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Glycemic Variability Measures Derived from CGMs in Pancreatic Diabetes and Type 2 Diabetes Mellitus

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ABSTRACT

Background: Using continuous glucose monitoring, compare glycemic variability (GV) indices between patients with fibrocalculous pancreatic diabetes (FCPD) and type 2 diabetes mellitus (T2D) (CGM).

Methods: We calculated GV indices in 61 patients with FCPD and T2D who were matched for HbA1c and diabetes duration. The CGM-derived measures of GV (SD, mean amplitude of glycemic excursion [MAGE], continuous overall net glycemic action [CONGA], absolute means of daily differences [MODD], M value, and coefficient of variance [percent CV]) and hypoglycemia (time spent below 70mg/dL, AUC below 70mg/dL, glycemic risk assessment diabetes equation hypoglycemia, Low Blood Glucose Index), and hyperglycemia (time spent above 180mg/dL at night [TSA > 180], AUC above 180mg/dL [AUC > 180], glycemic risk assessment diabetes equation hyperglycemia, High Blood Glucose Index [HBGI], and J index).The relationship between GV indices and HbA1c, diabetes duration, and demographic and biochemical data was also investigated.

Results: Except for M value, all of the CGM-derived GV parameters (SD, MAGE, CONGA, MODD, and percent CV) were substantially greater in the FCPD group than in the T2D group ($P<0.05$). The FCPD group had significantly greater levels of hyperglycemia (TSA >180, AUC >180, HBGI, and J index) than the T2D group ($P<0.05$). The levels of hypoglycemia in the two groups were not significantly different. In both groups, all hyperglycemia markers had a favourable connection with HbA1c.

Conclusions: T2D is linked to lower GV, whereas FCPD is linked to higher GV. Higher postprandial glycemic excursions were discovered in patients with FCPD, which could have treatment implications.

Keywords: CGM, fibrocalculous pancreatic diabetes, glycemic variability, hypoglycemia, MAGE, type 2 diabetes

INTRODUCTION

FCPD, a unique kind of secondary diabetes seen in individuals with tropical calcificpancreatitis, accounts for a significant number of pancreatogenic diabetes cases in India, with the highest prevalence recorded in southern India. [1] A typical patient with FCPD has a lean phenotype, insulin-dependent but ketosis-resistant diabetes, and brittle glycemic control. [2,3] Underlying pancreatic inflammation causes the death of not just beta cells but also islet

alpha and pancreatic polypeptide (PP) cells, resulting in poor glucagon counterregulation and decreased PP levels, all of which contribute to hyperglycemia. [4] This contributes to the onset of difficult-to-control "brittle" illness, which is characterised by large fluctuations in plasma glucose.In addition, reduced incretin secretion due to nutritional indigestion, exocrine insufficiency, insulin resistance, and other type 2 diabetes mellitus (T2D) risk factors further alter glucose metabolism. [4,5]

Brittle glycemic control may contribute to higher glycemic variability (GV) and a greater risk of hypoglycemia in these individuals, as well as other types of pancreatic diabetes. [6] During self-monitoring of blood glucose (SMBG), patients with pancreatogenic diabetes related to genetic pancreatitis had a significant rate of hypoglycemia and GV.[7] GV may impart an independent risk for the development of micro- and macrovascular problems, according to data from a few studies.[8,9] Wide swings in blood glucose levels have been linked to oxidative stress and endothelial dysfunction, both of which are important factors in the development of diabetes complications.[10]

Glycated haemoglobin A1c (HbA1c) is a combined measure of overall glucose exposure, however it does not provide enough information on GV because patients with equal HbA1c levels can have vastly different GV and glucose stability.[11,12] SMBG offers distinct capillary blood glucose values but lacks useful information on glycemic trends and swings, and it commonly misses nocturnal hypoglycemia. Continuous glucose monitoring (CGM), on the other hand, gives integrated information on glucose levels as well as several GV indicators. [13] Furthermore, CGMs record real-time glycemic levels and trends over several days and give a significant number of blood glucose records that may be analysed in depth. [14]

The many elements of GV dynamics have not been adequately explored in FCPD, and there is a lack of data on the measurement of GV and hypoglycemia in FCPD utilising CGM and comparisons with T2D patients. Information on GV and hypoglycemia aids in the development of prevention strategies and the evaluation of various GV-reduction treatment regimens. As a result, the goal of this study was to compare GV and hypoglycemia in patients with FCPD using CGM to those in patients with T2D.

MATERIALS AND METHODS

STUDY DESIGN

Subjects and requirements for participation.

The diagnosis of FCPD was made once all of the following criteria were met: (a) evidence of chronic pancreatitis, such as pancreatic calculi on radiography or at least three of the following: abnormal pancreatic morphology by ultrasonography or CT scan/chronic abdominal pain since childhood/steatorrhea/abnormal exocrine pancreatic function test; (b) diabetes defined by the ADA criteria; and (c) absence of other causes of chronic pancreatitis, such as pancreatic carcinoma/tumors, autoimmune disorders.[15]

Patients with T2D and FCPD who had registered at our diabetes clinic were contacted by phone and invited to take part in the trial. Patients who agreed to take part in the trial had to go through a screening process to see if they were eligible. We enrolled 61 patients with FCPD and 61 patients with T2D. Patients with FCPD or T2D who were 18 to 60 years old, had a HbA1c level of 6% to 13%, and were willing to wear a CGM device for at least 3 days met the inclusion criteria. Except for seven individuals with FCPD, all were given numerous subcutaneous doses of insulin.Patients with T2D were given either OAD or an OAD plus insulin combination. In the previous three months, patients with diabetic ketoacidosis, major surgery, severe infection, renal failure (GFR 1.5mg/dL), and/or severe hypoglycemia were excluded. Patients with T2D who were given incretin analogues were excluded from the study. Patients with FCPD who had their pancreas removed were not included in the study. Prior to the study, patients had to be on a consistent treatment regimen for at least one month. The researchers gathered information on

diabetes duration, insulin dosage, and oral antidiabetic drugs, as well as previous HbA1c levels, hypoglycemic episodes, chronic complications, and hospitalisation for infection, surgery, or ketoacidosis.

STUDY MEASURES

All of the participants were asked to provide a detailed clinical history as well as the necessary demographic information. All of the subjects' height, weight, BMI, and blood pressure were measured. For CGM, all of the patients were admitted to the hospital for three days. All of the patients were provided a typical diabetic diet with a median calorie consumption of 1600 kcal per day, and their calorie intake and treatment regimen were not changed during CGM. During their hospitalization, all of the subjects had CGM for 3 to 5 days.During this time, bedside finger prick glucose monitoring was also done. The timing and doses of insulin injections and oral medicines were kept track of. The final analysis included only those individuals who had at least 36 hours of CGM data. Because of differences between CGM and SMBG readings, premature sensor failure, or technical concerns during CGM measurement, data from 11 patients (6 in the FCPD group and 5 in the T2D group) were discarded.

Measures of glycemic variability. GlyCulator2 available at https://apps.konsta.com.pl/app/glyculator/was used to estimate the following CGM-derived measures of GV, hypoglycemia, and hyperglycemia.[16]

Glycemic variability*:* The standard deviation of the sensor results, the mean amplitude of glycemic excursion (MAGE), the continuous overall net glycemic action (CONGA), the absolute means of daily differences (MODD), the M value, and the coefficient of variation were all calculated (percent CV). [17]

Hypoglycemia*:* Time spent below 70mg/dL (TSB<70), AUC below 70mg/dL (AUC<70), and Low Blood Glucose Index are all used in the Glycemic Risk Assessment Diabetes Equation (GRADE hypo) (LBGI). [18,19]

Hyperglycemia: Time spent over 180mg/dL at night (TSA > 180), AUC above 180mg/dL (AUC > 180), High Blood Glucose Index (HBGI), and J index are all used in the glycemic risk assessment diabetes equation (GRADE hyper). [18-20]

Other investigations*:* Fasting plasma glucose (FPG), HbA1c, lipids, and serum creatinine were all measured using fasting samples. The BioRaD VARIANT^{TM} II TURBO Hemoglobin Testing System was used to calculate HbA1c.

STATISTICAL ANALYSIS

For categorical variables, the data is provided as n (percent) and for continuous variables, the mean SD. SPSS 21.0 for Windows was used for all statistical analyses (SPSS Inc, Chicago, IL, USA). The differences between the two groups were assessed using Chisquare and the Student's t-test. The connection between measurements of GV and biochemical/demographic variables was assessed using Pearson's and Spearman's coefficients.Multivariate logistic regression analysis was used to determine the independent determinants of MAGE, with MAGE as the dependent variable and age, BMI, diabetes duration, and HbA1c as independent factors for both groups independently. A statistically significant P value of <0.05 was used.

RESULTS

BASELINE CHARACTERISTICS

The baseline characteristics of the study participants are shown in Table 1. Both groups were matched in terms of sex and diabetes duration. BMI was lower in the FCPD group than in the T2D group ($p < 0.05$), and patients in the FCPD group were substantially younger at the time of diagnosis ($p<0.05$) than those in the T2D group. The HbA1c levels [NGSP (percent)] in the two groups were not substantially different (8.6 ± 1.6 vs 8.3 ± 2.2, $p = 0.2$). The difference in

FPG and postprandial glucose levels between the two groups was not significant (p = 0.7).The FCPD group had significantly lower total cholesterol, triglyceride, and low-density lipoprotein levels than the T2D group (p<0.05). Dipeptidyl peptidase-4 inhibitors (n = 24), sulfonylureas (n = 37), -glucosidase inhibitors (α-GI, n = 9), insulin therapy (n = 18), thiazolidinediones (n = 2), and sodium-glucose cotransporter 2 inhibitors (n = 10) were among the glucose-lowering agents used in the T2D group, with some patients taking a combination of these drugs. Metformin (n = 9), sulfonylureas (n = 6), and insulin (n = 45) were the glucose-lowering medications used in the FCPD group.

Table 1. Baseline Characteristics of the Study Participants.

	FCPD	T2D	*P* value
n	55	56	
Age (y)	34.8 ± 6.8	45.1 ± 11.9	0.001
Male, *n* (%)	34 (61.8%)	30 (53.6%)	0.44
BMI (kg/m²)	18.8 ± 3	24.4 ± 3.9	<0.05
Diabetes duration (y)	5.5 ± 2.6	6.0 ± 5.6	0.52
FPG (mg/dL)	178 ± 76.9	171 ± 109.3	0.68
PPG (mg/dL)	233.3 ± 77.9	228 ± 95.2	0.76
HbA1c (%)	8.6 ± 1.6	8.3 ± 1.9	0.37
Total cholesterol (mg/dL)	167 ± 38	188 ± 33	<0.05
Triglycerides (mg/dL)	146 ± 36	193 ± 73	0.001
HDL (mg/dL)	40 ± 9.5	41 ± 8.7	0.41
LDL (mg/dL)	92 ± 26	116 ± 33	0.001
Mean CGM sensor value	198 ± 64	180 ± 61	0.13

Abbreviations: BMI, body mass index; CGM, continuous glucose monitoring; FCPD, fibrocalculous pancreatic diabetes; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PPG, postprandial glucose; T2D, type 2 diabetes mellitus.
n (%) for categorical variables and mean ± SD for continuous variables. *P* value for chi-square or Student's *t*-test.

Table 2. Comparison of Glycemic Variability Measures Between Two Groups of Patients.

GV index	FCPD	T2D	*P* value
SD	62.5 ± 22.7	47.3 ± 22.3	0.001
MAGE	150.8 ± 56.2	116.8 ± 48.8	0.001
MODD	65.7 ± 28.8	48.5 ± 21.7	<0.05
CONGA–6	51.0 ± 20.1	38.0 ± 17.0	0.001
%CV	32.8 ± 11.9	26.7 ± 10.9	<0.05
M value	279.9 ± 115.5	243.6 ± 118.9	0.13

Abbreviations: CONGA, continuous overall net glycemic action; %CV, coefficient of variance; FCPD, fibrocalculous pancreatic diabetes; GV, glycemic variability; MAGE, mean amplitude of glycemic excursion; MODD, absolute means of daily differences; SD, standard deviation of the mean of the sensor values; T2D, type 2 diabetes mellitus; *P* value < 0.05 significant.

GLYCEMIC VARIABILITY METRICS

The mean 24-hour glucose concentrations did not differ significantly across groups (198mg/dL vs 180mg/dL, p = 0.13). Table 2 shows the results of a between-group comparison of various GV metrics. In general, the FCPD group's CGM-derived measures of GV showed more derangement. The FCPD group had considerably greater MAGE than the T2D group (150.8 ± 56.2 vs 116.8 ± 48.8, p= 0.001). (Figure 1).The FCPD group had a considerably higher SD of 24-hour glucose readings than the T2D group (62.5 ± 22.7 vs 47.3 ± 22.3, p = 0.001). In percent CV, MODD, and CONGA-6, there were significant between-group differences, with the FCPD group having greater values than the T2D group (p < 0.05). The M values, on the other hand, were not different amongst the groups. Figure 2 depicts a typical CGM graph for people with FCPD and T2D.

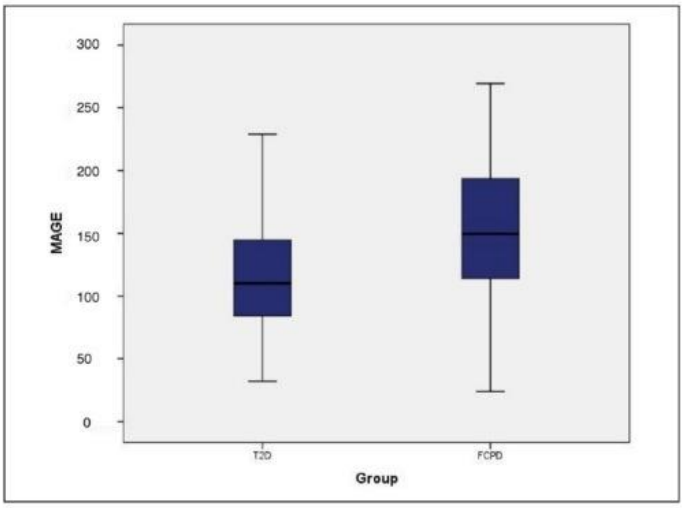

Figure 1. Comparison of MAGE between the two groups. FCPD, fibrocalculous pancreatic diabetes; MAGE, mean amplitude of glycemic excursion; T2D, type 2 diabetes mellitus.

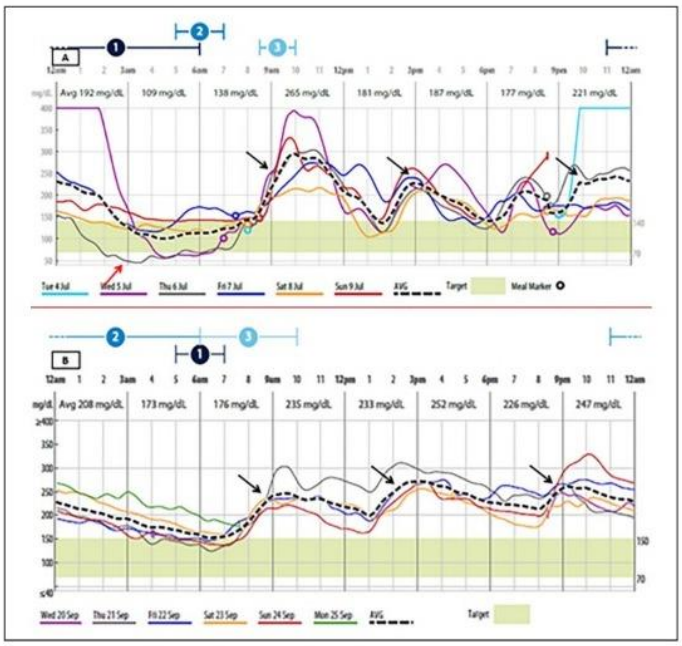

Figure 2: A typical CGM graph of patients with(a) FCPD and (b) T2D.
Dotted black lines represent integrated CGM curve; black arrows represent postprandial glucose excursions; red arrow represents hypoglycemia. Note marked post prandial excursions in FCPD patient; both patients have HbA1C of 9.4%.
CGM, continuous glucose monitoring; FCPD, fibrocalculous pancreatic diabetes; HbA1C, glycated hemoglobin A1c; T2D, type2 diabetes mellitus.

HYPOGLYCEMIA AND HYPERGLYCEMIA AS DETERMINED BY CGM

MEASURES OF HYPOGLYCEMIA

Nocturnal hypoglycemia wasobserved in 24 patients with FCPD and in 14 patients withT2D. Three patients in the FCPD group and two patients in the T2D group experienced severe nocturnal hypoglycemia

Table 3. Comparison of CGM-Derived Measures of Hypoglycemia and Hyperglycemia Between Two Groups of Patients.

	FCPD	T2D	*P* value
Hypoglycemia			
GRADE_hypo	7.97 ± 17.7	6.92 ± 19.2	0.24
TSB <70	3.49 ± 6.2	3.57 ± 9.7	0.16
AUC <70	0.51 ± 1.1	0.55 ± 1.9	0.14
LBGI	0.98 ± 1.6	1.0 ± 2.6	0.25
Hyperglycemia			
GRADE_hyper	85.4 ± 22.3	79.4 ± 28.4	0.37
TSA >180	68.5 ± 26.4	42.1 ± 31.4	0.001
AUC >180	46.4 ± 45.3	31.4 ± 40.8	<0.05
HBGI	14.9 ± 11.8	11.1 ± 10.8	<0.05
J index	73.6 ± 40.1	57.3 ± 37.8	<0.05

Abbreviations: AUC, area under curve; AUC > 180, AUC above 180 mg/dL; AUC < 70, AUC below 70 mg/dL; FCPD, fibrocalculous pancreatic diabetes; GRADE_hyper, glycemic risk assessment diabetes equation hyperglycemia; GRADE_hypo, glycemic risk assessment diabetes equation hypoglycemia; HBGI, High Blood Glucose Index; LBGI, Low Blood Glucose Index; T2D, type 2 diabetes mellitus; TSA > 180, time spent above 180 mg/dL; TSB < 70, time spent below 70 mg/dL; *P* value < 0.05 significant.

during CGM. The duration of hypoglycemia (<70 mg/dL) did not differ significantly between the two groups. Table 3 compares hypoglycemia and hyperglycemia markers determined from CGMs between groups. In the mean GRADE hypo (7.97 vs 6.94, p = 0.14), there were no significant differences between groups. Similarly, there were no significant differences in the duration of glucose levels below 70 mg/dL, AUC <70, or LBGI between the groups.

MEASURES OF HYPERGLYCEMIA

The FCPD group had more dysregulation in CGM-derived hyperglycemia markers. In contrast to hypoglycemia, patients with FCPD had a substantially longer period of glucose levels above 180 mg/dL (68.5±26.4 vs 42.1±31.4, p<0.05). The FCPD group had significantly greater AUC >180, HBGI, and J index than the T2D group (p< 0.05). GRADE hyper, on the other hand, showed no significant between-group differences (85.4±22.3 vs 79.4±28.4, p = 0.37).

CORRELATES AND DETERMINANTS OF GV

In both groups, there were no significant relationships between HbA1c levels and diabetes duration, as measured by SD, percent CV, and MAGE. In the FCPD group, MAGE was inversely associated to BMI, but not in the T2D group. In the T2D group, there were significant inverse associations between HbA1c levels and all four hypoglycemia markers, but not in the FCPD group. In contrast, in both groups, all five hyperglycemic indices exhibited a significant positive and moderate (r^2 = 0.3-0.6) connection with HbA1c levels (data not shown).In all groups, a multivariate logistic regression analysis was used to identify characteristics that contributed to greater MAGE levels. In the FCPD group, HbA1c levels and BMI were significant predictors of MAGE. In the FCPD group, a model that included HbA1c levels and BMI explained 90% of the variance in MAGE. In the T2D group, greater HbA1c levels and diabetes duration were predictive of higher MAGE (p<0.05).

DISCUSSION

We used CGM to assess GV and hypoglycemia in patients with FCPD and compared them to patients with T2D in this study. The most relevant conclusion of our study was that patients with FCPD have more GV than individuals with T2D, as measured by CGM-derived measurements. Furthermore, CGM-derived hyperglycemic indices were considerably higher in the FCPD group. This is the only study that we are aware of that compares GV between people with FCPD and those with T2D.

The mean of the absolute differences between glucose readings obtained on two consecutive days is used to calculate MODD, which is a measure of inter-day GV. CONGA-6 is an estimate of intra-day GV calculated over a 6-hour period, reducing the need for meticulous surveillance of patients' activities. The M value calculates intra-day GV based on a small number of glucose levels and ignores glycemic excursions between readings. [21,22]

FCPD, a prevalent kind of pancreaticogenic diabetes seen in India, encompasses a wide range of conditions, from mild hyperglycemia to overt diabetes, and from requiring merely OAD to requiring insulin for survival.[23] According to recent findings, pancreatogenic diabetes is frequently misclassified as T2D, which could have long-term consequences.[24,25] Our findings show that, when compared to T2D, FCPD is linked with higher GV, as evidenced by significant GV metrics such MAGE, SD, CONGA, and percent CV. This discovery emphasises the need of distinguishing between the two types of diabetes.

Despite the fact that pancreaticogenic diabetes is regarded "British," data on GV assessment with CGM is limited. Our findings on general GV indicators are consistent with those of a previous CGM study involving 11 patients with pancreatogenic diabetes, which found that GV in pancreatic diabetes is comparable to that of type 1 diabetes mellitus (T1D) and greater than that of type 2 diabetic mellitus (T2D).[26] In another study, patients with pancreatogenic diabetes related to hereditary pancreatitis experienced substantial fluctuation in capillary blood glucose and high hypoglycemia levels during SMBG.[7]

The LBGI and HBGI are two metrics that are used to calculate the risk of hypoglycemia and hyperglycemia, respectively. The duration of hypoglycemia and hypoglycemic exposure are represented by TSB 70 mg/dL and AUC 70 mg/dL, respectively. The duration of hyperglycemia and hyperglycemic exposure are represented by TSA > 180 mg/dL and AUC >180 mg/dL, respectively. [21,22]

In past studies, people with diabetes who had their pancreas removed experienced high rates of hypoglycemia.[27-29] Despite the fact that the FCPD group had more hypoglycemia episodes, there were no significant differences in hypoglycemic indices between the two groups. This difference could be explained by three factors: (a) the relative preservation of endocrine and exocrine function as well as counterregulatory responses in FCPD compared to complete pancreatectomy.[30,31] In this regard, it's worth noting that a previous study found that exocrine and endocrine pancreatic abnormalities were preserved in FCPD when compared to T1D. [32] (b) During the study, frequent blood glucose monitoring may have reduced or prevented hypoglycemic events. (c) Because both groups' HbA1c levels were high, hypoglycemic episodes may have been reduced. A comparison of hypoglycemic indices between the two groups with HbA1c readings close to the goal range (7%), for example, could have been more instructive.

The FCPD group exhibited more dysregulation in CGM-derived indices of hyperglycemia, according to our findings. This could indicate that the FCPD group's higher GV was mostly attributable to greater postprandial glucose excursions than the T2D group. This is consistent with the prior finding that postprandial glucose contributes significantly to overall glycemic exposure. The FCPD group has a lower insulin secretory capability than those with T2D, which contributes to higher postprandial glucose excursions.Another reason for postprandial hyperglycemia could be the destruction of additional pancreatic islet cells, notably PP, which leads to hepatic insulin resistance.[33] In addition, postprandial hyperglycemia in FCPD may be caused by faulty incretin responses and impaired insulin sensitivity, as seen in T2D.[34] The result that FCPD patients exhibit higher post-meal glucose increases could have prognostic and therapeutic implications. In individuals with a HbA1c of less than 7.5 percent, postprandial hyperglycemia is the leading cause of overall glycemic exposure, and it is also thought to be an independent risk factor for cardiovascular disease.[35] This finding could have therapeutic implications because these patients demand more prandial insulin than those with T2D.[36]

Wide blood glucose level variations with bouts of hyperglycemia or hypoglycemia characterise

GV and glycemic instability, which are associated with FCPD and other forms of pancreatogenic diabetes. Glycemic instability is caused by impaired counterregulation caused by muted glucagon and catecholamine responses, nutritional malabsorption, poor incretin response, and reduced hepatic gluconeogenesis.[37] Higher GV has clinical implications such as the difficulty to maintain rigorous glycemic control, an increased risk of hypoglycemia, and a possible link to higher rates of vascular problems. It has been discovered that severe hypoglycemia is preceded by a greater GV, implying that lowering GV could lower the risk of severe hypoglycemia.[38]GV is thought to contribute to vascular problems of diabetes in its own right, in addition to being linked to poorer glycemic control.[39] As a result, doctors consider GV evaluation to be a significant part of diabetic therapy.

Beyond the information supplied by HbA1c levels alone, CGM gives additional information on the quality of glycemic control and the size of glycemic excursions.[40] The value of CGM in detecting hypoglycemia is widely understood; in one study, hypoglycemic events detected with CGM were five times higher than those detected with SMBG in patients with pancreaticogenic diabetes.[41] Predictive low-glucose suspend with CGM and sensor-augmented continuous subcutaneous insulin infusion improved glycemic control and reduced hypoglycemia in patients with pancreaticogenic diabetes after complete pancreatectomy, according to another study.[28] After pancreatic resection, CGM employing an artificial endocrine pancreas improved glycemic control and reduced hypoglycemia in pancreatogenic diabetes.[42]

The application of CGM during hospitalisation, which may differ from that of ambu- latory home values, is one of the study's weaknesses. Dietary prescriptions in the hospital may differ from those at home, which could affect GV measures. Because hypoglycemia is a greater hazard in patients who maintain stricter glycemic control, higher HbA1c levels may have prevented correct measurement of hypoglycemic indices in the two groups. To address these shortcomings, studies with bigger sample sizes and stronger glycemic controls should be done.

CONCLUSION

Finally, our CGM-based comparison study showed that patients with FCPD have higher GV than those with T2D. Patients with FCPD had a greater postprandial glycemic excursion. Beyond achieving HbA1c-targeted glycemic control, treatment methods for FCPD must address GV and postprandial hyperglycemia. Finally, our CGM-based comparison study showed that patients with FCPD have higher GV than those with T2D. Patients with FCPD had a greater postprandial glycemic excursion. Beyond achieving HbA1c-targeted glycemic control, treatment methods for FCPD must address GV and postprandial hyperglycemia.

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