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Experience with Continuous Glucose Monitoring System in Children and Adolescents With Type 1 Diabetes in Kuwait

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Abstract

Objectives: To investigate the efficacy of using retrospective continuous glucose monitoring systems (rCGMS) in improving glycemic control defined, by glycosylated hemoglobin (HbA1c), and to assess glucose variability, and hyperglycemia in children and adolescents with Type 1 Diabetes Mellitus (T1DM) in a tertiary care center in Kuwait.

Methods: Children and adolescents with T1DM aged<18 years old were recruited for rCGM. Inclusion criteria: a baseline HbA1c >7.0% and being on multiple daily injections (MDI) of insulin. rCGMS was fixed for 3-6 days and then children attended clinic for data download. Results were used to review/ modify treatment. The glucose sensor was re-inserted after a 12-week interval. The change in HbA1c, mean daily CGMS standard deviations (SD), area under the curve (AUC) and events of hypoglycemia and hyperglycemia recorded at baseline and at 12 weeks, were compared. Mean absolute difference (MAD) was used for calibration accuracy.

Results: The study cohort included 33 (60.6% females) children and adolescents. Their mean age was 12.3±4.5 years, and mean duration of T1DM 6.6±4.1 years. HbA1c was 9.4±1.5% at baseline and 9.1±1.3 at 12 weeks with an absolute reduction of 0.4% (p=0.04). Those with baseline HbA1c >9.5% demonstrated a significant absolute reduction of 0.7%. The change in hyperglycemia and hypoglycemia AUC was not statistically significant and MAD was 5% (p=0.01).

Conclusion: The use of rCGM may improve glycemic control in children and adolescents with sub-optimally controlled T1DM and may offer an opportunity to guide intensive insulin therapy.

Keywords: Continuous glucose monitoring; Type 1 diabetes; Metabolic control

Introduction

Despite advances in medical technology and pharmacotherapy, e.g. insulin analogues and insulin pump therapy; overall control of diabetes, particularly amongst children and adolescents, worldwide remains poor [1]. Current standards of care recognize the importance of Diabetes Self-Management Training (DSMT) and the need for individuals with diabetes to be actively involved in management to improve their glycemic control [1-3].

The aim of intensive therapy is to reduce the physiologic injury associated with hyperglycemia and high glucose variability [3]. Self-monitoring of blood glucose (SMBG) is essential for successful diabetes self-management and optimal glycemic control in people with type 1 diabetes [4,5]. However, many patients in frequently check post-prandial or overnight blood glucose level [4,6]. Furthermore, SMBG suffers from a number of potential sources of error, and glucose variability cannot be appreciated using SMBG [6-8].

Optima glycemic control is difficult to achieve particularly in children. It is estimated that only 9.7%- 37% of children with diabetes achieve a glycated hemoglobin (HbA1c) of less than 7.5% (53mmol /mol) [1,9,10]. However, HbA1c may not be the best predictor of outcomes. Recent studies suggests that glucose variability may play a more significant role in the risk of developing diabetic complications [11-15].

Retrospective continuous glucose monitoring (r-CGM) systems can record glucose patterns for six days and downloads can provide assistance to health care professionals (HCP) to adjust the patient's insulin therapy [16]. The efficacy of CGMS on glycemic control has been proven in many studies [3,8,17-20].

Recommended indications for the use of CGMS for patients with T1DM [3] include, hypoglycemic unawareness, frequent hypoglycemia, preconception and pregnancy, according to the American Association of Clinical Endocrinologists.

The aim of this pilot prospective cohort study, is to investigate the efficacy of r-CGMS for the adjustment of insulin therapy to improve glycemic control in poorly controlled children and adolescent with T1DM, in Dasman Diabetes Institute (DDI)

Methods

This study was done in the Dasman diabetes Institute. Children and adolescents with T1DM were enrolled in the study according to the inclusion criteria numerated in Table 1. There were excluded if they have used any type of CGM (retrospective or real-time) previously, In the last 3 months? Suboptimal control was defined as an HbA1c greater than 7.5% (58.5mmol/mol) [21]. Recurrent hypoglycemia and/or hypoglycemia unawareness.

Table 1: Inclusion criteria for recruitment of study participants.

Inclusion Criteria
Age <18 years old
On MDI
Duration of diabetes > 1 year
Sub-optimal glycemic control HbA1c > 7.5%, or Recurrent hypoglycemia and/or hypoglycemia unawareness with HbA1c<7.5%
Regular attendance to pediatric DDI clinic (define regularity)
SMBG at least 3 times a day

rCGMS is also called the iPro® device consists of two parts: iPro2 Recorder and the sensor iPro® recorder is a retrospective recording device, i.e. there is no real-time display of the sensor readings and therefore no action to be taken accordingly. It works as a blind-Type recording. The second part is the sensor (Enlite 2), which is an enzyme-tipped catheter inserted subcutaneously. Such a sensor has a three to six days' life-span 35 [22].

Calibration is needed for the device, and is performed with four capillary blood-glucose measurements daily. This is done by measuring blood sugar using a regular glucometer and entering the value into the device. CGMS download is performed a week later. The results were saved in PDF files and were sent to the patient's Health care provider (HCP) to adjust their management plans accordingly

The study was carried out over a period of 24 weeks. Children and adolescents who were enrolled in the study wore the iPro® device for 3-6 days during week 1. They were then seen in week 2 for the download and subsequent therapy adjustment. rCGMS was repeated again after 3 months, and the impact of insulin adjustment was evaluated using downloads (Figure 1).

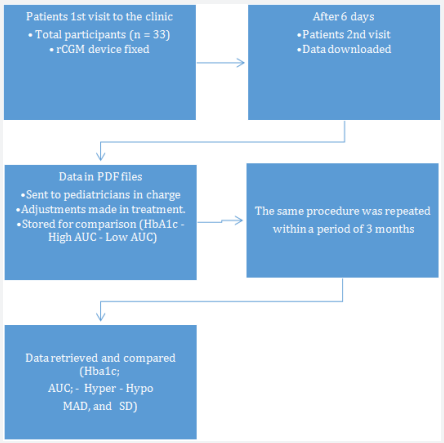

Figure 1: Flowchart of study design.

Data were collected from the electronic health record of patients. Data collected included demographics, HbA1c, and rCGM download. The latter included several parameters, such as high Area Under Curve (AUC), low AUC, and SD. AUC provides more insight into how much time the patient's blood glucose was high or low, as well as the severity of excursions outside of the target range. The closer that AUC is to zero, the more that blood glucose remained within the target range. For calibration accuracy MAD used; which is computed as the average of the absolute values of the differences between sensor readings and reference blood glucose values [23].

The primary outcome was the improvement of glycemic control as measured by HbA1c change. Secondary outcome measures were to detect

a. Postprandial hyperglycemia using Area under the Curve (AUC),

b. Hypoglycemia and

c. Glucose variability.

Statistical analysis

Descriptive statistics (frequencies, mean, SD) were used to describe the sample's demographics and characteristics. Mean HbA1c before vs after, was analyzed using paired t-tests with P≤0.05 defining significance. HbA1c was assessed for all participants (n=33), AUC's, were assessed only for participants who completed the study (n=23).

Results

A total of thirty three children and adolescents with T1D were recruited. There were 20 (60.6%) females and 13 (39.4%) males creating a male-to-female-ratio of 0.7. Kuwaiti nationals

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constituted 63.3% of them. Their mean age was 12.3±4.5 years, mean BMI was 21.0±5.0 Kg/M2 and the mean duration of diabetes was 6.6±4.1 years (Table 2).

Table 2: Characteristics of children and adolescents enrolled in the study.

Total number of participants	33
Male-to-female ratio	0.7 (13:20)
Age (mean±SD)	12.3±4.5 years
Age range (years)	5 (minimum)-18 (maximum)
Mean duration of T1D (years)	6.6±4.1
BMI (kg/m2)	20.6±5.4
Baseline HbA1c (%)	9.4±1.5
Baseline HbA1c < 8.0 %	5 (15.2%)
Baseline HbA1c 8.0 – 9.5%	12 (36.4%)
Baseline HbA1c > 9.5%	16 (48.5%)

The study cohort had a baseline HbA1c of 9.4±1.5%. Treatment adjustments was made by corresponding treating physicians in the light of the results of rCGM. HbA1c was repeated three months later to yield 9.1±1.3%. The absolute difference, 0.3%, was statistically significant (P <0.05). Further analysis of data of 29 children with no hypoglycemia unawareness or recurrent hypoglycemia showed a reduction of HA1c from 9.8±1.1 at base line to 9.4±1.1 after three months (p =0.029) (Figure 2).

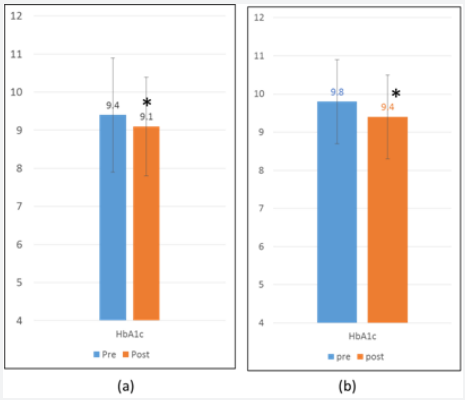

Figure 2: HbA1c before and after treatment adjustment based on the results of rCGM for all study cohort (a) and for children and adolescents with T1D with no hypoglycemia unawareness or recurrent hypoglycemia (b).

The effect of age, baseline glycemic control and gender was examined (Figure 3). Children and adolescents with baseline HbA1c > 9.5% demonstrate a statistically significant absolute reduction of 0.7% from baseline 10.5±1.0% to 9.8±1.2% (p 0.009). Male patients had higher HbA1c than females before and after treatment adjustments. However, they showed a larger drop in HbA1c with 0.5% from 9.8±1.9% to 9.3±1.5% vs girls who dropped their HbA1c by 0.3% from 9.2±1.1% to 8.9±1.3% although both changes did not reach statistical significance. Children below 12 years of age showed non-statistically significant improvement of HbA1c of only 0.2% from 8.9±1.1% to 8.7±1.0%. Children and adolescents aged 12 years and above reported 0.5% absolute reduction of baseline HbA1c from 9.9±1.6% to 9.4±1.5% although the drop was not statistically significant as well (Table 3).

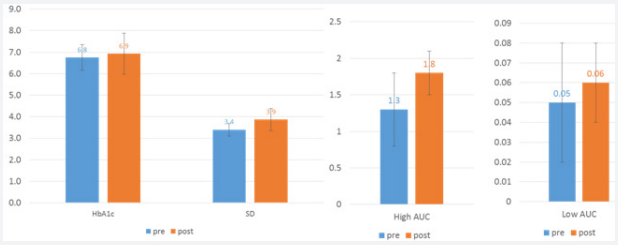

Figure 3: HbA1c before and after treatment adjustment based on the results of rCGM for all study cohort stratified according to age (a) glycemic control at baseline (b), and gender (c).

Table 3: Results of children and adolescents with T1D before and after treatment adjustment based on results of rCGM.

	Before		After		P value
	Mean	SD	Mean	SD	
HbA1c	9.4	1.5	9.1	1.3	0.044*
High AUC	3.52	1.75	3.31	1.56	0.406
Low AUC	0.04	0.04	0.06	0.07	0.247
SD	4.61	1.42	4.46	0.83	0.551
MAD	19.87	8.5	15.35	7.16	0.017*

The improvement in the mean hyperglycemia AUC from CGMS at baseline (3.6±1.9) and after three months (3.3±1.6), and the change in mean low AUC from baseline of 0.0396±0.04 to 0.058±0.07 after three months were not statistically significant. Moreover, the difference between the mean SD of CGM glucose readings during the entire CGMS recording at baseline (4.7±1.7) and after three months (4.5±0.8) was not statistically significant (p =0.551) (Figure 4).

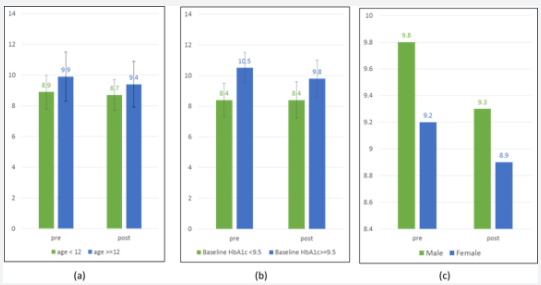

Figure 4: HbA1c before and after treatment adjustment based on the results of rCGM for all study cohort stratified according to age (a) glycemic control at baseline (b), and gender (c).

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Discussion

CGMS is engineered to monitor continuous glucose concentrations in the interstitial fluid of subcutaneous tissue. The system records glucose values within the range 2.2-22.2mmol/l [24]. HbA1C reflects average glycaemia over several months and has strong predictive value for diabetes complications [21]. It is the primary target for glycemic control and is a good indicator for general improvement in the blood glucose levels, as revealed from the DCCT and UKPDS where intensive glycemic control in type1 and type 2 diabetes reduce microvascular complications [25] The technology of CGM has been very helpful as the information gained from it provide a clear window to look at the glucose profiles and excursions.

There was a statistically significant improvement in HbA1c in children and adolescents with suboptimal glycemic control following r-CGM. This finding is consistent with other studies. Both Kaufman et al. & Chase [18,26] have assessed the effectiveness of CGM in a similar population of children and adolescents [18,26]. They both concluded that CGM can be used in those with suboptimal glycemic control with a significant reduction of HbA1c at 3 months. The magnitude of HbA1c improvement in this study for the cohort was an absolute drop of 0.3%. This is comparable to what has been described by Kaufman and Chase who found an absolute reduction of 0.2% and 0.36% in there cohorts respectively [18,26].

Despite the fact that a randomized control trial (RCT) that was carried out in adult, adolescents and children over 6 months has demonstrated that CGM is less beneficial in in children [4]. A significant reduction in HbA1c of 0.4% was seen in adults with baseline HbA1C≥7.0%, but was not seen in children. They also showed that children and adolescents were less likely to use CGM frequently [4]. Parental satisfaction with CGM was, however, demonstrated by Mauras et al. [27] in a study of 146 children with mean age of 7.4 years [27] although they failed to show any statistically significant improvement in HbA1c. Other studies found no significant difference in HbA1c after the use of CGM [28].

The hypoglycemia AUC was used as the principal measure of hypoglycemia improvement as it integrates both the duration and the severity of hypoglycemia episodes, which was demonstrated by [29]. They also found that CGM is a useful guiding tool to be used in the modification of insulin therapy to patients with diabetes.

This study has failed to show any significant difference in high, low AUC or SD before or after the use of CGM. The results of the study went in agreement with a RCT by Yates et al in that high AUC did not change between CGM and SMBG [30]. They also found that high AUC was not associated with HbA1c. Although not statistically significant, the low AUC actually increased after the use of CGM. This agrees with Langendam et al review of 22 RCTs that found that CGM use increased the risk of hypoglycemia. In contract, another 6 months RCT in adults and children concluded that CGM was effective in reducing episodes of hypoglycemia [4,31].

Conclusion

Tight glycemic control in pediatrics is hardly achieved without increasing the risk of hypoglycemia. SMBG is not helpful in detecting asymptomatic glucose excursion. CGM is a relatively new technology that aims to give a better insight into the glucose profile to appreciate the asymptomatic changes and assess the current therapy. This study investigated the efficacy of CGMS in therapy adjustment and improving glycemic control in children and adolescent with poorly controlled T1DM.

Despite the limitation of sample size, there was statistical significant reduction in HbA1c. The changes in hyperglycemia, hypoglycemia AUC and SD did not show any significance. Thus, our findings suggest that 6-day CGM may offer opportunities to improve HbA1c in pediatric patients with T1DM.

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Conflict of Insterest

There are no economic interest or any conflict of interest.

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