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Original Research Article

Impact of continuous glucose monitoring with diabetic education on glycemic variability and HbA1c

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ABSTRACT

Background: Continuous glucose monitoring (CGM) is an invasive technique which can be used in both outpatient and inpatient settings and can be used for assessing the glycemic variability among individuals with diabetes. It is an effective tool in diabetic management for evaluating the hypoglycemic, hyperglycemic and euglycemic events.
Methods: The study was both retrospective and prospective which was conducted at Believers Church Medical College Hospital, Thiruvalla after getting approval from the institutional ethical committee and patient consent was also taken. Patients with uncontrolled diabetes and those with suspicion of hypoglycaemia were taken from the patients attending the diabetic clinic from 26 July 2017. The study duration was from 26 July 2017 to 19 October 2019 (2 years).
Results: The study revealed the importance of CGM in the therapeutic management of diabetic patients by monitoring the individual patients and leading to an individualization of therapeutic regimen. It also helped to analyse the effect of each antidiabetic agent in the individual patients and thereby preventing the further occurrence of hypoglycemic and hyperglycemic stages in the individuals and will help to maintain a euglycemic stage in each individual and thus improving the patient's quality of life.
Conclusions: Hence it is concluded from this study that CGM has an important role in the better therapeutic management in diabetic patients as it helps in individualisation of therapy based on each patient in a better glycaemic control leading to a euglycemic state resulting in statistically significant HbA1c reduction.

Keywords: Continuous glucose monitoring, Diabetes mellitus, HbA1c, Type 2 diabetes mellitus

INTRODUCTION

Real time continuous glucose monitoring (CGM) is an emerging technology, on which few randomized controlled trials have been performed worldwide. It is a minimally invasive and a painless procedure which can be done on an outpatient basis and a maximum of 14 days glucose monitoring can be done. Many clinically useful information can be obtained like hyperglycemic excursion, hypoglycemic episodes and meal related glucose surge and proper therapeutic as well as diabetic education can be initiated on an individual basis to overcome the issues which each patient experiences. So, it can be considered as one of the effective tool in diabetic management.

The CGM have involved patients with a high level of involvement in their diabetes self-care management. Use

of CGM successfully, patients need to have advanced diabetic self-management skills. Continuous glucose monitor is a device used for monitoring blood glucose on a continuous basis in people with either type 1 or type 2 diabetes. A continuous glucose monitor takes the reading during pre-set intervals with a small electrode placed under the skin and held in place by an adhesive. A transmitter attached to the electrode sends data to a separate receiver.[1] A limitation of continuous glucose monitor systems is that glucose levels are measured from the interstitial fluids rather than the blood. As it takes time for glucose to travel from bloodstream into intestinal fluids there is an inherent lag between the current blood glucose level and the level of glucose measured by the continuous glucose monitor. This lag time varies based on the person and device and is generally 5-20 minutes.[2] Interstitial fluid glucose generates an electric current when it is oxidized in a reaction catalyzed by glucose oxidase.[3] Electric current data are transmitted to a receiver and then converted into glucose level that can be measured in mg/dL.[4] While it has not eliminated the risk of severe hypoglycemia, CGM allows patients to reduce HbA1c level without increasing the risk of severe hypoglycaemia.[5] In a multi-centre clinical trial funded by juvenile diabetes research foundation (JDRF), an improvement of 0.5% after 6 months of CGM use was seen in those patients above age of 25. In well controlled patients, CGM can substantially reduce the exposure to biochemical hypoglycemia, while helping to maintain HbA1c level within normal range. Real time CGM leads to an improvement in glycemic control without an associated worsening in the hypoglycemic events, is in direct contrast to other intervention studies such as DCCT in hypoglycemia, while helping to maintain HbA1c level within normal range.[6] Real time CGM leads to an improvement in glycemic control without an associated worsening in the hypoglycemic events, is in direct contrast to other intervention studies such as DCCT in which intermittent capillary glucose monitoring had been used to guide the intensification of metabolic control and points to promise this new technology offer for people with T1DM. Because of the lag of interstitial glucose below blood glucose, when the glucose level is declining the interstitial glucose can be in the normal range even through blood glucose is low when glucose is falling rapidly, physiological lag leads to underestimation by rate change indicator in the CGM device. In practice the patient feels hypoglycemic or suspects that the glucose is declining, but this is not corroborated by the sensor, they should disregard the sensor data and carry out a finger glucose measurement.[7]

GV has a more specific triggering effect on oxidative stress than sustained hyperglycemia.[8,9] Blood glucose values is accessed easily without effort, but also because indicators in the equipment provides insightful information that enables the diabetes is managed more proactively and effectively than with SMBG.[10,11] Key causes of severe hypoglycemia are asymptomatic hypoglycemia or hypoglycemic unawareness and nocturnal hypoglycemia.[12] These conditions impede patients' perception of hypoglycemia when it is occurring and, thus, limits their ability to take necessary and timely action. Impaired hypoglycemic awareness results from frequent hypoglycemic events (severe and non-severe).[13] Nocturnal hypoglycemia accounts for a significant proportion of hypoglycemic events and often goes undetected.[14] In an earlier study of 70 patients using CGM, data revealed hypoglycemic unawareness in 62.5% patients with type 1 diabetes mellitus (T1DM) and 46.6% of patients with type 2 diabetes mellitus (T2DM) - 73.7% of all episodes occurred during the night.[15] Nocturnal hypoglycemia is particularly concerning among adults and children after physical exercise.[16] In the report by Gomez et al, the severity of hypoglycemia is elevated during recovery from exercise for at least 24 hours, with the greatest risk of nocturnal hypoglycemia occurring after afternoon activity. In another study it is demonstrated that, the significant relationship between glucose fluctuations and macrovascular complications.[17] Furthermore, hypoglycemic episodes increased incidence and mortality of cardiovascular events of patients with advanced T2DM.[17,18]

CGM improves the capability to detect rapid hypoglycemia and hyperglycemia events which are usually missed by intermittent blood glucose measurements, and allows the possibility of evaluating glycemic variability diabetic patients, which is a promising marker for the prevention of complications and bad outcomes in critically ill patients.[19-22] CGMs that showed the highest accuracy and reliability performances are those based on one of two types of technology: transcutaneous (or needle-type) systems, where the amperometry biosensor is situated on the tip of a thin needle directly implanted in the subcutaneous tissue.[17,23,24]

The limitation of HbA1c measurements that hinder its usefulness in daily diabetes self-management. For example, it does not reflect intra- and inter-day glycemic excursions that may lead to hypoglycemia or postprandial hyperglycemia. Nor does it reflect the occurrence or degree of daily glucose variability, which has been shown to be a consistent predictor of hypoglycaemia.[25-27]

Monnier and colleagues have shown that glycemic variability might trigger adverse biological events and oxidative stress in patients with type 2 diabetes.[28]

Hypoglycemia during the insulin therapy has been shown to increase the risk of mortality, but can potentially be minimized with more frequent monitoring of the blood glucose level. Current technological advances relate to user-friendly software, interface, and displays and to better data management/analysis software, extending to artificial intelligence and automatic CGM real-time data transfer through Internet, smartphones including IoT devices.[29-31]

T1DM is also linked to a drastic drop of blood glucose (BG) during exercise, which potentially increases the risk of hypoglycaemia.[32,33]

METHODS

The study was both retrospective and prospective which was conducted at Believers church medical college hospital, Thiruvalla. Patients with uncontrolled diabetes and those with suspicion of hypoglycemia were taken from the patients attending the diabetic clinic from 26th July 2017. This study was approved by the institutional ethical committee and patient consent was also taken. The study duration was from July 2017 to October 2019 (2 years).

Inclusion criteria

- Patients with type 1 or type 2 diabetes who are on Insulin mainly premixed insulin, sulfonylureas, metformin, DPP-4 inhibitors and SGLT2 inhibitors.

Exclusion criteria

- Authors have excluded bedridden patients, those with dementia, stroke patients and gestational diabetes mellitus (GDM).

Demographic data was obtained from the computerized database. Each prescription about the oral hypoglycemic agents (OHA) and insulin were also obtained from the patient and also from the databases.

Patients were closely monitored and advised regarding the dietary and lifestyle modifications and monitoring of hypoglycemic events, if any. Diabetic education was initially given during the attachment of CGM device. The diabetic education include, Benefits of CGM in glycaemic control, pathophysiology of diabetes, complications in DM and its prevention, action of insulin and oral hypoglycemic agent, symptoms and management of hypoglycaemia and uncontrolled hyperglycaemia, blood glucose testing, glucometer using training, injection (how to use injection- insulin), diet control, foot care, physical exercises in diabetes, smoking cessation, weight maintenance in DM etc.

Telephonic communication was actively done regarding the CGM related issues with the diabetic educator and patient was advised to monitor glucose levels using a glucometer if he/she doubts the occurrence of hypoglycemic events.

RESULTS

The study was composed of all diabetic patients and among them 44 patients, 23 (52%) were male and 24 (48%) Female were followed up after diabetic education along with CGM (Figure 1).

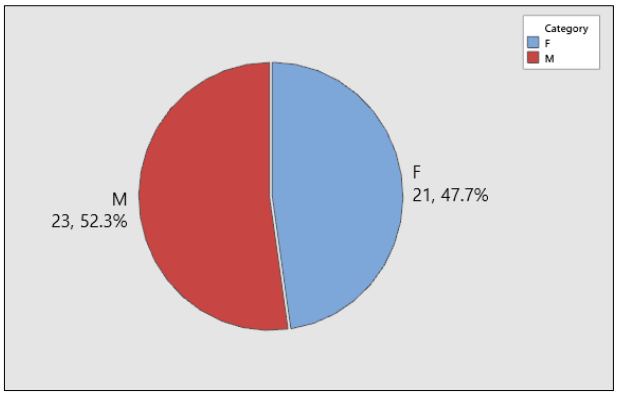

Figure 1: Gender distribution of the study population (n=44).

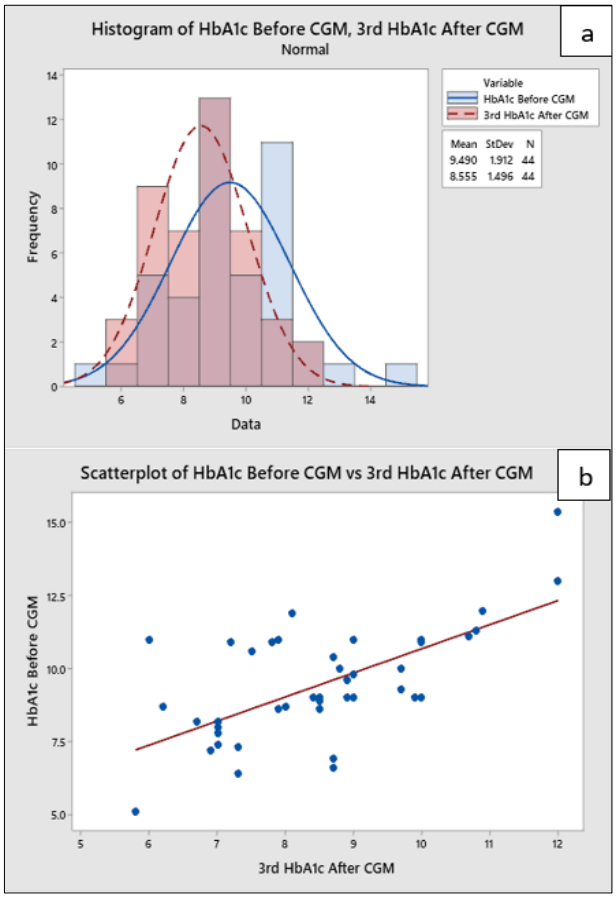

Figure 2: (a) Comparison of mean of HbA1c before and after CGM using t test (t=4.184, p<0.001) and (b) Correlation of mean of HbA1c before and after CGM (n=44) (r=0.645 (p<0.001)

The 3rd HbA1c value, 2nd measure after CGM (8.56±1.50) was significantly lower (t=4.184 and p<0.01) the HbA1c before CGM (9.49±1.91) when compared using the t test. The correlation between the HbA1c before CGM and second measurement after CGM were significantly positively correlating (r=0.645 and p<0.01) when Pearson correlation statistics is used (Figure 2).

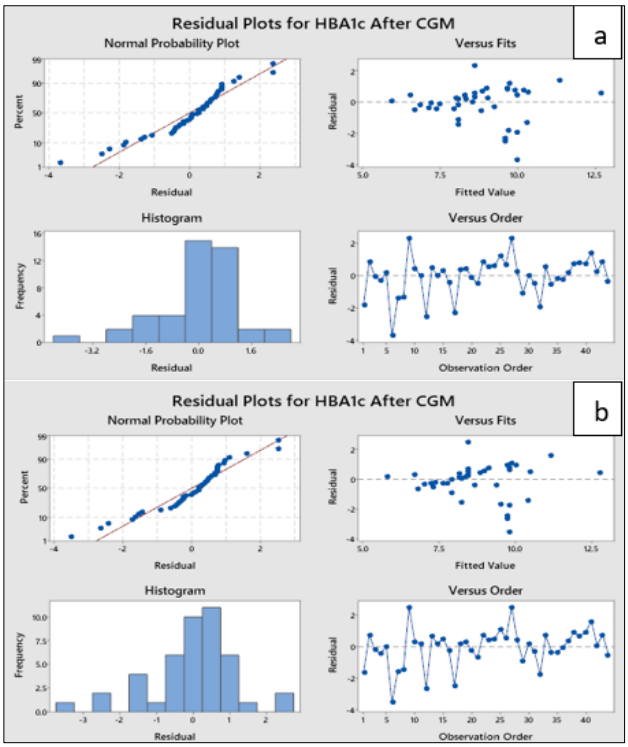

Figure 3: Residual plot for HbA1c after CGM.

Post CGM predictive equations were derived using the complete data and male and female subjects separately and showed an approximate 1 percent decrease HbA1c in post CGM for a pre CGM HbA1c of 10.5%. (Figure 3, Equation 1-3).

Predictive regression equation for the post HbA1c values in all subjects

HBA_{1c} after CGM $= 2.321+0.6813\ HbA_{1c}$ Before CGM Eqn:1

Predictive regression equation for the post HbA1c Values in male and female subjects

Gender

F HBA_{1c} After CGM $= 2.440+0.6864\ HbA_{1c}$ Before CGM Eqn:2

M HBA_{1c} After CGM $= 2.119+0.6864\ HbA_{1c}$ Before CGM Eqn:3

The association of the insulin therapy with the glycemic events (Euglycemia, hypo and hyperglycemia) was verified and found that the hypoglycemia, euglycemia and hyperglycemia are associated with the insulin therapy when insulin was used as one of the treatment modalities (Table 1). The percentage of hyperglycemic events where more when all the four treatment modalities were used, while the percentage of hypoglycemic events where less than the hyperglycemic and euglycemic events.

Table 1: Association of different therapy with the glycemia.

		% Euglycemia		% Hypoglycemia		% Hyperglycemia	
		Observed	**Chi-Sq**	**Observed**	**Chi-Sq**	**Observed**	**Chi-Sq**
Insulin	N	368.76	207.187	167.23	54.3545	373.45	1400.26
	Y	876.75	p<0.001	331.95	p<0.001	2312.95	p<0.001
Metformin	Y	890.04	229.436	292.05	14.4465	1733.38	226.683
	N	355.47	p<0.001	207.13	p<0.001	953.02	p<0.001
Sulphonyl urea	Y	405.93	150.984	131.8	111.178	960.12	218.508
	N	839.58	p<0.001	367.38	p<0.001	1726.28	p<0.001
DPP4	Y	1018.91	504.015	414.81	218.74	2297.93	1357.22
	N	226.6	p<0.001	84.37	p<0.001	388.47	p<0.001

DISCUSSION

The study population comprised 44 subjects between the age of 20 to 80 years with 52% male and 48% female subjects. Similar studies conducted in the United Kingdom investigated 91 patients within the age group of 35±10 years including 42 % females and 58% males. A randomized control trial conducted during the period of October 2014 and May 2016 at endocrinology practices in the United States included 158 adults with type 1 diabetes who were using multiple daily insulin injections, [mean age, 48 years; 44% women; mean baseline HbA1c level, 8.6%; and median diabetes duration, 19 years (IQR 10-31 years)], 155 (98%) completed the study.

In the current study, HbA1c was compared and correlated as, the 3rd HbA1c value, second measure after CGM (8.56±1.50) was significantly lower (t=4.184 and p<0.01) the HbA1c before CGM (9.49±1.91) when compared using the t-test. The correlation between the HbA1c before CGM and second measurement after CGM were significantly positively correlated (r=0.645 and p<0.01) when Pearson correlation statistics are used. Similar studies which conducted in United States showed that

Mean reduction in HbA1c level from baseline at 12 weeks was 1.1% and at 24 weeks was 1.0% in the CGM group and 0.5% and 0.4%, respectively, in the control group with primary analysis repeated-measures ($p<0.001$). At 24 weeks, the adjusted treatment group difference in mean change in HbA1c level was -0.6% (95% CI, -0.8% to -0.3%; $p<0.001$). Greater improvement of HbA1c in the CGM group also was reflected in multiple participant-level secondary, exploratory, and post hoc HbA1c outcomes. In a study conducted in United Kingdom on continuous subcutaneous glucose monitoring and close correlation between mean glucose and time spent in hyperglycemia and HbA1c showed that, the fraction of time spent in hyperglycemia also closely correlated to HbA1c ($r= 0.626$, $p<0.0001$) which is agreement with the current study Nielson JK et al.[34]

In the current study shown that insulin therapy alone has no role in occurrences of hyper, hypo and euglycemia it may vary with other parameters. But insulin therapy can reduce hypoglycemic effects. the similar study shown that there was a consistent significant reduction of hypoglycemia risk associated with insulin glargine, compared with NPH insulin, in terms of overall symptomatic (11%; $p<0.001$) and nocturnal (26%; $p<0.001$) hypoglycemia Rosenstock J et al.[35]

The other study with conducted in the UK showed that metformin has lower risk to develop hypoglycemia but sulphonyl urea have comparatively high risk in developing hypoglycemia as compare to other OHA, The study population of 50048 type 2 diabetic subjects, six cases of lactic acidosis during current use of oral antidiabetic drugs were identified, yielding a crude incidence rate of 3.3 cases per 100000 person-years in metformin users and 4.8 cases per ten lakh person-years in users of sulfonylureas. The study had a total of 2025 case subjects with hypoglycemia and 7278 matched control subjects. Use of sulfonylureas was associated with a materially elevated risk of hypoglycemia. The adjusted odds ratio for current use of sulfonylureas compared with present metformin use was 2.79 (95% CI 2.23-3.50) Bodmer M.[36]

This study showed that for DDP 4 there no significant relation between occurrences of hypoglycemia, hyperglycemia. The similar study conducted in the also shows the same results, in more than seven thousand patients exposed to any DPP4-i and about one thousand five hundred patients exposed to vildagliptin were compared to ten thousand patients exposed to IS. Eight patients (0.11%) from the DPP4-i cohort and none from the vildagliptin cohort (0.0%) were hospitalized for hypoglycemia versus 130 patients (1.30%) from the insulin secretagogues (IS) cohort (138 hospitalizations) ($p=0.02$ and $p<0.0001$, respectively). Consistent results were found when considering only treatment initiations for all compared cohorts, so hypoglycemia was remarkably less frequent in patients exposed to any DPP4-i or to vildagliptin versus IS. These real-life data should be considered in the benefit/risk evaluation of the drugs Detournay B.[37]

Oral vildagliptin is a useful option as monotherapy or as add on therapy for patients with type 2 diabetes Croxtail JD et al.[38] sitagliptin therapy did not cause a clinically significant increase in the incidence of hypoglycemia and sitagliptin and metformin combination was associated with fewer hypoglycemic episodes than a combination of glipizide + metformin despite similar levels of HbA1c Nauck MA et al.[39]

In this study it is showed that the diabetic education has important role in glycemic control. The HbA1c value before and diabetic education shows significance. The similar study which conducted in the Binjai city of north Sumatra, Indonesia says that there was a significant reduction in HbA1c levels. The statistical analysis using t-test found that there was a significant difference of HbA1c value between pre and post education among type 2 diabetes mellitus patients ($p<0.005$), diabetes self-management education in PHC of Binjai city can reduce the HbA1c level in type 2 diabetes mellitus patients Rusdiana et al.[40]

Hence it is concluded from this study that CGM has an important role in the better therapeutic management in diabetic patients as it helps in individualization of therapy based on each patient in a better glycemic control leading to a euglycemic state resulting in statistically significant HbA1c reduction.

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