ORIGINAL ARTICLE

Continuous Glucose Monitoring in 2012

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Introduction

THE EVIDENCE ON CONTINUOUS GLUCOSE MONITORING (CGM) expanded in several deficient areas in the last year. Two studies in the pediatric age group covering toddlers and preschool children demonstrated feasibility and safety of long-term CGM use in this particularly vulnerable population. However, both studies in young children, as well as a large survey of a pediatric database, demonstrated considerable difficulties associated with the routine use of CGM in youngsters, mostly related to poor compliance with the sensor use. Therefore, the first consensus guidelines for the pediatric age group considered various obstacles currently preventing successful use of CGM in all pediatric patients, but predominantly focused on proven benefits that compliant children and adolescents with type 1 diabetes obtain with regular use of CGM. More data supporting efficacious use of CGM in an adult population provided evidence for successful patient-led use of this technology, and confirmed long-term benefits in type 2 diabetes. CGM proved useful for evaluating glycemia during exercise and after pancreatic transplantation. Finally, the Endocrine Society guidelines on the use of CGM nicely summarized recent evidence and proposed current standards for routine use of CGM.

Feasibility of prolonged continuous glucose monitoring in toddlers with type 1 diabetes

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Pediatric Diabetes 2012; 13: 301–307

Aims

To evaluate the feasibility of sustained use of continuous glucose monitoring in children less than 4 years of age.

Methods

Patients with type 1 diabetes less than 4 years of age were enrolled in five participating centers. Baseline data were obtained during a run-in period with blinded continuous glucose monitoring (CGM). FreeStyle Navigator® (n=21) or Paradigm® (n=2) CGM device, blood glucose meters, and strips were provided at the beginning of the 6 months study period. Written instructions for routine daily use of CGM were given to the parents. Visits were scheduled at 1, 4, 8, 13, 19, and 26 weeks, with additional calls between them to adjust diabetes management. HbA1c level was determined at baseline and follow-up visits (except at the 1-week visit). Parents or guardians completed the CGM satisfaction scale questionnaire at the last visit. Insertion sites were carefully inspected and changes recorded at each visit. Hypoglycemia was considered severe if associated with age-specific signs or symptoms of neuroglycopenia recovering upon administration of glucose.

Results

The run-in period was successfully completed by 23 out of 29 participants (35% girls) with mean age of 3.0 ± 0.8 years (range 1.0–3.9); 2 (9%) being $1 \leq 2$ yr, 9 (39%) being $2 \leq 3$ years, and 12 (52%) being $3 \leq 4$ years. Median duration of diabetes was 0.7 year, 10 (43%) were using an insulin pump, and 13 were on multiple daily injections (MDI); mean ($\pm$ SD) HbA1c was $8.0 \pm 0.8\%$. Three dropped out during the study, 20 completed the entire 26 weeks with a median sensor use of 6.5 (25th, 75th percentile: 6.0, 7.0) days/week in the first 4 weeks and 4.7 (2.6, 6.6) days/week during 22–26 weeks. Mean HbA1c was $7.9 \pm 0.8\%$ at baseline and $8.0 \pm 0.8\%$ at 26 weeks. With an average item score of 4.1 on a 5-point Likert scale, parents reported very high satisfaction at the end of the study. Four severe instances of hypoglycemia were reported, all in a 3.5-year-old child, and only one of them while

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on CGM. No severe skin reactions were reported. Sixteen of the 23 children reported skin reactions at least once during the study: 8 (35%) moderate and 8 (35%) mild reactions. Eight of them reported skin reactions as a reason for reduced CGM use.

Conclusions

This study demonstrated that a CGM device can be safely and successfully worn by children with T1D younger than 4 years for a prolonged period of time with high parental satisfaction. Further evidence with more focus on metabolic control is needed.

Comment

Few clinical studies in diabetes enroll preschool children and even fewer toddlers as these age groups represent particularly vulnerable patient populations. Therefore, this pilot feasibility study is very important (1). Its focus was clearly on preventing hypoglycemia, as less than 2% of all CGM measurements were below 70 mg/dl. The fact that the HbA1c did not change therefore reflects the way parents were instructed to react on the CGM data. Only one child experienced severe hypoglycemia. Additionally, an average HbA1c of 8% without severe hypoglycemia or a significant percentage of glucose values below 70 mg/dl may represent a reasonable metabolic control for this age group. That said, an increasing amount of evidence indicates that chronic hyperglycemia clearly damages the developing brain, and better ways to achieve sustained normoglycemia in this age group are desperately needed. The use of CGM can reduce time spent in hypoglycemia in preadolescents and adolescents with T1D aged 10 to 18 years, with a concomitant improvement in metabolic control (2). However, it may take an artificial pancreas to fully accomplish this goal in the youngest patient group.

A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years

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Diabetes Care 2012; 35: 204–210

Aims

To evaluate the impact of continuous glucose monitoring (CGM) on metabolic control in prepubertal school children with type 1 diabetes (T1D).

Methods

Inclusion criteria were diabetes for at least 1 year, age 4 to <10 years, HbA1c $\geq 7\%$, and at least 3 injections of insulin per day. A blinded CGM was worn for 2 to 4 weeks during the run-in period. Only participants who wore the CGM successfully were eligible for randomization to either CGM or standard care. A Free Style Navigator CGM device or Medtronic MiniMed sensor-augmented insulin pump was provided, along with blood glucose meter and strips to the CGM group and only blood glucose meter and strips to the control group. All were instructed to measure blood glucose ≥ 4 times a day. Detailed written instructions were provided on the use of CGM and decision making based on continuous and blood glucose measurements. Visits were scheduled at 1, 4, 8, 13, 19, and 26 weeks for both groups, with one phone contact between visits. After visits at 13 and 26 weeks, a blinded CGM was used in the control group for a minimum of 96 hours. Questionnaires were completed before the study and at 26 weeks. The primary outcome was a decrease in HbA1c for $\geq 0.5\%$ with no severe hypoglycemia.

Results

A total of 146 participants (46% female) aged 4.0 to 9.9 (mean $\pm$ SD, 7.5 ± 1.7), with median diabetes duration of 3.5 years and 64% using insulin pumps, were randomized: 74 to the CGM group and 72 to the control group. Baseline HbA1c was $7.9\% \pm 0.8$ in both groups, with the same total insulin dose of 0.8 ± 0.2 units/kg. None of the metabolic parameters changed during the study and the primary endpoint at 26 weeks did not differ between the groups (19% in the CGM and 28% of participants in the control group, $p=0.17$). A slight decrease of $-0.1 \pm 0.6\%$ in HbA1c was observed in both groups. Glucose >250 mg/dl was observed in both groups for $>20\%$ of the day. Severe hypoglycemia occurred in three participants (total 3 events) in the CGM group and five participants (total 6 events) in the control group ($p=0.80$), with an incidence rate of 8.6 and 17.6 per 100 patient-years, respectively. Participants in both groups had glucose <60 mg/dl for $<1\%$ of the day at week 26. No ketoacidosis or severe skin reactions were reported. Only 41% of participants wore the sensor ≥ 6 days/week during the 6 months of the study; however, these participants had slightly greater decrease in HbA1c ($-0.3 \pm 0.7\%$ vs $0.0 \pm 0.5\%$, $p=0.01$). Parents generally reported high satisfaction with CGM at 26 weeks (mean score 3.9 out of 5-point Likert-type scale).

Conclusions

No metabolic benefit was demonstrated with a 6-month use of CGM in children with T1D aged 4 to <10 years. The incidence of severe hypoglycemia was low and comparable between the groups. High parental satisfaction was reported. Negative results may be related to persistent fear of hypoglycemia.

Comment

This study (3) is in general agreement with the landmark Juvenile Diabetes Research Foundation (JDRF) study where children and adolescents did not benefit from the use of CGM (4). The frequency of sensor use at the end of

the study was also comparable between the two trials. However, several trials conducted in Europe or Australia demonstrated significant benefit of CGM on metabolic control also in children and/or adolescents with T1D, including the first RCT with CGM, where a post-hoc insulin tolerance test (ITT) analysis of 27 adolescents in the CGM group and 27 in the control group demonstrated a statistically significant difference in the reduction of HbA1c levels after 3 months ($-0.72 \pm 1.13\%$ vs $-0.05 \pm 0.78\%$, adjusted $p=0.0447$) (5). Importantly, per protocol analysis of the pediatric age groups in the JDRF trial (6), as well as in the present trial, including only patients with the sensor use of ≥ 6 days/week demonstrated a significant decrease in HbA1c in pediatric population, comparable to the decrease in HbA1c calculated in the recent meta-analysis (7). It therefore seems that appropriate age-group-specific strategies, as well as better sensing devices, are needed to overcome significant psychosocial barriers in the pediatric age group.

Continuous glucose monitoring in children, adolescents, and adults with type 1 diabetes mellitus: analysis from the prospective DPV diabetes documentation and quality management system from Germany and Austria

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Pediatric Diabetes 2012; 13: 12–14

Aims

To determine the frequency, duration, and impact of continuous glucose monitoring (CGM) on glycemic control and rate of hypoglycemia in children and young adults in Germany and Austria.

Methods

A total of 144,385 sensor days from 2,874 patients (1,395 were younger than 18 years), using CGM between January 2008 and September 2010, were analyzed from 59,920 patients registered in the DPV (Diabetessoftware zur prospektiven Verlaufsdokumentation) database. Three groups—no CGM, CGM for less than 30 days, and CGM use for more than 30 days—were analyzed using multivariable linear regression analysis.

Results

In the analyzed cohort, 56% were on multiple daily injections (MDI) with four to eight injections per day, 8% had

three, and 1% had two injections per day, while 44% used an insulin pump. In addition, 77% of children below the age of 6 years used an insulin pump. CGM was used in 2.3% of pediatric and 4.8% of all patients, in 67.7% for less than 30 days, 13.0% for 30–60 days, and only in 19.3% for > 60 days. HbA1c improved significantly during the observation period in pediatric patients ≤ 18 years ($p < 0.031$). HbA1c was significantly higher in older children ($p < 0.014$), being $7.38 \pm 0.95\%$ ≤ 6 years of age, 7.66 ± 1.09 in 6 to ≤ 12 years of age, and 8.32 ± 1.63 in adolescents. HbA1c was significantly higher in children on MDI using long-acting insulin analogs ($p < 0.0001$) and in children with a higher insulin dose ($p < 0.0001$). In adults, a lower HbA1c was associated with CGM use ($p < 0.036$), younger age ($p < 0.0001$), and shorter duration of diabetes ($p < 0.0184$). More than 30 days of CGM use was associated with a significantly better HbA1c as compared to CGM use for < 30 days or no CGM ($p < 0.002$). Pediatric and adult patients using CGM for < 30 days had significantly more hypoglycemia ($p < 0.0011$) as compared with those without CGM, whereas prolonged CGM use for > 30 days was not significantly different in the rate of hypoglycemia as compared to less frequent or no use of CGM.

Conclusions

The use of CGM is limited to less than 5% of young patients with T1D in Germany and Austria. CGM use is associated with a significant decrease in HbA1c in adults but not in children. The rate of hypoglycemia was not reduced in any age group.

Comment

This large observational study from one of the largest T1D registries demonstrates a beneficial effect of CGM use in young adults (8), in line with most published randomized controlled trials, observational studies, and meta-analyses. An increase in hypoglycemia associated with short but not long-term CGM use may be due to the CGM selection criteria, which includes high incidence of severe hypoglycemia. The use of CGM in pediatric population was limited to only 2.3% with mostly short-term use and may not represent its entire potential; however, no impact on metabolic control corroborates data from several pediatric RCTs and emphasizes the need for age-specific strategies for the use of CGM in younger age-groups. Large prospective studies are necessary to further investigate strategies for optimal use of CGM in pediatric population.

Sensor augmented pump therapy from onset of type 1 diabetes: late follow-up results of the Pediatric Onset Study

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Pediatric Diabetes 2012; 13: 515–18

Aims

This follow-up study reports data on metabolic control and beta-cell (β -cell) function one year after the completion of the ONSET trial.

Methods

One-hundred and thirty-one participants (49.6% boys, age at onset 8.9 ± 4.3 years) of the original 154 patients were re-evaluated 24 months after the diagnosis of type 1 diabetes. Sixty-two of them were using a sensor-augmented insulin pump (SAP) (Paradigm REALTime, Medtronic MiniMed Inc.) therapy in the treatment group and 67 insulin pump therapy (MiniMed Paradigm® 515/715, Medtronic MiniMed Inc) with conventional self-monitoring of blood glucose in the control group. As predefined in the study protocol, a voluntary follow-up visit at 24 months after diabetes onset was offered to all study patients with measurement of HbA1c, blood glucose, and C-peptide levels at fasting conditions, measured in a central laboratory.

Results

All data from the second year were available for 124 of the 131 participants. The SAP was used by 58 participants from the primary group and 7 from the control group (total 65 participants, 52.4%), and 57 participants from the control group continued with insulin pump therapy (46.0%). Two participants from the control group used multiple daily injections (1.6%). HbA1c was similar in the 62 participants from the primary SAP group ($7.6 \pm 1.3\%$) as compared to the 69 participants from the control group ($7.7 \pm 1.2\%$, $p=0.493$). HbA1c below 7.5% was observed in 48.8% of participants with no significant difference ($p=0.436$) between the SAP and the control group (52.5% vs. 45.6%). Fasting C-peptide at 24 months was not significantly different between the primary SAP and the control group (0.13 ± 0.17 vs. 0.09 ± 0.10 nmol/L; $p=0.121$). Participants who used ≥ 1 sensor per week during the first year had smaller C-peptide reduction at 24 months compared to participants with irregular or no sensor use (0.02 ± 0.18 nmol/L vs. 0.07 ± 0.11 nmol/L, $p=0.046$; C-peptide values: 0.14 ± 0.17 nmol/L vs. 0.09 ± 0.13 nmol/L). Relative C-peptide loss remained significantly lower during the second year (30.0% vs. 41.3%, $p=0.005$). The frequency of sensor use was significantly ($p=0.033$) associated with the relative C-peptide change over 24 months in multiple linear regression analysis. There was no difference in the insulin requirement.

Conclusion

Frequent sensor use in SAP therapy during the first year of diabetes was associated with a smaller loss of C-peptide at 24 months of the disease.

Comment

This study demonstrates a small but significant and sustained preservation of β -cell function associated with the frequent use of continuous glucose monitoring from the disease onset (9). The overall decrease of C-peptide was lower than reported in a recent analysis of 4,411 pediatric patients (10), possibly related to the relatively good metabolic control for this age group. Longitudinal follow-up from the Diabetes Control and Complications Trial demonstrated an association between higher C-peptide at the study entry and less microvascular complications, as well as less severe hypoglycemia with the preservation of C-peptide secretion. The result of the present study therefore has potentially important implications. A larger trial specifically designed to study this important question, including glucose variability and patients using multiple daily injections, is warranted.

Use of continuous glucose monitoring in the pediatric age group: Consensus statement from the European Society for Pediatric Endocrinology, the Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes

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Pediatr Diabetes 2012; 13: 215–28

Aims

To present a consensus statement on the use of continuous glucose monitoring (CGM) in pediatric age groups.

Methods

Clinical experts reviewed the literature and provided evidence-based recommendations according to the American Diabetes Association (ADA) criteria. Important papers identified for each topic were assigned a level of evidence and verified by the entire expert panel. Evaluated topics included types of sensors, accuracy and reliability, current practice, efficacy and safety, patient selection, quality of life, cost-effectiveness, and future possibilities.

Results

Seventy-nine reports were evaluated and rated. Evidence-based recommendations were provided where high level of

evidence existed. Expert-opinion consensus recommendations were provided for areas still lacking evidence of acceptable quality.

Recommendations on efficacy are as follows

- 1 Real-time (RT)-CGM can be used effectively for lowering HbA1c (grade A and B evidence), reaching target HbA1c, and reducing the mean absolute glycemic excursion (MAGE) in the pediatric population with T1D without increasing the frequency of severe hypoglycemia.
- 2 RT-CGM can be used effectively for reducing severe hypoglycemia (grade A evidence) and shortening the time spent in hypoglycemia (grade A evidence) in the pediatric population with T1D.
- 3 The effectiveness of RT-CGM in the pediatric population with T1D is significantly related to the amount of sensor use (grade A and B evidence). Therefore, efforts for increased adherence with sensor use are paramount in this age group (expert opinion).
- 4 SAP is an effective means to treat youth of all ages at the onset of the disease (grade A evidence).
- 5 SAP treatment is effective in lowering HbA1c levels in children and adolescents with T1D who have elevated HbA1c values on MDI therapy using standard blood glucose monitoring (grade A evidence).
- 6 Intermittent, retrospective, or real-time CGM may be of use in children and adolescents with T1D to detect the dawn phenomenon, post-prandial hyperglycemia, asymptomatic and nocturnal hypoglycemia, and in evaluating the effects of major changes in treatment regimens (grade B evidence).
- 7 The development of more pediatric-oriented devices for RT-CGM is warranted, along with additional well-designed RCTs in the whole pediatric age-group spectrum (expert opinion).

Conclusions

Solid evidence demonstrates that benefits on metabolic control require near-continuous use of CGM. Education related to the use of CGM and age-specific implementation approach may be important to optimize clinical benefit. Realistic expectations and effective strategies to overcome the difficulties in using current CGM devices may contribute to the overall success. Finally, improved CGM devices with better sensors and more automated decision support with the ultimate goal of an artificial pancreas are desirable.

Comment

This presents expert guidelines (5) that are important in the view of a relative paucity of high-quality evidence from RCTs in pediatric population. Recent studies with limited patient population may not provide the whole spectrum of relevant data, especially in relation to the relatively poor long-term compliance in this age group. Larger RCTs with a special focus on appropriate age-specific treatment implementation and sustained adherence to near-continuous use of CGM may provide better information on the clinical efficacy of CGM in pediatric age group.

Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: the in-clinic ASPIRE study

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Diabetes Technol Ther 2012; **14**: 205–209

Aims

To evaluate the efficacy of automatic suspension of insulin delivery during induced hypoglycemia among subjects with type 1 diabetes on insulin-pump therapy.

Methods

An in-clinic, randomized crossover study of 50 type 1 DM subjects on insulin-pump therapy were sequentially assigned to either a sensor-augmented insulin pump with or without a low glucose suspend (LGS) feature turned on or off. When the LGS is turned on, all insulin delivery is automatically suspended for 2 hours following a sensor glucose (SG) value ≤ 70 mg/dL. Subjects fasted overnight and exercised until their plasma glucose, measured by yellow springs instrument (YSI), reached a value ≤ 85 mg/dL, with a washout period lasting 3 to 10 days between sessions. Sessions were done with the LGS feature turned on (LGS-On) or with continued insulin delivery regardless of the SG value (LGS-Off). The patients were randomly assigned to LGS-On or LGS-Off sessions. YSI glucose data were used to compare the duration and severity of hypoglycemia from successful LGS-On or LGS-Off sessions as well as the risk of rebound hyperglycemia after insulin delivery suspension. If any YSI glucose went < 50 mg/dL or > 300 mg/dL, the session was terminated and the subject had to repeat the study on another day.

Results

Fifty subjects attempted 134 sessions, 98 of which were successful. The mean $\pm$ SD hypoglycemia duration was less during LGS-On than during LGS-Off, being 138.5 ± 76.78 vs. 170.7 ± 75.91 min., $p = 0.006$. During LGS-On, compared to LGS-Off sessions, the mean end-observation YSI glucose was higher (91.4 ± 41.84 vs. 66.2 ± 13.48 mg/dL, $p < 0.001$). Most (53.2%) end-observation YSI glucose levels in LGS-On sessions were in the 70–180 mg/dL range, and none were > 250 mg/dL. Correlation between the SG and YSI values in the 40–70 mg/dL range was good with the mean and median absolute difference being 12 ± 8.6 mg/dL and 11.2 mg/dL, respectively.

Conclusion

Automatic suspension of insulin delivery in subjects using sensor-augmented pump therapy significantly reduced the duration and severity of induced hypoglycemia, without causing rebound hyperglycemia.

Comment

The ultimate goal of effective diabetes management is the prevention of hypoglycemia, with strategies that try to reduce both the duration and severity of hypoglycemia. This study provides evidence that an LGS feature, when programmed to suspend insulin delivery for two hours if any SG value of ≤ 70 mg/dL is detected, is beneficial in reducing the duration and severity of hypoglycemia without causing significant rebound hypoglycemia (11). This proof of concept study is extremely important in the first step of the artificial pancreas to prevent severe hypoglycemia.

This study involved a rigorous protocol, with a narrowly defined target of hypoglycemia being 50–70 mg/dL, which may limit the application of this study in real-life patients who may choose to suspend insulin delivery at different thresholds. In addition, subjects were discontinued from the session if any YSI glucose fell below 50 mg/dL during the experimental protocol. Of the 134 sessions, 29 had to be discontinued from significant hypoglycemia (defined as < 50 mg/dL) during the run-in phase. Analysis of this group of subjects with the LGS feature turned on would have been beneficial but the session was terminated per protocol.

Assessment of patient-led or physician-driven continuous glucose monitoring in patients with poorly controlled type 1 diabetes using basal-bolus insulin regimen (a 1-year multi-center study)

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Diabetes Care 2012; 35: 965–971

Aims

To compare the effect of two modes of use of CGM, patient-led or physician-driven vs. a control group with SMBG alone, for one year in subjects with poorly controlled type 1 diabetes.

Methods

Patients with type 1 diabetes aged 8–60 years with A1c $\geq 8\%$ were randomly assigned equally to three groups: Group 1, patient-led CGM; Group 2, physician-driven CGM; and Group 3, control group with conventional SMBG. Outcomes for glucose control were assessed at one year for each mode of intervention. Entry criteria to enroll in this study were that each patient had to wear CGM for a 10-day test period to confirm their ability and willingness to use CGM. In Group 1 (patient-led), use of CGM was managed entirely by patients themselves. In Group 2, use of CGM was prescribed by the patient's physician, who asked the patient to use the sensors intermittently, according to guidelines based on glucose outcomes. Two-week sensor use per month during the first 3 months, thereafter continuing either in the same manner or with more intensive use during the following 3 months, if at any visit the patient presented one of the following criteria: A1c $> 7.5\%$, > 4 mild hypoglycemic episodes per week, or at least one severe hypoglycemic episode. Thus, use of sensors could be gradually increased every 3 months to 20, 25, or even 30 days per month.

Results

Screening of 257 subjects with type 1 diabetes was carried out, with 197 randomized and 178 patients completing the study; mean age 36 ± 14 years, A1c $8.9\% \pm 0.9\%$. A1c improved equally in both CGM groups and was reduced compared to the control group. Group 1 vs. Group 3: -0.52% , $p=0.0006$; Group 2 vs. Group 3: -0.47% , $p=0.0008$; Group 1 & 2 vs. Group 3: -0.50% , $p<0.0001$. The incidence of hypoglycemia was similar in the three groups. Physical health score, based on SF-36 questionnaire, improved in both experimental CGM groups ($p=0.004$). Sensor consumption was 34% lower in the physician-led group than in the patient-led group (median consumption: Group 1, 3.42 per month (2.2–3.91) vs Group 2, 2.25 per month (1.27–2.99), $p=0.001$).

Conclusion

Patient-led and physician-driven CGM provides similar long-term improvement in glucose control in patients with poorly controlled, type 1 diabetes, defined as an HbA1c $\geq 8.0\%$ entering this study. The physician-driven CGM mode used fewer sensors with no significant difference in HbA1c at the end of the trial, compared to the patient-led CGM group.

Comment

CGM again has been shown to improve long-term glycemic control compared to standard SMBG in type 1 patients who are sub-optimally controlled based on an A1c of $\geq 8.0\%$ entering this trial (12). The CGM group was divided into a physician-led CGM recommendation vs. a patient-led regarding frequency of use. Both of these groups had equal reduction in HbA1c with compliance in the physician-driven group adhering slightly greater with 65% vs. 57% of the prescribed times in the physician-driven group vs. patient-driven group. It was determined that CGM requirements varied widely from one patient to another in order to achieve the goal, with half the patients in the physician-driven group requiring 15–20 days a month, with the remainder needing CGM for 25–30 days a month at the end of the study. Observations suggest that the initial prescription, CGM 15 days a month followed by incremental use if needed, may be more agreeable and cost effective under this physician-driven group plan.

This study underscored the value of a test period during which patients are invited to use sensors, before starting long-term CGM, to evaluate their technical skills and their motivation to use CGM. Patients unwilling to use the CGM device on a long-term basis, after a 10-day test period in the study, were younger, less compliant with SMBG, and probably less likely to use CGM than those finally included in this study. Thus, a test period may be useful to ensure selection of patients motivated to use CGM.

Other findings included that CGM is more effective in patients treated with CSII. In summary, the physician-driven group achieved equal glycemic control with 35% fewer sensors used during this one-year trial.

Effects of performing resistance exercise before versus after aerobic exercise on glycemia in type 1 diabetes

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Aims

To determine the effects of exercise order on acute glycemic responses in individuals with type 1 diabetes performing both aerobic and resistance exercise in the same session.

Methods

Twelve physically active individuals with type 1 diabetes (A1c $7.1\% \pm 1\%$) performed aerobic exercise (45 min of running at 60% Vo_{2peak}) before 45 min of resistance training (AR; three sets of eight using seven different exercises) or performed resistance exercise before aerobic exercise (RA). Plasma glucose was measured during exercise and for 60 min after exercise. Interstitial glucose was measured by CGM, 24 hours before, during, and 24 hours after exercise.

Results

Significant declines in blood glucose were seen in aerobic exercise (AR) but not in resistant exercise (RA) throughout the first exercise modality, resulting in higher glucose levels in RA (AR = 5.5 ± 0.7 vs. RA = 9.2 ± 1.2 mmol/L, $p = 0.006$ after 45 min of exercise). Glucose subsequently decreased in resistance exercise and increased in aerobic exercise over the course of the second 45-min exercise bout, resulting in levels that were not significantly different by the end of exercise (AR = 7.5 ± 0.8 , RA = 6.9 ± 1.0 mmol/L, $p = 0.46$). The duration (105 vs. 48 min) and severity (area under the curve 112 vs. 69 units-min) of hypoglycemia were not significantly greater after AR compared to RA.

Conclusion

Performing resistance exercise before aerobic exercise improves glycemic stability throughout the exercise and reduces the duration and severity of postexercise hypoglycemia for individuals with type 1 diabetes.

Comment

Hypoglycemia post exercise is very common in patients with type 1 diabetes. This study clearly illustrates that resistance exercise does not result in increased hypoglycemia either by itself or if performed before aerobic exercise in patients with type 1 diabetes (13). Use of CGM in this study was done to confirm this finding. Furthermore, beneficial effects from this sequence of resistance exercise first before aerobic exercise confirmed no significant hypoglycemia in the subsequent 12-hour glycemic trends post exercise. It is hypothesized that resistance exercise causes glucose levels to increase during exercise, producing postexercise hyperglycemia, if exercise is sustained for 12 or more minutes. It is postulated that the mode of action is catecholamine release being four times greater during moderate intensity resistant exercise than has been shown in individuals without diabetes; however, this was not studied in this population. Other release of hormones, including growth hormone and lactate,

may also explain these results. This study is limited by its small size of only 12 participants but does provide guidelines to individuals with type 1 diabetes who are having problems with hypoglycemia during routine exercise times.

In summary, the findings suggest that trained individuals with type 1 diabetes who performed both resistance and moderate aerobic exercise should consider performing resistance exercise first, if they tend to develop exercise-associated hypoglycemia either during or after their exercise period.

Short- and long-term effects of real-time continuous glucose monitoring on patients with type 2 diabetes

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Aim

To determine whether short-time, real-time continuous glucose monitoring has long-term glycemic effects in patients with type 2 diabetes who are not on prandial insulin.

Methods

One hundred adults with type 2 diabetes who were not on prandial insulin were randomized into two groups; an experimental group used 12 weeks of intermittent, real-time CGM (RT-CGM) followed by 40 weeks of SMBG vs. a control group prescribed SMBG four times a day for the entire 52-week period. The experimental group was told to wear a CGM for a two-week period with a one-week period off for the first 12 weeks for a total of 8 weeks of CGM use. They were given no instruction on how to interpret the results and what to do with these results. All subjects received diabetes care from their regular provider without any therapeutic intervention from the study team. Patients eligible for this study were aged ≥ 18 years, diagnosed with type 2 diabetes for at least 3 months, had an initial A1c $\geq 7.0\%$ but $\leq 12.0\%$, and were treated with diet and exercise alone or other glucose-lowering therapies except prandial insulin.

Results

There was a significant difference in A1c at the end of the three-month active intervention, which was sustained during follow-up. The mean A1c decreased by 1.0, 1.2, 0.8, and 0.8% in the RT-CGM group vs. 0.5, 0.5, 0.5, and 0.2% in the SMBG group at 12, 24, 38, and 52 weeks respectively ($p=0.04$). There was a significantly greater decline in A1c over the course of the study for the RT-CGM group than for the SMBG group after adjusting for covariates ($p<0.0001$). Subjects who used RT-CGM protocol (greater than 48 days) improved the most ($p<0.0001$). The improvement in the RT-CGM group oc-

curred without a greater intensification of medication compared with those in the SMBG group.

Conclusion

Subjects with type 2 diabetes not on prandial insulin who used RT-CGM intermittently for 12 weeks significantly improved glycemic control at 12 weeks and sustained the improvement in A1c without RT-CGM during the 40-week follow-up period compared to those who used only SMBG.

Comment

This study confirms that type 2 patients not on prandial insulin, who have suboptimal control of diabetes, are able to view CGM tracings and make changes either in their lifestyle or to adherence of medications that result in significantly greater A1c reduction than SMBG alone (14). The use of CGM was done specifically in patients not on prandial insulin and was done only for a maximum of 8 out of the first 12 weeks of the study, and the reduction in A1c was sustained at one year. Clearly, greater use of CGM in the experimental group resulted in a greater drop in A1c, both at 12 weeks and one year. There was no significant change in medication intervention at the end of the study in either of the two groups. The type of changes made by these patients is not known, but most likely involves changes in their lifestyle, dietary consumption of food, and possible adherence to medication.

Hypoglycemia assessed by continuous glucose monitoring is associated with preclinical atherosclerosis in individuals with impaired glucose tolerance

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Aim

To evaluate measured episodes of hypoglycemia during CGM and its relationship with early manifestation of vascular atherosclerosis in glucose-tolerant and intolerant individuals (IGT).

Methods

An oral glucose tolerance test was performed in 79 nondiabetic subjects with each individual undergoing CGM for 72 hours. Cardiovascular risk factors and ultrasound measurement of carotid intima media-thickness (IMT) were evaluated.

Results

Individuals had a worse cardiovascular risk profile, including higher IMT, and greater time significantly spent in hypoglycemia than glucose-tolerant individuals. In univariate analysis adjusted for gender, minutes spent in hypoglycemia significantly correlated with age ($R=0.26$; $p=0.01$), waist circumference ($R=0.33$; $p=0.003$), 2-h glucose ($R=0.58$;

$p < 0.0001$), and 2-h insulin ($R = 0.27$; $p = 0.02$). In a stepwise multivariate regression analysis, the variable significantly associated with IMT was minutes spent in hypoglycemia ($R^2 = 0.252$; $p < 0.001$) and ISI Index ($R^2 = 0.89$; $p = 0.004$), accounting for 34.1% of the variation.

Conclusion

Episodes of hypoglycemia may be considered as a new potential cardiovascular risk factor for glucose-intolerant individuals (IGT).

Comment

This is the first study evaluating the association between episodes of hypoglycemia assessed by CGM under real-life conditions and preclinical atherosclerosis in nondiabetic subjects with different degrees of glucose tolerance (15). The findings suggest that IGT individuals have asymptomatic episodes of hypoglycemia and spend more than two hours per day below hypoglycemic threshold of less than 70 mg/dL. These hypoglycemic episodes were significantly correlated with 2-h, post-load plasma glucose and insulin levels, thus raising the possibility that hypoglycemia occurs during the late post-prandial period as a consequence of a prolonged release of insulin in response to elevated glucose. In this study, the number of asymptomatic episodes of hypoglycemia could be considered a new potential cardiovascular risk factor for IGT individuals. However, it is not known whether these episodes of hypoglycemia are part of normal variability in IGT individuals or whether such episodes affect the risk of progression to overt cardiovascular disease.

Continuous glucose monitoring: an endocrine society clinical practice guideline

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Aim

To formulate practice guidelines for determining settings in which patients are most likely to benefit from the use of continuous glucose monitoring (CGM).

Methods

These evidence-based guidelines were developed using the grading of recommendations, assessment, development, and evaluation (GRADE system) to describe both the strength of recommendations and quality of evidence. This task force of experts had one group meeting, several conference calls, and e-mail communications to develop this consensus. Committees

and members of the Endocrine Society, the Diabetes Technology Society, and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines.

Summary of Recommendations

- 1 *Real-time continuous glucose monitoring (RT-CGM) in adult hospital settings*
 - 1.1 They recommend against the use of RT-CGM alone for glucose management in the hospital setting until further studies provide sufficient evidence for its accuracy or safety in those settings. (Recommended with very low quality of evidence.)
- 2 *RT-CGM in children and adolescent outpatients*
 - 2.1 They recommend that RT-CGM, with currently approved devices, be used in children and adolescents with type 1 diabetes (T1DM) who have achieved A1c levels $< 7.0\%$, because it will assist in maintaining target A1c levels while limiting the risk of hypoglycemia. (Recommended with high quality of evidence.)
 - 2.2 They recommend RT-CGM devices be used in children and adolescents with T1DM, who have an A1c level $\geq 7.0\%$ and are able to use these devices on a near-daily basis. (Recommended with moderate quality of evidence.)
 - 2.3 They make no recommendation for or against the use of RT-CGM by children with T1DM less than eight years of age.
 - 2.4 They suggest treatment guidelines be provided to patients to allow them to safely and effectively take advantage of the information provided to them by RT-CGM. (Weak recommendation with very low quality of evidence.)
 - 2.5 They suggest intermittent use of CGM systems designed for short-term, retrospective analysis in pediatric patients with diabetes for evaluation of nocturnal hypoglycemia, dawn phenomenon, post-prandial hyperglycemia, and in patients with hypoglycemic unawareness or in patients making changes to their insulin regimen. (Weak recommendation with very low quality of evidence.)
- 3 *Real-time RT-CGM in adult population*
 - 3.1 They recommend that RT-CGM devices be used by adult patients with T1DM who have A1c levels of at least 7% and who have demonstrated they can use these devices on a near-daily basis. (Recommended with very high quality of evidence.)
 - 3.2 They recommend that RT-CGM device be used in adult patients with T1DM who have A1c levels $> 7\%$ and who have demonstrated they can use these devices on a near-daily basis. (Recommended with very high quality of evidence.)
 - 3.3 They suggest that intermittent use of CGM systems, designed for short-term retrospective analysis, may be of benefit in adult patients with diabetes to detect nocturnal hypoglycemia, the dawn phenomenon, or post-prandial hyperglycemia, and to assist in the management of hypoglycemic unawareness and when significant changes are made to their diabetes regimen, such as instituting new insulins or switching from MDI to pump therapy. (Weak recommendation with very low quality of evidence.)

TABLE 1. DIFFERENCES IN HbA1c FROM FIVE RECENT META-ANALYSES COMPARING CGM VERSUS SMBG

Reference	Overall	T1D	T2D	CGM alone	SAP
Pickup ⁷	-0.30	-0.30	—	—	—
Gandhi ¹⁷	-0.27	-0.50 ^a	-0.70 ^a	—	—
Szyposwka ¹⁸	-0.25	—	—	—	-0.26
Langendam ¹⁹	—	—	—	-0.2	-0.7
Yeh ²⁰	-0.26	—	—	—	-0.68

All values represent mean difference; the unit is in percentage.

^aResult includes adults only.

T1D, type 1 diabetes; T2D, type 2 diabetes; CGM, continuous glucose monitoring; SAP, sensor-augmented pump.

Comment

This task force used the GRADE system to make recommendations for the use of RT-CGM in hospital patients, pediatric outpatients, and adult outpatients (16). Their level of evidence is based on randomized control trials, confirming whether their recommendation is justified based on outcome studies. They graded these recommendations accordingly, based on consensus recommendation versus a weak recommendation with the quality of the evidence in the literature to validate these recommendations. They analyzed all the major research studies published through 2011 to make the above recommendations. It is worthy to note that there were no recommendations considered for patients with type 2 diabetes.

Conclusion

Increasing amount of data prompted four new meta-analyses comparing the use of CGM with SMBG (17–20). Despite very different approaches comparing separately different age groups, type of diabetes, CGM versus SMBG, sensor-augmented pump (SAP) versus MDI with SMBG, or SAP versus CSII with SMBG, overall difference in HbA1c stayed firmly around -0.3% (Table 1), demonstrating a significant benefit to CGM.

Reduction in HbA1c with CGM was bigger in patients with poor control, when used more often and when used by adults. There was no difference in the rate of severe hypoglycemia; some analyses indicated a lower exposure to overall hypoglycemia, however, the data on hypoglycemia was limited.

CGM as a treatment modality is slowly reaching maturity. The overall clinical benefit is likely still below its full potential as several technical, behavioral, and psychosocial barriers impede its routine use. Improvement in the technologies of CGM, along with increasing experience of its use in different patients' groups, will possibly further increase its impact on metabolic control.

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tronic, Novo Nordisk, GluSense, and Diamyd. He has received honoraria for participating on the speaker's bureaux of Eli Lilly, Novo Nordisk, Bayer, and Medtronic, and consulting fees as a member of scientific advisory boards from Bayer, LifeScan, Eli Lilly, Sanofi-Aventis, and Medtronic.

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