Diabetes Technology and Therapy in the Pediatric Age Group

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Introduction

AMONG ALL THE AGE GROUPS, achieving goal HbA1c while avoiding hypoglycemia presents perhaps the greatest challenge in the pediatric age group. Recent data from the Type 1 Diabetes (T1D) Exchange report the highest mean HbA1c in children and adolescents with a peak of 9.2% in 17-year-olds (1). In contrast, data from European registries suggest that HbA1c has decreased over the past decades (2,3), although mean HbA1c remains well above the goal of 7.5% established by ISPAD (4) and recently updated by the ADA (5). Data on severe hypoglycemia (SH) are somewhat more encouraging. Data from Australia (6) and Germany and Austria (3,7) demonstrate a decrease in SH in youth with T1D. Notably, in these datasets the association of SH with HbA1c has flattened across the span of HbA1c, contrary to the DCCT data in which SH increased in a curvilinear fashion with lower HbA1c (8).

A number of reasons exist for the relatively poorer outcomes in pediatric as compared to adult T1D patients, including the physiologic changes associated with puberty and the developmental transition from parental focused diabetes self-care to patient self-care, among others. The need for improved diabetes care, combined with the adaptability of younger people to newer technology, has fueled extensive research with diabetes technology in the past year. Although the role of technology in pediatric diabetes care is well established, research specific to this population is required to establish its safety, acceptability, and effectiveness for children.

We conducted a Medline search for articles dealing with the following topics: diabetes technology, insulin pump therapy (CSII), continuous glucose monitoring (CGM), closed-loop systems, and new therapies in T1D relating to the pediatric age group (0–18 years). We focused on key articles that offer some insight into these issues and were published between July 1, 2014, and June 30, 2015.

In the last year, studies reviewed below evaluated the impact of modern technology on improved metabolic control with evidence of marked disparities in insulin treatment method and diabetes outcomes between different ethnic groups. Another study demonstrated that the accuracy of blood glucose meters affects glucose control and hypoglycemia rate. Some of the studies evaluated the implications and advantages of using the real-time continuous glucose monitoring (CGM) that provides 24-hour continuous glucose measurements in pediatric patients with T1D, in children at risk for T1D, and as a tool for evaluation of prediabetes in obese children. In the last year, different prototypes of closed-loop systems were evaluated. Results about the safety and efficacy of these systems in different settings at home and at diabetes camp, and in very young children are reviewed below. Other reviewed studies evaluated the impact of administration of metformin on BMI and insulin sensitivity in adolescents with T1D, and the effect of oral insulin on immune responses in children at high risk for T1D.

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Key Articles Reviewed for this Article**Contrasting the clinical care and outcomes of 2,622 children with type 1 diabetes less than 6 years of age in the United States T1D Exchange and German/Austrian DPV registries**

Maahs DM¹, Hermann JM², DuBose SN³, Miller KM³, Heidtmann B⁴, DiMeglio LA⁵, RamiMerhar B⁶, Beck RW³, Schober E⁶, Tamborlane WV⁷, Kapellen TM⁸, Holl RW², for the DPV Initiative and the T1D Exchange Clinic Network

Diabetologia 2014; **57**: 1578–85

Racial-ethnic disparities in management and outcomes among children with type 1 diabetes

Willi SM¹, Miller KM², DiMeglio LA³, Klingensmith GJ⁴, Simmons JH⁵, Tamborlane WV⁶, Nadeau KJ⁷, Kittelsrud JM⁸, Huckfeldt P⁹, Beck RW², Lipman TH¹, T1D Exchange Clinic Network

Pediatrics 2015; **135**: 424–34

Accuracy of blood glucose meters for self-monitoring affects glucose control and hypoglycemia rate in children and adolescents with type 1 diabetes

Boettcher C, Dost A, Wudy SA, Flechtner-Mors M, Borkenstein M, Schiel R, Weitzel D, Bechtold-Dalla Pozza S, Wolf J, Holl W, German/Austrian Diabetes Prospective Documentation Initiative

Diabetes Technol Ther 2015; **17**: 275–82

Youth and parent measures of self-efficacy for continuous glucose monitoring: survey psychometric properties

Rasbach LE^{1,2}, Volkening LK¹, Markowitz JT¹, Butler DA¹, Katz ML¹, Laffel LMB¹

Diabetes Technol Ther 2015; **17**: 327–34

Early hyperglycemia detected by continuous glucose monitoring in children at risk for type 1 diabetes

Steck AK, Dong F, Taki I, Hoffman M, Klingensmith GJ, Rewers MJ

Diabetes Care 2014; **37**: 2031–33

Continuous glucose monitoring and its relationship to hemoglobin A1c and oral glucose tolerance testing in obese and prediabetic youth

Chan CL¹, Pyle L², Newnes L¹, Nadeau KJ¹, Zeitler PS¹, Kelsey MM¹

J Clin Endocrinol Metab 2015; **100**: 902–10

A remote monitoring system for artificial pancreas support is safe, reliable, and user-friendly

Oron T, Farfel A, Muller I, Miller S, Atlas E, Nimri R, Phillip M

Diabetes Technol Ther 2014; **16**: 699–705

MD-Logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial

Nimri R¹, Muller I¹, Atlas E¹, Miller S¹, Fogel A¹, Bratina N², Kordonouri O³, Battelino T^{2,4}, Danne T³, Phillip M^{1,5}

Diabetes Care 2014; **37**: 3025–32

Feasibility of overnight closed loop therapy in young children with type 1 diabetes aged 3–6 years: comparison between diluted and standard insulin strength

Elleri D¹, Allen JM¹, Tauschmann M¹, El-Khairi R¹, Benitez-Aguirre P^{1–3}, Acerini CL¹, Dunger DB¹, Hovorka R¹

BMJ Open Diabetes Res Care 2014; **2**: e000040

A randomized trial of a home system to reduce nocturnal hypoglycemia in type 1 diabetes

Maahs DM¹, Calhoun P², Buckingham BA³, Chase HP¹, Hramiak I⁴, Lum J², Cameron F⁵, Bequette BW⁵, Aye T³, Paul T⁴, Slover R¹, Wadwa RP¹, Wilson DM³, Kollman C², Beck RW², In Home Closed Loop Study Group

Diabetes Care 2014; **37**: 1885–91

Overnight glucose control with an automated, unified safety system in children and adolescents with type 1 diabetes at diabetes camp

Ly TT^{1,2}, Breton MD³, Keith-Hynes P³, De Salvo D¹, Clinton P¹, Benassi K¹, Mize B³, Chernavsky D³, Place J⁴, Wilson DM¹, Kovatchev BP³, Buckingham BA¹

Diabetes Care 2014; **37**: 2310–16

Effects of high-dose oral insulin on immune responses in children at high risk for type 1 diabetes: the Pre-POINT randomized clinical trial

Bonifacio E^{1–3}, Ziegler AG^{3,4}, Klingensmith G⁵, Schober E⁶, Bingley PJ⁷, Rottenkolber M⁸, Theil A¹, Eugster A¹, Puff R⁴, Peplow C⁴, Buettner F⁹, Lange K¹⁰, Hasford J⁸, Achenbach P^{3,4} for the Pre-POINT Study Group

JAMA 2015; **313**: 1541–49

Effects of low dose metformin in adolescents with type 1 diabetes mellitus: a randomized, double-blinded placebo-controlled study

Nadeau KJ, Chow K, Alam S, Lindquist K, Campbell S, McFann K, Klingensmith G, Walravens P

Pediatr Diabetes 2015; **16**: 196–203

Contrasting the clinical care and outcomes of 2,622 children with type 1 diabetes less than 6 years of age in the United States T1D Exchange and German/Austrian DPV registries

Maahs DM¹, Hermann JM², DuBose SN³, Miller KM³, Heidtmann B⁴, DiMeglio LA⁵, RamiMerhar B⁶, Beck RW³, Schober E⁶, Tamborlane WV⁷, Kapellen TM⁸, Holl RW², for the DPV Initiative and the T1D Exchange Clinic Network

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Diabetologia 2014; **57**: 1578–85

Background

Children <6 years of age present multiple challenges for T1D care. Limited data exist on HbA1c, SH, or DKA outcomes in this age group or whether differences exist between countries. This study aimed to compare participant characteristics, treatment modalities, and clinical outcomes in reg-

istry participants in the Type 1 Diabetes Exchange (T1DX) in the United States and the Prospective Diabetes Follow-up Registry (DPV) in Germany and Austria.

Methods

HbA1c, SH, and DKA and frequencies of attaining HbA1c <7.5% (ISPAD goal) and <8.5% (ADA goal prior to 2014) were compared between registries.

Results

Insulin pump use was more frequent (74% vs. 50%, $p < 0.001$) and HbA1c was lower (7.4% vs. 8.2%, $p < 0.001$) in the DPV compared to the T1DX registry. HbA1c was lower for both pump and injections users in the DPV. Children in the DPV were more likely to achieve the 7.5% and 8.5% targets (56% vs. 22% and 90% vs. 66%, $p < 0.001$ for both). In contrast, SH did not differ between registries or by HbA1c category (<7.5%, 7.5 to <8.5%, $\geq 8.5\%$), whereas DKA increased with HbA1c.

Conclusions

The DPV data indicate that an HbA1c <7.5% can be frequently achieved in children <6 years of age with T1D. Improved metabolic control was associated with less DKA without increasing SH. Less frequent use of insulin pumps in the T1DX did not fully explain the suboptimal control in the T1DX, but may relate to the higher HbA1c target previously set by the ADA, which is now harmonized with the ISPAD goal of <7.5%.

Comment

Both the DPV and T1DX registries were established with an objective to improve the care of children with T1D by collecting clinical outcome data on a large population and sharing best practices. Although T1D has increased worldwide in this youngest age group, it remains a relatively rare patient population and requires multicenter collaboration for a sufficient sample size to make comparisons to serve as the basis for improving care. In this article, the U.S. children had higher HbA1c than the German and Austrian children. However, SH did not differ between registries nor did it increase at lower HbA1c (a higher HbA1c to prevent SH had previously been given as a reason for a higher HbA1c goal). DKA predictably increased with higher HbA1c.

A number of possible explanations for the higher HbA1c are explored, including pump use, which did not fully explain the difference between registries. The higher HbA1c previously set by the ADA is another and in 2014 it was harmonized with the <7.5% goal set by ISPAD. Further data are required to determine whether the now lower HbA1c goal (or other interventions) will translate to improved outcomes in the <6-year-old population in the United States. These data serve as an additional reminder of the power of large registries, including transnational comparisons, to identify shortcomings in diabetes care and identify targets for intervention studies.

Limitations of this study include lack of a central laboratory for HbA1c measurement, differences in data collection methodology (e.g., the DPV includes 70–90% of potential patients, whereas the T1DX includes a smaller percentage of potential participants), and the cross-sectional nature of the data, which should be considered hypothesis generating. Development of new drugs, devices, and technologies, and strategies to improve care of all children with T1D, including the youngest and most vulnerable, are needed.

Racial-ethnic disparities in management and outcomes among children with type 1 diabetes

Willi SM¹, Miller KM², DiMeglio LA³, Klingensmith GJ⁴, Simmons JH⁵, Tamborlane WV⁶, Nadeau KJ⁷, Kittelsrud JM⁸, Huckfeldt P⁹, Beck RW², Lipman TH¹, T1D Exchange Clinic Network

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Pediatrics 2015; **135**: 424–34

Background

Racial/ethnic disparities are documented in diabetes treatments and outcomes, although it is controversial whether the

disparities are due to socioeconomic status (SES) or other factors. The Type 1 Diabetes Exchange (T1DX) Clinical Registry examined racial/ethnic differences in diabetes therapies and outcomes.

Methods

The cohort included 10,704 participants <18 years with T1D ≥1 year (8,841 non-Hispanic whites, 697 non-Hispanic blacks, and 1,166 Hispanic, including 214 high-income [>\$100,000/year/household] non-Hispanic black and Hispanic families). Diabetes therapies and outcomes were compared.

Results

Insulin pump use was higher in non-Hispanic white (61%) than in non-Hispanic black (26%) or Hispanic (39%) participants after adjustment for gender, age, diabetes duration, and SES. Mean HbA1c was higher in non-Hispanic black than in Hispanic or non-Hispanic white participants (9.6%, 8.7%, 8.4%). More non-Hispanic black participants had DKA and severe hypoglycemia in the past year than Hispanic or non-Hispanic white participants who did not differ after adjustment for SES.

Conclusions

Marked disparities in insulin treatment method and diabetes outcomes, even after SES adjustment, exist between non-Hispanic black versus Hispanic and non-Hispanic white children. Barriers to insulin pump use and optimal glycemic control beyond SES should be explored in all ethnic groups.

Comment

It has been over 20 years since the publication of the Diabetes Control and Complications Trial demonstrated that intensive management significantly reduced vascular complications of type 1 diabetes (T1D). Data from the T1D Exchange registry indicate that only one quarter of children and adolescents with T1D in the United States achieve the hemoglobin A1c (HbA1c) goal of <7.5% (9). Although the importance of tight glucose control is clear, achieving this goal remains elusive in pediatric diabetes.

Willi and the T1D Exchange provide important data documenting disparities in management and outcomes particularly in non-Hispanic black (NHB) children and adolescents with T1D. This large cohort, although not a population representative cohort, included 10,704 participants from 60 pediatric sites in 31 states. The large sample size of this study, including 697 NHB and 1,166 Hispanic participants, enables investigation of factors such as socioeconomic status (SES), parental education, and insurance status that could explain outcome differences (HbA1c, severe hypoglycemia, and diabetic ketoacidosis) by racial-ethnic group. For example, 214 high-income (>\$100,000) NHB families were included, providing sufficient power for stratified analyses by these potential explanatory variables; a limitation of previous reports has been smaller sample sizes.

Higher HbA1c, SH, and DKA in the NHB as compared to non-Hispanic white (NHW) and Hispanic participants were the main findings. Moreover, insulin pump use,

which is considered by most pediatric endocrinologists to be the best way to deliver insulin, was highest in the NHW population. No significant differences existed between the Hispanic and NHW populations after adjustment for age, gender, T1D duration, and SES, but in the NHB population the disparities in outcomes persisted.

A number of hypotheses to explain higher reported HbA1c in the NHB population have been proposed, including a biologic “glycation gap” between NHW and NHB populations such that for an equivalent mean blood glucose the NHB population has a higher HbA1c than the NHW population. A potentially definitive study to define the association of mean blood glucose with HbA1c by race-ethnicity is in process by the same T1D Exchange group. Participants will wear a continuous glucose monitor (CGM) over 3 months to measure glucose every 5 minutes. These data will be used to determine whether a difference exists in the relationship of mean CGM glucose with HbA1c between the NHB and NHW populations. While genetic differences may exist in glycation to explain part of the 1.2% mean difference in HbA1c between NHB and NHW participants reported in this study, it remains to be seen if it will fully explain this disparity.

Cultural, socioeconomic, and provider-related factors may underlie the racial-ethnic disparities in the outcomes. Treatment differences by race-ethnicity in use of insulin pumps (3.6 times higher in NHW than NHB and 1.9 times higher in NHW than Hispanic youth) and self-monitoring of blood glucose were described. Further research efforts including intervention studies to determine the best possible care for all youth with T1D in the United States are needed.

Accuracy of blood glucose meters for self-monitoring affects glucose control and hypoglycemia rate in children and adolescents with type 1 diabetes

Boettcher C, Dost A, Wudy SA, Flechtner-Mors M, Borkenstein M, Schiel R, Weitzel D, Bechtold-Dalla Pozza S, Wolf J, Holl W, German/Austrian Diabetes Prospective Documentation Initiative

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Diabetes Technol Ther 2015; **17**: 275–82

Background

Self-monitoring of blood glucose (SMBG) is one of the most important elements of diabetes therapy. To investigate the accuracy of SMBG devices, the standard provided by the International Organization for Standardization (ISO) is widely used. Another method to specify glucose meter performance is via error grids according to Clarke et al. (10) or Parkes et al. (11) that inform the clinician about the severity of errors. The aim of this study was to investigate the accuracy of blood glucose (BG) meters for SMBG and its

influence on HbA1c levels and the frequency of hypoglycemic coma.

Methods

This study is based on the German/Austrian Diabetes software für prospektive Verlaufsbeobachtung (DPV) documentation system, a project that comprises quality assurance and scientific research. Self-measured and simultaneously obtained laboratory BG values from 9,163 patients with T1D younger than 18 years of age were analyzed by investigating their compliance with the ISO criteria (versions 2003 and 2013) and by error grid analyses. Regression models were used to evaluate the effects on glucose control and hypoglycemia rates.

Results

Comparison of SMBG values with local laboratory results according to the old and new ISO criteria showed that the required $\geq 95\%$ of BG values within target were not met under the “real-life conditions”; 78.7–94.7% of the SMBG values met the old and 79.7–88.6% met the new ISO criteria. Patients on pump therapy had more outliers than those using injection therapy (old ISO criteria, OR = 1.302, 95% CI 1.084–1.564, $p = 0.0051$; new ISO criteria, OR = 1.155, 95% CI 1.011–1.318, $p = 0.033$). In Clarke and Parkes error grid analyses, the percentages of SMBG values in Zone A ranged between 92.8% and 94.6% (Clarke) and between 92.2% and 95.0% (Parkes). Logistic regression analysis showed that pump therapy was associated with worse results compared with injection therapy (Clarke, OR = 1.286, 95% CI 1.066–1.551, $p = 0.0089$; Parkes, OR = 1.376, 95% CI 1.148–1.650, $p = 0.0007$). Age, gender, diabetes duration, and year of treatment had no significant influence on the proportion of BG values within target for both ISO standards, and these parameters were also not related to the proportions of BG values in Zone A in the error grid analyses. A significant association was found between the deviation of SMBG values from the laboratory-obtained glucose levels and adjusted mean HbA1c levels as a marker of glycemic control: patients measuring “far too low” (Q5) (cutoff, ≥ 0.8 mmol/L) with their SMBG devices showed the highest HbA1c levels (mean, 8.1% [65 mmol/mol]), differing significantly from Q1 (cutoff, -0.6 mmol/L), Q2 (cutoff, -0.1 mmol/L), Q3 (cutoff, 0.3 mmol/L), and Q4 (cutoff, 0.8 mmol/L). Those patients who measured “identical or almost identical” (Q3) or “too high” (Q2) exhibited the lowest HbA1c levels (mean, 7.7% [61 mmol/mol]). Performing “far too high” was associated with the highest rate of hypoglycemic coma in comparison with the other deviation quintiles.

Conclusions

This large study showed that under “real-life conditions” the current SMBG devices failed to meet the accuracy criteria of old and new ISO and also failed to meet the desired percentages of Zone A results in Clarke and Parkes error grid analyses. Large deviations of the SMBG values from the “true” glucose levels resulted in higher HbA1c levels and markedly increased rates of hypoglycemic events.

Comment

Patients with diabetes and their caregivers expect the available glucose-meter devices to work properly and accurately in order to help them to control their diabetes management. Over the last years several publications have pointed out that not all previously approved glucose-meter devices conform to the current and/or planned ISO standards (12,13), which may have an impact on clinical decision making and glucose control. The current study, which reflects the “real-life conditions” of pediatric patients using their own SMBG devices, emphasizes this issue.

Confounders may contribute to the inaccuracy and interfere with the blood glucose measurements, including lot-to-lot variability of test strips; interference from lack of calibration, temperature, humidity, or poor storage of strips; and patient factors, such as medication and anemia.

With increased use of pump therapy and continuous glucose monitoring (CGM), the use of the pump “bolus calculator” and calibration of the CGM that are based on SMBG values can increase the chance of “inaccurate” values that would consequently lead to inappropriate insulin dose suggestions, with greater deviations from the real required dose of insulin. Patients who measured “far too low” had higher HbA1c values probably because of unnecessary consumption of readily absorbable carbohydrates to raise the blood glucose level that resulted in hyperglycemia and subsequently elevated HbA1c levels.

A great concern is also for those measuring “too high” with administration of additional unnecessary insulin doses especially in children, placing them at higher risk for hypoglycemia with serious possible sequelae of coma and seizures.

These deviations of SMBG values from the “true” glucose levels lead to a clinically relevant increase of hypoglycemic events with a negative impact on HbA1c levels. Therefore, new stricter international regulations for SMBG devices have to be reconsidered, since patients with diabetes rely on these devices in decision making about their treatment.

Youth and parent measures of self-efficacy for continuous glucose monitoring: survey psychometric properties

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This manuscript is also discussed in the article on: Diabetes Technology and the Human Factor, p. S-105.

Background

This study aimed to fill a current research gap by developing a psychometric evaluation of youth and parent measures of self-efficacy related to CGM use in pediatric T1D patients.

Methods

Youth ($n=120$) with T1D for ≥ 1 year enrolled in a 2-year randomized clinical trial comparing CGM use with and without the addition of a family-focused CGM behavioral intervention. CGM self-efficacy (CGM-SE) surveys were completed at randomization after a 1-week run in to assess CGM tolerability. Comparisons of predictive validity included the youth in the control arm to assess CGM use and HbA1c outcomes at 3 and 6 months.

Results

CGM-SE surveys had acceptable internal consistency (Cronbach's $\alpha=0.80$ for youth and 0.82 for parents). Youth with higher baseline CGM-SE (>80) had significantly greater CGM use and lower HbA1c after 3 and 6 months compared to those with lower CGM-SE (≤ 80).

Conclusions

The CGM-SE surveys appear to have strong psychometric properties. CGM self-efficacy may be a tool to assess likelihood of CGM adherence and improvement in glucose control in youth with T1D.

Comment

A common challenge with new therapies in diabetes is the translation from research to clinical use. Adherence to use of CGM in children with diabetes has been reduced compared to adults in research (14), but similar benefit has been noted in children if CGM are used as directed (15). More recent data indicate that CGM use remains low in the pediatric population in the T1D Exchange at 5–13% (1), although these data are based on last-generation CGM devices.

Therefore, the challenge remains on how to increase clinical use of CGM so that this technology can benefit the greatest number of children and their families. The CGM-SE tool developed by Laffel and colleagues may be one method to determine whether prospective CGM users are likely to succeed with CGM use. Future work may also include development of programs to improve CGM self-efficacy among those children and parents with low scores so that CGM can be used successfully and more patients can reap its benefits. For the full benefit of diabetes technology to be realized in pediatrics, more studies such as these are required to determine how to best translate technology from research studies to clinical use.

Early hyperglycemia detected by continuous glucose monitoring in children at risk for type 1 diabetes

Steck AK, Dong F, Taki I, Hoffman M, Klingensmith GJ, Rewers MJ

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Diabetes Care 2014; **37**: 2031–33

Background

CGM was used as a new approach to define early hyperglycemia and to diagnose T1D in children with positive islet antibodies (Ab).

Methods

A Dexcom SEVEN CGM was worn by 14 Ab+ and 9 Ab− subjects in the Diabetes Autoimmunity Study in the Young (DAISY).

Results

The Ab+ subjects had more hyperglycemia (>140 mg/dL) than Ab− subjects (18% vs. 9%) with higher maximum daytime glucose values and increased glycemic variability. Mean HbA1c was 5.5% in the Ab+ subjects, among whom ≥18–20% CGM time >140 mg/dL predicted progression to diabetes.

Conclusions

CGM can detect early hyperglycemia in Ab+ children at high risk to progress to diabetes. Use of CGM to predict progression of diabetes requires further validation.

Comment

Current diagnostic tests to predict progression to diabetes include oral glucose tolerance tests (OGTT) and HbA1c measurement. Unfortunately, OGTTs are highly variable and repeat OGTT tests can be a logistical challenge. HbA1c is easier to measure, but less sensitive than OGTTs (16). Therefore, better tests are required to predict who will progress to diabetes. As CGM technology has improved accuracy, reduced burden on the patient, and lowered cost, it presents itself as a possible alternative to OGTTs and HbA1c with an added benefit of obtaining “free-living” glucose data on patients. Further data are required to better understand how to use CGM data to risk stratify progression to diabetes. It should also be noted that these results were obtained with earlier generation CGM technology, which has improved since this study was performed, suggesting that better results are possible in the future.

Continuous glucose monitoring and its relationship to hemoglobin A1c and oral glucose tolerance testing in obese and prediabetic youth

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Background

There has been significant controversy over the optimal method of diagnosing prediabetes and type 2 diabetes (T2D)

in the pediatric population. Studies in adolescents comparing HbA1c to 2-hour glucose and fasting plasma glucose (FPG) have reported poor agreement among these tests in classifying youth with dysglycemia, and HbA1c has been reported to have low sensitivity for identifying prediabetes and diabetes, as defined by oral glucose tolerance test (OGTT). The aim of this study was to evaluate whether HbA1c or the OGTT is a better predictor of “free-living” glucose levels as measured by continuous glucose monitoring (CGM).

Methods

A cross-sectional study of youth 10–18 years old, body mass index (BMI) ≥85th percentile, with diabetes risk factors, not on medications for glucose management.

The participants (*n*=118) were recruited from primary care and pediatric endocrinology clinics around Denver, Colorado. HbA1c, FPG, and 2-hour glucose were collected and all participants wore a blinded iPro CGM for 72 hours. The ability of HbA1c and 2-hour glucose to predict abnormal CGM area under the curve (AUC) was evaluated.

Patients with normal glucose levels (HbA1c < 5.7%, FPG <100 mg/dL, 2-hour glucose <140 mg/dL) were selected, and mean and SD CGM AUC were calculated. The remaining subjects were classified as having an abnormal CGM AUC if their AUC was greater than mean 2 SDs of the normal subjects. Logistic regression models were used to assess the ability of HbA1c, FPG, and 2-hour glucose to predict an abnormal CGM AUC by comparing the area under the receiver operating characteristic (ROC) curves. The cutoff value for HbA1c and 2-hour glucose that maximized sensitivity and specificity for identifying abnormal CGM AUC was determined.

Results

CGM data of 48 hours were collected on 98 obese youth. There were no differences in age, Tanner staging, or lipids among those with normal or prediabetes HbA1c. There were significant differences between normal glycemic youth and youth with prediabetes for CGM outcomes. When categorized by HbA1c, differences were highly significant (*p*<0.0001) for night average, night peak glucose, and night AUC, but not for CGM SD or excursions >200 mg/dL. When categorized by 2-hour glucose, differences were highly significant (*p*<0.0001) for percentage of time ≥140 mg/dL, but not for night-average glucose, minimum-sensor glucose, and night AUC. Participants with prediabetes had on CGM significantly higher average glucose, AUC, peak glucose, and percent of time spent >120 mg/dL and >140 mg/dL (*p*<0.01) than youth with normal HbA1c or normal OGTT. HbA1c had a greater magnitude of correlation to CGM average glucose, AUC, and minimum glucose; 2-hour glucose had a greater magnitude of correlation to CGM SD, peak glucose, and percent of time spent >140 mg/dL and >200 mg/dL. There were no differences in the strength comparisons between 2-hour glucose and HbA1c correlations to CGM outcomes.

Conclusions

These results confirm that obese youth in their “free-living” environments frequently have elevated glucoses, as

measured by CGM, and despite normal HbA1c, FPG, and 2-hour glucose, they have higher glucose distributions than in normal-weight, healthy individuals. In obese youth, HbA1c and 2-hour glucose performed equally well at predicting “free-living” glucose levels on CGM, suggesting that both are acceptable tests for dysglycemia screening.

Comment

We all wish for the gold-standard screening test for predicting prediabetes and diabetes in youth. This study demonstrated that HbA1c did not outperform 2-hour glucose in predicting abnormal glucose outcomes. HbA1c correlated more highly to measures of average and overnight glucose, whereas 2-hour glucose correlated more highly to peak glucose and variability. Thus, HbA1c reflects a measure of average glycemia, whereas 2-hour glucose reflects the response to a glucose challenge, potentially each test reflecting different underlying pathologic mechanisms for progression to T2D. Although there were no significant differences between 2-hour glucose and HbA1c in predicting CGM outcomes, both measures outperformed FPG in predicting several CGM outcomes. FPG has little added value to HbA1c or 2-hour glucose in determining abnormal glycemia under “free-living” circumstances. Thus, prediabetes and diabetes can be defined as states of progressive dysglycemia, as reported in this study.

We can also learn from this study that obese youth in their “free-living” environments frequently have elevated glucoses, as measured by CGM. This “silent” hyperglycemia may contribute to an increased cardiovascular risk. Limitations of this study include the small sample size of individuals with diabetes (a larger sample of individuals with diabetes would have allowed further comparison of CGM trends between individuals with prediabetes vs. diabetes), the limited number of CGM variables that were included, and the relevance of these findings to populations in other countries.

A remote monitoring system for artificial pancreas support is safe, reliable, and user-friendly

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Diabetes Technol Ther 2014; **16**: 699–705

This manuscript is also discussed in the article on: Diabetes Technology and the Human Factor, p. S-106.

Background

The widespread use of the Internet and smartphones has further augmented the development of telemedicine systems aimed at improving glycemic control and patient care. The increasing use of continuous glucose monitoring (CGM) devices, as well as the progress in the development of artificial pancreas (AP) systems, suggests a new role for tele-

medicine in the management of diabetes. The MD-Logic AP (MDLAP) algorithm applies fuzzy logic theory mimicking lines of reasoning of diabetes caregivers, in addition to real-time learning abilities and safety modules designed to prevent hypoglycemia episodes and prolonged hyperglycemia episodes. The aim of this study was to evaluate the ability of the remote monitoring and control diabetes management system (MDRS) to function as a reliable, remote monitoring system for future AP at-home studies and, in addition, to assess the MDRS ability to prevent or shorten nocturnal hypoglycemia episodes without the use of an AP at home.

Methods

In this prospective, case-control, randomized study, patients with type 1 diabetes (T1D, $n = 18$) aged 8–24 years with a mean HbA1c level of $7.5 \pm 0.6\%$ treated nightly over a 2-week period by the MDRS were compared with patients treated with sensor-augmented pump (SAP) therapy ($n = 19$). The performance of the MDRS, the number and duration of hypo- or hyperglycemia episodes, and the efficacy of the MDRS in detecting them were analyzed. Parents of the study participants completed the hypoglycemia fear survey, attitude, and satisfaction questionnaires.

Results

One hundred eighty-seven nights (80.6%) were valid for the per-protocol analysis in the MDRS group and 166 nights (71.5%) were valid in the control group. During the 13 nights of the study, the MDRS provided continuous monitoring with no major malfunctions of the system disrupting the connection between the patients and the control and command (C&C) center.

There was no difference between the study and control groups in regard to the number of hypoglycemia events and time spent in hypoglycemia, as well as in other parameters of glucose control. Without the use of an AP, the MDRS did not significantly prevent nocturnal hypoglycemia episodes. The overall impression of the MDRS users was favorable.

Conclusions

The MDRS is an efficient and reliable system that allows continuous monitoring of the patients using it, thus enabling the supervising medical personnel to intervene when needed. Without the use of an AP, the current alarm design of the MDRS did not significantly prevent or shorten nocturnal hypoglycemia episodes. The patients and their parents found the system reliable and user-friendly although having a considerable number of false alarms that were mostly related to the CGM device.

Comment

The idea of remote monitoring of T1D patients is now becoming a reality owing to the widespread use of CGM devices in conjunction with current telecommunication technology. In this feasibility study, the possibility of using a remote monitoring system that is supervised by medical personnel for everyday use was tested. As the MDRS provides continuous monitoring of the patients and continuously delivers technical data to the C&C

center, the technical malfunctions were detectable in real time, thus enabling the supervising personnel to intervene according to specific requirements or needs, predefined conditions, and clinical judgment. The MDRS looks suitable for future AP at-home studies and can provide the additional safety layer that is currently required and may relieve patients' and parents' fears, especially during the nights. In the current study, the inability of the MDRS to prevent the detected hypoglycemia episodes relies on the alarm design of the system and the study protocol. Further studies are required to test the hypothesis that by adjusting the alarms and intervention protocol to an open-loop setting, more hypoglycemia episodes could have been prevented or shortened.

It has become clear that remote monitoring systems such as the MDRS are desired by patients and their caregivers and should be considered for patients treated with SAP therapy or future AP systems. However, we have to remember that the MDRS depends greatly on the performance of the CGM. Thus, development of sensors that are more reliable and accurate are required for such a system to be effective.

MD-Logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial

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This manuscript is also discussed in the article on: Closing the Loop, p. S-36.

Background

The closed-loop insulin delivery system has been tested in hospital settings for day and night glycemic control in patients with type 1 diabetes (T1D).

The MD-Logic system was designed to have several safety layers and fault detection capabilities to suit the requirements for automated control of overnight insulin delivery. The aim was to evaluate the ability of the MD-Logic system to operate safely and efficiently during “free-life” conditions at home over a period of 6 weeks.

Methods

Patients with T1D aged 12–43 years ($n=24$) with an average HbA1c $7.5 \pm 0.8\%$ (58.1 ± 8.4 mmol/mol) were ran-

domly assigned to participate in two overnight crossover periods, each period of consecutive nights over 6 weeks at patients' homes. One period was under closed loop and the second under sensor-augmented pump (SAP) therapy. The primary end point was overnight time spent with sensor glucose levels <70 mg/dL (3.9 mmol/L). Secondary end points included the time spent at target range (70 – 140 mg/dL) and time spent in relatively high and low glucose levels, >240 and <50 mg/dL, respectively.

Results

During the study, subjects in the closed-loop arm reduced the time spent at hypoglycemia by a median of 40.2% as compared with subjects in the SAP arm ($p=0.02$), while the percentage of time spent within 70 – 140 mg/dL (3.9 – 7.8 mmol/L) increased by a median of 21.8% ($p=0.003$). The time spent in relatively high blood glucose >240 mg/dL (13.3 mmol/L) was reduced by a median of 52.2% ($p=0.001$). Although fewer total overnight insulin doses were delivered per subject on nights when the closed loop was used compared with SAP nights ($p=0.04$), the mean overnight glucose level was significantly reduced by a median of 15 mg/dL ($p=0.008$). The number of hypoglycemic events per night was low for both groups, but the mean area under the curve for nocturnal hypoglycemic events was 62.5% lower in the closed-loop group than in the control group ($p=0.036$). All tested parameters of hyperglycemia demonstrated a significant improvement during the closed-loop nights. A significant positive relation was found between the mean overnight glucose and the mean daily glucose for both closed-loop and SAP therapy. A significant improvement was found in the percentage of glucose readings within 70 – 180 mg/dL during the days after closed loop compared with the days after SAP nights ($p=0.006$). The average daytime glucose levels were also reduced by a median of 10.0 mg/dL ($p=0.017$), while total day insulin doses were lower ($p=0.038$). No severe adverse events occurred during closed-loop control.

Conclusions

The MD-Logic automated insulin delivery system proved to be a safe and effective tool for overnight treatment of T1D. Glycemic control with MD-Logic showed significantly reduced nocturnal hypoglycemia, with increased time within range and lower mean glucose levels, when used during long-term real-life conditions in patients' homes.

Comment

Hypoglycemia remains the major concern and obstacle with respect to methods for open-loop control of nocturnal blood glucose. The overnight closed loop has the potential to mitigate the risk of nocturnal hypoglycemia and has an added value over the low glucose suspension (LGS) in maintaining tighter overnight glycemic control, reducing hyperglycemia, improving glucose variability, and reducing patient fasting blood glucose, and thus may consequently improve the daytime control. It seems that the reduction in the risk of hypoglycemia was accompanied by overall better glycemic control.

The limitations of the study include the small number of participants, and the inability to determine the long-term impact of the MD-Logic system on HbA1c and quality of life. Also, since the system was evaluated among teens and adults with T1D who were motivated patients with relatively good glycemic control, it is now necessary to evaluate whether the system can reduce the rate of hypoglycemia among patients who are prone to nocturnal hypoglycemia, for those who are poorly controlled and less motivated, and also in the toddler age.

Feasibility of overnight closed loop therapy in young children with type 1 diabetes aged 3–6 years: comparison between diluted and standard insulin strength

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Background

Closed-loop insulin delivery systems combine glucose-sensing and insulin-delivery components to modulate delivery of insulin in a glucose-responsive fashion. The efficacy and safety of closed-loop therapy has been demonstrated in clinical studies performed in adolescents and children older than 6 years. The aim of this feasibility study was to evaluate overnight closed-loop therapy with model predictive control in young children with type 1 diabetes (T1D) and to compare closed loop using diluted vs. standard insulin strength.

Methods

Children with T1D ($n=11$) aged 3.75–6.96 years with diabetes duration of 2.2 ± 1 years, treated with insulin pump therapy, with HbA1c level of 60 ± 14 mmol/mol were studied at a clinical research facility on two occasions. In random order, participants received closed loop with diluted insulin aspart (20 IU/mL) or closed loop with standard aspart (100 IU/mL) from 17:00 until 8:00 the following morning. Children consumed an evening meal at 17:00 and an optional bedtime snack identical on both occasions.

Meals and carbohydrate content were chosen by the children and their families based on individual preferences and reflecting usual practice at home. Meals were accompanied by insulin boluses calculated using participants' standard insulin pump bolus calculator settings and premeal finger-stick glucose levels. Basal rates on insulin pump were adjusted every 15 min as directed by a model-predictive-control algorithm informed by a real-time glucose sensor values. Overnight sensor glucose levels were also recorded at home

before each study visit while children maintained their usual exercise and eating patterns and standard insulin pump settings were applied.

Results

Plasma glucose levels remained within the target range of 70–145 mg/dL for 72% and 83% of the time, respectively, when closed loop with standard insulin strength and closed loop with diluted insulin was applied ($p=0.328$). No difference was found in the mean plasma glucose concentration (122 ± 23 vs. 122 ± 24 mg/dL, $p=0.993$). A trend toward reduced time spent in hypoglycemia (glucose < 70 mg/dL) was observed during closed loop with diluted insulin. Sensor-based assessment indicated significant reduction of time < 63 mg/dL ($p=0.028$) and a reduced low blood glucose index ($p=0.026$). Insulin infusion rates were not different during the two interventions and resulted in similar plasma insulin levels.

No episode of hypoglycemia requiring treatment occurred during either intervention.

One asymptomatic episode of hypoglycemia (< 63 mg/dL) occurred in one participant during closed loop with diluted insulin as compared with 6 episodes in 5 participants during closed loop with standard insulin ($p=0.09$). All these episodes resolved with no carbohydrate intake within 15–45 min. All measurements of glycemic variability showed a tendency toward reduced variability during closed loop with diluted insulin, although these differences were not statistically significant.

Conclusions

Closed-loop therapy using a model predictive control approach can be safely and effectively applied for overnight glucose control in young children aged 3–6 years with T1D. A tendency toward reduced hypoglycemia and reduced glucose variability using diluted insulin was observed.

Comment

Previous studies have reported the efficacy and safety of closed-loop therapy in adolescents and children older than 6 years (17–20). Younger children are more prone to hypoglycemic seizures especially overnight, and the developing brain appears to be more susceptible to the adverse effects of severe hypoglycemia. High insulin sensitivity, unpredictable food intake, and physical activity complicate insulin dose adjustments in young children with T1D, resulting in large glycemic fluctuations. Infants and young children also require very small doses of insulin that challenge the accuracy of subcutaneous insulin administration with standard concentration. Fear of hypoglycemia is common and is associated with increased psychological burden and reduced quality of life for children and their families, leading to higher than optimal glucose levels as an attempt to prevent hypoglycemia. Therefore, the closed-loop system may be particularly beneficial for this group of preschool children. This study demonstrated attainment of safe and efficacious overnight glucose control during overnight closed loop.

The novelty of the current study was the implementation of the closed-loop system in the young age group and the use of diluted insulin to enhance the accuracy of delivery of small insulin doses that indeed demonstrated a tendency to reduced hypoglycemia and glycemic variability. However, the results of the study are limited due to the small number of patients included in the study, and need to be explored in larger studies. Also, we need to consider the difficulties related to the use of insulin dilution in daily life, including the need to prepare diluted insulin every 7–14 days and the major danger of dosing errors.

A randomized trial of a home system to reduce nocturnal hypoglycemia in type 1 diabetes

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This manuscript is also discussed in the article on: Closing the Loop, p. S-32–33.

Background

Overnight hypoglycemia is frequent in people with T1D and can result in seizures, loss of consciousness, or death. It remains a barrier to tight glucose control and is feared by patients with T1D and their families. An in-home trial was performed to determine whether a predictive low glucose suspend (PLGS) algorithm to suspend insulin pump delivery based on CGM glucose would result in reduced overnight hypoglycemia.

Methods

After a run-in phase, 45 individuals aged 15–45 years with T1D were randomized nightly to either PLGS or control for 42 nights. Proportion of nights with CGM glucose <60 mg/dL was the primary outcome.

Results

Overnight hypoglycemia was reduced by 48% with PLGS vs. control (21% vs. 33% of nights, $p < 0.001$). Median hypoglycemia AUC was reduced by 81% and hypoglycemia >2 hours was reduced 74%. Overnight time with CGM glucose >180 mg/dL and morning blood glucose >250 mg/dL did not differ. Morning ketosis was <1% in both arms of the study.

Conclusions

Use of an overnight PLGS system reduces overnight hypoglycemia without an increase in morning hyperglycemia or ketosis.

Comment

The use of a PLGS system represents the second step in the artificial pancreas roadmap (21). The first step, threshold suspension of insulin with a low CGM glucose, has been commercially available since 2009 in many countries and since 2013 in the United States. A PLGS system should reduce time spent hypoglycemic compared to open loop or a threshold suspend system as it reduces insulin in advance of hypoglycemia instead of waiting for hypoglycemia to occur to stop insulin delivery. This study demonstrates that this is indeed the case as compared to open-loop control and that PLGS can do so without increasing ketosis or morning hyperglycemia. Future studies are required to determine the effect on HbA1c and hypoglycemia of an overnight (or 24 hours a day) PLGS system in longer periods and in younger and older populations. The authors note that no difference in hypoglycemia prevention existed between the control and active nights of the system until 2–3 hours after activation of the system. Unsurprisingly, the PLGS system is unable to prevent hypoglycemia due to insulin dosed before the system activation. This argues that a PLGS system should be used 24 hours a day for a patient to gain the greatest benefit in hypoglycemia prevention. However, even overnight use, should regulatory agencies approve this first, promises benefit for people with T1D. While diabetes care providers and our patients wait for a fully closed loop to mitigate both hypoglycemia and hyperglycemia, overnight PLGS should provide benefit while more advanced technologies await regulatory approval and commercial development.

Overnight glucose control with an automated, unified safety system in children and adolescents with type 1 diabetes at diabetes camp

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Diabetes Care 2014; **37**: 2310–16

This manuscript is also discussed in the article on: Closing the Loop, p. S-34.

Background

The study's objective was to assess the safety and efficacy of an automated unified safety system (USS) in providing overnight closed loop (OCL) in children and adolescents with T1D at diabetes camps.

Methods

The Diabetes Assistant (DiAs) USS with Dexcom G4 Platinum glucose sensor (Dexcom) and t:slim insulin pump

(Tandem Diabetes Care). An in-patient study to assess safety was performed in 12 participants followed by the main camp study in 20 who were randomized to either OCL or sensor augmented pump (control condition) nightly over the course of the diabetes camp.

Results

Participants completed 54 OCL and 52 control nights. In an intent-to-treat analysis, percent time in range 70–150 mg/dL was 62% vs. 55% ($p=0.23$) for OCL versus control nights. In a per protocol analysis, median percent time in range was 73% vs. 52% ($p=0.037$) in OCL versus control nights. Less time was spent in hypoglycemia during OCL compared to control nights.

Conclusions

The DiAs USS algorithm improved time spent in range and reduced nocturnal hypoglycemia in children and adolescents with T1D in a diabetes camp setting.

Comment

Current FDA guidelines for research on artificial pancreas devices advise progression from highly monitored hospital studies to determine safety with progression next to hotel or camp studies that offer the opportunity to continue to have a high level of safety monitoring but a bridge to activities that patients would have in a home setting. In fact, diabetes camps such as the camp used in this study provide a greater challenge with increased physical activity and often a wider variety of diet than may be encountered in the home setting. Studies such as this by Ly advance the field of study and prepare the way for the pivotal, longer term outpatient studies that will be required for regulatory approval. These data demonstrate a significant reduction in nocturnal hypoglycemia in the OCL versus control when faced with the challenge of increased demands of diabetes camp. Depending on the analysis, more time was also spent in target. The next few years promise results from out-patient studies that are needed to assure safety, improved glucose outcomes, and reduced burden for patients with T1D from artificial pancreas devices.

Effects of high-dose oral insulin on immune responses in children at high risk for type 1 diabetes: the Pre-POINT randomized clinical trial

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This manuscript is also discussed in the article on: Immune intervention for type 1 diabetes. p. S-70.

Background

Type 1 diabetes (T1D) can be detected in asymptomatic individuals by the presence of islet autoantibodies that develop with a peak incidence at around 1 year of age. Autoantibodies against insulin are the first to appear, followed by the expansion of autoimmunity to other antigens before the onset of diabetes. Interferon- γ -producing CD4⁺ T cells directed against proinsulin and CD8⁺ T cells directed against insulin are also found in patients with T1D. The human leukocyte antigen (HLA) class II DR4-DQ8 haplotype is found in most children who develop T1D. Oral administration of insulin reduced the development of diabetes in an animal model, probably by stimulation of immune tolerance with induction of insulin-specific regulatory T cells. Antigen-specific therapy with insulin before the development of autoantibodies may induce protective immune responses that prevent the emergence of autoimmunity and T1D in genetically at-risk children. The aim of the study was to assess whether oral insulin in children autoantibody-negative, genetically at-risk can induce a potentially tolerogenic protective immune response to an autoantigen without causing adverse effects.

Methods

The Pre-POINT study was a double-blind, placebo-controlled, dose-escalation, phase 1/2 clinical pilot study conducted at four outpatient sites in Germany, Austria, the United States, and the United Kingdom. In this study, islet autoantibody-negative children ($n=25$) aged 2–7 years with a family history of T1D and susceptible HLA class II genotypes were enrolled. Children were randomized to receive oral insulin ($n=15$) or placebo ($n=10$) once daily for 3–18 months. Children in the insulin group were randomized to receive insulin in 1 of 5 study blocks. Children in block 1 received 2.5 mg of insulin for 6 months, followed by 7.5 mg for 3–12 months; those in block 2 received 2.5 mg for 6 months, followed by 22.5 mg for 3–12 months; those in block 3 received 7.5 mg for 6 months, followed by 67.5 mg for 3–12 months; those in block 4 received 22.5 mg for 3–12 months; and those in block 5 received 67.5 mg for 3–12 months. The main outcomes were an immune response to insulin, measured as serum IgG and saliva IgA binding to insulin, and CD4⁺ T-cell proliferative responses to insulin.

A secondary outcome measure was the gene expression profile of CD4⁺ T cells responding to insulin.

Results

Increases in IgG binding to insulin, saliva IgA binding to insulin, or CD4⁺ T-cell proliferative responses to insulin were observed in 2 of 10 (20%) placebo-treated children and in 1 of 6 (16.7%) children treated with 2.5 mg of insulin, 1 of 6 (16.7%) treated with 7.5 mg, 2 of 6 (33.3%) treated with 22.5 mg, and 5 of 6 (83.3%) treated with 67.5 mg ($p=0.02$). Insulin-responsive T cells displayed regulatory T-cell features after oral insulin treatment. No hypoglycemia, IgE responses to insulin, autoantibodies to glutamic acid decarboxylase or insulinoma-associated antigen 2, or diabetes were observed. Analysis of the gene expression profiles under insulin-stimulated and proinsulin-stimulated proliferation of single-cell-sorted CD4⁺ T cells from insulin-treated children showed a cluster of cells that expressed *FOXP3* (forkhead box P3) without CD127 or cytokines (*FOXP3* signature cells), a typical profile of *FOXP3*⁺ regulatory T cells. Analysis of the quantitative gene expression data from all genes examined discretely clustered the insulin-responsive CD4⁺ T cells from the children who received 67.5 mg of insulin away from the remainder of the insulin-responsive CD4⁺ T cells.

Adverse events were reported in 12 insulin-treated children (67 events) and 10 placebo-treated children (35 events). Infections were the most frequently reported adverse events.

However, there were no signs of hypoglycemia or allergic symptoms after receiving oral insulin. No changes in blood cell counts or blood chemistry values were observed.

Conclusions

The Pre-POINT pilot study demonstrated that daily oral administration of 67.5 mg of insulin, compared with placebo, to genetically at-risk for T1D healthy children without signs of islet autoimmunity resulted in an immune response without hypoglycemia. The immune response observed in insulin-treated children did not display the features typically associated with T1D, such as a dominant proinflammatory *IFNG* CD4⁺ T-cell response.

Comment

The organ-specific destruction of β -cell in T1D is mediated by T helper-1 lymphocyte and develops owing to the interaction between susceptibility genes, environmental factors, and some other risk factors. In order to try to prevent T1D, large multinational investigations have been designed and conducted to evaluate primary prevention trials. Primary prevention is treatment in infants with increased genetic risk before development of symptoms. The primary prevention studies include several dietary manipulations, such as infant formulas free of either cow's milk or bovine insulin, delayed exposure of gluten-containing foods, and vitamin D supplementation. Because primary prevention is directed at individuals who have no clinical signs of autoimmune diseases or metabolic impairment, and because it is uncertain whether they will develop T1D, the designed interventions must be effective, safe, and free of side effects. To date, all primary prevention trials have been

dietary interventions designed to interrupt putative environmental factors of T1D. So far, none of the specific dietary factors has been shown to be an unequivocal risk factor for β -cell-targeted autoimmune diseases or T1D, and their effects have still been contradictory (22).

Secondary prevention is targeted at individuals with persistent islet autoantibodies. In the DPT-1 study, subjects positive for anti-islet cell autoantibodies and anti-insulin autoantibodies without impaired glucose tolerance were randomly allocated to receive oral insulin 7.5 mg per day or placebo (23). The original study demonstrated that there was no delay in the clinical onset of T1D. A *post hoc* analysis indicated that a considerable delay in the clinical onset of T1D was achieved in a subgroup of individuals with high-titer anti-insulin autoantibodies. A 13-year follow-up also revealed that the β -cell function was preserved for so long as the oral insulin was taken (24).

In the present study, the administration of oral insulin in children genetically at risk, autoantibody negative, was evaluated as a way of induction of protective immune response to an autoantigen. The T-cell responses to insulin were complementary to the antibody responses at the highest insulin dose. The treatment with oral insulin appeared to induce insulin-responsive and proinsulin-responsive regulatory T cells, and responses seen with oral insulin were not the dominant proinflammatory interferon- γ responses associated with T1D and observed in islet autoantibody-positive children. The findings appear to be consistent with the notion that oral exposure to an antigen can promote regulatory T-cell responses to the antigen. In the study a moderate number of *IL21*-expressing insulin-responsive CD4⁺ T cells in insulin-treated children was also detected. *IL-21*⁺ T cells promote B-cell responses to antigens, and *IL21* gene-expressing CD4⁺ T cells responding to the vaccine antigen tetanus toxoid were observed, supporting the notion that orally administered insulin acted as a vaccine.

The novelty of the study is that it is the first trial to administer an autoantigen to genetically at-risk children without signs of autoimmunity. However, these children represent less than 1% of children who ultimately develop T1D, and it is possible that the immune efficacy findings may not be the same in children with lower genetic risk.

This study has other limitations: the small sample size, the short follow-up duration, the enrolled children were older than the peak incidence age of islet autoantibody seroconversion (9 months–2 years), and the evidence that insulin doses were not adjusted for body weight. Although the researchers included a combination of assays designed to detect weak responses to determine efficacy, these assays have not been externally validated. Therefore, the findings of immune efficacy should be interpreted with caution.

The findings of this study support the need for larger studies including trials to determine whether oral insulin can prevent islet autoimmunity and progression to diabetes in such children.

Effects of low dose metformin in adolescents with type 1 diabetes mellitus: a randomized, double-blinded placebo-controlled study

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Background

Insulin resistance increases in adolescence, complicating glucose control and potentially increasing CVD risk in adolescents with T1D. Metformin is a potential adjunct to insulin therapy in T1D to improve insulin sensitivity and glucose control. The investigators hypothesized that metformin in addition to insulin would improve metabolic parameters in adolescents with T1D.

Methods

Participants aged 13–20 years ($n=74$) were randomized to either metformin or placebo for 6 months. HbA1c, insulin dose, waist circumference, BMI, BP, and fasting lipids were measured.

Results

Significant decreases in insulin dose, BMI z -score, and waist circumference decreased at 3 and 6 months compared to baseline in the metformin group, and total insulin dose and SBP increased at 3 months and total insulin dose at 6 months in the placebo group. There was no significant change in HbA1c between the metformin or placebo groups.

Conclusions

Low-dose metformin likely improves BMI and insulin sensitivity in adolescents with T1D. The reduction in waist circumference suggests a benefit on fat distribution. More detailed research, including mechanistic studies, are needed to determine the potential impact of metformin on CVD and glucose control in adolescents with T1DM.

adjustment to achieve lower blood glucoses as part of the study protocol. Additional multicenter studies are in progress, including hyperinsulinemic-euglycemic clamp studies to investigate the insulin resistance and potential benefits from metformin therapy. Based on present evidence, data do not suggest a sustained improvement in glucose control as measured by HbA1c, but instead potential benefit on CVD risk factors. It remains an open question as to whether these possible benefits are worth initiating metformin therapy in adolescents with T1D or not.

Author Disclosure Statement

Dr. David Maahs' institute received research funds from Medtronic, Dexcom and Roche. He is on the Scientific Advisory Board for Insulet and a consultant for Abbott.

Dr. Shlomit Shalitin has no competing financial interests.

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Comment

The challenge of achieving goal glucose control is nowhere more apparent in adolescents. One physiologic difference is that of pubertal insulin resistance for which increased doses of insulin are required. Metformin is an appealing adjunctive to insulin treatment as a low-cost, safe, and once- or twice-daily oral medication to improve glucose control and CVD risk factors in adolescents with T1D. This study is similar to previous studies indicating improvement in some variables such as total daily insulin dose, BMI, and waist circumference, but not with others such as HbA1c. Perhaps this is not a surprise as the addition of metformin led to a decrease in insulin dose, but not a reduction in mean blood glucose. This was likely because of a lack of intensive dose

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