ORIGINAL ARTICLE

Continuous Glucose Monitoring in 2018

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Introduction

ADVANCED TREATMENT MODALITIES are generally associated with considerable additional costs for the payer. As the costs of medical care for diabetes represent an increasing share in most health-care budgets (1), payers design various strategies to limit the access to expensive treatment modalities. It is exceedingly rare that a novel, efficient, and safe treatment modality can incur cost reduction. Continuous glucose monitoring (CGM) seems to position itself into this uncommon category (2). Now unequivocally accepted as safe and efficient, and recommended in all clinical guidelines from all professional associations (3), CGM enters various public and private insurance systems with the proven potential to reduce acute morbidity and absenteeism, adding considerably to the total reduction of costs related to diabetes.

The current article discusses recent clinical evidence associating CGM with reduction in morbidity related to glucose variability and hyper- and hypoglycemia, with the focus on well-being of people with diabetes (PWD) and, during pregnancy complicated by diabetes, also on their offspring. Indeed, CGM is “transforming diabetes management step by step” (4), among PWD as well as diabetes care providers. The CGM metric of time in target range (TIR) becomes more widely adopted, and its use combined with time in hypoglycemia can provide a more personalized approach to diabetes management. As always, PWD will have to decide whether CGM is their “best friend or spy” (5). CGM influences physical, emotional, and relational aspects of everyday life. Diabetes care providers can help reduce the burden of CGM with sensible delivered training and realistic expectations for PWD. Complementing the quality of life (QOL) outcomes in adults with diabetes, CGM use has been associated with less adolescent and parental distress compared to no technology use, along with lower glycosylated hemoglobin (HbA1c) (6). Empowerment and relational partnerships in diabetes care can optimize contentment and success with CGM. PWD seem to be perfectly ready—let’s make sure that we, diabetes care providers, don’t lag behind.

Key Articles Reviewed for the Article

Effect of continuous glucose monitoring on glycemic control, acute admissions, and quality of life: a real-world study

Charleer S, Mathieu C, Nobels F, De Block C, Radermecker RP, Hermans MP, Taes Y, Vercammen C, T’Sjoen G, Crenier L, Fieuws S, Keymeulen B, Gillard P; on behalf of RESCUE Trial Investigators

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Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomized controlled trial

Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D, Hermanns N

Lancet 2018; **391**: 1367–1377

Continuous glucose monitoring for hypoglycemia avoidance and glucose counterregulation in long-standing type 1 diabetes

Rickels MR, Peleckis AJ, Dalton-Bakes C, Naji JR, Ran NA, Nguyen HL, O'Brien S, Chen S, Lee I, Schutta MH

J Clin Endocrinol Metab 2018; **103**: 105–114

Continuous glucose monitoring in healthy children aged 2–8 years

Sundberg F, Forsander G

Diabetes Technol Ther 2018; **20**: 113–116

Revisiting the relationships between measures of glycemic control and hypoglycemia in continuous glucose monitoring data sets

Gimenez M, Tannen AJ, Reddy M, Moscardo V, Conget I, Oliver N

Diabetes Care 2018; **41**: 326–332

Clinically significant cognitive impairment in older adults with type 1 diabetes

Chaytor NS, Barbosa-Leiker C, Ryan CM, Germine LT, Hirsch IB, Weinstock RS

J Diabetes Complications 2019; **33**: 91–97.

Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicenter international randomised controlled trial

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Continuous glucose monitoring results in lower HbA1c in Malaysian women with insulin-treated gestational diabetes: a randomized controlled trial

Paramasivam SS, Chinna K, Singh AKK, Ratnasingam J, Ibrahim L, Lim LL, Tan ATB, Chan SP, Tan PC, Omar SZ, Bilous RW, Vethakkan SR

Diabet Med 2018; **35**: 1118–1129

Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): a multicentre randomized controlled trial

Voormolen DN, DeVries JH, Sanson RME, Heringa MP, de Valk HW, Kok M, van Loon AJ, Hoogenberg K, Bekedam DJ, Brouwer TCB, Porath M, Erdsieck RJ, NijBijvank B, Kip H, van der Heijden OWH, Elving LD, Hermesen BB, Potter van Loon BJ, Rijnders RJP, Jansen HJ, Langenveld J, Akerboom BMC, Kiewiet RM, Naaktgeboren CA, Mol BWJ, Franx A, Evers IM

Diabetes Obes Metab 2018; **20**: 1894–1902

Continuous glucose monitoring in pregnant women with type 1 diabetes: benefits for mothers, using pumps or pens, and their babies

Feig DS, Murphy HR

Diabet Med 2018; **35**: 430–435

Relative contributions of preprandial and postprandial glucose exposures, glycemic variability, and non-glycemic factors to HbA1c in individuals with and without diabetes

Færch K, Alsema M, David J, Mela DJ, Borg R, Vistisen D

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Ann Intern Med 2017; **167**: 365–374

Contribution of basal and postprandial hyperglycemia in type 2 diabetes patients treated by an intensified insulin regimen: impact of pump therapy in the OPT2MISE trial

Reznik Y, Habteab A, Castaneda J, Shin J, Joubert M

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Hu YM, Zhao LH, Zhang XL, Cai HL, Huang HY, Xu F, Chen T, Wang XQ, Guo AS, Li JA, Su JB

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A prospective multicenter evaluation of the accuracy of a novel implanted continuous glucose sensor: PRECISE II

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Diabetes Technol Ther 2018; **20**: 197–206

Effect of continuous glucose monitoring on glycemic control, acute admissions, and quality of life: a real-world study

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This manuscript is also discussed in the article on Technology and Pregnancy, page S-101, and the article on Practical Implementation of Diabetes Technology: It Is Time, page S-148.

Aims

Randomized controlled trials evaluating real-time CGM use in type 1 diabetes (T1D) demonstrate improved glycemic control; however, limited prospective data are available on routine home use. Belgian health-care authority granted CGM reimbursement for an initial period of 3 years as a pilot program, with selected centers being legally obliged to prospectively analyze the impact of reimbursement on clinical outcome parameters. This prospective, observational, multicenter, cohort study assessed the impact of CGM in real-world settings on glycemic control, hospital admissions, work absenteeism, and QOL.

Methods

Data from all patients who started in the reimbursement program with a standardized clinical follow-up in 17 specialized diabetes centers selected by the Belgian health-care authority between September 2014 and December 2016 were analyzed. Patients were expected to use CGM >70% of the time and upload their RT-CGM data monthly. Every patient who entered the reimbursement program was included, without exception, after signing the informed consent. The primary endpoint was change in HbA1c between baseline and 12 months after start of CGM reimbursement. Secondary endpoints were effect of CGM on admissions for acute diabetes complications (hypoglycemia and/or ketoacidosis), work absenteeism, QOL, glucose variability (coefficient of variation), percentage of time in hypoglycemia (<70 mg/dL; <3.9 mmol/L), range (70 to 180 mg/dL; 3.9 to 10 mmol/L), and hyperglycemia (>250 mg/dL; >13.9 mmol/L). Sensors used were Enlite Sensor (Medtronic, Northridge, CA) (n=382; 75%), Dexcom G4 PLATINUM (Dexcom, Inc., San Diego, CA) (n=121; 24%), and FreeStyle Navigator II (Abbott Diabetes Care, Alameda, CA) (n=8; 2%). Prespecified clinical data were collected from a period of 12 months before until 14 months after the start of the reimbursement program.

Results

Out of 515 people with T1D on continuous subcutaneous insulin infusion (CSII) who benefited from the CGM reim-

bursement, 417 (81%) had 12 months (or more) of follow-up, 46 (9%) had <12 months of follow-up, and 52 (10%) stopped using CGM. Most patients were female (299; 59%), highly educated (296; 64%), and Caucasian (493; 97%), with a long history of T1D, and 5.7 ± 4.6 years of CSII use at baseline. The main indication for starting CGM was hypoglycemia (289; 56%), followed by inadequate glycemic control (132; 26%). CGM use was $87.5 \pm 8.2\%$ of time over the 12-month period. Most frequent reasons for discontinuation were alarm fatigue (18; 35%), <70% usage of CGM (17; 33%), local and/or technical problems (16; 31%), and no apparent benefit for patient and/or physician (12; 23%). Baseline HbA1c was $7.7 \pm 0.9\%$ (61 ± 9.8 mmol/mol) and decreased to $7.4 \pm 0.8\%$ (57 ± 8.7 mmol/mol) at 12 months ($P < 0.0001$). Subjects who started CGM because of insufficient glycemic control showed a greater decrease in HbA1c at 4, 8, and 12 months (from $8.2 \pm 0.9\%$ [66.0 ± 9.8 mmol/mol] before reimbursement to $7.6 \pm 0.8\%$ [60.0 ± 8.7 mmol/mol] after 12 months; $P < 0.0001$), whereas patients who were using CGM because of hypoglycemia had a slight decrease in HbA1c (from $7.5 \pm 0.8\%$ [58.0 ± 8.7 mmol/mol] to $7.4 \pm 0.8\%$ [57.0 ± 8.7 mmol/mol]; $P = 0.001$). The percentage of values <70 mg/dL (3.9 mM) was $5.6 \pm 3.8\%$ in the first 2 weeks compared with $4.5 \pm 3.2\%$ after 12 months ($P = 0.002$), independent of baseline HbA1c. Mean coefficient of variation (95% confidence interval) decreased slightly from 38.7% (95% CI 38.0%–39.4%) in the first 2 weeks to 37.9% (95% CI 37.2%–38.6%) at 12 months ($P = 0.02$). In the year preceding reimbursement, 16% of patients were hospitalized for severe hypoglycemia or ketoacidosis in contrast to 4% ($P < 0.0005$) the following year, with a decrease in admission days from 54 to 18 per 100 patient-years ($P < 0.0005$), representing a nationwide cost reduction of €345,509 during the trial period. In the same period, work absenteeism decreased and QOL improved significantly, with strong decline in fear of hypoglycemia. Based on effect sizes, improvement in QOL was largest in patients who had problems with hypoglycemia and weakest in patients with insufficient and variable glycemic control.

Conclusions

The nationwide reimbursement of CGM for selected people with T1D using CSII in specialized diabetes centers improved glycemic control and lowered risk of acute diabetes-related hospitalizations. Additionally, it decreased fear of hypoglycemia and led to significantly higher QOL. These results support the benefit of CGM use in a real-world setting.

Comments

The pervasive effectiveness of CGM observed in this study may be attributable to several factors. Mean sensor use (87.5%) was higher than in most random, controlled trials (RCTs) and observational studies, which is repeatedly associated with higher effectiveness of CGM. The specific design of the study, dictated by the Belgian health authorities, selected highly motivated patients and professional teams (the attrition was very low), who were able to maintain the CGM benefits throughout the study. We need to keep in mind the trial has limitations of an observational study without a prospective control

group: specific training, education, and more intense contact with dedicated health-care professionals may have contributed to the favorable outcomes (2). Nevertheless, the nationwide cost reduction of €345,509 during the trial period (without the savings from less work-days lost and other secondary cost savings) may outweigh CGM-related costs and put the CGM therapy into the “cost saving” binder of insurance systems. If so, the Belgian real-world study deserves the attribute “landmark.”

Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomized controlled trial

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Background

The effectiveness of real-time CGM in avoidance of hypoglycemia among high-risk individuals with T1D treated with multiple daily insulin injections (MDI) is unknown. This study ascertained the incidence and severity of hypoglycemia with the use of CGM in this cohort of PWD.

Methods

This multicenter, open-label, parallel, randomized controlled trial with a 6-month study period and a 4-week run-in included 149 adults with T1D for >1 year who were using MDI, from 12 specialized diabetes practices in Germany. All had a history of having at least one severe hypoglycemia event requiring third-party assistance for recovery in the previous year or of having impaired hypoglycemia awareness (score of 4 or more by Clarke). All participants wore a masked CGM (Dexcom G4 with software 505) for 4 weeks during the run-in, 74 were subsequently randomized to CGM, and 74 to standard care for 22 weeks. The primary outcome was the number of hypoglycemic events measured by CGM during the follow-up phase (weeks 22–26) compared with baseline run-in period of 4 weeks. Hypoglycemic event was defined as glucose value of 3.0 mmol/L (≤ 54 mg/dL) or lower for at least 20 min, preceded by a minimum of 30 min with glucose values greater than 3.0 mmol/L (> 54 mg/dL). The primary outcome analysis was done by negative binomial regressions analysis with adjustments for the number of hypoglycemic events during the baseline phase and the duration of the follow-up phase.

Results

The analysis dataset included 141 participants (control group, n=66; CGM group, n=75) who completed the baseline and follow-up phases. CGM participants wore a sensor for 90.7% of study days assessed (88 days). The frequency of self-monitoring of blood glucose (SMBG) was significantly lower in the CGM group than in the control groups (3.7 ± 1.9 vs 6.0 ± 1.3 ; $P < 0.0001$). The mean number of hypoglycemic events per 28 days defined by CGM was reduced from 10.8 (SD 10.0) to 3.5 (4.7) in CGM group and from 14.4 (12.4) to 13.7 (11.6) in the control group. Incidence of hypoglycemic events decreased by 72% for CGM participants (incident rate ratio [IRR] 0.28 [95% CI 0.20–0.39]; $P < 0.0001$). Analysis of the intention-to-treat population by use of multiple imputation generated similar results. Twenty-five (33.3%) of CGM group participants had no hypoglycemic events during the follow-up phase compared with 5 (7.6%) of 66 control group participants, corresponding to an odds ratio of 6.1 [95% CI 2.2–17.1]; $P = 0.0006$ for avoidance of hypoglycemia with CGM. The percentage of hyperglycemic values was increased slightly in both study groups with no significant between-group differences. Glycemic variability was significantly reduced in the CGM group (from 39.3% at baseline to 34.1% at follow-up). The incidence of all severe hypoglycemia events during follow-up was 0.64 (SD 1.92) vs 1.18 (SD 3.46) events per patient-year (IRR 0.36 [95% CI 0.15–0.88]; $P = 0.0247$) in the CGM vs control groups. A significant between-group effect was observed for the hypoglycemia distress subscale score of the T1-DDS questionnaire.

Conclusions

Results from this study indicate that regular use of CGM can minimize both biochemical and clinical hypoglycemia without increasing HbA1c in individuals with T1D with impaired hypoglycemia awareness or severe hypoglycemia treated by MDI.

Comments

Impressive and highly clinically relevant results from the HypoDE study are important, and not only because of their obvious face value: in the context of some other similar recent studies—for example, IN CONTROL and HypoCOMPaSS (7)—the German study clearly demonstrates that it takes more than just distributing a CGM device to a PWD. Traditional systemized education for SMBG-centered self-management of T1D cannot empower PWD for the successful use of CGM. Throughout the ongoing story of technology use in diabetes, even large RTCs demonstrate dichotomous results; only studies run by diabetes care centers experienced with the use of technology (or, for a matter of fact, studies in which PWDs did not get any instructions on how to use CGM) demonstrated consistent success. Therefore, it may not be just the CGM-specific education itself but rather the CGM “attitude” and “culture” that distinguish successful CGM RTCs from those that did not show any added value. There is, however, one important consideration: the hypoglycemia-centered diabetes community is confronted

with an increasing amount of evidence that it is in fact hyperglycemia that damages the brain in young (8), adult (9), and elderly (10) patients. We can therefore expect that future RCTs will focus on time in range (TIR) rather than on the extremes of glycemic excursions (11,12).

Continuous glucose monitoring for hypoglycemia avoidance and glucose counterregulation in long-standing type 1 diabetes

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Aims

To determine whether the use of real-time CGM over 18 months as a strategy to avoid hypoglycemia could improve glucose counterregulation in patients with long-standing type 1 diabetes (T1D) who have severe hypoglycemia and hypoglycemic unawareness.

Methods

Participants were adults 25–70 years of age, with T1D for >10 years who had undetectable c-peptide, were naïve to CGM use, were on intensive diabetes management, and had hypoglycemic unawareness based on Clarke score and HYPO score of severe hypoglycemia in the past year. Eleven patients with a mean 31 years' duration of diabetes were studied longitudinally in the Clinical and Translational Research Center of the University of Pennsylvania prior to and both 6 and 18 months after initiation of real-time CGM (DexCom n=7; Medtronic n=4) were compared with 12 nondiabetic control participants. The primary outcome was endogenous glucose production response to insulin-induced hypoglycemia using a paired hyperinsulinemic stepped-hypoglycemic and euglycemic clamps with infusion of 6,6-²H₂-glucose.

Results

In these 11 patients with T1D using real-time CGM, hypoglycemia awareness (Clarke score) and severity (HYPO score and severe events) improved as early as 6 months and persisted through 18 months ($P<0.01$ for all) without a change in HbA1c (baseline, $7.2\% \pm 0.2\%$). Glycemic variability improved as well, as quickly as within 6 months, and remained stable through the end of the study. In response to insulin-induced hypoglycemia, endogenous glucose production did not change from baseline to 6 months (0.44 ± 0.08 vs 0.54 ± 0.07 mg/kg·min) but improved after 18 months (0.84 ± 0.15 mg/kg·min; $P<0.05$ vs before CGM), but remaining less than in controls (1.39 ± 0.11 mg/kg·min;

$P \leq 0.01$ vs all). Other counterregulation hormones (epinephrine, norepinephrine, glucagon, pancreatic polypeptide) did not change over the 18-month study.

Conclusion

Real-time CGM can improve hypo-awareness and reduce the burden of problematic hypoglycemia in patients with long-standing T1D, but with only modest improvement in the endogenous glucose production response that is required to prevent or correct low blood glucose. Other counterregulatory hormones did not change over the 18-month study.

Comments

Recurrent severe hypoglycemia and hypoglycemia unawareness are a major complication to a subset of people with long-standing type 1 diabetes, especially those who are c-peptide negative, have marked glycemic variability, and have frequent exposure to hypoglycemia. Fortunately, the use of real-time CGM can markedly reduce exposure to hypoglycemia in well-trained persons using intensive insulin management by reducing the risk of severe hypoglycemia. Unfortunately, in this small study of 11 participants who underwent a hypoglycemia challenge, glucose counterregulatory hormones did not change with only a moderate improvement of endogenous glucose production at 18 months. Thus, the best treatment at this time for people suffering from hypoglycemic unawareness and severe hypoglycemia is to wear real-time CGM and avoid any hypoglycemia, preferably using hybrid closed-loop systems.

Continuous glucose monitoring in healthy children aged 2–8 years

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Diabetes Technol Ther 2018; **20**: 113–116

Aims

Normal glycemic patterns have been described in older children and adults. CGM studies have also been performed in older children and teenagers; however, no such data are available for small children. The purpose of this study was to generate the information that has been missing on CGM-derived glycemic levels and patterns during the daily lives of healthy children aged 2–8 years, helping researchers and clinicians in their decisions related to T1D in this age group.

Methods

Siblings of insulin-treated children with diabetes using CGM were invited to participate in this study. Inclusion criteria were age 2–7.99 years, BMI standard deviation score (SDS) within ± 2 SDS, no illness and on no medication, HbA1c <42 mmol/mol (<6.0%), fasting plasma glucose

<5.6 mmol/L (<100 mg/dL), and a postprandial 2-h plasma glucose <7.8 mmol/L (<140 mg/dL) after a challenge with a carbohydrate-rich meal consisting of pancakes and jam (at least 1.75 g carbohydrates per kilogram body weight). Participants used a Dexcom G4 (Dexcom, Inc., San Diego, CA) CGM for 7 days. Sensors were applied by a trained research nurse after anesthesia with topical lidocaine (EMLA; AstraZeneca PLC, London, UK) and regularly calibrated by the parents with SMBG.

Results

All 15 participating children provided valid data from more than 6 days. No data had to be excluded due to concurrent illness or medication. Sensor glucose levels were mainly within 4–7.8 mmol/L (72–140 mg/dL); 9% were <4 mmol/L (72 mg/dL), 3% <3.5 mmol/L (63 mg/dL), and 1% >9.0 mmol/L (162 mg/dL). Zero percent of sensor glucose values was >11.1 mmol/L (200 mg/dL). Three children provided more low sensor glucose values than the rest of the group. The glycemic pattern was very stable, with mean glucose $\pm$ SD of 1.0 ± 0.2 , and coefficient of variation (CV) of 18.87%. Sensor glucose levels were slightly higher in the evening and lower in the morning.

Conclusions

Twenty-four-hour glycemia and measures of glycemic variability as determined by CGM in healthy children aged 2–8 years were reported.

Comments

Normative data are crucial for understanding physiological range and variability of measured variables in individuals. This may be of particular importance in the preschool pediatric population with several additional vulnerabilities and risks, particularly related to the developing brain. The number of low plasma glucose values was unevenly distributed, with three children having more values <4.0 mmol/L (72 mg/dL) than the rest of children. With this study design limited by age-specific ethical considerations, it is impossible to distinguish between outlying values caused by physiological variations, sensor quality, or calibration-related errors. Importantly, there was no values registered above 11 mmol/L (200 mg/dL) and only 1% >9 mmol/L (>162 mg/dL), indicating that in children with T1D values above 10 mmol/L (180 mg/dL), a common “clinically chosen threshold,” should be strictly avoided.

Revisiting the relationships between measures of glycemic control and hypoglycemia in continuous glucose monitoring data sets

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Aims

The inverse relationship between HbA1c and severe hypoglycemia, identified in The Diabetes Control and Complications Trial (DCCT), influenced clinical decision making in diabetes for more than 3 decades. This analysis investigated the relationship between hypoglycemia and HbA1c in a large T1D cohort on MDI or insulin pump therapy using blinded CGM data (the Juvenile Diabetes Research Foundation [JDRF]-CGM trial). The impact of real-time CGM on these relationships at different biochemical thresholds of hypoglycemia were assessed.

Methods

CGM data were obtained from the JDRF CGM randomized control trial, freely accessible from the Jaeb Center for Health Research. One-week baseline blinded CGM data were used to assess time in hypoglycemia in all individuals. Endpoint data from the CGM intervention group were used to assess the impact of CGM. Percentage of time spent below 3.9, 3.3, 3.0, and 2.8 mmol/L (70, 60, 54, and 50 mg/dL) were calculated and quadratic regression model plots drawn. Relationships were analyzed visually, and ANOVA was used to assess relationships between glycemia and time below threshold.

Results

Of the 448 individuals included in the baseline analysis (54.9% female, age 25.1 ± 15.8 years, HbA1c $7.44 \pm 0.86\%$), 231 individuals were assigned to the CGM intervention group, and data from 155 individuals were available at 26 weeks (blinded CGM data with a minimum of 6 days were available for 185 individuals in the control group). J-shaped relationships were observed for all biochemical hypoglycemia thresholds, with the lowest hypoglycemia risk occurring at HbA1c values between 8.1% and 8.6% (65–70 mmol/mol). The use of an average of 5 days/week of CGM changed substantially the shapes of the 3.3, 3.0, and 2.8 mmol/L curves, becoming flattened U-shaped curves with reduced variation in time spent below hypoglycemia threshold with change in HbA1c. The regression curves for time spent at <3.3, <3.0, and 2.8 mmol/L had low R² values and were not significant. The CGM nadir points for the 2.8, 3.0, and 3.3 mmol/L curves were reduced to 7.3% (56 mmol/mol), 7.4% (57 mmol/mol), and 7.7% (61 mmol/mol), respectively. In the CGM group, Kruskal–Wallis analysis only identified significant difference for the 3.9 mmol/L threshold ($P < 0.01$), with no variance of hypoglycemia across HbA1c categories identified for the 3.3, 3.0, or 2.8 mmol/L thresholds.

Conclusions

The relationship between hypoglycemia and HbA1c in a population with type 1 diabetes is J-shaped. Lower HbA1c values were still associated with increased hypoglycemia risk only for the higher threshold of 3.9 mmol/L (70 mg/dL), but not at lower thresholds. Real-time CGM may reduce the percentage time spent in hypoglycemia, changing the relationship between HbA1c and hypoglycemia.

Comments

The use of CGM weakens the relationship between HbA1c and hypoglycemia and may even avoid the currently accepted thresholds for hypoglycemia (3.0 mmol/L or 54 mg/dL). Therefore, CGM enables achievement of a lower HbA1c and reduced hypoglycemia risk simultaneously, as already demonstrated by several RCTs. The increased hypoglycemia risk at higher HbA1c values is consistent with the persistent risk of SH an HbA1c >8.5% (>69 mmol/mol) in the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up data. This fact is of particular clinical relevance, as it is not consistently remembered that people with higher HbA1c values are at a higher risk for hypoglycemia and need routine access to CGM. Moreover, insulin pump use in the JDRF dataset was associated with a lower risk of hypoglycemia across the whole range of HbA1c, corroborating the DCCT/EDIC cohort results. Mild biochemical hypoglycemia is likely to remain more frequent at the extremes of HbA1c, but as the use of CGM abolished the relationship between HbA1c and hypoglycemia at <3.3, <3.0, and <2.8 mmol/L (60, 54, and 50 mg/dL), both in the quadratic regression curves and in ANOVA, it is not more likely to progress to clinically significant hypoglycemia and can be efficiently managed. Therefore, 3.9 mmol/L (70 mg/dL) can be considered a safe hypoglycemia threshold for action in routine clinical use of CGM. With the fact in mind that the JDRF trial was published in 2008, a decade ago, the current CGM technology is even more efficient. This important reanalysis of the data therefore brings crucial messages for our day-to-day diabetes care routine.

Clinically significant cognitive impairment in older adults with type 1 diabetes

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J Diabetes Complications 2019; **33**: 91–97.

Aims

Little is known about cognition in older adults with type 1 diabetes. This study aimed to identify correlates of clinically significant cognitive impairment. One study used the cutoff for cognitive impairment as performance ≥ 1.5 standard deviations below normative data on two or more tests and reported cognitive impairment in 28% of their cohort (mean age 49 years). The strongest diabetes-related predictors were higher mean HbA1c over the prior 14 years and retinopathy

or/and polyneuropathy measured 5 years prior. No published data were available on the prevalence or correlates of clinically significant cognitive impairment in older adults with T1D.

Methods

T1D Exchange Clinic Network enrolled 201 participants, ≥ 60 years old, with diabetes duration of ≥ 20 years, from 18 diabetes centers between August 2013 and April 2014. Neuropsychological testing (Symbol Digit Modalities Test, Trail Making Test, Hopkins Verbal Learning Test–Revised, and the Grooved Pegboard Test) was conducted only when capillary blood glucose was >70 mg/dL. The Dexcom SEVENPLUS CGM was used in blinded mode for 14 days (two sensors). Demographic and diabetes-related variables (e.g., sex, education, age, diabetes duration, age of diagnosis), microvascular complications (retinopathy, neuropathy, and nephropathy), HbA1c, severe hypoglycemic events within the past 12 months, hypoglycemia unawareness, depression symptoms, and functional status were collected.

Results

Median (interquartile range [IQR]) age at study entry was 66 (63–71) years, ranging from 60 to 86 years; diabetes duration was 39 (29–50) years ranging from 20 to 73; and age at diabetes diagnosis was 30 (17–37) years ranging from 5 to 57 years. The majority of the sample (74%) was diagnosed at >18 years. Clinically significant cognitive impairment (≥ 2 cognitive tests ≥ 1.5 SD below normative data) occurred in 48% of the sample. The prevalence of impairment was highest on a test of executive functioning (Trails B = 38.6% impaired) and lowest on verbal recognition memory (Hopkins Verbal Learning Test–Revised recognition memory = 14.1% impaired). After controlling for age, gender, education, and diabetes duration, we found that hypoglycemia unawareness, recent severe hypoglycemic events, any microvascular complication, higher HbA1c, and higher CGM average nocturnal glucose were all associated with increased odds of clinically significant cognitive impairment (Odds ratios [ORs] = 1.01–2.61), while CGM nocturnal % time below 60 mg/dL was associated with decreased odds of cognitive impairment (OR = 0.94). Diabetes duration, diagnosis age, daytime CGM, and lifetime severe hypoglycemic events were not related to cognitive impairment status.

Conclusions

Community residing, nondemented, older adults with T1D had a 48% clinically significant cognitive impairment, despite the vast majority having no impairment in activities of daily living (mild cognitive impairment), compared with reported 16% in general population of older than 60 years. Similar to findings of younger adults with T1D, those with clinically significant cognitive impairment in this older population were more likely to have a higher HbA1c and at least one microvascular complication. Lifetime frequency of severe hypoglycemic events was not associated with cognitive impairment, consistent with findings from the Diabetes Control and Complications Trial and later 18-year follow-up that did not find greater cognitive decline in those with a history of severe hypoglycemic episodes.

Comments

The population of older adults with T1D continues to increase and nearly 50% of them may have clinically significant cognitive impairment, considerably increasing the individual burden of the disease. It is conceivable that cognitive decline associated with aging or other age-related conditions increases the likelihood of making a self-management error that leads to a severe hypoglycemic event. Additionally, it is possible that cognitive impairment results in a reduced ability to monitor, detect, or interpret the early signs of hypoglycemia and/or react appropriately to avoid severe hypoglycemia. Those with cognitive impairment had higher HbA1c and higher mean CGM glucose at night, consistent with prior data linking higher HbA1c to greater cognitive impairment. Importantly, a recent longitudinal study in pediatric population including a final population of 118 children with T1D and 58 healthy matched controls demonstrated lower axial diffusivity (a presumed measure of myelination) in children with T1D compared to healthy participants at baseline ($P=0.022$) and at 18 months ($P=0.015$) (8). In children with T1D, lower lifetime exposure to hyperglycemia (the average of all HbA1c measurements >42 mmol/mol [$>6\%$] from diagnosis to baseline) was associated with higher fractional anisotropy (a measure of white matter development) at 18 months ($P=0.037$), and fractional anisotropy was in turn significantly correlated with performance IQ ($r=0.29$; $P<0.002$) and full-scale IQ ($r=0.23$; $P<0.02$). These findings suggest that brain myelination in children is affected by average excess levels of glucose rather than by a cumulative hyperglycemic effect from the age of diagnosis (no correlation of fractional anisotropy with disease duration). As lower exposure to hyperglycemia correlates with better white matter maturation and higher IQ in children, so lower HbA1c and lower average nocturnal CGM glucose correlate with less clinically significant cognitive impairment in older adults with (mostly) adult-onset T1D.

Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial

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Lancet 2017; **390**: 2347–2359

This manuscript is also discussed in the article on Technology and Pregnancy, page S-101.

Aims

Neonatal outcomes attributed to maternal hyperglycemia remain suboptimal in pregnant women with T1D, despite the recommended striving for optimal glucose control. The aim in this study was to examine the effectiveness of CGM on maternal glucose control, and obstetric and neonatal health outcomes.

Methods

In this multicenter, open-label, randomized controlled trial, women aged 18–40 years with T1D for a minimum of 12 months on intensive insulin therapy were recruited. Participants were pregnant (≤ 13 weeks and 6 days' gestation) or planning pregnancy (two separate trials) from 31 hospitals in Canada, England, Scotland, Spain, Italy, Ireland, and the United States. In both trials, participants were randomly assigned to either CGM in addition to SMBG or SMBG alone. Randomization was stratified by insulin delivery (pump or injections) and baseline HbA1c. The primary outcome was change in HbA1c from randomization to 34 weeks' gestation in pregnant women and to 24 weeks or conception in women planning pregnancy. Secondary outcomes included obstetric and neonatal health outcomes, assessed with all available data without imputation.

Results

From March 2013 to March 2016, 325 women were randomly assigned (215 pregnant, 110 planning pregnancy) to either SMBG with CGM (108 pregnant and 53 planning pregnancy) or SMBG alone (107 pregnant and 57 planning pregnancy). The primary outcome, difference in HbA1c, was lower in pregnant women using CGM (mean difference -0.19% [95% CI -0.34 to -0.03]; $P=0.0207$), with more

time in target of 3.5–7.8 mmol/L (63–140 mg/dL) (68% vs 61%; $P=0.0034$) and less time in hyperglycemia (27% vs 32%; $P=0.0279$) than did pregnant control participants, with comparable severe hypoglycemia episodes (18 CGM and 21 control) and time spent in hypoglycemia (3% vs 4%; $P=0.10$). The use of CGM significantly improved neonatal outcomes, with lower incidence of large for gestational age (odds ratio [OR] 0.51 [95% CI 0.28 to 0.90]; $P=0.0210$), fewer neonatal intensive care admissions lasting more than 24 h (0.48 [0.26 to 0.86]; $P=0.0157$), fewer incidences of neonatal hypoglycemia (0.45 [0.22 to 0.89]; $P=0.0250$), and 1-day shorter length of hospital stay ($P=0.0091$). No apparent benefit was found for CGM in women planning pregnancy. The frequency of CGM use was median 6.1 days per week (IQR 4.0–6.8) in pregnant participants and 6.2 days per week (IQR 5.2–6.9) in participants planning pregnancy. Sensor use was highest in later gestation, with a median of 6.5 days (IQR 3.9–7.0) at 25–34 weeks. Adverse events occurred in 51 (48%) of CGM participants (with skin reactions occurring in 49 participants—48% of all adverse events) and 43 (40%) of control participants in the pregnancy trial, and in 12 (27%) of CGM participants and 21 (37%) of control participants in the planning pregnancy trial. Serious adverse events occurred in 13 (6%) participants in the pregnancy trial (8 [7%] CGM, 5 [5%] control) and in 3 (3%) of participants in the planning pregnancy trial (2 [4%] CGM and 1 [2%] control). The most common serious adverse events were gastrointestinal (nausea and vomiting in 4 participants during pregnancy and 3 participants planning pregnancy).

Conclusions

Reduced exposure to maternal hyperglycemia with the use of CGM during pregnancy in women with T1D is associated with improved neonatal outcomes. CGM should be offered to all pregnant women with T1D.

Comment

This study is the first to indicate potential for improvements in neonatal outcomes from CGM use in pregnancies complicated by T1D. This story of “sweet success” (13) came only with dedication and skill of diabetes care providers supporting participants to incorporate CGM data into their diabetes routines, as they have some 500 additional unscheduled contacts related to sensor use (sensor issues mean 2.1 [SD 2.8] per participant in the CGM group vs 0.1 [SD 0.3] per participant in the control group; $P<0.0001$) and to sensor-related diabetes management issues (26 [SD 5.3] vs 0.2 [SD 0.7]; $P<0.0001$), with CGM frustrations affecting more than 80% of women (connectivity issues, alarms, and calibration errors, and almost 50% experiencing skin reactions, such as bleeding, erythema, and discomfort). This unexpected difference in unscheduled contacts prompted a *post hoc* analysis adding the total number of unscheduled non-sensor-related contacts to the main ANCOVA model: the CGM treatment effect estimate remained significant. Higher TIR with the CGM use translated to an additional 1.7 h/day in target and approximately 1 h/day less in hyperglycemia during pregnancy.

Day-to-day exposure to maternal hyperglycemia and reduced glucose variability measured directly with CGM might be more relevant for neonatal outcomes than surrogate markers such as HbA1c (14).

Health-economic analyses are required to ascertain the costs of CGM and its implementation into antenatal care; from this trial, 6 pregnant women need CGM treatment for preventing one neonatal intensive care admission and one large for gestational age neonate, and 8 for preventing one neonatal hypoglycemia. Taking the high costs of perinatal interventions into the equation, CGM treatment during pregnancy may prove cost-saving.

Continuous glucose monitoring results in lower HbA1c in Malaysian women with insulin-treated gestational diabetes: a randomized controlled trial

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Diabet Med 2018; 35: 1118–1129

Aims

To determine whether the use of masked (blinded) CGM would improve HbA1c with less hypoglycemia in women with insulin-treated gestational diabetes mellitus (GDM).

Methods

Fifty women with insulin-treated GDM were randomized to either masked CGM (Medtronic iPro2 Enlite 6-day sensor) at 28, 32, and 36 weeks' gestation (Group 1, CGM, $n=25$) or typical antenatal care without CGM (group 2, control, $n=25$). Each participant performed seven-point capillary blood glucose (CBG) profiles a minimum of 3 days per week and recorded all hypoglycemic events (symptomatic as well as asymptomatic CBG <3.5 mmol/L; nonfasting <4.0 mmol/L). HbA1c was measured at 28, 33, and 37 weeks. Diabetes in group 1 mothers was treated based on both CGM and CBG data; mothers in group 2 were managed based on CBG data alone.

Results

Both groups had similar baseline HbA1c ($5.1 \pm 0.3\%$ vs $5.3 \pm 0.5\%$; $P=0.124$) as well as total insulin dose and BMI. Mean HbA1c remained unchanged throughout the trial in the CGM group and increased significantly in controls as pregnancy advanced. Mean HbA1c in the CGM group was lower at 37 weeks compared with controls ($5.2 \pm 0.4\%$ vs $5.6 \pm 0.6\%$; $P<0.006$). 92% of the CGM group achieved an HbA1c $<5.8\%$ at 37 weeks compared to 68% of the control group ($P=0.012$). Neither group experienced severe hypoglycemia.

Conclusion

The use of masked CGM just three times in the third trimester may be useful in the management of insulin-treated GDM by effectively improving HbA1c compared with usual antenatal care without increasing severe hypoglycemia.

Comment

Publications on the use of CGM in the management of insulin-treated GDM are limited. This small prospective, open-label, randomized controlled study of women with insulin-dependent GDM showed that the use of masked CGM just three times in the third trimester can aid the health-care practitioner in managing the insulin titration with improvement in HbA1c while minimizing the risk of severe hypoglycemia. CGM has now become the standard of care in managing many people with insulin requiring diabetes. The question now is whether real-time CGM is beneficial for the majority of patients with insulin-requiring diabetes in pregnancy.

Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): a multicentre randomized controlled trial

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Diabetes Obes Metab 2018; **20**: 1894–1902

This manuscript is also discussed in the article on Technology and Pregnancy, page S-101.

Aim

To determine the effectiveness of additional use of masked CGM in pregnancies complicated by insulin requiring diabetes.

Methods

This study was a nationwide, multicenter, open-label, randomized, controlled trial to study pregnant women with type 1 or type 2 diabetes who were undergoing insulin therapy at gestational age <16 weeks or women who were undergoing insulin treatment for gestational diabetes at gestational age <30 weeks. Participants were randomized (1:1) to intermittent use of retrospective CGM for 5–7 days every 6 weeks or to standard treatment. Primary outcome was macrosomia, defined as birth weight above the 90th percentile, with secondary outcomes being glycemic control and maternal and neonatal complications.

Results

Three hundred pregnant women on insulin with type 1 (n=109), type 2 (n=82), or with gestational (n=109) diabetes were randomized to either CGM (n=147) or standard treatment (n=153). No difference was seen in any pregnancy outcomes, with the incidence of macrosomia being 31.0% in the CGM group and 28.4% in the standard treatment group (relative risk 1.06 [95% CI 0.83–1.37]). HbA1c levels were similar between treatment groups.

Conclusions

In insulin-requiring diabetes in pregnancy, use of intermittent masked CGM every 6 weeks did not reduce the risk of macrosomia or other pregnancy outcomes. HbA1c also did not change.

Comment

Masked (retrospective) CGM should improve glucose profiles over time in insulin requiring diabetes if the

health-care providers are competent at interpreting the glucose profiles and adjusting basal and bolus insulin appropriately. In this large multicenter, nationwide study, masked CGM was done only every 6 weeks. Insulin adjustments must be done weekly in pregnancy due to the marked changes in insulin resistance, especially in the second and third trimester. For this reason, masked CGM should not help with reducing macrosomia or other pregnancy outcomes when using CGM every 6 weeks; it must be done weekly. In addition, one must try to get the 1 h postmeal glucose to be <6.7 mmol/L (<120 mg/dL) instead of <7.8 mmol/L (<140 mg/dL) to prevent macrosomia. The target in this study was <7.8 mmol/L (<140 mg/dL) at 1 h post-eating.

Continuous glucose monitoring in pregnant women with type 1 diabetes: benefits for mothers, using pumps or pens, and their babies

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Diabet Med 2018; 35: 430–435

Aims

Current publications on the use of CGM during pregnancy in women with type 1 diabetes are reviewed.

Methods

The authors searched current literature for randomized controlled trials using CGM during pregnancy in women with type 1 diabetes and found the three published studies listed below:

Murphy HR, Rayman G, Lewis K, et al. Effectiveness of CGM in pregnant women with diabetes: randomised clinical trial. *BMJ* 2008; 337: a1680.

Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. The effect of real-time CGM in pregnant women with diabetes: a randomized controlled trial. *Diabetes Care* 2013; 36: 1877–1883.

Feig DS, Donovan LE, Corcoy R, et al. CGM in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. *Lancet* 2017; 390: 2347–2359 (discussed earlier in this article, on page S-21, and in the article on Technology and Pregnancy, page S-101).

Results

Murphy et al. in the UK randomized 71 pregnant women (46 with T1D; 25 with T2D) to periodic masked CGM every 4–6 weeks in addition to 7–10 SMBG per day. The CGM group had a significant drop in HbA1c (5.8% vs 6.4%; $P=0.007$) with a

reduction in large-for-gestational-age (LGA) infants (13% vs 18%; $P=0.05$), with no increase in hypoglycemia and no difference in admission to neonatal intensive care (NICU). Secher et al. in Denmark randomized 154 women (123 with T1D and 31 with T2D) to real-time CGM for 6 days on 5 occasions at 8, 12, 21, 27, and 33 weeks gestation vs usual care. Glycemic outcomes in both cohorts were the same (HbA1c 6.1% in both arms; glucose time in target 4 to 8 mmol/L 58% in both arms). There was no difference in reduction of LGA infants (45% vs 34% $P=0.19$) or severe neonatal hypoglycemia (36% vs 40%; $P=0.62$). The study by Feig et al. in the UK randomized only T1D women who were planning pregnancy or already pregnant early in the first trimester to real-time CGM all the time vs usual care with SMBG 7 times a day. The mean difference in HbA1c was small, 0.2%, favoring the CGM group ($P=0.04$) with additional time in range (3.5 to 7.8 mmol/L) of 100 minutes per day at 34–36 weeks gestation with 72 min per day less in hyperglycemia (>7.8 mmol/L). Neonatal outcomes improved in the CGM group with LGA infant rate of 53% vs 69% ($P=0.02$) and severe neonatal hypoglycemia requiring IV glucose being 15% vs 28% ($P=0.025$) and NICU admit >24 hrs 27% vs 43% ($P=0.0157$).

Conclusion

The use of CGM in pregnant women with type 1 diabetes is associated with improved glycemic control and neonatal outcomes in the most recent publications, although the rates of LGA infants and neonatal hypoglycemia remain too high. Further research is needed to decrease these complications.

Comment

Tight control of glucose in pregnancy is crucial to prevent macrosomia as well as other neonatal complications including neonatal hypoglycemia. Real-time CGM along with frequent SMBG allows the patient and the health-care provider to titrate the basal insulin and bolus insulin to preprandial glucose <5 mmol/L (<90 mg/dL) and 1 h postmeal <6.7 mmol/L (<120 mg/dL). In achieving these goals, macrosomia and neonatal hypoglycemia are extremely rare.

Relative contributions of preprandial and postprandial glucose exposures, glycemic variability, and non-glycemic factors to HbA1c in individuals with and without diabetes

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Nutr Diabetes 2018; 8: 38

Aims

To determine the associations of preprandial glucose exposure and postprandial glucose exposure (PPG) as well as

other factors in the variance in HbA1c in individuals with and without T2D.

Methods

Participants willing to wear masked CGM 4 times over 12 weeks were recruited from the A1c-Derived Average Glucose study. Three groups were included in this analysis: without T2D (n=77), with noninsulin treated T2D and HbA1c <6.5% (n=63), and HbA1c ≥6.5% (n=34). In linear regression models, the study team estimated the associations of the glycemic exposures with HbA1c and calculated the proportion of variance in HbA1c explained by glycemic and nonglycemic factors (age, sex, body mass index, and ethnicity).

Results

The glycemic and nonglycemic factors in the CGM analysis explained 35% of the variance in HbA1c in people with no DM, 49% in subjects with T2D and HbA1c <6.5%, and 78% in people with T2D and HbA1c ≥6.5%. In non-DM subjects, only PPG exposure was associated with HbA1c ($P<0.05$). In the T2D group with HbA1c <6.5%, all glycemic measures were associated with HbA1c ($P<0.05$), with preprandial glucose and PPG accounting for 14% and 18%, respectively. In the T2D with HbA1c ≥6.5% group, both preprandial glucose and PPG exposures accounted for more than 50% of the variation in HbA1c, with equal contributions.

Conclusion

Based on CGM analysis, PPG was strongly predictive of HbA1c in people with no DM. In T2D with a HbA1c ≥6.5%, preprandial glucose and PPG exposure contributed equally to HbA1c.

Comment

HbA1c is affected by glucose exposure over time as well as red blood cell turnover and nonglycemic factors including age, sex, body mass index, and ethnicity. If one has prediabetes, one should use lifestyle intervention including diet and exercise to minimize postprandial glucose exposure. If one has type 2 diabetes with a HbA1c ≥6.5%, one has to address both the preprandial and postprandial glucose exposure using lifestyle change and pharmacological agents.

Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial

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Ann Intern Med 2017; **167**: 365–374

Aims

The effect of CGM, proven to be beneficial for adults with T1D, has not been well evaluated in people with T2D receiving insulin with MDI.

Methods

This RCT, performed in 25 endocrinology practices in North America, randomly assigned 158 adults with T2D for a median of 17 years (IQR 11–23 years), aged 35–79 years (mean age 60 years, SD 10; 52% of participants ≥60 years), on MDI, with HbA1c from 7.5% to 9.9% (mean 8.5%) to either CGM (n=79, Dexcom G4 Platinum CGM System, algorithm software 505) or usual care (control group, n=79; SMBG averaging 2 or more times per day, asked to perform at least 4 times daily). The primary outcome was HbA1c reduction at 24 weeks.

Results

The 24-week primary outcome visit was completed by 77 participants (97%) in the CGM group (medium CGM wear 6.7 days per week [SD 1.0] in month 6) and 75 (95%) in the control group. Mean HbA1c levels decreased to 7.7% in the CGM group and 8.0% in the control group at 24 weeks (adjusted difference in mean change, −0.3% [95% CI −0.5% to 0.0%]; $P=0.022$). The CGM group averaged 6.7 days (SD 0.9) of CGM use per week. Biochemical CGM hypoglycemia was infrequent, limiting the ability to assess the effect of CGM on reducing hypoglycemia. No cases of severe hypoglycemia occurred in either group. The treatment groups did not differ in the quality-of-life measures. However, CGM Satisfaction Scale at the end of the trial indicated high satisfaction with CGM, reflected also in the high frequency of use. The treatment effect was greater in participants with the highest baseline HbA1c (at least 9.0%; reduction of 1.4% in the CGM group vs 0.7% in the control group) who are at greatest risk for complications.

Conclusions

A high percentage of adults who received MDI for T2D used CGM on a daily or near-daily basis for 24 weeks and experienced improved glycemic control. These results support an additional efficient management option for insulin-treated patients with T2D.

Comment

Clinicians in this trial did not make periodic substantial insulin adjustments despite persistent hyperglycemia and infrequent hypoglycemia, reflected in the minimal increase in daily insulin dose. Individuals with T2D often have less advanced diabetes management skills (such as carbohydrate counting, insulin sensitivity factors, and

appropriate correction timing) and less empowerment for self-management, which would limit their ability to use CGM optimally. High CGM use and high satisfaction with CGM in this trial suggest that even greater glycemic benefits could be obtained if clinicians incorporated treat-to-target insulin titration algorithms or expanded shared decision making based on CGM data. Clear and clinically meaningful benefit of CGM in individuals with T2D receiving MDI demonstrated in this trial should improve the access to routine CGM in this patient population, allowing them to set more ambitious targets for time in range without an increased risk of hypoglycemia.

Contribution of basal and postprandial hyperglycemia in type 2 diabetes patients treated by an intensified insulin regimen: impact of pump therapy in the OPT2MISE trial

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Aims

To determine the contribution of basal hyperglycemia and postprandial hyperglycemia in patients with type 2 diabetes treated with MDI of insulin before randomization and after 6 months of CSII.

Methods

Participants (n=259) in the OPT2MISE trial were placed on masked CGM after completion of an 8-week run-in period of titration on MDI and then 6 months after being randomized to CSII (n=131). The hyperglycemic area under the curve (AUC) during the 24-h basal period (AUC-B) and the postprandial period (AUC-P) were compared using ANOVA based on contribution to total hyperglycemia in HbA1c groups (group 1, <8%; group 2, 8%–8.4%; group 3, 8.5%–8.9%; group 4, 9%–9.4%; and group 5, ≥9.5%). Changes in AUC-B and AUC-P were examined after 6 months of pump therapy in 131 randomized subjects for whom CGM recordings were available.

Results

In patients on MDI therapy post-8-week forced titration, HbA1c correlated with AUC-B but not with AUC-P. AUC-B was 21.6% to 54.8% lower in group 4 to 1 ($P=0.0138$ and $P=0.0002$, for groups 1 and 4, respectively) compared with group 5. In contrast, AUC-P did not differ between HbA1c groups ($P=0.10$). After switching to CSII, AUC-B and AUC-P decreased by 21% and 17%, respectively.

Conclusions

In the OPT2MISE study, basal hyperglycemia was the major determinant of overall exposure to hyperglycemia in

type 2 diabetes with MDI failure. Once randomized to CSII, both basal and postprandial hyperglycemia were equally decreased.

Comment

If patients are failing MDI, one should consider CSII to better manage their diabetes. CSII allows one to control basal hyperglycemia when people are not eating and to control mealtime excursions with bolus insulin premeal and over time for high-fat meals. As a result, CSII allows one to better manage both basal hyperglycemia and postprandial hyperglycemia compared with MDI.

Association of glycemic variability evaluated by continuous glucose monitoring with diabetic peripheral neuropathy in type 2 diabetic patients

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Endocrine 2018; **60**: 292–300

Aims

This study investigated the association of diabetic peripheral neuropathy (DPN) with glycemic variability using CGM in a large-scale sample of patients with type 2 diabetes.

Methods

A large group of patients with type 2 diabetes (n=982) were enrolled in a cross-sectional study where all patients were screened for DPN and wore a masked CGM system (Medtronic Gold) for 4 days in the hospital between February 2011 and January 2017. Multiple glycemic parameters were analyzed from the CGM profiles including mean amplitude of glycemic excursions (MAGE), mean of daily differences (MODD), standard deviation of glucose (SD), and 24-h mean glucose. Other possible risk factors for DPN were also examined.

Results

Out of the 982 patients with type 2 diabetes, 197 patients (20.1% of the screened population) were diagnosed as having DPN by both physical exam and abnormal nerve conduction. Upon analysis of CGM tracings, these patients had higher MAGE, MODD, SD, and 24-h mean glucose than patients without DPN ($P<0.001$). Using univariate and multiple logistic regression analyses, MAGE, diabetes duration, homeostatic model assessment of insulin resistance (HOMA-IR), and HbA1c were found to be independent contributors to DPN with corresponding odds ratios [95% CI] of 4.57 [3.48–6.01], 1.10 [1.03–1.17], 1.24 [1.09–1.41], and 1.33 [1.15–1.53],

respectively. The optimal MAGE cutoff value for predicting DPN was 4.60 mmol/L with the corresponding sensitivity being 64.47%, and the specificity being 75.54%.

Conclusion

Increased glycemic variability assessed by MAGE in addition to conventional risk factors including diabetes duration, HOMA-IR, and HbA1c are significant independent contributors to DPN in patients with type 2 diabetes.

Comments

DPN is one of the most common complications of type 2 diabetes. Conventional risk factors have been duration of diabetes, insulin resistance, and glycemic control as measured by HbA1c. This study identified glycemic variability assessed by MAGE as one of the strongest contributors to DPN, most likely from oxidative stress and other factors. Future studies need to validate whether controlling glycemic variability can prevent or improve DPN.

Outcome prediction in acute stroke patients by continuous glucose monitoring

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Aims

To determine the relationships between glucose parameters obtained using CGM at the onset of acute stroke and clinical outcomes in these acute stroke patients.

Methods

This is a prospective single-center observational study that enrolled 100 consecutive patients with acute ischemic stroke or intracerebral hemorrhage within the first 24 h after onset. On the first morning of the admission, a masked CGM device (Medtronic iPro2) was attached for the initial 72 h. CGM tracings provided values for eight glucose parameters: maximum, minimum, mean, and SD of blood glucose levels; AUC > 8 mmol/L of sensor glucose; time spent with > 8 mmol/L of sensor glucose; coefficient of variation (%CV); and presence of time at < 4 mmol/L over the 72 h. The primary outcome measure was correlation of these 8 glycemic parameters with death or dependency at 3 months (modified Rankin scale score ≥ 3).

Results

The study group included a total of 100 patients with acute ischemic stroke (n = 58) or intracerebral hemorrhage (n = 42). Sensor-recorded glucose levels varied between 5.2 ± 1.4 and

11.4 ± 3.2 mmol/L over 72 hours, with AUC > 8 mmol/L of blood glucose of 0.7 ± 1.4 min $\times$ mmol/L, time spent > 8 mmol/L of blood glucose of $31.7 \pm 32.7\%$, %CV of $15.5 \pm 5.4\%$, and presence of hypoglycemia (< 4 mmol/L) in 20% of overall patients. Mean glucose level (adjusted odds ratio 1.60 [95% CI 1.12–2.28]/ 1 mmol/L), AUC more than 8 mmol/L of blood glucose (2.13 [1.12–4.02]/ 1 min $\times$ mmol/L), and time spent more than 8 mmol/L of blood glucose (1.25, 1.05–1.50/ 10%) were related to death or dependency for overall patients, and also for patients with acute ischemic stroke (2.05, 1.15–3.65; 2.38, 1.04–5.44; 1.85, and 1.10–3.10, respectively), but not for those with intracerebral hemorrhage. Patients with early neurological deterioration within 7 days had higher HbA1c ($P = 0.01$), mean glucose ($P = 0.03$), AUC > 8 mmol/L ($P = 0.04$), and time spent > 8 mmol/L ($P < 0.001$). Only the time spent > 8 mmol/L was significantly correlated to neurological deterioration on multivariate analysis.

Conclusions

High mean glucose levels as well as time spent at more than 8 mmol/L (> 144 mg/dL) and AUCs more than 8 mmol/L (> 144 mg/dL) during the initial 72 hours of acute stroke were associated with death or dependency at 3 months after acute stroke.

Comment

Hyperglycemia (> 8 mmol/L; > 144 mg/dL) in the first 72 hours of an acute stroke, specifically ischemic stroke, is associated with poor outcomes. Unfortunately, we do not know whether controlling glucose to a near normal range without hypoglycemia in the first 72 hours upon admission will prevent the death and neurological deterioration that is common in acute ischemic stroke victims. Future randomized controlled trials are needed to answer whether glucose should be controlled in acute stroke victims.

Glucose sensor-augmented continuous subcutaneous insulin infusion in patients with diabetic gastroparesis: an open-label pilot prospective study

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Aims

Blood glucose levels out of target can be a cause and consequence of delayed gastric emptying in people with diabetes. Whether or not improved glycemic control increases risks of hypoglycemia or improves HbA1c levels and gastrointestinal symptoms in diabetic gastroparesis is unknown. This GLUMIT-DG study examined the safety and potential effectiveness of CSII and CGM in individuals with poorly controlled diabetes and gastroparesis.

Methods

Forty-five patients (age 18 ± 70 years, diabetes for >2 years) with T1D or T2D and gastroparesis with HbA1c $>8\%$ from the NIDDK Gastroparesis Consortium were included in a 24-week (with additional 8 weeks screening period and 8 weeks run-in), open-label pilot prospective study administering CSII plus CGM. Participants had symptoms for >1 year with Gastroparesis Cardinal Symptom Index scores >18 , confirmed with gastric scintigraphy before registration with $>60\%$ 2-hour and/or $>10\%$ 4-hour retention. Meal bolus insulin recommendations included: (i) bolus initiation 15 ± 30 minutes after eating, using CGM to detect increasing glucose levels indicating the onset of meal absorption, (ii) using the dual-wave bolus with a small first wave ($10 \pm 20\%$ total meal dose) followed by a second wave ($80 \pm 90\%$) over 4–6 hours, and (iii) considering temporary basal rate increases instead of meal boluses if CGM suggested longer periods of delayed meal absorption. The primary safety outcome was combined numbers of mild, moderate, and severe hypoglycemic events at screening and after 24 weeks of treatment. Secondary outcomes included glycemic excursions on CGM, HbA1c, gastroparesis symptoms, quality of life, and liquid meal tolerance.

Results

The rates of combined mild, moderate, and severe hypoglycemic events were similar during the screening/run-in (1.9

per week) and treatment (2.2/week) phases, with a relative risk of 1.18 ([95% CI 0.8–1.64], $P=0.33$). CGM time in hypoglycemia (<70 mg/dL) decreased from 3.9% to 1.8% ($P<0.0001$), time in euglycemia (70–180 mg/dL) increased from 44.0% to 52.0% ($P=0.02$), time in severe hyperglycemia (>300 mg/dL) was reduced from 14.2% to 7.0% ($P=0.005$), and HbA1c fell from $9.4 \pm 1.4\%$ to $8.3 \pm 1.3\%$ ($P=0.001$) on CSII with CGM. Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) survey symptom scores decreased from 29.3 ± 7.1 to 21.9 ± 10.2 with lower nausea/vomiting, fullness/early satiety, and bloating/distention scores ($P<0.001$). PAGI-QOL scores improved from 2.4 ± 1.1 to 3.1 ± 1.1 ($P<0.0001$), and the tolerated volumes of liquid nutrient meals rose from 420 ± 258 mL to 487 ± 312 mL ($P=0.05$) at 24 weeks.

Conclusions

In patients who had poorly controlled diabetes and gastroparesis, CSII plus CGM appeared to be safe, with minimal risks of hypoglycemic events and associated improvements in glycemic control, gastroparesis symptoms, quality of life, and meal tolerance. These results support the safety, feasibility, and potential benefits of improving glycemic control in individuals with diabetic gastroparesis.

Comment

Concerns that intensifying insulin therapy in diabetic gastroparesis might cause hypoglycemia due to mismatches consequent to delayed nutrient absorption prompted investigators in this study to select combined weekly mild, moderate, and severe hypoglycemic episodes before and during CSII plus CGM as their primary outcome. To match postprandial nutrient absorption to short-acting insulin analog pharmacokinetics in diabetic gastroparesis, dual-wave CSII feature and/or temporary basal rate increases were the treatment modality. These two distinctly CSII features, monitored by CGM, likely caused observed improvements in glycemic control, gastroparesis symptoms, and quality of life. This study provides further evidence that when CSII is used by experienced diabetes care providers, able to train participants for the use of advanced CSII features adjusted to particular individual needs, and especially with concomitant use of CGM, most clinically relevant outcomes are significantly improved.

The effect of continuous glucose monitoring in preventing inpatient hypoglycemia in general wards: the glucose telemetry system

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Aim

The use of CGM devices in hospital was investigated to determine whether CGM readings can be successfully transmitted from the patient's bedside to a central monitoring device in the nurses station and whether the CGM alarms on the central monitoring device can prevent hypoglycemic events.

Methods

This was a small, nonrandomized, pilot study that enrolled 5 insulin-treated general medicine patients with T2D who were at higher risk for hypoglycemia. All participants from one hospital floor were placed on real-time CGM (Dexcom G 4). The CGM values were transmitted via bluetooth to the Apple iPhone at the bedside and then to an Apple iPad located centrally at the nursing station using DexCom Follow and Share 2 software. CGM low alerts were set up at glucose <85 mg/dL. The primary outcome was prevention of hypoglycemia.

Results

Two patients had three actions of prevention of potential hypoglycemia (CGM BG <70 mg/dL for >20 minutes) captured by central alarm at <85 mg/dL, allowing the nursing team to administer oral carbohydrates. Two other patients experienced a single hypoglycemic event despite the CGM alerts: one was off the ward in a radiology suite and the other occurred when the nurse was not at the nursing station. No patients had CGM glucose value <54 mg/dL. Overall, participants were monitored with CGM for an average of 4 ± 1.6 days.

Conclusions

In this small pilot study, use of CGM in hospitalized patients can be successfully transmitted to a monitoring device in the nursing station, improving patient surveillance in insulin-treated patients with diabetes.

Comments

Diabetes is very common in the hospital, with up to 25% of patients having known diabetes and another 10%–25% having hyperglycemia. As a result, both hyperglycemia and hypoglycemia are common, with prevalence rates of hypoglycemia in patients as high as 30%, which in turn can cause adverse events including mortality and prolonged length of stay. As a result, we need better surveillance of glucose readings to prevent hypoglycemia and manage hyperglycemia. In this small pilot using CGM at the bedside, one is able to measure CGM at the bedside and transfer the readings to a central nursing station with the prevention of three hypoglycemia events. Further studies are needed to validate the accuracy of CGM in the hospital and ICU and show if it is cost-effective to use CGM instead of POC BG testing to manage glucose safely and efficiently in hospital to near normal glycemia with minimal hypoglycemia.

A prospective multicenter evaluation of the accuracy of a novel implanted continuous glucose sensor: PRECISE II

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Aims

Persistent use of CGM improves glycemic control in individuals with both T1D and T2D; however, many patients struggle to achieve consistent adherence. Moreover, the attrition rate of CGM is high in several environments, commonly associated with frustrations related to sensor wear and/or malfunction. PRECISE II aimed at evaluating the accuracy and safety of an updated Eversense system, which included a modified algorithm and a new sensor configuration, in individuals with T1D and T2D.

Methods

The CGM system consists of an implantable, fluorescence-based, cylindrical glucose sensor (3.5 × 18.3 mm), a transmitter, and a mobile medical application that displays glucose information on a mobile device in real time. The sensor contains core electronics and optics that are sealed in epoxy within a polymethyl methacrylate (PMMA) encasement. The sensor is activated by receiving radio frequency power from the transmitter to measure interstitial fluid glucose every 5 min. A 100-μm thick copolymer matrix is embedded to the outside of the PMMA encasement as the indicator hydrogel; selective, fully reversible binding between glucose and the covalently attached molecular complex increases fluorescence intensity measured by the sensor's optical system, thus detecting changes in glucose concentrations. The optical system's LED and two photodiodes are powered by a ferrite antenna substrate. The encoded glucose data are sent to the transmitter for generating a glucose reading and to check the integrity of the system. The implantable sensor has a silicone collar impregnated with 1.75 mg of dexamethasone acetate that elutes an average of 3 μg per day over the life of the sensor, to attenuating local inflammatory response and prolonging the sensor life. The system provides a sensor replacement alert when the oxidative degradation of the glucose recognition chemistry causes insufficient sensitivity to glucose.

This was a 90-day, nonrandomized, prospective, blinded, single-arm multicenter study of the implantable CGM system, conducted from January to July 2016 at eight sites in the United States, enrolling individuals >18 years of age with a clinically confirmed diagnosis of T1D or T2D for >1 year. Endocrinology specialists without surgical training inserted all

sensors in the upper arm through a 5–8 mm incision into a dilator-prepared subcutaneous pocket with a special inserter. The incision was closed with Steri-Strips thereafter. Bilateral sensors were placed to 15 participants for assessing inpatient variability and the compression effect. SMBG was performed by Contour Next USB (Ascensia Diabetes Care, Parsippany, NJ). Participants were asked to wear the transmitters over the sensors and to calibrate twice daily. All CGM values and glucose-related alerts were blinded to both the participants and investigators for the duration of the study. On 4 days the accuracy was tested inpatient comparing the CGM glucose values with bedside Yellow Springs glucose analyzer, also during three hyperglycemia and hypoglycemia challenges. The primary effectiveness endpoint was the mean absolute relative difference (MARD) for paired sensor and Yellow Springs Instruments (YSI) reference glucose measurements during clinic visits at 90 days postinsertion across a range of 40–400 mg/dL.

Results

Ninety participants ($n=75$ single sensor and $n=15$ bilateral sensors) had sensors inserted and were included in the primary effectiveness and safety populations, and 82 (91%) completed the study with day 90 data collection (5 got the sensor replacement alert before day 90, ending glucose data collection). The median transmitter wear time for the participants was 23.4 hours per day. The primary effectiveness endpoint of MARD over the glucose range of 40–400 mg/dL was 8.8% (95% CI 8.1%–9.3%), with 93.3% of CGM values within ± 20 mg/dL or 20% of YSI reference values (referred to as 20/20%) over the total YSI glucose range of 40–400 mg/dL. CGM readings within 20/20% of the reference values measured during compression (92.3%) were similar to those measured without compression (93.4%) ($P=0.88$); similarly, exercise conditions (95.1%) had no effect on accuracy compared with nonexercise (93.2%) ($P=0.35$). Clarke error grid analysis showed 99.3% of measurements in the clinically acceptable error zones A (92.8%) and B (6.5%), none in zones C and E, and 0.7% in zone D. A strong between-sensors correlation among the 15 participants with bilateral sensors (9974 matched pairs) scored at paired absolute relative difference of 8.8% (95% CI 7.4%–12.3%). The system correctly identified 93% and 96% of hypoglycemic and hyperglycemic events per YSI. Based on Kaplan–Meier analysis, the sensor survival probability at day 90 for the 106 implanted sensors was 91%. A total of 14 device-related adverse events among 7 participants included 9 events of bruising, erythema, or pain/discomfort, one syncopal episode after insertion of the device and one episode of paresthesia or tingling. There were 2 events wherein a small element of the PMMA encasement possibly remained under the skin. A serious adverse event represented one event of inability to remove the sensor by the investigator; a general surgeon chose to use general anesthesia for the removal procedure. There were no infections at insertion or removal, with no skin reactions due to the adhesive patch. For all 90 participants, no dexamethasone was detectable in plasma (< 2 ng/mL) before insertion or at day 90.

Conclusions

The PRECISE II trial demonstrated that the Eversense CGM system provided accurate glucose readings through the intended 90-day sensor life with a favorable safety profile.

Comments

This trial improved the recently published results for the 180-day PRECISE trial (15), where the MARD value against reference glucose values > 4.2 mmol/L was 11.1% (95% CI 10.5–11.7). Similarly, the hypoglycemia detection rate by the system was improved compared with the 81% in the PRECISE trial (15). With the overall MARD below 10%, the implantable Eversense CGM now clearly ranks among routinely clinically applicable CGM systems. More importantly, PWDs who used the implantable sensor during the trial provided almost surprisingly positive feedback with a considerable majority of participants (93% of first-time users and 77% previous CGM users) expressing the readiness to continue using the Eversense system to help manage their diabetes more effectively (16). Implantable sensors, particularly when the 6 months or longer longevity and functionality are reached, will likely become the CGM of choice with a considerable proportion of PWDs. As soon as this implantable CGM technology matures and the manufacturing capacity is scaled up to the market needs, we all will face another “game changer.”

Conclusion

As the technical development of CGM advances with unprecedented swiftness from implantable sensors on one side to less-invasive technologies on the other, along with the development of algorithms for professionals and PWDs, it is the penetration of CGM use that is improving glycemic control and improving outcomes. In addition to the Belgium Health Authority follow-up study, several other reports demonstrate cost savings for PWD using CGM therapy.

An economic evaluation of CGM cost-effectiveness for people with T1D and impaired awareness of hypoglycemia performed in North West London Clinical Commissioning Groups in England ($n=3032$ PWDs with impaired hypoglycemia awareness) estimated that the net additional cost (deducting the offsets from lower hypoglycemia-related costs, reduced SMBG strip usage, avoided near-term HbA1c-related complications, and insulin pump usage) for regular CGM use would amount to approximately \$1081 per person per year in the first 4 years (17), without taking into account the loss of working days and other indirect costs. Another study utilized Optum Clinformatics® Data Mart (OptumInsight, Eden Prairie, MN) database of commercially insured and Medicare Advantage subscribers and their dependents (initial sample: CGM, $n=1027$, non-CGM, $n=32,583$; after final matching: 283 PWD in each group and no significant differences between the CGM and non-CGM groups) and estimated more than \$4200 lower 1-year cost (without durable medical equipment) with the use of CGM when compared with individuals not using CGM ($P<0.05$). The majority of this cost difference was in medical costs, with about \$2200 lower costs in the “outpatient other facility” category, and almost \$2000 lower costs, on average, in the “inpatient hospital” category. These lower inpatient costs were corroborated with fewer hospital admissions ($P<0.05$) and a tendency toward shorter lengths of stay during the post-index period ($P=0.08$) (18). Both of these studies were performed by CGM companies and may contain various biases.

Another company-sponsored national analysis (using the CORE model) in Spain estimated the incremental cost-effectiveness ratio for the use of sensor-augmented pumps of €25,394/QALY (19), which is below the Spanish national insurance threshold for reimbursement. Finally, a more affordable variant—the intermittent glucose monitoring or “Flash” glucose monitoring—received public reimbursement in several countries in the European Union (including the United Kingdom) and the United States (20).

CGM is now standard of care for most people with T1D as well as poorly controlled T2D and diabetes in pregnancy, with significant improvement in glycemic control with minimizing hypoglycemia and improving clinical outcomes. Diabetes health-care providers, based on solid clinical evidence and apparently acceptable cost-effectiveness ratios, should do more to help PWD use CGM effectively and with as little nuisance as possible.

Author Disclosure Statement

B.B. received consultancy and speaker fees from Adocia, Astra Zeneca, Bayer, Diasome, Intarcia, Janssen, Mannkind, Medtronic, Novo Nordisk, and Sanofi. B.B.’s employer, Atlanta Diabetes Associates, has received research and grant support from Abbott, Becton Dickson, Boehringer Ingelheim, Diasome, DexCom, Janssen, Lilly, Mannkind, Medtronic, Novo Nordisk, Sanofi, and Senseonics.

T.B. served on advisory boards of Novo Nordisk, Sanofi, Eli Lilly, Boehringer, Medtronic, and Bayer Health Care. T.B.’s employer University of Ljubljana and University Medical Center Ljubljana received research grant support, with receipt of travel and accommodation expenses in some cases, from Abbott, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz, and Diamyd. T.B. received honoraria for participating on the speaker’s bureaux of Eli Lilly, Bayer, Novo Nordisk, Medtronic, Sanofi, and Roche. T.B. owns stock in DreaMed Diabetes.

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