Comparison of CGM-Derived Measures of Glycemic Variability Between Pancreatogenic Diabetes and Type 2 Diabetes Mellitus

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Abstract

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

Methods: We measured GV indices using CGM (iPro™2 Professional CGM, Medtronic, USA) data in 61 patients each with FCPD and T2D who were matched for glycated hemoglobin A1c (HbA1c) and duration of diabetes. GlyCulator2 software was used to estimate 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 [%CV]), hypoglycemia (time spent below 70 mg/dL, AUC below 70 mg/dL, glycemic risk assessment diabetes equation hypoglycemia, Low Blood Glucose Index), and hyperglycemia (time spent above 180 mg/dL at night [TSA > 180], AUC above 180 mg/dL [AUC > 180], glycemic risk assessment diabetes equation hyperglycemia, High Blood Glucose Index [HBGI], and J index). The correlation of GV indices with HbA1c, duration of diabetes, and demographic and biochemical parameters were also assessed.

Results: All the CGM-derived measures of GV (SD, MAGE, CONGA, MODD, and %CV), except M value, were significantly higher in the FCPD group than in the T2D group ($P < 0.05$). Measures of hyperglycemia (TSA > 180, AUC > 180, HBGI, and J index) were significantly higher in the FCPD group than in the T2D group ($P < 0.05$). The measures of hypoglycemia were not significantly different between the two groups. All the hyperglycemia indices showed a positive correlation with HbA1c in both groups.

Conclusions: FCPD is associated with higher GV than is T2D. The findings of higher postprandial glycemic excursions in patients with FCPD could have potential therapeutic implications.

Keywords

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

Introduction

Fibrocalculous pancreatic diabetes (FCPD), a unique form of secondary diabetes observed in patients with tropical calcific pancreatitis, accounts for a substantial proportion of cases of pancreatogenic diabetes in India with the highest prevalence reported in southern India.¹ Lean phenotype, insulin-requiring but ketosis-resistant diabetes, and brittle glycemic control characterize a typical patient with FCPD.^{2,3} Underlying pancreatic inflammation results in the loss of not only beta cells but also

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islet alpha and pancreatic polypeptide (PP) cells, with reduced levels of glucagon ensuing in impaired counterregulation and decreased PP levels contributing to hyperglycemia.⁴ This contributes to the development of difficult to control “brittle” disease, which is associated with wide excursions in plasma glucose. In addition, impaired incretin secretion due to nutrient indigestion, exocrine insufficiency, presence of insulin resistance, and other coexisting risk factors for type 2 diabetes mellitus (T2D) further disrupt the glucose metabolism.^{4,5}

Brittle glycemic control could contribute to higher glycemic variability (GV) and higher risk of hypoglycemia among these patients and other causes of pancreatogenic diabetes.⁶ In fact, a high rate of hypoglycemia and GV was observed during self-monitoring of blood glucose (SMBG) in patients with pancreatogenic diabetes due to hereditary pancreatitis.⁷ Data from a few studies suggest that GV may confer an independent risk for the development of micro- and macrovascular complications.^{8,9} Wide fluctuations in blood glucose levels have been shown to be associated with oxidative stress and endothelial dysfunction, which are key factors in the development of complications in diabetes.¹⁰

Glycated hemoglobin A1c (HbA1c) is an integrated measure of overall glucose exposure, but it does not provide sufficient information on GV as patients with similar HbA1c levels may differ significantly in terms of GV and glucose stability.^{11,12} SMBG provides discrete capillary blood glucose levels but fails to provide meaningful information on glycemic trends and fluctuations, and nocturnal hypoglycemia is frequently missed by SMBG. In contrast, continuous glucose monitoring (CGM) provides integrated information on glucose levels and various parameters of GV.¹³ In addition, CGM record real-time glycemic values and trends over multiple days and provide a large number of blood glucose recordings permitting detailed analysis.¹⁴

The different aspects of GV dynamics have not been well studied in FCPD, and data on the assessment of GV and hypoglycemia in FCPD using CGM and its comparison with patients with T2D are lacking. Information on GV and hypoglycemia helps in planning preventive strategies and the evaluation of various therapeutic regimens to reduce GV. Therefore, this study aimed to assess GV and hypoglycemia in patients with FCPD using CGM and compare them with those in patients with T2D.

Materials and Methods

Study Design

Subjects and eligibility criteria. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from each subject prior to the study. This study was performed in accordance with the Declaration of Helsinki. The diagnosis of FCPD was based on the fulfillment of all the following criteria: (a) evidence of chronic pancreatitis: 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 according to the criteria of the ADA; and (c) absence of other causes of chronic pancreatitis, such as pancreatic carcinoma/tumors, autoimmune disorders, pancreatic ischemia, hyperparathyroidism/hypercalcemia, alcohol, hypertriglyceridemia, and biliary disease.¹⁵

Patients with T2D and FCPD, who were registered at our diabetic clinic, were contacted over the phone to invite them to participate in the study. Patients who were willing to participate in the study went through a screening process to determine their eligibility. We enrolled 61 patients with FCPD and 61 patients with T2D, between February 2016 and December 2018. Inclusion criteria were patients with FCPD or T2D who were aged 18 to 60 years, with HbA1c level 6% to 13%, and were willing to use a CGM device for at least 3 days. All but seven patients with FCPD were being treated with insulin using multiple subcutaneous injections. Patients with T2D were administered either OAD or a combination of OAD and insulin. Patients with a history of diabetic ketoacidosis, major surgery, severe infection, renal dysfunction (GFR <60 mL/min and serum creatinine >1.5 mg/dL), and/or severe hypoglycemia in the past 3 months were excluded. T2D patients who were administered incretin analogs were excluded. Patients with FCPD who had undergone pancreatic resection were excluded from the study. Patients had to be on a stable treatment regimen at least 1 month prior to the study. Data on diabetes duration, insulin dosage and oral antidiabetic medications, past HbA1c values, hypoglycemic episodes, chronic complications, and hospitalization for infection, surgery, or ketoacidosis were acquired.

Study measures. A comprehensive clinical history and necessary demographic data were obtained from all the participants. Height, weight, BMI, and blood pressure were recorded for all the subjects. All the patients were hospitalized for 3 days for CGM. A standard diabetic diet with a median calorie of 1600 kcal per day was given to all the patients, and calorie intake and treatment regimen were not altered during CGM. All the participants underwent CGM (iPro™2 Professional CGM, Medtronic, USA) for 3 to 5 days during hospitalization. Bedside finger prick glucose monitoring was also performed during this period. Record of timing/doses of insulin injections and oral medications was maintained. Only those patients who had at least 36 hours of CGM data were included in the final analysis. Data from 11 patients (6 in FCPD group and 5 in T2D group) were excluded because of discrepancies between CGM and SMBG readings, premature sensor failure, or technical issues during CGM measurement.

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: SD of the mean of the sensor values, mean amplitude of glycemic excursion (MAGE), continuous overall net glycemic action (CONGA), absolute means of daily differences (MODD), *M* value, and coefficient of variance (%CV).¹⁷

Hypoglycemia: Glycemic risk assessment diabetes equation (GRADE_hypo), time spent below 70mg/dL (TSB < 70), AUC below 70mg/dL (AUC < 70), and Low Blood Glucose Index (LBGI).^{18,19}

Hyperglycemia: Glycemic risk assessment diabetes equation (GRADE_hyper), time spent above 180mg/dL at night (TSA > 180), AUC above 180mg/dL (AUC > 180), High Blood Glucose Index (HBGI), and *J* index.¹⁸⁻²⁰

Other investigations: Fasting samples were collected for estimation of fasting plasma glucose (FPG), HbA1c, lipids, and serum creatinine. HbA1c was estimated using BioRad VARIANT™ II TURBO Hemoglobin Testing System.

Statistical Analysis. Data are reported as *n* (%) for categorical variables and mean ± SD for continuous variables. All statistical analyses were performed using SPSS 21.0 for Windows (SPSS Inc, Chicago, IL, USA). Chi-square and Student's *t*-test were used to assess the differences between the two groups. Pearson's and Spearman's coefficients were used to evaluate the correlation between measures of GV and biochemical/demographic variables. To ascertain the independent determinants of MAGE, multivariate logistic regression analysis was performed using MAGE as dependent variable and age, BMI, duration of diabetes, and HbA1c as independent variables for both groups separately. *P* value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of the study participants. Both the groups were matched for sex and the duration of diabetes. However, BMI was lower in the FCPD group than in the T2D group (*P* < 0.05); patients in the FCPD group were significantly younger than those in the T2D group at the time of diagnosis (*P* < 0.05). HbA1c levels [NGSP (%)] were not significantly different between the two groups (8.6 ± 1.6 vs 8.3 ± 2.2 , *P* = 0.2). FPG and postprandial glucose values were not significantly different between the two groups (*P* = 0.7). Total cholesterol, triglyceride, and low-density lipoprotein levels were significantly lower in the FCPD group than in the T2D group (*P* < 0.05). Glucose-lowering agents in the T2D group comprised dipeptidyl peptidase-4 inhibitors (*n* = 24), sulfonylureas (*n* = 37), α -glucosidase inhibitors (α -GI, *n* = 9), insulin therapy (*n* = 18), thiazolidinediones (*n* = 2), and sodium glucose cotransporter 2 inhibitors (*n* = 10), with some patients taking combination of these drugs. Glucose-lowering agents in the FCPD group comprised metformin (*n* = 9), sulfonylureas (*n* = 6), and insulin (*n* = 45).

Table 1. Baseline Characteristics of the Study Participants.

	FCPD	T2D	<i>P</i> value
<i>n</i>	55	56	
Age (y)	34.8 ± 6.8	45.1 ± 11.9	0.001
Male, <i>n</i> (%)	34 (61.8%)	30 (53.6%)	0.44
BMI (kg/m ²)	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, fibrocalculus 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	<i>P</i> 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
<i>M</i> value	279.9 ± 115.5	243.6 ± 118.9	0.13

Abbreviations: CONGA, continuous overall net glycemic action; %CV, coefficient of variance; FCPD, fibrocalculus 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.

Measures of Glycemic Variability

There was no significant between-group difference in mean 24-hour glucose concentrations (198mg/dL vs 180mg/dL, *P* = 0.13). Table 2 provides the between-group comparison of different measures of GV. In general, CGM-derived measures of GV displayed greater derangement in the FCPD group. MAGE was significantly higher in the FCPD group than in the T2D group (150.8 ± 56.2 vs 116.8 ± 48.8 , *P* = 0.001) (Figure 1). The SD of the 24-hour glucose levels was significantly higher in the FCPD group than in the T2D group (62.5 ± 22.7 vs 47.3 ± 22.3 , *P* = 0.001). Similarly, significant between-group differences were noted in %CV, MODD, and CONGA-6, with the FCPD group having higher values than the T2D group (*P* < 0.05). However, *M* values were not different between the groups. A typical CGM graph of patients with FCPD and T2D is shown in Figure 2.

Figure 1. Comparison of MAGE between the two groups. FCPD, fibrocalculus 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 postprandial excursions in FCPD patient; both patients have HbA1c of 9.4%. CGM, continuous glucose monitoring; FCPD, fibrocalculus pancreatic diabetes; HbA1c, glycated hemoglobin A1c; T2D, type 2 diabetes mellitus.

Hypoglycemia and Hyperglycemia as Determined by CGM

Measures of hypoglycemia. Nocturnal hypoglycemia was observed in 24 patients with FCPD and in 14 patients with T2D. 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, fibrocalculus 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 two groups did not differ significantly with respect to the duration of hypoglycemia (<70 mg/dL). Table 3 provides between-group comparison of CGM-derived indicators of hypoglycemia and hyperglycemia. No significant between-group differences were observed in the mean GRADE_hypo (7.97 vs 6.94, $P = 0.14$). Similarly, the durations of glucose levels below 70 mg/dL, AUC < 70, and LBGI were not significantly different between the groups.

Measures of hyperglycemia. CGM-derived indicators of hyperglycemia showed greater derangement in the FCPD group. In contrast to hypoglycemia, duration in which glucose levels were above 180 mg/dL was significantly higher among patients with FCPD (68.5 ± 26.4 vs 42.1 ± 31.4 , $P < 0.05$). AUC > 180, HBGI, and J index were all significantly higher in the FCPD group than in the T2D group ($P < 0.05$). However, significant between-group differences were not observed with GRADE_hyper (85.4 ± 22.3 vs 79.4 ± 28.4 , $P = 0.37$).

Correlates and Determinants of GV

No significant correlations were observed between HbA1c levels and the duration of diabetes with SD, %CV, and MAGE in both the groups. MAGE correlated inversely with BMI in the FCPD group but not in the T2D group. Significant inverse correlations were observed between HbA1c levels and all the four indices of hypoglycemia in the T2D group but not in the FCPD group. Conversely, all the five hyperglycemic indices showed significant positive and moderate ($r^2 = 0.3$ - 0.6) correlation with HbA1c levels in both the groups (data not shown). Multivariate logistic regression

analysis was performed to identify factors contributing to higher MAGE values in both the groups. HbA1c levels and BMI were significant predictors of MAGE in the FCPD group. A model including HbA1c levels and BMI explained 90% of the variance in MAGE in the FCPD group. HbA1c levels and the duration of diabetes were predictors of higher MAGE in the T2D group ($P < 0.05$).

Discussion

In this study, we assessed GV and hypoglycemia in patients with FCPD using CGM and compared them with those in patients with T2D. The most important finding of our study was that patients with FCPD experience a greater degree of GV as assessed by CGM-derived measures than do patients with T2D. In addition, CGM-derived indices of hyperglycemia were significantly higher in the FCPD group. To our knowledge this is the first study comparing GV between patients with FCPD and those with T2D.

MODD is a measure of inter-day GV and represents the mean of the absolute differences between glucose values measured on two successive days. CONGA-6 is an estimate of intra-day GV, assessed during a 6-hour period, decreasing the dependence on the rigorous tracking of patients' habits. *M* value measures intra-day GV based on few glucose values and does not consider glycemic excursions in-between readings.^{21,22}

FCPD, a common form of pancreatogenic diabetes observed in India, represents a wide spectrum of diseases ranging from mild hyperglycemia to overt diabetes and only requiring OAD to requiring insulin for survival.^{1,23} Recent reports suggest that cases of pancreatogenic diabetes are often misclassified as T2D with potential long-term implications.^{24,25} Our results indicate that FCPD, compared with T2D, is associated with elevated GV as indicated by important measures of GV, such as MAGE, SD, CONGA, and %CV. This finding underscores the importance of differentiating these two forms of diabetes.

Although pancreatogenic diabetes is considered as "brittle," data on evaluation of GV using CGM are sparse. Our findings with regard to the general indicators of GV are consistent with those of a previous CGM study involving 11 patients with pancreatogenic diabetes which reported that GV in pancreatic diabetes is as large as that in type 1 diabetes mellitus (T1D) and greater than that observed in T2D.²⁶ In another study, high variability in capillary blood glucose and high hypoglycemia levels were observed during SMBG in patients with pancreatogenic diabetes secondary to hereditary pancreatitis.⁷

LBGI and HBGI are metrics that are specifically designed to calculate the risk of hypoglycemia and hyperglycemia. TSB < 70 mg/dL and AUC < 70 mg/dL represent the duration of hypoglycemia and hypoglycemic exposure, respectively. TSA > 180 mg/dL and AUC > 180 mg/dL represent the duration of hyperglycemia and hyperglycemic exposure, respectively.^{21,22}

High rates of hypoglycemia were observed in previous studies in patients with diabetes following pancreatic resection.²⁷⁻²⁹ Although the frequency of hypoglycemic episodes was higher in the FCPD group, we did not observe significant differences in hypoglycemic indices between the two groups. This discordance could be attributed to three factors: (a) relative preservation of endocrine and exocrine function and counterregulatory responses in FCPD compared to that following total pancreatectomy.^{30,31} In this regard, it is interesting to note that an earlier study demonstrated relative preservation of exocrine and endocrine pancreatic dysfunction in FCPD in comparison with T1D.³² (b) Frequent monitoring of blood glucose during the study might have reduced/prevented hypoglycemic episodes. (c) Hypoglycemic episodes might have been lower as the mean HbA1c levels of both the groups were high. HbA1c values close to the target range ($< 7\%$) could have provided a more informative comparison of hypoglycemic indices between the two groups.

We observed that CGM-derived measures of hyperglycemia had greater derangement in the FCPD group. This potentially suggests that higher GV in the FCPD group was predominantly due to greater postprandial glucose excursions than in the T2D group. This is in accordance with the previous observation suggesting that postprandial glucose significantly contributes to overall glycemic exposure. Reduced insulin secretory capacity than those with T2D is a major contributor to greater postprandial glucose excursions in the FCPD group. Destruction of other pancreatic islet cells specifically PP leading to hepatic insulin resistance could be another mechanism responsible for postprandial hyperglycemia.³³ In addition, defective incretin responses and reduced insulin sensitivity observed in T2D may also play a role in postprandial hyperglycemia in FCPD.³⁴ This finding of greater post-meal glucose increments in FCPD could have prognostic and therapeutic implications. Postprandial hyperglycemia is the predominant contributor to overall glycemic exposure in patients with HbA1c lower than 7.5% and is also considered to be an independent risk factor for cardiovascular disease.³⁵ The potential therapeutic implication of this observation is that these patients have higher prandial insulin requirements than those with T2D.³⁶

GV and glycemic instability, associated with FCPD and other forms of pancreatogenic diabetes, are characterized by wide blood glucose level fluctuations with periods of hyperglycemia or hypoglycemia. Impaired counterregulation due to blunted glucagon and catecholamine responses, nutrient malabsorption, defective incretin response, and diminished hepatic gluconeogenesis contribute to this glycemic instability.³⁷ Clinical implications of higher GV include inability to achieve strict glycemic control, higher risk of hypoglycemia, and a possible association with higher rates of vascular complications. It has been observed that severe hypoglycemia is preceded by a higher GV signifying that reducing GV may also reduce the risk of severe hypoglycemia.³⁸ Besides being associated with poorer glycemic control, GV is believed to independently contribute to vascular complications of diabetes.³⁹ Thus, the

assessment of GV is considered to be an important aspect of diabetes management among clinicians.

CGM provides additional information on the quality of glycemic control and the magnitude of glycemic excursions beyond that provided by HbA1c levels alone.⁴⁰ The importance of CGM in identifying hypoglycemia is well recognized; in a previous study, hypoglycemic events identified with CGM were five times higher than during SMBG in patients with pancreatogenic diabetes.⁴¹ In another study, predictive low-glucose suspend using CGM and sensor-augmented continuous subcutaneous insulin infusion improved glycemic control and reduced hypoglycemia in patients with pancreatogenic diabetes following total pancreatectomy.²⁸ CGM using artificial endocrine pancreas during perioperative period improved glycemic control and reduced hypoglycemia in pancreatogenic diabetes after pancreatic resection.⁴²

The limitations of this study include application of CGM during hospitalization, which might differ from that of ambulatory home values. Dietary prescription during hospitalization could be different from that at home and potentially impact GV measurements. Higher HbA1c levels may have precluded the accurate assessment of hypoglycemic indices in the two groups as hypoglycemia is a bigger threat in patients who maintain stricter glycemic control. Studies with larger sample sizes and stricter glycemic controls should be conducted to address these limitations.

In conclusion, this CGM-based comparative study demonstrated that patients with FCPD display higher GV than those with T2D. Postprandial glycemic excursion was also higher in patients with FCPD. Treatment strategies in FCPD must address GV and postprandial hyperglycemia beyond attaining HbA1c-targeted glycemic control.

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Declaration of Conflicting Interests

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References

1. Barman KK, Premalatha G, Mohan V. Tropical chronic pancreatitis. *Postgrad Med J*. 2003;79:606-615.
2. Mittal N, Mehrotra R, Agarwal G, et al. The clinical spectrum of fibrocalculous pancreatic diabetes in north India. *Natl Med J India*. 2002;15(6):327-331.
3. Jyotsna VP, Singh SK, Gopal D, et al. Clinical and biochemical profiles of young diabetics in North-Eastern India. *J Assoc Physicians India*. 2002;50:1130-1134.
4. Hart PA, Bellin MD, Andersen DK, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. *Lancet Gastroenterol Hepatol*. 2016;1(3):226-237.
5. Andersen DK, Korc M, Petersen GM, et al. Diabetes, pancreatogenic diabetes, and pancreatic cancer. *Diabetes*. 2017;66(5):1103-1110.
6. Cui Y, Andersen DK. Pancreatogenic diabetes: special considerations for management. *Pancreatology*. 2011;11(3):279-294.
7. Dytz MG, Marcelino PA, de Castro Santos O, et al. Clinical aspects of pancreatogenic diabetes secondary to hereditary pancreatitis. *Diabetol Metab Syndr*. 2017;9:4.
8. Cardoso CRL, Leite NC, Moram CBM, Salles GF. Long-term visit-to-visit glycemic variability as predictor of micro- and macrovascular complications in patients with type 2 diabetes: the Rio de Janeiro Type 2 Diabetes Cohort Study. *Cardiovasc Diabetol*. 2018;17(1):33.
9. Kilpatrick ES, Rigby AS, Atkin SL. Effect of glucose variability on the long-term risk of microvascular complications in type 1 diabetes. *Diabetes Care*. 2009;32(10):1901-1903.
10. Saisho Y. Glycemic variability and oxidative stress: a link between diabetes and cardiovascular disease? *Int J Mol Sci*. 2014;15:18381-406.
11. Kuenen JC, Borg R, Kuik DJ, et al.; ADAG Study Group. Does glucose variability influence the relationship between mean plasma glucose and HbA1c levels in type 1 and type 2 diabetic patients? *Diabetes Care*. 2011;34(8):1843-1847.
12. Tylee TS, Trencle DL. Glycemic variability: looking beyond the A1C. *Diabetes Spectr*. 2012;25(3):149-153.
13. Wright EE, Gavin JR. Clinical use of professional continuous glucose monitoring. *Diabetes Technol Ther*. 2017;19(S2):S12-S15.
14. Rodbard D. Continuous glucose monitoring: a review of successes, challenges, and opportunities. *Diabetes Technol Ther*. 2016;18(suppl 2):S3-S13.
15. Mohan V, Alberti KGMM. Diabetes in the tropics. In: Alberti KGMM, Defronzo RA, Keen H, Zimmet P, eds. *International Textbook of Diabetes Mellitus*. Chichester: John Wiley and Sons Ltd; 1999:177-196.
16. Czerwoniuk D, Fendler W, Walenciak L, Mlynarski W. GlyCulator: a glycemic variability calculation tool for continuous glucose monitoring data. *J Diabetes Sci Technol*. 2011;5(2):447-451.
17. Siegelar SE, Holleman F, Hoekstra JB, DeVries JH. Glucose variability; does it matter? *Endocr Rev*. 2010;31:171-182.
18. Hill NR, Hindmarsh PC, Stevens RJ, Stratton IM, Levy JC, Matthews DR. A method for assessing quality of control from glucose profiles. *Diabet Med*. 2007;24(7):753-758.
19. Kovatchev BP, Clarke WL, Breton M, Brayman K, McCall A. Quantifying temporal glucose variability in diabetes via

- continuous glucose monitoring: mathematical methods and clinical application. *Diabetes Technol Ther.* 2005;7(6):849-862.
20. Wójcicki JM. "J"-index. A new proposition of the assessment of current glucose control in diabetic patients. *Horm Metab Res.* 1995;27(1):41-42.
 21. Suh S, Kim JH. Glycemic variability: how do we measure it and why is it important? *Diabetes Metab J.* 2015;39(4):273-282.
 22. Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. *Lancet Diabetes Endocrinol.* 2019;7(3):221-230.
 23. Shivaprasad C, Anish K, Aiswarya Y, et al. A comparative study of the clinical profile of fibrocalculous pancreatic diabetes and type 2 diabetes mellitus. *Diabetes Metab Syndr.* 2019;13:1511-1516.
 24. Woodmansey C, McGovern AP, McCullough KA, et al. Incidence, demographics, and clinical characteristics of diabetes of the exocrine pancreas (Type 3c): a retrospective cohort study. *Diabetes Care.* 2017;40(11):1486-1493.
 25. Bhattamisra SK, Siang TC, Rong CY, et al. Type-3c diabetes mellitus, diabetes of exocrine pancreas - an update. *Curr Diabetes Rev.* 2019;15:1-13.
 26. Kon A, Tando Y, Yanagimachi, et al. Analysis of glycemic variability and insulin resistance in patients with pancreatic diabetes using a continuous glucose monitoring system. *Hiroaki Med J.* 2012;63(2):116-126.
 27. Maeda H, Hanazaki K. Pancreatogenic diabetes after pancreatic resection. *Pancreatol.* 2011;11(2):268-276.
 28. Scott ES, Fulcher GR, Clifton-Bligh RJ. Sensor-augmented CSII therapy with predictive low-glucose suspend following total pancreatectomy. *Endocrinol Diabetes Metab Case Rep.* 2017;2017. pii: 17-0093.
 29. Barbier L, Jamal W, Dokmak S, et al. Impact of total pancreatectomy: short- and long-term assessment. *HPB (Oxford).* 2013;15(11):882-892.
 30. Yajnik CS, Kanitkar SV, Shelgikar KM, Naik SS, Alberti KG, Hockaday D. Pancreatic C-peptide response to oral glucose in fibrocalculous pancreatic diabetes. Improvement after treatment. *Diabetes Care.* 1990;13(5):525-527.
 31. Suzuki S, Kajiyama H, Takemura A, Shimazaki J, Nishida K, Shimoda M. The clinical outcomes after total pancreatectomy. *Dig Surg.* 2017;34(2):142-150.
 32. Sidhu SS, Shah P, Prasanna BM, Srikanta SS, Tandon RK. Chronic calcific pancreatitis of the tropics (CCPT): spectrum and correlates of exocrine and endocrine pancreatic dysfunction. *Diabetes Res Clin Pract.* 1995;27(2):127-132.
 33. Brunicaudi FC, Chaiken RL, Ryan AS, et al. Pancreatic polypeptide administration improves abnormal glucose metabolism in patients with chronic pancreatitis. *J Clin Endocrinol Metab.* 1996;81(10):3566-3572.
 34. Knop FK. Incretin hormones and beta cell function in chronic pancreatitis. *Dan Med Bull.* 2010;57(7):B4163.
 35. Ceriello A. Postprandial hyperglycemia and cardiovascular disease: is the HEART2D study the answer? *Diabetes Care.* 2009;32(3):521-522.
 36. Ketema EB, Kibret KT. Correlation of fasting and postprandial plasma glucose with HbA1c in assessing glycemic control; systematic review and meta-analysis. *Arch Public Health.* 2015;73:43.
 37. Makuc J. Management of pancreatogenic diabetes: challenges and solutions. *Diabetes Metab Syndr Obes.* 2016;9:311-315.
 38. Uemura F, Okada Y, Torimoto K, Tanaka Y. Relation between hypoglycemia and glycemic variability in type 2 diabetes patients with insulin therapy: a study based on continuous glucose monitoring. *Diabetes Technol Ther.* 2018;20(2):140-146.
 39. Liang S, Yin H, Wei C, Xie L, He H, Liu X. Glucose variability for cardiovascular risk factors in type 2 diabetes: a meta-analysis. *J Diabetes Metab Disord.* 2017;16:45.
 40. Kohnert KD, Heinke P, Vogt L, Salzsieder E. Utility of different glycemic control metrics for optimizing management of diabetes. *World J Diabetes.* 2015;6(1):17-29.
 41. Ruxer J, Mozdzan M, Loba J, Barański M, Ruxer M, Markuszewski L. [Usefulness of continuous glucose monitoring system in detection of hypoglycaemic episodes in patients with diabetes in course of chronic pancreatitis]. *Pol Arch Med Wewn.* 2005;114(4):953-957.
 42. Okabayashi T, Nishimori I, Yamashita K, et al. Continuous postoperative blood glucose monitoring and control by artificial pancreas in patients having pancreatic resection: a prospective randomized clinical trial. *Arch Surg.* 2009;144(10):933-937.