ORIGINAL ARTICLE

Diabetes Technology and Therapy in the Pediatric Age Group

David M. Maahs¹, Rayhan Lal¹, and Shlomit Shalitin^{2,3}

Introduction

WE CONTINUE TO SEE TREMENDOUS advances in both research and clinical translation of diabetes technology and therapeutics in the pediatric age group. This year's selection of manuscripts in the article spans the full range of ages in pediatrics and includes novel glucose monitoring and closed-loop systems as well as translation of medications commonly used in adults into the pediatric population. As new technologies are researched and applied clinically, reports on use of current diabetes technologies including the effectiveness of pumps compared to multiple daily injections, use of continuous glucose monitoring (CGM) in preterm infants and data on intermittently scanned CGM (isCGM) become available. These real-world data (1) are very important for clinicians and researchers to better understand how to most effectively translate new developments to best solve the challenges our patients face on a daily basis. Further data are reported on closed-loop control systems, including predicted low-glucose suspend systems and multiple studies in which closed-loop systems were challenged by exercise, as this is a real-world problem for children and adolescents with diabetes and more data are required to best manage this in an outpatient setting.

In addition to diabetes technology, this year's articles remind us of the long-term complications of diabetes and the increased future risk of cardiovascular disease and mortality (2–4). Reports are included on therapies translated from adult to pediatric populations in studies designed to decrease the risk of long-term vascular complications. Finally, because the delay, prevention, and curing of diabetes remain the ultimate goals in diabetes research, the international TrialNet Oral Insulin trial is summarized and raises hypotheses to focus future research in type 1 diabetes (T1D).

To select these 13 articles focused on diabetes technology and therapeutics in the pediatric age group, 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, 2017, and June 30, 2018.

Key Articles Reviewed for the Article

Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes

Karges B, Schwandt A, Heidtmann B, Kordonouri O, Binder E, Schierloh U, Boettcher C, Kapellen T, Rosenbauer J, Holl RW

JAMA 2017; **318**: 1358–1366

¹Stanford Medical Center, Department of Pediatrics, Division of Endocrinology and Diabetes, Stanford, CA

²Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

³Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Continuous glucose monitoring in very preterm infants: a randomized controlled trial

Galderisi A, Facchinetti A, Steil GM, Ortiz-Rubio P, Cavallin F, Tamborlane WV, Baraldi E, Cobelli C, Trevisanuto D

Pediatrics 2017; **140**: e20171162

Effect of financial incentives on glucose monitoring adherence and glycemic control among adolescents and young adults with type 1 diabetes: a randomized clinical trial

Wong CA, Miller VA, Murphy K, Small D, Ford CA, Willi SM, Feingold J, Morris A, Ha YP, Zhu J, Wang W, Patel MS

JAMA Pediatr 2017; **171**: 1176–1183

Flash glucose measurements in children with type 1 diabetes in real-life settings: to trust or not to trust?

Szadkowska A, Gawrecki A, Michalak A, Zozulińska-Ziółkiewicz D, Wojciech Fendler W, Młynarski W

Diabetes Technol Ther 2018; **20**: 17–24

Reduction in hypoglycemia with the predictive low-glucose management system: a long-term randomized controlled trial in adolescents with type 1 diabetes

Abraham MB, Nicholas JA, Smith GJ, Fairchild JM, King BR, Ambler GR, Cameron FJ, Davis EA, Jones TW; on behalf of the PLGM Study Group

Diabetes Care 2018; **41**: 303–310

Closed-loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: the artificial pancreas ski study

Breton MD, Cherňavsky DR, Forlenza GP, DeBoer MD, Robic J, Wadwa RP, Messer LH, Kovatchev BP, Maahs DM

Diabetes Care 2017; **40**: 1644–1650

Optimizing hybrid closed-loop therapy in adolescents and emerging adults using the MiniMed 670G system

Messer LH, Forlenza GP, Sherr JL, Wadwa RP, Buckingham BA, Weinzimer SA, Maahs DM, Slover RH

Diabetes Care 2018; **41**: 789–796

Closed-loop glucose control in young people with type 1 diabetes during and after unannounced physical activity: a randomised controlled crossover trial

Dovc K, Macedoni M, Bratina N, Lepej D, Nimri R, Atlas E, Muller I, Kordonouri O, Biester T, Danne T, Phillip M, Battelino T

Diabetologia, 2017; **60**: 2157–2167

Safety and feasibility of the OmniPod hybrid closed-loop system in adult, adolescent, and pediatric patients with type 1 diabetes using a personalized model predictive control algorithm

Buckingham BA, Forlenza GP, Pinsky JE, Christiansen MP, Wadwa RP, Schneider J, Peyser TA, Dassau E, Lee JB, O'Connor J, Layne JE, Ly TT

Diabetes Technol Ther 2018; **20**: 257–262

ACE inhibitors and statins in adolescents with type 1 diabetes

Marcovecchio ML, Chiesa ST, Bond S, Daneman D, Dawson S, Donaghue KC, Jones TW, Mahmud FH, Marshall SM, Neil HAW, Dalton RN, Deanfield J, Dunger DB; for the AdDIT Study Group

N Engl J Med 2017; **377**: 1733–1745

Effect of metformin on vascular function in children with type 1 diabetes: A 12-month randomized controlled trial

Anderson JJA, Couper JJ, Giles LC, Leggett CE, Gent R, Coppin B, Peña AS

J Clin Endocrinol Metab 2017; **102**: 4448–4456

Randomized, double-blind, placebo-controlled dose-finding study of the dipeptidyl peptidase-4 inhibitor linagliptin in pediatric patients with type 2 diabetes

Tamborlane WV, Laffel LM, Weill J, Gordat M, Neubacher D, Retlich S, Hettema W, Hoesl CE, Kaspers S, Marquard J

Pediatric Diabetes 2018; **19**: 640–648

Effect of oral insulin on prevention of diabetes in relatives of patients with type 1 diabetes: a randomized clinical trial

Writing Committee for the Type 1 Diabetes TrialNet Oral Insulin Study Group, Krischer JP, Schatz DA, Bundy B, Skyler JS, Greenbaum CJ

JAMA 2017; **318**: 1891–1902

INSULIN PUMPS

Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes

Karges B¹, Schwandt A^{2,3}, Heidtmann B⁴, Kordonouri O⁵, Binder E⁶, Schierloh U⁷, Boettcher C⁸, Kapellen T⁹, Rosenbauer J¹⁰, Holl RW³

¹Division of Endocrinology and Diabetes, Medical Faculty, RWTH Aachen University, Aachen, Germany; ²Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm, Germany; ³German Center for Diabetes Research (DZD), Neuherberg, Germany; ⁴Children's Hospital Wilhelmstift, Hamburg, Germany; ⁵Diabetes Center for Children and Adolescents, Children's Hospital Auf Der Bult, Hannover, Germany; ⁶Department of Pediatrics, Medical University of Innsbruck, Innsbruck, Austria; ⁷Department of Pediatrics, Centre Hospitalier de Luxembourg, Luxembourg City, Luxembourg; ⁸Division of Paediatric Endocrinology and Diabetology, Center of Child and Adolescent Medicine, Justus Liebig University Giessen, Giessen, Germany; ⁹Hospital for Children and Adolescents, University of Leipzig, Leipzig, Germany; ¹⁰Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center at the University of Düsseldorf, Düsseldorf, Germany

JAMA 2017; **318**: 1358–1366

This manuscript is also discussed in the article on Insulin Pumps, page S-32.

Background

The use of insulin pumps for intensive insulin therapy among patients with type 1 diabetes (T1D) has substantially increased. The aim of this study was to determine whether rates of short-term diabetes complications, namely severe hypoglycemia and diabetic ketoacidosis (DKA), are lower

with insulin pump therapy compared with insulin injection therapy in children, adolescents, and young adults with T1D.

Methods

A population-based cohort study was conducted between January 2011 and December 2015 in 446 diabetes centers participating in the Diabetes Prospective Follow-up Initiative in Germany, Austria, and Luxembourg. Study participants were patients younger than 20 years of age with T1D and diabetes duration > 1 year, treated with insulin pump therapy or with multiple daily insulin injections. The main outcomes were rates of severe hypoglycemia and DKA during the most recent treatment year. Secondary outcomes included glycated hemoglobin levels, insulin dose, and body mass index.

Results

Of 30,579 patients (53% male) with a mean age of 14.1 ± 4.0 years, 14,119 (46.2%) used pump therapy (median duration, 3.7 years) and 16,460 used insulin injections (median duration, 3.6 years). Patients using pump therapy ($n = 9814$) were matched with patients using injection therapy ($n = 9814$). Compared with injection therapy, pump therapy was associated with lower rates of both severe hypoglycemia (9.55 vs 13.97 per 100 patient-years; $P < 0.001$) and DKA (3.64 vs 4.26 per 100 patient-years; $P = 0.04$). Glycated hemoglobin levels and total daily insulin doses were also lower with pump therapy than with injection therapy (8.04% vs 8.22%; $P < 0.001$ and 0.84U/kg vs 0.98U/kg; $P < 0.001$, respectively). No significant difference was observed for body mass index between the two treatment regimens.

Conclusions

Among young patients with T1D, insulin pump therapy was associated with improved clinical outcomes determined by reduced risks of short-term diabetes complications including severe hypoglycemia and DKA as well as better glycemic control during the most recent year of therapy compared with insulin injection therapy.

Comments

Pump therapy with rapid-acting insulin allows for a more physiologic insulin replacement and may thus contribute to improved metabolic control, thereby reducing the risk of long-term complications. Previous large registry data (5–7) already demonstrated better glycemic control in children with T1D treated with insulin pump therapy compared with children treated with multiple daily injections. However, the association of pump therapy compared to injection therapy with the risk of acute diabetes complications has not been studied comprehensively. Several studies reported an increased risk of DKA associated with insulin pump therapy in pediatric patients with diabetes (8,9) raising concerns about the safety of pump therapy. The results of this study favor pump therapy, with lower rates of acute complications (severe hypoglycemia, hypoglycemic coma, and DKA) and with lower glycated hemoglobin (HbA1c) levels reflecting improved metabolic control.

In the current study, all patients continuously used either pump therapy or injection therapy during the entire observation period of 12 months, thus excluding treatment crossover. The present study strengths include its prospective design, the very large sample size of a population of more than 30,000 young patients with T1D, and the statistical methodology that included a matched-pair approach that allowed a direct comparison of hypoglycemia and DKA frequencies in pump users and injection users. Whereas previous randomized clinical trials have been too small to assess the risk of these short-term diabetes complications, this study provides outcome data in clinical use that are likely representative of pediatric patients with T1D.

In the present study, the reduced risk of severe hypoglycemia with pump therapy was associated with lower total daily insulin dose. The use of rapid-acting insulin analogues with pump therapy allows for more flexible therapy with lower glycemic variability, leading to lower rates of acute and long-term diabetes complications. Prevention of DKA is an integral part of diabetes education and should be emphasized in patients treated with pump therapy, thereby reducing their incidence of DKA.

The study limitations include its nonrandomized, observational design that may be prone to selection bias.

Another limitation is lack of other data relevant to glycemic control, hypoglycemia, and DKA as: the intensity of diabetes education, data about the socio-demographic characteristics of the study population and family support, and the lack of data regarding the use of continuous glucose monitoring.

¹NICU, Departments of Women's and Child's Health and ²Endocrinology Section, Department of Pediatrics, Yale University, New Haven, CT; ³Information Engineering, University of Padova, Padova, Italy; ⁴Boston Children's Hospital, Boston, MA; ⁵Independent Statistician, Padova, Italy

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Background

Very preterm infants (≤ 32 weeks gestation or birth weight ≤ 1500 g) are at risk for morbidity, mortality, and neurologic consequences from abnormal blood sugar. The aim of this study was to assess whether glucose administration guided by continuous glucose monitoring (CGM) was more effective than standard of care in maintaining euglycemia in very preterm infants.

Methods

Within the first 48 hours of life, 50 very preterm infants were randomly assigned to receive computer-guided intravenous dextrose driven by CGM or standard of care glucometer. The primary outcome was time spent with blood sugar of 72–144 mg/dL. Secondary outcomes included time with blood sugar < 47 mg/dL (severe hypoglycemia), 47–71 mg/dL (mild hypoglycemia), 145–180 mg/dL (mild hyperglycemia), > 180 mg/dL (severe hyperglycemia), glucose variability, and clinical outcomes.

Results

Those in the group using CGM-mediated dextrose delivery spent 84% time in range vs 68% for the standard of care group ($P < 0.001$). There was a statistically significant reduction in time spent in severe hypoglycemia ($P = 0.007$), mild hypoglycemia ($P = 0.04$), and severe hyperglycemia ($P = 0.04$) with reduction in glucose variability (mean $\pm$ SD 21.6 ± 5.4 mg/dL vs 27 ± 7.2 mg/dL, $P = 0.01$; coefficient of variation $22.8\% \pm 4.2\%$ vs $27.9\% \pm 5.0\%$, $P < 0.001$).

Conclusions

CGM-guided titration of intravenous dextrose can successfully increase time in range, reduce hypoglycemia, and minimize glycemic variability in preterm infants during the first week of life.

Comments

There is some evidence for long-term negative neurodevelopmental outcomes in neonates with severe hypoglycemia (10). Very preterm infants have an even greater risk of poor neurological outcomes. To reduce hypoglycemia as a possible risk factor in these patients, Galderisi and colleagues performed a randomized controlled trial at the University Hospital of Padua of a system that uses CGM to control the delivery rate of intravenous (i.v.) dextrose via a proportional-integrative-derivative (PID) controller. Infants born before 32 weeks of gestation or with birth weight below 1500 grams and less than 48 hours old were randomized to receive 7 days blinded CGM and standard-of-care i.v. dextrose or an unblinded CGM with alarms and i.v. dextrose delivered according to

BLOOD GLUCOSE MONITORING

Continuous glucose monitoring in very preterm infants: a randomized controlled trial

Galderisi A^{1,2}, Facchinetti A³, Steil GM⁴, Ortiz-Rubio P⁴, Cavallin F⁵, Tamborlane WV², Baraldi E¹, Cobelli C³, Trevisanuto D¹

the PID controller. Outcomes were based on CGM data from a Dexcom G4P.

An important issue brought up in the paper is that detachment of the device more than once occurred in two subjects who discontinued the intervention as per protocol. This is very important for informed consent in other neonatal CGM studies.

The authors conclude that delivery of dextrose by a controller using CGM data improved measures of glucose by the same CGM. While these results demonstrate technology proof of concept, it must be noted that there was no effect on the short-term clinical outcomes the team evaluated. As the Dexcom G6 no longer requires calibration, use of this technology in the neonatal intensive care unit may significantly decrease the burden of managing glucose for health-care providers. Larger studies will be needed to assess whether there are long-term clinical benefits for these children.

Effect of financial incentives on glucose monitoring adherence and glycemic control among adolescents and young adults with type 1 diabetes: a randomized clinical trial

Wong CA^{1,2}, Miller VA³, Murphy K⁴, Small D^{2,5}, Ford CA³, Willi SM⁶, Feingold J⁷, Morris A⁸, Ha YP⁸, Zhu J^{2,8}, Wang W^{2,8}, Patel MS^{2,8,9,10}

¹Department of Pediatrics, Duke Clinical Research Institute, Duke-Margolis Center for Health Policy, Duke University, Durham, NC; ²Leonard Davis Institute of Health Economics, Center for Health Incentives and Behavioral Economics at the University of Pennsylvania, Philadelphia, PA; ³Division of Adolescent Medicine, The Children's Hospital of Philadelphia, Perelman School of Medicine and University of Pennsylvania, Philadelphia, PA; ⁴Division of Pediatric Endocrinology, The Children's Hospital of Philadelphia, Philadelphia, PA; ⁵Department of Statistics, The Wharton School, University of Pennsylvania, Philadelphia, PA; ⁶Division of Pediatric Endocrinology, The Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA; ⁷Medical student, Icahn School of Medicine at Mount Sinai, New York, NY; ⁸Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; ⁹Department of Medicine, Crescenzo Veterans Affairs Medical Center, Philadelphia, PA; ¹⁰Health Care Management, The Wharton School, University of Pennsylvania, Philadelphia, PA

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This manuscript is also discussed in the article on Self-Monitoring of Blood Glucose, page S-4.

Background

For those with type 1 diabetes, glucose control often worsens during the transition to young adulthood, which may lead to complications later in life. The aim of this study was to determine the effect of financial incentives on adherence to glucose checks and the effect on glycemic control in adolescents and young adults with type 1 diabetes (T1D).

Methods

The BE IN CONTROL (Behavioral Economic Incentives to Improve Glycemic Control Among Adolescents and Young Adults with T1D) study was a 6-month, two-arm, randomized clinical trial with 3-month intervention and follow-up periods. Ninety participants with T1D and HbA1c > 8.0% were randomized to receive either standard of care for 6 months or 3 months of an incentive program followed by 3 months standard of care. The daily blood glucose monitoring goal was four or more checks per day with one or more readings of 70–180 mg/dL. The incentive was \$60/month, from which \$2 was subtracted for every day goals were not met. During the following 3 months, the incentive was discontinued. The primary outcome was change in HbA1c at 3 months. Secondary outcomes included frequency of glucose monitoring and change in HbA1c at 6 months.

Results

During the first 3-month period, daily adherence to glucose checks was significantly greater ($P = 0.003$) in the incentive group (50.0%) vs the control group (18.9%). The difference was not maintained after the incentive was removed over the subsequent 3 months. HbA1c did not significantly differ between groups at 3 or 6 months.

Conclusions

Adolescents and young adults with T1D displayed improved glucose monitoring adherence during a 3-month daily financial incentive. This did not translate into significantly improved glycemic control.

Comments

There is a tremendous need to address glycemic control in adolescents and young adults (11,12). The BE IN CONTROL study assessed the effect of financial incentives on adherence to glucose checks and glycemic controls. During the first 3-month period, daily adherence to glucose checks was significantly greater in the incentive group. The difference was not maintained after the incentive was removed, and HbA1c did not significantly differ between groups at 3 or 6 months. The incentivized behavior did increase, but the authors conclude that increasing glucose checks in isolation did not improve glycemic control.

The results are fascinating and do suggest that incentivizing desired actions is efficacious while the intervention persists. Economic factors are often highlighted in health-care disparities research, but targeted research on interventions is more limited. One criticism of the current study is the way behavior was incentivized. It is frequently more useful to positively reinforce good behaviors than punish undesired behaviors. The phrasing here was that the subjects would lose money if they did not check. It may have been more useful to suggest a \$2 reimbursement for the desired behavior. Additionally, it is possible the wrong behavior was incentivized. Since the primary outcome was HbA1c, incentivizing mealtime boluses or glucose reading within target may have had a more direct effect on

glycemic control. It is not clear how long a behavior must be incentivized to persist. If the correct behavior is incentivized and improves glycemic control, it may be cost feasible for payers.

Flash glucose measurements in children with type 1 diabetes in real-life settings: to trust or not to trust?

Szadkowska A¹, Gawrecki A², Michalak A¹, Zozulińska-Ziółkiewicz D², Wojciech Fendler W^{1,3}, Młynarski W¹

¹Departments of Pediatrics, Oncology, Hematology and Diabetology and ³Biostatistics and Translational Medicine, Medical University of Lodz, Lodz, Poland; ²Department of Internal Medicine and Diabetology, Poznan University of Medical Science, Poznan, Poland

Diabetes Technol Ther 2018; **20**: 17–24

Background

Maintaining a high frequency of self-monitoring of blood glucose (SMBG) is the cornerstone for meeting HbA1c goals, preventing serious hypoglycemia, and associated with significantly lower rates of diabetic ketoacidosis. CGM offers efficient glycemic control with a reduced need for manual tests and associated inconveniences. A new intermittently scanned CGM (isCGM) system (Abbott Diabetes Care, Alameda, CA), FreeStyle Libre (FSL), was proposed as an alternative. The main aim of the study was to establish the clinical accuracy of a Flash glucose-monitoring device FSL in reference to the glucometer in children with type 1 diabetes (T1D) in a real-world setting during a summer camp. The secondary objective was to assess the children's attitude toward the device and its possible association with measurement accuracy.

Methods

This was a prospective, single-arm study conducted during an annual summer camp for children and adolescents with T1D. During the camp, children (n = 79, 8–18 years of age) were provided with FSLs for 12 days. Supervised glucose testing was carried out at eight time points on days 3, 7, and 11 of the study. Glycemia was estimated using FSL and measured with a personal glucometer within 2 minutes, and glucose trend arrows were recorded. On the last day, a custom-designed questionnaire was administered to assess the degree of satisfaction with isCGM use.

Results

The study participants (n = 78; 43% boys) had a median age of 12.8 years (interquartile range [IQR] 11.6–14.7 years), with a median diabetes duration of 5.8 years (IQR 3.8–8.5 years). Their median HbA1c at inclusion was 7.5% (IQR 7.0%–8.0%) or 58.5 mmol/mol (IQR 53–63.9 mmol/mol); 88.6% were treated with insulin pump therapy. During the summer camp, children wore the sensors for a median time of 10.5 days (IQR 10 to complete 11 days), and 10 sensors were replaced in eight children due to detachment. Mean absolute relative difference (MARD) between the FSL and the gluc-

ometer was 13.5%–12.9%. FSL was the most accurate in stable glycemic conditions (MARD 11.4%–10.4%), less accurate when glycemia was falling >2 mg/(dL·min) [0.111 mmol/(L·min): MARD 22.6%–18.6%; $P < 0.001$ vs stable conditions], and when the device could not determine the glucose trends (16.5%–16.3%; $P = 0.01$ vs stable conditions). The FSL was less accurate during the day than during the night (MARD 14.9%–14% vs 11.2%–10.6%; $P < 0.0001$). The Surveillance Error Grid methodology was used to evaluate paired results: 80.36% of FSL readings were associated with no clinical risk, 18.73% were associated with slight risk, and one high-risk measurement was detected. Sixty-eight (87.2%) children expressed a willingness to continue isCGM use. Most of the participants regarded the discretion and painlessness of measurements as key advantages and its inaccuracy, as perceived by the children, as a disadvantage.

Conclusions

The FSL isCGM device offers good accuracy in comparison with capillary blood glucose in children and adolescents with T1D. However, the performance of isCGM is strongly affected by the glycemia change trend at the time of measurement. Therapeutic decisions should not be solely based on measurements flagged by a rapid change flag on the FSL isCGM. Such measurements should first be verified by using a blood glucose measurement.

Comments

FSL offers a factory-calibrated sensor that can be worn for 14 days without manual calibration by using blood testing, a reader combined with a standard glucometer, and dedicated software. The user receives a current glucose measurement along with historic results from the preceding 8 hours by scanning the sensor with the FreeStyle reader. The glucose trends are displayed as arrows on the reader along with alerts. The device requires active scanning by the user, and it does not report alerts in real time. So far, only one study tested the accuracy of FSL in a pediatric population that examined the use of FSL in home-based conditions, and the data obtained by isCGM were hidden from participants (13).

Initial observations suggested that FSL users may rely solely on flash glucose monitoring (FGM) and not perform SMBGs. This raises the question whether isCGM is accurate enough to replace standard glucometers, or should it be just a complementary addition to SMBG. The current study demonstrated that most FSL readings were localized in zone A or B of the error grids for more than 98% of cases, which means that they would not impact clinical decisions in a severe manner. Most of the children expressed willingness to continue using this device. It is possible that the good reception of isCGM may result from its minimal invasiveness when compared with standard blood glucose measurements and added value in the form of easily interpretable glucose trend arrows. Therefore, it can be a good compromise in those young patients who do not perform frequent SMBG and do not want to use the CGM. However, the main limitations of this device are the requirement of compliance of active scanning by the user

and the lack of alarms, which may be crucial for those patients with hypoglycemic unawareness and during the night hours. The main limitations of the study are its short (12 days) duration and comparing FSL readings only with the Contour Plus One glucometer measurements. Comparing results of the FSL with Yellow Springs Instrument (YSI), which is widely accepted as a method for reference measurements, and system calibration by most manufacturers of blood glucose monitoring systems would be more accurate. Studies with longer observation times are needed to evaluate whether FSL could provide lasting improvement in glycemic outcomes.

We have to consider that when glucose levels were falling rapidly, the FSL reading differed by up to 20% from blood glucose measurements. This difference may be due to the lag time between glucose concentrations in the interstitial fluid reaching those in the blood. Therefore, patients and parents have to be instructed to confirm the measurements with SMBG in such situations and also in situations of glucose levels in the hypoglycemic range or when the patient's sensations are inadequate to the device readings.

Reduction in hypoglycemia with the predictive low-glucose management system: a long-term randomized controlled trial in adolescents with type 1 diabetes

Abraham MB^{1,3}, Nicholas JA^{1,2}, Smith GJ², Fairchild JM⁴, King BR⁵, Ambler GR⁶, Cameron FJ⁷, Davis EA^{1,3}, Jones TW^{1,3}; on behalf of the PLGM Study Group

¹Children's Diabetes Centre, Telethon Kids Institute, The University of Western Australia, Perth, Australia; ²Department of Endocrinology and Diabetes, Princess Margaret Hospital for Children, Perth, Australia; ³Division of Paediatrics, Medical School, The University of Western Australia, Perth, Australia; ⁴Department of Endocrinology and Diabetes, Women's and Children's Hospital, Adelaide, Australia; ⁵Department of Endocrinology and Diabetes, John Hunter Children's Hospital, Newcastle, Australia; ⁶Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead and Clinical School, The University of Sydney, Sydney, Australia; ⁷Department of Endocrinology and Diabetes, The Royal Children's Hospital, Melbourne, Australia

Diabetes Care 2018; **41**: 303–310

This manuscript is also discussed in the article on Insulin Pumps, page S-32.

Background

Short-term studies with automated systems that suspend basal insulin for predicted hypoglycemia reduce hypoglycemia, but long-term efficacy and safety have not been established.

Methods

A 6-month, multicenter, randomized controlled trial was carried out in children and adolescents with T1D, comparing

the use of Medtronic MiniMed 640G pump with predictive low-glucose management (PLGM) with sensor-augmented pump therapy (SAPT) alone. The percentage time in hypoglycemia with sensor glucose (SG) <3.5 mmol/L (63 mg/dL) was the primary outcome.

Results

Seventy-four subjects were randomized to SAPT and 80 subjects to PLGM in an intent-to-treat analysis. The time with SG <3.5 mmol/L was 3.0% in the SAPT group and 2.8% in the PLGM group at baseline. PLGM was associated with a reduction in hypoglycemia compared with SAPT (% time SG <3.5 mmol/L SAPT vs PLGM, 2.6 vs 1.5; $P < 0.0001$), as was time with SG <3 mmol/L ($P < 0.0001$). This reduction was seen during both day and night ($P < 0.0001$). Hypoglycemic events (SG <3.5 mmol/L for >20 min) also declined with PLGM vs SAPT (139 vs 227 events/patient-year; $P < 0.001$). There was no difference in HbA1c at 6 months (SAPT $7.6 \pm 1.0\%$ vs PLGM $7.8 \pm 0.8\%$; $P = 0.35$). No PLGM-related serious adverse events were reported, and quality of life measures in did not change in either the parent group or the participant group.

Conclusions

PLGM reduced hypoglycemia without deterioration in HbA1c in children and adolescents with T1D.

Comments

Progress in diabetes technology has been rapid and relentless, although still slower than people with T1D who desire a fully automated, burden-free, inexpensive, and reliable technology would wish. Predictive low-glucose suspend systems mark an important advance that sensibly shuts off insulin when hypoglycemia is predicted (14). The MiniMed 640G system available in many parts of the world preceded the 670G hybrid closed-loop system (15) and adds protection against hypoglycemia. Data such as these by Abraham and colleagues add important data from a longer study (6 months) to support the use of predicted low-glucose suspend. Although systems that dose insulin will increasingly be used, for some people this step on the pathway may be a start as the technologies develop and user experience expands.

CLOSED-LOOP INSULIN DELIVERY SYSTEMS

Closed-loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: the artificial pancreas ski study

Breton MD¹, Chervinsky DR¹, Forlenza GP², DeBoer MD¹, Robic J², Wadwa RP², Messer LH², Kovatchev BP¹, Maahs DM^{2,3}

¹Center for Diabetes Technology, University of Virginia, Charlottesville, VA; ²Barbara Davis Center for Childhood Diabetes, University of Colorado Denver, Aurora, CO; ³Department of Pediatrics, Stanford University, Stanford, CA

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This manuscript is also discussed in the article on Decision Support Systems and Closed Loop, page S-42, and the article on Advances in Exercise, Physical Activity, and Diabetes Mellitus, page S-112.

Background

Intense exercise challenges type 1 diabetes (T1D) management. Closed-loop control (CLC) systems improve glycemic control during physical activity of limited intensity and short duration. However, CLC data are limited for extended vigorous outdoor exercise among adolescents.

Methods

Skiing presents unique metabolic challenges: intense prolonged exercise, cold, altitude, and stress/fear/excitement. Thirty-two adolescents with T1D (10–16 years of age) participated in a randomized controlled trial during two 5-day ski camps (5 h skiing/~day) in Virginia and Colorado. Participants were randomly assigned to the University of Virginia CLC system or remotely monitored sensor-augmented pump (RM-SAP). The CLC and RM-SAP groups were paired by age and hemoglobin A1c (HbA1c) and remotely monitored by the study team 24 h/day.

Results

Percent time in range (70–180 mg/dL) improved using CLC: 71.3 vs 64.7% (+6.6% [95% confidence interval 1–12]; $P=0.005$) compared with physician-monitored open loop. Maximum effect was reported late at night. Both hypoglycemia exposure and carbohydrate treatments improved overall ($P=0.001$ and $P=0.007$) and during the daytime, although ski level effects were strong ($P=0.0001$ and $P=0.006$). The two groups were balanced in terms of ski/snowboard proficiency, but there was a very strong effect by site (experienced in Colorado and naive in Virginia). No adverse events were reported with CLC, and feedback from participants was strongly positive.

Conclusions

CLC in adolescents with T1D reduced hypoglycemia and improved glycemic control during prolonged intensive winter sports, including challenges of altitude and cold.

Comment

In the past decade, artificial pancreas research has progressed from single day, hospital-based, single participant studies to the first U.S. FDA approval of a first-generation hybrid closed-loop system for people with T1D. Future iterations of artificial pancreas systems will improve usability and performance. One challenge for current systems is exercise (16,17). While much work is needed to improve current systems performance, this study makes clear that existing systems do better than open-loop control as far as hypoglycemia prevention and time in range. This study design placed the bar high with a control group of sensor-augmented pump therapy that was remotely monitored by a physician 24 h/day for the duration of the study. How the CLC system (71% time in

range) would compare with typical glucose control in a free-living skiing situation is uncertain, but undoubtedly the glucose control would not be as tight as in this comparison group (64% time in range during the study), as these participants had a mean HbA1c of 8.5% at entry to the study. Moreover, studies such as these are required to test artificial pancreas systems in settings that mimic user's real-life activity. Future iterations of these devices will increasingly be tested in challenging situations to provide insight on how to further improve their ability to benefit people with diabetes.

Optimizing hybrid closed-loop therapy in adolescents and emerging adults using the MiniMed 670G system

Messer LH¹, Forlenza GP¹, Sherr JL², Wadwa RP¹, Buckingham BA³, Weinzimer SA², Maahs DM³, Slover RH¹

¹Barbara Davis Center for Childhood Diabetes, University of Colorado, Anschutz Medical Campus, Aurora, CO; ²Department of Pediatrics, Yale School of Medicine, New Haven, CT; ³Department of Pediatrics, Stanford University School of Medicine, Stanford, CA

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This manuscript is also discussed in the article on Diabetes Technology and the Human Factor, page S-138.

Background

The MiniMed 670G System is the first globally available commercial hybrid closed-loop (HCL) system for management of type 1 diabetes (T1D). Insulin delivery patterns and time-in-range metrics were investigated in HCL “Auto Mode” and open-loop (OL) “Manual Mode” in adolescents and young adults with T1D. We examined system alerts, usage profiles, and operational parameters with the objective of providing guidance for optimal clinical use of the system.

Methods

We analyzed data from 31 adolescent and young adult participants (14–26 years old) at three clinical sites in the 670G pivotal trial. Participants completed a 2-week run-in period in OL (insulin pump with CGM), followed by a 3-month in-home study phase with HCL functionality (Auto Mode) enabled. Data were compared between baseline OL and HCL use after 1 week, 1 month, 2 months, and 3 months.

Results

Compared with baseline OL, carbohydrate-to-insulin (C-to-I) ratios were more aggressive for all meals with HCL, although total daily insulin dose and ratio of basal to bolus was unchanged over the duration of the study. HbA1c decreased 0.75% and time in range increased 14% with use of Auto Mode after 3 months ($P<0.001$). Time in Auto Mode declined from 87% to a final use rate of 72% (–15%). The main causes of Auto Mode exit were sensor/insulin delivery alerts and hyperglycemia.

Conclusions

For adolescents and young adults who transition to the MiniMed 670G System, health-care providers should anticipate immediate C-to-I ratio adjustments and assess active insulin time. Users should anticipate occasional Auto Mode exits and should follow system instructions and bolus for meals to reduce exits. Ongoing clinical guidance and education from providers will be required for 670G optimization.

Comment

Landmark advances have been made in the past few years in the commercial availability of diabetes technology to the pediatric population. The MiniMed 670G system was the first HCL system available and lowered HbA1c in both adult and pediatric participants of the clinical trial. This paper by Messer adds to our understanding of how to initiate these systems in this population and provides anticipatory guidance on what education and dose adjustments will maximize usability (18,19). Providers should consider initial C-to-I adjustments to dose more insulin with meals and snacks and to shortening active insulin time. It will be especially important that users of the 670G have realistic expectations about this first-generation system and what efforts are required to remain in Auto Mode (i.e., closed loop) such as required calibration, bolusing for meals and snacks, and how to troubleshoot system challenges. The 670G marks a tremendous advance in diabetes technology, yet the 15% decline in time in Auto Mode over 3 months while in a fully supported, industry-sponsored clinical trial raises questions about what real-world clinical use might be in this patient population. Given the clear benefit with respect to increased time in range and lower HbA1c and hypoglycemia, improving usability remains a primary goal for next generation artificial pancreas systems.

Closed-loop glucose control in young people with type 1 diabetes during and after unannounced physical activity: a randomised controlled crossover trial

Dovc K¹, Macedoni M², Bratina N¹, Lepej D³, Nimri R⁴, Atlas E⁵, Muller I⁵, Kordonouri O⁶, Biester T⁶, Danne T⁶, Phillip M^{4,7}, Battelino T^{8,9}

¹Department of Paediatric Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia; ²Department of Paediatrics – Diabetes Service Studies, University of Milan, Ospedale dei Bambini Vittore Buzzi, Milan, Italy; ³Department of Pulmonology, University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia; ⁴The Jesse and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Centre for Childhood Diabetes, Schneider Children's Medical Centre of Israel, Petah Tikva, Israel; ⁵DreaMed Diabetes Ltd, Petah Tikva, Israel; ⁶Diabetes Centre for Children and Adolescents, Kinder- und Jugendkrankenhaus Auf der Bult, Hannover, Germany; ⁷Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; ⁸Department of Paediatric En-

docrinology, Diabetes and Metabolic Diseases, University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia; ⁹Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

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This manuscript is also discussed in the article on Decision Support Systems and Closed Loop, page S-42, and the article on Advances in Exercise, Physical Activity, and Diabetes Mellitus, page S-112.

Background

Hypoglycemia associated with exercise remains a challenge for patients with T1D. This study tested the safety and performance of the Glucositter fuzzy-logic controller on young people with T1D engaging in a regimented exercise routine conducted in the hospital.

Methods

During four visits at a single site in Slovenia, individuals with T1D experienced with pump use were randomized to perform two separate exercise routines with closed- or open-loop insulin delivery. The participants performed unannounced exercise that was either moderate intensity (55% of VO₂ max) or moderate intensity with integrated high-intensity sprints (55/80% of VO₂ max). Closed-loop insulin delivery occurred from 3 p.m. on the day of exercise to 1 p.m. the next day. The primary outcome was glucose control during the exercise period and the following night.

Results

Twenty participants with T1D performed all activities. Neither group experienced hypoglycemia below 60mg/dL. However, closed-loop insulin delivery increased time in range to 84.1% vs 68.7% for the open-loop group ($P=0.0057$) with a decrease in required insulin ($P=0.0123$).

Conclusions

Closed-loop insulin delivery resulted in no hypoglycemia during this in-hospital trial. There was a significant increase in time in range for closed-loop versus open-loop insulin delivery.

Comment

Despite evidence of the benefits of exercise for those with T1D (20), there remains a risk of hypoglycemia both during the activity and the following night (21). Dovc and colleagues tested the performance of the Glucositter fuzzy-logic controller on young people with T1D engaging in unannounced exercise routines conducted in the hospital. The study was well designed with objective measurements of exercise intensity. If hypoglycemia can be prevented during exercise, weight loss becomes more likely as the individual does not have to consume additional calories to treat lows. Additionally, the decrease in insulin with greater time in range implies improved insulin sensitivity or increased glucose utilization by insulin-independent mechanisms. One can hypothesize that this profile improves the efficacy of exercise in those with T1D.

Safety and feasibility of the OmniPod hybrid closed-loop system in adult, adolescent, and pediatric patients with type 1 diabetes using a personalized model predictive control algorithm

Buckingham BA¹, Forlenza GP², Pinsky JE³, Christiansen MP⁴, Wadwa RP², Schneider J⁵, Peyser TA⁵, Dassau E⁶, Lee JB⁷, O'Connor J⁷, Layne JE⁷, Ly TT⁷

¹Division of Endocrinology, Department of Pediatrics, Stanford School of Medicine, Stanford, Palo Alto, CA; ²Barbara Davis Center for Diabetes, University of Colorado School of Medicine, Aurora, CO; ³Sansum Diabetes Research Institute, Santa Barbara, CA; ⁴Diablo Clinical Research, Walnut Creek, CA; ⁵ModeAGC LLC, Palo Alto, CA; ⁶Harvard John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, MA; ⁷Insulet Corporation, Billerica, MA

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Background

The current study assesses the Insulet model predictive control algorithm in youth, adolescents, and adults with type 1 diabetes (T1D). Insulet's system utilizes the OmniPod patch pump, Dexcom G4 CGM, and a model predictive control algorithm running on a tablet for automated insulin delivery.

Methods

This was a multicenter safety and feasibility trial with 1-week use of only sensor and pump followed by 36 hours on the closed-loop system. Subjects with T1D who were 6–65 years of age with hemoglobin A1c level of 6%–10% were eligible. Physical activity was limited, and announced meals ranged from 30 to 90 grams of carbohydrates. Primary endpoints included percent time with sensor glucose < 70 mg/dL and > 250 mg/dL.

Results

Adults receiving 80% bolus had 0.7% time < 70 mg/dL, 69.5% time 70–180 mg/dL, and 8% time > 250 mg/dL; adults receiving full bolus 0.7% time < 70 mg/dL, 73.0% time 70–180 mg/dL, and 3.6% time > 250 mg/dL; adolescents 2% time < 70 mg/dL, 72.6% time 70–180 mg/dL, and 4.9% time > 250 mg/dL; and pediatric patients 2% time < 70 mg/dL, 70.1% time 70–180 mg/dL, and 6.7% time > 250 mg/dL.

Conclusions

The authors conclude that the device is safe for further testing in those with T1D.

Comments

Following FDA approval of the Medtronic 670G in September 2016 (22), both Insulet and Tandem have been at work creating closed-loop insulin delivery systems. Insulet's system utilizes the OmniPod patch pump, Dexcom CGM, and a model predictive control algorithm running on a tablet for automated insulin delivery. This

was a proof of concept for the algorithm and not the commercial system, which will undoubtedly be designed very differently on final release. As the first human trial of this system, the initial group of 24 adult subjects received a reduced 80% meal bolus, while another 10 adults, 12 adolescents, and 12 pediatric age patients received full meal boluses.

Importantly, carbohydrate intake was restricted to 30–90 grams and exercise was limited. While these are very restrictive conditions, it is a necessary first step in assessing safety. The investigation is significant, as some individuals prefer the patch pump design to a tethered pump. Additionally, it is the first test of a commercial model predictive control insulin delivery system. Currently, both Insulet and Tandem are paring with Dexcom, who is now producing a sensor that does not require calibration. This will provide significant competition for the Medtronic 670G system, wherein the Guardian 3 sensor requires at least one calibration every 12 hours.

OTHER TREATMENTS FOR DIABETES

ACE inhibitors and statins in adolescents with type 1 diabetes

Marcovecchio ML¹, Chiesa ST⁴, Bond S³, Daneman D⁸, Dawson S³, Donaghue KC⁹, Jones TW¹⁰, Mahmud FH⁸, Marshall SM⁶, Neil HAW⁷, Dalton RN⁵, Deanfield J⁴, Dunger DB^{1,2}; for the AdDIT Study Group

¹The Department of Paediatrics and ²the Wellcome Trust–Medical Research Council Institute of Metabolic Science, University of Cambridge, UK; ³The Cambridge Clinical Trials Unit, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, UK; ⁴Cambridge, the National Centre for Cardiovascular Prevention and Outcomes, University College London, UK; ⁵The Well Child Laboratory, Evelina London Children's Hospital, St. Thomas' Hospital, London, UK; ⁶The Institute of Cellular Medicine (Diabetes), Faculty of Clinical Medical Sciences, Newcastle University, Newcastle upon Tyne, UK; ⁷The Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK; ⁸The Department of Paediatrics, Hospital for Sick Children, and University of Toronto, Toronto, Australia; ⁹The Institute of Endocrinology and Diabetes, Children's Hospital at Westmead, and University of Sydney, Sydney, Australia; ¹⁰The Telethon Kids Institute, University of Western Australia, Perth, Australia

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Background

Rapid increases in the excretion of albumin during puberty precede the development of microalbuminuria and macroalbuminuria in adolescent patients with type 1 diabetes (T1D). These changes are associated with dyslipidemia, hypertension, increased levels of high-sensitivity C-reactive protein, increased aortic and carotid intima-media thickness, and altered retinal vasculature. The aim was to evaluate whether adolescents with high levels of albumin excretion

might benefit from therapy with angiotensin-converting enzyme (ACE) inhibitors and statins.

Methods

The trial was a double-blind, randomized, placebo-controlled trial at 32 centers in three countries (the United Kingdom, Canada, and Australia) designed to explore the effects of two medications with different mechanisms of action in a population of adolescents with T1D. Adolescents aged 10–16 years were screened ($n=4407$), and 1287 were identified with values in the upper third of the albumin/creatinine ratios. Patients ($n=443$) underwent randomization to one of four regimens: ACE inhibitor plus placebo, statin plus placebo, ACE inhibitor plus statin, or placebo plus placebo. The primary outcome for both interventions was the change in albumin excretion, assessed by albumin/creatinine ratio calculated from three early-morning urine samples obtained every 6 months over 2–4 years, and expressed as the area under the curve. Secondary outcomes included the development of microalbuminuria, progression of retinopathy, changes in the glomerular filtration rate, lipid levels, and measures of cardiovascular risk assessed by the carotid intima-media thickness, and levels of high-sensitivity C-reactive protein and asymmetric dimethylarginine.

Results

Overall adherence to the drug regimen was 75%, and there were no significant differences in the rate of serious adverse events between groups. The change in albumin excretion was not affected by ACE inhibitor therapy, statin therapy, or the combination of the two. The use of an ACE inhibitor was associated with a lower incidence of microalbuminuria than was the use of placebo, although it was not statistically significant. Significant reductions were observed in total, low-density lipoprotein, and non-high-density lipoprotein cholesterol levels and triglyceride levels, as well as in the ratio of apolipoprotein B to apolipoprotein A1, with the use of statins. However, neither medication caused significant changes in carotid intima-media thickness, other cardiovascular markers, the glomerular filtration rate, or the progression of retinopathy.

Conclusions

Neither ACE inhibitor nor statin therapy over a period of 2–4 years altered the primary outcome of the change in repeated measures of the albumin-to-creatinine ratio among adolescents with T1D.

measures of the albumin-to-creatinine ratio among adolescents with T1D.

Recent data from the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study indicate that even intermittent microalbuminuria may predict cardiovascular risk (23). In the current study, lower rates of progression to microalbuminuria were observed with the ACE inhibitor than with placebo, and although this finding was not significant, it may be of clinical relevance, since it was related to reduction in the variability of albumin-to-creatinine ratio.

The main study strengths are the large sample size and double-blind, randomized, placebo-controlled trial design. The main study limitation is the relatively short duration of exposure to the trial drugs. Despite the absence of response with respect to the carotid intima-media thickness in this trial, long-term follow-up of the cohort will be important to assess whether early intervention during this critical period of adolescence with ACE inhibitors or statins will result in a later effect, as reported in other trials of patients with type 2 diabetes (T2D) of glucose-lowering, lipid-lowering, or blood-pressure-lowering interventions in which reduced vascular complications emerged beyond the duration of the original trials (24,25). The concept of a “metabolic memory,” meaning that diabetic vascular stresses persist after glucose normalization, has been supported for both T1D and T2D. Mechanisms for propagating this memory appear focused on the nonenzymatic glycation of cellular proteins and lipids and on an excess of cellular reactive oxygen and nitrogen species, in particular originating at the level of glycated mitochondrial proteins and perhaps acting in concert with one another to maintain stress signaling independent of glucose levels. Thus, there is a need for early aggressive treatment aiming to “normalize” metabolic control together with the addition of agents that reduce cellular reactive species and glycation in order to minimize long-term diabetic complications. Therefore, follow-up of the present cohort will be essential to evaluate the long-term potential benefits of early intervention with ACE inhibitors and statins.

Comments

The study hypothesis was that adolescents with high levels of albumin excretion have an increased glomerular filtration rate, dyslipidemia, and increased arterial stiffness, aortic intima-media thickness, and cardiac autonomic dysfunction. Therefore, they might benefit from ACE inhibitors and statins that may lower the rate of cardiovascular risk factors as hypertension and dyslipidemia. The present study demonstrated that neither ACE-inhibitor nor statin therapy over a relatively short period of time (2–4 years) altered the change in repeated

Effect of metformin on vascular function in children with type 1 diabetes: a 12-month randomized controlled trial

Anderson JJA^{1,2}, Couper JJ^{1,2}, Giles LC³, Leggett CE^{1,4}, Gent R⁵, Coppin B⁶, Peña AS^{1,2}

¹Discipline of Paediatrics, Robinson Research Institute, University of Adelaide, North Adelaide, South Australia, Australia; ²Endocrinology and Diabetes Department, Women's and Children's Hospital, North Adelaide, South Australia, Australia; ³School of Public Health, Faculty of Health and Medical Sciences, University of Adelaide, North Adelaide, South Australia, Australia; ⁴Pharmacy, Women's and Children's Hospital, North Adelaide, South Australia, Australia; ⁵Medical Imaging, Women's and Children's Hospital, North Adelaide, South Australia, Australia;

⁶Flinders Medical Centre, Bedford Park, South Australia, Australia

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Background

Patients with T1D have three times the risk for cardiovascular causes of death as matched controls, despite good glycemic control. Therefore, they need additional strategies to improve cardiovascular health. Vascular dysfunction is a critical event in the development of cardiovascular disease (CVD) and is detectable years before CVD develops. Vascular function is impaired in children with T1D, and the early vascular changes in function and structure are potentially reversible. The aim of the study was to evaluate the effect of metformin on vascular health in children with T1D and with a weight above the average.

Methods

In this 12-month double-blind, randomized, placebo-controlled trial, children (n=90) aged 8–18 years with T1D of at least 6-month duration, and with a body mass index (BMI) >50th percentile for age and sex were randomly allocated in a 1:1 ratio to metformin (up to 1 g twice a day) or placebo. The main outcome was the vascular function measured by brachial artery ultrasound (flow-mediated dilatation/glyceryl trinitrate-mediated dilatation [GTN]). Other outcomes included HbA1c, insulin dose, BMI, body composition, waist circumference, mean of three consecutive blood pressures, fasting lipid profile, high-sensitivity C-reactive protein, adiponectin, leptin, and early morning urinary albumin/creatinine ratio.

Results

Ninety participants (41 boys) were enrolled. Mean age of participants was 13.6 ± 3.5 years. Median (interquartile range) HbA1c was 8.7% (8.1–9.9) (72 mmol/mol [65–85]) and mean BMI z-score was 0.89 ± 0.57 . Fifty-four participants had normal BMI (BMI 50%–84%), 25 were overweight (BMI 85%–95%), and 11 were obese (BMI >95%). Ten patients discontinued intervention, and one was lost to follow-up. Median (95% confidence interval [CI]) adherence, evaluated by electronic monitoring, was 75.5% (65.7–81.5), without group differences. On metformin, GTN improved, independent of HbA1c, by 3.3 percentage units ([95% CI 0.3–6.3]; $P=0.03$) and insulin dose was reduced by 0.2 U/kg/d ([95% CI 0.1–0.3] $P=0.001$) during 12 months, with effects from 3 months. There was a significant benefit in adjusted (age, sex) HbA1c at 3 months for the metformin group (8.4% [95% CI 8.0–8.8]) (68 mmol/mol [95% CI 64–73]) vs placebo group (9.3% [95% CI 9.0–9.7]) (78 mmol/mol [95% CI 75–83]) ($P=0.001$), and this was primarily responsible for the overall benefit of metformin compared with placebo during the study period. There were no effects on carotid/aortic intima-media thickness, BMI, lipids, blood pressure, or other cardiovascular risk factors. Gastrointestinal side effects were more common in the metformin group compared with placebo (incidence rate ratio 1.65 [95% CI 1.08–2.52]; $P=0.02$), with no difference in hypoglycemia or diabetic ketoacidosis.

Conclusions

The study findings demonstrated the benefit of metformin on vascular smooth muscle function, HbA1c, insulin dose, and estimated insulin sensitivity during 12 months in children with T1D who are above the average weight as well as the drug's good safety profile.

Comments

Data regarding complementary therapies (used in addition to insulin) in adults with T1D that do not attain the target glycemic control have already been reported (26,27). In pediatric T1D patients, however, there are limited data on this topic. Studies in the adult patients with type 2 diabetes showed that metformin treatment improves glycemic control and reduces cardiovascular mortality without weight gain or risk of hypoglycemia (28,29). Previously it was reported that among overweight adolescents with T1D, the addition of metformin to insulin did not improve glycemic control after 6 months (30). A recent systematic review and meta-analysis of randomized controlled trials conducted on children aged 6 to 19 years diagnosed with T1D examined the effect of adding metformin to standard insulin therapy. The evidence did not support use of metformin in T1D adolescents to improve HbA1c. However, metformin provided modest reduction in the daily insulin dose and BMI (31).

The current study was for longer duration (1 year) and demonstrated improved glycemic control as well as a good safety profile during the trial. This study contributes important knowledge of metformin use in children with T1D—in addition to improved glycemic control, reduction in insulin, and an increase in estimated insulin sensitivity, it has shown an effect on vascular function and support of CVD benefit of metformin in adolescent T1D. Since most of the patients were not overweight, the results can be applied to patients of a wider weight range. The main limitation was that the duration of only 12 months did not provide the opportunity to detect changes in vascular structure, only changes in vascular function. Change in vascular structure likely requires several years of follow-up in T1D (32,33).

Randomized, double-blind, placebo-controlled dose-finding study of the dipeptidyl peptidase-4 inhibitor linagliptin in pediatric patients with type 2 diabetes

Tamborlane WV¹, Laffel LM², Weill J³, Gordat M⁴, Neubacher D⁵, Retlich S⁵, Hettema W⁵, Hoessl CE⁵, Kaspers S⁶, Marquard J⁶

¹Department of Pediatrics, Yale School of Medicine, New Haven, CT; ²Joslin Diabetes Center, Harvard Medical School, Boston, MA; ³Hôpital Jeanne de Flandre, Lille, France; ⁴Boehringer Ingelheim, Reims, France; ⁵Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; ⁶Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany

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Background

The limited treatment options currently available for youth with T2D stand in contrast to the number of new medications (e.g., dipeptidyl peptidase-4 [DPP-4] inhibitors, glucagon-like peptide-1 [GLP-1] agonists, and sodium glucose co-transporter 2 [SGLT2] inhibitors) that have been approved for use in adults with T2D. Linagliptin is a potent DPP-4 inhibitor and is eliminated predominantly by nonrenal excretion and can be prescribed to adult patients with T2D without adjusting the dose according to kidney function. The aim of this study was to provide the pharmacokinetics (PK)/pharmacodynamics (PD) data to inform the choice of the appropriate dose of linagliptin to be used in the pediatric patients with T2D.

Methods

Thirty-nine patients 10–18 years of age with T2D were included in a double-blind, randomized, placebo-controlled study that compared linagliptin 1 mg and 5 mg once daily (approved for use in adults with T2D) with placebo. The primary efficacy endpoint was the change from baseline in HbA1c after 12 weeks of treatment. The key pharmacodynamic endpoint was DPP-4 inhibition during steady-state.

Results

Compared with placebo, there was a dose-dependent reduction in mean HbA1c of 0.48% and 0.63% with linagliptin 1 mg and 5 mg, respectively, with corresponding decreases in mean fasting plasma glucose of 5.6 and 34.2 mg/dL. Median DPP-4 inhibition was 38% with linagliptin 1 mg and 79% with linagliptin 5 mg. Geometric mean trough levels of linagliptin were 3.80 nmol/L and 7.42 nmol/L in the 1 mg and 5 mg groups, respectively. The levels were slightly higher than those in adult patients with T2D, probably due to higher plasma DPP-4 concentrations in the study population. There were no drug-related adverse events during treatment with either dose of linagliptin.

Conclusions

Overall, the results are consistent with the clinical efficacy and safety profile that has been reported for linagliptin in adult patients with T2D, favoring linagliptin 5 mg over 1 mg. Linagliptin was well tolerated and induced dose-dependent DPP-4 inhibition that was accompanied by corresponding reductions in HbA1c and fasting plasma glucose levels in children with T2D.

Comments

The SEARCH for Diabetes in Youth Study demonstrated that 27% of youth with T2D participating in that study had poor glycemic control with HbA1c $\geq 9.5\%$ (≥ 80 mmol/mol) (34), and the Pediatric Diabetes Consortium T2D Registry has shown that rescue therapy with insulin, in metformin treatment failures, rarely lowers HbA1c to $< 7.5\%$ (< 58 mmol/mol) (35), the target level recommended by the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes. Therefore, new therapies in addition to metformin

and insulin are required in youth with T2D below 18 years of age.

Overall, the results from this trial are consistent with the clinical efficacy and safety profile that has been reported for linagliptin in adult patients with T2D, favoring linagliptin 5 mg over 1 mg. Although the number of patients enrolled in the current study was sufficient for the assessment of the key PD outcome of DPP-4 inhibition, the main limitation is the small sample size, which makes the generalization of data difficult. However, the findings of the current study support the need for evaluation of the long-term safety and efficacy (including further PK data) of linagliptin 5 mg in a phase 3 study in pediatric patients with T2D.

Effect of oral insulin on prevention of diabetes in relatives of patients with type 1 diabetes: a randomized clinical trial

Writing Committee for the Type 1 Diabetes TrialNet Oral Insulin Study Group, Krischer JP¹, Schatz DA², Bundy B¹, Skyler JS³, Greenbaum CJ⁴

¹University of South Florida, Tampa, FL; ²University of Florida, Gainesville, FL; ³University of Miami, Miami, FL; ⁴Benaroya Research Institute, Seattle, WA

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This manuscript is also discussed in the article on Immune Intervention in Type 1 Diabetes, page S-95.

Background

Patients with type 1 diabetes (T1D) face major lifestyle changes and increased morbidity and mortality. Therefore, preventing or delaying the onset of diabetes would provide major public health benefit. The objective of this study was to determine whether oral insulin delays onset of T1D in autoantibody-positive relatives of patients with T1D.

Methods

Between March 2, 2007, and December 21, 2015, relatives with at least two autoantibodies, including insulin autoantibodies and normal glucose tolerance, were enrolled in nine countries worldwide. The main study group (n=389) had first-phase insulin release on an intravenous glucose tolerance test that was higher than the threshold. The secondary stratum 1 (n=55) included individuals with an antibody profile identical to the main study group but who had first-phase insulin release that was lower than the threshold. Secondary strata 2 (n=114) and strata 3 (n=3) had different autoantibody profiles and first-phase insulin release threshold combinations. Participants were randomized to receive 7.5 mg/day of oral insulin (n=283) or placebo (n=277). The primary outcome was time to diabetes in the main study group. A one-sided threshold of 0.05 determined significance, and one-sided 95% confidence intervals (95% CI) are reported.

Results

A total of 560 randomized participants were enrolled in the trial (median enrollment age, 8.2 years; interquartile range

[IQR] 5.7–12.1 years; 60% male, $n=170$; 90.7% white non-Hispanic; 57.6% with a sibling with T1D). Of those enrolled, 550 participants completed the trial, including 389 participants (median age 8.4 years; 245 boys [63%]) in the main study group. T1D was diagnosed in 58 subjects (28.5%) in the oral insulin group and 62 (33%) in the placebo group during a median follow-up of 2.7 years (IQR 1.5–4.6 years) in the main study group. There was no significant difference in time to T1D between the oral insulin and placebo groups (hazard ratio 0.87 [95% CI 0–1.2]; $P=0.21$). In secondary stratum 1 ($n=55$), T1D was diagnosed in 13 participants (48.1%) in the oral insulin group and 19 participants (70.3%) in the placebo group, with a significantly longer time to T1D with oral insulin (HR 0.45 [95% CI 0–0.82]; $P=0.006$). For between-group comparisons among the 116 participants in the other secondary strata, the hazard ratio for time to T1D was 1.03 (95% CI 0–2.11; $P=0.53$), and the hazard ratio for the entire cohort of 560 participants was 0.83 (95% CI 0–1.07; $P=0.11$), which were not significantly different. With 254 events, infection was the most common adverse event ($n=134$ for oral insulin group; $n=120$ for placebo), but no significant study-related adverse events occurred.

Conclusions

In this trial of oral insulin vs placebo among autoantibody-positive relatives of patients with T1D, 7.5 mg/day of oral insulin did not delay or prevent the development of T1D over 2.7 years. These findings do not support oral insulin as used in this study for T1D prevention.

Comments

Although the results of this investigation were disappointing in that they do not provide hope for prevention therapy for those who are antibody positive, much was learned from this well-performed study. Congratulations are in order for the research teams and study participants for the effort required for this decade-long project, which demonstrates feasibility for such multinational research in early prevention of T1D. Over 130,000 participants were screened to find the 560 randomized participants. While the overall findings were negative, the intervention was safe. Moreover, there will be ongoing debate and further analyses regarding the prespecified secondary stratum in which there was a statistically significant delay to T1D of 31 months. More mechanistic studies on samples from the trial promise to add insight into results and help refine hypotheses for future study.

TrialNet and others have developed a stage of T1D schema (36) that emphasizes the need to intervene early in the pathophysiologic course of T1D to preserve beta-cells and avoid the acute and long-term complications that come once T1D develops. This study highlights the importance of developing shorter-term markers of T1D progression to allow for more rapid studies. Future research may also take a multidrug approach with a goal of a personalized approach based on better understanding of what is increasingly being understood as a heterogeneous disease process requiring tailored approaches.

Author Disclosure Statement

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S.S. has no competing financial interests.

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