Therapeutic Use and Diagnostic Potential of Continuous Glucose Monitoring Systems (CGMS) in Adolescents

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Abstract Glucose meters provide quantitative information about blood glucose concentration that is discontinuous. Continuous glucose monitoring systems (CGMS) using sensors provide time sequences data, including “quantity,” and adding direction, rate of change and rate of acceleration. Therefore CGMS appear more informative, efficacious and safe as meters when used for treatment choices. Recently some important improvements are achieved in consistency, ease of use and incorporation with other technologies. From the therapeutic point, ambulatory sensors are currently approved and used with success to treat diabetic patients on insulin therapy. CGMS can provide the data needed to prevent hypoglycemia. In addition, CGMS technology is expanding its benefits for diagnostic use and behavior modification in prediabetes especially in high risk adolescents like those with obesity with or without family history of diabetes, metabolic syndrome, cystic fibrosis and thalassemia. This mini-review clarifies both the therapeutic and diagnostic capabilities and potential use of CGMS to diagnose and manage glycemic abnormalities in adolescents. Moreover it summarizes the results of studies that compare CGMS to other diagnostic tools, namely intermittent capillary glucose monitoring using glucometers, fasting venous glucose measurement, oral glucose tolerance test (OGTT) and measurement of glycated hemoglobin (HbA1C) in the management of these adolescents. The possible early diagnosis of glycemic abnormalities using CGMS in adolescents and their timely management to prevent progression to diabetes appears to be an attractive future therapeutic approach.

Keywords Continuous Glucose Monitoring (CGM), Adolescents, Diabetes, Prediabetes, Diagnosis, Monitoring

1. Introduction

Puberty is associated with insensitivity to insulin in both sexes, across all ethnic groups, returning to almost pre-pubertal levels in young people above 16 years of age. This is compensated by an increase in insulin secretion. (1,2,3) The speed of growth is correlated to the rise in fasting serum insulin in pubertal adolescents without diabetes. (4-7) The marked increase in the secretion of growth hormone (GH), and insulin-like growth factor-I (IGF-I) associated with the pubertal growth spurt can explain in part increased insensitivity to insulin. (4,5) These physiological changes make the adolescent more vulnerable to glycemic anomalies. This concept is supported by the facts that in adolescents with type 2 diabetes (DM2) have significant deterioration of glycemic control during this pubertal period. (8-12) and those with type 1 DM (DM 1) the insulin requirements increase by between 30% and 50% during puberty. (8-12) In addition, there is increased prevalence of prediabetes {impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) } especially those with obesity and/or family history of DM2. Adolescents aged 12-15 years (peak pubertal insensitivity to insulin) have a significantly higher rate of prediabetes than those aged 16-19 years. (13-18)

Prediabetes is a recognized risk factor for both T2DM and cardiovascular disease and is associated with retinopathy, a 2-fold increased incidence of micro albuminuria, and neuropathy. Concerns have been raised about the potential effect of prediabetes on morbidity in adolescents. (19-21) Adolescents with hyperinsulinemia have a 4-fold higher prevalence than those without cardio-metabolic risk factors. (22-29) In addition, a study performed 117 obese children and adolescents (mean age: 12.7 years Out of 33 children with IGT at baseline, 15 (45.5%) reverted to normal glucose tolerance, 10 (30.3%) continued to have IGT, and 8 (24.2%) developed T2DM. Severe obesity, weight gain, IGT, and black race emerged as the best predictors of developing T2DM, whereas baseline fasting glucose, insulin level, and C-peptide level were not predictive. (30) A higher rate of reversion (75%) from IGT to normal glucose tolerance was demonstrated in 128 obese white European adolescents...
followed up for a mean of 3.9 years. Only 16% continued to have IGT, 2% developed DM 2. The 2-hour glucose levels by OGTT at baseline were significantly higher in the adolescents who continued to have IGT and were the highest in adolescents who developed diabetes. (31,32)

In 2009, an International Committee composed of experts from the American Diabetes Association, the European Association for the Study of Diabetes and the International Diabetes Federation recommended that prediabetes testing include the Hb A1C test, fasting blood sugar test and oral glucose tolerance test. (33)

According to the American Diabetes Association recommendations it would be helpful to consider monitoring patients with impaired fasting glucose or HbA1c (5.7%-6.4%) or previously impaired fasting glucose (IFG) every year. Monitoring should include at least annual reassessment of FPG and/or an OGTT. For individuals where progression is suspected, annual measurements of FPG and HbA1C, with 2-hour OGTT, should all be conducted. The AACE recommends HbA1C primarily for screening and monitoring and not for prediabetes identification. This is because the A1C test can be misleading or inaccurate in some populations. (33-40)

In a multiethnic cohort study conducted between 2005 and 2010, 1156 obese children and adolescents (40% boys) underwent an oral glucose tolerance test (OGTT) and HbA1c measurement. In 21% of these patients, HbA1c levels were 5.7%-6.4%. Among children classified as being at increased risk for diabetes on the basis of their HbA1c values, only 47% were categorized as being at increased risk on the basis of their OGTT results. Moreover, 27% of children with HbA1c levels below 5.7% were diagnosed with prediabetes on the basis of OGTT results. (17)

Agreement is poor between HbA1c levels and OGTT results. It appears that given the low sensitivity and specificity of these tests, HbA1c alone is a poor diagnostic tool for prediabetes in obese children and adolescents. The ADA panel acknowledged that concordance is not perfect among HbA1c, fasting plasma glucose, and 2-hour fasting plasma glucose levels in adults. Nonetheless, long-term data on HbA1c elevation and risk for retinopathy, combined with practical considerations on the use of HbA1c, led the ADA to recommend its use. (17,18)

2. Continuous Glucose Monitoring Systems (CGMS) Versus Glucometers as Monitoring Tools of Glycemia

CGMS are a developing technology that allows frequent glucose measurements (every 5 min) and have the ability to monitor glucose trends in real time. The use of CGMS affords information about the direction, magnitude, duration and frequency of fluctuations in blood glucose levels. Compared with conventional intensified glucose monitoring, defined as three to four blood glucose measurements per day, CGM provides much greater view of glucose levels throughout the day. (1)

These two types of blood glucose monitors differ in many ways: 1) an intermittent blood glucose monitor (IGM) measures discrete glucose levels accurately, whereas a continuous monitor provides multiple glucose levels of fair accuracy; 2) IGM detects the current blood glucose levels but does not predict future glucose levels, whereas with a CGMS, trends in glucose levels have predictive competence; 3) with an IGM, it is easy to study every measured blood glucose value, but with CGMS the numerous data generated is difficult to be studied point by point, and 4) an IGM requires effort to operate, whereas a CGMS does not.

CGM has the potential to improve detection of hyperglycemic excursions as well as asymptomatic hypoglycemia to improve management of glucose levels in diabetes patients. Although CGMS becomes an important tool in diabetes management, still its potential use as a diagnostic tool is not fully determined. (1)

3. Approval of Use of CGMS in Children and Adolescents

The US Food and Drug Administration (FDA) has expanded the approval of the Dexcom G4 Platinum CGMS to include use in children aged 2 to 17 years of age, despite reduced accuracy compared with adults. The G4 Platinum (Pediatric) system is the first CGM system approved for young children. Another currently available CGM system, Medtronic's Enlite, is approved for ages 16 and older but is being studied in children as young as 2 years. (41-43) (Table 1)
4. Accuracy of a New Real-time Continuous Glucose Monitoring Algorithm

In 2008, the Clinical and Laboratory Standards Institute published POCT05-A, which provides recommendations for study design and parameters of interest in the performance evaluation of CGM systems. (44) CGMS performance was evaluated numerically and clinically. Numerical evaluation was performed for sub analyses using mean absolute relative difference (MARD) and precision absolute relative difference (PARD). Mean absolute relative difference is the average of the absolute differences between paired capillary BG and interpolated CGM readings and is expressed as a percentage of the corresponding capillary BG readings. Precision absolute relative difference was calculated in a similar fashion, but instead of sensor-to-BG differences, sensor-to-sensor differences were calculated, with the mean of the interpolated and the non-interpolated CGM readings replacing the capillary BG readings. (45) These parameters were calculated as averages of all of the experiment’s MARD and PARD results and as aggregated MARD and PARD of all individual absolute relative differences.

In one study, two sensors of each of the three CGM systems (Navigator, Guardian and seven plus CGMS) were compared in a setting following POCT05-A recommendations. The Navigator CGM system achieved more accurate results than the Guardian or the Seven Plus with respect to MARD and PARD. Performance in the hypoglycemic range was markedly worse for all CGM systems when compared with BG results. (46) Chen Z et al, evaluated the accuracy of CGMS during OGTT in the detection of blood glucose changes in glucose in 49 out-patients with fasting plasma glucose of 3.9-11.0 mmol/L. (20) The correlation indices between CGMS values and the venous blood glucose (VBG) values during the entire OGTT and in phases of stable, rapidly rising and falling glucose levels were 0.928, 0.901, 0.924 and 0.902, respectively (P<0.001). CGMS values showed good consistency with VBG values measured during OGTT confirming the efficiency of CGMS in detection the rapidly changing blood glucose during OGTT. (47)

Zhou et al. studied the relationship between HbA1c, and 24 h mean blood glucose (MBG) from CGM (3 days) in in 742 Chinese subjects with different glucose tolerance status. (48) OGTT classified the participants as non-diabetic subjects, including those with normal glucose regulation (NGR; n=121) and impaired glucose regulation (IGR; n=209), or newly diagnosed type 2 diabetes (n=343). The levels of HbA1c and 24 h MBG significantly increased with presence of glucose intolerance (NGR<IGR<type 2 diabetes; both, P<0.001). When HbA1c was 6.5%, the mean calculated 24 h MBG was 7.2 mmol/L, and when HbA1c was 7.0%, the mean 24 h MBG was 7.8 mmol/L mg/dL). This study provided the reference data of the relationship between HbA1c and CGM in Chinese subjects. (48)

Collectively these studies provided good evidence of improving accuracy of CGMS in detecting glycemic abnormalities across different glucose different states. The drawback of CGMS use include the relatively higher cost of its use as well as the discomfort of inserting the sensor for few days and requirement for trained staff for education, insertion and downloading the data.

5. Proposed Reference Values of Glycemic Parameters for CGM

To establish reference values of glycemic parameters for continuous glucose monitoring, Zhou et al studied 48 individuals with normal glucose regulation using CGMS for 3 days. (49) Indices in CGMS were analyzed, including mean level of 24 h blood glucose (BG) values (24 h MBG) and its standard deviation (SDBG), percentage of time above 7.8 mmol/L or below 3.9 mmol/L, area under the curve (AUC) of BG above 5.6 mmol/L, the largest amplitude of glycemic excursions (LAGE), mean amplitude of glycemic excursions (MAGE) and absolute means of daily differences (MODD). (49,50) (Table 2).
In addition, Kang et al. described some CGMS criteria denoting deterioration of glucose regulation, the intraday and day-to-day blood glucose excursions become increasingly fluctuant. (51) The amplitude of glycemic excursion is lower in the NGT group than in the T2DM group, however, the frequency of glycemic excursion is higher in the NGT subject than in the T2DM subjects. The glycemic excursion profile of the IGR subjects is between the NGR and T2DM subjects. (3) The characteristics of glycemic excursion of the IGT group are similar to those of the T2DM group, and the characteristics of the IFG group are similar to those of the NGT group. (4) The loss of postprandial glycemic control precedes evident deterioration in fasting phase of IGR.

Rodbard reviewed a systematic approach to the interpretation of continuous glucose monitoring data for use by clinical researchers and clinicians to evaluate the quality of glycemic control, glucose variability including within- and between-day variability, the day-to-day stability of glycemic patterns, and changes in response to therapy. (52, 53)

Collectively, these results supported that the favorable use of CGMS profile to reflect the overall BG regulation and the different feature of glycemic excursions in detail.

6. Use of CGMS for better Monitoring and Control of Diabetes in Adolescents

Self-monitoring of blood glucose is essential to optimize glycemic control in DM 1. CGM systems measure interstitial fluid glucose levels to provide semi-continuous information about glucose levels, which identifies fluctuations that would not have been identified with conventional self-monitoring. Through minimally invasive sensor-based CGM, individuals can manage their blood glucose (BG) levels more aggressively to lower their Hb A1C level and possibly reduce the risk of hypoglycemia. However, tighter glycemic control poses the risk of hypoglycemia. CGM with more accurate glucose sensor and calibration algorithm with increased performance at lower BG levels appears to approach these targets.

A systematic review and meta-analysis of 14 relevant trials including a total of 1268 type 1 diabetic patients, assessing the efficiency and safety of CGM, particularly its real-time system, showed a favorable effect on glycemic control and decreases the incidence of hypoglycemic episodes in both pediatric and adult patients with type 1 diabetes. (54)

In 72 adult and adolescent subjects the efficacy of the Paradigm® REAL-Time (PRT) sensor-augmented pump system (Medtronic Diabetes, Northridge, CA) was investigated. A retrospective analysis (24 weeks) of the data set was performed to evaluate a new calibration algorithm utilized in the Paradigm® Veo™ insulin pump (Medtronic Diabetes) and to compare these results to performance metrics calculated for the PRT. The Veo calibration algorithm decreased the overall mean absolute relative difference by greater than 0.25 to 15.89%, with hypoglycemia sensitivity increased from 54.9% in the PRT to 82.3% in the Veo (90.5% with predictive alerts); however, hyperglycemia sensitivity was decreased only marginally from 86% in the PRT to 81.7% in the Veo. (55) It appears that the Veo calibration algorithm, with sensor improves hypoglycemia detection, while retaining accuracy at high glucose levels.

Other Authors reviewed 22 randomized controlled trials (RCTs) comparing retrospective or real-time CGM with conventional self-monitoring of blood glucose (SMBG) levels or with another type of CGM system in patients with type 1 diabetes mellitus with a primary outcomes were glycemic control, e.g. level of glycosylated HbA1c and health-related quality of life. The search identified 1366 references. Twenty-two RCTs meeting the inclusion criteria of this review were identified. The results of the meta-analyses (across all age groups) indicate benefit of CGM for patients starting on CGM sensor augmented insulin pump therapy compared to patients using multiple daily injections of insulin (MDI) and standard monitoring blood glucose (SMBG). After six months there was a significant larger decline in HbA1c level for real-time CGM users starting insulin pump therapy compared to patients using multiple daily injections (MDI) and SMBG. They concluded that higher compliance of wearing the CGM device improves Hb A1C to a larger extent. (56)

Yeh et al reviewed 33 randomized, controlled trials in
children or adults that compared continuous subcutaneous insulin infusion (CSI) with MDI (n=19), real-time continuous glucose monitoring (rt-CGM) with SMBG (n=10), or sensor-augmented insulin pump use with MDI and SMBG (n=4). They decided that for glycemic control, rt-CGM is superior to SMBG and sensor-augmented insulin pumps are superior to MDI and SMBG without increasing the risk for hypoglycemia (57)

7. The Potential Use of CGMS in the Early Diagnosis of Glycemic Abnormalities in Adolescents (New Use for an CGMS Tool)

i. The Classic Diagnostic Criteria for Prediabetes

A standardized diagnosis of prediabetes in adolescents can be made using impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), metabolic syndrome criteria, or A1C values; any of these 3 approaches appears acceptable.

1. IFG/IGT criteria: Prediabetes is identified by IFG (glucose levels 100-125 mg/dL [5.6-6.9 mmol/L]) and/or IGT (glucose levels 140-199 mg/dL [7.8-11 mmol/L]) following a 2-hour 75-g oral glucose tolerance test (OGTT) given in the morning (after an appropriate overnight fast). Before the OGTT test, patients should be receiving adequate carbohydrate intake, should not be physically active during the test, and must not be smokers. IGT is considered a more important risk than IFG. (37-40, 58)

2. A1C criteria: A1C values between 5.5% and 6.4% should be a signal to conduct more specific glucose testing. FPG or OGTT should be used for the definitive identification of prediabetes. (37)

3. Metabolic syndrome criteria: The presence of metabolic syndrome, based on National Cholesterol Education Program IV Adult Treatment Panel III (NCEP ATP III) criteria and also known as insulin resistance syndrome, is a prediabetes equivalent. The San Antonio Heart Study analyzed the risks associated with metabolic syndrome, NCEP risk factor categories, and 2-hour glucose values and found very high risk in patients with both IFG and metabolic syndrome. Patients with normal fasting glucose levels and metabolic syndrome, as well as those with IFG without metabolic syndrome, were also found to be at increased risk. (58) Metabolic syndrome, however, predicts future diabetes better than IFG. (37-39)

Approximately one-half of patients with IGT meet the NCEP ATP III criteria for the diagnosis of metabolic syndrome. Three of 5 metabolic syndrome criteria are sufficient for identification; however, recent evidence suggests that even 2 of 5 metabolic syndrome criteria may be adequate. (42-44) These criteria include the presence of systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, Plasma triglycerides ≥ 150 mg/dL; HDL cholesterol < 35 mg/dL in men or < 39 mg/dL in women; Body mass index > 30 kg/m2 or waist-hip ratio > 0.9 in men or > 0.85 in women, and urinary albumin excretion rate ≥ 20 mcg/min or albumin/creatinine ratio ≥ 30 mg/g

ii. CGMS for early diagnosis of glycemic abnormalities

The deficiency in islet β cell secretion and insulin sensitivity are the two important pathophysiological mechanisms of diabetes responsible for glycemic disorders. Glucose variability that can be monitored by CGMS could be an independent risk factor for diabetes development and complications in addition to average glucose. (58)

Chen et al. and Wang et al studied different groups with different OGTT response ranging from: normal glucose regulation (NGR) to (IGM) to diabetes. (58, 59) Groups were monitored using the CGMS for consecutive 72 hours. The multiple parameters of glycemic variability included the standard deviation of blood glucose (SD), mean of blood glucose (MBG), high blood glucose index (HBGI), mean of daily differences (MODD) and mean amplitude of glycemic excursions (MAGE). Results showed that the respective values of MBG, HBGI, MODD and MAGE were all increased progressively (all p < 0.05), while their oral disposition indices were decreased progressively (p < 0.05). Increased glycemic variability parameters were consistently associated with decreased oral disposition index in subjects across the range of glucose tolerance from the NGR to IGM to DM group. Qian et al showed that Chinese NGT subjects with a 1-h plasma glucose > or = 11.1 mmol/l are characterized by metabolic abnormalities, which may be caused by the impairment of early insulin release rather than aggravated insulin resistance. (60) These studies pointed out to the potential use of CGMS as an early diagnostic tool for glycemic abnormalities that can not be detected early using the old tools (FPG,OGTT and HbA1C)

8. The Potential Use of CGMS to Diagnose Early Glycemic Abnormalities in High Risk Adolescents

1. Morbid obesity

Childhood obesity is epidemic in developed countries and is accompanied by an increase in the prevalence of type 2 diabetes (T2DM). In obese adolescents pancreatic beta-cells may not be able to cope with insulin resistance leading to hyperglycemia and T2DM.

Brufani et al. screened 510 overweight/obese (8-13 years) children and adolescents. Using OGTT, IGT was the most frequent alteration (11.2%), with a higher prevalence in adolescents than in children. Silent DM 2 was identified in two adolescents (0.4%). HOMA-IR and glucose-stimulated insulin levels were higher in patients with IGT than
individuals with normal glucose tolerance. Multivariate analysis showed that age, fasting glucose, and insulin resistance influenced independently plasma glucose at 120 min of OGTT. (61)

Morandiet al. (62) screened 817 obese children and adolescents (8-18.4 years) and reported 39 children (4.7%) with IGT. Cambuli et al. (68) during 1-year observational study conducted on 736 (535 overweight/obese and 201 normal weight) diagnosed IFG in (7.66%) , IGT in 3.18% and T2D in 0.18%. These reports supported high prevalence of glucose metabolism alterations among children and adolescents with overweight. (62, 63)

Elawwa et al. assessed the 72-h CGM, OGTT and calculated homeostatic model assessment (HOMA), and the quantitative insulin sensitivity check index (QUICKI) in 13 adolescents with simple obesity (BMI SDS=4 ± 1.06). OGTT revealed 3 cases (23%) with IFG (FG >5.6 mmol/L), 4 cases (30%) with IGT ( 2h blood glucose >7.8 <11.1 mmol/L), and none with diabetes. Using CGMS, IFG was detected in 4 cases, the maximum serum blood glucose 2h or more after meal was >7.8 and <11.1 mmol/L (IGT) in 9 children (69%) and >11.1 mmol/L (diabetes) in one case (7.6%). No glycemic abnormality was detected using HbA1C (5.7 ± 0.3%). 11/13 patients had HOMA values >2.6 and QUICKI values <0.35 denoting insulin resistance. (64)

2. First degree relatives of individuals with type 2 DM

First-degree relatives of individuals with DM 2 and obesity are at increased risk of developing hyperglycemia. Jensen et al. investigated 531 first-degree relatives with no known history of diabetes (aged 44.1 +/- 0.7 years; BMI 29.0 +/- 0.3 kg/m2). (65-66) They identified diabetes in 19% (n = 100), and impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) in 36% (n = 191). Thus, only 45% (n = 240) had normal glucose tolerance (NGT). Both insulin resistance and impaired beta-cell function are associated with impaired glucose metabolism in all ethnic groups.

Madhu et al. investigated glycemic profiles by CGMS in 20 obese first-degree relatives of type 2 diabetes mellitus patients and found 3 (15%) NGT, 7 (35%) IFG, and 8 (40%) IGT subjects showed excursions in the diabetes range, whereas 18 (90%) NGT and 17 (85%) pure IFG subjects showed excursions in the IGT range. (65) These studies denoted that in obese children and adolescents, CGMS appears superior and more sensitive compared to FBG, OGTT and HbA1C in detecting early glycemic abnormalities.

3. Polycystic ovary syndrome (PCO)

In a controlled study, Tao et al. investigated glucose homeostasis using OGTT and CGMS tolerance in women with PCO versus age-matched healthy women with normal menstruation. (67) The peaking time of post-breakfast plasma glucose level of the PCOS group was significantly longer than that of the control group. CGMS diagnosed an abnormal mode of daily glucose change characterized by a delayed peak of post-breakfast plasma glucose level.

Zhu et al. (68) compared CGM data in two groups of women with PCO and evaluated the influence of hyperandrogenemia on glucose metabolism. CGMS showed that the minimal blood glucose and mean blood glucose as well as the percentage of time for hypoglycemia were significantly higher in hyperandrogenemia group. This may place them at increased risk for developing DM 2. However, the use of CGMS in adolescents with PCO has not been studied.

4. Cystic fibrosis

A long pre-diabetic phase of abnormal glucose tolerance is described in subjects with cystic fibrosis (CF) since childhood. Seventeen children with CF and 14 controls were investigated (mean age 13.3 years). (67)

All subjects underwent OGTT and CGMS monitoring for 3 days. On the basis of OGTT, children were classified as NGT, IGT, IGT plus at least one glucose value above 200 mg/dl at intermediate OGTT points (IGTC 200) and CFRD. Subjects with CF underwent another OGTT after 2.5 years. Baseline OGTT revealed 3/17 (17.6%) children with CF with at least one glucose value above 200 mg/dl, while CGMS revealed (35.3%) with glucose excursions above 200 mg/dl. None of the controls showed glucose over 200 mg/dl either at OGTT or at CGMS. At the 2.5-year follow-up OGTT, all the six subjects who had diabetic glucose excursion (i.e. > 200 mg/dl) at baseline CGMS presented IGTC 200 or CFRD. In logistic regression analysis, CGMS diabetic excursion was the strongest predictor of IGT/C200 and CFRD. This study suggested that CGMS is a useful tool to predict glucose metabolism derangements in children affected by CF. (69)

Thirty eight children with CF > 10 years , with normal OGTT, were grouped into 2 groups according to the max CGM glucose value obtained during 3-days CGMS monitoring. Group 1 <11 mmol/l (n= 26) and Group 2 ( n=12) ≥11 mmol/l. Group 2 patients exhibited a significant impairment in lung function: FEV1, 68.2±25.6% vs. 87.3±17%, p=0.02 and FVC, 86.1±31.7% vs. 99.3±13.4%, p=0.021, as well as a higher rate of colonization by P. aeruginosa: 83.3% vs. 44%, p=0.024. (70)

Paired oral glucose tolerance tests (OGTTs) and CGMS monitoring was undertaken in 102 children and adolescents with cystic fibrosis (age 9.5–19.0 years) at baseline (CGM1) and after 12 months (CGM2). CGM validity was assessed by reliability, reproducibility, and repeatability. In this cohort of children and adolescents with cystic fibrosis, CGM performed on two occasions over a 12-month period was reliable, reproducible, and repeatable. In addition, authors reported that CGM in the normal glucose tolerance (NGT) and impaired glucose tolerance (IGT) stages may allow earlier diagnosis of CF-related diabetes. (71)

It appears that under certain circumstances, OGTT screening, used to diagnose CF-related diabetes (CFRD), fails to reveal early glucose tolerance abnormalities and CGM may aid the early diagnosis of glucose abnormalities and could be useful to avoid the deterioration of lung function related to glycemic abnormalities.
5. Thalassemia major

Both insulin deficiency and resistance are reported in patients with β-thalassemia major (BTM). The use of continuous blood glucose monitoring (CGM), among the different methods for early detection of glycemic abnormalities.(72-74)

Rimondi et al. investigated the value of using CGMS in six TM patients with abnormal glucose homeostasis after an oral glucose tolerance test (OGTT). (70) Two-hour OGTT glucose values and CGMS fluctuations were classified as normal if <7.8 mmol/L, impaired if 7.8 to 11.1 mmol/L, diabetic if >11.1 mmol/L. The TM patients spent from 1 to 23% of the time with a blood glucose level from 7.8 to 11.1 mmol/L. In five patients the CGMS confirmed the impaired glucose tolerance diagnosis and in one patient the CGMS excluded the diagnosis of diabetes.

Similarly, Soliman et al. (71) studied 16 adolescents with TM (19.75 ± 3 years) using OGTT and CGMS for 3 days. Using OGTT 25% had IFG, 12.5% had IGT and one of them had diabetes. Using CGMS the maximum BG (3h postprandial) 25% had diabetes and 56% had IGT. Serum ferritin concentrations were correlated significantly with the fasting BG and the 2-h blood glucose levels in the OGTT as well as with the average BG recorded by CGM.

Collectively, these results demonstrate that the CGMS is a useful method to detect the variability of glucose fluctuations and offers an opportunity for better assessment of glucose homeostasis in TM patients. Proper and early iron chelation or the use of intensive iron chelation in those with high iron load the new oral chelators has been shown to decrease or reverse these glycemic abnormalities. (72-74)

6. Adolescents on high dose corticosteroid therapy

Impaired glucose tolerance (IGT) and steroid-induced diabetes have been reported with systemic use of pharmacological doses of corticosteroids. The effects of glucocorticoids on carbohydrate metabolism may be dose related. Elawwa et al. assessed OGTT and 72-h continuous blood glucose concentrations by CGMS, and calculated the Homeostatic model assessment (HOMA), and the quantitative insulin sensitivity check index (QUICKI) in 10 children and adolescents receiving pharmacological doses of oral prednisolone for more than 3 weeks. The mean cumulative dose of prednisolone given was 1601.3± 984.8 mg, the mean duration of therapy = 84 ± 14 days. The OGTT and the average glucose level recorded by CGMS were normal in all patients. Using CGMS , 4 cases had maximum glucose level > 11.1 mmol/L (Diabetic range), and the other six had BG > 7.8 mmol/L, 3-hours after meal (IGT). This pilot study showed that CGMS is superior to OGTT in detection glycemic abnormalities in these patients. (75)

8. Conclusions

Prediabetic states are prevalent among children and adolescents. Moreover, the prevalence of prediabetes has increased markedly over recent decades. Screening for prediabetes and monitoring of glycemic abnormalities seems to be meaningful in adolescents who have a parental history of diabetes, are extremely obese, especially in adolescents of certain ethnic groups and affected by special systemic diseases like thalassemia and CF.

When used properly, continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens appears to be a useful tool to lower HbA1C in selected adolescents with type 1 diabetes. Success correlates with adherence to ongoing use of the device. CGM may be a useful supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes.

The use of CGMS in the diagnosis of early dysglycemia (prediabetes) especially in high risk adolescents appears to be and promising approach. Many studies reported significant value of using CGMS as a diagnostic tool compared to other known tools, namely oral glucose tolerance test (OGTT) and measurement of HbA1C in high risk groups. These studies reported that subcutaneous CGM is safe and offered detailed insight into glucose homeostasis in different groups of high risk patients.

Those categories of patients include adolescents with obesity with or without family history of type 2 diabetes mellitus, polycystic ovary syndrome (PCO), cystic fibrosis, and thalassemia major. Early diagnosis of glycemic abnormalities in these patients offers an opportunity of early prevention of progression to a diabetic state.

Further long-term controlled studies are needed to support the already present evidences and to elucidate the different diagnostic CGMS criteria and validate the use of CGMS for diagnosing prediabetes in adolescents

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