.

Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, Denver, Colorado, USA. rosanna.fiallo-scharer@uchsc.edu

Abstract
OBJECTIVE: To determine whether mixing insulin glargine (IG) with a rapid-acting insulin (RAI) analogue in the same syringe had any deleterious effects on glycemic control in children with type 1 diabetes mellitus.

STUDY DESIGN: Data from 55 children mixing the IG with a RAI analogue was collected for 6 months before and 6 months after the insulin mixing began. Data from a control group of 55 children not mixing the insulins was collected at similar intervals. Parameters evaluated included hemoglobin A1c (HbA1c) values, number of non-severe and severe hypoglycemic events, number of diabetic ketoacidosis (DKA) events, and blood glucose distribution patterns.

RESULTS: After 6 months of study, HbA1c values were equivalent for the control and test groups (8.54+/-1.14 vs 8.61+/-1.14, respectively; P=1.0000). Percentages of blood glucose values in, above, and below the target range did not vary significantly in the groups. There were no significant differences in the groups in the occurrence of non-severe or severe hypoglycemic events or of DKA events.

CONCLUSION: There were no significant differences in glycemic control between children who mixed IG in the same syringe with a RAI analogue compared with children who took separate injections.

PMID: 16647408 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, Substances, Grant SupportPublication Types:
Controlled Clinical Trial
Research Support, N.I.H., Extramural
MeSH Terms:
Adolescent
Child
Diabetes Mellitus, Type 1/drug therapy*

Diabetic Ketoacidosis/chemically induced
Drug Combinations
Female
Humans
Hypoglycemia/chemically induced
Injections
Insulin/administration & dosage*
Insulin/adverse effects
Insulin/analogs & derivatives*
Male
Matched-Pair Analysis
Patient Compliance
Prospective Studies
Regression Analysis
Substances:
Drug Combinations
glargine
Insulin
Grant Support:
M01 RR00069/RR/NCRR NIH HHS/United States
17.Endocr Pract. 2006 Jan-Feb;12 Suppl 1:105-9.

Insulin treatment in type 1 diabetes.
Bolli GB.

Department of Medicine, University of Perugia, Italy.

Abstract
OBJECTIVE: To present key aspects and strategies for use of insulin therapy in patients with type 1 diabetes mellitus.

METHODS: Limitations and advantages of various insulin regimens are discussed, and issues pertaining to insulin analogues are reviewed.

RESULTS: Rapid-acting insulin analogues provide better and safer postprandial glucose coverage than does human regular insulin. Premixed insulin preparations do not provide the flexibility to address the individual needs of patients adequately to control postprandial glucose excursions. Because of its peak, short duration, and high variability, NPH insulin is inappropriate for patients with type 1 diabetes and patients with type 2 diabetes who require continuous basal coverage. Continuous infusion of soluble insulin by means of an insulin pump is currently the most physiologic approach available for treatment of type 1 diabetes. Use of insulin glargine or insulin detemir with a rapid-acting insulin analogue at meals is an effective and reasonable alternative to insulin pump therapy.

CONCLUSION: Both rapid-acting and long-acting insulin analogues improve glycemic control. This improvement involves controlling hemoglobin A1c levels, reducing glucose excursions, and decreasing hypoglycemia, particularly during the night. Clinicians should prescribe insulin regimens that yield physiologic results in patients with type 1 diabetes.

PMID: 16627392 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Comparative Study
Review
MeSH Terms:
Blood Glucose/analysis
Diabetes Mellitus, Type 1/drug therapy*
Hemoglobin A, Glycosylated/analysis
Humans
Insulin/analogs & derivatives
Insulin/blood
Insulin/therapeutic use*
Insulin Infusion Systems
Insulin, Long-Acting/therapeutic use
Insulin, NPH/therapeutic use
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Insulin, Long-Acting
glargine
insulin detemir
Insulin
insulin LISPRO
Insulin, NPH
18.Diabetes Res Clin Pract. 2006 Jun;72(3):277-83. Epub 2006 Apr 17.

Actual usage and clinical effectiveness of insulin preparations in patients with Type 1 diabetes mellitus in Japan: CoDiC-based analysis of clinical data obtained at multiple institutions (JDDM 3).

Kanatsuka A, Kawai K, Hirao K, Oishi M, Takagi H, Kobayashi M; Japan Diabetes Clinical Data Management Study Group.

Diabetes Center, Chiba Central Medical Center, Wakaba-ku, Japan. azumaka@yahoo.co.jp

Abstract
To clarify the actual usage of insulin preparations and their effectiveness on glycaemic control in patients with Type 1 diabetes mellitus in Japan, we analyzed clinical data collected via CoDiC, an electronic system for diabetes data collection and management, at 28 institutes. Of 18,470 diabetic patients registered with CoDiC in June, 2003, 12,279 patients were being treated with insulin preparations and/or oral hypoglycemic agents, with 861 of these patients having Type 1 diabetes mellitus and 11,418 patients having Type 2 diabetes. Three analytical surveys were carried out with the Type 1 diabetes patients. Study I: Cross-sectional survey on the treatment in 2002. Six hundred and thirteen patients received intensive conventional insulin treatment (ICT). The number of patients receiving rapid-acting insulin analogue (RA) was greater than that of patients receiving regular insulin (R). Serum CPR was lower in the patients with ICT than in the patients with conventional insulin treatment (CT). Study II: Survey on the changes in the actual usage and clinical effectiveness of insulin preparations, based on the data input in 2001 and 2002. The number of patients with ICT using RA insulin markedly increased. Study III: Analysis of the participants' clinical course over the 18-month period of the study from the time of first consultation. The dose of insulin increased during the term. The average HbA1c level fell drastically and

reached to 7.5% over the first 9 months of the study and then remained between a range of 7.5% and 8% for the rest of the study period. In conclusion, ICT is actively performed and the RA insulin analogues are widely used in Type 1 diabetic patients in Japan. Basal-bolus therapy should be used to treat Type 1 diabetic patients with postprandial serum CPR of less than 0.5 ng/ml. It is difficult to obtain the ideal glycaemic control in Type 1 diabetic patients with the currently available insulin preparations.

PMID: 16616794 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Meta-Analysis
Multicenter Study
Research Support, Non-U.S. Gov't
MeSH Terms:
Adult
Blood Glucose
Blood Pressure/drug effects
Body Mass Index
Cholesterol/blood
Clinical Trials as Topic
Cross-Sectional Studies
Database Management Systems
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 1/epidemiology*
Dose-Response Relationship, Drug
Follow-Up Studies
Hemoglobin A, Glycosylated/analysis
Humans
Insulin/therapeutic use*
Japan/epidemiology
Middle Aged
Pharmaceutical Preparations/classification
Treatment Outcome
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Pharmaceutical Preparations
Insulin
Cholesterol
19.Clin Ther. 2005;27 Suppl B:S75-88.

Biphasic insulin aspart 30: literature review of adverse events associated with treatment.
Davidson J, Vexiau P, Cucinotta D, Vaz J, Kawamori R.

Endocrine and Diabetes Associates of Texas, Dallas, TX 75230, USA.
jdavidson@medicalcitydallas.com

Abstract

BACKGROUND: Biphasic insulin aspart 30 (BIAsp 30 [30% soluble, rapid-acting insulin aspart and 70% protamine-bound insulin aspart], NovoLog Mix 70/30, Novo Nordisk, Bagsvaerd, Denmark), a premixed insulin analogue, addresses both the prandial and basal aspects of glucose regulation when used once or twice daily in patients with type 1 or type 2 diabetes. It provides overall glycemic control similar to biphasic human insulin 30 (BHI 30, 30% human insulin and 70% neutral protamine Hagedorn [NPH] insulin) in patients with type 1 or type 2 diabetes.

OBJECTIVE: The aim of this review was to evaluate the safety profile associated with BIAsp 30 in patients with type 1 or type 2 diabetes versus that of comparator insulin products, including BHI 30 and biphasic insulin lispro 25 (Mix 25 [25% biphasic insulin lispro and 75% protaminated lispro], Humalog Mix 75/25, Eli Lilly and Company, Indianapolis, Indiana), together with the basal insulins, including NPH insulin and insulin glargine (Lantus, Sanofi-Aventis Pharmaceuticals, Paris, France).

METHODS: Data from human clinical studies published in peer-reviewed journals or as conference proceedings that reported safety results in patients with type 1 or type 2 diabetes who were treated with BIAsp 30 versus comparator insulins were evaluated. To locate the appropriate articles, a MEDLINE search was performed for all years up to February 2005, using the following key words: biphasic insulin aspart, BIAsp 30, biphasic insulin, and premixed insulin. Additional papers were identified by examining the reference lists in these papers as well as our own personal reference files. Results from 17 publications were analyzed. The analysis included >2600 patients with type 2 diabetes (mean [range] age, 58 [36-70] years; duration of diabetes, 11.8 [9-17] years; and baseline glycosylated hemoglobin [HbA1c], 8.6% [7.5%-9.9%]). It also included 104 patients with type 1 diabetes (mean [range] age, 44.5 [30-58] years; duration of diabetes, 16 [2-30] years; and baseline HbA1c, 8.4% [7.2%-10.4%]).

RESULTS: Hypoglycemia occurred in 43% to 57% of patients receiving BIAsp 30 versus 32% to 57% of patients receiving BHI 30 and 28% of patients receiving NPH insulin. Major hypoglycemic events were uncommon in most studies; but when they did occur, they were reported less frequently in patients receiving BIAsp 30 (2%-8% of patients) than in patients receiving BHI 30 (2%-14% of patients). Furthermore, patients treated with BIAsp 30 were at lower risk of experiencing minor nocturnal hypoglycemia than patients receiving comparator insulin; in 1 study, the relative risk (BIAsp 30 vs BHI 30) was calculated to be 0.63 (95% CI, 0.37 to 1.09). The adverse event (AE) profile, weight gain during treatment, and formation of cross-reactive antibodies were not different between BIAsp 30 and BHI 30. AEs were reported in 36% to 90% of patients receiving BIAsp 30, 38% to 88% of patients receiving BHI 30, and 51% of patients receiving Mix 25. The use of oral antidiabetic drugs in combination with BIAsp 30 did not alter the safety profile of BIAsp 30.

CONCLUSION: The flexible and convenient treatment regimen offered by BIAsp 30, together with its ability to improve postprandial glucose control, is associated with a safety profile comparable to that of BHI 30 and NPH insulin, with a lower risk of major and nocturnal hypoglycemic events.

PMID: 16519039 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:

Review
MeSH Terms:
Adult
Aged
Clinical Trials as Topic
Cross Reactions
Diabetes Complications/chemically induced*
Diabetes Complications/immunology
Diabetes Mellitus, Type 1/drug therapy
Diabetes Mellitus, Type 1/immunology
Diabetes Mellitus, Type 2/drug therapy
Diabetes Mellitus, Type 2/immunology
Female
Humans
Hypoglycemia/blood
Hypoglycemic Agents/adverse effects*
Hypoglycemic Agents/therapeutic use
Insulin/adverse effects
Insulin/analogs & derivatives*
Insulin/therapeutic use
Male
Middle Aged
Randomized Controlled Trials as Topic
Weight Gain/drug effects
Substances:
Hypoglycemic Agents
insulin aspart
Insulin
20.Diabet Med. 2006 Mar;23(3):285-92.

Improved glycaemic control with insulin glargine plus insulin lispro: a multicentre, randomized, cross-over trial in people with Type 1 diabetes.
Ashwell SG, Amiel SA, Bilous RW, Dashora U, Heller SR, Hepburn DA, Shutler SD, Stephens JW, Home PD.

University of Newcastle upon Tyne, Newcastle upon Tyne, UK. s.g.ashwell@ncl.ac.uk

Abstract
AIMS: To compare blood glucose control using insulin glargine + insulin lispro with that on NPH insulin + unmodified human insulin in adults with Type 1 diabetes managed with a multiple injection regimen.

METHODS: In this 32-week, five-centre, two-way cross-over study, people with Type 1 diabetes (n = 56, baseline HbA1c 8.0 +/- 0.8%) were randomized to evening insulin glargine + mealtime insulin lispro or to NPH insulin (once- or twice-daily) + mealtime unmodified human insulin. Each 16-week period concluded with a 24-h inpatient plasma glucose profile.

RESULTS: HbA1c was lower with glargine + lispro than with NPH + human insulin [7.5 vs. 8.0%, difference -0.5 (95% CI -0.7, -0.3) %, P < 0.001]. This was confirmed by an 8% lower 24-h plasma glucose area under the curve (AUC) (187 vs. 203 mmol l(-1) h(-1), P = 0.037), a 24% reduction in plasma glucose AUC > 7.0 mmol/l1 (47 vs. 62 mmol l(-1) h(-1), P = 0.017) and a 15% lower post-prandial plasma glucose AUC (75 vs. 88 mmol l(-1) h(-1), P = 0.002).

There was no reduction in night-time plasma glucose AUC or increase in plasma glucose area < 3.5 mmol/l. Monthly rate of nocturnal hypoglycemia was reduced by 44% with glargine + lispro (0.66 vs. 1.18 episodes/month, P < 0.001).

CONCLUSIONS: Compared with NPH insulin + unmodified human insulin, the combination of insulin glargine with a rapid-acting insulin analogue as multiple-injection therapy for Type 1 diabetes improves overall glycaemic control as assessed by HbA1c and 24-h plasma glucose monitoring to a clinically significant degree, together with a reduction in nocturnal hypoglycemia.

PMID: 16492212 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Comparative Study
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adult
Area Under Curve
Blood Glucose/analysis*
Blood Glucose Self-Monitoring
Cross-Over Studies
Diabetes Mellitus, Type 1/drug therapy*
Drug Therapy, Combination
Female
Hemoglobin A, Glycosylated/analysis
Humans
Hypoglycemia/blood
Hypoglycemic Agents/adverse effects
Hypoglycemic Agents/therapeutic use*
Insulin/adverse effects
Insulin/analogs & derivatives
Insulin/therapeutic use*
Insulin, NPH/adverse effects
Insulin, NPH/therapeutic use
Male
Treatment Outcome
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
glargine
Insulin
insulin LISPRO
Insulin, NPH
21.Pediatr Endocrinol Rev. 2003 Sep;1(1):9-21.

Rational use of insulin analogues in the treatment of type 1 diabetes mellitus.

Bolli GB.

University of Perugia, Section of Internal Medicine, Endocrinology and Metabolism, Perugia, Italy. gbolli@unipg.it

Abstract
Long-term near-normoglycaemia in Type 1 diabetes protects against the onset and/or progression of microangiopathic complications. To successfully reach the goal while avoiding the risk of hypoglycemia and hypoglycemia unawareness, insulin therapy has to be physiological. Mealtime insulin should be given as a bolus injection before, or both before and after, a meal. In addition, basal insulin between meals should be replaced by an insulin preparation with a square wave action profile. Rapid-acting insulin analogues are the mealtime insulin preparations of choice. Either continuous subcutaneous insulin infusion (CSII), or once day injection of the long-acting insulin analogue glargine is required to optimally replace basal insulin. In Type 1 diabetes the benefits of mealtime treatment with rapid-acting insulin analogues become apparent only to the extent to which replacement of basal insulin is optimised at the same time. This has been difficult in the past with the peak insulin NPH, but it is nowdays easier with the nearly peakless long-acting insulin analogue glargine. As compared to NPH, glargine reduces the risk for nocturnal hypoglycemia, and at the same time improves HbA1c similarly to CSII.

PMID: 16437009 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Diabetes Mellitus, Type 1/drug therapy*
Humans
Hypoglycemic Agents/therapeutic use*
Insulin/analogs & derivatives*
Insulin/therapeutic use
Treatment Outcome
Substances:
Hypoglycemic Agents
glargine
Insulin
22.Acta Diabetol. 2005 Dec;42(4):156-61.

Metabolic control and educational status in children with type 1 diabetes: effects of a summer camp and intensive insulin treatment.
Karagüzel G, Bircan I, Erisir S, Bundak R.

Department of Pediatrics, Division of Pediatric Endocrinology, School of Medicine, Akdeniz University, Antalya, Turkey. gulaykg@akdeniz.edu.tr

Abstract

Our aim was to evaluate prospectively, in our diabetic patients, the impacts of a summer camp and intensive insulin treatment (IIT) on both metabolic control and disease-related educational level. Twenty-five patients participated in a 7-day-long summer camp. Before the camp, all patients were on therapy with short-acting human insulin (SAI) and intermediate-acting insulin (IAI) twice daily. On arrival, their insulin therapy regimen was changed by IIT including either SAI or rapid-acting insulin analogue (RAI) three times before meals supplemented by IAI at bedtime. Following the camp, all participants were given IIT with RAI plus IAI. Frequency of hypoglycemia, insulin dose, body mass index (BMI) and glycohaemoglobin (HbA1c) levels were assessed at pre-camp and post-camp controls. To evaluate the effectiveness of camp-assisted education, all participants were regularly tested. We observed significant elevations in total daily dose of insulin and BMI at months 3 and 6 when compared with the pre-camp values but, by month 12, they were not significantly different from precamp values. The mean HbA(1c) level decreased significantly at months 6 and 12. Severe hypoglycaemic episodes and ketoacidosis were not detected during the camp and the following year. Significant improvements in knowledge about diabetes and self-management were determined at the end of the camp, after 6 and 12 months. Camp-assisted IIT with RAI improved metabolic control of diabetic children. Additionally, camp-assisted education has a positive effect on disease-related educational level and self-management.

PMID: 16382302 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adolescent
Blood Glucose/drug effects
Blood Glucose/metabolism*
Body Mass Index
Camping*
Child
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy
Diabetes Mellitus, Type 1/rehabilitation*
Educational Status
Female
Hemoglobin A, Glycosylated/metabolism
Humans
Hypoglycemic Agents/therapeutic use
Insulin/therapeutic use*
Male
Patient Selection
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Insulin
23.Horm Metab Res. 2005 Nov;37(11):702-7.

Efficacy and safety of insulin glulisine in patients with type 1 diabetes.

Dreyer M, Prager R, Robinson A, Busch K, Ellis G, Souhami E, Van Leendert R.

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Abstract
Insulin glulisine (glulisine), a human insulin analogue with a rapid-acting time-action profile, has been developed to fulfil the mealtime (bolus) insulin requirement in patients with diabetes. The aim of this multinational, multi-centre, controlled, open-label, randomized, parallel-group study was to compare the efficacy and safety of insulin glulisine (glulisine) to that of insulin lispro (lispro) in adults diagnosed with Type 1 diabetes. Of the 683 patients randomized, 672 received treatment (339 patients received glulisine, 333 patients received lispro). Over the 26-week study, a similar reduction in mean HbA1c occurred in both groups (adjusted mean change from baseline -0.14% in both groups). The basal insulin dose was relatively unchanged from baseline in the glulisine group but increased in the lispro group (glulisine: 0.12 IU vs. lispro: 1.82 IU; p = 0.0001). As a consequence, total daily insulin dose decreased in the glulisine group but increased in the lispro group (glulisine: -0.86 IU vs. lispro: 1.01 IU; p = 0.0123). There was no relevant difference between the two groups in the reporting of symptomatic hypoglycemia (overall, nocturnal and severe). This study demonstrates that glulisine provides equivalent glycaemic control to lispro. The clinical relevance of any difference in total daily insulin dose remains to be established.

PMID: 16308840 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adult
Antibodies, Bacterial/blood
Blood Glucose/analysis
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Drug Hypersensitivity/epidemiology
Escherichia coli/immunology
Female
Humans
Insulin/adverse effects
Insulin/analogs & derivatives*
Insulin/therapeutic use
Insulin Antibodies/blood
Male
Middle Aged
Substances:
Antibodies, Bacterial
Blood Glucose
Insulin Antibodies

Insulin
insulin glulisine
24.Endocr Pract. 2005 Jan-Feb;11(1):11-7.

Optimized Basal-bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human insulin in combination with Basal insulin glargine.

Garg SK, Rosenstock J, Ways K.

Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, Denver, Colorado 80262, USA.

Erratum in:

Endocr Pract. 2005 Mar-Apr;11(2):145.

Abstract
OBJECTIVE: To compare the efficacy and safety of insulin glulisine (GLU), a new rapid-acting insulin analogue, injected 0 to 15 minutes before or immediately after meals, with regular human insulin (RHI), injected 30 to 45 minutes before meals.

METHODS: Patients with type 1 diabetes (N = 860) received once-daily insulin glargine and subcutaneous injections of either GLU (premeal or postmeal) or premeal RHI in this open-label, randomized, controlled, multicen-ter, parallel-group, 12-week study.

RESULTS: Baseline to endpoint changes in mean gly-cated hemoglobin (as A1c equivalents) (A1c) occurred in the premeal GLU, postmeal GLU, and premeal RHI groups (-0.26%, -0.11%, and -0.13%, respectively). The reduction in A1c was greater for the premeal GLU group in comparison with the RHI group (P = 0.02) and the post-meal GLU group (P = 0.006); no significant between-treatment difference was found for postmeal GLU versus RHI. Overall, blood glucose profiles were similar in all 3 treatment groups but were significantly lower for premeal GLU 2-hour postbreakfast measurements (premeal versus postmeal GLU, P = 0.0017; premeal GLU versus RHI, P = 0.0001) and 2-hour postdinner measurements (premeal GLU versus RHI, P = 0.0001; premeal versus postmeal GLU, P = 0.0137). Severe hypoglycemic episodes were comparable for premeal GLU, postmeal GLU, and pre-meal RHI groups (8.4%, 8.4%, and 10.1%, respectively). Body weight increased (+0.3 kg) in the RHI and premeal GLU groups; however, weight decreased in the postmeal GLU group (-0.3 kg; between-treatment difference, P = 0.03).

CONCLUSION: Better A1c reductions were obtained with premeal GLU, but postmeal administration of GLU was as safe and effective as premeal GLU or RHI in combination with insulin glargine and was not associated with weight gain.

PMID: 16033730 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Multicenter Study
Randomized Controlled Trial

Research Support, Non-U.S. Gov't
MeSH Terms:
Adult
Blood Glucose Self-Monitoring
Body Weight/drug effects
Diabetes Mellitus, Type 1/drug therapy*
Eating
Female
Hemoglobin A, Glycosylated/metabolism
Humans
Hypoglycemia/chemically induced
Hypoglycemic Agents/administration & dosage*
Hypoglycemic Agents/adverse effects
Insulin/administration & dosage*
Insulin/adverse effects
Insulin/analogs & derivatives*
Male
Middle Aged
Postprandial Period
Substances:
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Insulin
insulin glulisine
25.Expert Opin Pharmacother. 2005 Apr;6(4):643-51.

Insulin glulisine: a new rapid-acting insulin analogue for the treatment of diabetes.
Garg SK, Ellis SL, Ulrich H.

Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, 4200 E. 9th Ave. B140, Denver, CO 80262, USA. Satish.Garg@uchsc.edu

Abstract
Insulin glulisine (Apidra, Sanofi-Aventis), a new and recently approved rapid-acting insulin analogue, mimics the pharmacokinetic and pharmacodynamic profiles of physiological human insulin, but has a rapid onset, peak effect at 1h, and a shorter duration of action (approximately 4 h). Its rapid-action properties are maintained across subject types. Formal clinical evaluations show that insulin glulisine can be administered safely and effectively pre- and postmeal. When injected immediately premeal, insulin glulisine provides superior postprandial blood glucose control compared with regular human insulin (RHI) injected 30 min premeal. These data highlight the flexibility in the dosing schedule with insulin glulisine. Clinical trials have demonstrated that insulin glulisine elicits a greater reduction in glycosylated haemoglobin at end point than RHI, in both type 1 and 2 diabetes mellitus. In addition, the safe administration of insulin glulisine by continuous subcutaneous insulin infusion has been demonstrated in patients with type 1 diabetes. In conclusion, insulin glulisine is an effective, safe and well-tolerated rapid-acting insulin analogue.

PMID: 15934890 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Clinical Trials as Topic/statistics & numerical data
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/blood
Diabetes Mellitus, Type 2/drug therapy*
Humans
Insulin/analogs & derivatives*
Insulin/pharmacokinetics
Insulin/therapeutic use
Substances:
Insulin
insulin glulisine
26.Postgrad Med. 2004 Nov;116(5 Suppl Exploring):13-20.

Type 1 diabetes mellitus: effective insulin strategies with less hypoglycemia.
Bolli GB.

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Abstract
Stringent glycemic control is important for preventing the development or progression of complications in type 1 diabetes. This goal may best be achieved by intensive insulin replacement therapy that closely follows the physiologic patterns of secretion observed in patients without diabetes. Premixed insulin formulations of human regular and NPH insulin are commonly used to control blood glucose levels throughout the day, but because these preparations do not mimic the physiologic profile of insulin release, hypo- and hyperglycemia may ensue. Using human regular insulin to control mealtime hyperglycemia is similarly problematic, and thus recently developed rapid-acting insulin analogues, such as lispro and aspart, are now preferred for prandial glucose control. In addition, regimens that combine insulins--eg, NPH insulin for meeting the demand for round-the-clock basal insulin secretion and a rapid-acting insulin analogue to cover mealtime insulin requirements--improve glycemic control, but increase risk of nocturnal hypoglycemia. The ideal basal insulin replacement should feature a uniform continuous release of insulin with a long duration to minimize hypoglycemia. Although such a profile may be achieved with a continuous subcutaneous insulin infusion, new basal insulin analogues, such as once daily, 24-hour insulin glargine, combined with mealtime lispro or aspart, offer comparable glycemic control without the drawbacks of insulin pump use in type 1 diabetes. Insulin glargine reduces the frequency of nocturnal hypoglycemia compared with NPH when used with rapid-acting analogues and thus facilitates optimal insulin replacement therapy.

PMID: 19667675 [PubMed - indexed for MEDLINE]

Related citations

MeSH Terms, SubstancesMeSH Terms:
Diabetes Mellitus, Type 1/drug therapy*
Humans
Hypoglycemia/prevention & control*

Hypoglycemic Agents/administration & dosage*
Insulin/administration & dosage*
Insulin/analogs & derivatives
Substances:
Hypoglycemic Agents
glargine
Insulin
27.Drugs. 2004;64(17):1957-74.

Insulin aspart: a review of its use in the management of type 1 or 2 diabetes mellitus.
Reynolds NA, Wagstaff AJ.

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Abstract
Insulin aspart (NovoRapid, NovoLog) is a short-acting insulin analogue, which has a faster onset and shorter duration of action than regular human insulin. Insulin aspart administered immediately before meals provided significantly greater improvements in glycosylated haemoglobin and better postprandial glycaemic control than regular human insulin administered 30 minutes before meals, when used in a basal-bolus regimen with neutral protamine Hagedorn (NPH) insulin, in randomised, nonblind studies in patients with type 1 diabetes mellitus. In patients with type 2 diabetes, insulin aspart provided similar glycaemic control to regular human insulin, administered in a basal-bolus regimen with NPH insulin. Small studies suggest that the use of insulin aspart in combination with oral hypoglycaemic agents may be beneficial. Insulin aspart, administered by continuous subcutaneous insulin infusion (CSII) provided better glycaemic control than insulin aspart multiple daily injection regimens in patients with type 1 (but not type 2) diabetes, and had similar efficacy to CSII with insulin lispro or regular human insulin in type 1 diabetes. Limited studies show insulin aspart to be effective in children, adolescents and young adults with type 1 diabetes. Insulin aspart had a tolerability profile similar to that of regular human insulin in clinical trials. The incidence of major or nocturnal hypoglycaemic events reported in patients receiving insulin aspart was lower than that of regular human insulin in several studies. In conclusion, insulin aspart, administered immediately before meals in a basal-bolus regimen with NPH insulin, provided better long-term glycaemic control than regular human insulin administered 30 minutes before meals in patients with type 1 diabetes, and was as effective as regular human insulin in patients with type 2 diabetes. A significantly lower risk of hypoglycemia was seen in several trials. Insulin aspart CSII provided better glycaemic control than insulin aspart multiple daily subcutaneous injection (MDI) in patients with type 1 (but not type 2) diabetes and had similar efficacy to CSII with insulin lispro or regular human insulin in type 1 diabetes. Insulin aspart is an effective and well tolerated alternative to regular human insulin and insulin lispro for the maintenance of glycaemic control in patients with type 1 or 2 diabetes.

PMID: 15329046 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Adolescent

Adult
Blood Glucose
Child
Clinical Trials as Topic
Diabetes Mellitus/blood
Diabetes Mellitus/drug therapy*
Drug Therapy, Combination
Humans
Hypoglycemic Agents/pharmacology*
Hypoglycemic Agents/therapeutic use*
Insulin/analogs & derivatives*
Insulin/pharmacology*
Insulin/therapeutic use*
Lipids/blood
Quality of Life
Substances:
Blood Glucose
Hypoglycemic Agents
Lipids
insulin aspart
Insulin
28.Diabetologia. 2004 Apr;47(4):622-9.

Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes.
Hermansen K, Fontaine P, Kukolja KK, Peterkova V, Leth G, Gall MA.

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Abstract
AIMS/HYPOTHESIS: The aim of the trial was to compare the efficacy and tolerability of two types of basal-bolus therapy, using either the soluble long-acting basal insulin analogue, insulin detemir, in combination with the rapid-acting analogue, insulin aspart, or NPH insulin in combination with mealtime regular human insulin.

METHODS: In this 18-week, 1:1 randomised, open-labelled, parallel trial, 595 patients with Type 1 diabetes mellitus received insulin detemir or NPH insulin in the morning and at bedtime in combination with mealtime insulin aspart or regular human insulin respectively.

RESULTS: Glycaemic control with insulin detemir/insulin aspart was improved in comparison with NPH insulin/regular human insulin (HbA1c: 7.88% vs 8.11%; mean difference: -0.22% point [95% CI: -0.34 to -0.10]; p<0.001). Self-measured 8-point plasma glucose profiles differed between the groups (p<0.001), with lower postprandial plasma glucose levels in the insulin detemir/insulin aspart group. Within-person day-to-day variation in plasma glucose was lower with insulin detemir/insulin aspart than with NPH insulin/regular human insulin (SD: 2.88 vs 3.12 mmol/l; p<0.001). Risk of overall and nocturnal hypoglycemia (23.00-06.00 hours) was, respectively, 21% (p=0.036) and 55% (p<0.001) lower in the insulin detemir/insulin aspart group than in the NPH insulin/regular human insulin group. Body weight (adjusted for baseline and change in HbA1c) was 1 kg lower with insulin detemir/insulin aspart than with NPH insulin/regular human insulin (p<0.001).

CONCLUSIONS/INTERPRETATION: Basal-bolus therapy using insulin detemir/insulin aspart offers a better balance of control and tolerability than with NPH insulin/regular human insulin. The low variability and more physiological action profiles generated with these insulin analogues resulted in improved glycaemic control with lower risk of hypoglycemia and no concomitant body weight increase.

PMID: 15298338 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adult
Blood Glucose/metabolism
Body Weight/physiology
Diabetes Mellitus, Type 1/drug therapy*
Endpoint Determination
Female
Hemoglobin A, Glycosylated/metabolism
Humans
Hypoglycemia/chemically induced
Hypoglycemia/epidemiology
Hypoglycemic Agents/administration & dosage
Hypoglycemic Agents/adverse effects
Hypoglycemic Agents/therapeutic use*
Insulin/administration & dosage
Insulin/adverse effects
Insulin/analogs & derivatives*
Insulin/therapeutic use*
Insulin, NPH/administration & dosage
Insulin, NPH/adverse effects
Insulin, NPH/therapeutic use*
Male
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
insulin aspart
insulin detemir
Insulin
Insulin, NPH
29.Diabet Med. 2004 Jul;21(7):769-75.

Hypoglycemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with Type 1 diabetes.

Heller SR, Colagiuri S, Vaaler S, Wolffenbuttel BH, Koelendorf K, Friberg HH, Windfeld K, Lindholm A.

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Abstract
AIMS: To compare the effects of the rapid-acting insulin analogue insulin aspart and soluble human insulin on hypoglycemia and glycaemic control in patients with Type 1 diabetes when injected immediately before meals as part of intensive insulin therapy.

METHODS: In this multinational, double-blind, randomised, crossover trial, 155 patients with Type 1 diabetes (HbA(1c) < 8.0%) were symmetrically randomised to two 16-week treatment periods on either type of insulin, both injected 0-5 min before meals. NPH insulin was given as basal insulin once or twice daily as needed, and insulin dosages were regularly adjusted using pre-defined algorithms to maintain tight glycaemic control. Treatment periods were separated by a 4-week washout.

RESULTS: The rate of major nocturnal (24.00-06.00 h) hypoglycaemic episodes was 72% lower with insulin aspart than with human insulin (0.067 vs. 0.225 events/month; P = 0.001). Total rate of major hypoglycemia did not differ significantly between treatments (insulin aspart/human insulin relative risk 0.72; 95% CI 0.47-1.09, P = 0.12). The rate of minor events was significantly reduced by 7% with insulin aspart (P = 0.048). Reductions in rate of hypoglycemia were achieved with maintained overall glycaemic control: Mean HbA(1c) remained constant, slightly below 7.7% on both treatments.

CONCLUSIONS: The use of insulin aspart in an intensive insulin regimen in patients with tightly controlled Type 1 diabetes led to clinically significant reductions in major nocturnal hypoglycemia with no deterioration in glycaemic control. Major nocturnal hypoglycemia appears to be a strong clinical indication for the use of rapid-acting insulin analogues during intensive insulin therapy.

PMID: 15209772 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adolescent
Adult
Aged
Blood Glucose/metabolism
Circadian Rhythm
Cross-Over Studies
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/complications

Diabetes Mellitus, Type 1/drug therapy*
Double-Blind Method
Drug Administration Schedule
Female
Hemoglobin A, Glycosylated/metabolism
Humans
Hypoglycemia/etiology
Hypoglycemia/prevention & control*
Hypoglycemic Agents/therapeutic use*
Insulin/analogs & derivatives*
Insulin/therapeutic use*
Insulin, NPH/therapeutic use
Male
Middle Aged
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
insulin aspart
Insulin
Insulin, NPH
30.Diabetes Care. 2003 Aug;26(8):2359-64.

A comparison of postprandial and preprandial administration of insulin aspart in children and adolescents with type 1 diabetes.
Danne T, Aman J, Schober E, Deiss D, Jacobsen JL, Friberg HH, Jensen LH; ANA 1200 Study Group.

Kinderkrankenhaus auf der Bult, Diabetes-Zentrum für Kinder und Jugendliche, Hannover, Germany. danne@hka.de

Abstract
OBJECTIVE: The aim of this study was to compare the glycemic control of preprandial versus postprandial injections of the new rapid-acting insulin analogue aspart in children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS: Forty-two children (aged 6-12 years) and 34 adolescents (13-17 years) were randomized to preprandial (immediately before meal start) and postprandial (immediately after a meal or a maximum of 30 min after meal start) treatment with insulin aspart (at least thrice daily) as part of a basal/bolus regimen in a multicenter study with an open labeled, two-period cross-over design (6-week periods). Of this group, 49% were boys, 55% were aged <or=13 years, and duration of diabetes was 4.4 years (range 1.0-9.4).

RESULTS: Glycemic control for postprandial treatment was not worse than preprandial treatment as assessed by fructosamine week 0 vs. 6 (mean +/- SD, preprandial 367 +/- 74 vs. 378 +/- 90 micro mol/l; postprandial 383 +/- 83 vs. 385 +/- 77 micro mol/l) and HbA(1c) (preprandial 7.9 +/- 1.3 vs. 8.0 +/- 1.5%; postprandial 8.0 +/- 1.4 vs. 8.3 +/- 1.5%, P = 0.14). The only statistically significant finding from the seven-point blood glucose profiles and derived parameters between preprandial and postprandial treatment was a lower postprandial glucose level 120 min after breakfast (mean +/- SEM, -2.08 +/- 0.74 mmol/l, P = 0.016). The relative risk of hypoglycemia (blood glucose <3.9 mmol/l) preprandially to postprandially

was not significantly different (mean 1.1; 95% CI 0.91-1.35; P = 0.31). Overall treatment satisfaction was equally high for both regimens with both patients and parents.

CONCLUSIONS: Although preprandial administration of insulin aspart is generally preferable, this study shows that in children and adolescents, postprandial administration of insulin aspart is a safe and effective alternative.

PMID: 12882862 [PubMed - indexed for MEDLINE]Free Article

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adolescent
Blood Glucose/drug effects
Child
Cross-Over Studies
Diabetes Mellitus, Type 1/drug therapy*
Female
Humans
Hypoglycemic Agents/administration & dosage*
Hypoglycemic Agents/adverse effects
Hypoglycemic Agents/pharmacokinetics
Insulin/administration & dosage*
Insulin/adverse effects
Insulin/analogs & derivatives
Insulin/pharmacokinetics
Male
Postprandial Period
Treatment Outcome
Substances:
Blood Glucose
Hypoglycemic Agents
insulin aspart
Insulin
31.Diabet Med. 2003 Aug;20(8):626-34.

Effect of the rapid-acting insulin analogue insulin aspart on quality of life and treatment satisfaction in patients with Type 1 diabetes.
Bott U, Ebrahim S, Hirschberger S, Skovlund SE.

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Abstract

AIMS: To compare quality of life (QoL) and treatment satisfaction in patients with Type 1 diabetes receiving the rapid-acting insulin analogue, insulin aspart (IAsp), with that in patients receiving soluble human insulin (HI).

METHODS: In this 6-month, multinational, randomized, open-label trial, 424 patients from German-speaking countries were subjected to psychometric assessment before and after randomization (ratio 2 : 1) to basal-bolus treatment with either IAsp (n = 283) or HI (n = 141). Patients on HI were advised to keep an injection-meal interval of 30 min, whereas patients on IAsp were advised to inject immediately before meals. Treatment satisfaction and diabetes-related QoL were assessed using validated instruments to measure the domains of patients' individual treatment goals, physical complaints, worries about the future, social relations, leisure time flexibility, daily hassles, diet restrictions, burdens and fear of hypoglycemia, blood glucose fluctuations, self-efficacy, and fear of insulin analogues.

RESULTS: After 6 months, IAsp was associated with significantly greater improvement in treatment satisfaction than HI in two different scales ($P < 0.01$), and in QoL with respect to diet restrictions ($P < 0.01$). Improved satisfaction was mainly due to increased dietary and leisure time flexibility ($P < 0.0001$). Twenty-three percent of the IAsp group vs. 14% of the HI group achieved small but important improvements of total QoL (between-group difference, $P < 0.06$). The number needed to treat (NNT) with IAsp for an important increase in QoL was calculated to be 10. Regression analyses of potential predictors of improvement in QoL highlighted patients intensely striving for physical strength ($P < 0.01$; NNT = 7) and patients feeling less protected against hypoglycemia ($P < 0.005$; NNT = 8) as being the most likely to benefit from IAsp.

CONCLUSIONS: Under these study conditions, IAsp improved treatment satisfaction and quality of life regarding diet restrictions when compared with human insulin. The 'numbers needed to treat' for important quality of life benefits indicate that the effect of IAsp in this regard is not trivial.

PMID: 12873289 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adult
Diabetes Mellitus, Type 1/drug therapy*
Female
Humans
Hypoglycemic Agents/therapeutic use*
Insulin/analogs & derivatives
Insulin/therapeutic use*
Male

Patient Satisfaction*
Quality of Life*
Regression Analysis
Treatment Outcome
Substances:
Hypoglycemic Agents
insulin aspart
Insulin
32.JAMA. 2003 May 7;289(17):2254-64.

Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review.
DeWitt DE, Hirsch IB.

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Abstract
CONTEXT: Newer insulin therapies, including the concept of physiologic basal-prandial insulin and the availability of insulin analogues, are changing clinical diabetes care. The key to effective insulin therapy is an understanding of principles that, when implemented, can result in improved diabetes control.

OBJECTIVE: To systematically review the literature regarding insulin use in patients with type 1 and type 2 diabetes mellitus (DM).

DATA SOURCES: A MEDLINE search was performed to identify all English-language articles of randomized controlled trials involving insulin use in adults with type 1 or type 2 DM from January 1, 1980, to January 8, 2003. Bibliographies and experts were used to identify additional studies.

STUDY SELECTION AND DATA EXTRACTION: Studies were included (199 for type 1 DM and 144 for type 2 DM, and 38 from other sources) if they involved human insulins or insulin analogues, were at least 4 weeks long with at least 10 patients in each group, and glycemic control and hypoglycemia were reported. Studies of insulin-oral combination were similarly selected.

DATA SYNTHESIS: Twenty-eight studies for type 1 DM, 18 for type 2 DM, and 48 for insulin-oral combination met the selection criteria. In patients with type 1 DM, physiologic replacement, with bedtime basal insulin and a mealtime rapid-acting insulin analogue, results in fewer episodes of hypoglycemia than conventional regimens. Rapid-acting insulin analogues are preferred over regular insulin in patients with type 1 DM since they improve HbA1C and reduce episodes of hypoglycemia. In patients with type 2 DM, adding bedtime neutral protamine Hagedorn (isophane) insulin to oral therapy significantly improves glycemic control, especially when started early in the course of disease. Bedtime use of insulin glargine results in fewer episodes of nighttime hypoglycemia than neutral protamine Hagedorn regimens. For patients with more severe insulin deficiency, a physiologic insulin regimen should allow lower glycemic targets in the majority of patients. Adverse events associated with insulin therapy include hypoglycemia, weight gain, and worsening diabetic retinopathy if hemoglobin A1C levels decrease rapidly.

CONCLUSIONS: Many options for insulin therapy are now available. Physiologic insulin therapy with insulin analogues is now relatively simple to use and is associated with fewer episodes of hypoglycemia.

PMID: 12734137 [PubMed - indexed for MEDLINE]Free Article

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Research Support, Non-U.S. Gov't
Review
MeSH Terms:
Ambulatory Care
Blood Glucose Self-Monitoring
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/drug therapy*
Humans
Hypoglycemic Agents/administration & dosage
Hypoglycemic Agents/adverse effects
Hypoglycemic Agents/therapeutic use*
Infusion Pumps, Implantable
Insulin/administration & dosage
Insulin/adverse effects
Insulin/analogs & derivatives*
Insulin/therapeutic use*
Insulin Infusion Systems
Randomized Controlled Trials as Topic
Substances:
Hypoglycemic Agents
Insulin

33.Curr Diab Rep. 2001 Oct;1(2):112-8.

New aspects of insulin therapy in type 1 and type 2 diabetes.

Dills DG.

University of Colorado Department of Medicine, University of Colorado Health Sciences Center, F-732 Anschutz Center for Advanced Medicine, 1635 N. Ursula Street, Aurora, CO 80010, USA. Diana.Dills@UCHSC.edu

Abstract
Tight control of the blood glucose level decreases the frequency of complications of both type 1 and type 2 diabetes mellitus. Until recently, the available short, intermediate, and long-acting forms of insulin could not readily be used to achieve tight glycemic control without introducing an unacceptably high risk of hypoglycemia or demanding an impracticably rigid lifestyle. With the introduction of faster-acting insulin analogues, lispro and aspart, and a peakless long-acting insulin analogue, glargine, the goal of safe and effective tight glycemic control may now be within reach for many patients. The use of these new insulins allows the clinician and patient an expanded range of options for achieving good control of fasting and postprandial blood glucose levels.

PMID: 12643106 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/drug therapy*
Humans
Hypoglycemic Agents/therapeutic use*
Insulin/therapeutic use*
Substances:
Hypoglycemic Agents
Insulin
34.Diabetes Res Clin Pract. 2002 Nov;58(2):115-21.

Insulin lispro therapy in pregnancies complicated by type 1 diabetes mellitus.
Persson B, Swahn ML, Hjertberg R, Hanson U, Nord E, Nordlander E, Hansson LO.

Department of Pediatrics, Karolinska Hospital, 171 76 Stockholm, Sweden.
bengt.persson@swipnet.se

Abstract
OBJECTIVE: To compare the efficacy and safety of preprandial administration of rapid-acting lispro analogue with regular short-acting insulin to pregnant women with type 1 diabetes.

STUDY DESIGN: Open randomised multicentre study. Women were treated with multiple insulin injections aiming at normoglycaemia. Blood glucose was determined six times daily, HbA(1c) every 4 weeks. Diurnal profiles of blood glucose were analysed at gestational week 14 and during the study period at weeks 21, 28 and 34.

PARTICIPANTS: 33 pregnant women with type 1 DM were randomised to treatment with lispro insulin (n=16) or regular insulin (n=17).

RESULTS: Blood glucose was significantly lower ($P<0.01$) after breakfast in the lispro group, while there were no significant group differences in glycemic control during the rest of the day. Severe hypoglycaemia occurred in two patients in the regular group but biochemical hypoglycaemia (blood glucose <3.0 mmol/l) was more frequent in the lispro than in the regular group (5.5 vs. 3.9%, respectively). HbA(1c) values at inclusion were 6.5 and 6.6% in the lispro and regular group respectively. HbA(1c) values declined during the study period and were similar in both groups. There was no perinatal mortality. Complications during pregnancy, route of delivery and foetal outcome did not differ between the groups. Retinopathy progressed in both groups, one patient in the regular group developed proliferative retinopathy.

CONCLUSION: The results suggest that it is possible to achieve at least as adequate glycemic control with lispro as with regular insulin therapy in type 1 diabetic pregnancies.

PMID: 12213353 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Multicenter Study
Randomized Controlled Trial
MeSH Terms:
Adult
Blood Glucose/drug effects
Blood Glucose/metabolism
Diabetes Mellitus, Type 1/drug therapy*
Diabetic Angiopathies/epidemiology
Diabetic Retinopathy/epidemiology
Drug Administration Schedule
Female
Hemoglobin A, Glycosylated/metabolism
Humans
Hypoglycemic Agents/administration & dosage
Hypoglycemic Agents/therapeutic use
Infant, Newborn
Insulin/administration & dosage
Insulin/analogs & derivatives*
Insulin/therapeutic use*
Parity
Pregnancy
Pregnancy Outcome
Pregnancy in Diabetics/drug therapy*
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Insulin
insulin, neutral
insulin LISPRO
35.Int J Clin Pract Suppl. 2002 Jul;(129):65-74.

Clinical strategies for controlling peaks and valleys: type 1 diabetes.
Bolli GB.

Department of Internal Medicine, University of Perugia, Italy.

Abstract
The DCCT and UKPDS have established that in type 1 and in type 2 diabetes respectively, long-term near-normoglycaemia protects against the onset and/or progression of microangiopathic complications. Therefore, insulin strategies to maintain long-term near-normoglycaemia are of key importance in the management of diabetes. To successfully achieve near-normoglycaemia, insulin therapy must mimic nature by providing a bolus of insulin at meal ingestion and by replacing basal insulin between meals and overnight

Mealtime insulin needs can be best met by subcutaneous (s.c.) injection of a rapid-acting insulin analogue such as insulin lispro or insulin aspart. Rapid-acting insulin analogues are preferred to human regular insulin for three reasons: convenience (meal-time injection, better adaptation of insulin dose to carbohydrate content of the meal); lower blood glucose 2 hours after meals; and less risk for late postprandial hypoglycaemia. However, in type 1 diabetes the benefits of mealtime treatment with rapid-acting insulin analogues become apparent only to the extent that replacement of basal insulin is optimised. The interprandial need for basal insulin can be best met by continuous s.c. insulin infusion (CSII). CSII is very good for basal insulin replacement because it uses a rapid-acting insulin analogue with low variability in s.c. absorption, resulting in a flat and peakless action profile. A second option for basal insulin replacement is s.c. injection of an insulin preparation with retarded action. The two most commonly used are NPH and insulin glargine. NPH exhibits an action profile with a peak 4 to 5 hours after injection and duration of action of 10 to 15 hours. Insulin glargine has a peakless action profile and lasts approximately 24 hours. To optimise replacement of basal insulin with NPH, a few units of NPH must be combined with rapid-acting analogues at meals and also given at bedtime (0.2 U/kg). With insulin glargine, 0.2 to 0.4 U/kg should be injected once or, in some patients, twice daily. Modern insulin strategies for intensive therapy should include use of a rapid-acting insulin analogue at meal-time, and use of CSII to replace basal insulin. Insulin glargine reproduces closely the pharmacokinetics and pharmacodynamics of CSII and should be considered for substitution of basal insulin, especially in type 1 diabetes.

PMID: 12166610 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Humans
Hypoglycemic Agents/administration & dosage*
Hypoglycemic Agents/pharmacokinetics
Injections, Subcutaneous
Insulin/administration & dosage*
Insulin/analogs & derivatives*
Insulin/metabolism
Insulin/pharmacokinetics
Insulin, NPH/administration & dosage
Insulin, NPH/pharmacokinetics
Postprandial Period/physiology
Substances:
Hypoglycemic Agents
basal insulin
insulin aspart
Insulin
insulin LISPRO
Insulin, NPH
36.Int J Clin Pract. 2002 Jul-Aug;56(6):460-6.

Insulin glargine (Lantus).

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owensdr@cardiff.ac.uk

Abstract
Insulin glargine (Lantus) is a long-acting, human insulin analogue that has been specifically designed to overcome the deficiencies of traditionally available 'intermediate-acting' insulins that are currently used for basal insulin supplementation. In contrast to NPH insulin, subcutaneous insulin glargine injected once daily provides a relatively constant basal level of circulating insulin with no pronounced peak. In patients with type 1 and type 2 diabetes, once-daily insulin glargine achieves equivalent glycaemic control to NPH insulin given once or twice daily In patients with type 1 diabetes, it is associated with significantly lower fasting blood glucose (FBG) levels, especially in those patients previously on twice-daily NPH insulin. Insulin glargine is well tolerated and elicits less hypoglycaemia, especially nocturnal episodes, than NPH insulin, with similar levels of glycaemic control. This benefit is seen in patients with both type 1 and type 2 diabetes, in particular those previously on a once-daily NPH insulin regimen. Patients with type 1 and type 2 diabetes have also reported higher levels of treatment satisfaction when treated with insulin glargine. Insulin glargine provides the opportunity to achieve target blood glucose levels more effectively and safely compared with NPH insulin, due to the reduced risk of hypoglycaemia, especially nocturnal hypoglycaemia. Insulin treatment needs to be individualised, with the dose of insulin glargine adjusted according to the blood glucose level as part of an aggressive regimen in an attempt to achieve near normoglycaemia without incurring episodes of hypoglycaemia. Insulin glargine should be used in combination with short-acting insulin analogues in patients with type 1 diabetes. In patients where oral hypoglycaemic agents are failing, insulin glargine can be added. The early introduction of insulin in patients with type 2 diabetes is to be encouraged.

PMID: 12166545 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Adult
Aged
Blood Glucose/metabolism
Delayed-Action Preparations
Diabetes Mellitus/blood
Diabetes Mellitus/drug therapy*
Diabetes Mellitus, Type 1/drug therapy
Diabetes Mellitus, Type 2/drug therapy
Humans
Insulin/analogs & derivatives*
Insulin/blood
Insulin/pharmacology
Insulin/therapeutic use*
Middle Aged

Substances:
Blood Glucose
Delayed-Action Preparations
glargine
Insulin
37.Horm Res. 2002;57 Suppl 1:46-53.

Experience with insulin analogues in children.
Danne T, Deiss D, Hopfenmüller W, von Schütz W, Kordonouri O.

Diabetes-Zentrum für Kinder und Jugendliche, Kinderkrankenhaus auf der Bult, Hannover, Germany. danne@hka.de

Abstract
Current data on rapid and long-acting insulin analogues in the paediatric age group is limited. While several studies indicate a benefit in reducing hypoglycaemia, particularly at night, with rapid or long-acting insulin analogue treatment, the effect on long-term glycaemic control remains controversial. The continuous glucose monitoring system offers a new option for tailoring treatment with insulin analogues to achieve optimal glycaemia. In 29 adolescents with diabetes this approach confirmed the non-inferiority of postprandial rapid-acting analogue administration compared to preprandial regular insulin, but revealed significant mealtime differences, with increased analogue requirement at breakfast and dinner. Although rapid- and long-acting insulin analogues may offer potential benefits for problems frequently encountered in paediatric diabetology, their value for the individual child still has to be tested in long-term observations in daily clinical practice.

PMID: 11979022 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Blood Glucose/analysis
Child
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 1/physiopathology
Drug Combinations
Humans
Infusion Pumps
Insulin/analogs & derivatives*
Safety
Substances:
Blood Glucose
Drug Combinations
Insulin
38.Diabetes Nutr Metab. 2001 Dec;14(6):349-57.

The potential role of insulin analogues in the treatment of children and adolescents with Type 1 diabetes mellitus.

Mohn A, Dunger DB, Chiarelli F.

Department of Paediatrics, University of Chieti, Italy. amohn@unich.it

Abstract
The main therapeutic challenge in the treatment of Type 1 diabetes is maintenance of near-normoglycaemia in order to prevent long-term complications and avoid hypoglycaemia. This goal is relevant from the onset of the disease and is feasible if physiological models of insulin replacement are used and patients are educated in the strategy of intensive insulin therapy. Although the use of available insulins within a multiple injection regimen has improved, metabolic control it is still far from being optimal. The recent introduction of insulin analogues with a short- and long-acting profile seems promising in improving metabolic control and quality of care. Insulin lispro and insulin aspart, the short-acting insulin analogues offer a better post-prandial profile, while insulin glargine the new long-acting insulin analogue might provide better overnight control. In fact, the theoretical combination of an acute prandial insulin peak with a flat interprandial and overnight plasma profile would closely mimic the 24-hr insulin profile of non-diabetic individuals. This would possibly lead to lower post-prandial blood glucose excursion and better fasting blood glucose associated with minimal risk of hypoglycaemia. The possible reduction of hypoglycaemia is especially important in children as recurrent episodes might represent a potential risk for cognitive impairment. However, recent clinical research on the short-acting insulin analogues demonstrates the difficulties of translating these theoretical benefits into clinical relevant advantages. This might happen to other insulin analogues and requires further and larger studies in order to fully exploit the theoretical advantages of insulin analogues in the paediatric population. Safety issues should also be carefully monitored when introducting analogues in long-term therapy.

PMID: 11853368 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Adolescent
Child
Circadian Rhythm
Diabetes Mellitus, Type 1/drug therapy*
Food
Hemoglobin A, Glycosylated
Humans
Insulin/analogs & derivatives*
Insulin/blood
Insulin/pharmacokinetics
Insulin/therapeutic use
Kinetics
Substances:
Hemoglobin A, Glycosylated
Insulin
39.Expert Opin Pharmacother. 2002 Feb;3(2):183-95.

Insulin aspart: promising early results borne out in clinical practice.

Heller S, Kurtzhals P, Verge D, Lindholm A.

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Abstract
The novel, rapid-acting insulin analogue insulin aspart (IAsp; Novo Nordisk) has been shown in preclinical studies to be more rapidly absorbed than human insulin (HI) when administered subcutaneously. IAsp reaches higher peak serum concentrations in a shorter time than HI, whilst maintaining a similar receptor binding and safety profile. The physiological pharmacokinetic profile of IAsp compared to that of HI has been demonstrated in both adult and paediatric populations and was accompanied by small but statistically significant reductions in HbA(1c), lower postprandial glucose excursions and a reduced risk of late postprandial and major nocturnal hypoglycaemia. Benefits may be maximised by dose optimisation, using bolus doses that result in effective postprandial glucose reduction, as well as higher and multiple basal insulin doses. The safety profile, including cardiovascular risk, is equivalent to HI.

PMID: 11829732 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, SubstancesPublication Types:
Research Support, Non-U.S. Gov't
Review
MeSH Terms:
Adolescent
Blood Glucose/analysis
Child
Clinical Trials as Topic
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy
Diabetes Mellitus, Type 2/blood
Diabetes Mellitus, Type 2/drug therapy
Drug Evaluation
Humans
Hypoglycemia/chemically induced
Hypoglycemic Agents/adverse effects
Hypoglycemic Agents/blood
Hypoglycemic Agents/pharmacokinetics*
Insulin/adverse effects
Insulin/analogs & derivatives
Insulin/blood
Insulin/pharmacokinetics*
Substances:
Blood Glucose
Hypoglycemic Agents
insulin aspart
Insulin
40.Diabetes Nutr Metab. 2001 Oct;14(5):292-304.

Intensive insulin treatment in diabetic children.

Ludvigsson J, Bolli GB.

Department of Health and Environment, Linköping University, Sweden.

Abstract
Intensification of insulin therapy which maintains long-term near-normoglycaemia (HbA1c<7.0%) strongly protects against onset and/or progression of diabetic microangiopathy in Type 1 diabetes mellitus of adults. Similar intensification of insulin therapy is needed in diabetic children as well, in order to prevent complications a few years after diabetes onset, ie very often in young age. Provided adequate psychosocial support and education are available, children should be treated with multiple daily injections of insulin or, when necessary, with continuous subcutaneous insulin infusion, along with blood glucose monitoring. Insulin regimens may differ from child to child and vary from day to day in the same child, depending on lifestyle and considering all the available insulin preparations. These include the short-acting insulin (both human regular and short-acting insulin analogues), the intermediate-acting insulin (NPH and Lente), as well as the new long-acting insulin analogue glargine. The latter seems a promising candidate to substitute of basal insulin. The concern that intensified insulin therapy increases the risk of hypoglycaemia, as indicated by the Diabetes Control and Complications Trial (DCCT), is no longer tenable. On the contrary, a physiological, flexible insulin regimen better than a fixed insulin regimen, usually the twice daily split-mixed regimen, protects against the risk of hypoglycaemia in relation to food ingestion, physical exercise and sleep. Thus, appropriate education should be delivered at diabetes onset to the child and parents in order to start the strategy of intensified insulin therapy as early as possible.

PMID: 11806471 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Blood Glucose/analysis*
Blood Glucose Self-Monitoring
Child
Diabetes Mellitus, Type 1/drug therapy*
Diabetic Angiopathies/prevention & control*
Drug Administration Schedule
Humans
Hypoglycemia/prevention & control
Hypoglycemic Agents/therapeutic use*
Injections
Insulin/therapeutic use*
Insulin Infusion Systems
Patient Education as Topic
Substances:
Blood Glucose
Hypoglycemic Agents
Insulin

41.Diabet Med. 2001 Nov;18(11):864-70.

Recent advances in treatment of youth with Type 1 diabetes: better care through technology.
Tamborlane WV, Bonfig W, Boland E.

Department of Paediatrics and the Children's Clinical Research Center, Yale University School of Medicine, New Haven, CT 06520, USA. William.Tamborlane@Yale.udu

Comment in:

Diabet Med. 2001 Nov;18(11):861-3.

Abstract
While treatment of Type 1 diabetes mellitus (T1DM) in children and adolescents is especially difficult, recent technological advances have provided new therapeutic options to clinicians and patients. The urgency to achieve strict diabetes control and the introduction of new and improved insulin pumps have been accompanied by a marked increase in use of continuous subcutaneous insulin infusion (CSII) therapy in youth with diabetes. Results of clinical outcome studies indicate that CSII provides a safe and effective alternative to multiple daily injection (MDI) therapy, even when employed in a regular clinic setting in a large number of children. The safety and efficacy of CSII is further enhanced by the introduction of lispro and aspart insulin. The sharper peaks and shorter duration of action of these very rapid-acting insulin analogues provides a means to achieve better control of post-prandial hyperglycaemia with less late post-prandial and nocturnal hypoglycaemia. Glargine insulin, a soluble and essentially peakless long-acting insulin analogue, may provide a better basal insulin for MDI regimens, but there are limited published data with this agent in children with T1DM. A number of systems for pulmonary delivery of insulin are in development and preliminary results of Phase III studies have been promising. Like CSII, inhaled insulin allows the child to take bolus insulin doses before each meal without having to take a premeal injection. A major obstacle to effective treatment is that self-monitoring of three to four blood glucose levels a day often misses the marked glycaemic excursions that characterize T1DM in young patients. On the other hand, new continuous glucose sensing systems provide a wealth of data that can be used to optimize basal and bolus therapy, regardless of how insulin is administered. Even more important, we may finally be at the threshold of development of a practically applicable artificial pancreas.

PMID: 11703429 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, Substances, Grant SupportPublication Types:
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Review
MeSH Terms:
Administration, Inhalation
Adolescent
Blood Glucose Self-Monitoring/instrumentation
Blood Glucose Self-Monitoring/methods
Diabetes Mellitus, Type 1/therapy*
Humans

Insulin/administration & dosage
Insulin/analogs & derivatives
Insulin Infusion Systems
Therapeutics/trends*
Substances:
Insulin
Grant Support:
RR06022/RR/NCRR NIH HHS/United States
42.Diabetes Res Clin Pract. 2001 Nov;54(2):105-14.

Glyaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study.
Tamás G, Marre M, Astorga R, Dedov I, Jacobsen J, Lindholm A; Insulin Aspart Study Goup.

National Centre for Diabetes Care, 1st Department of Medicine, Diabetes Unit, Semmelweis University, Medical Faculty, Korányi Sándor utca 2A, H-1083, Budapest, Hungary. tamgyu@bell.sote.hu

Abstract
Insulin aspart (IAsp), is a rapid-acting analogue of human insulin (HI), for use in the meal related treatment of diabetes mellitus. The degree of glycaemic control achieved by IAsp in comparison with HI after algorithm-driven dose optimisation was tested over 3 months. The prospective, multicentre, randomised, open-label study with parallel groups was performed in 48 centres in 11 countries and included 423 basal-bolus treated patients with Type 1 diabetes. Main outcome measures were blood glucose control assessed by HbA1c, nine-point self-monitored blood glucose profiles, insulin dose, quality of life, hypoglycaemia and adverse events. An algorithm-driven increase occurred in the dose and number of daily injections of basal insulin, particularly in the IAsp group. After 12 weeks of treatment, HbA1c was significantly lower in IAsp compared to HI treated subjects by 0.17 (95% CI 0.30-0.04) ($P<0.05$). Comparison of the blood glucose profiles showed lower blood glucose levels with IAsp after breakfast (mean 8.4 vs 10.1 mmol/l; $P<0.0001$) and dinner (8.2 vs 9.3 mmol/l; $P<0.01$). There were no differences between treatments in the incidence of hypoglycaemic episodes or in the adverse event profiles. The WHO Diabetes Treatment Satisfaction Questionnaire score for perceived hyperglycaemia was lower with Iasp ($P=0.005$), and patients found the insulin aspart treatment more flexible ($P=0.022$). The current study underlines the need for optimising the basal insulin regimen in order to take full advantage of the pharmacodynamics of IAsp.

PMID: 11640994 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Multicenter Study
Randomized Controlled Trial
MeSH Terms:
Adult
Aged

Blood Glucose/metabolism*
Diabetes Mellitus, Type 1/blood*
Diabetes Mellitus, Type 1/drug therapy*
Fasting
Female
Hemoglobin A, Glycosylated/metabolism
Humans
Hypoglycemia/chemically induced
Hypoglycemia/epidemiology
Hypoglycemic Agents/adverse effects
Hypoglycemic Agents/therapeutic use*
Insulin/adverse effects
Insulin/analogs & derivatives
Insulin/therapeutic use*
Male
Middle Aged
Postprandial Period
Quality of Life
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
insulin aspart
Insulin
43.Clin Pharmacokinet. 2001;40(9):641-59.

Clinical pharmacokinetics and pharmacodynamics of insulin aspart.
Lindholm A, Jacobsen LV.

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Abstract
Insulin aspart is a novel rapid-acting insulin analogue with improved subcutaneous absorption properties when compared with soluble human insulin. Pharmacokinetic studies show an absorption profile with a time to reach peak concentration (t(max)) about half that of human insulin, a peak plasma drug concentration (Cmax) approximately twice as high and shorter residence time. The potency and bioavailability of insulin aspart are similar to those of human insulin. The pharmacokinetics of insulin aspart have been studied in healthy Caucasian and Asian-Japanese volunteers, in patients with type 1 and 2 diabetes mellitus, and in children with diabetes, with both pre- and postprandial administration and during continuous subcutaneous insulin infusion (CSII). The pharmacokinetic profile was similar to that of another rapid-acting insulin analogue, insulin lispro, on the basis of published information for that agent. Pharmacodynamic studies show a smaller excursion of postprandial glucose with insulin aspart injected subcutaneously just before the meal compared with soluble human insulin injected 30 minutes before the meal in patients with type 1 diabetes mellitus, and an equivalent control in patients with type 2 diabetes displaying residual insulin production. In a treatment study, glucose excursions evaluated from 24-hour glucose profiles showed less variability with insulin aspart compared with human insulin. Adverse events, including hypoglycaemia-induced ventricular repolarisation and hypoglycaemic threshold and awareness, did not differ between insulin aspart and human insulin. The available data suggest that subcutaneous injections of insulin aspart just before

meals better mimic the endogenous insulin profile in blood compared with human insulin, resulting in improved glucose control in a meal-related insulin regimen. This review summarises the clinical pharmacokinetics and pharmacodynamics of insulin aspart in relation to human insulin and insulin lispro.

PMID: 11605714 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Adult
Area Under Curve
Biological Availability
Blood Glucose/drug effects
Child
Clinical Trials as Topic
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 1/metabolism
Diabetes Mellitus, Type 2/drug therapy*
Diabetes Mellitus, Type 2/metabolism
Female
Humans
Hypoglycemic Agents*/pharmacokinetics
Hypoglycemic Agents*/pharmacology
Hypoglycemic Agents*/therapeutic use
Insulin*/analogs & derivatives*
Insulin*/pharmacokinetics
Insulin*/pharmacology
Insulin*/therapeutic use
Intestinal Absorption
Male
Tissue Distribution
Substances:
Blood Glucose
Hypoglycemic Agents
insulin aspart
Insulin
insulin LISPRO
44.Int J Clin Pract Suppl. 2001 Sep;(123):47-50.

Insulin pump therapy and rapid acting insulin: what have we learned?
Zinman B.

Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, University of Toronto, Canada.

Abstract
Approximately 80 years after the discovery and first human use of insulin, we are still striving to replace insulin in a physiological manner. The development of insulin analogues with superior pharmacokinetics has made mimicking of meal and basal insulin requirements

by subcutaneous injection more feasible. Administration by continuous subcutaneous insulin infusion (CSII) has provided additional flexibility in meal timing and modifying basal insulin replacement in response to circadian rhythms. Several studies have documented improved glycaemic control with CSII using a rapid-acting analogue such as insulin lispro, compared with regular human insulin. Lower postprandial glucose peaks and improved HbA1c levels were seen with insulin lispro by CSII. In addition, the frequency of hypoglycaemia was significantly reduced and the counter-regulatory hormone responses were maintained. The use of insulin lispro in CSII, compared with regular human insulin, resulted in improved hepatic glucose output in response to glucagon. The potential for problems of hyperglycaemia and ketoacidosis with interruption of insulin delivery by CSII has been studied. One study showed accelerated development of hyperglycaemia and ketosis with insulin lispro compared with regular human insulin while another showed no difference but return to normal glycaemia was faster when insulin lispro was administered. The use of CSII in the US has grown from 6,600 in 1990 to over 100,000 patients currently. With improved insulins, better methods of delivery and advances in glucose monitoring we will continue progress towards physiological insulin replacement and reduce the long-term complications of diabetes.

PMID: 11594299 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Humans
Hypoglycemia/prevention & control
Hypoglycemic Agents/administration & dosage*
Insulin/administration & dosage*
Insulin/analogs & derivatives
Insulin Infusion Systems*/adverse effects
Substances:
Hypoglycemic Agents
Insulin
insulin LISPRO
45.Exp Clin Endocrinol Diabetes. 2001;109 Suppl 2:S317-32.

Physiological insulin replacement in type 1 diabetes mellitus.
Bolli GB.

Department of Internal Medicine, University of Perugia, Italy. gbolli@dimisem.med.unipg.it

Abstract
The DCCT and UKPDS studies have definitely established that in type 1 as well as in type 2 diabetes mellitus, long-term near-normoglycaemia strongly protects against onset and/or progression of microangiopathic complications. Therefore, implementation of insulin strategies to maintain long-term near-normoglycaemia is of key importance in the management of diabetes mellitus. To successfully reach the goal of near-normoglycaemia, insulin therapy has to be physiological, i.e. it has to mimic nature by providing a bolus of

insulin at meal ingestion, and by replacing the need for basal insulin between meals and during the night. The meal-time insulin needs can be best met by s.c. injection of a short-acting insulin analogue (lispro, aspart). Short-acting insulin analogues should be preferred to human regular insulin for three main reasons. First, convenience (meal-time injection, better adaptation of insulin dose to carbohydrate content of the meal); second, lower blood glucose 2-hour after meals; third, less risk for late post-prandial hypoglycaemia. However, the benefits of meal-time treatment with short-acting insulin analogues become apparent only by the extent to which replacement of basal insulin is optimised as well. The interprandial (especially nocturnal) need for basal insulin can be best met by the continuous s.c. insulin infusion by an external minipump, the gold standard of basal insulin replacement. Continuous s.c. insulin infusion in the basal state is so good because it uses a short-acting insulin analogue (low variability in s.c. absorption, flat and peak-less action profile), not insulin preparations with retarded action (high variability of s.c. absorption, peak of action) likewise the model of multiple daily insulin injections. A second choice option is s.c. injection of an insulin preparation with retarded action. At present, the long-acting insulin analogue glargine is the retarded insulin preparation of choice because its action profile is flat, peakless and long-lasting (approximately 24 hours). This is in contrast with the peak action profile of NPH insulin which exhibits a short duration of action (10-15 h). Thus, the modern insulin strategies for intensive therapy always include use of a short-acting insulin analogue at meal-time, and use of either continuous s.c. insulin infusion, or a s.c. injection of insulin glargine to replace basal insulin. Insulin glargine reproduces closely the pharmacokinetics and pharmacodynamics of continuous s.c. insulin infusion, and should always be preferred to NPH in all insulin-requiring diabetic patients, both type 1 and type 2.

PMID: 11460580 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Blood Glucose/analysis
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 1/physiopathology
Humans
Insulin/physiology
Insulin/therapeutic use*
Patient Education as Topic
Substances:
Blood Glucose
Insulin
46.Diabetes Obes Metab. 2000 Oct;2(5):307-11.

Impact of insulin lispro on HbA1c values in insulin pump users.
Garg SK, Anderson JH, Gerard LA, Mackenzie TA, Gottlieb PA, Jennings MK, Chase HP.

Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, Denver 80262, USA.

Abstract

AIM: To compare the therapeutic efficacy of the short-acting insulin analogue insulin lispro (Humalog) with that of buffered regular human insulin (Velosulin) in patients on insulin pump therapy.

PATIENTS AND METHODS: Sixty-two (45 women and 17 men) young patients with type 1 diabetes using insulin pump therapy were compared while using buffered regular human insulin for a mean +/- s.e.m. of 20.1+/-1.2 months or insulin lispro for a mean +/- s.e.m. of 19.7+/-0.5 months. The initial mean +/- s.e.m. age and duration of diabetes were 29.1+/-0.9 and 17.7+/-0.9 years, respectively. The mean HbA1c values, basal insulin dosages, premeal insulin dosages and number of low blood sugars were recorded during treatment with both insulins.

RESULTS: Mean +/- s.e.m. HbA1c values were significantly lower ($p < 0.001$; paired Wilcoxon t-test) during insulin lispro treatment (7.4+/-0.1%) as compared to treatment with buffered regular human insulin (7.9+/-0.1%). Total units of insulin (mean +/- s.e.m.)/kg/day was significantly ($p = 0.03$) lower (0.61+/-0.02) during the insulin lispro treatment period as compared to the buffered regular human insulin treated period (0.65+/-0.03). Total mean +/- s.e.m. (U/kg/day) of basal insulin administered per day was higher when patients received insulin lispro treatment (0.44+/-0.02 vs. 0.42+/-0.01 for buffered regular human insulin treated period; $p = 0.002$). The premeal insulin boluses (mean +/- s.e.m.) for the two treatment groups were significantly different with less insulin required for the insulin lispro treatment period for all three meals ($p < 0.001$, t-test). The number of mild/moderate and severe hypoglycaemic episodes were similar in the two groups.

CONCLUSION: We conclude that use of insulin lispro in pump therapy significantly lowers HbA1c values in comparison to therapy with buffered regular human insulin insulin without increasing hypoglycaemic episodes.

PMID: 11225746 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, Substances, Grant SupportPublication Types:
Clinical Trial
Comparative Study
Controlled Clinical Trial
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
MeSH Terms:
Adult
Biological Markers/analysis
Blood Glucose/metabolism
Diabetes Mellitus, Type 1/blood*
Diabetes Mellitus, Type 1/drug therapy*
Female
Hemoglobin A, Glycosylated/analysis*
Humans
Hypoglycemic Agents/administration & dosage
Hypoglycemic Agents/therapeutic use
Insulin/administration & dosage
Insulin/analogs & derivatives*

Insulin/therapeutic use*
Insulin Infusion Systems*
Male
Middle Aged
Substances:
Biological Markers
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Insulin
insulin LISPRO
Grant Support:
MO1RR00069/RR/NCRR NIH HHS/United States
47.Diabet Med. 2000 Nov;17(11):762-70.

Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: a randomized controlled trial.
Home PD, Lindholm A, Riis A; European Insulin Aspart Study Group.

Human Diabetes and Metabolism Research Centre, University of Newcastle upon Tyne, UK. philip.home@newcastle.ac.uk

Abstract
AIMS: To compare the efficacy of insulin aspart, a rapid-acting insulin analogue, with that of unmodified human insulin on long-term blood glucose control in Type 1 diabetes mellitus.

METHODS: Prospective, multi-centre, randomized, open-labelled, parallel-group trial lasting 6 months in 88 centres in eight European countries and including 1,070 adult subjects with Type 1 diabetes. Study patients were randomized 2:1 to insulin aspart or unmodified human insulin before main meals, with NPH-insulin as basal insulin. Main outcome measures were blood glucose control as assessed by HbA1c, eight-point self-monitored blood glucose profiles, insulin dose, quality of life, hypoglycaemia, and adverse events.

RESULTS: After 6 months, insulin aspart was superior to human insulin with respect to HbA1c with a baseline-adjusted difference in HbA1c of 0.12 (95% confidence interval 0.03-0.22) %Hb, $P < 0.02$. Eight-point blood glucose profiles showed lower post-prandial glucose levels (mean baseline-adjusted -0.6 to -1.2 mmol/l, $P < 0.01$) after all main meals, but higher pre-prandial glucose levels before breakfast and dinner (0.7-0.8 mmol/l, $P < 0.01$) with insulin aspart. Satisfaction with treatment was significantly better in patients treated with insulin aspart (WHO Diabetes Treatment Satisfaction Questionnaire (DTSQ) baseline-adjusted difference 2.3 (1.2-3.3) points, $P < 0.001$). The relative risk of experiencing a major hypoglycaemic episode with insulin aspart compared to human insulin was 0.83 (0.59-1.18, NS). Major night hypoglycaemic events requiring parenteral treatment were less with insulin aspart (1.3 vs. 3.4% of patients, $P < 0.05$), as were late post-prandial (4-6 h) events (1.8 vs. 5.0% of patients, $P < 0.005$).

CONCLUSIONS: These results show small but useful advantage for the rapid-acting insulin analogue insulin aspart as a tool to improve long-term blood glucose control, hypoglycaemia, and quality of life, in people with Type 1 diabetes mellitus.

PMID: 11131100 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adult
Blood Glucose/metabolism*
Blood Glucose Self-Monitoring
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 1/psychology
Female
Hemoglobin A, Glycosylated/analysis
Humans
Hypoglycemia/epidemiology
Hypoglycemic Agents/adverse effects
Hypoglycemic Agents/therapeutic use*
Insulin/adverse effects
Insulin/analogs & derivatives*
Insulin/therapeutic use*
Male
Patient Satisfaction
Quality of Life*
Questionnaires
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
insulin aspart
Insulin
48.Diabet Med. 2000 May;17(5):371-5.

Post-prandial administration of the insulin analogue insulin aspart in patients with Type 1 diabetes mellitus.
Brunner GA, Hirschberger S, Sendlhofer G, Wutte A, Ellmerer M, Balent B, Schaupp L, Krejs GJ, Pieber TR.

Department of Internal Medicine, Karl-Franzens University, Graz, Austria. gernot.brunner@kfunigraz.ac.at

Abstract
AIMS: In intensified insulin therapy, the recent development of short-acting insulin analogues with a very rapid onset of action forces a new discussion in terms of the optimal injection-meal interval. This study evaluated prandial glycaemia in patients with Type 1 diabetes following the subcutaneous injection of soluble human insulin (HI) and the insulin

analogue insulin aspart (IAsp) at different injection-meal intervals and investigated whether administration of IAsp after the meal might provide satisfactory metabolic control.

METHODS: In a randomized, double-blind, double-dummy, four-period crossover study, 20 Type 1 diabetic patients were investigated. Prandial insulin was administered 15 min before the start of the meal (HI(-15min)), immediately before the meal (HI(0min); IAsp(0min)) and 15 min after the start of the meal (IAsp(+15min)).

RESULTS: Plasma glucose excursions from baseline levels during the 4 h (PGexc) were highest with HI(0min) (17.9 mmol.l(-1).h; $P < 0.05$ vs. other treatments) and were not statistically different for HI(-15min), IAsp(0min) and IAsp(15min) (13.6, 11.9 and 14.2 mmol.l(-1).h, respectively). Maximum concentration of plasma glucose (PGmax) was lowest with IAsp(0min) (11.2 mmol/l; $P < 0.05$ vs. other treatments). PGmax was comparable with HI(-15min), HI(0min) and IAsp(+15min) (13.3, 14.1 and 13.2 mmol/l, respectively).

CONCLUSIONS: With regard to prandial glycaemia IAsp(+15min) is as effective as HI(-5min) and superior to HI(0min). Thus, post-prandial dosing of the insulin analogue IAsp offers an attractive and feasible therapeutic option for well-controlled patients with Type 1 diabetes mellitus.

PMID: 10872536 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adult
Blood Glucose/metabolism
Cross-Over Studies
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Double-Blind Method
Female
Food*
Humans
Hypoglycemic Agents/administration & dosage*
Hypoglycemic Agents/therapeutic use
Insulin/administration & dosage*
Insulin/analogs & derivatives*
Insulin/therapeutic use
Male
Middle Aged
Substances:
Blood Glucose
Hypoglycemic Agents
insulin aspart
Insulin
49.Journ Annu Diabetol Hotel Dieu. 1999:165-77.

[My approach to the management of a type I diabetic treated with short-acting insulin analogue]
[Article in French]

Colombel A, Charbonnel B.

Clinique d'Endocrinologie, Maladies Métaboliques, Hôtel Dieu, Nantes.

PMID: 10732416 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Blood Glucose/analysis
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Hemoglobin A/analysis
Humans
Hypoglycemia/chemically induced
Hypoglycemic Agents/therapeutic use*
Infusion Pumps
Insulin/analogs & derivatives*
Insulin/therapeutic use
Patient Satisfaction
Quality of Life
Substances:
Blood Glucose
Hypoglycemic Agents
Insulin
insulin LISPRO
Hemoglobin A
50.Rom J Intern Med. 1998 Jan-Jun;36(1-2):85-96.

Safety and efficacy of insulin lispro in patients with diabetes mellitus.
Cheta D, Strachinariu R, Trifan E, Nicolau A, Ionescu-Tîrgoviste C, Georgescu M, Ghenof M, Mincu I, Uta D, Ristic S. N. C. Paulescu Institute, Clinic of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania.

Abstract
Lispro is a human insulin analogue with a very rapid onset of action, and a shorter duration of activity than soluble insulin. In order to assess the therapeutical value of lispro, we have had an open-label, non-comparative study, for 12 weeks, involving 19 IDDM patients. The treatment regimen with lispro and Humulin N has been adapted depending on each patient characteristics. Patients attended three visits, and the main metabolic control parameters included values of hemoglobin Alc, fasting and postprandial blood glucose monitoring. The patients themselves monitored their blood glucose using a glucometer. The mean age value of 19 patients (8 females and 11 males) was 22.32 (+/- 13.59) years. In patients previously receiving insulin treatment, therapy with lispro insulin significantly reduced postprandial

glucose values. Lispro has been administered t.i.d. in 14 patients, and b.i.d. in 5 patients. At visit 1, mean value of HbAlc was 10.32% (+/- 1.63%); at visit 3, mean HbAlc was 9.90% (+/- 1.59%). Total insulin daily dose and the rate of short and long acting insulin did not change from visit 1 to visit 3. There has been reported only one serious adverse event during the study: a ketoacidosis due to a technical dosing error. Ten patients have reported mild hypoglycemic episodes. The outcomes of clinical study and of Quality of Life Questionnaire suggests that lispro--the first human insulin analogue used in humans--is effective, safe, and it is broadening beneficially the spectrum of insulins.

PMID: 10660973 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
MeSH Terms:
Adolescent
Adult
Aged
Blood Glucose/analysis
Blood Glucose/drug effects
Child
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Female
Hemoglobin A, Glycosylated/analysis
Hemoglobin A, Glycosylated/drug effects
Humans
Hypoglycemic Agents/administration & dosage
Hypoglycemic Agents/adverse effects*
Insulin/administration & dosage
Insulin/adverse effects
Insulin/analogs & derivatives*
Male
Middle Aged
Safety
Time Factors
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Insulin
insulin LISPRO
51.Acta Diabetol. 1998 Dec;35(4):183-93.

Prevention and treatment of hypoglycaemia unawareness in type 1 diabetes mellitus.
Bolli GB.

Di. M.I.S.E.M., University of Perugia, Italy.

Abstract
Unawareness of hypoglycaemia (reduced ability/failure to recognize hypoglycaemia symptoms at the physiological threshold of 3.0 mmol/l) occurs frequently in type 1 diabetes mellitus, and patients are then at risk for severe hypoglycaemia. Unawareness of hypoglycaemia is the result of earlier frequent episodes of hypoglycaemia (iatrogenic). Likewise, a history of hypoglycaemia induces unawareness, while meticulous prevention of hypoglycaemia can reverse hypoglycaemia unawareness. Therefore, it is essential that insulin therapy regimens for type 1 diabetes mellitus be designed not only to maintain near-normoglycaemia, but also to minimize hypoglycaemia. Such a goal is feasible as long as (1) a rational plan of insulin therapy is adopted, including appropriate use of the short-acting insulin analogue lispro, (2) blood glucose is properly monitored, (3) blood glucose targets are individualized, and (4) education programs are widely implemented.

PMID: 9934816 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Research Support, Non-U.S. Gov't
Review
MeSH Terms:
Awareness*
Blood Glucose/analysis
Diabetes Mellitus, Type 1/complications*
Humans
Hypoglycemia/blood
Hypoglycemia/etiology*
Hypoglycemia/prevention & control
Hypoglycemia/psychology*
Substances:
Blood Glucose
52.Diabet Med. 1998 Jul;15(7):592-600.

Use of the short-acting insulin analogue lispro in intensive treatment of type 1 diabetes mellitus: importance of appropriate replacement of basal insulin and time-interval injection-meal.

Del Sindaco P, Ciofetta M, Lalli C, Perriello G, Pampanelli S, Torlone E, Brunetti P, Bolli GB.

Dipartimento di Medicina Interna e Scienze Endocrine e Metaboliche, Università di Perugia, Italy.

Abstract
To establish whether lispro may be a suitable short-acting insulin preparation for meals in intensive treatment of Type 1 diabetes mellitus (DM) in patients already in chronic good glycaemic control with conventional insulins, 69 patients on intensive therapy (4 daily s.c. insulin injections, soluble at each meal, NPH at bedtime, HbA1c <7.5%) were studied with an open, cross-over design for two periods of 3 months each (lispro or soluble). The % HbA1c and frequency of hypoglycaemia were assessed under four different conditions (Groups I-IV). Lispro was always injected at mealtime, soluble 10-40 min prior to meals (with the exception of Group IV). Bedtime NPH was continued with both treatments. When lispro replaced

soluble with no increase in number of daily NPH injections (Group I, n = 15), HbA1c was no different (p = NS), but frequency of hypoglycaemia was greater (p < 0.05). When NPH was given 3-4 times daily, lispro (Group II, n = 18), but not soluble (Group III, n = 12) decreased HbA1c by 0.35 +/- 0.25% with no increase in hypoglycaemia. When soluble was injected at mealtimes, HbA1c increased by 0.18 +/- 0.15% and hypoglycaemia was more frequent than when soluble was injected 10-40 min prior to meals (Group IV, n = 24) (p < 0.05). It is concluded that in intensive management of Type 1 DM, lispro is superior to soluble in terms of reduction of % HbA1c and frequency of hypoglycaemia, especially for those patients who do not use a time interval between insulin injection and meal. However, these goals cannot be achieved without optimization of basal insulin.

PMID: 9686700 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Randomized Controlled Trial
MeSH Terms:
Adult
Blood Glucose/metabolism
Body Weight
Cross-Over Studies
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Female
Food*
Hemoglobin A, Glycosylated/metabolism
Humans
Hypoglycemia/chemically induced
Hypoglycemic Agents*
Insulin/administration & dosage*
Insulin/adverse effects
Insulin/analogs & derivatives*
Insulin/therapeutic use
Male
Solubility
Time Factors
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Insulin
insulin LISPRO
53.Diabet Med. 1998 Mar;15(3):247-9.

Human insulin analogue [LYS(B28), PRO(B29)]: the ideal pump insulin?
Schmauss S, König A, Landgraf R.

Department of Internal Medicine, Innenstadt Klinikum, University of Munich, Germany.

Abstract
The short-acting insulin analogue lispro ([LYS(B28), PRO(B29)] is absorbed from the subcutis more rapidly than soluble insulin (S). To compare the clinical effectiveness of lispro vs S, 11 Type 1 patients using continuous subcutaneous insulin infusion (CSII) therapy (6 F, 5 M, age 30 +/- 2.5 years, diabetes duration 14 +/- 1.0 years, BMI 24.0 +/- 0.8 kg m(-2), HbA1c 6.5 +/- 0.2%) were studied in an open, randomized, crossover study for 6 months (3 months lispro and 3 months S or vice versa). During lispro treatment mean fasting and 2 h postprandial blood glucose were lower compared to the S phase (fasting 6.5 +/- 0.4 vs 7.5 +/- 0.4 mmol l(-1) (NS), postprandial 6.8 +/- 0.3 vs 8.3 +/- 0.3 mmol l(-1), p = 0.03). In patients treated first with lispro HbA1c levels improved from 6.3 +/- 0.2% to 5.7 +/- 0.3%; On reversion to S HbA1c increased to 6.2 +/- 0.2%. In the group treated first with S, HbA1c fell (6.7 +/- 0.4% vs 6.5 +/- 0.3%) and then improved further to 6.3 +/- 0.3% with lispro. None of these changes were significant. There was no significant difference with respect to hypoglycaemic or other adverse events. It can be concluded that lispro in CSII therapy is safe and may improve postprandial glucose excursions.

PMID: 9545126 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adult
Blood Glucose/metabolism
Body Mass Index
Cross-Over Studies
Diabetes Mellitus, Type 1/drug therapy*
Fasting
Female
Hemoglobin A, Glycosylated/metabolism
Humans
Hypoglycemic Agents/administration & dosage
Hypoglycemic Agents/therapeutic use*
Insulin/administration & dosage
Insulin/analogs & derivatives*
Insulin/therapeutic use
Insulin Infusion Systems*
Male
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Insulin
insulin LISPRO
54.Artif Organs. 1998 Jan;22(1):32-42.

Enhanced, simplified glucose sensors: long-term clinical application of wearable artificial endocrine pancreas.

Shichiri M, Sakakida M, Nishida K, Shimoda S.

Department of Metabolic Medicine, Kumamoto University School of Medicine, Japan.

Abstract
At present, 2 major problems should be solved before long-term application of the wearable artificial endocrine pancreas, the development of a reliable and stable glucose monitoring system and the development of a subcutaneous insulin infusion algorithm. With either a miniaturized extracorporeal glucose monitoring system based on microdialysis sampling method or a ferrocene-mediated needle-type glucose sensor covered with highly biocompatible membrane, poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (poly[MPC-co-BMA]) membrane, subcutaneous glucose concentrations could be monitored for 7 days without any in vivo calibrations, followed by 14 days with one point calibration. Considering the management and safety of the insulin delivery route, subcutaneous insulin infusion is obligatory. With the subcutaneous insulin infusion algorithm using a short acting insulin analogue (Insulin Lispro), near physiological glycemic control could be established in diabetic patients without showing any delayed hyperinsulinemia or hypoglycemia. The wearable artificial endocrine pancreas is now recognized as an excellent therapeutic tool for regulating blood glucose excursions physiologically in ambulatory diabetic patients on a long-term basis.

PMID: 9456224 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Animals
Biosensing Techniques*
Blood Glucose/metabolism*
Blood Glucose Self-Monitoring/instrumentation
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/therapy
Diabetes Mellitus, Type 2/blood
Diabetes Mellitus, Type 2/therapy
Ferrous Compounds/chemistry
Humans
Insulin/administration & dosage
Insulin/analogs & derivatives*
Insulin Infusion Systems/trends*
Membranes, Artificial
Methacrylates/chemistry
Phosphorylcholine/analogs & derivatives
Phosphorylcholine/chemistry
Polyvinyl Alcohol/chemistry
Randomized Controlled Trials as Topic
Rats
Substances:
Blood Glucose
Ferrous Compounds

Membranes, Artificial
Methacrylates
ferrocene
Phosphorylcholine
Insulin
poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate)
insulin LISPRO
Polyvinyl Alcohol
55.Clin Ther. 1997 Nov-Dec;19(6):1408-21.

Efficacy of insulin lispro in combination with NPH human insulin twice per day in patients with insulin-dependent or non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group.

Vignati L, Anderson JH Jr, Iversen PW.

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, USA.

Abstract
A common treatment regimen for patients with either insulin-dependent diabetes mellitus (IDDM) or non-insulin-dependent diabetes mellitus (NIDDM) is a combination of rapid-acting insulin and intermediate-acting insulin administered twice each day. It is usually recommended that regular human insulin be injected 30 to 45 minutes before a meal. In practice, patients often inject regular human insulin closer to mealtime, causing a higher post-prandial serum glucose level and an increased potential for hypoglycemia in the postabsorptive period. Insulin lispro, a rapid-acting insulin analogue, is best injected just before a meal because of its more rapid absorption and shorter duration of action. In 707 randomized patients, 379 with IDDM and 328 with NIDDM, we studied the effect of twice-daily insulin lispro or regular human insulin in combination with NPH human insulin (isophane insulin) on premeal, 2-hour postprandial, and bedtime glycemic control. Assessments were based on the results of a seven-point blood glucose profile, the insulin dose (by formulation and time of administration), the incidence and frequency of hypoglycemic episodes, and the glycated hemoglobin value. Treatment with insulin lispro resulted in lower postprandial glucose levels and smaller increases in glucose level after the morning and evening meals compared with treatment with regular human insulin. Overall glycemic control, frequency of hypoglycemic events, and total insulin dose were not different between the two groups. Insulin lispro in combination with NPH human insulin in a twice-per-day regimen allows injection closer to mealtime and improves post-prandial glycemic control without increasing the risk of hypoglycemia.

PMID: 9444449 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Randomized Controlled Trial
MeSH Terms:
Adolescent
Adult
Blood Glucose/metabolism

Cross-Over Studies
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/blood
Diabetes Mellitus, Type 2/drug therapy*
Drug Therapy, Combination
Female
Hemoglobin A, Glycosylated/metabolism
Humans
Hypoglycemic Agents/adverse effects
Hypoglycemic Agents/therapeutic use*
Insulin/adverse effects
Insulin/analogs & derivatives*
Insulin/therapeutic use
Insulin, NPH/adverse effects
Insulin, NPH/therapeutic use*
Male
Middle Aged
Postprandial Period
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Insulin
insulin LISPRO
Insulin, NPH
56.N Z Med J. 1997 Nov 28;110(1056):435-8.

Lispro insulin as premeal therapy in type 1 diabetes: comparison with Humulin R.
Daniels AR, Bruce R, McGregor L.

Whitiora Diabetes Clinic, Middlemore Hospital, Auckland.

Abstract
AIMS: To determine the efficacy, tolerability and safety of the short-acting insulin analogue lispro compared with regular short-acting insulin, Humulin R as premeal therapy in type 1 diabetes mellitus and to assess the safety of lispro administered for one year.

METHODS: The study was part of an international multicentre crossover study (IOAG) in which 1008 patients were randomised. Twenty patients from Auckland, with insulin dependent diabetes mellitus, received lispro for 3 months and Humulin R for 3 months in a crossover design. At the end of the crossover period, 19 patients elected to participate in an open label continuation of lispro therapy. Humulin N, L or U was used as basal insulin therapy.

RESULTS: Lispro and Humulin R in combination with Humulin N, L or U did not significantly differ with respect to glycaemic control or incidence of hypoglycaemia. Glycosylated haemoglobin (HbA1C) improved from 8.6% at baseline to 7.6 +/- 0.9 (Humulin R) and 7.7 +/- 1.1% (lispro). During the open label continuation of lispro plus the usual basal insulin HbA1C deteriorated to 8.6% after 12 months.

CONCLUSIONS: In this short-term comparison, lispro and Humulin R were well tolerated, while glycaemic control, incidence of hypoglycaemia and adverse effects were similar.

PMID: 9418839 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adolescent
Adult
Aged
Blood Glucose/analysis
Child
Cross-Over Studies
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 1/metabolism
Female
Follow-Up Studies
Hemoglobin A, Glycosylated/metabolism
Humans
Hypoglycemia/chemically induced
Hypoglycemic Agents/therapeutic use*
Incidence
Insulin/analogs & derivatives*
Insulin/therapeutic use*
Male
Middle Aged
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Insulin
insulin LISPRO
57.Wien Med Wochenschr. 1997;147(9):222-5.

[Insulin therapy and sports]
[Article in German]

Aigner A.

Institut für Sportmedizin des Landes Salzburg.

Abstract
Physical work effects a transitory enhanced affinity of insulin to its receptor in the stressed muscles and thereby a better efficiency. Therefore, in sports lasting for 30 min and more the

basal and/or bolus doses of insulin have to be reduced in order to prevent hypoglycemia. An alternative supply of additional carbohydrates prior to physical work is often not practicable. Injections of insulin into areas of the body not involved in muscular work do not give sufficient warranty against hypoglycemic reactions. A new short-acting insulin-analogue (Lispro) shows a reduced effect on blood glucose levels after 3 h as compared to regular insulin. Therefore, it could be of advantage for insulin dependent diabetics doing their exercise at this time.

PMID: 9281236 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
English Abstract
Review
MeSH Terms:
Blood Glucose/metabolism
Combined Modality Therapy
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 1/physiopathology
Diabetic Diet
Exercise/physiology*
Humans
Insulin/administration & dosage*
Insulin/adverse effects
Insulin/analogs & derivatives
Muscle, Skeletal/drug effects
Muscle, Skeletal/physiopathology
Receptor, Insulin/physiology
Sports*
Substances:
Blood Glucose
Insulin
insulin LISPRO
Receptor, Insulin
58.Diabet Med. 1996 Jul;13(7):625-9.

Prandial glycaemia after a carbohydrate-rich meal in type I diabetic patients: using the rapid acting insulin analogue [Lys(B28), Pro(B29)] human insulin.
Heinemann L, Heise T, Wahl LC, Trautmann ME, Ampudia J, Starke AA, Berger M.

Department of Nutrition and Metabolism, WHO Collaborating Centre for Diabetes, Heinrich-Heine-University of Düsseldorf, Germany.

Abstract
The time-action profile of the insulin analogue insulin lispro ([Lys(B28), Pro(B29)] human insulin) with its rapid onset and short duration of action might be more suitable to limit hyperglycaemic excursions after a meal rich in rapidly absorbable carbohydrates in comparison to regular human insulin. A randomized, double-blind study was performed in 10 Type I diabetic patients with good metabolic control (HbA1c 7.0 +/- 0.5%). After a baseline period of 3 h (blood glucose clamped at 6.7 mmol l-1, i.v. insulin infusion of 0.2 mU kg-1

min-1 throughout the study), the patients ate a pizza, drank a cola and had a carbohydrate-rich dessert (total carbohydrate content 140 g). Immediately before the meal 15.4 +/- 3.5 U of either insulin preparation were injected subcutaneously. Blood glucose concentrations were monitored continuously thereafter. Following the injection of insulin lispro the area under the blood glucose curve after the meal was 78% of that of regular insulin (1.76 +/- 0.34 vs 2.26 +/- 0.68 mol l-1 *240 min-1; $p < 0.01$). Maximal blood glucose excursions were higher and were reached later after regular insulin as compared to insulin lispro (11.9 +/- 2.8 vs 9.9 +/- 1.4 mmol l-1; $p < 0.05$; 66 +/- 37 vs 41 +/- 7 min; $p < 0.05$). Maximal individual differences in the blood glucose excursions (regular human insulin minus insulin lispro) were 4.8 +/- 2.2 mmol l-1 ($p < 0.0001$ against zero) after 110 +/- 37 min. In Type 1 diabetic patients prandial blood glucose excursions after a carbohydrate rich meal were reduced after preprandial injection of insulin lispro in comparison to human regular insulin.

PMID: 8840095 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adult
Blood Glucose/metabolism
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 1/epidemiology
Diabetes Mellitus, Type 1/physiopathology
Dietary Carbohydrates/administration & dosage
Dietary Carbohydrates/metabolism*
Double-Blind Method
Eating/physiology
Glucose Clamp Technique
Humans
Hypoglycemic Agents/pharmacokinetics
Hypoglycemic Agents/pharmacology
Hypoglycemic Agents/therapeutic use*
Insulin/analogs & derivatives*
Insulin/blood
Insulin/pharmacokinetics
Insulin/pharmacology
Insulin/therapeutic use
Patient Compliance
Time Factors
Substances:
Blood Glucose
Dietary Carbohydrates
Hypoglycemic Agents
Insulin
insulin LISPRO
59.Exp Clin Endocrinol Diabetes. 1996;104(1):25-30.

Intensive insulin therapy with insulin lispro in patients with type 1 diabetes reduces the frequency of hypoglycemic episodes.

Pfützner A, Küstner E, Forst T, Schulze-Schleppinghoff B, Trautmann ME, Haslbeck M, Schatz H, Beyer J.

III. Med. Klinik, Innere Medizin & Endokrinologie, Mainz.

Abstract

In a randomized, open-label, controlled cross-over trial, 107 patients with type 1 diabetes were treated with either regular human insulin or insulin lispro, a rapid-acting insulin analogue. After a lead-in period of 2 to 4 weeks, the patients were randomized to receive intensified insulin treatment with one of the insulins. NPH-human insulin was used for basal substitution in both groups. The crossover took place after 3 months of treatment. Efficacy and safety of the drugs were established by the assessment of hemoglobin A1c, pretest blood glucose, 1 and 2-hour postprandial glucose excursions, number of hypoglycemic episodes, daily insulin doses, body weight, insulin antibodies, and the number and severity of adverse events. A questionnaire comprised of four primary domains was used to measure some quality of life aspects of the patients. Both treatment regimens were well tolerated. While no differences were seen in the hemoglobin A1c values, there was a trend for a decrease in the pretest blood glucose levels and significant decreases of the 1 and 2-hour postprandial glucose excursions in the patients treated with insulin lispro. The number of hypoglycemic episodes was also significantly lower in the insulin lispro treatment period. The evaluation of the quality of life questionnaire revealed an improvement in the patients treatment satisfaction for the insulin lispro group. During treatment with insulin lispro, the basal insulin doses increased slightly. However, the total daily insulin doses decreased to a greater extent with insulin lispro as compared to regular human insulin. Human insulin-specific antibody binding values at endpoint were not different for the two treatments. In conclusion, intensive insulin treatment with insulin lispro therapy results in improved postprandial glycemic control and HbA1c levels at least equal to the treatment with regular human insulin but with less hypoglycemia and more treatment satisfaction for the patient.

PMID: 8750567 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Multicenter Study
Randomized Controlled Trial
MeSH Terms:
Adult
Aged
Amino Acid Sequence
Blood Glucose/drug effects
Blood Glucose/metabolism*
Cross-Over Studies
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Eating

Female
Hemoglobin A, Glycosylated/analysis
Humans
Hyperglycemia/chemically induced
Hyperglycemia/epidemiology
Hyperglycemia/prevention & control*
Hypoglycemic Agents/therapeutic use*
Incidence
Insulin/adverse effects
Insulin/analogs & derivatives*
Insulin/chemistry
Insulin/therapeutic use*
Male
Middle Aged
Molecular Sequence Data
Recombinant Proteins/therapeutic use
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Recombinant Proteins
Insulin
insulin LISPRO
60.Diabet Med. 1996 Jan;13(1):47-52.

Pre-meal insulin analogue insulin lispro vs Humulin R insulin treatment in young subjects with type 1 diabetes.
Garg SK, Carmain JA, Braddy KC, Anderson JH, Vignati L, Jennings MK, Chase HP.

Department of Paediatrics, University of Colorado Health Sciences Center, Denver, USA.

Abstract
The present prospective one-year randomized study was conducted to compare soluble human insulin, with a new rapid-acting human insulin analogue, lispro, with respect to postprandial glucose excursions, frequency of hypoglycaemic episodes, glucose control, and long-term safety in 39 subjects (20 females, 19 males) with Type 1 diabetes. The duration of diabetes, gender distribution, and age were similar in the two groups. The total number of hypoglycaemic episodes was significantly less ($p < 0.04$, Wilcoxon rank sum test) in subjects receiving insulin lispro compared with regular human insulin over the 12-month period. The 2-h postprandial glucose excursion at 1 year was also significantly less ($p < 0.05$, ANOVA) in the group treated with insulin lispro. The reductions in the total number of hypoglycaemic episodes and in the postprandial glucose excursion with use of insulin lispro may be beneficial for the long-term management of subjects with Type 1 diabetes. However, the greatest benefit identified by the subjects receiving insulin lispro was the greater convenience of the rapid-acting analogue.

PMID: 8741812 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Amino Acid Sequence
Analysis of Variance
Blood Glucose/drug effects
Blood Glucose/metabolism
Child
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Drug Administration Schedule
Eating
Female
Hemoglobin A, Glycosylated/analysis
Humans
Hypoglycemia/chemically induced
Hypoglycemia/epidemiology
Hypoglycemic Agents/adverse effects
Hypoglycemic Agents/chemistry
Hypoglycemic Agents/therapeutic use*
Insulin/adverse effects
Insulin/analogs & derivatives*
Insulin/chemistry
Insulin/therapeutic use*
Male
Molecular Sequence Data
Prospective Studies
Recombinant Proteins/therapeutic use
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Recombinant Proteins
Insulin
insulin LISPRO
61.Horm Metab Res. 1995 Sep;27(9):421-4.

Insulinkinetic and -dynamic in diabetic patients under insulin pump therapy after injections of human insulin or the insulin analogue (B28Asp).
Wiefels K, Hübinger A, Dannehl K, Gries FA.

Diabetes-Forschungsinstitut an der Heinrich Heine Universität Düsseldorf, Germany.

Abstract
In this double blind randomized study we compared the insulinkinetic, insulindynamic and the frequency of hypoglycemic events after s.c. injection of human insulin and the insulin analogue (B28Asp). Fourteen c-peptide negative patients treated with continuous subcutaneous insulin infusion (CSII) were included in the study. Their mean age was 42.9 (range 26-60 yrs), duration of diabetes 18.5 (5-29) and mean duration of CSII 6.3 yrs (3-10).

Serum free insulin (FIRI) was determined from 8:00 to 11:00 h, and blood glucose from 7:00 to midnight. Maximum FIRI values were obtained after 45 min for (B28Asp) and after 90 min for Actrapid HM. Maximum blood glucose increase (Tmax) was obtained 60 min after injection of (B28Asp) and 90 min after Actrapid HM. The AUCBC was greater after administration of Actrapid HM compared to (B28Asp) ($p < or = 0.05$). A total number of 16 hypoglycemias (BG < or = 3.3 mmol.l-1) were registered. 8 episodes were induced equally by (B28Asp) and by Actrapid HM. We conclude that in insulin dependent diabetic patients the insulin analogue (B28Asp) showed a faster absorption and less hyperinsulinemia than Actrapid HM after s.c. administration. The corresponding BG-values were higher after s.c. administration of Actrapid HM compared to (B28Asp). These findings in patients support the concept of a more physiological effect of rapid acting insulin analogues than of regular insulin.

PMID: 8557242 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adult
Blood Glucose/metabolism
Cross-Over Studies
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 1/metabolism*
Double-Blind Method
Female
Humans
Hypoglycemia/blood
Hypoglycemia/chemically induced
Hypoglycemic Agents/administration & dosage
Hypoglycemic Agents/pharmacokinetics*
Hypoglycemic Agents/therapeutic use
Infusion Pumps, Implantable
Insulin/administration & dosage
Insulin/analogs & derivatives*
Insulin/pharmacokinetics
Insulin/therapeutic use
Insulin Infusion Systems
Male
Middle Aged
Substances:
Blood Glucose
Hypoglycemic Agents
insulin aspart
Insulin
62.Diabetologia. 1995 Jan;38(1):106-11.

Exercise-induced hypoglycaemia in IDDM patients treated with a short-acting insulin analogue.

Tuominen JA, Karonen SL, Melamies L, Bolli G, Koivisto VA.

Second Department of Medicine Helsinki University Central Hospital, Finland.

Abstract

In order to examine the effect of short-acting insulin analogue on the exercise-induced hypoglycaemia in insulin-dependent diabetes mellitus (IDDM) patients we compared the glycaemic response of 40 min cycle ergometer exercise performed either shortly (40 min) or later (180 min) after a breakfast meal and subcutaneous injection of either short-acting insulin analogue [Lys(B28) Pro(B29)] or soluble human insulin (Humulin Regular) in ten IDDM patients with long duration of the disease. Both preparations had been used 1 month before respective studies. Changes in blood glucose, insulin and counterregulatory hormones were assayed. As compared to human insulin, after the analogue injection the peak insulin concentration came earlier, was 56% higher ($p < 0.05$) and disappeared faster, and the postprandial blood glucose response was lower ($p < 0.05$). In the analogue-treated patients the exercise-induced hypoglycaemia was 2.2-fold greater ($p < 0.01$) during the early exercise, but 46% less ($p < 0.05$) during late exercise as compared to the treatment with human insulin. Serum insulin or analogue concentration at the beginning of the exercise correlated closely with the fall in blood glucose during exercise ($r = 0.74$, $p < 0.01$; $r = 0.73$, $p < 0.02$, respectively). In the analogue-treated patients, fasting serum glucagon and adrenalin concentrations were higher than during human insulin therapy ($p < 0.05$) and remained so throughout the study.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 7744214 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Research Support, Non-U.S. Gov't
MeSH Terms:
Adult
Blood Glucose/analysis
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/complications*
Exercise*
Female
Glucagon/blood
Humans
Hypoglycemia/blood
Hypoglycemia/drug therapy
Hypoglycemia/etiology*
Insulin/blood
Insulin/therapeutic use*
Male
Substances:
Blood Glucose
Insulin
Glucagon
63.Br J Clin Pharmacol. 1991 Nov;32(5):563-7.

Preventive effects of octreotide (SMS 201-995) on diabetic ketogenesis during insulin withdrawal.

Diem P, Robertson RP.

Department of Medicine, University of Bern, Switzerland.

Abstract
1. Exogenous somatostatin inhibits glucagon secretion and prevents ketoacidosis in diabetic patients, but has the therapeutic disadvantage of requiring continuous intravenous infusion to exhibit these effects. 2. Consequently, we examined the effect of subcutaneous administration of the long-acting somatostatin analogue octreotide (SMS 201-995) on early ketogenesis in diabetic ketoacidosis. On two separate occasions insulin was withdrawn over a period of 9 h from seven type I diabetic patients. On the second occasion the patients were given 50 micrograms octreotide s.c. before the insulin withdrawal and every 3 h during insulin withdrawal. 3. Differences in integrated free fatty acid responses (4706 +/- 1227 mumol l-1 h vs 3026 +/- 835 mumol l-1 h, AUC, P = NS) were not significant, but the peak increments of acetoacetate (1413 +/- 354 mumol l-1 vs 612 +/- 176 mumol l-1, P less than 0.05), beta-hydroxybutyrate (2180 +/- 475 mumol l-1 vs 922 +/- 246 mumol l-1, P less than 0.01) and the decrements in plasma bicarbonate (-8 +/- 1 mumol l-1 vs -4 +/- 1 mumol l-1, P less than 0.05) and pH (-0.07 +/- 0.01 vs -0.03 +/- 0.01, P less than 0.05) were significantly less with octreotide. 4. At the same time peak increments of glucagon were lower with octreotide treatment (329 +/- 206 pg ml-1 vs 39 +/- 30 pg ml-1, P less than 0.05). 5. We conclude that, despite accelerated lipolysis and provision of substrate for ketogenesis during insulin withdrawal, this somatostatin analogue significantly reduces ketogenesis resulting from insulin deprivation, probably secondary to decreasing glucagon secretion. This drug may be useful in short term prophylactic treatment of diabetic patients during periods of increased risk for ketoacidosis.

PMID: 1954071 [PubMed - indexed for MEDLINE]PMCID: PMC1368631Free PMC Article

Related citations

Publication Types, MeSH Terms, Substances, Grant SupportPublication Types:
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
MeSH Terms:
Adult
Blood Glucose/analysis
Diabetes Mellitus, Type 1/drug therapy
Diabetic Ketoacidosis/drug therapy
Diabetic Ketoacidosis/prevention & control*
Fatty Acids, Nonesterified/blood
Glucagon/blood
Humans
Insulin/therapeutic use*
Ketone Bodies/blood
Octreotide/therapeutic use*
Substances:
Blood Glucose
Fatty Acids, Nonesterified

Ketone Bodies
Insulin
Octreotide
Glucagon
Grant Support:
M01-RR-00400/RR/NCRR NIH HHS/United States
64.Diabetes Care. 1991 Jul;14(7):571-7.

Comparison of subcutaneous soluble human insulin and insulin analogues (AspB9, GluB27; AspB10; AspB28) on meal-related plasma glucose excursions in type I diabetic subjects.
Kang S, Creagh FM, Peters JR, Brange J, Vølund A, Owens DR.

Department of Medicine, University of Wales College of Medicine, Cardiff, United Kingdom.

Abstract
OBJECTIVE: To compare postprandial glucose excursions and plasma free insulin-analogue levels after subcutaneous injection of three novel human insulin analogues (AspB10; AspB9, GluB27; and AspB28) with those after injection of soluble human insulin (Actrapid HM U-100).

RESEARCH DESIGN AND METHODS: Six male subjects with insulin-dependent diabetes, at least 1 wk apart and after an overnight fast and basal insulin infusion, received 72 nmol (approximately 12 U) s.c. of soluble human insulin 30 min before, or 72 nmol of each of the three analogues immediately before, a standard 500-kcal meal.

RESULTS: Mean basal glucoses were similar on the 4 study days. Compared to human insulin (6.3 +/- 0.8 mM), mean +/- SE peak incremental glucose rises were similar after analogues AspB10 (5.4 +/- 0.8 mM) and AspB9, GluB27 (5.4 +/- 0.7 mM) and significantly lower after analogue AspB28 (3.6 +/- 1.2 mM, P less than 0.02). Relative to soluble human insulin (100% +/- SE21), incremental areas under the glucose curve between 0 and 240 min were 79% +/- 34 (AspB10, NS), 70% +/- 29 (AspB9, GluB27, NS), and 43% +/- 23 (AspB28, P less than 0.02). Basal plasma free insulin levels were similar on the 4 study days. Plasma free insulin-analogue levels rose rapidly to peak 30 min after injection at 308 +/- 44 pM (AspB10); 1231 +/- 190 pM (AspB9, GluB27) and 414 +/- 42 pM (AspB28) and were significantly higher than corresponding (i.e., 30 min postmeal) plasma free insulin levels of 157 +/- 15 pM (P less than 0.02 in each case).

CONCLUSIONS: Plasma profiles of the insulin analogues were more physiological than that of human insulin after subcutaneous injection. All three analogues given immediately before the meal are at least as effective as soluble human insulin given 30 min earlier. These analogues are promising potential candidates for short-acting insulins of the future.

PMID: 1914797 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:

Clinical Trial
Comparative Study
Controlled Clinical Trial
MeSH Terms:
Adult
Blood Glucose/metabolism*
Diabetes Mellitus, Type 1/blood*
Diabetes Mellitus, Type 1/drug therapy
Diet
Humans
Injections, Subcutaneous
Insulin/administration & dosage
Insulin/analogs & derivatives*
Insulin/blood
Insulin/therapeutic use*
Male
Substances:
Blood Glucose
insulin aspart
insulin, Asp(B10)-
Insulin
insulin, Asp(B9)-Glu(B27)-
65.Diabet Med. 1989 Mar;6(2):103-11.

Somatostatin analogues in diabetes mellitus.
Davies RR, Turner SJ, Alberti KG, Johnston DG.

Ninewells Hospital and Medical School, Dundee, UK.

Abstract
Growth hormone (GH) has long been considered to have importance in diabetes. With poor control in Type 1 diabetes GH levels are high and may aggravate poor metabolic control. Pharmacological suppression of GH release at this stage might reverse the metabolic changes, with the possible added benefit of lower plasma insulin concentrations. Diabetic patients with life-long GH deficiency rarely develop retinopathy, while pituitary ablation in patients with retinopathy often leads to improvement. Growth hormone release inhibiting factor, somatostatin, has a short plasma half-life, and multiple effects on the endocrine system and on the gastrointestinal tract, making it unsuitable for clinical use as a GH suppressant. Long-acting analogues have a long half-life, but remain non-specific in their effects. In Type 2 diabetes the analogue Octreotide suppresses insulin and glucagon release, leaving glucose levels either unchanged or somewhat elevated. Gastrointestinal side-effects have been common, but may diminish with long-term treatment. In Type 1 diabetes insulin requirement is decreased by Octreotide, but as in Type 2 diabetes GH suppression has been observed consistently only when the drug was given at bed-time. The decrease in insulin requirement may reflect suppression of glucagon release and/or gut effects. Amelioration of the 'dawn phenomenon' has not proved possible, and hypoglycaemia has proved a particular problem with Octreotide given subcutaneously at night. The lack of effective GH suppression (particularly in patients with proliferative retinopathy), lack of specificity, and the gut and hypoglycaemic side-effects, argue strongly against a clinical role for the current somatostatin analogues in diabetes mellitus.

PMID: 2564819 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Research Support, Non-U.S. Gov't
Review
MeSH Terms:
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/blood
Diabetes Mellitus, Type 2/drug therapy*
Growth Hormone/physiology
Humans
Octreotide/therapeutic use*
Somatostatin/analogs & derivatives*
Somatostatin/therapeutic use*
Substances:
Somatostatin
Octreotide
Growth Hormone
66.Scand J Gastroenterol Suppl. 1986;119:166-9.

Somatostatin analogue SMS 201-995 in type I diabetes mellitus. Initial experience after repeated administration.
Plewe G, Nölken G, Krause U, del Pozo E, Beyer J.

Abstract
We have recently obtained encouraging short-term results after a single subcutaneous injection of the long-acting somatostatin analogue SMS 201-995 in acromegalic patients. Increased growth hormone (GH) levels may be involved in the pathogenesis of proliferative retinopathy in type I diabetes mellitus. In this study we thus investigated the effect of 3 X 50 micrograms SMS 201-995 daily on the metabolic control and hormone secretion of eight type I diabetics over a 3-day period. GH levels decreased by 32% (p less than 0.05) and somatomedin C levels by 31% (p less than 0.01) on the 3rd day of treatment compared with a control day. The insulin requirements during conventional subcutaneous insulin therapy were reduced by 28% (p less than 0.01) in seven patients without deterioration of metabolic control (mean blood glucose levels, 153.8) versus 154.7 mg/dl). Triiodothyronine, thyroxine, glucagon, prolactin, luteinizing hormone and follicle-stimulating hormone showed no significant changes. We conclude that SMS 201-995 could be an excellent tool for further clinical investigation and therapy of diabetic vascular complications.

PMID: 2876502 [PubMed - indexed for MEDLINE]

Related citations

- Adding the MeSH terms “children” and “adolescents” leads to 19 hits:

Results: 19
1.Drugs. 2009 May 29;69(8):1035-57. doi: 10.2165/00003495-200969080-00006.

Insulin glulisine: a review of its use in the management of diabetes mellitus.
Garnock-Jones KP, Plosker GL.

Wolters Kluwer Health/Adis, 41 Centorian Drive, Mairangi Bay, North Shore 0754, Auckland, New Zealand. demail@adis.co.nz

Abstract
Insulin glulisine (Apidra) is a human insulin analogue approved for the improvement of glycaemic control in adults, adolescents and children with diabetes mellitus. It has similar binding properties, and is associated with a faster onset but similar level of glucose disposal, to regular human insulin (RHI). Insulin glulisine and insulin lispro have similar effects on glucose levels. Insulin glulisine is effective when compared to other short- and rapid-acting insulins, demonstrating either noninferiority, no significant difference, or superiority in primary endpoints in studies involving patients with type 1 and type 2 diabetes. It is more effective and has a faster onset and shorter duration of activity than RHI. Insulin glulisine is as effective as insulin lispro in patients with type 1 diabetes; however, there is a need for further, well designed head-to-head comparisons with insulin lispro in patients with type 2 diabetes and with insulin aspart in patients with type 1 or type 2 diabetes to fully establish the place of insulin glulisine in the management of diabetes. Insulin glulisine has a flexible administration period, as it can be administered immediately before or after meals. Hypoglycaemia, a common risk with insulins, occurs at a similar rate among recipients of insulin glulisine to that seen with other insulins. Thus, insulin glulisine is an effective and well tolerated option for the treatment of patients with type 1 and type 2 diabetes.

PMID: 19496630 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Adolescent
Adult
Blood Glucose/drug effects
Child
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/drug therapy*
Humans
Hypoglycemia/chemically induced
Hypoglycemic Agents/adverse effects
Hypoglycemic Agents/pharmacokinetics
Hypoglycemic Agents/pharmacology*
Insulin/adverse effects
Insulin/analogs & derivatives*
Insulin/pharmacokinetics
Insulin/pharmacology
Substances:
Blood Glucose
Hypoglycemic Agents
Insulin
insulin glulisine
2.Diabet Med. 2008 Sep;25(9):1030-5.

Effects of fat supplementation on glycaemic response and gastric emptying in adolescents with Type 1 diabetes.

Lodefalk M, Aman J, Bang P.

Paediatric Endocrinology and Diabetes Unit, Department of Woman and Child Health, Karolinska Institute, Stockholm, Sweden. mskorre@hem.utfors.se

Abstract

AIMS: To compare the glycaemic response to meals with different fat content in adolescents with Type 1 diabetes mellitus (T1DM) and to investigate associations with gastric emptying.

METHODS: In this randomized, cross-over study, paired results were obtained from seven adolescents with T1DM who ingested on different days two meals with the same carbohydrate and protein content, but different fat and energy content (2 and 38 g fat, 320 and 640 kcal, respectively). Paracetamol was mixed into the meals and gastric emptying was estimated by the paracetamol absorption method. All subjects were normoglycaemic and given 7 IU insulin aspart at commencement of ingestion. Postprandial blood samples were taken during 4 h.

RESULTS: The areas under the curves for plasma glucose and serum paracetamol concentrations were larger after the low-fat than after the high-fat meal during the first 2 h ($P = 0.047$ and $P = 0.041$, respectively). The difference between meals in time-to-peak in glucose and paracetamol concentrations did not reach statistical significance (high-fat vs. low-fat meal: 210 min (120-240) vs. 120 min (50-240), $P = 0.080$ and 120 min (75-180) vs. 60 min (60-120), $P = 0.051$, respectively). Changes in glucose concentrations correlated with simultaneous changes in paracetamol concentrations ($P < 0.001$).

CONCLUSIONS: For the first time, we have shown that the initial glycaemic response is reduced after a meal with higher compared with a meal with lower fat content in adolescents with T1DM given a rapid-acting insulin analogue preprandially. The type and dose of preprandial insulin may need adjustment to the fat content of the meal to reach postprandial normoglycaemia.

PMID: 19183308 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Acetaminophen/pharmacokinetics
Adolescent
Area Under Curve
Blood Glucose/metabolism*
Cross-Over Studies
Diabetes Mellitus, Type 1/metabolism*
Dietary Fats/administration & dosage*
Female
Gastric Emptying/physiology
Humans

Hypoglycemic Agents/pharmacology*
Insulin/pharmacology*
Intestinal Absorption
Lipid Metabolism/physiology
Male
Postprandial Period
Substances:
Blood Glucose
Dietary Fats
Hypoglycemic Agents
Acetaminophen
Insulin
3.Arch Pediatr. 2006 Sep;13(9):1275-82. Epub 2006 Aug 22.

[Rational use of insulin analogues in the treatment of type 1 diabetic children and adolescents: personal experience]
[Article in French]

Dorchy H.

Clinique de diabétologie, hôpital universitaire des enfants Reine Fabiola, 15, avenue J.-J.-Crocq, 1020 Bruxelles, Belgique. hdorchy@ulb.ac.be

Abstract
In the last decade, four fast- and long-acting insulin analogues have been created. Due to the pharmacokinetic characteristics of insulin analogues, they provide an insulin profile closer to normal physiology than can be achieved with human insulins. However, they do not necessarily improve glycated haemoglobin, but they allow better quality of life. In the two daily insulin injection regime, fast-acting analogues are very useful to rapidly correct hyperglycaemia, to allow sleeping in and eating something sweet. In the basal-bolus regime (> or =4 insulin injections), long-acting analogues reduce nocturnal hypoglycaemias and improve fasting blood glucose. In the two insulin regime (2 or > or =4 injections), rapid-acting human insulin must not be systematically replaced by a fast-acting analogue. On the other hand, insulin dose alteration must be triple: retrospective, according to numerous previous experiments, in order to enjoy more freedom for meals, sports, etc.; prospective according to programmed changes in meals and sports; with only a "touch" of compensatory adaptation according to actual glycaemia.

PMID: 16920339 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
English Abstract
Review
MeSH Terms:
Adolescent
Child
Delayed-Action Preparations
Diabetes Mellitus, Type 1/drug therapy*
Hemoglobin A, Glycosylated/analysis

Humans
Hypoglycemic Agents/therapeutic use*
Insulin/analogs & derivatives*
Insulin/therapeutic use*
Substances:
Delayed-Action Preparations
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Insulin
4.Diabet Med. 2006 Aug;23(8):879-86.

Twice-daily compared with once-daily insulin glargine in people with Type 1 diabetes using meal-time insulin aspart.
Ashwell SG, Gebbie J, Home PD.

University of Newcastle upon Tyne, Newcastle upon Tyne, UK. s.g.ashwell@ncl.ac.uk

Abstract
AIM: To compare blood glucose control when using insulin glargine twice daily at breakfast- and dinner-times with insulin glargine once daily at dinner time, in unselected people with Type 1 diabetes using insulin aspart at meal-times.

METHODS: In this 8-week, two-way, cross-over study, 20 people with Type 1 diabetes were randomized to insulin glargine injection once daily at dinner-time or twice daily at breakfast- and dinner-times, both plus meal-time insulin aspart. Each 4-week treatment period concluded with a 24-h inpatient metabolic profile.

RESULTS: Insulin doses, HbA1c, fructosamine concentration and pre-breakfast self-monitored blood glucose (SMBG) concentration did not differ between treatment periods. SMBG concentrations after breakfast, after lunch and before dinner were lower with twice-daily compared with once-daily dinner-time glargine [9.3 +/- 0.5 (+/- se) vs. 6.7 +/- 0.5 mmol/l, P = 0.003; 10.2 +/- 0.9 vs. 7.0 +/- 0.9 mmol/l, P = 0.024; 9.6 +/- 0.5 vs. 6.6 +/- 0.5 mmol/l, P = 0.001]. Mean 24-h SMBG concentration was lower with twice-daily glargine (7.1 +/- 0.5 vs. 8.8 +/- 0.5 mmol/l, P = 0.031). Within-day variability of SMBG concentration was lower with twice-daily glargine (sd 3.2 +/- 0.2 vs. 4.0 +/- 0.3 mmol/l, P = 0.044). Plasma free insulin concentration was higher in the afternoon with twice-daily glargine (21.9 +/- 1.4 vs. 16.1 +/- 1.3 mU/l, P = 0.009), but lower overnight (12.1 +/- 1.7 vs. 17.8 +/- 1.7 mU/l, P = 0.030), compared with once-daily injection. Plasma glucose concentration overnight was higher with twice-daily compared with once-daily glargine (mean 9.0 +/- 0.4 vs. 6.6 +/- 0.4 mmol/l, P = 0.001).

CONCLUSIONS: Blood glucose concentration rises in the late afternoon in association with falling plasma insulin levels towards the end of the 24-h period after insulin glargine injection in some people with Type 1 diabetes using once-daily glargine at dinner-time plus a rapid-acting insulin analogue at meal-times. This is prevented by twice-daily injection of insulin glargine.

PMID: 16911626 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Comparative Study
Randomized Controlled Trial
MeSH Terms:
Adolescent
Adult
Aged
Blood Glucose/metabolism
Cross-Over Studies
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Drug Administration Schedule
Female
Humans
Hypoglycemic Agents/administration & dosage*
Hypoglycemic Agents/blood
Insulin/administration & dosage
Insulin/analogs & derivatives*
Insulin/blood
Male
Middle Aged
Treatment Outcome
Substances:
Blood Glucose
Hypoglycemic Agents
glargine
Insulin
5.J Pediatr. 2006 Apr;148(4):481-4.

Mixing rapid-acting insulin analogues with insulin glargine in children with type 1 diabetes mellitus.
Fiallo-Scharer R, Horner B, McFann K, Walravens P, Chase HP.

Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, Denver, Colorado, USA. rosanna.fiallo-scharer@uchsc.edu

Abstract
OBJECTIVE: To determine whether mixing insulin glargine (IG) with a rapid-acting insulin (RAI) analogue in the same syringe had any deleterious effects on glycemic control in children with type 1 diabetes mellitus.

STUDY DESIGN: Data from 55 children mixing the IG with a RAI analogue was collected for 6 months before and 6 months after the insulin mixing began. Data from a control group of 55 children not mixing the insulins was collected at similar intervals. Parameters evaluated included hemoglobin A1c (HbA1c) values, number of non-severe and severe hypoglycemic events, number of diabetic ketoacidosis (DKA) events, and blood glucose distribution patterns.

RESULTS: After 6 months of study, HbA1c values were equivalent for the control and test groups (8.54+/-1.14 vs 8.61+/-1.14, respectively; P=1.0000). Percentages of blood glucose values in, above, and below the target range did not vary significantly in the groups. There were no significant differences in the groups in the occurrence of non-severe or severe hypoglycemic events or of DKA events.

CONCLUSION: There were no significant differences in glycemic control between children who mixed IG in the same syringe with a RAI analogue compared with children who took separate injections.

PMID: 16647408 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, Substances, Grant SupportPublication Types:
Controlled Clinical Trial
Research Support, N.I.H., Extramural
MeSH Terms:
Adolescent
Child
Diabetes Mellitus, Type 1/drug therapy*
Diabetic Ketoacidosis/chemically induced
Drug Combinations
Female
Humans
Hypoglycemia/chemically induced
Injections
Insulin/administration & dosage*
Insulin/adverse effects
Insulin/analogs & derivatives*
Male
Matched-Pair Analysis
Patient Compliance
Prospective Studies
Regression Analysis
Substances:
Drug Combinations
glargine
Insulin
Grant Support:
M01 RR00069/RR/NCRR NIH HHS/United States
6.Acta Diabetol. 2005 Dec;42(4):156-61.

Metabolic control and educational status in children with type 1 diabetes: effects of a summer camp and intensive insulin treatment.
Karagüzel G, Bircan I, Erisir S, Bundak R.

Department of Pediatrics, Division of Pediatric Endocrinology, School of Medicine, Akdeniz University, Antalya, Turkey. gulaykg@akdeniz.edu.tr

Abstract
Our aim was to evaluate prospectively, in our diabetic patients, the impacts of a summer camp and intensive insulin treatment (IIT) on both metabolic control and disease-related educational level. Twenty-five patients participated in a 7-day-long summer camp. Before the camp, all patients were on therapy with short-acting human insulin (SAI) and intermediate-acting insulin (IAI) twice daily. On arrival, their insulin therapy regimen was changed by IIT including either SAI or rapid-acting insulin analogue (RAI) three times before meals supplemented by IAI at bedtime. Following the camp, all participants were given IIT with RAI plus IAI. Frequency of hypoglycaemia, insulin dose, body mass index (BMI) and glycohaemoglobin (HbA1c) levels were assessed at pre-camp and post-camp controls. To evaluate the effectiveness of camp-assisted education, all participants were regularly tested. We observed significant elevations in total daily dose of insulin and BMI at months 3 and 6 when compared with the pre-camp values but, by month 12, they were not significantly different from precamp values. The mean HbA(1c) level decreased significantly at months 6 and 12. Severe hypoglycaemic episodes and ketoacidosis were not detected during the camp and the following year. Significant improvements in knowledge about diabetes and self-management were determined at the end of the camp, after 6 and 12 months. Camp-assisted IIT with RAI improved metabolic control of diabetic children. Additionally, camp-assisted education has a positive effect on disease-related educational level and self-management.

PMID: 16382302 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adolescent
Blood Glucose/drug effects
Blood Glucose/metabolism*
Body Mass Index
Camping*
Child
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy
Diabetes Mellitus, Type 1/rehabilitation*
Educational Status
Female
Hemoglobin A, Glycosylated/metabolism
Humans
Hypoglycemic Agents/therapeutic use
Insulin/therapeutic use*
Male
Patient Selection
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Insulin
7.Drugs. 2004;64(17):1957-74.

Insulin aspart: a review of its use in the management of type 1 or 2 diabetes mellitus.

Reynolds NA, Wagstaff AJ.

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Abstract
Insulin aspart (NovoRapid, NovoLog) is a short-acting insulin analogue, which has a faster onset and shorter duration of action than regular human insulin. Insulin aspart administered immediately before meals provided significantly greater improvements in glycosylated haemoglobin and better postprandial glycaemic control than regular human insulin administered 30 minutes before meals, when used in a basal-bolus regimen with neutral protamine Hagedorn (NPH) insulin, in randomised, nonblind studies in patients with type 1 diabetes mellitus. In patients with type 2 diabetes, insulin aspart provided similar glycaemic control to regular human insulin, administered in a basal-bolus regimen with NPH insulin. Small studies suggest that the use of insulin aspart in combination with oral hypoglycaemic agents may be beneficial. Insulin aspart, administered by continuous subcutaneous insulin infusion (CSII) provided better glycaemic control than insulin aspart multiple daily injection regimens in patients with type 1 (but not type 2) diabetes, and had similar efficacy to CSII with insulin lispro or regular human insulin in type 1 diabetes. Limited studies show insulin aspart to be effective in children, adolescents and young adults with type 1 diabetes. Insulin aspart had a tolerability profile similar to that of regular human insulin in clinical trials. The incidence of major or nocturnal hypoglycaemic events reported in patients receiving insulin aspart was lower than that of regular human insulin in several studies. In conclusion, insulin aspart, administered immediately before meals in a basal-bolus regimen with NPH insulin, provided better long-term glycaemic control than regular human insulin administered 30 minutes before meals in patients with type 1 diabetes, and was as effective as regular human insulin in patients with type 2 diabetes. A significantly lower risk of hypoglycaemia was seen in several trials. Insulin aspart CSII provided better glycaemic control than insulin aspart multiple daily subcutaneous injection (MDI) in patients with type 1 (but not type 2) diabetes and had similar efficacy to CSII with insulin lispro or regular human insulin in type 1 diabetes. Insulin aspart is an effective and well tolerated alternative to regular human insulin and insulin lispro for the maintenance of glycaemic control in patients with type 1 or 2 diabetes.

PMID: 15329046 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Adolescent
Adult
Blood Glucose
Child
Clinical Trials as Topic
Diabetes Mellitus/blood
Diabetes Mellitus/drug therapy*
Drug Therapy, Combination
Humans

Hypoglycemic Agents/pharmacology*
Hypoglycemic Agents/therapeutic use*
Insulin/analogs & derivatives*
Insulin/pharmacology*
Insulin/therapeutic use*
Lipids/blood
Quality of Life
Substances:
Blood Glucose
Hypoglycemic Agents
Lipids
insulin aspart
Insulin
8.Diabet Med. 2004 Jul;21(7):769-75.

Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with Type 1 diabetes.

Heller SR, Colagiuri S, Vaaler S, Wolffenbuttel BH, Koelendorf K, Friberg HH, Windfeld K, Lindholm A.

Northern General Hospital, Sheffield S5 7AU, UK. S.Heller@sheffield.ac.uk

Abstract

AIMS: To compare the effects of the rapid-acting insulin analogue insulin aspart and soluble human insulin on hypoglycaemia and glycaemic control in patients with Type 1 diabetes when injected immediately before meals as part of intensive insulin therapy.

METHODS: In this multinational, double-blind, randomised, crossover trial, 155 patients with Type 1 diabetes (HbA(1c) < 8.0%) were symmetrically randomised to two 16-week treatment periods on either type of insulin, both injected 0-5 min before meals. NPH insulin was given as basal insulin once or twice daily as needed, and insulin dosages were regularly adjusted using pre-defined algorithms to maintain tight glycaemic control. Treatment periods were separated by a 4-week washout.

RESULTS: The rate of major nocturnal (24.00-06.00 h) hypoglycaemic episodes was 72% lower with insulin aspart than with human insulin (0.067 vs. 0.225 events/month; P = 0.001). Total rate of major hypoglycaemia did not differ significantly between treatments (insulin aspart/human insulin relative risk 0.72; 95% CI 0.47-1.09, P = 0.12). The rate of minor events was significantly reduced by 7% with insulin aspart (P = 0.048). Reductions in rate of hypoglycaemia were achieved with maintained overall glycaemic control: Mean HbA(1c) remained constant, slightly below 7.7% on both treatments.

CONCLUSIONS: The use of insulin aspart in an intensive insulin regimen in patients with tightly controlled Type 1 diabetes led to clinically significant reductions in major nocturnal hypoglycaemia with no deterioration in glycaemic control. Major nocturnal hypoglycaemia appears to be a strong clinical indication for the use of rapid-acting insulin analogues during intensive insulin therapy.

PMID: 15209772 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adolescent
Adult
Aged
Blood Glucose/metabolism
Circadian Rhythm
Cross-Over Studies
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/complications
Diabetes Mellitus, Type 1/drug therapy*
Double-Blind Method
Drug Administration Schedule
Female
Hemoglobin A, Glycosylated/metabolism
Humans
Hypoglycemia/etiology
Hypoglycemia/prevention & control*
Hypoglycemic Agents/therapeutic use*
Insulin/analogs & derivatives*
Insulin/therapeutic use*
Insulin, NPH/therapeutic use
Male
Middle Aged
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
insulin aspart
Insulin
Insulin, NPH
9.Diabetes Care. 2003 Aug;26(8):2359-64.

A comparison of postprandial and preprandial administration of insulin aspart in children and adolescents with type 1 diabetes.
Danne T, Aman J, Schober E, Deiss D, Jacobsen JL, Friberg HH, Jensen LH; ANA 1200 Study Group.

Kinderkrankenhaus auf der Bult, Diabetes-Zentrum für Kinder und Jugendliche, Hannover, Germany. danne@hka.de

Abstract
OBJECTIVE: The aim of this study was to compare the glycemic control of preprandial versus postprandial injections of the new rapid-acting insulin analogue aspart in children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS: Forty-two children (aged 6-12 years) and 34 adolescents (13-17 years) were randomized to preprandial (immediately before meal start) and postprandial (immediately after a meal or a maximum of 30 min after meal start) treatment with insulin aspart (at least thrice daily) as part of a basal/bolus regimen in a multicenter study with an open labeled, two-period cross-over design (6-week periods). Of this group, 49% were boys, 55% were aged <or=13 years, and duration of diabetes was 4.4 years (range 1.0-9.4).

RESULTS: Glycemic control for postprandial treatment was not worse than preprandial treatment as assessed by fructosamine week 0 vs. 6 (mean +/- SD, preprandial 367 +/- 74 vs. 378 +/- 90 micro mol/l; postprandial 383 +/- 83 vs. 385 +/- 77 micro mol/l) and HbA(1c) (preprandial 7.9 +/- 1.3 vs. 8.0 +/- 1.5%; postprandial 8.0 +/- 1.4 vs. 8.3 +/- 1.5%, P = 0.14). The only statistically significant finding from the seven-point blood glucose profiles and derived parameters between preprandial and postprandial treatment was a lower postprandial glucose level 120 min after breakfast (mean +/- SEM, -2.08 +/- 0.74 mmol/l, P = 0.016). The relative risk of hypoglycemia (blood glucose <3.9 mmol/l) preprandially to postprandially was not significantly different (mean 1.1; 95% CI 0.91-1.35; P = 0.31). Overall treatment satisfaction was equally high for both regimens with both patients and parents.

CONCLUSIONS: Although preprandial administration of insulin aspart is generally preferable, this study shows that in children and adolescents, postprandial administration of insulin aspart is a safe and effective alternative.

PMID: 12882862 [PubMed - indexed for MEDLINE]Free Article

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adolescent
Blood Glucose/drug effects
Child
Cross-Over Studies
Diabetes Mellitus, Type 1/drug therapy*
Female
Humans
Hypoglycemic Agents/administration & dosage*
Hypoglycemic Agents/adverse effects
Hypoglycemic Agents/pharmacokinetics
Insulin/administration & dosage*
Insulin/adverse effects
Insulin/analogs & derivatives
Insulin/pharmacokinetics
Male
Postprandial Period

Treatment Outcome
Substances:
Blood Glucose
Hypoglycemic Agents
insulin aspart
Insulin
10.Horm Res. 2002;57 Suppl 1:46-53.

Experience with insulin analogues in children.
Danne T, Deiss D, Hopfenmüller W, von Schütz W, Kordonouri O.

Diabetes-Zentrum für Kinder und Jugendliche, Kinderkrankenhaus auf der Bult, Hannover, Germany. danne@hka.de

Abstract
Current data on rapid and long-acting insulin analogues in the paediatric age group is limited. While several studies indicate a benefit in reducing hypoglycaemia, particularly at night, with rapid or long-acting insulin analogue treatment, the effect on long-term glycaemic control remains controversial. The continuous glucose monitoring system offers a new option for tailoring treatment with insulin analogues to achieve optimal glycaemia. In 29 adolescents with diabetes this approach confirmed the non-inferiority of postprandial rapid-acting analogue administration compared to preprandial regular insulin, but revealed significant mealtime differences, with increased analogue requirement at breakfast and dinner. Although rapid- and long-acting insulin analogues may offer potential benefits for problems frequently encountered in paediatric diabetology, their value for the individual child still has to be tested in long-term observations in daily clinical practice.

PMID: 11979022 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Blood Glucose/analysis
Child
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 1/physiopathology
Drug Combinations
Humans
Infusion Pumps
Insulin/analogs & derivatives*
Safety
Substances:
Blood Glucose
Drug Combinations
Insulin
11.Diabetes Nutr Metab. 2001 Dec;14(6):349-57.

The potential role of insulin analogues in the treatment of children and adolescents with Type

1 diabetes mellitus.

Mohn A, Dunger DB, Chiarelli F.

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Abstract
The main therapeutic challenge in the treatment of Type 1 diabetes is maintenance of near-normoglycaemia in order to prevent long-term complications and avoid hypoglycaemia. This goal is relevant from the onset of the disease and is feasible if physiological models of insulin replacement are used and patients are educated in the strategy of intensive insulin therapy. Although the use of available insulins within a multiple injection regimen has improved, metabolic control it is still far from being optimal. The recent introduction of insulin analogues with a short- and long-acting profile seems promising in improving metabolic control and quality of care. Insulin lispro and insulin aspart, the short-acting insulin analogues offer a better post-prandial profile, while insulin glargine the new long-acting insulin analogue might provide better overnight control. In fact, the theoretical combination of an acute prandial insulin peak with a flat interprandial and overnight plasma profile would closely mimic the 24-hr insulin profile of non-diabetic individuals. This would possibly lead to lower post-prandial blood glucose excursion and better fasting blood glucose associated with minimal risk of hypoglycaemia. The possible reduction of hypoglycaemia is especially important in children as recurrent episodes might represent a potential risk for cognitive impairment. However, recent clinical research on the short-acting insulin analogues demonstrates the difficulties of translating these theoretical benefits into clinical relevant advantages. This might happen to other insulin analogues and requires further and larger studies in order to fully exploit the theoretical advantages of insulin analogues in the paediatric population. Safety issues should also be carefully monitored when introducting analogues in long-term therapy.

PMID: 11853368 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Adolescent
Child
Circadian Rhythm
Diabetes Mellitus, Type 1/drug therapy*
Food
Hemoglobin A, Glycosylated
Humans
Insulin/analogs & derivatives*
Insulin/blood
Insulin/pharmacokinetics
Insulin/therapeutic use
Kinetics
Substances:
Hemoglobin A, Glycosylated
Insulin
12.Expert Opin Pharmacother. 2002 Feb;3(2):183-95.

Insulin aspart: promising early results borne out in clinical practice.

Heller S, Kurtzhals P, Verge D, Lindholm A.

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Abstract
The novel, rapid-acting insulin analogue insulin aspart (IAsp; Novo Nordisk) has been shown in preclinical studies to be more rapidly absorbed than human insulin (HI) when administered subcutaneously. IAsp reaches higher peak serum concentrations in a shorter time than HI, whilst maintaining a similar receptor binding and safety profile. The physiological pharmacokinetic profile of IAsp compared to that of HI has been demonstrated in both adult and paediatric populations and was accompanied by small but statistically significant reductions in HbA(1c), lower postprandial glucose excursions and a reduced risk of late postprandial and major nocturnal hypoglycaemia. Benefits may be maximised by dose optimisation, using bolus doses that result in effective postprandial glucose reduction, as well as higher and multiple basal insulin doses. The safety profile, including cardiovascular risk, is equivalent to HI.

PMID: 11829732 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Research Support, Non-U.S. Gov't
Review
MeSH Terms:
Adolescent
Blood Glucose/analysis
Child
Clinical Trials as Topic
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy
Diabetes Mellitus, Type 2/blood
Diabetes Mellitus, Type 2/drug therapy
Drug Evaluation
Humans
Hypoglycemia/chemically induced
Hypoglycemic Agents/adverse effects
Hypoglycemic Agents/blood
Hypoglycemic Agents/pharmacokinetics*
Insulin/adverse effects
Insulin/analogs & derivatives
Insulin/blood
Insulin/pharmacokinetics*
Substances:
Blood Glucose
Hypoglycemic Agents
insulin aspart
Insulin

13.Diabetes Nutr Metab. 2001 Oct;14(5):292-304.

Intensive insulin treatment in diabetic children.

Ludvigsson J, Bolli GB.

Department of Health and Environment, Linköping University, Sweden.

Abstract
Intensification of insulin therapy which maintains long-term near-normoglycaemia (HbA1c<7.0%) strongly protects against onset and/or progression of diabetic microangiopathy in Type 1 diabetes mellitus of adults. Similar intensification of insulin therapy is needed in diabetic children as well, in order to prevent complications a few years after diabetes onset, ie very often in young age. Provided adequate psychosocial support and education are available, children should be treated with multiple daily injections of insulin or, when necessary, with continuous subcutaneous insulin infusion, along with blood glucose monitoring. Insulin regimens may differ from child to child and vary from day to day in the same child, depending on lifestyle and considering all the available insulin preparations. These include the short-acting insulin (both human regular and short-acting insulin analogues), the intermediate-acting insulin (NPH and Lente), as well as the new long-acting insulin analogue glargine. The latter seems a promising candidate to substitute of basal insulin. The concern that intensified insulin therapy increases the risk of hypoglycaemia, as indicated by the Diabetes Control and Complications Trial (DCCT), is no longer tenable. On the contrary, a physiological, flexible insulin regimen better than a fixed insulin regimen, usually the twice daily split-mixed regimen, protects against the risk of hypoglycaemia in relation to food ingestion, physical exercise and sleep. Thus, appropriate education should be delivered at diabetes onset to the child and parents in order to start the strategy of intensified insulin therapy as early as possible.

PMID: 11806471 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Blood Glucose/analysis*
Blood Glucose Self-Monitoring
Child
Diabetes Mellitus, Type 1/drug therapy*
Diabetic Angiopathies/prevention & control*
Drug Administration Schedule
Humans
Hypoglycemia/prevention & control
Hypoglycemic Agents/therapeutic use*
Injections
Insulin/therapeutic use*
Insulin Infusion Systems
Patient Education as Topic
Substances:
Blood Glucose
Hypoglycemic Agents

Insulin
14.Diabet Med. 2001 Nov;18(11):864-70.

Recent advances in treatment of youth with Type 1 diabetes: better care through technology.
Tamborlane WV, Bonfig W, Boland E.

Department of Paediatrics and the Children's Clinical Research Center, Yale University School of Medicine, New Haven, CT 06520, USA. William.Tamborlane@Yale.udu

Comment in:

Diabet Med. 2001 Nov;18(11):861-3.

Abstract
While treatment of Type 1 diabetes mellitus (T1DM) in children and adolescents is especially difficult, recent technological advances have provided new therapeutic options to clinicians and patients. The urgency to achieve strict diabetes control and the introduction of new and improved insulin pumps have been accompanied by a marked increase in use of continuous subcutaneous insulin infusion (CSII) therapy in youth with diabetes. Results of clinical outcome studies indicate that CSII provides a safe and effective alternative to multiple daily injection (MDI) therapy, even when employed in a regular clinic setting in a large number of children. The safety and efficacy of CSII is further enhanced by the introduction of lispro and aspart insulin. The sharper peaks and shorter duration of action of these very rapid-acting insulin analogues provides a means to achieve better control of post-prandial hyperglycaemia with less late post-prandial and nocturnal hypoglycaemia. Glargine insulin, a soluble and essentially peakless long-acting insulin analogue, may provide a better basal insulin for MDI regimens, but there are limited published data with this agent in children with T1DM. A number of systems for pulmonary delivery of insulin are in development and preliminary results of Phase III studies have been promising. Like CSII, inhaled insulin allows the child to take bolus insulin doses before each meal without having to take a premeal injection. A major obstacle to effective treatment is that self-monitoring of three to four blood glucose levels a day often misses the marked glycaemic excursions that characterize T1DM in young patients. On the other hand, new continuous glucose sensing systems provide a wealth of data that can be used to optimize basal and bolus therapy, regardless of how insulin is administered. Even more important, we may finally be at the threshold of development of a practically applicable artificial pancreas.

PMID: 11703429 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, Substances, Grant SupportPublication Types:
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Review
MeSH Terms:
Administration, Inhalation
Adolescent
Blood Glucose Self-Monitoring/instrumentation
Blood Glucose Self-Monitoring/methods
Diabetes Mellitus, Type 1/therapy*

Humans
Insulin/administration & dosage
Insulin/analogs & derivatives
Insulin Infusion Systems
Therapeutics/trends*
Substances:
Insulin
Grant Support:
RR06022/RR/NCRR NIH HHS/United States
15.Clin Pharmacokinet. 2001;40(9):641-59.

Clinical pharmacokinetics and pharmacodynamics of insulin aspart.
Lindholm A, Jacobsen LV.

Department of Clinical Pharmacology, Huddinge Hospital, Karolinska Institute, Stockholm, Sweden. andl@novonordisk.com

Abstract
Insulin aspart is a novel rapid-acting insulin analogue with improved subcutaneous absorption properties when compared with soluble human insulin. Pharmacokinetic studies show an absorption profile with a time to reach peak concentration (t(max)) about half that of human insulin, a peak plasma drug concentration (Cmax) approximately twice as high and shorter residence time. The potency and bioavailability of insulin aspart are similar to those of human insulin. The pharmacokinetics of insulin aspart have been studied in healthy Caucasian and Asian-Japanese volunteers, in patients with type 1 and 2 diabetes mellitus, and in children with diabetes, with both pre- and postprandial administration and during continuous subcutaneous insulin infusion (CSII). The pharmacokinetic profile was similar to that of another rapid-acting insulin analogue, insulin lispro, on the basis of published information for that agent. Pharmacodynamic studies show a smaller excursion of postprandial glucose with insulin aspart injected subcutaneously just before the meal compared with soluble human insulin injected 30 minutes before the meal in patients with type 1 diabetes mellitus, and an equivalent control in patients with type 2 diabetes displaying residual insulin production. In a treatment study, glucose excursions evaluated from 24-hour glucose profiles showed less variability with insulin aspart compared with human insulin. Adverse events, including hypoglycaemia-induced ventricular repolarisation and hypoglycaemic threshold and awareness, did not differ between insulin aspart and human insulin. The available data suggest that subcutaneous injections of insulin aspart just before meals better mimic the endogenous insulin profile in blood compared with human insulin, resulting in improved glucose control in a meal-related insulin regimen. This review summarises the clinical pharmacokinetics and pharmacodynamics of insulin aspart in relation to human insulin and insulin lispro.

PMID: 11605714 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Review
MeSH Terms:
Adult

Area Under Curve
Biological Availability
Blood Glucose/drug effects
Child
Clinical Trials as Topic
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 1/metabolism
Diabetes Mellitus, Type 2/drug therapy*
Diabetes Mellitus, Type 2/metabolism
Female
Humans
Hypoglycemic Agents*/pharmacokinetics
Hypoglycemic Agents*/pharmacology
Hypoglycemic Agents*/therapeutic use
Insulin*/analogs & derivatives*
Insulin*/pharmacokinetics
Insulin*/pharmacology
Insulin*/therapeutic use
Intestinal Absorption
Male
Tissue Distribution
Substances:
Blood Glucose
Hypoglycemic Agents
insulin aspart
Insulin
insulin LISPRO
16.Rom J Intern Med. 1998 Jan-Jun;36(1-2):85-96.

Safety and efficacy of insulin lispro in patients with diabetes mellitus.
Cheta D, Strachinariu R, Trifan E, Nicolau A, Ionescu-Tîrgoviste C, Georgescu M, Ghenof M, Mincu I, Uta D, Ristic S.

N. C. Paulescu Institute, Clinic of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania.

Abstract
Lispro is a human insulin analogue with a very rapid onset of action, and a shorter duration of activity than soluble insulin. In order to assess the therapeutical value of lispro, we have had an open-label, non-comparative study, for 12 weeks, involving 19 IDDM patients. The treatment regimen with lispro and Humulin N has been adapted depending on each patient characteristics. Patients attended three visits, and the main metabolic control parameters included values of hemoglobin Alc, fasting and postprandial blood glucose monitoring. The patients themselves monitored their blood glucose using a glucometer. The mean age value of 19 patients (8 females and 11 males) was 22.32 (+/- 13.59) years. In patients previously receiving insulin treatment, therapy with lispro insulin significantly reduced postprandial glucose values. Lispro has been administered t.i.d. in 14 patients, and b.i.d. in 5 patients. At visit 1, mean value of HbAlc was 10.32% (+/- 1.63%); at visit 3, mean HbAlc was 9.90% (+/- 1.59%). Total insulin daily dose and the rate of short and long acting insulin did not change from visit 1 to visit 3. There has been reported only one serious adverse event during the study: a ketoacidosis due to a technical dosing error. Ten patients have reported mild hypoglycemic episodes. The outcomes of clinical study and of Quality of Life Questionnaire

suggests that lispro--the first human insulin analogue used in humans--is effective, safe, and it is broadening beneficially the spectrum of insulins.

PMID: 10660973 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
MeSH Terms:
Adolescent
Adult
Aged
Blood Glucose/analysis
Blood Glucose/drug effects
Child
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Female
Hemoglobin A, Glycosylated/analysis
Hemoglobin A, Glycosylated/drug effects
Humans
Hypoglycemic Agents/administration & dosage
Hypoglycemic Agents/adverse effects*
Insulin/administration & dosage
Insulin/adverse effects
Insulin/analogs & derivatives*
Male
Middle Aged
Safety
Time Factors
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Insulin
insulin LISPRO
17.Clin Ther. 1997 Nov-Dec;19(6):1408-21.

Efficacy of insulin lispro in combination with NPH human insulin twice per day in patients with insulin-dependent or non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group.
Vignati L, Anderson JH Jr, Iversen PW.

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, USA.

Abstract
A common treatment regimen for patients with either insulin-dependent diabetes mellitus (IDDM) or non-insulin-dependent diabetes mellitus (NIDDM) is a combination of rapid-acting insulin and intermediate-acting insulin administered twice each day. It is usually recommended that regular human insulin be injected 30 to 45 minutes before a meal. In

practice, patients often inject regular human insulin closer to mealtime, causing a higher post-prandial serum glucose level and an increased potential for hypoglycemia in the postabsorptive period. Insulin lispro, a rapid-acting insulin analogue, is best injected just before a meal because of its more rapid absorption and shorter duration of action. In 707 randomized patients, 379 with IDDM and 328 with NIDDM, we studied the effect of twice-daily insulin lispro or regular human insulin in combination with NPH human insulin (isophane insulin) on premeal, 2-hour postprandial, and bedtime glycemic control. Assessments were based on the results of a seven-point blood glucose profile, the insulin dose (by formulation and time of administration), the incidence and frequency of hypoglycemic episodes, and the glycated hemoglobin value. Treatment with insulin lispro resulted in lower postprandial glucose levels and smaller increases in glucose level after the morning and evening meals compared with treatment with regular human insulin. Overall glycemic control, frequency of hypoglycemic events, and total insulin dose were not different between the two groups. Insulin lispro in combination with NPH human insulin in a twice-per-day regimen allows injection closer to mealtime and improves post-prandial glycemic control without increasing the risk of hypoglycemia.

PMID: 9444449 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Randomized Controlled Trial
MeSH Terms:
Adolescent
Adult
Blood Glucose/metabolism
Cross-Over Studies
Diabetes Mellitus, Type 1/blood
Diabetes Mellitus, Type 1/drug therapy*
Diabetes Mellitus, Type 2/blood
Diabetes Mellitus, Type 2/drug therapy*
Drug Therapy, Combination
Female
Hemoglobin A, Glycosylated/metabolism
Humans
Hypoglycemic Agents/adverse effects
Hypoglycemic Agents/therapeutic use*
Insulin/adverse effects
Insulin/analogs & derivatives*
Insulin/therapeutic use
Insulin, NPH/adverse effects
Insulin, NPH/therapeutic use*
Male
Middle Aged
Postprandial Period
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents

Insulin
insulin LISPRO
Insulin, NPH
18.N Z Med J. 1997 Nov 28;110(1056):435-8.

Lispro insulin as premeal therapy in type 1 diabetes: comparison with Humulin R.

Daniels AR, Bruce R, McGregor L.

Whitiora Diabetes Clinic, Middlemore Hospital, Auckland.

Abstract
AIMS: To determine the efficacy, tolerability and safety of the short-acting insulin analogue lispro compared with regular short-acting insulin, Humulin R as premeal therapy in type 1 diabetes mellitus and to assess the safety of lispro administered for one year.

METHODS: The study was part of an international multicentre crossover study (IOAG) in which 1008 patients were randomised. Twenty patients from Auckland, with insulin dependent diabetes mellitus, received lispro for 3 months and Humulin R for 3 months in a crossover design. At the end of the crossover period, 19 patients elected to participate in an open label continuation of lispro therapy. Humulin N, L or U was used as basal insulin therapy.

RESULTS: Lispro and Humulin R in combination with Humulin N, L or U did not significantly differ with respect to glycaemic control or incidence of hypoglycaemia. Glycosylated haemoglobin (HbA1C) improved from 8.6% at baseline to 7.6 +/- 0.9 (Humulin R) and 7.7 +/- 1.1% (lispro). During the open label continuation of lispro plus the usual basal insulin HbA1C deteriorated to 8.6% after 12 months.

CONCLUSIONS: In this short-term comparison, lispro and Humulin R were well tolerated, while glycaemic control, incidence of hypoglycaemia and adverse effects were similar.

PMID: 9418839 [PubMed - indexed for MEDLINE]

Related citations

Publication Types, MeSH Terms, SubstancesPublication Types:
Clinical Trial
Comparative Study
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
MeSH Terms:
Adolescent
Adult
Aged
Blood Glucose/analysis
Child
Cross-Over Studies
Diabetes Mellitus, Type 1/drug therapy*

Diabetes Mellitus, Type 1/metabolism
Female
Follow-Up Studies
Hemoglobin A, Glycosylated/metabolism
Humans
Hypoglycemia/chemically induced
Hypoglycemic Agents/therapeutic use*
Incidence
Insulin/analogs & derivatives*
Insulin/therapeutic use*
Male
Middle Aged
Substances:
Blood Glucose
Hemoglobin A, Glycosylated
Hypoglycemic Agents
Insulin
insulin LISPRO
19.Diabet Med. 1996 Jan;13(1):47-52.

Pre-meal insulin analogue insulin lispro vs Humulin R insulin treatment in young subjects with type 1 diabetes.
Garg SK, Carmain JA, Braddy KC, Anderson JH, Vignati L, Jennings MK, Chase HP.

Department of Paediatrics, University of Colorado Health Sciences Center, Denver, USA.

Abstract
The present prospective one-year randomized study was conducted to compare soluble human insulin, with a new rapid-acting human insulin analogue, lispro, with respect to postprandial glucose excursions, frequency of hypoglycaemic episodes, glucose control, and long-term safety in 39 subjects (20 females, 19 males) with Type 1 diabetes. The duration of diabetes, gender distribution, and age were similar in the two groups. The total number of hypoglycaemic episodes was significantly less ($p < 0.04$, Wilcoxon rank sum test) in subjects receiving insulin lispro compared with regular human insulin over the 12-month period. The 2-h postprandial glucose excursion at 1 year was also significantly less ($p < 0.05$, ANOVA) in the group treated with insulin lispro. The reductions in the total number of hypoglycaemic episodes and in the postprandial glucose excursion with use of insulin lispro may be beneficial for the long-term management of subjects with Type 1 diabetes. However, the greatest benefit identified by the subjects receiving insulin lispro was the greater convenience of the rapid-acting analogue.

PMID: 8741812 [PubMed - indexed for MEDLINE]

Related citations

COMMENTS FROM INDIVIDUAL MEDICAL PROFESSIONALS

I would like to comment on the importance of glucose monitoring. I have insight into this topic both as a fire department paramedic who responds frequently to diabetic emergencies, as well as being the parent of a well-controlled 18-year-old Type 1 diabetic.

First, with regard to glucose monitoring in general, there is no question that more frequent monitoring and attention to glucose levels results in better glucose level control. Patients that I see with the greatest frequency of low blood sugar emergencies are typically those with the least frequency of glucose testing. In some instances, this is due to lack of education or motivation, and in some other cases, it is due to lack of resources - for instance, patients on public assistance who are only allotted 3-4 test strips per day. Those diabetics that I encounter who maintain good control over glucose levels check their blood glucose more frequently.

Secondly, with regard to Continuous Glucose Monitoring (CGM), I believe that is a valuable tool, especially in conjunction with an insulin pump. Because finger-stick glucose monitoring provides only a "snapshot" of blood glucose levels, it does not provide trending data (blood glucose going up or down). Availability of trending data will facillitate better control of blood glucose.

Better control of blood glucose levels will result in fewer emergency responses and fewer long-term health issues and costs. I support anything which will allow this to happen.

Eric Adman, Paramedic
7815 NE 192 St
Kenmore, WA 09028
Paramedic, Shoreline Fire Department

To Whom it Concerns~

My niece has directed me to your site in order to provide support/concern regarding the proposal to possibly cut funding, for supplies needed for regular glucose monitoring for Type 1 diabetics. I am a physical therapist that works in home healthcare, and witnesses firsthand the problems that occur when diabetics DON'T closely monitor their glucose levels. These problems/complications end up costing the healthcare system/payers much more than the cost for supplies! Not to mention their lives +/or limbs! So MANY of the patients that I work with deal with the ill effects/secondary complications of chronic-often preventable-illnesses, with diabetes being one of the more difficult and devastating.

It's been not only heartbreaking, but quite an eye opener to observe my niece take on the challenges of caring for her son (diagnosed 2 years ago) with Type 1 diabetes. He couldn't have more committed and capable parents. His mother has educated herself and her child thoroughly on the disease, and has worked closely with the physicians in establishing the best care/monitoring possible for her son's needs. However, as a growing, active child there are variables that present that are beyond their "control" (i.e. hormone changes/growth spurts, body temperature/weather, changes in activity and stress/emotional levels, etc). If he wasn't monitored as regularly as he is, they could lose him to dangerous "highs or lows" that put him at risk for seizure and death. I can't even imagine how children that DON'T have such support can make it through childhood without irreversible damage.

Diabetes is a severe disease that takes time, commitment, means, diligence, intuition, long sleepless nights, tears and continuing education to keep up with. Families that struggle just to keep food on the table and their kids in school will be devastated to lose the support needed to aid in their struggle with this diagnosis! Despite "these tough economic times" and the need to make cuts "across the board", I urge you to reconsider cuts that so negatively impact the lives - LITERALLY-of those who are the most vulnerable and unfortunate among us. I also urge you to look into other studies before making your final determination. My understanding is that the study supporting this proposal doesn't even include input by an endocrinologist...?! I think you would be hard pressed to find a pediatric endocrinologist that would support this.
I have sent copy of this letter to some of our elected officials in order to share how ridiculous some of the cuts/strategies to balance budgets is getting. I'm guessing there aren't any politicians out there that would support cutting coverage for medical supplies that save children's lives.....

Thank you for your consideration.
~C. Childs, PT

To Continuous Glucose Monitoring Taskforce:

This letter is from Louise Suhr, Glycemic Team ARNP and Dawn Corl, Diabetes CNS at Harborview Medical Center in Seattle WA. We use Professional (not Real Time) Continuous Glucose Monitoring (CGMS) on outpatients who have been referred for:

Elevated A1c
Hypoglycemic episodes or unawareness
Unexplained blood glucose excursions
DKA
Poor glycemic control
Discrepancies between records and A1c

We find professional (blinded to the patient) CGMS to be an extremely valuable tool in both medication adjustments that best match the patient's insulin needs as well as patient educational opportunity when reviewing downloads and patient logs. We have been using this tool for the last 2 years and have consistently been impressed with its efficacy to pinpoint exactly the causes of uncontrolled diabetes - such as timing of insulin with meals, mismatch of basal and nutritional needs, effects of snacks, etc. Every patient who has had professional CGMS also has had significant changes in medication recommendations. We also found nocturnal hypoglycemia to be much more prevalent that we had imagined. The risks associated with this test are truly minimal. The costs are far less that an equivalent Holter monitoring test, yet always produce beneficial results that prevent the more costly complications of uncontrolled diabetes.

We strongly advocate coverage of professional CGMS for Medicaid patients.

Sincerely,
Dawn Corl, Diabetes CNS
Louise Suhr, Glycemic Team ARNP

In my opinion it is too expensive and only people c insurance will be able to afford it. Money should be used to provide a hbg machine to poor people who cannot afford one and may have costly complications in the future due to this lack, rather than continuous glucose monitoring for the well to do to reduce their A1c from 6.8 to 6.4 thereby meeting their endocrinologist's goal for them. Heaven help us c this health care system that is currently in place.

Dawn Giberson, RN BSN CDE CPH

Dear Health Technology Assessment team evaluating Glucose Monitoring for children with diabetes,

I have read through your Draft Evidence Report regarding Glucose Monitoring and find it significantly flawed. Implementation of the recommendations would cause serious harm to Washington State citizens with type 1 diabetes and their families.

In this regard several points are worth considering. It is critically important to distinguish between the newer technology involving continuous glucose monitoring (CGM) and "standard" home glucose monitoring involving test strips. While it is extremely likely that the evolution of CGM technology will enhance clinical care for individuals with type 1 diabetes in the future, it is at least a reasonable position for the state to take to wait for further data about this technology before formal adaption. This is in contrast to the recommendations regarding "standard" home glucose monitoring for which your position is not reasonable. Potentially limiting the use of standard home glucose monitoring for children with diabetes is an egregious misuse of the notion of "evidence-based medicine".

Evidence based medicine is a process by which the impact of a procedure or therapy on clinical outcomes is rigorously evaluated by review of published studies addressing the area. Using evidence based medicine approaches requires multiple well designed studies that demonstrate a clinically relevant measureable harm, or a clinically relevant measureable benefit. Some, like the use of beta blockers post-MI are consistently shown to be of benefit and other procedures, like stents when bypass surgery results in better outcomes can show harm. However, the ABSENCE of well designed clinical trials that rigorously evaluate clinical relevant outcomes does not mean that the procedure or therapy has no value. It only means that it hasn't been well tested. Moreover, there is appears to be a selective use of rigorous evaluation in the draft documents. For example, the statement that "several lines of evidence have suggested an association between glucose monitoring and increased discomfort, inconvenience and worsening of depression scores" is included with no reference(s) and no critical evaluation of the data.

In the case of home blood glucose monitoring, you report a lack of evidence suggesting benefit on HbA1c or severe hypoglycemia or quality of life. While this may be true, it is important to recognize that studies formally testing this will NEVER be done using current state of the art care. Why? Because it would be unethical to randomize a child with diabetes to not testing their blood glucose frequently. The major advance for individuals living with type 1 diabetes over the past decades is the ability to keep blood glucoses in a more normal range – a fact in which the DCCT trial convincingly demonstrated decades ago directly resulted in better short term outcomes (retinopathy, nephropathy) and decades later still showed better long term outcomes (cardiovascular disease). I assume that the health technology board agrees with this evidence based information that "tight diabetes control" is associated with improved, measureable and clinically relevant outcomes.

Given that, it is worthwhile asking how is it does the board think that individuals with diabetes try to obtain "tight diabetes control"? It is through multiple injections of different types of

insulin, or insulin pumps, accompanied by anticipation and consideration of every moment of every day's food intake and activity level. Most importantly, it is by frequently checking the glucose level so that appropriate adjustments can be made. When should this be done? **As often as it takes to give the child and their parent reassurance that they are safe**. The ADA "minimum" recommendations are to check before each meal to help decide how much insulin to take for that meal and bedtime. But this minimum ignores the reality of living with diabetes which requires frequent assessment of blood glucose at other times of the day and night. First, few individuals with or without diabetes eat only three times a day, so understanding how much insulin is needed for food at other times requires blood glucose assessment. Second, individual's activity has a huge impact on their diabetes and their lives. Checking blood glucose before, during, and after exercise makes the difference between a child who is able to actively participate in sports and school activities and a child whose life is limited due to diabetes. Checking blood glucose before getting behind a wheel or operating machinery, allows a teen or young adult with diabetes to develop independence and pursue the jobs of their choice without risking themselves, their friends, or others on Washington state roads. Checking blood glucose before bed or in the middle of the night relieves the fear of the child and parent that hypoglycemia will occur overnight.

The real fear of hypoglycemia and its impact on people's lives should not be underestimated. Why is hypoglycemic unawareness such a devastating complication of diabetes? Because confusion, seizures, coma, and death can come without warning. Home glucose monitoring is the only tool individuals have. The fear of hypoglycemia or recurrent hyperglycemia on their child's long term health already results in parents limiting their outside jobs to devote time to their "diabetes job" of constantly monitoring their kids. How can the state even consider telling a mother of an 18 month old with diabetes not too check her glucose when the child is being difficult. How is the mother to know if the child has a blood glucose of 55 mg/dl, a blood glucose of 450 mg/dl, or if the child is just starting the normal "terrible twos"?

All of the above point to the impact of glucose testing on glycemic parameters and quality of life. Why then are the studies not convincingly demonstrating that more frequent testing improves quality of life? The health technology assessment board needs to ask themselves how sensitive or specific are our crude measures of quality of life even given validated questionnaires. Why are the studies not convincingly demonstrating that more frequent testing improves hypoglycemia? Because severe hypoglycemia is fortunately not a common event (largely due to the ability to test!) and less severe hypoglycemia is unreliable to measure in clinical trial in the absence of continuous glucose monitoring.

Perhaps most important is for the health technology board to reflect how limiting the ability of individuals with diabetes to test their blood glucose contradicts an important ethical foundation, that of patient autonomy and empowerment. Having diabetes means that your body has betrayed you. You feel helpless, hopeless, and out of control of your life. Checking blood glucose as needed gives people assurance, confidence, and puts them in control once again. This allows for productive lives. Why would the state even consider limiting access to such a tool?

I would challenge any member of the health technology assessment board to live with a child with diabetes for a week and still conclude that there is no "evidence" that frequent checking blood glucose improves lives.

Sincerely,

Carla Greenbaum MD
Director, Diabetes Program
Benaroya Research Institute,
Seattle, WA
Clinical Associate Professor
University of Washington
Member, American Diabetes Association Leadership Council

Note: the views expressed are my own. I am not speaking on behalf of the Benaroya Research Institute, the University of Washington, or the ADA.

December 10, 2010

Washington State Health Care Authority
shtap@hca.wa.gov

To Whom It May Concern,

I would like to comment on the Health Technology Assessment: "Glucose Monitoring Self-Monitoring in Patients Under the Age of 18." The 130 page review by the authors is impressive. However, it should be appreciated that the review on home blood glucose monitoring covers different eras and locations around the world and thus the data are not necessarily applicable to diabetes management in Washington State as we enter 2011. I also have decided not to comment about continuous glucose monitoring (CGM), as this is a relatively new technology. Even though some of my own research is quoted in the CGM discussion, I feel that diabetes patients have more to lose by the misinterpretation of data surrounding traditional home glucose monitoring.

As for my credentials, I am not a pediatric endocrinologist. but as a Professor of Medicine at the University of Washington with a specialty in endocrinology and diabetes, I do see teenagers with type 1 diabetes. Additionally, I have had type 1 diabetes for 46 years, my younger brother has type 1 diabetes, and my 9-year-old nephew was diagnosed at the age of 3. Taken together, these factors give me a well-rounded perspective on the use of home blood glucose monitoring in children 18 years of age and younger.

Home blood glucose monitoring is a relatively young technology, at least compared to insulin therapy. Before we had home blood glucose monitoring insulin dosing was a pure guesswork and overall control was quite poor. It took us several decades to learn how to best use home blood glucose monitoring and even today the technology is far from perfect. Yet, without it, there would be no way to safely manage type 1 diabetes in patients of any age. It is difficult to imagine how parents in the 1960s and 1970s (including mine) struggled to determine whether an unusual behavior in their child was due to a falling glucose level just preceding a hypoglycemic seizure or attributable to some other normal stress. Fortunately, today's parents of children with diabetes can use home blood glucose monitoring to make these distinctions more easily.

As correctly pointed out in your report, we have minimal data about home blood glucose monitoring as an *individual factor* for the successful management of type 1 diabetes. However, our landmark studies examining the importance of glucose control in reducing the vascular complications of diabetes would not have been possible without the ability to measure point-of-care glucose levels outside of the physician's office or hospital. The international controversy right now is the impact of home blood glucose monitoring in individuals with *type 2 diabetes not receiving insulin*. There is no controversy in national or international academics about the value of home blood glucose monitoring for individuals receiving insulin therapy, mainly because of the risk of hypoglycemia. Even our best efforts to normalize blood glucose carry this risk—it is part of life for individuals with type 1 diabetes. In King County alone there are 1200 ambulance calls each year for hypoglycemia. Although it is usually benign and easily treated, "severe hypoglycemia" (requiring the assistance of another person) still occurs far too frequently. Studies

in the past 4 years have estimated death from hypoglycemia to account from 6-10% of all deaths in type 1 diabetes. Children are especially vulnerable to long-term neurological changes.

Home blood glucose monitoring is considered such an integral part of modern-day management of type 1 diabetes that an IRB evaluating a randomized study comparing diabetes control in patients using it compared to those not using it would deem the study unethical, especially in light of current evidence-based A1C targets. The most quoted studies of home blood glucose monitoring generally use home blood glucose monitoring as one element of an "intensive therapy" program, making it difficult if not impossible to single out its effects. Our initial data from the Helmsley Foundation's T1D Exchange show the same relationships (data not yet published) with mean and median frequency of testing in children under 18 years old at 5 to 7 times daily (N=365). And as previous reviews have shown, there is a strong negative relationship between home blood glucose testing and HbA1c.

It should also be appreciated that the epidemiological relationships we have reported in terms of A1C and the risk of severe hypoglycemia would not been possible to elucidate without home blood glucose monitoring. There is agreement that we now have excellent data showing that over the past 3 decades both hemoglobin A1c levels have improved and at the same time the risk for severe hypoglycemia has decreased. The figure at the end of this letter illustrates how much better we do in reducing severe hypoglycemia in today's era of insulin therapy. Although we cannot definitively attribute this to home blood glucose monitoring alone, the only other major change in therapy during this period has been the introduction of insulin analogues.

The figure represents the entire population of the DCCT (in the late 1980s and early 1990s). There were approximately 62 episodes of severe hypoglycemia per 100 patient years. As noted correctly in your report, the risk was 55 episodes per 100 patient-years for an A1C of 7.6%.. When we looked at the rate of severe hypoglycemia in the Juvenile Diabetes Research Foundation sensor study in those individuals not using CGM, ie, simply using insulin therapy with home blood glucose monitoring, the rate of severe hypoglycemia was less than 20 episodes per 100 patient years. I can't imagine that number being so low if patients were giving their insulin without sufficient home blood glucose monitoring, especially prior to eating (the mean frequency of testing was 7 per day). We are past evidence here. This is common sense.

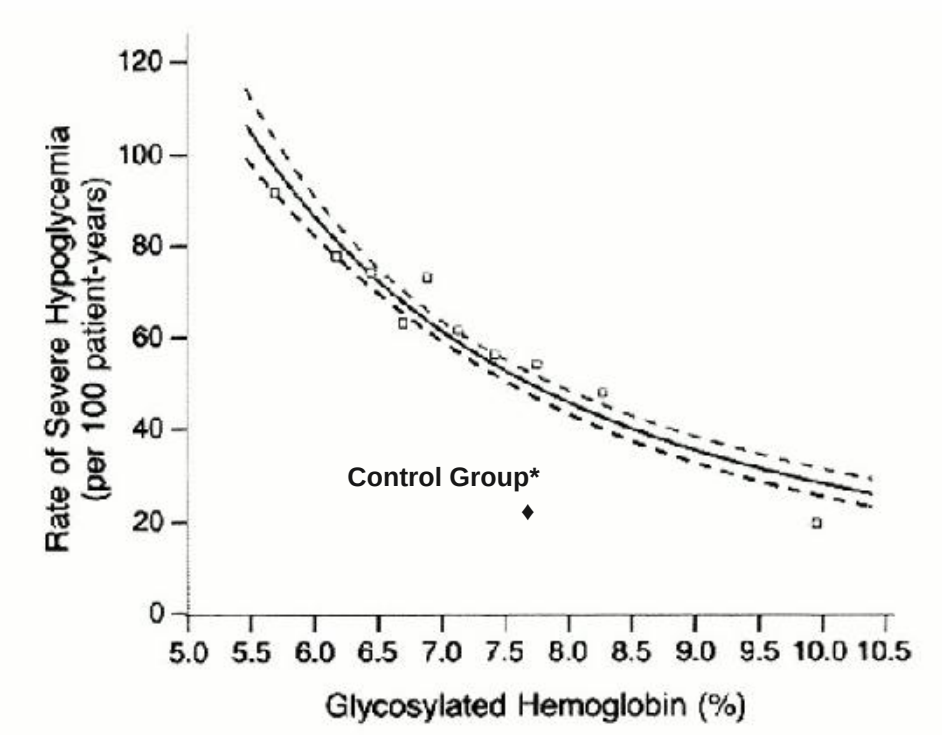
Recently we learned the "clock starts ticking" regarding the development of microvascular complications upon the diagnosis of diabetes no matter the age. This refutes decades-old data suggesting that the timeline for starting the risk for microvascular complications did not start until after puberty, At the same time, we also appreciate that in the very young children hypoglycemia has a much more detrimental effect on brain development. Greater neuro-cognitive changes are true with the geriatric population, the point being that hypoglycemia is more dangerous in the very young and in the very old. Why we would even consider limiting home glucose monitoring for these important populations?

I would be more than happy to discuss this with you in more detail. Around the world, home blood glucose monitoring is considered to be the most fundamental aspect of type 1 diabetes

therapy. It is now established as a necessary therapy for children in third-world countries and a major mission of the International Diabetes Federation is to secure glucose monitoring supplies for every individual with type 1 diabetes worldwide. I'm not exactly sure why this would be different in Washington State. Indeed, I regret having to say that as a resident of Washington State for the past 20 years, I am actually embarrassed that our state is considering this particular health care policy.

Sincerely,

Irl B. Hirsch, M.D.
Professor of Medicine
University of Washington School of Medicine



This line was published as part of the DCCT primary paper, N Engl J Med 1993;329, 977-986.
The ♦ comes the control group of the JDRF Continuous Sensor study (subjects only used home blood glucose monitoring with or without insulin pump therapy).

Dear Decision Makers,

In an era of cost containment it is essential that the individuals making the decisions about life and death should have knowledge of the issues surrounding their decisions. Glucose monitoring, especially in type 1 diabetes, where insulin is essential to life, is itself essential. Simply said taking insulin without knowing what the current glucose is like playing Russian Roulette. An individual must know their glucose number to calculate how much insulin to administer to correct a high glucose or a low glucose and they must also know how much carbohydrates they are eating to know how much insulin to give themselves, this combination of information is a corner stone of preventative medicine in diabetes. Without the knowledge of the glucose the child will simply be guessing and if he/she are smart they will always give themselves too little insulin otherwise they risk hypoglycemic seizure which can kill them and possibly a loved one, for example if they happen to be driving a car. That by itself leads to hyperglycemia which has been proven to significantly increase the risk of complications later in life and therefore increasing the cost of healthcare in the adult population. You see Diabetes is a condition and unless it is care for it can become kidney disease costing 60-70K per year or blindness or heart disease or loss of limbs all increasing the burden on Medicare. The Scandinavians have over the last 50 years saved a tremendous amount of healthcare dollars by simply implementing excellent foot care for their population in diabetes, this is how and where we should be investing our healthcare dollars, and not by simply eliminating care.

I can understand limiting glucose testing strips for those who are not insulin dependent, type 2's taking only non-hypoglycemic oral agents, although I do disagree with the concept of limiting glucose strips altogether, limiting glucose strips (less than 4 per day) for a child should be considered the same as handing a loaded gun to that child, a punishable criminal offense. You say show me the research, well although large bodies of research may not exist in this group, simple concepts can be transferred from a slew of studies that do provide the understanding that not know what your blood sugar happens to be and taking insulin blind is dangerous no matter the age of that individual.

Please consider the risk of death in children who will not have glucose monitoring available.

Thank you!

Dori Khakpour RD CD CDE
Diabetes Research Nutrition Coordinator
University of Washington Medical Center
Diabetes Care Center
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4225 Roosevelt Way NE, Suit 101
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Phone: 206-598-4882
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We are about to embark on a grant funded CGM project to assess whether CGM is efficacious in a community health care setting. CGM saves healthcare provider time in assessing insulin dosing and self-management. If we are going to manage a large population of people using insulin with a small number of experts capable of managing insulin, we need the tools to do so. CGM can be done in 3-5 days with data that would otherwise take over a month to evaluate.

Ginny - Make a Dif
Virginia O'Kelly RD, CDE
Make a DIF (Diabetes Intervention & Follow-up)
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662-6000 ext 1141
gokelly@cvch.org
"It is the mission of Columbia Valley Community Health to provide access to improved health and wellness with compassion and respect for all."

I would greatly, greatly encourage greater coverage and support of continuous glucose monitoring devices. As a woman living with type 1 diabetes, the CGM is a great tool for me to catch my lows in the middle of the night (which I might not wake up from) or extreme highs throughout the day that end up making me very ill. Although a finger poke can do the same, it cannot alert you as you begin to trend one way or another. It only catches the number at that one instance. As a director of a diabetes camp, I also know how much these devices benefit parents of children with diabetes. Most of all of the children I know who have had seizures due to low blood sugars, have them in the middle of the night when they are unaware. And most parents I know, get up 4 times a night to check on their child with diabetes because they are afraid for them. The CGM offers support to parents already facing an extremely challenging disease, as well as protects children from the severe damages that could result in an overnight low. While I see much area for improvement and believe it is of great importance for doctor's to inform their patients that their CGM should not be taking the place of a finger poke, overall, I believe the benefits outweigh the negatives. This is a natural step in the progression toward a functional, closed loop system, and hopefully someday an artificial pancreas. For diabetes research and technology to proceed with the great strides it has been taking, the option of a CGM is a must.

Thank you,
Alyssa Olsen

Alyssa Olsen
Associate Manager, Youth Programs
American Diabetes Association
1730 Minor Ave, Suite 920
Seattle, WA 98101
Phone: (206) 282-4616 ext. 7202
Fax: (206) 903-8107

I am a Physician Assistant and CDE working in endocrinology and diabetes. I cannot stress how important it is to have patients monitor frequently- our medication adjustments and insulin therapy depend on those numbers, keep our patients (and roads) safe.

Please consider these comments.

Megan O'Neill [megan.s.oneill@gmail.com]

I would like to add my two cents to this conversation.

While I think that frequent finger stick blood sugar monitoring is key, and that got me through a pregnancy, continuous blood sugar monitoring has a big role in keeping diabetics safe.
I have a continuous glucose monitor now, and while its technology still isn't ideal, the ability to alert me to rapidly rising or dropping blood sugars has kept me out of dire straits many times.
This technology needs some improvement, but it adds an important benefit of safety.

Sincerely,
Kim Schrier, M.D.
Pediatrician
Type 1 diabetic

Hello & thank you for reading my comment:

Diabetics who test their blood sugar level at least 4 times a day are healthier, with less costly physical complications, then those who do less or do not test at all. One huge barrier is the cost of most strips... **$1 per strip is outrageous**. I was diagnosed with Type 1 Diabetes at the age of 7 and I have tested over 10 times a day for decades, constantly appalled by the cost, yet always putting my health first. I am not the norm. Millions go without this very valuable action for keeping their health in check.

Please make a reasonable cap on the cost of blood glucose test strips.
Reasonable cost of test strips = diabetics testing more often = The resulting improvement in health statistics, not only would improve the lives of millions of diabetics, but would save our country thousands if not millions of dollars....less amputations, less kidney failure, less cardiovascular disease, less strokes, less blindness, less neuropathy.

Thank you for doing all you can to place an industry wide cap on the price of blood glucose strips.

Dr. Jody Stanislaw, N.D.
Naturopathic doctor, 208-309-3239

To Whom It May Concern,

My name is Andrew Swanson, an RN and type 1 diabetic since the age of 13, diagnosed 11 years ago. Since then I have been through many battles with my blood sugars and am constantly involved in learning how my body reacts to external interventions. In the course of my relationship with my diabetes the most useful knowledge that I have had available is the trend that my blood sugars follow throughout the course of a day. Without the ability to monitor these trends, my current practice of tight and effective management would be minimal to almost impossible. From a basic management stand point there is no information more valuable than the blood sugar trends one experiences. With the recent discussion at hand involving insurance coverage of glucose testing strips, I would like to offer my thoughts on the subject.

The knowledge of blood sugar trends determines how one individual's day by day events effect blood sugar levels. These daily events involve eating, exercising, even sleeping. I realized because of efficient glucose testing that I have a morning spike in my blood sugar levels. Without this knowledge I would start everyday with uncontrolled levels that would be hard to normalize throughout the day. It is also very important to consider the generally adolescent age of type 1 diabetics upon diagnosis which leads to many hormonal and basic body functions that also effect blood sugar levels. With so many factors that can influence blood sugar levels at any age, but especially in adolescence, the only way to truly understand an individual's diabetes is to follow a close assessment of their blood sugar levels.

This battle of blood sugar normalization is not something that can relax in assessment over time. Whether it is impacted by the food i am eating, the exercise I am practicing, whether the insulin I am using is still effective or any number of other factors, I need to have knowledge of my blood sugars. This allows proper primary and preventative planning with my doctor's input to avoid complications and hospitalizations related to this chronic condition.

On a long term basis, the mismanagement of blood sugar levels can lead to multiple hospitalizations and the presentation of more debilitating chronic conditions including peripheral vascular disease, blindness, amputations and kidney disease. To limit the amount of testing availability to a diabetic can cause not only a decreased quality of life, but an increase in healthcare costs for the individual and the system.

I urge you to consider the personal and systemic implications this decision means for the long term health of our country. It is a fight many individuals have to face everyday. Please make my daily life and that of many others easier to manage and full of future potential.

Thank you for your consideration,

--
Andy R Swanson, BAH, BSN, RN
VA Hospital RN
Only Phone: 206-399-8195

COMMENTS FROM INDIVIDUALS

Hello. My name is Brant Baetz. I am 41, married, a father of 2 girls, and living in Ballard. I was surprised to be diagnosed with Type 1 diabetes 5 years ago.

I practice tight control, exercise, watch what I eat, and follow my doctors instructions very carefully. I test with a finger stick monitor at least 5 times a day. This disease is RELENTLESS. Even testing this frequently, I still find myself more often than I would like in precarious situations with my blood sugar, being either surprised by highs or brought to a screeching halt by lows. These situations I know are damaging to my physical and mental health (frustration and ensuing depression).

Blood glucose monitoring is clearly one of the most important ways I treat my diabetes. The option of a Continuous Glucose Monitor is very exciting. A device to replace the "spot checks" and warn me when my blood sugar is fluctuating unexpectedly l will allow me to take action immediately to correct. With this device I can be warned before my blood sugar reaches dangerous levels.

I have been educated on the CGM by the Diabetes Care Center at the UW, and I believe that a CGM is what I need to effectively treat this chronic disease. I want one and am working on my health insurance situation right now to get one. If only it wasn't so expensive!

Bottom line - I have not seen a better tool for me to treat my diabetes.

Best Regards,
Brant Baetz

To whom it may concern,

I'd like to weigh in on this topic. I've been a type 1 diabetic for just over 10 years now. I've used glucometers since day one. Managing the disease is difficult enough estimating carbs in meals and how they absorb in the bloodstream let alone getting an accurate meter reading. Currently I'm using two technologies a continuous device along with a traditional finger stick glucometer. Keeping a healthy balance is indeed difficult. Avoiding hypo/hyper glycemic states is a daily struggle. Being type 1 I feel as if my specific disease state is overshadowed by the type 2 diabetics in the press. Their side effects of poor management are detrimental over the long term, type 1 can actually go into a coma with poor management very easily.
With the rise in the disease we need continued support of research and development of a more accurate and less invasive means of glucose monitoring. Earning good health is a two way street. I'm committed to help find a cure and manage the disease while on this journey.

Best Regards,
Ted C. Bearor

As a parent of two children with type 1 diabetes, I can tell you from personal experience that Glucose Monitoring is not only very important to their control of blood glucose levels but it is critical to their survival. Without several checks per day, 6 to 8, children especially would/could suffer severe episodes of Hypo or hyperglycemia resulting in numerous hospital visits and/or coma/death. Unfortunately, for diabetics to have a healthy life, blood glucose monitoring is not an option, it is a requirement. I am very upset that this is even a discussion point. Unless you have experienced a severe low episode resulting in near death and seizures of your own child, maybe you cannot even imagine how asinine or ridiculous it is to even question the importance of Glucose Monitoring.

Thank you,

Rob Berg

To Whom It May Concern –

I am writing today in response to the Health Technology Assessment study on glucose monitoring for children with Type 1 diabetes. I am deeply concerned that the study could be foreshadowing a decision by the Washington State Health Care Authority to limit the number of blood glucose tests covered for children with Type 1 diabetes. I strongly urge you to continue coverage of blood glucose test strips and to encourage patients with the disease to follow aggressive testing regimens, as said regimens are recognized as the best option for monitoring glucose levels to maintain good health.

Blood glucose monitoring is absolutely essential to the management of Type 1 diabetes. The study does not seem to reflect an appropriate understanding of Type 1 diabetes. It is an autoimmune disease where the cells that produce insulin are destroyed, requiring a person with diabetes to take insulin injections to make up for the insulin one's body no longer produces. Blood glucose monitoring is *the compass* that guide's a diabetics decisions on how much insulin is required to maintain safe blood glucose levels.

As someone who has lived with Type 1 diabetes for more than 20 years, I can tell you that blood glucose testing is critical to my ability to determine how much insulin I need throughout the day. Regular testing allows me to respond appropriately to any adverse events that occur, such as dangerously high or low blood sugars, which can occur unexpectedly in spite of the best planning and management. On average, I test between four to six times a day, exceeding that number in times of illness or extreme physical activity.

I simply cannot imagine managing my diabetes based on the data provided by one test a day. What the study failed to recognize is a glucose test is a snapshot in time of the glucose level. Glucose levels change rapidly throughout any given day with the intake of food, physical activity, stress, etc. Constant monitoring is the only tool we have to ensure we're adjusting our insulin and food intake in response to our body's needs.

Please ensure individuals with Type 1 diabetes have access to the appropriate tools to manage this disease. Do not threaten the number of blood glucose tests a patient can do in a day by limiting coverage for test strips. Whatever cost savings the state can achieve by limiting access to tests strips will not come close to the costs of unmanaged diabetes.

If you have any questions or would like more information about the diabetes management regimen my endocrinologist and I have developed please do not hesitate to contact me, I would be happy to share more about my experience.

Thank you for your time and consideration.

Sincerely,

Tiffany Butler
206-446-8718
tiffanymbutler@live.com

Dear Sir or Madam,

I am writing today in response to the Health Technology Assessment study on glucose monitoring for children with Type 1 diabetes. I am deeply concerned that the study could be foreshadowing a decision by the Washington State Health Care Authority to limit the number of blood glucose tests covered for children with Type 1 diabetes. I strongly urge you to continue coverage of blood glucose test strips and to encourage patients with the disease to follow aggressive testing regimens, as said regimens are recognized as the best option for monitoring glucose levels to maintain good health.

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My wife has lived with Type 1 diabetes for over twenty years, and in the four years that I've known her, I've come to appreciate a few key insights about life with this disease, with one foremost among them: effective day-to-day management, or the lack of it, is the single strongest influence on a patient's quality of life. I don't intend to demean the importance of looking at the long-term incidences of side effects or survivability statistics--surely these are incredibly important. But I think that one aspect missing from this study which must be part of a meaningful and wise policy decision is the effect of regular, intra-day testing and treatment adjustment in making the disease livable.

Without the constant adjustment to her treatment that is possible with after-meal testing, my wife's blood sugar would fluctuate more severely than it already does, leaving her feeling nauseous virtually all the time. When we've been in situations away from home where we've run out of strips and testing has been impossible, she's lost evenings and days to feelings of illness that have left her fatigued and unable to concentrate on her work. I hate to think what life would be like if she had to live that way all the time. A treatment regimen that aims to help people with this disease should consider not just survivability, but the need to help those people function well enough to work and make a contribution to their society.

Should you be interested, either of us would be willing to speak to someone at length to share our experience. Thanks very much for considering my comments.

Best regards,

Will Butler, Seattle
206-914-6392

I have been diabetic for 34 years. I have been on an insulin pump for the last 14 years. During that time I have used a continuous glucose monitoring device. This is an excellent source of information for a diabetic and very important for any treatment plan of a diabetic who is having trouble regulating their blood sugar. Having been diabetic for so long I can tell you that all the medicine and finger sticking gets old. It is not easy to always be on your toes and on top of how many carbs you may be eating. the CGM can let you know that your blood sugar is either going up or down and can keep an ugly episode from happening. It is an incredibly important piece of medical equipment and I will be first in line when they have an implantable pump/cgm combination ready to go.

Thank you,

Samantha Corbin

Sir,

Thank you for this message. However I do not attach any significance to blood glucose tests. I have been diabetic almost 70 years. I had one 16 year stretch in which I did not check myself in any way. I just regulated my diabetes by how much exercise I did, how much I ate, and how much insulin I needed. I took two shots a day for over 66 years. At least 45,000 shots. If my BG gets low in the night I still wake up. If I could still get beef pork insulin, I am sure I would never have to use the BG tests. I use Humalog insulin, which I have to take about three hours before I need it. If I take a dose of more than six units, it will react sometime between 3 and 12 hours later.

I hope what I have written will be helpful in your research. I am the only one I know of who has trouble with Humalin Insulin.

E. B. "Van" Corley

Continuous Glucose Monitoring is the ONLY way to catch upcoming highs and lows. When you finger stick to test, you capture the moment T of your blood level. You don't know if you are tending up or more dangerously down.

I am an active type 1 diabetic, I race my road bike and I run Marathons and 1/2 Marathons. I cannot afford to test while I train or race. I don't even bother taking my tester with me during those times. But I always make sure I have my CGM. Even if not always accurate, it will give me a sense of confirming, and validating what I feel. I most cases, when I doubt, I will treat with carbs as it only takes one low for game over.

With CGM low and high alarming, I feel a sense of extra security when I am out on long 100 or 200 miles rides. But the CGM also allows me to bring my senses to reality, even in the most intense efforts of my training and racing. It makes me test! My A1c today is 5.8% and I know for sure it wouldn't be that level if I didn't have the CGM on me. When I don't ware it, I feel naked, I feel vulnerably.

Do not question the efficacy of a CGM on an active person like me. It has saved my life a couple of times now. More work and research needs to be funded to allow for even better and better accuracy. Also better insertion as it can hurt a lot, and every time I insert one, I feel bad for the poor little children to use it. If my son had type 1, I would without a doubt put him on CGM.

Thank you for considering my tail as proof of success on CGMs.

-- Thierry Douet

I wish to comment on the value of intensive glucose testing for Type I diabetics.

I am a 70 year old Caucasian male. My training includes a Ph.D. in biochemistry at the University of California. My mother was a nutritionist also trained at the University of California, and she taught me at an early age about food groups. I have had Type I diabetes for 30 years. I have absolutely no secondary complications. For example, I had a test for retinopathy a year ago showing no damage. My hemoglobin A1c tests run on the order of 6 or lower. My present doses of insulin are less than ½ a unit per kilogram of body mass, lower in fact, than in newly found diabetics in the so called honey moon stage. I work physically several hours a day, splitting and hauling firewood, or riding my bike 10 or twenty miles. I could still ride 50 or miles in a day. My diet is strict, but we prepare food which is very tasty and enjoyable to eat. At a height of 5 foot 4 inches, my weight is about 138 lbs., stripped, in the morning, before breakfast.

The cornerstones of my exceedingly good health are diet, exercise, weight control, glucose monitoring, and insulin doses, varied as needed.

I find the results showing comparisons between groups with so called tight control versus non tight control to be flawed. There is no mention about the willingness and ability of the participants to very carefully control what they eat, and how much exercise they get. One example is the higher incidence of hypoglycemia seen among the group with intensive control. Based on what I know about conventional diets and availability of food, I would venture to say that many of these children continue to eat corn products, potato products, ordinary bread, soft drinks, pizza, pasta, as well as cookies, cakes, ice cream, and all the other high glycemic index foods which make up the average American diet. I saw a television show about how a dog could sense when a boy was going hypo glycemic. But I could also see why the boy was having problems. The whole family was overweight. One shot showed the family sitting down to dinner. Included in the boy's meal were an apple and a plate full of pasta. I never eat pasta, and save my apples for when my blood sugar is low. I will explain below why his diet leads to hypoglycemia.

People talk of children trying to have a "normal life" like non diabetic children. I'm sorry, that does not work. A diabetic is not normal and cannot lead a healthy life eating a "normal" diet. (Of course, the non diabetic also damages his/her health eating a "normal" diet.)

What happens with the tight control group is that they eat high glycemic index foods, then test and find a high blood sugar, they take insulin to bring it down, and overdose on insulin. By eating low glycemic index foods (a lot of home grown vegetables, and some fruit, plant proteins, no animal fats), while I still have high blood sugars from time to time, the insulin I take reduces my blood sugar more slowly because of the low glycemic foods supply calories which will last. Occasionally I give into a craving and have something sweet. The follow up with a dose of regular insulin often leads to a hypoglycemic episode.

My life is very dependent on glucose self monitoring, and I would love to go to an implanted electrode and continuous monitoring, especially when biking long distances. Many activities depend on having a blood sugar in the 80 to 124 range. These include thinking, sleeping well, bike riding, heavy work, sex (below .8 g/l, no climax), and so forth. Life would be hell without frequent monitoring.

I test in the middle of the night (at my age one always gets up to urinate), first thing on waking to determine what insulin dose I will take, mid morning to see how I did with breakfast (my major meal of the day), early afternoon to know if I have a high enough blood sugar level to continue to function well, early evening to determine what and how much to eat, and finally at bedtime. All of the tests can be followed by adjustments, either with a piece of fruit, or an injection of regular insulin. Sometimes, as with biking or heavy exercise, extra testing is needed. Note that I said a piece of fruit. A whole apple is too much. About half an apple is the maximum dose. I have created for myself a table of how many units of insulin I need to bring blood sugar down from various levels. That is modified by my understanding of the glycemic content of what I have eaten. That table is memorized by now. I also have on my table the number of calories needed to go up by a certain amount, and some quantities of healthy foods needed to obtain those calories.

Another item not being considered in the studies of intensive monitoring is the quality of life. Life as a Type I diabetic is a roller coaster. Anything you can do to smooth it out makes life saner. And that requires frequent testing and a low glycemic index diet.

Finally, when you study all this, do you consider the financial and societal costs of blindness, kidney failure, amputation, heart failure, loss of nerve sensitivity, and all the other complications from uncontrolled diabetes.

I wish that at least one of the people in your studies had type I diabetes, which he/she had successfully managed for 10 or 20 years or 30 years as have. That leads to much understanding, which the people reporting in the study seem to be totally unaware of.

There is no cure for diabetes. I expect to live with this for the rest of my life, which I hope with the care I am giving, will be about 30 years. I have a system which works. Don't ask me to change it. And as far as the juveniles in your study, give them real help in changing to a healthy diet/life style.

Stephen A. Douglass, Ph.D.
206-780-0982
stephen.a.douglass@earthlink.net
15399 Sunrise Drive NE
Bainbridge Island, WA 98110

To Whom It May Concern –

I am writing today in response to the Health Technology Assessment study on glucose monitoring for children with Type 1 diabetes. I am deeply concerned that the study could be foreshadowing a decision by the Washington State Health Care Authority to limit the number of blood glucose tests covered for children with Type 1 diabetes. I strongly urge you to continue coverage of blood glucose test strips and to encourage patients with the disease to follow aggressive testing regimens, as said regimens are recognized as the best option for monitoring glucose levels to maintain good health.
Blood glucose monitoring is absolutely essential to the management of Type 1 diabetes. The study does not seem to reflect an appropriate understanding of Type 1 diabetes. It is an autoimmune disease where the cells that produce insulin are destroyed, requiring a person with diabetes to take insulin injections to make up for the insulin one's body no longer produces. Blood glucose monitoring is *the compass* that guide's a diabetics decisions on how much insulin is required to maintain safe blood glucose levels.

As someone who has dear friends with Type 1 diabetes, I can tell you that blood glucose testing is critical to their ability to determine how much insulin they need throughout the day. Regular testing allows them to respond appropriately to any adverse events that occur, such as dangerously high or low blood sugars, which can occur unexpectedly in spite of the best planning and management. On average, they test between four to six times a day, exceeding that number in times of illness or extreme physical activity.

I simply cannot imagine that they could appropriately manage their diabetes based on the data provided by one test a day. What the study fails to recognize is a glucose test is a snapshot in time of the glucose level. Glucose levels change rapidly throughout any given day with the intake of food, physical activity, stress, etc. Constant monitoring is the only tool we have to ensure we're adjusting our insulin and food intake in response to our body's needs.

Please ensure individuals with Type 1 diabetes have access to the appropriate tools to manage this disease. Do not threaten the number of blood glucose tests a patient can do in a day by limiting coverage for test strips. Whatever cost savings the state can achieve by limiting access to tests strips will not come close to the costs of unmanaged diabetes.

Thank you for your time and consideration.

Adam Erickson l Staffing Consultant l College Recruiting

I'm writing to provide some input on the Glucose Monitoring assessment being done by the HTA.

I am a 47yr old male, lifelong Washington resident, diagnosed with Type I Diabetes in Yakima at age 11 (1974). I have have been Insulin Dependent since June of 1974 and experienced life as a Diabetic *__without__* glucose monitoring for the first 7yrs, until early 1981. The remaining 30yrs I have benefitted not only daily, but often hourly from the access insurance gave me to monitor my BG. I was fortunate as a young teen to have a Physician (Dr. James Dodge, Yakima) who at the time specialized in Diabetes care and aggressively encouraged myself and others to make use of the then newly available home glucose monitors. My first device was called the Glucoscan 2000, and I still have it in the cupboard, because it *__changed my life__* in that it saved my life.

I had been Diabetic long enough to recall using test tube as well as reagent strip urine analysis, but in spite of their accuracy the data was 4hours old by the time I received it, making management of my blood sugar a crap-shoot at best. Glyco-Hemoglobin blood tests had become standard procedure for my doctor visits in the late 70s/early 80s, but the numbers were never great, ranging between 8 & 15 as I recall. If you're not a diabetic, you can only imagine how crappy one's quality of life is when their sugar is out of control, but family members of a diabetic can attest that it does make one miserable to live with. The home blood testing improved my ability to manage this a great deal, but only so much as it was used regularly. In the early days we only tested at Breakfast and Dinner, with an occasional bedtime check. Life was better, but nowhere near normal.

In 1986 I graduated from University and moved to Seattle. By October I was randomized into the 'Experimental' group of the DCCT (Diabetes Control and Complications Trial) at the UW and began intensive treatment to control my blood sugar. My A1-C upon entering the DCCT was still hovering around 8%, which for the time wasn't too bad, but I would eventually find out how much better it (and my quality of life) could get. One of the benefits of being in that study was access to newer glucose monitoring tools, enough strips to test regularly, and the encouragement to do it. The goal I was given as part of the intensive therapy group was an A1-C of 6 to 6.5%. I eventually found that I could achieve 6.5%, and do so safely, *__only__* by regularly monitoring my blood glucose. There were challenges with bringing it down to improve how I felt and my quality of life, but also risk of going too low. REGULAR daily monitoring is the ONLY thing that made it possible to approach near normality without dangerous risk. The ONLY thing. Without glucose monitoring it would have been impossible at best, and a risk to my life at worst.

As the study progressed I found that I needed to test at least 10x/day to stay on top of swings to my sugar and achieve my goal. It not only required checking before meals, but also after, and in the hours between at a bare minimum. If I eat a large banana for instance, my blood sugar can jump from slightly low (70) to high (180) within 20 minutes, and a glass of fruit juice can act even faster. Conversely, even with today's fast acting insulins, if my glucose is already high (>200) it can take 2hrs or more to bring it back into a range that is both healthy and feels good, and close monitoring to not overshoot and go low. As I said, if you've never felt what 250 feels like, you have no clue about the effect it has on quality of life.

Today my A1-C averages between 5.9%-6.1% because I have learned to know at all times what my glucose is. The more often I know what it is, the better I can maintain it. Whether I use a CGM (Continuous monitor) or Intermittent monitoring with a Blood Glucose Monitor, ***frequency*** is the common key. Without a good deal of frequency I could never achieve such near normal blood sugars, could not safely attempt to, and would lose the quality of life that is only ***near*** normal. High blood sugar hurts more than nerve endings, Kidneys, heart, and eyes. It also hurts while it's present. It's like having fibro myalgia that you can avoid if you're simply afforded the tools to manage your glucose, and the necessary tools include frequent glucose monitoring.

I pray you'll consider the experience of a 35+yr veteran living with Type 1 diabetes as valuable input for your analysis.

Sincerely,

Steve Fuchs
17218 159th Ave NE
Woodinville, WA 98072
425-486-0128
m 206-940-1167

Addendum to letter above:

I forgot to add a few facts about the efficacy of my history with frequent blood glucose monitoring:
After almost 37yrs with IDDM:

a) My Ophthalmologist tells me my eyes are as healthy and clear as a non-diabetic. I have never had retinopathy nor been treated for any eye complications
b) My Kidney function is completely normal – no complications from diabetes now nor ever before.
c) A recent EKG showed my heart to be without side-effects from diabetes, and my blood pressure is very normal
d) A recent checkup determined my reflexes, circulation, and sensation in both feet to be excellent and unaffected by my diabetes – the nurse even commented about how much hair I have on the tops of my feet, which indicates healthy circulation.
e) I have never experienced symptoms of Diabetic Neuropathy.
f) Testing of my ANS (Autonomic Nervous System) as part of some research showed it to be very normal.
g) In the 31yrs using glucose monitoring, I have never needed help because of a severe low (which I did a few times before testing my blood)
h) I have never lost consciousness as a result of unknown blood sugar
i) I have never lost control of a vehicle as a result of unknown blood sugar

Given that I take 70-90 units of insulin daily, that's no easy task.
Frequently monitoring my blood glucose enabled that quality of life with diabetes.

Steve Fuchs

hello sir/maam,
to whom it may concern, i am a person who suffers from diabetes and unfortunately, there are millions of us in this country who would greatly benefit from the use and advancements of utilizing a continuous glucose monitoring device. it is incredibly important for diabetics to check their glucose levels frequently to asses their health. self monitoring of blood sugar levels has been one of the most essential tools diabetics have currently of preventing deadly and devastating complications. however, i strongly believe a continuous glucose monitoring device is immensely more effective in keeping people with diabetes healthier, thus saving the state and the entire country millions of dollars in already distressed economic times. the continuous glucose monitoring devices show real-time, accurate glucose readings that really display how a person is dealing with their diabetes. self monitoring devices require time, expensive test strips(which many diabetics cannot afford), and it only gives a person's glucose reading at the time of the test. a person with diabetes can either not check their glucose levels, or they can check anywhere from 3-15 times a day to see how they are doing. this is an incredibly painful ordeal if one has to do this every single day for the rest of their lives.

a continuous glucose monitor would relieve a lot of those pains and hassles for diabetics, hence making it easier to keep himself or herself much healthier. since diabetes currently has no cure and can only be managed with medications, food, and exercise, it is of great importance that people who suffer from this disease have the best tools possible at their disposal to care for themselves so they will not suffer nor be a burden to their family or society. please help diabetics find a way to pay for test strips at a more affordable cost or make continuous glucose monitors easily available through coverage under insurance plans. it is also much safer for diabetics if they are aware of their glucose levels at all times, so that they can make needed adjustments to their medications, activity levels, food intake, and stress levels. diabetes is not only a issue about people's health, but it is also an issue about safety and financial costs to people, society, and the government. if people do not have insurance, social services from the government and private charities often help to pay for the astronomical costs of good health care. it is much better to prevent expensive complications than to treat far advanced problems that often have irreversible consequences.

too many people have already lost their eyesight, limbs, fingers. toes, and other parts of their body due to diabetes. it is a very heavy burden to live with this illness, and any tool that can help to alleviate further suffering would be massively successful in saving lives and money in the future. please do what you can to help save your neighbor, your mom, your friend, and anyone else that you might know that is inflicted with this horrible disease. time is not on our side, and millions of people are being diagnosed ever year with diabetes. i truly believe that continuous glucose monitoring devices will be revolutionary in the way people with diabetes take care of themselves.

please help save my life and millions of others like me from anguish due to diabetes. we are at the mercy of this disease and often times, it is a battle many of us have not won. every day is a fight for our life, and every person deserves to live a life with happiness, goodness, and dignity, regardless of whether they are healthy or not. thank you for your time and consideration.

sincerely, anne gimotea

Dear Senator Haugen and/or SHTAP Committee Member,

I am writing from Freeland, WA to protest any limitation on testing supplies for juvenile type 1 diabetics in need of state aid. These children are quite possibly the most vulnerable in our diabetic community.

This study seems to not understand the volatile nature of type1 diabetes in children. Children with type1 produce no insulin of their own. This is caused when the immune system attacks and kills the insulin producing beta-cells in their bodies. Without continuous insulin my niece's 10 year old son will die. They need to check blood sugars consistently through the day to know where his blood sugars are and determine how much insulin is needed for every carb eaten or to correct for any problems. Variables that cannot be controlled and that alter blood sugars include hormonal surges, infections, activity, temperature and emotions. Additionally, these factors are not consistent in their impact on our children's blood sugars. My grand nephew Ethan's sugars climb during soccer, but plummet during baseball. His family uses frequent blood sugar checks to prevent dangerous highs, which can cause, in the short term Ketoacidosis and coma, or the long term complications we all hear about. Frequent checks also catch lows, which left untreated, can lead to a seizure and even death. The simplest way to manage blood sugars is a finger poke to check in with your child and a dose adjustment to keep him in a target range. Self monitoring is cost effective.

Any pediatric endocrinologist would tell you that one blood sugar check a day, as suggested by the study, will certainly endanger and likely kill type 1 diabetic kids. I'm sure this is not your goal and cannot be your recommendation.

I beg you to do everything in your power to ensure that this study. "Glucose Monitoring: Self Monitoring in Patients under 18 years Old," is not used to limit access to blood glucose monitoring supplies for children with type1, who are dependent on state assistance. You would be asking a parent to endanger the life of their child, it would be worse than suggesting they not wear a seat belt, or a bicycle helmet. At this phase, the best protection these children have from the risks of this disease is frequent monitoring and quick adjustments to variances in blood sugars.

Thank you for your consideration.

Jo Hansen
1720 Scenic Ave
Freeland, WA 98249

I understand that there has been testimony by medical professions who are not pediatric endocrinologists that limiting glucose testing strips will not threaten the health of juvenile diabetics.

My grandson has JD and some days his glucose is very volatile, and he needs testing up to 12 times to stabilize his condition.His situation is not uncommon. Limiting access to test strips would be immediately dangerous to these children and carry long-term debilitating effects to children who survive.

Please consider this piece regarding a long-term study from Diabetic Living magazine:

STAY IN CONTROL
Research continues to validate the benefits of tight blood glucose control after the conclusion of the landmark Diabetes Control and Complications Trial(DCCT). The trial ended in 1993 but more than 1370 of its 1441 participants enrolled in a long-term follow-up study-- Epidemiology of Diabetes Intervention and Complications(EDIC).People under tight control continue to show long-term benefits to the eyes, heart, kidney, and nerves, even after their treatment iss monitored less and becomes less rigorous. The latest data from the EDIC report that intensive treatment participants experienced a 42 percent reduction in risk of cardiovascular events and a 64 percent reduction in neuropathy.

Even if you could save money by limiting glucose testing and putting children's lives in danger, the state would pay more in the future for the debilitating conditions that are the long-term effects of poor blood glucose monitoring.

Thank you.

Nancy Hansen
7822 115th Ave., SE, Newcastle WA 98027

Dear Senator Nelson,

I am the aunt of a child with juvenile diabetes, now more commonly referred to as type1. I am horrified to read that the results of the state Health Care Authorities recent study are being considered as a rational to promote severe limitations on testing supplies for juvenile type1 diabetics in need of state aid, quite possibly the most vulnerable of our diabetic community. In reading this study it seems to grossly misunderstand to volatile nature of type1 diabetes in children. Children with type1 produce no insulin of their own. This is caused when the immune system attacks and kills the insulin producing beta-cells in their bodies. Without continuous insulin my son will die. We need to check blood sugars consistently through the day to know where his blood sugars are and determine how much insulin is needed for every carb eaten or to correct for any problems. If you are not aware, variables that cannot be controlled for that alter blood sugars include hormonal surges, infections, activity, temperature and emotions. Additionally, these factors are not consistent in their impact on our children's blood sugars. My son Ethan's sugars climb during soccer, but plummet during baseball. So we use frequent blood sugar checks to prevent dangerous highs, which can cause, in the short term Ketoacidosis and coma, or the long term complications we all hear about. Frequent checks also catch lows, which left untreated, can lead to a seizure and even death. The simplest way to manage blood sugars is a finger poke to check in with your child and a dose adjustment to keep him in a target range. My nephew is checked between 10 & 12 times per day, more when he is ill, starting a new activity, the weather changes etc….. when blood sugars are really unpredictable. This we do to keep him safe for today and give him the chance to live a long and healthy life.

When my sister told Ethan of this possibility he asked, "but what if I have a low blood sugar and I already tested?" He is 10 and when his blood sugar drops he knows that he must treat it with carbohydrates and then recheck and make sure his sugar is back in a safe range so he can go on with his day. There is no magic equation that tells us what exactly how many carbs he needs, so we treat his low and recheck. That higher number allows our kids to know that this disease, which can kill them, is at least for the moment in check and he is safe to be 10 again. Any pediatric endocrinologist would tell you that one blood sugar check a day, as suggested by the study, will certainly endanger and likely kill type 1diabetic kids. And that is wrong.

I beg you to do everything in your power to ensure that this study. "Glucose Monitoring: Self Monitoring in Patients under 18 years Old," is not used to limit access to blood glucose monitoring supplies for children with type1, who are dependent on state assistance. You would be asking a parent to endanger the life of their child, it would be worse than suggesting they not wear a seat belt, or a bicycle helmet. At this phase, the best protection these children have from the risks of this disease is frequent monitoring and quick adjustments to variances in blood sugars…..period. Our family offers you a visit to our home, to spend the day learning what it is like to care for and live with type1 diabetes. Further, we can talk and I can tell you what a typical day is like, for our nephew. Either of these options will provide you an opportunity to truly understand why doing frequent blood sugar checks is the best way to manage this disease, keep our kids safe, out of the emergency room and ensure they have a long, healthy and relatively normal life.
Thank You for Your Time. Respectfully,
Tanya Hansen

To Whom It May Concern -

I am writing to express my deep concern about a potential decision being considered by the Washington State Health Care Authority that would limit the number of blood glucose tests covered for children with Type 1 diabetes. I strongly urge you to keep coverage for blood glucose test strips and to encourage patients with the disease to aggressively monitor their disease to maintain the best possible health.

The tighter a person with Type 1 diabetes can control their blood glucose, the better the chances are to avoid long term health complications. I read the section of the Health Technology Assessment about this issue and think that the study does not adequately reflect an appropriate understanding of Type 1 Diabetes (T1D). T1D is an auto-immune disease where the body destroys the cells in the pancreas that produce insulin. The only way to survive is to inject insulin to make up for the lack of produced insulin. To figure out how much insulin to give, you balance the amount of carbohydrates consumed, the activity level of the individual, the amount of insulin already in effect in the body and most importantly - the blood glucose reading.

The blood glucose reading is how you know if your control is working or not. Most people with T1D do between 4 and 6 tests each day, which involves pricking a finger (or toe) and placing a drop of blood onto a test strip connected to a small machine. The test usually takes about 10 seconds to complete. The machines are in dozens of brands and sell over the counter at every pharmacy.

What the study fails to realize, in my opinion, is that a blood glucose (BG) reading once a day is not a constant number. Your BG can change rapidly and requires constant monitoring to make sure that you dose your insulin appropriately. If you run low or high for prolonged periods of time, you can do real damage to your brain or kidneys. BG tests are inexpensive and easy to do. When a patient does them on a habitual basis, they have tighter control over their disease and can ward off long term complications.

Please make sure that the Health Care Authority does not limit the number of BG tests that a patient can do in a day. The goal ought to be providing the best care possible at the lowest possible cost. Whatever cost savings you achieve from denying BG tests will pale compared to the costs of unmanaged diabetes. Providing the support and reimbursement necessary for people to manage their disease should be the desirable outcome.

I have had T1D for more than 35 years. My son, age 5, also has the disease. If you have any questions about the way in which we deal with the disease or manage it on a day to day basis, I'd be happy to make us available.

Thank you for your time and I look forward to your response.

Jeremy Johnston
7555 NW 23rd Street
Seattle, WA 98117
(206) 240-3133

RE: Health Technology Assessment: Glucose Monitoring

To whom it may concern,

As a 37-year-old who has had Type-I diabetes for 36 years, I cannot stress how important blood glucose testing is to overall health and management of the disease. I often say there are two key breakthroughs in Diabetes in the last two centuries, 1) inject-able insulin, and 2) at-home blood sugar checking. Without both, I would be dead, literally.

I am not sure why this question is coming up for study, but I cannot stress enough how important blood sugar testing is. For a non-diabetic, imagine living a whole day without the ability to feel (wear rubber gloves around the house for a while and see how it feels). For us, the testing is a way to feel how we are doing and take immediate and decisive action. We simply have no other meaningful option. Left untreated, both the short and long term effects of high blood sugars are well known, and are obviously high impact and high cost to the health infrastructure.

From a cost perspective, I can comment on a few points. First, I have no idea why the cost for the strips are so high. I am quite convinced that the prices are falsely elevated because the insurance companies and manufacturers know how important they are. If you want to target cost reduction, go to them and force them to bring down the prices. Reduction in consumption is simply not an option. Second, having had diabetes for 36 years, and still having both eyes, kidneys and feet and a 5.8 A1C indicates I, and my parents back in the day, are doing something right. Given the price of a single hospital stay costs about 5 years worth of strips, and an amputation or kidney transplant costing considerably more, it stands to reason that if you are taking good care of yourself, with frequent glucose monitoring, your overall health care costs will be lower. This is a no brainer.

That's my $0.02.

Respectfully,
Brad Joss
Mercer Island, WA

Dear Senator Nelson,

I understand the difficulty of budget cuts, but if you chose to limit testing supplies for diabetes, you are creating a life-threatening scenario for hundreds of thousands of children in Washington State.

Type 1 diabetes is in my family. I have seen the physical effects of blood sugar that is too high or low, and I know the consequences if it goes unchecked. I've seen the need to measure—not just guess—the amount of insulin or glucose to provide a child. I have seen parents go above and beyond to care for their child, so he or she will have a healthy life as an adult.

If you approve this recommendation, you threaten not only the health of these children, but their families and communities that support them.

Consider your life if you could brake your car only once per day: You can swerve, you can drive in low gear, but you're not safe. That's what you're doing by limiting test strips. Don't do this to our children; don't do this to our state.

Respectfully,
Sondra Kornblatt
--
Sondra Kornblatt
Author
"Restful Insomnia: How to Get the Benefits of Sleep, Even When You Can't"
"A Better Brain at Any Age"

P.O. Box 31403
Seattle, WA 98103
(206) 992-1811
www.restfulinsomnia.com

To: Health Technology Assessment Team
From: Jeff and Kristen Kuhns
Re: Glucose Monitoring for children with diabetes
Date: December 8, 2010

As the parents of a daughter with type 1 autoimmune diabetes, we are alarmed to read your Draft Evidence Report regarding glucose monitoring. It appears that your evaluation of continuous monitors, a relatively new and still developing technology, has resulted in a judgment on the value of SMBG. It is imperative that your team understand and acknowledge that frequent SMBG is a critical component of diabetes management, so that this report does not go unchallenged.

Certainly the premise in the Topic Summary that "the role of glucose monitoring is unclear" is contrary to everything we have been taught and practiced over the past 18 years! Our daughter was diagnosed at age three in 1992, just as the DCCT study results were released. Consequently, we learned from our initial hospital stay about the importance of keeping blood sugar levels as close to normal as possible in order to prevent or delay the onset of complications. Trying to mimic the pancreatic function of insulin secretion has given us a new appreciation for the human body's ability to perform this delicate balancing act. The disease requires a 24/7 effort to stabilize blood sugar levels through insulin, carbohydrates, exercise, stress, illness, etc. which one can only hope to manage with regular blood glucose measurements. In fact, we found that the younger our daughter was, the more frequent blood sugar tests were necessary. Her lower body weight, coupled with her inability to recognize high and low blood sugar symptoms, meant we had to monitor 10-12 times or more a day to keep her safe. Now that she is grown, she typically checks 6-8 times a day.

While it is apparent that the HTA team has invested considerable time in this effort and cited numerous studies, the conclusion of the group is nonsensical. Best practice methodology requires families follow intensive insulin therapy protocol and it would be unethical to attempt anything less. It is a well accepted fact that one of the primary tools families have at their disposal for managing blood sugar level is SMBG and tight control is a prevention strategy that works. Suggesting that there is no evidence of improved effectiveness "beyond one test a day" for children ages 12 and under is frankly inflammatory to families living with type 1 diabetes.

Please consider restating your premise so that it is clear on what issue your team is opining. This is an opportunity to recognize the challenges families with type 1 diabetes face and to ensure that state of the art tools are readily available to families in need.

We are happy to address any follow-up questions you may have.
Sincerely,

Kristen and Jeff Kuhns
5462 East Mercer Way
Mercer island, WA 98040
206-236-1537
kuhnsfamily@seanet.com

I was diagnosed 3 years ago at the age of 50 with Type 1 diabetes. I also have gasteoparesis which affects my ability to determine if my blood sugar is low. I currently have a continuous blood glucose monitor and need this device to tell me when I am getting a low blood sugar. I am constantly woken up in the middle of the night by this device. I have also been on the freeway multiple times driving when this device has alerted me to a low. I am not sure if I could survive without the device. Currently WA state law says insurance should be paying for treatment recommended by your Dr. for diabetes. I had to fight my insurance company and appeal in order to get my monitor back after I was laid off of work and had a change to my insurance. This resulted in several months without this device. Which made everything worse (due to stress). Currently I still have to do a blood stick to verify the reading my monitor is giving me. If I did not have this device I would have had to go to the emergency room/call for a paramedic many times over which would have resulted in an increase cost to my insurance over the cost of the sensors. I am not sure what the current issue is you are dealing with but can't imagine there even should be an issue. Glucose monitoring for diabetics is a must.

Please let me know if you have any questions. Thanks!

Cheryl Laurenzo

To the members of the Washington State Health Care Authority -

As a mother of a child with Type 1 diabetes, I was sickened to read about the recent Health Care Authority's study. It appears you are promoting limits on testing supplies for children affected by diabetes in need of state aid.

The study seems to grossly misunderstand the nature of Type 1 diabetes, which is an unpreventable autoimmune disease in which a person's immune system destroys the insulin-producing cells in the pancreas. Because of this autoimmune attack, the body is unable to produce insulin, and s/he must take insulin through injections in order to stay alive. Blood glucose testing is imperative to determine how to balance blood sugars (by either administering insulin or consuming glucose) throughout the day, and to respond appropriately to any adverse events that occur, such as dangerously high or low blood sugars, which can occur unexpectedly in spite of painstaking planning and management (which every Type 1 diabetes parent does).

A child with Type 1 diabetes who is limited to one blood glucose test each day, as seems to be suggested by the study as good policy, will under certain terms die. Please consult any pediatric endocrinologist and they will certainly confirm this fact that without reservation.

My ten-year-old son requires a minimum of six to ten daily blood glucose tests to maintain life and keep him feeling okay. There are days on which regulating his blood sugar in a manner that does not seriously and permanently damage his eyes, kidneys, cardiovascular system, or brain takes 10-15 tests. When my son was diagnosed at the age of 3 ½, more frequent testing was required as a standard because of the lack of his ability to recognize and communicate symptoms related to dangerously high or low blood glucose levels.

I beg you to ensure that the "Glucose Monitoring: Self-monitoring in Patients Under 18 Years Old" study is not used to severely limit access to blood glucose monitoring for those children with Type 1 diabetes who are dependent on state assistance.

If you would like more information about living with and managing a child who has Type 1 diabetes, I would be more than willing to gather several families to speak with you. I also invite any of you to spend a typical day with me and I will show you firsthand what it takes to keep my son alive, safe and feeling well.

Respectfully,
Suzanne Leamer

To whom it may concern,

I strongly urge you to uphold funding for more extensive daily glucose monitoring for children with Type 1 Diabetes. The necessity of more frequent testing of blood sugar levels is clear when one looks at the developing bodies and lifestyles (constant changes of activity level throughout a typical day) of young Diabetes patients. Allowing for only a single test a day would greatly increase the number of serious complications and ultimately cost the health care system even more than preventative maintenance would cost. This appears to be a short-term savings that will be followed by greatly increased long term costs, and that isn't even taking into consideration the severely reduced quality of life for both these kids and their families!
Please continue funding blood sugar level monitoring at a level that covers what each child needs to stay healthy.

Sincerely,
Nancy Lewis-Williams 206-463-1272
Vashon WA

Dear Committee Members,

My older brother has been a diabetic since 1955, my mother (deceased - 1999) since the late 1970s, my nephew since 2000 and I since 1967. Our family knows very well that intensive diabetes management, which includes glucose monitoring, is essential to keep blood glucose near normal range. My brother and I became diabetics when testing meant hassling with urine and testape, which didn't measure glucose levels accurately. Bruce, my brother, is now suffering from the effects of living with diabetes for over 50 years without strict control of his glucose levels.

Also, the research you are reporting cites evidence that there is no benefit to testing babies with type 1 diabetes more than once per day. Again, you do not understand that intensive diabetes management is essential to keep blood glucose near normal range. The type 1 diabetics I know take multiple daily injections that require multiple blood glucose checks, even very young children. If I need to choose the sub-group of type 1 diabetics to advocate for for a minimum number of strips per day, I request that at least 8-10 are prescribed for young children. We must give them a healthy start in life to continue living in a healthy body.

If I may advocate for all type 1 diabetics, I would like each type 1 diabetic be allowed all the glucose test strips needed to keep glucose levels low. I hope you agree.

Thank you very much.
Lucia M. Linn
6847 37th Avenue NE
Seattle, WA 98115
206 683 0673

Dear Senator Nelson,

I am the parent of a child with juvenile diabetes, now more commonly referred to as type1. I am horrified to read that the results of the state Health Care Authorities recent study are being considered as a rational to promote severe limitations on testing supplies for juvenile type1 diabetics in need of state aid, quite possibly the most vulnerable of our diabetic community.

In reading this study it seems to grossly misunderstand to volatile nature of type1 diabetes in children. Children with type1 produce no insulin of their own. This is caused when the immune system attacks and kills the insulin producing beta-cells in their bodies. Without continuous insulin my son will die. We need to check blood sugars consistently through the day to know where his blood sugars are and determine how much insulin is needed for every carb eaten or to correct for any problems. If you are not aware, variables that cannot be controlled for that alter blood sugars include hormonal surges, infections, activity, temperature and emotions. Additionally, these factors are not consistent in their impact on our children's blood sugars. My son Ethan's sugars climb during soccer, but plummet during baseball. So we use frequent blood sugar checks to prevent dangerous highs, which can cause, in the short term Ketoacidosis and coma, or the long term complications we all hear about. Frequent checks also catch lows, which left untreated, can lead to a seizure and even death. The simplest way to manage blood sugars is a finger poke to check in with your child and a dose adjustment to keep him in a target range.

We check our son between 10 & 12 times per day, more when he is ill, starting a new activity, the weather changes etc….. when blood sugars are really unpredictable. This we do to keep him safe for today and give him the chance to live a long and healthy life.

When I told Ethan of this possibility he asked, "but what if I have a low blood sugar and I already tested?" He is 10 and when his blood sugar drops he knows that he must treat it with carbohydrates and then recheck and make sure his sugar is back in a safe range so he can go on with his day. There is no magic equation that tells us what exactly how many carbs he needs, so we treat his low and recheck. That higher number allows our kids to know that this disease, which can kill them, is at least for the moment in check and he is safe to be 10 again.

Any pediatric endocrinologist would tell you that one blood sugar check a day, as suggested by the study, will certainly endanger and likely kill type 1diabetic kids. And that is wrong.

I beg you to do everything in your power to ensure that this study. "Glucose Monitoring: Self Monitoring in Patients under 18 years Old," is not used to limit access to blood glucose monitoring supplies for children with type1, who are dependent on state assistance. You would be asking a parent to endanger the life of their child, it would be worse than suggesting they not wear a seat belt, or a bicycle helmet. At this phase, the best protection these children have from the risks of this disease is frequent monitoring and quick adjustments to variances in blood sugars…..period.

I offer you a visit to our home, to spend the day learning what it is like to care for and live with type1 diabetes. Further, we can talk and I can tell you what a typical day is like, for our son. Either of these options will provide you an opportunity to truly understand why doing frequent blood sugar checks is the best way to manage this disease, keep our kids safe, out of the emergency room and ensure they have a long, healthy and relatively normal life.

Thank You for Your Time.

Respectfully,
Lieschan Lopuszynski

To Whom it May Concern:

As a person with Diabetes one of the important things is being able to test frequently in order to have control of my blood sugars. Without frequent testing it is not possible to manage my diabetes in the way that helps me avoid complications and other problems that arise from diabetes such as high blood sugars and low blood sugars, etc. and being able to treat highs and lows effectively.

Now saying this, children with diabetes are much more prone to highs and lows and need to test even more frequently. This idea of testing only once a day is ludicrous and not only is unsafe but endangers the very life of the child with diabetes.

I know this idea came to save money but it is dangerous and just plain wrong. Whoever came up with this idea to only allow one test strip a day has no idea what they are talking about and this idea needs to be squashed.

Please ban this idea once and for all.

Please show you care about keeping all children with diabetes safe and stop this ludicrous idea.

Sincerely,
Kathryn Mack

By the People, For the People,

I understand there's a new study in town which suggests children receiving state aid should receive a significant reduction in their access to diabetes testing supplies.

Is this for real? There really are death panels? Is it some distorted new sin tax? On juvenile diabetes?
In all seriousness, a friend of mine would be **directly affected** by this lark, not to mention the hell brought down on his entire family. Can you *imagine?*

What ever happened to women and children first?

Well, thank you for your time, and thank you for the sober and reflective consideration and redress of this vicious matter.

In pursuit of those elusive *American Values* I keep hearing bandied about,

Karyn Martin

As a parent of a child with Type 1 Diabetes, I implore those who have undertaken this study to look closer into the safety, cost and health impact of blood glucose monitoring.
Without 6-8 blood glucose checks a day/night, my child's health and safety are impaired significantly. Blood glucose levels too low, and my child with succumb to seizures, brain damage, and die. Blood glucose levels too high, and irreparable damage is done to his organs, including loss of eye site and limb loss. How much does it cost the health care system to take care of my son with those kinds of health issues??

The research is extremely clear - multiple blood glucose readings are essential to good diabetes management.

Rebecca McFarland [mcfarland.r@mail.wsd.wednet.edu]

Senator Oemig,

During your campaign your message was; if you have any questions or concerns, please let me know. Well, that time has come.

I have some very serious concerns about an issue that will soon be before the Washington Senate. Based on the findings of one single recent study it is being suggested that children receiving state aid should receive significant reduction in their access to diabetes testing supplies.

I have a nephew diagnosed 2 years ago with Juvenile Diabetes (also known as Type 1). I have witnessed the monumental changes this diagnosis has brought to my brother's entire family. They test my nephews blood sugar 8-12 times daily following the protocol given them by Children's Hospital here in Seattle. They are fortunate to have good health insurance coverage and a high income which allows them to do this as the supplies are very expensive. Each test strip over the counter costs one dollar ($1). It is no wonder that their might be motivation to limit the amount of test strips the children receiving state funds should receive. However, I am horrified to read that the results of the state Health Care Authorities recent study are being considered as a rational to promote severe limitations on testing supplies for juvenile type1 diabetics in need of state aid, quite possibly the most vulnerable of our diabetic community.

In reading this study it seems to grossly misunderstand to volatile nature of type1 diabetes in children. Children with type1 produce no insulin of their own. This is caused when the immune system attacks and kills the insulin producing beta-cells in their bodies. Without continuous insulin these children will die. My brother and his wife need to check my nephew's blood sugars consistently through the day to know where his blood sugars are and to determine how much insulin is needed for every carb eaten or to correct for any problems. They weigh and measure everything he eats. If you are not aware, variables that cannot be controlled for that alter blood sugars include hormonal surges, infections, activity, temperature and emotions. Additionally, these factors are not consistent in their impact on our children's blood sugars.

My nephew's sugars climb during soccer, but plummet during baseball. So they use frequent blood sugar checks to prevent dangerous highs, which can cause, in the short term Ketoacidosis and coma, or the long term complications we all hear about blindness, loss of limbs etc. Frequent checks also catch lows, which left untreated, can lead to a seizure and even death. The simplest way to manage blood sugars is a finger poke to check in with your child and a dose adjustment to keep him in a target range.

Any pediatric endocrinologist would tell you that one blood sugar check a day, as suggested by the study, will certainly endanger and likely kill type 1diabetic kids. This is wrong!
I beg you to do everything in your power to ensure that this study. "Glucose Monitoring: Self Monitoring in Patients under 18 years Old," is not used to limit access to blood glucose monitoring supplies for children with type1 Diabetes, who are dependent on state assistance.

You would be asking a parent to endanger the life of their child, it would be worse than suggesting they not wear a seat belt, or a bicycle helmet. At this phase, the best protection these children have from the risks of this disease is frequent monitoring and quick adjustments to variances in blood sugars…..period. Children who have been diagnosed with Type 1 Diabetes face enough challenges and complications in their young lives without adding this additional burden. Type 1 Diabetes is not brought on by lifestyle, inactivity or poor diet. Through no fault of their own these children's young bodies are simply unable to produce insulin. Let us not endanger their lives and add to the burdens they and their families already face due to their disease. My husband, my son (voting absentee from college in California), my daughter (who voted for the first time this last election) and I are all very concerned about this issue having witnessed my nephew struggle with his diagnosis. We appreciate your attention to this issue and the opportunity for our kids to witness first-hand, democracy in action.

Respectfully,
Dorota McHenry and family

To Whom It May Concern -

I am writing today in response to the Health Technology Assessment study on glucose monitoring for children with Type 1 diabetes. I am deeply concerned that the study could be foreshadowing a decision by the Washington State Health Care Authority to limit the number of blood glucose tests covered for children with Type 1 diabetes. I strongly urge you to continue coverage of blood glucose test strips and to encourage patients with the disease to follow aggressive testing regimens, as said regimens are recognized as the best option for monitoring glucose levels to maintain good health.

What the study fails to recognize is that a glucose test is a snapshot in time of the glucose level, and glucose levels change rapidly throughout any given day. Constant monitoring is the only tool diabetics have to ensure they are adjusting insulin and food intake in response to their body's needs. I challenge the state to also examine the potential (and highly likely) increased cost of the consequences of poorly managed diabetes in the form of hospital or emergency room visits and treatment of those patients reliant upon state-sponsored health care. Managing Type 1 diabetes responsibly with only one test per day is simply not possible, and whatever cost savings the state can achieve by limiting access to tests strips will not come close to the costs of poorly managed diabetes.

Thank you for your time and consideration.

Sincerely,
Meryl C. Mims

My name is Jami and I live in Everett, WA. My Sister and I both have Type 1 Diabetes. Together we have had this disease for over 35 years. My Sister Amy takes multiple medications and has had several eye surgeries due to the effects of high blood sugars. The importance of keeping her blood sugar in a normal range is critical. We both have the insulin pump through Medtronic Mini Med. We both love it but it is not enough to keep our sugars in a normal range all the time. We both looked into the continuous glucose monitoring system to help keep our blood sugars in check throughout the day. It was too expensive for both of us. Our medical supplies right now are very expensive even with our medical insurance. It is very important for Type 1 diabetics to be able to afford the tools to achieve an excellent A1C. We need to be comfortable with keeping our blood sugars in a normal range by being able to look at our pump to see if we are going up or going down. There is a constant fear of passing out when trying to keep your blood sugars around 100-120. We would like to see more coverage for people living with this disease. We deserve to live a normal life and avoid medical complications that can be easily corrected with a simple device that could change so many lives.

I am thankful for being able to share this and I am excited for changes ahead for well deserved Type 1 and Type 2 Diabetics!

Jami Pratt

To Whom It May Concern –

I am writing today in response to the Health Technology Assessment study on glucose monitoring for children with Type 1 diabetes. I am deeply concerned that the study could be foreshadowing a decision by the Washington State Health Care Authority to limit the number of blood glucose tests covered for children with Type 1 diabetes. I strongly urge you to continue coverage of blood glucose test strips and to encourage patients with the disease to follow aggressive testing regimens, as said regimens are recognized as the best option for monitoring glucose levels to maintain good health.

Blood glucose monitoring is absolutely essential to the management of Type 1 diabetes. The study does not seem to reflect an appropriate understanding of Type 1 diabetes. It is an autoimmune disease where the cells that produce insulin are destroyed, requiring a person with diabetes to take insulin injections to make up for the insulin one's body no longer produces. Blood glucose monitoring is *the compass* that guide's a diabetics decisions on how much insulin is required to maintain safe blood glucose levels.

As someone who has dear friends with Type 1 diabetes, I can tell you that blood glucose testing is critical to their ability to determine how much insulin they need throughout the day. Regular testing allows them to respond appropriately to any adverse events that occur, such as dangerously high or low blood sugars, which can occur unexpectedly in spite of the best planning and management. On average, they test between four to six times a day, exceeding that number in times of illness or extreme physical activity.

I simply cannot imagine that they could appropriately manage their diabetes based on the data provided by one test a day. What the study fails to recognize is a glucose test is a snapshot in time of the glucose level. Glucose levels change rapidly throughout any given day with the intake of food, physical activity, stress, etc. Constant monitoring is the only tool we have to ensure we're adjusting our insulin and food intake in response to our body's needs.

Please ensure individuals with Type 1 diabetes have access to the appropriate tools to manage this disease. Do not threaten the number of blood glucose tests a patient can do in a day by limiting coverage for test strips. Whatever cost savings the state can achieve by limiting access to tests strips will not come close to the costs of unmanaged diabetes.

Thank you for your time and consideration.

Sincerely,
Danielle S. Regan

To the members of the Washington State Health Care Authority -

As a person with Type 1 diabetes, I was alarmed to read about the state Health Care Authority's recent study that seems designed to promote sharp limits on testing supplies for diabetics in need of state aid.

The study seems to grossly misunderstand the nature of Type 1 diabetes (formerly called Juvenile Diabetes), which is an unpreventable autoimmune disease in which a person's immune system destroys the insulin-producing cells in the pancreas. Because of this autoimmune attack, a type 1 diabetic's body produces no insulin, and s/he must take insulin through injections in order to stay alive. Blood glucose testing is imperative to determine how much insulin must be administered throughout the day, and to respond appropriately to any adverse events that occur, such as dangerously high or low blood sugars, which can occur unexpectedly in spite of the best planning and management.

A type 1 diabetic child who is limited to one blood glucose test each day, as seems to be suggested by the study as good policy, will DIE. Any pediatric endocrinologist will tell you that without reservation.

In order to keep myself healthy, I perform a blood glucose test a minimum of six to ten times a day. This is imperative in attempting to maintain blood sugar levels that maintain health. Some days, during illness for example, it might take 10-15 tests. For very young children, especially infants and toddlers, more frequent testing has to be the standard because of their poor ability to recognize and communication symptoms related to dangerously high or low blood glucose levels.

I beg you to ensure that this study, "Glucose Monitoring: Self-monitoring in Patients Under 18 Years Old", is not used to severely limit access to blood glucose monitoring for those children with type 1 diabetes who are dependent on state assistance.

If you would like more information about living with type 1 diabetes, I would be happy to speak with you. Let’s do what’s right for children with diabetes to ensure they are safe and healthy.

Thank you for your time.

Respectfully,
Ann Ripley
206-729-0342
riple@comcast.net

To Whom it May Concern

I want to give you my thoughts on glucose monitoring. I have a 9 year old daughter that was diagnosed with diabetes two years ago. Glucose monitoring is what keeps her health going in the right direction. Without it I don't know how we could come close to managing her health and knowing whether or not her glucose levels were in a safe place so as too preserve her body. We look forward to the day when she can have continuous monitoring to avoid the low blood sugars that sometimes occur.

I look to my brother as an example of how not to manage blood sugars. He rarely tests and 25 years after being diagnosed is experiencing many complications. I believe that knowledge is power. It is impossible to manage diabetes without knowing where you are and where you are headed.

Jessica Royce

Subject: Public Comment for: Glucose Monitoring
From:shannonvalleylumber@hotmail.com
Date: Fri, 10 Dec 2010 12:27:33 -0800
To: shtap@hca.wa.gov

To Whom It May Concern –

I am writing today in response to the Health Technology Assessment study on glucose monitoring for children with Type 1 diabetes. I am deeply concerned that the study could be foreshadowing a decision by the Washington State Health Care Authority to limit the number of blood glucose tests covered for children with Type 1 diabetes. I strongly urge you to continue coverage of blood glucose test strips (min.4-6 per day) and to encourage patients with the disease to follow aggressive testing regimens, as said regimens are recognized as the best option for monitoring glucose levels to maintain good health.

My younger daughter was diagnosed twenty years ago with type 1 diabetes when she was a child. Her ability to test her blood glucose level whenever she needed to was paramount to her ability to continue attending public school and participate in extra curricular activities. Now as an adult, it helps keep her body in check so she can remain healthy enough to carry a child. Without the ability to closely monitor her blood glucose levels as a child, there is no way her body would have maintained enough strength to be the healthy adult she is today. My brother in-law was also diagnosed with type 1 diabetes as a child before blood glucose monitoring strips were available. His body is now failing due to the lack of blood glucose control through-out his life. He suffers from multiple complications. He had a kidney transplant by age 50, he has lost two toes and suffers from gout. This is not the life I want for my daughter or any other child already suffering and attempting to cope with a very difficult disease.
Diabetes complications are **far more costly** than the test strips.

Thank you for your consideration

Shannon Scott
shannonvalleylumber@hotmail.com

To Whom It May Concern –

I am writing today in response to the Health Technology Assessment study on glucose monitoring for children with Type 1 diabetes. I am deeply concerned that the study could be foreshadowing a decision by the Washington State Health Care Authority to limit the number of blood glucose tests covered for children with Type 1 diabetes. I strongly urge you to continue coverage of blood glucose test strips and to encourage patients with the disease to follow aggressive testing regimens, as said regimens are recognized as the best option for monitoring glucose levels to maintain good health.

My younger sister was diagnosed twenty years ago with type 1 diabetes when we were children. Her ability to test her blood glucose level whenever she needed was paramount to her ability to continue attending public school and participate in extra curricular activities. Now as an adult, it helps keep her body in check so she can remain healthy enough to carry a child. Without the ability to closely monitor her blood glucose levels as a child, there is no way her body would have maintained enough strength to be the healthy adult she is today. Our uncle was also diagnosed with type 1 diabetes as a child -before blood glucose monitoring was available to the public. His body in now failing due to the lack of blood glucose control thought his life. He had a kidney transplant by age 50, he has lost two toes and suffers from gout. This is not the life I want for my sister or any other child already suffering and attempting to cope with a very difficult disease.

Thank you for your consideration

Stephanie Scott
ss7rose@yahoo.com

To the members of the Washington State Health Care Authority -

As a mother of a child with Type 1 diabetes, I was alarmed to read about the state Health Care Authority's recent study that seems designed to promote sharp limits on testing supplies for diabetics in need of state aid.

The study seems to grossly misunderstand the nature of Type 1 diabetes (formerly called Juvenile Diabetes), which is an unpreventable autoimmune disease in which a person's immune system destroys the insulin-producing cells in the pancreas. Because of this autoimmune attack, a type 1 diabetic's body produces no insulin, and s/he must take insulin through injections in order to stay alive. Blood glucose testing is imperative to determine how much insulin must be administered throughout the day, and to respond appropriately to any adverse events that occur, such as dangerously high or low blood sugars, which can occur unexpectedly in spite of the best planning and management.

A type 1 diabetic child who is limited to one blood glucose test each day, as seems to be suggested by the study as good policy, will die. Any pediatric endocrinologist will tell you that without reservation.

My child requires a minimum of six to eight daily blood glucose tests to maintain life and keep her feeling okay, and that is generally only when we are using continuous glucose monitoring to supplement finger pokes (what the state-commissioned study calls SMBG). There are days on which regulating her blood sugar in a manner that does not seriously and permanently damage her eyes, kidneys, cardiovascular system, or brain takes 10-15 tests. For very young children, especially infants and toddlers, more frequent testing has to be the standard because of their poor ability to recognize and communication symptoms related to dangerously high or low blood glucose levels.

I beg you to ensure that this study, "Glucose Monitoring: Self-monitoring in Patients Under 18 Years Old", is not used to severely limit access to blood glucose monitoring for those children with type 1 diabetes who are dependent on state assistance.

If you would like more information about living with and managing a child with type 1 diabetes, I would be happy to speak with you. I also invite any of you to come spend a day with my family, to get a sense of what is really involved in keeping a child with diabetes safe and healthy, so that you can come to any discussions of state health care policy regarding diabetes with accurate information and a realistic perspective.

Thank you for your time.

Respectfully,

JoAnn Silkes

We have a 16 year old son who was diagnosed with Type 1 when he was 14. He utilizes an insulin pump for insulin delivery and tests his blood glucose with a meter and test strips at least 10 times, but usually more, per day. We hope to use a continuous glucose monitoring system in the near future, but are prevented at this time due to cost.

Intensive insulin therapy is essential to minimizing further organ damage or failure as well as ensuring our son's overall health into old age. Through intensive testing and insulin therapy, he has been able to maintain an A1C of 5.6 for the last year. We strongly believe that continuous glucose monitoring could help him lower his A1C yet more. Our goal is that he maintain as close to normal blood glucose levels at all times, and thereby greatly reduce the chances that he will develop another autoimmune disease or any other type of disease in the future. Vigilant glucose monitoring along with insulin therapy is the key to achieving that goal.

Only when armed with accurate blood glucose information as a result of frequent testing or continuous monitoring, can we fight the unpredictable nature of this disease and ensure that our son lives a healthy and normal life.

Thank you for your time,
Tony and Laurel Smith

Having been diagnosed at age 50 as a Type 1 I was all for whatever worked best to control this disease. I purchased a CGM which was not cheap and not covered by insurance. I used it for about 6 months. What it did do was show me trends. I am not on a pump and part of that decision came from wearing the CGM. I don't want to be attached to something full time. But the CGM was great for showing me things like spiking up to 200 at midnight. From that data I changed my long acting shots from one a day to two. It was great for showing me how my body reacted to food and the insulin I was taking. You understand that if you eat certain food you numbers will go up but if you take the right amount of insulin they will go back down. It helped me understand that pizza was slow to process and sugar (juice, candy, etc.) was much faster. With pizza I can do two shots about 1 hour apart and get the same results as someone on a pump. It helps when my schedule changes.

I have a terrible time when I travel. I believe it shows me how stress changes my numbers. It's not something I want to rely on all the time but it's a great tool for understanding more. No, it's not accurate but neither are strips. I can take tests on three meters and end up with three numbers possibly 30 points apart. I test and takes shots probably 8 times a day. My A1C is 6.0. The CGM is a great teaching tool. It's pretty accurate between 80 and 200.

I never had any complications or issues when using it. Yes it hurts to insert it but that last a second or two. It's was comfortable and always worked correctly.

I think the big issue with kids is getting them to want to take care of themselves and understanding they shouldn't be embarrassed. If you need to check your sugar check it or take a shot. It doesn't matter where you are or who see you. You are the important one, not them. I had a guy on an airplane ask me once "What if I don't like needles?" I told him not to watch.

Thanks for the opportunity to comment. I find most of the research is done on younger people. That's a little frustrating. I should be important too.

Wendy Smith

I am writing today in response to the Health Technology Assessment study on glucose monitoring for children with Type 1 diabetes. I'm deeply troubled that the study may be used to justify a reduction in coverage for test strips. Please ensure individuals with Type 1 diabetes have access to the appropriate tools to manage their disease. I urge you not to threaten the number of blood glucose tests a patient can do in a day by limiting coverage for test strips. Whatever cost savings the state can achieve by limiting access to tests strips will not even compare to the costs of treating complications resulting from unmanaged diabetes.

Emily Sproule
Staffing Associate | Microsoft Office Division | 425.538.7368 | emispro@microsoft.com

Hello,

Having become familiar with the needs and tragic outcomes of diabetics inability to control their blood sugar, I am urging you to support advances in glucose monitoring as it is both an definite increase in the quality of life of those with diabetes, and is also a wise investment in helping to avoid of delay the extremely high costs associated with the complications of the disease.

Thank You,
John Sullivan

President

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jbs@thebuildingpermitcompany.com
www.thebuildingpermitcompany.com

To whom it may concern:

I am writing today in response to the Health Technology Assessment study on glucose monitoring for children with Type 1 diabetes. I'm deeply troubled that the study may be used to justify a reduction in coverage for test strips. Please ensure individuals with Type 1 diabetes have access to the appropriate tools to manage their disease. I urge you not to threaten the number of blood glucose tests a patient can do in a day by limiting coverage for test strips. Whatever cost savings the state can achieve by limiting access to tests strips will not even compare to the costs of treating complications resulting from unmanaged diabetes.

Thank you,

Liz Taylor
Staffing Consultant | Microsoft Office Division | (w) 425.707.5677 | (e) lizwest@microsoft.com

Hello HTA,

Having a type I diabetic daughter I am all to familiar with the hell these folks go through their entire lives from this horrible auto immune disease. The sure way to mitigate the effects of it are to carefully monitor one's blood sugar. For most type I's this is five to ten times per day.

The cost of the monitoring strips is unconscionable at about $1.00 each. The manufacture's know they have a captive audience of around six million people in the US with type I and they are milking the situation for all the money they can get out of it. Type I's alone will consume 30-60 million strips per day every day. Quite a cash cow for the strip manufactures.

It is time to regulate the cost of these strips and encourage diabetics to use them often to control their blood sugar which in turn prevents much more serious problems, like loss of sight, diabetic ulcers, loss of limbs, etc. The cost of treating an impaired diabetic is astronomical. Much of this can be prevented with constant blood glucose monitoring which can be strongly encouraged if the cost of monitoring is reasonable, like 5 cents per strip that costs 1 cent to manufacture.

Please consider mandating the low cost of monitoring strips to ease the financial and health care cost burden on these type I's who through no fault of their own must live with this awful condition.

Sincerely,

Chris Warner
3514 NW 67th St.
Seattle WA 98117
206-782-1277

To whom it may concern:

I wish to comment on the Health Technology Assessment of Glucose Monitoring. I am alarmed to read that so little value is being ascribed to frequent monitoring of blood glucose levels for children and youth with type 1 diabetes.

The Diabetes Control and Complications Trial has shown the benefits of intensive diabetes management in terms of reduction of long-term complications. Intensive management consists of administering multiple doses of insulin to match levels of food intake and exercise. Blood glucose readings are an essential part of this equation. Perhaps, in theory, one could eat the exact same meals at the exact same times, get exactly the same level of exercise at the same each day, never get sick and maintain a constant level of stress. In this case it might be possible to control blood glucose without testing multiple times a day. But of course this is not reality. Toddlers with diabetes develop colds and fevers which increase blood sugar levels. Children won't eat the same number of carbohydrates every day. High school-aged youth get stressed over college applications, unfair curfews and broken hearts and the stress plays a significant role in variations in blood sugar levels.

I have grown up in a family with type 1 diabetes. My brother was diagnosed at age 5, in 1955. I can remember the "dark ages" when there was no way to monitor blood sugar levels. Either my brother passed out and was carried home in the back of a station wagon (hypoglycemia), or we could measure sugar in his urine that indicated that his blood sugar levels had been far too high earlier in the day. It was a nightmare, and my brother is now paying the price for this in terms of complications. I have a twenty one year old son with type 1 diabetes and I am so grateful that he is able to monitor his blood sugar frequently throughout the day. Multiple checks and an insulin pump have allowed him to travel abroad, crossing time zones and changing his schedule of eating, sleeping and exercise. Without testing he would have no way to determine how much insulin was needed to control his blood sugars. Testing is a way to give people with diabetes and their families some of the control over their lives that those without diabetes enjoy.

Intensive insulin control comes at the price of more frequent hypoglycemia, but this should not be viewed as a reason NOT to check blood glucose levels. These checks are necessary to detect hypoglycemia before an individual is unable to help himself, i.e., before a teen gets behind the wheel of a car, before a mother puts a cranky toddler to bed, or before a boy scout with diabetes passes out on a hike.

My family has good medical insurance. When my son's test strips run out before insurance will pay for more, we have the means to buy more strips out of pocket. Please do not penalize children and families without these resources by taking away the tools they need to perform adequate testing.

Thank you for your consideration.

Most sincerely,

Christine Webber

To whom it may concern,

I write this message from Greece, as an American student with type-1 diabetes. I am 21 years old and have had type-1 diabetes for 9 years, and am here to write about the Health Technology Assessment of Glucose Monitoring. Since developing the disease, I have longed for more freedom from this tyrannous disease, and one of my chief sources of freedom has been the ability to test my glucose levels, at will, several times a day. I test my glucose levels often, eight to ten times a day, not because I enjoy the process. How could I? To test my blood sugar requires me to prick one of my fingers with a needle, and when the blood is drawn, I risk disturbing others and hearing their complaints. But I do this because of the freedom it gives me, and for the long term health benefits.

The report being written cannot find many studies which show that testing glucose levels more than once a day is beneficial to health. I would hope so. In order to see if it is beneficial, people with type-1 diabetes would be compelled, in order to make the test scientifically sound, to test only once a day. The thought of doing that is so abominable to a diabetic, and puts him or her at such risk, that such tests would be entirely unethical.

From personal experience, I can attest to how testing my glucose levels eight to ten times a day is not enjoyable, or convenient, or inexpensive. But I can say that it is necessary, and the mere thought of testing less than that is horrific to me. It might be theoretically possible for someone with type-1 diabetes to need only test once a day, if they were to keep the conditions the same daily. But, the life of a diabetic is not a Newtonian scientific model, where every facet of life can be precisely calculated and foreseen. There is chaos in having diabetes. There are days where my blood sugars are consistently high, even when everything else is the same. There are also days when my blood sugars also tilt to lower numbers, again, even when all else remains constant. There have been times where I have not accounted for how many test strips are available, and during those times, I feel like a wolf without a nose, or a blind eagle, losing a faculty which makes a meaningfully free life possible.

Glucose levels should be tested eight-to-ten times a day for healthy living. For families with few financial resources and children with type-1 diabetes, the very idea of them permitting their children to test once a day and no more, out of sheer financial necessity, is barbarous, horrific and inexcusable. It is wholly unfair to those families to deny them a medical necessity. Those children will invariably have worse health than if they were able to test eight to ten times a day, and cripple their chances of living a normal, healthy life. It is a waste- not just for those children, but also for the country to be denied such manpower. Sonia Sotomayor, for example, has type-1 diabetes.

It is simply astonishing to me that this study is being seriously considered, when the only way to vindicate or dismiss its claims would be to put type-1 diabetics are such a grave health risk. For all the pain and inconvenience testing glucose levels causes, type-1 diabetics still test numerous times a day because it is necessary for good health. If it wasn't, we'd be the first ones to test less!

Sincerely,
Clark Webber

To the members of the Washington State Health Care Authority -

As a mother of a child with Type 1 diabetes, I was alarmed to read about the state Health Care Authority's recent study that seems designed to promote sharp limits on testing supplies for diabetics in need of state aid.

The study seems to grossly misunderstand the nature of Type 1 diabetes (formerly called Juvenile Diabetes), which is an unpreventable autoimmune disease in which a person's immune system destroys the insulin-producing cells in the pancreas. Because of this autoimmune attack, a type 1 diabetic's body produces no insulin, and s/he must take insulin through injections in order to stay alive. Blood glucose testing is imperative to determine how much insulin must be administered throughout the day, and to respond appropriately to any adverse events that occur, such as dangerously high or low blood sugars, which can occur unexpectedly in spite of the best planning and management.

A type 1 diabetic child who is limited to one blood glucose test each day, as seems to be suggested by the study as good policy, will die. Any pediatric endocrinologist will tell you that without reservation.

My child requires a minimum of six to eight daily blood glucose tests to maintain life and keep her feeling okay, and that is generally only when we are using continuous glucose monitoring to supplement finger pokes (what the state-commissioned study calls SMBG). There are days on which regulating her blood sugar in a manner that does not seriously and permanently damage her eyes, kidneys, cardiovascular system, or brain takes 10-15 tests. For very young children, especially infants and toddlers, more frequent testing has to be the standard because of their poor ability to recognize and communication symptoms related to dangerously high or low blood glucose levels.

I beg you to ensure that this study, "Glucose Monitoring: Self-monitoring in Patients Under 18 Years Old", is not used to severely limit access to blood glucose monitoring for those children with type 1 diabetes who are dependent on state assistance.

If you would like more information about living with and managing a child with type 1 diabetes, I would be happy to speak with you. I also invite any of you to come spend a day with my family, to get a sense of what is really involved in keeping a child with diabetes safe and healthy, so that you can come to any discussions of state health care policy regarding diabetes with accurate information and a realistic perspective.

Thank you for your time.

Respectfully,
Melinda Woods, mother of 13 year old Darrien

Blood glucose monitoring is a critical step in combating this horrible disease. What I wouldn't do to be able to monitor myself closer and avoid constant pricking of my fingers. Unless one has to take on this endeavor daily, I don't think that the real need for this research should be dismissed. Diabetes is unfortunately the disease of our time and will only continue to get worse. The better chances we have of monitoring ourselves around the clock, the better we can win at the "head game" of numbers that we are constantly dealing with.

Regards,

Beth Woolford
Seattle, WA