Original Article

Evaluation of accuracy of ambulatory glucose profile in an outpatient setting in children with type 1 diabetes

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ABSTRACT

Background: In children with type 1 diabetes, intensive diabetes management has been demonstrated to reduce long-term microvascular complications. At present, self-monitoring of blood glucose (SMBG) by patients at home and glycated hemoglobin estimation every 3 months are used to monitor glycemic control in children. Recently, ambulatory glucose profile (AGP) is increasingly being used to study the glycemic patterns in adults. However, accuracy and reliability of AGP in children have not been evaluated yet. **Objectives:** To assess the accuracy of AGP data in children with type 1 diabetes mellitus when compared with laboratory random blood sugar (RBS) levels, capillary blood glucose (CBG) measured by glucometer in the hospital, and SMBG monitored at home. **Methods:** Paired RBS, CBG, and AGP data were analyzed for 51 patients who wore AGP sensors for 2 weeks. Simultaneous venous and CBG samples were collected on day 1 and day 14. SMBG at home was checked and recorded by the patients for optimizing insulin doses. Accuracy measures (mean absolute deviation, mean absolute relative difference (MARD), and coefficient of linear regression of AGP on RBS, CBG, and home-monitored SMBG were calculated. **Results:** Seventy paired RBS, CBG, and AGP data and 362 paired home-monitored SMBG and AGP data were available. The MARD was 9.56% for AGP over RBS and 15.07% for AGP over CBG. The linear regression coefficient of AGP over RBS was 0.93 and that of AGP over CBG was 0.89 ($P < 0.001$). The accuracy of AGP over SMBG was evaluated over four ranges: <75, 76–140, 141–200, and >200 mg/dl. **Conclusion:** In this study, AGP data significantly correlate with RBS and CBG data in children with type 1 diabetes. However, a large number of samples in a research setting would help to document reproducibility of our results.

Key words: Accuracy of ambulatory glucose profile, ambulatory glucose profile, glucose profile in children

Introduction

It is well known that in type 1 diabetes mellitus, optimal glycemic control is extremely important to prevent or postpone long-term complications. In general, glycemic control in children with type 1 diabetes is monitored by measuring glycated hemoglobin (HbA1C) and self-monitoring of blood glucose (SMBG). As demonstrated in various studies, HbA1C correlates well with long-term complications.[1] However, HbA1C is only a measure of mean blood glucose over the previous 2–3 months and not a representation of diurnal patterns of glucose variability. Research has demonstrated that in patients with diabetes, glycemic variability is an independent risk factor

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Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.190546

Cite this article as: Hulse A, Rai S, Prasanna Kumar KM. Evaluation of accuracy of ambulatory glucose profile in an outpatient setting in children with type 1 diabetes. Indian J Endocr Metab 2016;20:643-7.

for developing long-term complications even when HbA1C is in normal range.[2-4]

When SMBG is used to understand glycemic patterns, ideally it should be recorded at pre- and post-meals and at midnight every day which comes to about seven pricks per day. This is not only stressful for a young child with diabetes but also incurs a huge cost to the family. As a result, many patients resort to a compromised SMBG recording where they check blood glucose 3–4 times/day. This may lead to erroneous recognition of patterns based on which insulin doses are adjusted. There are various studies demonstrating the fact that SMBG recording may miss significant hypoglycemic episodes, particularly nocturnal hypoglycemia as well as postprandial hyperglycemia which can be captured by continuous glucose monitoring (CGM).[5,6]

CGM helps to identify glycemic patterns which may not be evident on SMBG record and assists patients achieve their goal of optimum glycemic control.[5,7] However, the data generated by CGM is enormous, and this sometimes poses difficulty for a clinician to interpret it. Therefore, a need for simpler and easily comprehensible summary of continuous glucose data which would reveal the important patterns of glycemic variability was recognized. Ambulatory glucose profile (AGP) (using FreeStyle Libre Flash Glucose Monitoring (FGM) system, Abbott Diabetes Care, Alameda, CA, USA) combines all the data from CGM over a period of 14 days and gives a summarized visual display of glycemic patterns. This system is sometimes referred to as FGM system as it measures glucose in the interstitial fluid every 15 min.

Accuracy and reproducibility of CGM in adults as well as in children have been established in various studies.[8-11]

Earlier versions of CGM sensors used capillary blood glucose (CBG) for calibration of the sensor. Typically, CBG and random blood sugar (RBS) are used as references to measure the accuracy of the sensor devices. There are differences in CBG (measured using glucometer) and RBS (plasma glucose measured by laboratory analyses) as glucose concentration in capillary and vein varies. Therefore, if CBG is used to calibrate CGM, it may affect the accuracy assessment of the sensor device. Newer sensor devices as used in our study (FreeStyle Libre FGM system, Abbott Diabetes Care, Alameda, CA, USA) are factory calibrated and do not require calibration using CBG. The accuracy of this system has been documented in adults.[12]

It is being used in several countries in adults, but its use in children is yet to be explored.[13,14]

The aim of this study is to evaluate the accuracy of AGP using FreeStyle Libre FGM system in comparison to RBS as well as CBG (monitored at hospital and home) in children.

Methods

This prospective study was conducted at two clinical sites in South India. A total of 51 subjects were enrolled after written informed consent was obtained from them. Ethical approval was obtained from the institutional review board. Children aged one to 18 years with type 1diabetes were included in the study. Those with known allergy to medical grade adhesive or isopropyl alcohol used to disinfect skin, those with extensive skin diseases at the proposed application sites and with associated diseases such as untreated hypothyroidism were excluded from the study.

The sensor was inserted over the upper arm of the study participants. Simultaneous capillary and venous blood glucose were measured on the day 1 and day 14 in the hospital. CBG was checked using glucometer (Accu-Chek active, Roche). Venous blood glucose was analyzed in the laboratory using Turbo Chem 100 (Awareness Technology Inc. USA) glucose analyzer. Day 14 samples could not be obtained in whom the sensor dislodged before 14 days. The subjects were also asked to continue checking SMBG at home during the sensor wear period using their own glucometer, 2–4 times a day (before meals and 2 h after meals). During this time, insulin doses were adjusted by the study participants or their parents based on their SMBG readings. The sensors were removed after 14 days.

The accuracy of the AGP data was also evaluated over four different SMBG ranges: <75 mg/dl, 76–140 mg/dl, 141–200 mg/dl, and >200 mg/dl to determine if there were differences in accuracy at various glucose concentrations. Clarke error grid analysis (EGA) was used to evaluate the point accuracy for AGP versus RBS and AGP versus CBG.

Statistical analysis

Categorical variables such as patient characteristics are presented as "*n*" and standard deviations. Accuracy measures such as mean absolute deviation, mean absolute relative difference (MARD), and coefficient of linear regression of AGP on RBS, and CBG were calculated. Accuracy measures were also calculated for AGP on home-monitored SMBG. Statistical analysis was done using Microsoft Excel Spreadsheet.

Results

Paired RBS, CBG, and AGP data were analyzed for 51 patients. The average sensor wear period was 10.6 days. Thirty-four (66.66%) study subjects completed 14 days

of sensor wear. Demographic characteristics of the study participants are listed in Table 1. Seventy paired RBS, CBG, and AGP data and 362 paired home-monitored SMBG, and AGP data were available. Two paired readings were excluded because the sensor readings were out of system's recordable range (<40 mg/dl or more than 500 mg/dl).

The linear regression coefficient of AGP over RBS was 0.93, and that of AGP over CBG was 0.89 ($P < 0.001$). Average MARD of AGP over RBS was 9.6%, and that of AGP over CBG was 15.07%. A detailed comparison of RBS, CBG, and AGP data are illustrated in Table 2.

The difference between AGP and home-monitored SMBG values were compared across different SMBG ranges as illustrated in Table 3. When SMBG was <75 mg/dl, only 65% of the AGP readings were within 20% of SMBG readings. Whereas, when SMBG was more than 200 mg/dl more than 77% of the AGP readings were within 20% of SMBG readings. The linear regression coefficient of AGP over SMBG was 0.93 ($P < 0.001$).

The Clarke EGA for paired values of AGP versus RBS yielded 75.9%, 22.5%, 1.6%, 0.0%, and 0.0% results in zones A, B, C, D, and E, respectively. Corresponding findings for AGP versus CBG included 54.9%, 43.5%, 0.0%, 0.0%, and 1.6% results in zones A, B, C, D, and E, respectively. Clinically, acceptable values are represented by dots in zone A and B of Clarke EGA in Figure 1a and b.

Major adverse reaction was not noticed in any of the study participants who wore the FGM sensor. Mild pain and irritation at the sensor insertion site were complained by five of the study participants.

Table 1: Demographic Characteristic of Study Participants

Demographic Characteristics	*n*=51
Age (years) (mean (SD))	10.44 (5.14)
Gender, *n* (%)	
Female	22 (43.13)
Male	29 (56.86)
BMI (kg/m^2) (mean (SD))	17.32 (4.07)
Diabetes duration (years) (mean (SD))	3.62 (3.67)
Age at Diagnosis (years) (mean (SD))	6.84 (3.93)
HbA1C (%) (mean (SD))	10.13 (2.04)
Insulin regimen, *n* (%)	
Split Mix	29 (56.86)
Basal Bolus	21 (41.17)
CSII	1 (1.96)

Table 2: Comparison of RBS, AGP and CBG data

	RBS vs. AGP	CBG vs. AGP	RBS vs. CBG
Linear Regression Coefficient (*r*) (*P*<0.001)	0.93	0.89	0.94
Mean Absolute Deviation (MAD) (mg/dl)	27.00	28.74	20.46
Mean Absolute Relative Difference (MARD) (%)	9.56	15.07	13.40
Median Absolute Relative Difference (%)	10.65	18.40	7.56

RBS: Random blood sugar, AGP: Ambulatory glucose profile CBG: Capillary blood glucose

Table 3: Comparison of AGP data across various SMBG ranges

SMBG (mg/dl) *n*=362	Paired SMBG and AGP data (*n*)	AGP data within 20% of SMBG *n* (%)
<75	37	24 (64.80)
76-140	96	68 (70.83)
141-200	83	61 (72.49)
>200	146	113 (77.30)

AGP: Ambulatory glucose profile, SMBG: self-monitoring of blood glucose

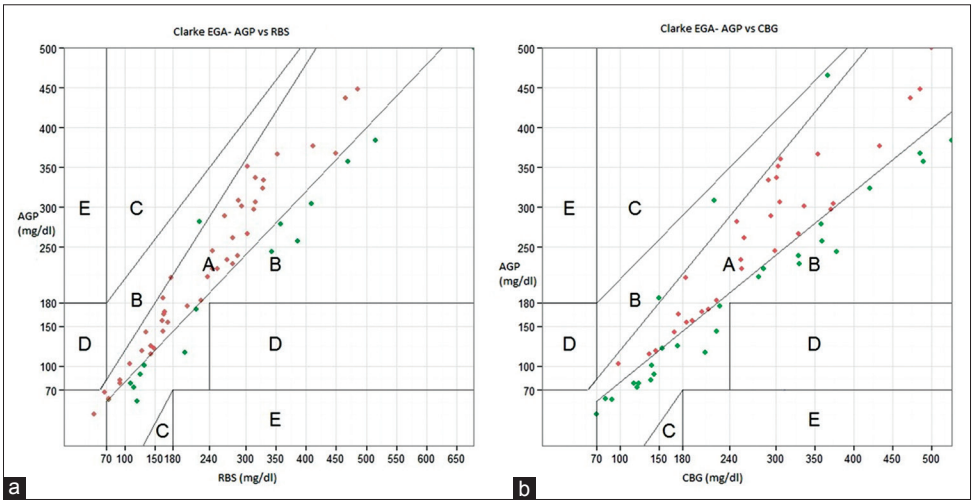

Figure 1: (a) Clarke EGA of paired AGP and RBS (used as reference) data in clinically significant zones A and B. (b) Clarke EGA of paired AGP and CBG (used as reference) data in clinically significant zones A and B

Discussion

This study was undertaken to evaluate the accuracy of AGP using FreeStyle Libre FGM system in comparison to plasma glucose and CBG measured at the hospital as well as at home environment, in children with diabetes. Feasibility and acceptability of AGP in our study subjects have been reported in a separate paper which is being submitted for publication.

The accuracy of CGM and FGM sensors have been studied against frequently sampled venous and capillary blood.[12,15,16] In this study, the linear regression coefficient of AGP over RBS was 0.93 and that of AGP over CBG was 0.89 which is comparable to a recently published study evaluating the performance and usability of "FGM system" involving adults.[12] In our study, MARD for AGP over RBS was 9.56% and that of AGP over CBG was 15.07%. MARD is a concise measure of the accuracy of a glucometer device. Earlier studies by Andelin *et al*., comparing CGM system (using CBG for calibration) have quoted MARD of 11.7% using capillary values as a reference and 13.7% using venous samples which is similar to the findings in this study.[16] Other studies comparing various CGM devices have quoted similar numbers.[15,16] In this study, MARD was lower when AGP was compared to RBS than when it was compared to CBG.

In this study, three different references (RBS, CBG, and SMBG) have been used to assess the accuracy of AGP. In the hospital setting, the reference method used was the plasma glucose analysis, whereas AGP sensor measures interstitial glucose. Many studies have compared interstitial glucose and plasma glucose and have found a good correlation between the two.[15-17] Our results too confirm these findings. Second, we compared capillary glucose checked at the hospital with a single glucometer with AGP glucose data and found a similar correlation. However, comparison with plasma glucose reference showed relatively better accuracy. Finally, testing the accuracy of AGP at home by the patients reflects the performance of AGP sensor in routine practical setting. Hence, the accuracy of AGP was assessed in reference to SMBG done at home by the patients. This method also facilitates more number of paired glucose data to be obtained at different time of the day which is difficult to obtain in the hospital without admitting the study subjects. However, in the home setting, since there is no supervision, the validity of the data is questionable. The Linear regression coefficient for AGP versus SMBG was 0.93.

In this study, glucose data obtained by AGP and SMBG were compared across various glucose ranges. In the lower range (SMBG <75 mg/dl), only 65% of the AGP data were within 20% of corresponding SMBG data, whereas more than 70% of the AGP data were within 20% of SMBG data when glucose levels were higher (>75 mg/dl). This is in line with other studies on CGM where it has been found that the accuracy may be compromised at lower glucose levels.[18] However, it is to be noted that this does not indicate the absolute accuracy, but the relative accuracy of AGP device in comparison with SMBG measurement by glucometer.

The main limitation of this study includes a small number of paired venous and capillary samples. This is because of practical difficulties as well as ethical issues involved with the procedure of multiple venous sampling in children. The study was performed in outpatient clinical setting and not in a research setting making it difficult to obtain multiple samples from the study participants. SMBG data obtained at home was not directly supervised but was counter checked and confirmed from individual glucometer records. In addition, SMBG at home was monitored using different glucometers used by individual patients which could have affected accuracy results. We could not check reliability over different periods in 2 weeks due to less number of samples. Earlier studies have mentioned that there is inconsistency in the results when the accuracy of CGM sensors are assessed at hospital and home environment.[19] In contrary to this, in our study, the accuracy of the AGP sensor was found to be similar both at hospital setting as well as at home environment (r = 0.89 for AGP vs. CBG and 0.93 for AGP vs. SMBG).

The results on AGP from this study provide a novel and painless modality of studying glycemic trends in children with diabetes. However, at lower glucose levels (<75 mg/dl), AGP values need to be interpreted with caution and should be confirmed by SMBG before clinical intervention.

Conclusion

The findings of the study revealed that AGP glucose data correlates well with corresponding RBS as well as CBG. Even at home setting, there is agreement between AGP glucose data and corresponding SMBG. However, a large number of samples in a research setting would help to document reproducibility of our results.

Acknowledgement

We would like to thank MERT for their financial support and Mrs. Ratna, co-ordinator at Bangalore Diabetes Hospital for her support in co-ordinating this study.

Financial support and sponsorship

Partial funding received from Medical Education Research Society (MERT), Bengaluru, Karnataka, India.

Conflicts of interest

There are no conflicts of interest.

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