Diabetes Technology and Therapy in the Pediatric Age Group

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Introduction

THE PAST YEAR SAW MARKED ADVANCES in research in pediatric diabetes with numerous studies investigating the use of closed-loop systems in the pediatric population. While such technologies are on the horizon for clinical use in pediatrics, other studies in the past year have highlighted the challenges with clinical implementation of insulin pump therapy, a technology that has been available for decades. The hope for an automated – or initially a semiautomated or hybrid closed-loop system requiring the user to give premeal boluses of insulin – is well deserved. These systems aim to improve glucose control and lower the burden of care for children with type 1 diabetes (T1D) and their families. However, initial systems will continue to require significant user involvement as well as experienced and informed pediatric diabetes teams for successful adoption of these diabetes technologies.

In addition, advances were seen in the use of a novel intranasal formulation of glucagon to treat hypoglycemia that simplifies the current injectable version of this potentially life-saving medication. A randomized trial on the benefits of metformin in overweight adolescents with T1D found no benefit on HbA1c, but other potential metabolic improvements. Technology was also studied using telehealth to improve diabetes outcomes by delivering care to rural populations and in pediatric patients struggling to achieve treatment goals.

Research in diabetes technology in pediatrics has accelerated in the past few years and with the advent of clinical availability of closed-loop technology promises to remain a rich field of investigation for years to come. Pediatric patients and their families should begin to reap the benefits of decades of work on these diabetes technologies to improve glucose control and lower the burden of care for diabetes.

We conducted a Medline search for articles on the following topics: diabetes technology, insulin pump therapy (continuous subcutaneous insulin infusion [CSII]), continuous glucose monitoring (CGM), closed-loop systems, and new therapies in T1D relating to the pediatric age group (0–18 years). This article focuses on key articles that were published between July 1, 2015 and June 30, 2016.

Key Articles Reviewed for the Article

Use of insulin pump therapy in children and adolescents with type 1 diabetes and its impact on metabolic control: comparison of results from three large, transatlantic paediatric registries

Sherr JL, Hermann JM, Campbell F, Foster NC, Hofer SE, Allgrove J, Maahs DM, Kapellen TM, Holman N, Tamborlane WV, Holl RW, Beck RW, Warner JT; for the T1D Exchange Clinic Network, the DPV Initiative, and the National Paediatric Diabetes Audit and the Royal College of Paediatrics and Child Health registries

Diabetologia 2016; 59: 87–91

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Characterization of metabolic responders on CSII treatment amongst children and adolescents in Denmark from 2007 to 2013

Overgaard Ingeholm I, Svensson J, Olsen B, Lyngsøe L, Thomsen J, Johannesen J; The Danish Study Group of Diabetes in Childhood (DSBD)

Diabetes Res Clin Pract 2015; **109**: 279–286

Effect of insulin dilution on lowering glycemic variability in pump-treated young children with inadequately controlled type 1 diabetes

Mianowska B, Fendler W, Tomasik B, Młynarski W, Szadkowska A

Diabetes Technol Ther 2015; **17**: 605–610

Predictive low-glucose insulin suspension reduces duration of nocturnal hypoglycemia in children without increasing ketosis

Buckingham BA, Raghinaru D, Cameron F, Bequette BW, Chase HP, Maahs DM, Slover R, Wadwa RP, Wilson DM, Ly T, Aye T, Hramiak I, Clarson C, Stein R, Gallego PH, Lum J, Sibayan J, Kollman C, Beck RW; for the In Home Closed Loop Study Group

Diabetes Care 2015; **38**: 1197–1204

Blood glucose fluctuation during Ramadan fasting in adolescents with type 1 diabetes: findings of continuous glucose monitoring

Kaplan W, Afandi B

Diabetes Care 2015; **38**: e162–163

Effect of lipohypertrophy on accuracy of continuous glucose monitoring in patients with type 1 diabetes

DeSalvo DJ, Maahs DM, Messer L, Wadwa RP, Payne S, Ly TT, Buckingham BA

Diabetes Care 2015; **38**: e166–167

Day and night closed-loop control using the integrated Medtronic hybrid closed-loop system in type 1 diabetes at diabetes camp

Ly TT, Roy A, Grosman B, Shin J, Campbell A, Monirabbasi S, Liang B, von Eyben R, Shanmugham S, Clinton P, Buckingham BA

Diabetes Care 2015; **38**: 1205–1211

Home use of an artificial beta cell in type 1 diabetes

Thabit H, Tauschmann M, Allen JM, Leelarathna L, Hartnell S, Wilinska ME, Acerini CL, Dellweg S, Benesch C, Heinemann L, Mader JK, Holzer M, Kojzar H, Exall J, Yong J, Pichierrri J, Barnard KD, Kollman C, Cheng P, Hindmarsh PC, Campbell FM, Arnolds S, Pieber TR, Evans ML, Dunger DB, Hovorka R; for the APCam Consortium and the AP@home Consortium

N Engl J Med 2015; **373**: 2129–2140

Use of an artificial pancreas among adolescents for a missed snack bolus and an underestimated meal bolus

Cherňavský DR, DeBoer MD, Keith-Hynes P, Mize B, McElwee M, Demartini S, Dunsmore SF, Wakeman C, Kovatchev BP, Breton MD

Pediatr Diabetes 2016; **17**: 28–35

Single- and dual-hormone artificial pancreas for overnight glucose control in type 1 diabetes

Haidar A, Rabasa-Lhoret R, Legault L, Lovblom LE, Rakheja R, Messier V, D'Aoust É, Falappa CM, Justice T, Orszag A, Tschirhart H, Dallaire M, Ladouceur M, Perkins BA

J Clin Endocrinol Metab 2016; **101**: 214–223

Automated hybrid closed-loop control with a proportional-integral-derivative based system in adolescents and adults with type 1 diabetes: individualizing settings for optimal performance

Ly TT, Weinzimer SA, Maahs DM, Sherr JL, Roy A, Grosman B, Cantwell M, Kurtz N, Carria L, Messer L, von Eyben R, Buckingham BA

Pediatr Diabetes 2016; **18**. [Epub ahead of print] DOI 10.1111/pedi.12399

Glucagon nasal powder: a promising alternative to intramuscular glucagon in youth with type 1 diabetes

Sherr JL, Ruedy KJ, Foster NC, Piché CA, Dulude H, Rickels MR, Tamborlane WV, Bethin KE, DiMeglio LA, Fox LA, Wadwa RP, Schatz DA, Nathan BM, Marcovina SM, Rampakakis E, Meng L, Beck RW; for the T1D Exchange Intranasal Glucagon Investigators

Diabetes Care 2016; **39**: 555–562

Effect of metformin added to insulin on glycemic control among overweight/obese adolescents with type 1 diabetes: a randomized clinical trial

Libman IM, Miller KM, DiMeglio LA, Bethin KE, Katz ML, Shah A, Simmons JH, Haller MJ, Raman S, Tamborlane WV, Coffey JK, Saenz AM, Beck RW, Nadeau KJ; for the T1D Exchange Clinic Network Metformin RCT Study Group

JAMA 2015; **314**: 224150

Seeing is believing: using Skype to improve diabetes outcomes in youth

Harris MA, Freeman KA, Duke DC

Diabetes Care 2015; **38**: 1427–1434

Use of telemedicine to improve adherence to American Diabetes Association standards in pediatric type 1 diabetes

Wood CL, Clements SA, McFann K, Slover R, Thomas JF, Wadwa RP

Diabetes Technol Ther 2016; **18**: 7–14

Use of insulin pump therapy in children and adolescents with type 1 diabetes and its impact on metabolic control: comparison of results from three large, transatlantic paediatric registries

Sherr JL¹, Hermann JM², Campbell F³, Foster NC⁴, Hofer SE⁵, Allgrove J⁶, Maahs DM⁷, Kapellen TM⁸, Holman N⁹, Tamborlane WV¹, Holl RW², Beck RW⁴, Warner JT¹⁰; for the T1D Exchange Clinic Network, the DPV Initiative, and the National Paediatric Diabetes Audit and the Royal College of Paediatrics and Child Health registries

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Diabetologia 2016; **59**: 87–91

This manuscript is also discussed in Article on Insulin Pumps, page S-19.

Background

Use of insulin pumps in pediatrics has expanded dramatically, but there is considerable variability by country in use of this diabetes technology. This study described differences in metabolic control and pump use in three large pediatric diabetes registries.

Methods

Data from 54,410 children during 2011 to 2012 were collected from the Prospective Diabetes Follow-up Registry (DPV), T1D Exchange (T1DX), and the National Paediatric Diabetes Audit (NPDA). Insulin delivery modality based on age, and ethnic minority status and the impact of pump use on HbA1c levels were compared.

Results

Overall mean HbA1c was higher in NPDA (8.9% ± 1.6%) than in the DPV (8.0% ± 1.6%) and T1DX (8.3% ± 1.4%). Conversely, pump use was lower in NPDA (14%) than in DPV (41%) or T1DX (47%). In a combined analysis, HbA1c

was lower in those using a pump than those using injection ($8.0\% \pm 1.2\%$ vs. $8.5 \pm 1.7\%$). Those with an ethnic minority status were less likely to be treated with a pump and boys were less likely using a pump than girls ($P < 0.001$ for all comparisons listed).

Conclusions

Substantial differences exist in metabolic control across three large transatlantic pediatric diabetes registries, due in part to the frequency of insulin pump therapy.

Comment

These data are consistent with previous reports showing a lower HbA1c in pediatric patients using insulin pumps vs. those using injections. Despite all five of the countries represented in this report having access to advanced pediatric diabetes care, remarkable differences are reported in the use of insulin pumps. The NPDA registry had the lowest use of pumps, which the authors suggest could be a result of national UK guidance. Also, the pattern of use of pumps differed by country with the DPV registry reporting the highest use of pumps in the <6-year-old population ($\sim 70\%$) whereas pump use was half of this in their adolescents. In contrast, in T1DX pump use was higher in adolescents than in the youngest age group.

Most troubling is that among the 20%–24% of children defined as ethnic minorities in each registry, use of pumps was much lower (22.1% vs. 34.5%, odd ratio (OR)=0.54, $P < 0.001$). Future investigations need to focus on the reasons for lower pump use among ethnic minorities, especially considering the association with of pump use with lower HbA1c and with the future possibility of a mechanical solution to the problems of managing T1D in pediatrics.

Characterization of metabolic responders on CSII treatment amongst children and adolescents in Denmark from 2007 to 2013

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Diabetes Res Clin Pract 2015; **109**: 279–286

Background

Continuous subcutaneous insulin infusion (CSII) has been shown to improve glucose control, but the benefit varies in individuals. This study aimed to identify and estimate the frequency of responders to CSII therapy and second, to characterize CSII users with good adherence to pump therapy in 463 children and adolescents with T1D.

Methods

Response was defined as a decrease in HbA1c of 1% or achieving an HbA1c <7.5% and good adherence as ≥ 7 boluses and ≥ 7 self-monitored blood glucoses daily.

Results

At 24 months of follow up 32% qualified as responders. Stratifying for age at onset, 45% of <6 year olds versus 32% of 6–12 year olds and 28% of 12–19 year olds qualified as responders ($P = 0.02$). Responders were characterized by HbA1c at pump onset, taking more boluses daily (7.6 ± 3.3 vs. 6.4 ± 3.2 , $P = 0.003$), and checking blood glucose more daily at follow up (6.9 ± 2.4 vs. 6.3 ± 2.5 , $P = 0.03$). Severe hypoglycemia decreased from 14.3 to 3.3 events per 100 person years. Twenty percent did not respond despite good adherence on CSII therapy.

Conclusions

At age <6 years, high or low HbA1c at pump initiation and number of daily boluses were associated with improved or near-normal metabolic outcome. Severe hypoglycemia incidence was reduced significantly.

Comment

Current enthusiasm for diabetes technology including pumps, CGM, and closed-loop systems in a variety of forms is well deserved. However, adoption of pump therapy ranged between 14%–47% in a recent 5 country registry report from Sherr (1). Reports such as these aim to provide more information on characteristics identifying responders versus nonresponders to pump therapy. The ultimate goal is to better understand how to implement diabetes technology to improve metabolic outcomes and quality of life for people with T1D. For diabetes technology to be widely adopted requires improved outcomes, reduced burden, and a favorable cost benefit among other factors.

Limitations of this report include the observational study design and its arbitrary, although reasonable, definition of a responder. Much more research is required to successfully translate current and future diabetes technologies to all people with T1D.

Effect of insulin dilution on lowering glycemic variability in pump-treated young children with inadequately controlled type 1 diabetes

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Diabetes Technol Ther 2015; **17**: 605–610

Background

Commercially available insulin (i.e., 100 units/mL [U100]) and insulin pumps (calibrated for insulin U100) are not diversified for different age groups. Therefore, in patients requiring very low hourly insulin infusion rates (<0.2 units/h),

insulin diluted to 10 units/mL (U10) or to 50 units/mL was suggested to optimize dosage.

The aim was to evaluate whether the switch to insulin diluted to 10 units/mL (U10) used with continuous subcutaneous infusion can limit technical problems and improve glycemic control in young children with inadequately controlled T1D.

Methods

In three children 3.8, 3.2, and 1.3 years old, treated with pump therapy, with a mean HbA1c level of $8.1\% \pm 0.17\%$ (65 ± 1.7 mmol/mol) and insulin dose of 8.80 ± 2.93 units/day, diluted U10 insulin was started. Patients were evaluated with continuous glucose monitoring and a quality of life questionnaire and surveyed for pump-related problems at baseline and after 3 and 9 months of U10 insulin therapy.

Results

After the patients started U10 insulin, no severe hypoglycemia, ketoacidosis, or skin infection at the infusion site occurred in any of the children. Significant improvements were noted for parameters of glycemic variability with continuous glucose monitoring. HbA1c levels dropped to $7.3\% \pm 1.00\%$ (56 ± 11.0 mmol/mol) after 3 months and to $6.7\% \pm 0.55\%$ (50 ± 6.1 mmol/mol) after 9 months ($P=0.12$). Technical difficulties were minimized.

Conclusions

The study results show that the use of U10 insulin decreased glycemic variability and facilitated insulin pump therapy in young children with inadequately controlled T1D. However, when implementation of diluted insulin is considered, selection of patients based on strict cooperation and capability of their parents is obligatory.

Comments

Diluted insulin is rarely used in insulin pumps in toddlers with T1D, and analyses of merits of insulin dilution vs. nondilution are lacking. The current study results showed that the use of U10 insulin allowed for better tailoring of insulin dosing. When U100 insulin is used, the lowest bolus can be set at 0.1 units, and the lowest basal rate at 0.05 units/h. With U10 the insulin pumps were able to deliver boluses with an accuracy of 0.01 units, and the actual basal rate could be 0.005 units/h. Thus, insulin delivery was more precise.

The authors suggest that children in whom we have to consider switching to U10 are those with an HbA1c level of $>7.5\%$ (58 mmol/mol), younger than 6 years (or weight <25 kg) with basal insulin rate for at least 2 h of the day <0.1 units/h, with average total daily insulin dose of <15 units/day, associated with frequent unexplained hyperglycemia (>250 mg/dL), high daily blood glucose fluctuations, or frequent need to remove air bubbles from the tubing.

However, we need to consider the disadvantage of using insulin U10 in a pump, since it is more prone to hazards as a result of calculation mistakes with the possibility of 10-fold misdosing of insulin (under- or

overdosing). Thus, when implementation of diluted insulin is considered, selection of patients based on strict cooperation and capability of their parents is obligatory.

The main limitation of the current study is the small number of participants.

The main application of using the diluted insulin in pumps seems to be in the very young age groups, in patients with increased insulin sensitivity, and perhaps during the “honey-moon” period when insulin requirement is low.

Predictive low-glucose insulin suspension reduces duration of nocturnal hypoglycemia in children without increasing ketosis

Buckingham BA¹, Raghinaru D², Cameron F³, Bequette BW³, Chase HP⁴, Maahs DM⁴, Slover R⁴, Wadwa RP⁴, Wilson DM¹, Ly T¹, Aye T¹, Hramiak I⁵, Clarson C⁶, Stein R⁶, Gallego PH⁶, Lum J², Sibayan J², Kollman C², Beck RW²; for the In Home Closed Loop Study Group

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Diabetes Care 2015; **38**: 1197–1204

Background

Nocturnal hypoglycemia is a barrier to tight glycemic control, especially in young children with T1D. An in-home randomized trial assessed the efficacy and safety of a continuous glucose monitor-based overnight predictive low-glucose suspend (PGLS) system.

Methods

Two groups of children (11–14 and 4–10 years of age) participated in a 42 night trial such that each night was randomized to either PLGS active (intervention night) or inactive (control night). The primary outcome was percent time <70 mg/dL overnight.

Results

Median time <70 mg/dL was reduced from 10.1% to 4.6% (54% reduction on intervention compared to control nights in 11–14 year olds and from 6.2% to 3.1% (50%) reduction in 4–10 year olds ($P<0.001$ for both). Mean overnight glucose was lower on control compared to intervention nights in both age groups (144 ± 18 vs. 152 ± 19 mg/dL ($P<0.001$) and 153 ± 14 vs. 160 ± 16 mg/dL ($P=0.004$). Mean morning glucose was 159 ± 29 vs. 176 ± 28 mg/dL ($P<0.001$) in the 11–14 year olds and 154 ± 25 vs. 158 ± 22 mg/dL ($P=0.11$) in the 4–10 year olds, respectively. No difference existed in either age group between intervention and control in morning blood ketones.

Conclusions

Use of an overnight PLGS system reduced hypoglycemia without an increase in morning ketosis, although mean glucose was slightly higher.

Comment

Per the Juvenile Diabetes Research Foundation (JDRF) road map, the first steps of the pathway to an artificial pancreas consist of suspension of insulin delivery once a low glucose is sensed to be followed by the suspension of insulin when a low glucose is predicted. These data, obtained in a home setting using a unique study design in which participants were randomized in a masked fashion nightly, demonstrate the safety and efficacy of PLGS systems in children down to 4 years of age.

At the time of design of this study, concerns existed about the potential of ketosis with insulin cessation for up to 2 hours (3 hours over the course of the night) to prevent hypoglycemia. No differences in ketones existed by intervention group. PLGS systems have been commercialized and are available in certain areas of the world and the concept of stopping or decreasing insulin to prevent hypoglycemia will be a component of fully closed-loop systems. The data in this study are quite similar to those published by this group in adults ages 15–45 years (2) and reiterate the importance of these systems being studied in the pediatric population prior to clinical use.

Blood glucose fluctuation during Ramadan fasting in adolescents with type 1 diabetes: findings of continuous glucose monitoring

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Diabetes Care 2015; **38**: e162–163

Background

Scant data exist on the safety and effect of fasting during Ramadan in adolescents with T1D. CGM was used to monitor the glucose profile to assess this and to provide data to inform clinical decision making.

Methods

Adolescents ($n=21$, 15 women, age 15 ± 4 years, T1D duration 6 ± 3 years) who intended to fast during Ramadan were asked to wear a CGM and report any episode of severe hypoglycemia or diabetic ketoacidosis or emergency room visit.

Results

Subjects were able to fast for 85% of the days with a total fasting time of 14.5 hours. There were no reported episodes of severe hypoglycemia or diabetic ketoacidosis or emergency room visits. Hypoglycemia during fasting hours was 14.2% vs. 2.5% during eating hours ($P<0.05$) whereas hyperglycemia was more common in the eating vs. fasting hours (12% vs. 17%, $P<0.05$).

Conclusions

These data add to those of other studies that the majority of patients with T1D could safely fast during Ramadan. Wide glucose fluctuations were noted during fasting and eating

hours and episodes of unreported hypoglycemia were clearly noted in the CGM data.

Comment

These data in adolescents add to those that indicate that the majority of patients with T1D can safely fast during Ramadan. However, symptomatic hypoglycemia was common. The authors note that for people with T1D, frequent glucose monitoring is required to safely fast and that trials are required to identify better insulin regimens to minimize glucose variability during the both fasting and eating hours. Use of diabetes technology, including real time CGM and iterations of automated insulin delivery, promise to make fasting safer for people with T1D.

Effect of lipohypertrophy on accuracy of continuous glucose monitoring in patients with type 1 diabetes

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Diabetes Care 2015; **38**: e166–167

Background

Repeated delivery of insulin locally can lead to lipohypertrophy and cause erratic and slower absorption of insulin as a result of the avascular nature of the adipose tissue. Lipohypertrophied tissue is commonly used for CGM sensor sites, although no data exist on sensor performance in such tissue. The performance of CGM sensors worn concurrently in lipohypertrophied and normal tissue was assessed.

Methods

Subjects with T1D ($n=19$, 48% male, HbA1c $7.5\% \pm 0.8\%$, average diameter of lipohypertrophy 8.1 ± 3.5 cm), with an area of lipohypertrophied tissue >3 cm in diameter wore two CGM sensors (Dexcom G4 Platinum), one in normal tissue and one in lipohypertrophied tissue. The CGM data were compared to blood glucose results (Bayer Contour Next meters).

Results

There were 89,853 sensor readings of which 1547 had corresponding meter readings. The median absolute relative difference (ARD) was 10.0% (4.3, 17.2) vs. 11.0% (4.9, 19.3) in normal tissue ($P<0.001$). For blood glucose (BG) <70 mg/dL, mean absolute difference (MAD) for sensors in lipohypertrophied tissue was 15 mg/dL ($n=49$) compared with 18 mg/dL ($n=48$) in normal tissue ($P=0.14$).

Conclusions

In this study, CGM sensors in lipohypertrophied tissue showed similar or slightly superior accuracy to sensors in normal tissue. More research is needed to quantify the risks of sensor use in lipohypertrophied tissue.

Comment

With the increased use of diabetes technology such as CGM and insulin pumps and the imminent clinical use of closed-loop technologies, research is needed on the effects of these systems on skin and adipose tissue in patients. In the pediatric population in particular having sites for pumps and CGM poses a challenge.

This research indicates that lipohypertrophied tissue could be used for CGM sensor placement with similar mean absolute relative difference (MARD) as in sensors placed in normal tissue. The authors caution that additional research is required, especially with long-term usage. With the rapid advance of diabetes technology that employs a subcutaneous placement, issues with skin and adipose tissue will continue to be a topic of great clinical relevance and highly pertinent to patient care.

Day and night closed-loop control using the integrated Medtronic hybrid closed-loop system in type 1 diabetes at diabetes camp

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Diabetes Care 2015; **38**: 1205–1211

Background

The hybrid closed-loop (HCL) system of Medtronic MiniMed Inc. (Northridge, CA) is a fully integrated system designed for continuous day and night HCL control with the algorithm incorporated within the insulin pump. The HCL system requires meal announcement with an estimate of carbohydrate intake and a premeal insulin bolus to optimize postprandial glucose excursions.

The aim was to test the feasibility and efficacy of the fully integrated Medtronic MiniMed HCL system (that consists of a fourth generation glucose sensor (4S), a sensor transmitter, and an insulin pump using a modified proportional-integral-derivative (PID) insulin feedback algorithm with safety constraints) in adolescents and adults with type 1 diabetes (T1D) over 48 h in an inpatient setting research center followed by a 6 day period at a diabetes camp.

Methods

Participants were eligible to participate if they were 14–40 years of age, had a diagnosis of T1D for at least 1 year, and had

been using an insulin pump for at least 3 months. Patients (n=8) were studied over 48 h in an inpatient setting, followed by a study of 21 subjects for 6 days at diabetes camp, randomized to either the closed-loop control group using the HCL system (study group) or to the group using the Medtronic MiniMed 530G with threshold suspend (control group).

Results

The mean age of the participants was 18.6 ± 3.7 years (range 15.3–31.4), duration of diabetes was 9.1 ± 4.7 years, HbA1c was $8.6\% \pm 1.5\%$ (range 5.9–11.6%) (70 ± 16 mmol/mol, range 41–103), and insulin dose was 0.8 ± 0.2 units/kg/day. During the camp session, subjects in the HCL group remained in closed loop for $93 \pm 3\%$ of the scheduled time. There was continuous sensor glucose data available for 98.9% of the time. Time off closed loop was attributed to sensor change or temporarily suspending HCL after infusion set failure.

The overall mean sensor glucose percent time in the range 70–180 mg/dL was similar between the groups (73.1% vs. 69.9%, control vs. HCL, respectively, $P=0.580$). Meter glucose values between 70–180 mg/dL were similar between the groups (73.6% vs. 63.2%, control vs. HCL, respectively, $P=0.086$).

The mean absolute relative difference of the 4S sensor was $10.8\% \pm 10.2\%$, when compared with plasma glucose values in the inpatient setting, and $12.6\% \pm 11.0\%$ compared with capillary Bayer Contour Next Link glucose meter values during 6 days at camp. The average daily insulin dose tended to decrease during the week of camp for both the control and the intervention groups.

There were no diabetic ketoacidosis or severe hypoglycemia events in the HCL group.

Conclusions

In this clinical study of the fully integrated system using an investigational PID algorithm, the system did not demonstrate improved glucose control compared with sensor-augmented pump therapy alone in a supervised setting. The system demonstrated good connectivity and improved sensor performance.

Comment

The hybrid closed-loop (HCL) system of Medtronic MiniMed Inc. (Northridge, CA) consists of a fourth generation sensor (4S) and uses a proportional-integral-derivative with insulin feedback (PID-IFB) algorithm with safety constraints to continuously modulate basal insulin delivery based on sensor glucose values.

This report describes the first clinical experience using the Medtronic HCL system with the 4S sensor and an investigational algorithm. The system performance was comparable to automated insulin suspension alone in a supervised setting. Over multiple days, there was improved performance of the system, achieving 70%–77% time in range.

The advantages of the integrated Medtronic hybrid closed-loop system include a system configuration that places the closed-loop controller on the pump and removes the need for an intermediary device that contains the algorithm. This reduces the need for connectivity between

a controller and the insulin pump, as well as between the controller and sensor, two points of potential interrupted communication in a multi-device system. The HCL system was also simple to navigate and use.

However, the system has several limitations: first, during closed-loop operation, both the carbohydrate/insulin ratio as well as the insulin sensitivity factor were algorithm derived. This did not reflect individualized patient-derived settings, and may have contributed to the postprandial hyperglycemia seen in the HCL group. Second, the automatic corrections did not correct glucose values into target as rapidly as patients expected with their own standard therapy, and contributed to the higher mean glucose values and the more prolonged postprandial hyperglycemia seen in the HCL group. Third, correction boluses were given automatically, and subjects were not able to see the amount to accept, reject, or adjust the bolus. Thus, patients complained that they did not feel comfortable not knowing how much insulin was given.

Therefore, in future versions of HCL systems, there are some features that have to be improved and implemented such as: the option of entering patient specific carbohydrate/insulin ratios in specific time blocks, use of new types of insulin with faster pharmacokinetics, use of algorithms that may have a lower threshold to initiate a correction dose as well as a lower correction dose target to allow for increased insulin dosing, and features of flexibility and adaptability to individuals with variable insulin sensitivities that may change with exercise, stress, illness, and menstrual cycle. Finally, it is necessary to test the system performance over a longer time period.

Home use of an artificial beta cell in type 1 diabetes

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This manuscript is also discussed in Article on Closing the Loop, page S-27.

Background

The artificial beta cell (closed-loop insulin delivery system) expands on the concept of sensor responsive insulin delivery. The closed-loop system differs from conventional pump therapy and threshold-suspend approaches in that it uses a control algorithm that autonomously and continually increases and decreases the subcutaneous delivery of insulin on the basis of real-time sensor glucose levels.

The aim was to evaluate the feasibility, safety, and efficacy of prolonged use of an artificial beta cell in the home setting. The primary end point was the proportion of time of glucose level between 70–180 mg/dL for adults and between 70–145 mg/dL for children and adolescents.

Methods

Participants were eligible to participate if they were treated with insulin-pump therapy for at least 6 months and were T1D adults aged ≥ 18 years with HbA1c level of 7.5%–10% (58–86 mmol/mole) and children and adolescents with T1D aged 6–18 years with HbA1c level $< 10\%$ (< 86 mmol/mole).

In two multicenter, crossover, randomized, controlled studies conducted under free-living home conditions, closed-loop insulin delivery was compared with sensor-augmented pump (SAP) therapy in 58 patients (25 children and adolescents). Participants used the closed-loop system for a 12 week period and SAP therapy (control) for a similar period. The closed-loop system was used day and night by 33 adults and overnight by 25 children and adolescents.

Results

Among adults, the proportion of time that the glucose level was in the target range was significantly greater during the intervention period than during the control period ($P < 0.001$). The mean glucose level was significantly lower with day-and-night use of the closed-loop system than with the control system ($P < 0.001$), as was the time spent above the target range ($P < 0.001$), and the area under the curve for the period with glucose level < 63 mg/dL ($P < 0.001$). Glucose variability, measured both as the standard deviation of the sensor glucose level and as the coefficient of variation of the sensor glucose level between days, was significantly lower with day-and-night use of the closed-loop system than with the control system. Higher basal insulin delivery during the intervention period than during the control period ($P < 0.001$) was offset by lower bolus delivery during the intervention period ($P = 0.002$).

Overnight end points were similar to those during the 24 hour period. In the daytime there was a lower mean glucose level, an increased proportion of time spent within the target range, and a reduced proportion of time spent above the target range or time that the glucose level was < 50 mg/dL with the closed-loop system than with the control therapy.

Among children and adolescents, proportion of nocturnal time that the glucose level was in the target range was significantly greater during the intervention period than during the control period ($P < 0.001$). The mean overnight glucose level was significantly lower with the closed-loop system than with the control system ($P < 0.001$), as was the time spent above the target range ($P < 0.001$). The proportion of time with sensor glucose level < 50 mg/dL was $< 1\%$.

Glucose variability was significantly less with the closed-loop system than with the control system. Nocturnal glucose levels were lower during the intervention period than during the control period without an increase in the total overnight insulin dose ($P=0.11$). Daytime insulin delivery and the total daily insulin dose were similar during the two study periods. The overnight closed-loop system was operating for a median of 9.3 h/day.

The 24 hour mean glucose level was significantly lower with overnight use of the closed-loop system than with the SAP therapy ($P=0.01$), and the proportion of time spent within the 70–180 mg/dL target range was significantly greater with the closed-loop system ($P<0.001$). The time that the glucose level was <50 mg/dL over the 24 hour period tended to be lower with the closed-loop system than with the control system ($P=0.05$). The hypoglycemia burden during the 24 hour period, as measured by the area under the curve with sensor glucose level <63 mg/dL, was significantly lower by 42% during the intervention period than during the control period ($P=0.03$). One adolescent had two severe hypoglycemic episodes (seizures) during the intervention period. During the two episodes, the participant was using SAP therapy.

Conclusions

Extended use of a closed-loop system at home over a period of 12 weeks during free daily living without close supervision was feasible in adults, children, and adolescents with T1D. Improvements in glucose control and reductions in the burden of hypoglycemia were observed as compared with SAP therapy.

Comment

Previous studies involving patients under home, free-living conditions have been limited to 1 week, day-and-night use of the closed-loop system in adults and to overnight use of a closed-loop system for 3–6 weeks in adolescents and adults. This study demonstrated the feasibility, safety, and efficacy of the application of closed-loop insulin delivery day and night in adults and overnight application in children and adolescents under free-living conditions over a long period of 12 weeks. In all age groups, the amount of time that the glucose level was within the target range was greater with use of the closed-loop system than with the control system and the mean glucose level was lower.

Systems with threshold-suspend control and predictive low-glucose suspend control may reduce the risk of hypoglycemia, but the systems are not designed to increase insulin delivery and therefore do not address the issue of hyperglycemia. The advantage of the closed-loop system is the responsive, graduated modulation of insulin delivery, both below and above the preset pump regimen, which allows for improvements in the proportion of time spent in target glucose range and the lowering of the mean glucose level without increasing the risk of hypoglycemia.

A dual-hormone system may provide additional protection against hypoglycemia but is currently limited by the need to reconstitute glucagon daily and by the use of a second pump to deliver glucagon through a separate infusion set, which increases the burden and complexity.

The strengths of the study include: the multicenter design with a large age range of patients, without restriction of participants' dietary intake or physical activity, and the demonstration of the advantages of the closed-loop system over a long period of time in the home setting without conditions of remote monitoring or close supervision.

It is hoped that with the use of faster insulin formulations and with development of more accurate glucose sensors and of special algorithms that can calculate the required meal bolus, glucose control in patients with T1D will be optimized with the additional ultimate aim of reduced burden of care.

Use of an artificial pancreas among adolescents for a missed snack bolus and an underestimated meal bolus

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Background

A large component of nonadherence among adolescents with T1D is omission of insulin for ingested carbohydrate at snacks and meals, both by missing boluses entirely and by underestimating the insulin needed for carbohydrate content. Artificial pancreas (AP) systems offer a potential solution for many issues of insulin omission during adolescence.

The aim was to evaluate the safety and performance of the AP in adolescents with T1D following insulin omission for mealtime carbohydrate.

Methods

Inclusion criteria were: age 13–18 years, diabetes duration ≥ 2 years, use of insulin pump ≥ 6 months, attainment of at least Tanner 2 pubertal stage, HbA1c $< 10.5\%$; and self-reported history of missing insulin for snacks or underbolusing for meals.

In a randomized, crossover trial, adolescents ($n=16$) were randomized on separate days (each admission lasted approximately 8 h), to receive either usual care (UC) through their home insulin pump or used an AP system (Diabetes Assistant platform, continuous glucose monitor, and insulin pump). Participants in both groups received an unannounced snack of 30 g carbohydrate, and 4 h later they received an 80 g lunch, for which both groups only received 75% of the calculated insulin dose to cover carbohydrates. On the UC day, they received their full high blood glucose correction factor at lunch.

Results

CGM sensors performed very reliably 98.7% of the time at a high accuracy; these performances led to the AP system functioning 97.6% of the time during the AP visit.

Primary outcome, time spent in near normoglycemia (70–180 mg/dL) was improved by the AP system (43.41% $\pm$ 6.53% vs. 18.92% $\pm$ 7.04%, $P=0.02$) overall, as well as for each meal. Furthermore, better control did not come at the cost of an increased risk for hypoglycemia (0.06 $\pm$ 0.06 vs. 0.13 $\pm$ 0.13 events/subject, NS) overall as well as per meal.

Overall glycemic control was improved by approximately 40 mg/dL (196.5 $\pm$ 10.2 mg/dL vs. 235.4 $\pm$ 14.2, $P=0.007$) overall, and percent time spent >250 mg/dL was reduced 2-fold (24.7% $\pm$ 6.1% vs. 49.9% $\pm$ 7.9%, $P=0.009$).

During the trial, there were no differences between groups in the rate of hypoglycemia <70 mg/dL. Mean blood glucose rose following a snack in the UC arm but did not change during AP use. A larger amount of insulin was delivered on closed-loop days compared to UC days (19.0 $\pm$ 1.4 U vs. 17.1 $\pm$ 1.2 U, $P=0.03$).

Conclusions

Adolescents with T1DM exhibited improved blood glucose control following insulin omission for carbohydrate on a closed-loop AP system as compared to UC. Given the prevalence of poor diabetes control in adolescence and the cost of high blood glucose values with respect to long-term complications, the AP may offer a means of improvement for diabetes care in this at-risk group.

Comment

AP systems are designed to respond to glucose excursions by adjusting the rate of insulin delivery. Almost all current systems monitor interstitial glucose levels sensed via CGM and track trends in these values to either identify current blood glucose values that are above or below a target range or predict impending high/low blood glucose based on blood glucose trends over time. The potential benefits of an AP system to compensate for glucose excursions is balanced by a need for safety that additional insulin delivery will not result in increased hypoglycemia.

This study demonstrated that in a common set of situations for adolescents with T1D—both omission of insulin for snacks and underbolusing for mealtime carbohydrate ingestion—the AP improved blood glucose control without causing hypoglycemia.

The study limitations include: the small number of participants, the short-term duration of the trial, and the applicability of the findings in poor controlled adolescents, since in this study the efficacy of the AP system was tested in a group of adolescents whose diabetes was relatively well controlled (average HbA1c 8.2%).

Single- and dual-hormone artificial pancreas for overnight glucose control in type 1 diabetes

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Background

The added benefit of glucagon to insulin-only closed-loop systems for overnight glucose control has not been fully explored. This study compared the efficacy of dual hormone (insulin and glucagon) artificial pancreas, single hormone (insulin) artificial pancreas, and conventional insulin pump therapy in a 3 center, 3 arm, open-label, randomized, crossover controlled trial over two nights after a high-carbohydrate/high-fat meal and a second after exercise in a home setting.

Methods

The study was from 9pm to 7am in 28 participants with T1D with the main outcome time between 4–8 mmol/L (72–144 mg/dL) between 11pm and 7am.

Results

Median interquartile range (IQR) percentage of time in target was 47% (36%–71%), 76% (65%–91%), and 81% (68%–93%) for conventional, single, and dual hormone artificial pancreas, respectively, and time <4 mmol/L (72 mg/dL) was lower on both single 5% (0%–13%, $P=0.004$) and dual hormone (1%, 0%–8%, $P<0.001$) artificial pancreas compared to conventional therapy (14%, 4%–28%). There were 14 hypoglycemic events on conventional therapy compared to 6 on single ($P=0.59$) and 3 on dual hormone artificial pancreas ($P=0.017$). None of the outcomes differed between single and dual hormone artificial pancreas arms.

Conclusions

Both single and dual hormone artificial pancreas systems provide better glucose control than conventional therapy. The dual hormone system did not increase overnight time in range, but an effect on hypoglycemia cannot be ruled out.

Comment

The topic of single (insulin only) vs. dual (insulin plus glucagon) artificial pancreas systems has been the subject of intense debate in the past several years. Studies such as this finally begin to provide data on the efficacy of these systems tested within a single research study. Not surprisingly, either single or dual hormone systems provide superior overnight glucose control compared to conventional therapy with an insulin pump. However, no difference existed in either time in target or hypoglycemia, although the authors conclude that a difference in hypoglycemia cannot be ruled out.

Much of the debate on the way forward with closed-loop technology as decreased since the publication of Kowalski's new roadmap (3) that distinguishes parallel pathways for automated insulin delivery (insulin only) and multihormonal therapy (insulin plus glucagon or other hormones such as amylin). It is certain that an insulin only automated delivery system will be on the market first. However, a basic principle of endocrinology is to replace hormones that are deficient making a multihormonal approach an ultimate goal. Fortunately, research continues on both pathways with commercial availability is on the horizon for insulin only systems. More data are needed to determine how the performance of multihormonal systems will justify the added complexity and potential additional costs compared to insulin only systems. This will likely remain a field of active research for years to come.

Automated hybrid closed-loop control with a proportional-integral-derivative based system in adolescents and adults with type 1 diabetes: individualizing settings for optimal performance

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Background

Automated insulin delivery is nearing commercial availability. The purpose of this study was to determine preliminary safety and efficacy of initialization parameters with the Medtronic hybrid closed-loop system.

Methods

An initial cohort of 9 adults followed by 15 adolescents were studied using a proportional-integral-derivative with insulin feedback algorithm in a supervised hotel-based protocol over 4–5 days.

Results

The overall mean percentage of time in range (70–180 mg/dL) and time spent < 70 mg/dL during hybrid closed loop was 71.8% and 2.0% in the adult and 69.8% and 2.5% in the adolescent cohort. Mean glucose values were 152 mg/dL in the adult and 153 mg/dL in the adolescent cohorts.

Conclusions

Closed-loop control using the Medtronic hybrid closed-loop system allows adaptive, real-time basal rate modulation. Individualized attention to initialization parameters will be required in clinical practice to optimize glucose control.

Comment

To date in the United States, progress in testing closed-loop technologies have proceeded along a pathway of studies under Food and Drug Administration (FDA) direction; initial human studies are based in hospital settings to allow for attentive supervision followed by transition to slightly less supervised camp or hotel studies and only then followed by out-patient trials and pivotal trials to obtain FDA approval. This study represents a prepivotal study using a Medtronic system to gain experience and data on use in adolescents and adults with T1D. Not surprisingly, very good glucose control was obtained. However, more importantly, these data provide the opportunity to tune systems prior to embarking on larger and longer pivotal trials. The authors also conclude that translation of these systems to clinical use will require individualization (those who believe that the initial systems will translate successfully to large clinical populations without extensive support may be disappointed). On another note, while the current FDA directive on the process for closed-loop research has accelerated research in the field, it remains to be seen how future research will proceed. A future question is what degree of modification of a system will require a full pivotal study vs. a more focused study?

Glucagon nasal powder: a promising alternative to intramuscular glucagon in youth with type 1 diabetes

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Background

Fear of hypoglycemia can prevent patients and their caregivers from striving for optimal metabolic control, especially

among parents of young children with T1D. Fear of hypoglycemia may be increased by the daunting task of treating such events with currently available glucagon emergency kits that require reconstitution of lyophilized powder in a diluent immediately prior to intramuscular injection by family members or others who may not be well trained in or comfortable with giving injections.

The current study was undertaken to assess the safety and pharmacokinetics and pharmacodynamics of intranasal glucagon compared with commercially available intramuscular glucagon in children and adolescents with T1D. The secondary aims were to verify whether adjustment of intranasal glucagon dosing would be needed based on age or weight for younger patients, as weight-based dosing is currently recommended for the intramuscular formulation.

Methods

The study included three cohorts of children ($n = 48$): 4–8, 8–12, and 12–17 years of age. Participants 12–17 years of age were randomly assigned in a 1:1 ratio to receive either 3 mg intranasal glucagon or 1 mg intramuscular glucagon (GlucaGen HypoKit, Novo Nordisk) for the first dosing visit, with the other glucagon preparation administered during the second dosing visit in a crossover fashion.

Studies in the 4–8 and 8–12-year age-groups were designed to compare the efficacy, safety, and pharmacokinetics of the 2 mg and 3 mg intranasal doses of glucagon with one another, as well as with weight-based dosing of intramuscular glucagon. During each visit, glucagon was given 5 min after the plasma blood glucose was < 80 mg/dL, and successful treatment (the primary efficacy outcome) was defined as a ≥ 25 mg/dL rise in plasma glucose from nadir within 20 min of receiving glucagon without receipt of additional actions to increase the blood glucose level.

Results

The primary outcome of a ≥ 25 mg/dL rise in plasma glucose within 20 min after glucagon administration was achieved in all 24 intramuscular dosing visits and in 58 of the 59 intranasal dosing visits. The mean maximal glucose concentrations achieved in all successful intranasal dosing visits ranged between 178–208 mg/dL across age cohorts, with mean maximal glucose in the intramuscular dosing visits ranging between 194–211 mg/dL across the age cohorts.

Plasma glucagon levels increased rapidly within 5 min of intranasal and intramuscular glucagon administration. Times to peak plasma glucose and glucagon levels were similar under both intramuscular and intranasal conditions.

Nausea occurred in 67% of participants who received intramuscular glucagon compared with 43% for the 3 mg intranasal dose and 39% for the 2 mg intranasal dose ($P = 0.05$ intramuscular vs. intranasal). Head/facial discomfort was reported by 24% of participants receiving the 3 mg intranasal dose, 17% receiving the 2 mg intranasal dose, and 13% receiving intramuscular ($P = 0.30$ intramuscular vs. intranasal).

Conclusions

In this phase 1, pharmacokinetic and pharmacodynamic study, intranasal administration of glucagon was a promising alternative for treatment of hypoglycemia to currently

available injected glucagon in youth with T1D. Given the similar frequency of adverse effects of the 2 and 3 mg intranasal doses in the two youngest cohorts, a single 3 mg intranasal dose appears to be appropriate for use across the entire age range (4–17 years).

Comment

Administration of the current available intramuscular glucagon is thought to be complex, and even among trained caregivers of patients with T1D, it was demonstrated that intranasal glucagon was administered in a more successful manner compared with the intramuscular device. The problems in preparing and injecting the current intramuscular glucagon emergency kits stand in stark contrast to the ease of using the single-dose, needle-free intranasal glucagon-dispensing device used in the study.

This study demonstrated that plasma glucagon concentrations rapidly increased to supraphysiologic levels over the first 20 min after administration in a similar fashion after both intranasal and intramuscular glucagon dosing, without significant differences in the side effects between both modes of therapy. As intranasal glucagon is absorbed passively through the nasal mucosa, no co-operation from an individual requiring rescue glucagon therapy is required.

Since this study was carried out in controlled research center settings and both intramuscular and intranasal glucagon were administered by trained professionals, it remains to be determined whether similar results will be seen in the real-life outpatient setting in a combative child or during seizures. It is encouraging that the new mode of intranasal glucagon administration may permit a larger number of caregivers to treat T1D patients with severe hypoglycemia.

Effect of metformin added to insulin on glycemic control among overweight/obese adolescents with type 1 diabetes: a randomized clinical trial

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Background

Observational studies show increasing numbers of overweight and obese individuals with T1D. For youth with T1D, being overweight or obese potentially has serious metabolic consequences, especially during adolescence. Previous studies assessing the effect of metformin (an oral glucose-lowering agent) on glycemic control in adolescents with T1D have been small, of short duration, or used nonstandard doses of metformin and have produced inconclusive results.

The aim of this study was to assess the efficacy and safety of the addition of metformin, 2000 mg/day, to basal-bolus insulin treatment in overweight and obese adolescents with T1D.

Primary outcome was change in HbA1c from baseline to 26 weeks adjusted for baseline HbA1c. Secondary outcomes included change in continuous glucose monitor indices, total daily insulin dose, BMI, waist circumference, body composition, blood pressure, and lipid profile.

Methods

A 6 month, multicenter, double-blind, placebo-controlled, randomized trial involving overweight and obese adolescents ($n = 140$), mean age of 15.3 ± 1.7 years, with mean duration of T1D of 7.0 ± 3.3 years, mean total daily insulin 1.1 ± 0.2 U/kg, and mean HbA1c $8.8\% \pm 0.7\%$.

Participants were randomized to receive metformin ($n = 71$) (≤ 2000 mg/d) or placebo ($n = 69$).

Results

At 13 week follow-up, reduction in HbA1c was greater with metformin (-0.2%) than placebo ($P = 0.02$). This differential effect was not sustained at 26 week follow-up when mean change in HbA1c from baseline was 0.2% in each group. At 26 week follow-up, total daily insulin/kg was reduced by at least 25% from baseline among 23% of participants in the metformin group vs. 1% of participants in the placebo group ($P = 0.003$), and 24% of participants in the metformin group and 7% of participants in the placebo group had a reduction in BMI Z-score of 10% or greater from baseline to 26 weeks ($P = 0.01$). Gastrointestinal adverse events were reported by more participants in the metformin group than in the placebo group ($P < 0.001$).

Conclusions

Among overweight adolescents with T1D, the addition of metformin to insulin did not improve glycemic control after 6 months. However, findings favored metformin only for insulin dose and measures of adiposity; conversely, metformin resulted in an increased risk for gastrointestinal adverse events.

Comment

Similar to the general population, there is an increased number of overweight and obese teens with T1D. These patients often develop insulin resistance, especially during puberty, with high doses of insulin required to overcome the insulin resistance, difficulties in glycemic control, and may further weight gain. In addition, among adolescents with T1D, insulin resistance has been associated also with increases in cardiovascular risk factors.

Metformin seemed to be a “promising” medication administered orally, that decrease hepatic glucose output and increases peripheral uptake of glucose, especially in the muscle. However, the results of this study were disappointing since they failed to show a sustained effect of metformin as an adjunct to basal-bolus insulin therapy on glycemic control after 26 weeks of administration. Metformin treatment failed to improve a number of clinical and biochemical risk factors for future cardiovascular disease including blood pressure, plasma lipid concentrations, and adipocytokines. Therefore, prescribing metformin to adolescents to improve glycemic control is not supported. However, metformin compared with placebo was associated with reductions in weight gain, BMI, body fat, and total daily insulin dose – potential benefits that may or may not justify use of metformin in these patients.

It will be interesting to evaluate whether the addition of a GLP-1 analogue (or other adjunct medications), although administered by injections, as an adjunct to basal-bolus insulin therapy in obese adolescents with T1D will show better results.

Seeing is believing: using Skype to improve diabetes outcomes in youth

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Background

Behavioral Family Systems Therapy (BFST) is a well-supported intervention designed to improve family functioning and adherence in youth with diabetes. Telemental health-care, or the delivery of psychological or behavioral health-care via communication networks, has been deployed to overcome a shortage of behavioral health resources and infrastructure.

Internet-based videoconferencing may be an effective method of overcoming obstacles to care by increasing the availability of expert or specialized services to address regional shortages of qualified providers.

The aim of this study was to compare the relative effectiveness of two modes of delivering of BFST for diabetes (BFST-D) to improve adherence and glycemic control among adolescents with T1D with suboptimal glycemic control.

The outcomes were: changes in youth- and parent-reported adherence and glycemic control, which were compared before and after the intervention and at follow-up assessment.

Methods

Inclusion criteria at enrollment required a diagnosis of T1D of at least 1 year of duration, age 12–19 years, HbA1c $\geq 9.0\%$ [≥ 74.9 mmol/mol]. Adolescents needed to reside

with and be accompanied by a primary caretaker for the duration of the study (7 months).

Adolescents and one adult caregiver were randomized to receive BFST-D via face to face (clinic) or Internet videoconferencing (Skype) condition. Participants completed up to 10 therapy sessions within a 12 week period.

Results

No statistically significant between-group differences at baseline were identified for patient age, duration of diabetes, socioeconomic status, sex, race/ethnicity, family composition, parental marital status, or HbA1c. Using an intent-to-treat analytic approach, no significant between-group differences were identified between the after, and follow-up assessments.

Results demonstrated that statistically significant improvements in adherence and glycemic control occurred from before to after the intervention, regardless of method; improvements were maintained at 3 month follow-up.

Conclusions

The findings of the study support the effectiveness of delivering BFST-D using Internet-based videoconferencing technology for addressing nonadherence and suboptimal glycemic control in adolescents with T1D. Further, the results add to the growing evidence that BFST-D can be effectively delivered in varied ways, potentially reducing barriers to care for youth and families.

Comment

Achieving optimal management of T1D is difficult particularly during adolescence, as youth assume increasing responsibility for their care. Numerous factors contribute to adherence difficulties during this critical developmental period, and family functioning is an important predictor of adherence and glycemic control. Behavioral Family Systems Therapy (BFST) is a well-supported intervention designed to improve family functioning and adherence in youth with diabetes. BFST is a structured, manualized intervention that includes four primary components: problem-solving, communication skills, cognitive restructuring, and family systems interventions. This study demonstrated that regardless of method (clinic or Skype), significant improvements in youth- and parent-reported adherence and glycemic control occurred, without a difference in treatment effect across conditions. Outcomes for youth with poor glycemic control were clinically meaningful and encouraging. However, most adolescents in the study remained in suboptimal glycemic control.

Using technology to deliver specialized behavioral health-care such as BFST-D has several potential advantages over traditional outpatient psychotherapy, including reducing burden to patients and improving accessibility to specialty providers.

Future studies should examine the durability of improvements over a longer time period, and to examine means of optimizing intervention outcomes to achieve better improvements in glycemic control.

Use of telemedicine to improve adherence to American Diabetes Association standards in pediatric type 1 diabetes

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Background

The American Diabetes Association (ADA) recommends that children with T1D be seen quarterly by a pediatric endocrinologist and a multidisciplinary team with educational, nutritional, and psychosocial support. However, access to care can be difficult in the western United States secondary to geographic barriers and uneven distribution of pediatric endocrinologists throughout the country.

The aim of the study was to determine if clinical visits using videoconferencing among youth 1–22 years of age with T1D in Wyoming are comparable to previous in-person visits with regard to HbA1c levels, change in HbA1c over a 1 year period, and number of clinic visits.

Methods

The Barbara Davis Center (BDC) (Aurora, CO) telemedicine program provides diabetes care to pediatric patients in Casper and Cheyenne, WY, via remote consultation with annual in-person visits. Over 27 months, 54 patients completed one year in the study.

Results

The studied population (n=70) was mostly male (70%), with a mean age of 12.1 ± 4.1 years, T1D duration of 5.4 ± 4.1 years, and median HbA1c of 9.0% (range 5.5%–13.5%). Approximately 50% of the patients used insulin pumps. Patients were mostly non-Hispanic white in ethnicity (87%), and the payer mix at the first telemedicine visit was mostly private insurance (63%). The majority of patients (56%) seen via telemedicine lived within 20 miles of the telemedicine site. The demographics of the patients who agreed to participate in the research were similar to those of the entire telemedicine population. However, when compared with nonoutreach patients seen in-person at the BDC, the telemedicine patients have higher HbA1c levels, included a larger proportion of non-Hispanic white patients (64% at the BDC), and included a smaller percentage of patients with private insurance (72% private insurance at the BDC).

There was no significant change between baseline and 1 year HbA1c levels for patients with data at both time points. Patients saw diabetes specialists an average of 2.0 ± 1.3 times per year in the year prior to starting telemedicine and 2.9 ± 1.3 times ($P < 0.0001$) in the year after starting telemedicine. Patients and families missed significantly less school and work time to attend appointments.

Conclusions

The BDC telemedicine program successfully met the needs of rural pediatric patients with T1D in Wyoming by minimizing travel for families and physicians while maintaining adherence to ADA guidelines. Patients could increase their access to diabetes care and potentially improve on compliance with the frequency of clinical visits recommended by the ADA. Decreased financial burden and increased access may improve overall diabetes care and compliance for rural patients.

Comment

Height and weight monitoring, HbA1c evaluation, age-specific nutrition and insulin adjustment, and sick-day management reviews are necessary on a quarterly basis. The delivery of care to pediatric T1D to geographically remote regions carries unique challenges and telehealth is one potential solution.

There are multiple reports of telemedicine technology being used to transmit blood glucose information to the diabetes care team and to connect school nurses and patients with diabetes care teams.

In this study, glycemic control was maintained in a noninferior manner, and patients were seen more frequently when telemedicine was offered. Also patients and families missed significantly less school and work time and were more satisfied. However, mean HbA1c did not change with use of telemedicine over a 1 year period of time.

The study limitations include: first, the observational nature and the lack of randomization of subjects to telemedicine or routine care limits the ability to comment on the effectiveness of videoconferencing as a

substitute for face-to-face visits. Second, patients were self-selected for analysis because if they did not follow-up in telemedicine, they did not fill out future surveys, and attrition rate was significant. Finally, the relatively small number of participants that were seen for at least one year cannot allow to generalize the findings.

Author Disclosure Statement

Dr. Shlomit Shalitin has no competing financial interests. David M. Maahs is on the advisory board for Insulet, a consultant for Abbott, and receives research support to his institution from Medtronic, Dexcom, and Roche.

References

1. Sherr JL, Hermann JM, Campbell F, Foster NC, Hofer SE, Allgrove J, Maahs DM, Kapellen TM, Holman N, Tamborlane WV, Holl RW, Beck RW, Warner JT; T1D Exchange Clinic Network, the DPV Initiative, and the National Paediatric Diabetes Audit and the Royal College of Paediatrics and Child Health registries. Use of insulin pump therapy in children and adolescents with type 1 diabetes and its impact on metabolic control: comparison of results from three large, transatlantic paediatric registries. *Diabetologia* 2016; **59**: 87–91.
2. Maahs DM, Calhoun P, Buckingham BA, Chase HP, Hramiak I, Lum J, Cameron F, Bequette BW, Aye T, Paul T, Slover R, Wadwa RP, Wilson DM, Kollman C, Beck RW; In Home Closed Loop Study Group. A randomized trial of a home system to reduce nocturnal hypoglycemia in type 1 diabetes. *Diabetes Care* 2014; **37**: 1885–91.
3. Kowalski A. Pathway to artificial pancreas systems revisited: moving downstream. *Diabetes Care* 2015; **38**: 1036–43.