ORIGINAL ARTICLE

Continuous Glucose Monitoring in 2014

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Introduction

CONTINUOUS GLUCOSE MONITORING (CGM) was used in 9% of 17,317 participants (6% of children <13 years old, 4% of adolescents 13 to <18 years, 6% of young adults 18 to <26 years, and 21% of adults ≥26 years) who replied to a CGM device use questionnaire 1 year after enrollment in the T1D Exchange clinic registry (1). This is the highest penetration in a large patient population reported so far, demonstrating the increased use of real-time CGM in an advanced medical environment. Moreover, CGM use was associated with lower HbA1c in children (8.3% vs. 8.6%, $p < 0.001$) and adults (7.7% vs. 7.9%, $p < 0.001$), but also with a more affluent social status (1). Interestingly, only a quarter of self-reported CGM users downloaded data from their device at least once per month (1), indicating that the general CGM use largely remains intuitive. Regular CGM device downloading is associated with a considerable improvement in metabolic control (2) and may be one of the important determinants of sustained and efficient routine CGM use in T1D, also for prevention of severe hypoglycemia. However, many controversies remain in the population of non-insulin-treated patients with T2D, where a well-designed clinical trial investigating the use of CGM is yet to arrive.

The present review focuses on the most recent articles describing factors that improve glycemic outcomes in persons using CGM as well as how CGM is being utilized to understand the progression of normal glucose tolerance to impaired glucose tolerance and to overt type 2 and type 1 diabetes in certain high-risk populations.

The effects of lowering nighttime and breakfast glucose levels with sensor-augmented pump therapy on hemoglobin A1c levels in type 1 diabetes

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This manuscript is also discussed in article on Diabetes Technology and Therapy in the Pediatric Age Group, p. S-99.

Aims

To evaluate the association of longitudinal data from day- and nighttime glucose control evaluated by CGM, with HbA1c.

Methods

Data from the STAR 3 study (3) were used. Briefly, patients with T1D who were 7–70 years old and not using an insulin pump were randomized to either multiple daily injections (MDI) with self monitoring of blood glucose (SMBG) or insulin pump with CGM (a sensor-augmented pump, SAP). The 196 patients (out of 244 randomized to use SAP) were included in the analysis based on having a minimum of 80% of CGM data available for at least 3 days at baseline and at 1 year. Time periods were daytime (6 a.m. till midnight) and overnight (midnight till 6 a.m.). Additionally, mean glucose values for each meal were calculated. Univariate linear regression and multivariable linear regression analyses were used to evaluate contributions from glucose levels at different times of the day to change in HbA1c.

Results

Improved both daytime and overnight CGM-glucose levels resulted in greatest improvement in HbA1c (–1.34% to 0.76%). With mean CGM-glucose levels improvement only overnight (no daytime improvement), the reduction in HbA1c was similar to the reduction for subjects who did not show a significant improvement at either time of day. Daytime-only improvement was associated with improvement of all three meal periods. Overnight-only CGM-glucose improvement resulted in significant improvement ($p < 0.01$) in the breakfast meal period. The decline in breakfast meal period CGM-glucose at 1 year was 26–22 mg/dL for those with overnight-only improvement, 9–32 mg/dL for those with no improvement overnight or during daytime, 41–20 mg/dL for those with daytime-only improvement, and 61–36 mg/dL for those with

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a combined daytime and overnight improvement. Mealtime CGM-glucose improvement resulted in a calculated reduction in HbA1c at breakfast (−0.68%), lunch (−0.66%), and dinner (−0.56%) (all $p < 0.0001$). Only the breakfast mealtime period improvement had a significant independent association with the 1-year HbA1c value (−0.46%, $p < 0.0001$), explaining 59% of the HbA1c improvement as demonstrated by the partial R^2 , when a multivariable linear regression model including changes in all three meal periods and overnight-only glucose improvement was used.

Conclusions

Improving breakfast meal period CGM-glucose levels had the greatest independent effect on lowering HbA1c levels in patients with type 1 diabetes. Improved overnight control had a protracted effect associated with lower CGM-glucose levels during the breakfast period.

Comment

Achieving continuous near-normoglycemia in patients with T1D is a desirable goal often difficult to achieve. Therefore, specific strategies focusing in the most critical periods of the day may bring faster benefit to a considerable proportion of patients. The present *post-hoc* data analysis from the STAR 3 study provides this important information: improving the overnight control is associated with better glucose control during the breakfast period, which in turn contributes for more than a half of HbA1c improvement (4). Interestingly, similar observation is described in overnight closed-loop insulin delivery studies, where better overnight glucose control on closed-loop insulin delivery resulted in lower daytime mean glucose (5). Focusing on overnight glucose control using an artificial pancreas also reduces hypoglycemia, representing the major obstacle in classical therapy strategies. As the overnight glucose control with an artificial pancreas represents an achievable goal (6,7), this may designate the shortest way to its use in routine clinical practice.

Quantitative estimation of insulin sensitivity in type 1 diabetic subjects wearing a sensor-augmented insulin pump

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Diabetes Care 2014; 37: 1216–23

Aims

Measures of insulin sensitivity are based on hyperinsulinemic–euglycemic clamp, intravenous glucose tolerance test, and oral glucose tolerance tests. All require the measurement of both plasma glucose and insulin concentrations and therefore cannot be used outside institutions. This study aimed at developing and validating a method to estimate insulin sensitivity from CGM sensor and insulin pump data.

Methods

Twelve subjects with T1D (5 females, aged 39.5 ± 14.2 years, BMI 25.7 ± 3.8 kg/m², HbA1c $\leq 8.5\%$ or 69 mmol/mol) were studied for 3 days in a clinical research center (CRC). A triple-tracer mixed-meal study protocol was performed once per day during breakfast, lunch, or dinner with blood samples collected at −180, −30, 0, 5, 10, 20, 30, 60, 90, 120, 150, 180, 240, 300, and 360 ($t=0$ corresponding to meal time), for measurement of plasma glucose and insulin concentrations in order to estimate insulin sensitivity with the oral minimal model. All subjects used an insulin pump and CGM. A mathematical model was developed to estimate insulin sensitivity from insulin delivery and CGM-glucose data, and a comparison between the oral minimal model estimation and the estimation based on insulin delivery and CGM-glucose data was performed.

Results

The correlation between the two measures of insulin sensitivity was very good ($r=0.825$; $p < 10^{-8}$). Insulin sensitivity based on insulin delivery and CGM-glucose data was consistently higher than the one estimated based on oral minimal model (13.86 ± 14.56 vs. 6.67 ± 5.63 dL/kg/min per $\mu\text{U/mL}$; $p < 10^{-3}$) with comparable diurnal variability.

Conclusions

The insulin sensitivity measure derived from CGM and insulin pump data was comparable to the one obtained by oral minimal model. Thus, using retrospective subcutaneous sensor and insulin delivery data with some anthropometric parameters for each subject provided, by an integral formula, the patient's insulin sensitivity for each meal. This can be used for precise adjustments of insulin-to-carbohydrate ratios in routine diabetes management and notably in closed-loop insulin delivery protocols.

Comment

Variations of insulin sensitivity during the day, with activity, stress, disease, and other factors, have long been a substantial challenge in routine management of T1D. Only the combination of an insulin pump with CGM provides retrospective data obtainable during regular life and sufficient for relatively precise estimation of current insulin sensitivity. The above study (8) validated a mathematical model for such minute-to-minute calculation of insulin sensitivity in individual patients with real-time CGM and insulin infusion data. The potential use of current individual insulin sensitivity is wide: from professional medical office-based therapy advisory systems, through hand-held patients' advisor utilities, likely integrated into an insulin pump or CGM device, to closed-loop insulin delivery systems. Indeed, every closed-loop system used in clinical studies is estimating insulin sensitivity with a more or less precise modeling. With increasing amount of clinical studies using closed-loop insulin delivery at patients' homes, a thorough validation of these algorithms will be possible in normal life conditions, finally bringing therapy advisors and artificial pancreas into routine diabetes management.

Parental sleep quality and continuous glucose monitoring system use in children with type 1 diabetes

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Aims

Caring for a child with T1D necessitates the devotion of substantial time and energy during days and nights, resulting, among other issues, also in partial sleep disruption related to fear from nocturnal hypoglycemia, and at least intermittent sleep deprivation. The study aimed at comparing objective and subjective sleep quality parameters and sleep–wake patterns of parents caring for children with T1D before and during routine use of CGM.

Methods

Data were collected approximately 1 week prior to CGMS use (pre-CGMS session) and 4–8 weeks following initiation of CGMS use (post-CGMS session). Pittsburgh Sleep Quality Index (PSQI) with seven subscale scores (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleep medications, and daytime dysfunction, with addition of questions about frequency of different reasons for sleep disruption) was applied along with actigraphy on nondominant wrist for seven consecutive nights accompanied with a sleep diary, also during pre- and post-CGMS session.

Results

Thirteen out of 20 parents completed both pre- and post-CGMS sessions. No differences were demonstrated between pre- and post-CGMS data in total PSQI or any of the PSQI scores, with total PSQI score <5 (severe sleep problems) documented in 6/13 parents pre- and post-CGMS use. The number of wake bouts recorded during the post-CGMS session was slightly greater than that of the pre-CGMS session (22.9 vs. 19.7 wake bouts per night, respectively, $p < 0.003$), along with total wake time per night being slightly longer during the post-CGMS session than during the pre-CGMS session (48.3 vs. 42.4 min, respectively, $p < 0.003$). This was accompanied by more awakening episodes reported by the parents in the post-CGMS session (1.0 vs. 1.6 times per night for pre- and post-CGMS sessions, respectively, $p < 0.003$), with 77% of parental nocturnal awakenings due to diabetes care in both pre- and post-CGMS sessions.

Conclusions

Parental sleep continuity worsened at the beginning of CGM use, although self-perception of sleep quality remained unchanged. Assisting parents to obtain realistic expectations regarding quality of sleep with initial CGM use seems reasonable.

Comment

This small observational study opens an important angle on QOL of parents caring for children with T1D (9). As every CGM device prompts to action as soon as glucose levels are outside a predefined range, effort related to diabetes management increases along with improved metabolic control and reduction in hypoglycemia. When CGM is used for a longer period of time by adults with T1D, several aspects of treatment satisfaction increase significantly, while no significant differences in children's health-related quality of life (HRQOL) or parents' proxy ratings are observed in a recent data analysis from the SWITCH randomized controlled trial (10). Managing expectations related to the CGM use is therefore critical, especially at the beginning. Every initial CGM training should include a thorough open discussion on possible additional burden related to continuous CGM use. If prepared in a realistic way, patients and caregivers accept CGM along with its possible nuisance and use it successfully for prolonged periods.

Real-time continuous glucose monitoring significantly reduces severe hypoglycemia in hypoglycemia-unaware patients with type 1 diabetes

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This manuscript is also discussed in article on Insulin Pumps, p. S-22 and in article on Diabetes Technology and the Human Factor, p. S-112.

Aims

A 1-year retrospective audit of CGM use in adult patients with impaired awareness of hypoglycemia (IAH) in two tertiary centers, aiming at evaluating its impact on severe hypoglycemia (SH).

Methods

Patients with IAH and Gold score >4 using MDI or CSII and a CGM for at least 12 months were selected. HbA1c, rate of SH, and Gold score were evaluated at baseline and 1 year.

Results

The mean age of 35 included patients (24 female) was 43.2 ± 12.4 years with a mean duration of T1D of 29.6 ± 13.6

years. CSII was started prior to CGM in 33 patients (median 40 months, range 8–352 months). The median rates of SH were reduced from 4.0 (interquartile range [IQR] 0.75–7.25) to 0.0 (0.0–1.25) episodes/patient-year ($p < 0.001$), and the mean ($\pm$ SD) rates were reduced from 8.1 ± 1.3 to 0.6 ± 1.2 episodes/year ($p = 0.005$). HbA1c was reduced from $8.1 \pm 1.2\%$ to $7.6 \pm 1.0\%$ over the year ($p = 0.005$). The mean Gold score was measured in 19 patients and did not change: 5.1 ± 1.5 vs. 5.2 ± 1.9 .

Conclusions

The use of CGM in adult patients with IAH despite the proper diabetes-related education and CSII can significantly reduce the rate of SH along with a significant improvement in HbA1c but no improvement in hypoglycemia awareness.

Comment

More than a third of patients with long-duration T1D have IAH with a several-fold increase of the risk for SH. Structured education about self-adjustment of insulin doses can improve IAH and reduce SH in approximately half of these patients. The use of CSII can further reduce SH for several folds, particularly in those with highest frequency of SH at CSII initiation. This retrospective audit demonstrated that the use of CGM can additionally reduce SH in patients already receiving proper education in CSII therapy (11). Despite its observational design, this study implies that CGM can both reduce SH and lower HbA1c in this highly vulnerable patient population.

Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes

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This manuscript is also discussed in article on Insulin Pumps, p. S-21.

Aims

The primary aim of this study was to determine the incidence of severe and moderate hypoglycemia with sensor augmented pump (SAP) therapy with a low-glucose insulin suspension function compared with standard insulin pump therapy. The primary outcome was the incidence of severe and moderate hypoglycemia.

Methods

Patients with impaired awareness of hypoglycemia (IAH) were selected with modified Clarke hypoglycemia unawareness score of at least 4. All were using an insulin pump for at least 6 months and had HbA1c 8.5% or lower. They were randomized with stratification by 5 age groups (4–7, 8–11, 12–17, 18–25, and 26–50 years) with random block size either to continue using the insulin pump or to use the SAP with low-glucose insulin suspension. At baseline, 3 months, and 6 months, a 6-day retrospective blinded CGM device was worn by all participants. A detailed diary of severe (seizures or coma) and moderate (requiring assistance from another person) hypoglycemia was kept throughout the study. Patients 12 years or older completed the modified Clarke questionnaire for hypoglycemia unawareness, and parents of participants aged 4–18 years completed the parent version. Hypoglycemic insulin clamp was performed in 15 patients to evaluate epinephrine response.

Results

Regular insulin pump therapy group consisted of 49 randomized patients with a baseline rate of severe and moderate hypoglycemia of 20.7 (95% CI, 13.8–30), and SAP with low-glucose insulin suspend group of 46 patients with a baseline rate of severe and moderate hypoglycemia of 129.6 (95% CI, 111.1–150.3) per 100 patient-months. The adjusted incidence rate per 100 patient-months, fitted using the 0-inflated Poisson model, was 34.2 (95% CI, 22.0–53.3) for the pump-only group and 9.5 (95% CI, 5.2–17.4) for the low-glucose insulin suspension group. The incidence rate ratio was 3.6 (95% CI, 1.7–7.5; $p < 0.001$), favoring the low-glucose insulin suspension group. Similar results were calculated for patients younger than 12 years: the adjusted incidence rate ratio, using the 0-inflated Poisson model, was 5.5 (95% CI, 2.0–15.7; $p < 0.001$), favoring the low-glucose insulin suspension group. HbA1c remained similar and stable in both groups: 7.4 (95% CI, 7.2–7.7) in the pump-only ($p = 0.46$) versus 7.5 (95% CI, 7.3–7.7) in the low-glucose insulin suspension group ($p = 0.10$). Significantly less time was recorded below 60 mg/dL (3.3 mmol/L) and below 70 mg/dL (3.9 mmol/L) on retrospective CGM with low-glucose insulin suspension. The hypoglycemia unawareness score improved significantly in both groups without a difference between them. No significant changes in epinephrine response to hypoglycemia were observed in the clamp study.

Conclusions

The use of SAP with automated low-glucose insulin suspension reduced the combined rate of severe and moderate hypoglycemia in patients with T1D, without changing HbA1c, hypoglycemia unawareness score, or hypoglycemic insulin clamp-induced epinephrine response.

Comment

The design of this important study has several peculiarities: the SAP with low-glucose insulin suspension was not compared to SAP but to regular pump therapy with an assumption that “real-time continuous glucose

monitoring has not been demonstrated to be effective in reducing hypoglycemia and is indeed unlikely to reduce nocturnal events during sleep" (12), hypoglycemic events were self-reported or reported by the parents, and the CGM data were limited to a maximum of 18 days in each group. Of notice, the statistical significance for the primary outcome measure was lost after the exclusion of 2 children with the highest baseline rates of moderate hypoglycemia in the sensitivity analysis. However, the strength and importance of this study remains in the outcome of severe hypoglycemia, which was abolished with the use of low-glucose insulin suspension, similarly to the larger randomized controlled trial investigating the same technology (13), indicating that this technology can help those with impaired awareness of hypoglycemia who are at the highest risk.

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

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Diabetes Care 2014; **37**: 2031–33

Aims

CGM was explored as a new approach to identify early hyperglycemia and diagnose T1D in children with positive islet autoantibodies (Ab+).

Methods

Retrospective CGM was applied every 3–6 months on regular study visits for 5–7 days within the Diabetes Autoimmunity Study in the Young (DAISY). Fourteen Ab+ children, free of signs or symptoms of diabetes, and nine antibody-negative (Ab–) age- and gender-matched subjects, with more than 96 hours of CGM data, were included.

Results

The mean age of all participants was 13.7 years. Ab+ subjects showed more hyperglycemia, with 18% time spent above 140 mg/dL (7.8 mmol/L), compared with 9% in Ab– subjects ($p=0.04$). Their average maximum daytime glucose value was higher (222 vs. 168 mg/dL [12.3 vs. 9.3 mmol/L], $p=0.011$), and they had increased glycemic variability (SD and CV) and increased AUC during the daytime. The mean HbA1c in the Ab+ subjects was 5.5% (37 mmol/mol). Six out of the 14 Ab+ subjects developed T1D within 6 months after the CGM. In ROC analysis among Ab+ subjects, 18% of CGM time spent above 140 mg/dL predicts progression to diabetes with 80% sensitivity and 78% specificity, while 20% of CGM time spent above 140 mg/dL predicts progression to diabetes with 60% sensitivity and 89% specificity.

Conclusions

CGM can detect early hyperglycemia in Ab+ children who are at high risk for progression to diabetes. Proposed CGM predictors of progression to diabetes require further validation.

Comment

Children with two or more diabetes-related antibodies positive have a 70% chance to develop T1D within 10 years; however, the variability is considerable. This small study (14) is the first to demonstrate that CGM can detect early hyperglycemia, predominantly during the day in postprandial periods. This likely relates to documented slow increase in HbA1c in these individuals prior to development of T1D; however, the glucose increase can be demonstrated much sooner with the CGM. The proposed threshold of 18–20% of glucose readings >140 mg/dL (7.8 mmol/L) for detecting T1D needs validation in larger cohorts; however, CGM may represent an easy, acceptable, and reliable way to detect early T1D.

Residual dysglycemia when at target HbA1c of 7% (53 mmol/mol) in persons with type 2 diabetes

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Diabetes Res Clin Pract 2014; **104**: 370–75

Aims

To understand the composition of the residual dysglycemia when HbA1c is between 6.5% (48 mmol/mol) representing the definition of diabetes, and 7% (53 mmol/mol) representing the recommended treatment goal.

Methods

One hundred persons with type 2 diabetes and an HbA1c <7% (53 mmol/mol) treated with diet alone and/or oral hypoglycemic agents underwent continuous glucose monitoring (CGM) and were further divided into two subgroups, 1 ($n=50$) and 2 ($n=50$), according to whether the HbA1c was <6.5% (48 mmol/mol) or 6.5–6.9% (48–52 mmol/mol), respectively. A similar analysis was performed in those on diet alone: subgroup A ($n=34$, HbA1c <6.5%, 48 mmol/mol) and subgroup B ($n=10$, HbA1c 6.5–6.9%, 48–52 mmol/mol). The residual dysglycemia determined from the CGM was assessed using glucose exposures defined as areas under curves (AUCs) and mean glucose values.

Results

Averaged 2-hour postprandial glucose value (averaged PPG, mmol/L, mean $\pm$ SD) and postprandial glucose exposure (AUC_{pp}, mean $\pm$ SD, mmol $\cdot$ [L⁻¹ hour]) were significantly higher in subgroup 2 (mean HbA1c = 6.7%, 50 mmol/mol) than in subgroup 1 (mean HbA1c = 6.0%, 42 mmol/mol); averaged

PPG = 8.1 ± 1.3 versus 7.3 ± 1.3 mmol/L ($p < 0.002$); AUCpp = 23.5 ± 8.6 versus 16.2 ± 8.6 ($p < 0.0001$). The percentages of persons with averaged PPG ≥ 7.8 mmol/L were 52% and 24% ($p < 0.01$) in subgroups 2 and 1, respectively. Similar results were observed in those (subgroups A and B) who were on diet alone. Basal glucose exposure (AUCs basal) as a whole over 24 hours was found to be equivalent in subgroup 2 versus 1 and the nocturnal glucose concentrations (mmol/L) were at essentially normal levels, that is, 6.0 ± 1.3 (subgroup 1) and 6.2 ± 1.2 (subgroup 2).

Conclusions

The residual dysglycemia in type 2 diabetes with HbA1c between 6.5% and 6.9% (48–52 mmol/mol) inclusive is mainly due to remnant abnormal postprandial glucose excursions. Consequently, HbA1c $< 6.5\%$ (48 mmol/mol) is an achievable goal with therapeutic measures aimed at reducing postmeal glucose when the HbA1c is at 7% (53 mmol/mol).

Comment

This study confirms that persons with type 2 diabetes with an HbA1c between 6.5% and 7% have hyperglycemia primarily from postprandial glucose excursions and not from fasting hyperglycemia (15). Thus, if one wants to lower HbA1c below 7%, one should use pharmacological agents that address postprandial glucose excursions such as incretins and avoid agents that lower fasting glucose and that may cause hypoglycemia. Medical nutrition therapy is also an option.

24-hour glycemic variations in drug-naïve patients with type 2 diabetes: a continuous glucose monitoring (CGM)-based study

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Aims

The 24-hour glycemic variability was investigated using CGM in people with type 2 diabetes prior to using any medications.

Methods

A total of 30 patients (8 females) with type 2 diabetes were included in this in-hospital study to analyze the 24-hour CGM data.

Results

The patients' median age was 58 years (interquartile range: 42–66 years), median BMI, 25.3 (22.6–27.3) kg/m²; and their median HbA1c value was 7.6 (6.7–8.8) %. The median range of postprandial glucose increases (Increase Range) was 83 (59–119) mg/dL after breakfast, 84 (66–106) mg/dL after

lunch, and 109 (84–120) mg/dL after dinner, with the time to glucose peaks (Peak Time) was 83 (59–110) minutes after breakfast, 70 (59–88) minutes after lunch, and 85 (65–99) minutes after dinner. There was a significant positive correlation between the HbA1c values and Increase Range after breakfast ($P = 0.021$), and after dinner ($P = 0.011$), and Peak Time observed after breakfast ($P < 0.0001$) and after dinner ($P = 0.006$). The patients were then stratified into the low-HbA1c (L) group and the high-HbA1c group (H) by a median HbA1c value of 7.6%. Their median SD was 30 (24–36) mg/dL in the L group and 47 (30–54) mg/dL ($P = 0.027$) in the H group; their median MAGE was 80.3 (65.0–94.7) in the L group and 105.3 (90.0–124.7) in the H group ($P = 0.010$). Increase Range and Peak Time after breakfast were shown to be significantly higher in the H group. The subjects were subsequently divided into four groups according to HbA1c levels: 1 ($< 7.0\%$, $n = 8$), 2 (7.0–7.9%, $n = 8$), 3 (8.0–8.9%, $n = 8$), and 4 ($> 9\%$, $n = 6$). The average glucose level, pre-meal glucose level, and postprandial peak glucose level demonstrated a stepwise increase from group 1 to group 4.

Conclusions

The Peak Time and the Increase Range were maximal after dinner in the investigated group of people with type 2 diabetes without medications. The greater the HbA1c values, the longer the Peak Time and the higher the Increase Range after breakfast and dinner. The average glucose level, pre-meal glucose level, and postprandial peak glucose level increased along with the increase in HbA1c level.

Comment

As expected, as HbA1c increases in drug-naïve patients with type 2 diabetes, the overall glucose rises as well as the postprandial glucose levels specifically postdinner and breakfast, as well as a shift to the time of the peak glucose postmeal. In this study, the median HbA1c was 7.6% with median average glucose of 137 with a median SD of 32.5 (16). The postprandial peaks occurred at 75–85 minutes postmeal. In a prior study in normal glucose-tolerant Japanese patients, the authors found that the median average glucose was 101 (96–106) mg/dL with a median SD being 16.5 (14–19) with postprandial peaks occurring at 40–50 minutes after the start of a meal. Thus, as HbA1c rises in patients with diabetes, one must address postprandial excursions as well as fasting hyperglycemia and know that the peak postprandial excursions occur earlier than the 120 minutes after the start of the meal that is referenced in many diabetes guidelines.

A comparison of Internet monitoring with continuous glucose monitoring in insulin-requiring type 2 diabetes mellitus

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Aims

To compare the effects on HbA1c levels in patients with type 2 diabetes treated with insulin of real-time continuous glucose monitoring (RT-CGM) or an internet blood glucose monitoring system (I-BGMS).

Methods

Fifty-seven patients with insulin-treated type 2 diabetes were randomized to either group 1 where they had the results of their self-monitoring of blood glucose level monitored biweekly using an I-BGMS, or group 2 using RT-CGM and monitored biweekly. Both groups uploaded data using a secure website and received feedback from their endocrinologist. HbA1c and laboratory test results were collected at 0, 3, and 6 months.

Results

The two groups did not differ significantly in the baseline parameters. After a 6-month follow-up period, A1C level were significantly improved in both I-BGMS and RT-CGM group: In the IBGMS group, the A1C level decreased from $8.79\% \pm 1.25\%$ to $7.96\% \pm 1.30\%$ ($p < 0.05$), and in the RT-CGM group it decreased from $8.80\% \pm 1.37\%$ to $7.49\% \pm 0.70\%$ ($p < 0.001$). Between-group difference in A1C levels was not significantly different at baseline, 3 months, or 6 months.

Conclusions

HbA1c levels were significantly improved in this 6-month randomized trial with the use of either I-BGMS or RT-CGM in patients with insulin-treated type 2 diabetes. There were no significant differences in A1C values between the two groups after 6 months.

Comment

This study was unfortunately underpowered with only 57 patients enrolled: 32 to RT-CGM and 25 to intermittent SMBG (17). A total of 17 patients withdrew from the study, 12 of whom were from the RT-CGM group, many citing discomfort with the Guardian Soft-sensor. BG strip utilization was higher in the RT-CGM group by 95 strips over 6 months, mostly for calibration of the CGM system. The overall difference in HbA1c between groups was 0.47 HbA1c points ($p = 0.081$), confirming that if more patients were enrolled in the study, there would have been a significant drop in HbA1c in the RT-CGM group compared to the intermittent SMBG group, confirming that use of CGM in patients with diabetes not at goal will help lower their HbA1c versus traditional intermittent SMBG.

The acute effects of interval- vs. continuous-walking exercise on glycemic control in subjects with type 2 diabetes: a cross-over, controlled study

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Aims

To determine whether interval-based exercise improves postprandial glucose tolerance and free-living glycemia more than oxygen-consumption- and time-duration-matched continuous exercise.

Methods

Ten subjects with type 2 diabetes participated in cross-over, controlled three 1-hour exercise interventions in a randomized order. These interventions were (a) interval-walking (IW; repeated cycles of 3 minutes of slow and fast walking), (b) continuous-walking (CW), and (c) control (CON). Oxygen consumption (VO_2) was measured continuously to match mean VO_2 between exercise sessions ($\sim 75\%$ VO_2 peak). Main outcome measure was a mixed meal tolerance test (MMTT; 450 kcal, 55% carbohydrate). This MMTT was performed with stable glucose isotopic tracers after each intervention, and glucose kinetics were measured during the following 4 hours. Free-living glycemic control was assessed for ~ 32 hours following the MMTT using continuous glucose monitoring (CGM).

Results

VO_2 was well-matched between the exercise interventions. IW decreased mean and maximal incremental plasma glucose during the MMTT when compared to CON (mean: 1.2 ± 0.4 vs. 2.0 ± 0.5 mmol/L, $p < 0.001$; maximal: 3.7 ± 0.6 vs. 4.6 ± 0.7 mmol/L, $p = 0.005$) and mean when compared to CW (1.7 ± 0.4 mmol/L, $p = 0.02$). No differences in mean or maximal incremental plasma glucose values were seen between CW and CON. Metabolic clearance rate of glucose during the MMTT was increased in IW compared to CW ($p = 0.049$) and CON ($p < 0.001$). CGM mean glucose was reduced in IW compared to CW for the rest of the intervention day (8.2 ± 0.4 vs. 9.3 ± 0.7 mmol/L, $p = 0.03$), whereas no differences were found between IW and CW the following day.

Conclusions

Interval-based exercise sessions (repeated cycles of slow and fast walking) improve glycemic control in T2DM subjects when compared to an oxygen-consumption- and time-duration-matched continuous exercise session (continuous walking).

Comment

It has been shown by other investigators as well as these investigators that interval-based exercise with slow and rapid activity will lower glucose greater than continuous exercise (18). Reasons for this finding are uncertain but could be due to multiple factors ranging from more energy intake in continuous exercise, greater peak exercise intensity in the cyclic group, or the cyclic exercise pattern allowing for more glucose uptake during periods of lower intensity exercise. Future studies are needed to evaluate the mechanism of glucose lowering in cyclic exercise versus continuous exercise. In the meantime, it may be worth diabetes patients not at goal to do cyclic exercise varying the intensity of exercise from low to high levels to better improve glucose.

Relationship between HbA1c and continuous glucose monitoring in Chinese population: a multicenter study

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Aims

Only scarce published reference data describe the relationship between HbA1c and 24-hour mean blood glucose (MBG) from continuous glucose monitoring (CGM) in Chinese populations. This relationship was investigated in adult Chinese subjects with different degrees of glucose tolerance.

Methods

Seven-hundred-and-forty-two individuals without history of diabetes were included in the study at 11 hospitals in urban areas across China from 2007 to 2009, and data of 673 subjects were included in the final analysis. Oral glucose tolerance test (OGTT) was used to classified participants into those with normal glucose regulation (NGR; n=121), impaired glucose regulation (IGR; n=209), or newly diagnosed type 2 diabetes (n=343). All participants underwent testing for HbA1c levels and wore a CGM system for three consecutive days. The 24-hour CGM-based MBG levels were calculated. Spearman correlations and linear regression analyses were utilized to quantify the relationship between glucose parameters.

Results

The levels of HbA1c and 24-hour MBG significantly increased with the presence of glucose intolerance (NGR < IGR < type 2 diabetes; all, $p < 0.001$). Analysis of the total population indicated that HbA1c strongly correlated with 24-hour MBG ($r = 0.735$). The correlation was also significant for the subgroup of participants with newly diagnosed type 2 diabetes ($r = 0.694$, $p < 0.001$). Linear regression analysis of the total study population was described by the following equation: 24-hour MBG mmol/L = $1.1986 \cdot \text{HbA1c} - 0.582$ (24-hour MBG mg/dL = $21.5646 \cdot \text{HbA1c} - 10.476$) ($R^2 = 0.670$, $p < 0.001$). The model fit was not improved by application of exponential or quadratic modeling. When HbA1c was 6.5%, the calculated 24-hour MBG was 7.2 (6.4–8.1) mmol/L (130 [115–146] mg/dL); when HbA1c was 7.0%, the 24-hour MBG was 7.8 (6.9–8.7) mmol/L (140 [124–157] mg/dL).

Conclusions

This reference data study demonstrated correlation between HbA1c and CGM-derived MBG in Chinese subjects with different glucose tolerance status.

Comment

The prevalence of diabetes in China from a 2010 national survey estimates that 11.6% of the adult population has diabetes. Thus, diabetes is a major public health problem in China. Data on correlation of mean blood glucose to HbA1c are needed to help providers tell patients what blood glucose goal is needed to obtain a reasonable HbA1c. This study in Chinese patients confirms that mean blood glucose by CGM correlates strongly with HbA1c from normal glucose tolerance to impaired glucose tolerance and over diabetes (19). Future studies on various ethnic groups should be done to see if the mean blood glucose over a 24-hour period is similar to this Asian population in regard to HbA1c values.

Conclusion

Severe hypoglycemia, particularly associated with impaired awareness of hypoglycemia, was the last major diabetes-related complication with few therapy options. In the last year, however, data from several studies demonstrate the ability of sensor-augmented insulin pumps with threshold low-glucose insulin suspension function to provide a significant reduction

in severe hypoglycemia (20). It is now time to reevaluate the health economic benefits of this therapy and make it more widely available to patients who struggle daily with hypoglycemia. The story with CGM in severe hypoglycemia also demonstrates time and again that only high-quality randomized controlled trials with intelligent designs and detailed retrospective audits can provide credible guidelines to healthcare providers and payers. Studies in this category are still largely missing for patients with different stages of T2D, where smaller trials suggest a multitude of possible benefits these patients' populations could obtain from CGM.

Psychosocial barriers, continuously highlighted in the literature (21), however, remain an intrinsic part of CGM-related therapies—as long as a therapeutic modality requires active participation from the patients, people will react to it in any imaginable way. Let's believe that the integration of CGM into the closed-loop insulin delivery that occurred in the past year will be another step closer to the routine use of CGM.

Author Disclosure Statement

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