

Continuous glucose monitoring to assess glucose variability in type 3c diabetes

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Abstract

Aim: The effectiveness of continuous glucose monitoring (CGM) in maintaining glycaemic control in type 1 diabetes mellitus and type 2 diabetes mellitus has been well demonstrated. However, the degree of glycaemic variability (GV) in people with type 3c diabetes mellitus has not been fully explored using CGM. This study aims to evaluate GV in type 3c diabetes mellitus participants and compare it to type 1 diabetes mellitus and type 2 diabetes mellitus.

Methods: Participants were grouped according to type of diabetes. GV, defined as percentage coefficient of variation (%CV), and other glycaemic indices were obtained using CGM (FreeStyle Libre, Abbott, Australia) from 82 participants across all three cohorts over a 14-day period. Comparison of baseline characteristics and GV were performed across all groups. Correlation of GV with C-peptide values, and whether pancreatic supplementation had an effect on GV were also assessed in the type 3c diabetes mellitus cohort.

Results: GV of type 3c diabetes mellitus participants was within the recommended target of less than %CV 36% ($p = 0.004$). Type 3c diabetes mellitus participants had the lowest GV among the three groups ($p = 0.001$). There was a trend for lower C-peptide levels to be associated with higher GV in type 3c diabetes mellitus participants ($p = 0.22$). Pancreatic enzyme supplementation in type 3c diabetes mellitus participants did not have an effect on GV ($p = 0.664$).

Conclusions: Although type 3c diabetes mellitus participants were the least variable, they had the highest mean glucose levels and estimated HbA_{1c}, which suggests that the concept of 'brittle' diabetes in type 3c diabetes mellitus is not supported by the results of CGM in this study and may be leading to poorer glycaemic control.

KEYWORDS

continuous glucose monitoring, C-peptide, diabetes mellitus, glycaemic variability

1 | INTRODUCTION

Hyperglycaemia arising in the setting of exocrine pancreatic dysfunction is termed type 3c diabetes mellitus.¹ Type 3c

diabetes mellitus covers a wide range of aetiologies, including acute and chronic pancreatitis, pancreatectomy or other pancreatic surgeries, pancreatic cancer, cystic fibrosis (CF), haemochromatosis, rare genetic disorders and idiopathic

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forms.¹ Frequently, type 3c diabetes mellitus is misdiagnosed as type 2 diabetes mellitus.² Type 3c diabetes mellitus is characterised by endocrine dysfunction affecting all islet cells, as well as exocrine dysfunction. In type 3c diabetes mellitus, destruction of β -cells leads to insulin deficiency and consequent hyperglycaemia via the loss of insulin action.³ Glucagon secretion from alpha cells is also reduced, diminishing the counter-regulatory response to hypoglycaemia.⁴ Disruption of other pancreatic islet cells such as pancreatic polypeptide and somatostatin cells also contributes to derangements in metabolic pathways.³ In addition, malabsorption of nutrients due to pancreatic exocrine insufficiency (PEI) leads to an impaired secretion of incretin, therefore further diminishing insulin release from remaining β -cells.⁵

HbA_{1c} has been the gold standard for assessing glycaemic control and has strong predictive value for the development of diabetes-related complications.^{6,7} However, HbA_{1c} reflects average glycemia over a period of 2–3 months, but does not reflect rapid short-term intra- and inter-day fluctuations in blood glucose levels or glycaemic excursions, known as glycaemic variability (GV).⁸ Individuals with the same HbA_{1c} reading may have significantly different diurnal variations in glucose levels. GV can be measured by different methods, including percentage coefficient of variation (%CV), mean amplitude of glycaemic excursion (MAGE), continuous overall net glycaemic action (CONGA), mean of daily difference (MODD) and others. There is currently a lack of a clear consensus on the standard method for measuring GV.⁹

Since continuous glucose monitoring (CGM) systems provide a more comprehensive overall blood glucose profile, clinicians have the necessary information to personalise management plans and empower people with diabetes to achieve better glycaemic management.¹⁰ Clinical use of CGM systems allows assessment of glycaemic control, which is defined by an increased time in desired range (TIR); lower GV; lower HbA_{1c} levels; and decreased frequency, magnitude and duration of hypoglycaemia.¹¹ However, most CGM systems only measure glucose levels for a period of 2–3 weeks in a single setting, hence continuous use of CGM is recommended.

Randomised control trials have shown improved glycaemic control in both people with type 1 diabetes mellitus and type 2 diabetes mellitus with higher initial HbA_{1c} using CGM compared to self-monitoring blood glucose methods.^{12–15} There is also strong evidence for the use of CGM in type 1 diabetes mellitus with hypoglycaemia unawareness or frequent hypoglycaemic events, including nocturnal hypoglycaemia.¹³ Many studies in type 1 diabetes mellitus and type 2 diabetes mellitus populations have found that CGM usage resulted in a reduction in mean HbA_{1c} level, increased TIR and reduced time spent in hypoglycaemia.^{16,17} However, the different aspects of GV

What's new?

- Currently, most research involving the use of continuous glucose monitoring in diabetes management has been limited to type 1 and 2 diabetes mellitus, with little evidence in type 3c diabetes mellitus.
- This study uses a flash monitoring system to compare the patterns of glycaemia across all three groups of diabetes.
- The results show that people with type 3c diabetes mellitus are not at an increased risk of unstable glycaemic variability as compared to people with type 1 or type 2 diabetes mellitus, as previously suggested.
- Our results suggest that glycaemic variability is not a barrier to achieving optimal glucose targets in people with type 3c diabetes mellitus.

and glycaemic control have not been well studied in type 3c diabetes mellitus.

People with type 3c diabetes mellitus are believed to have more 'brittle' glycaemic control, which could contribute to higher GV and a higher risk of frequent hypoglycaemia due to the loss of insulin secretion and counter-regulatory glucagon secretion.¹⁸ There is limited literature that specifically studies the effectiveness of CGM use in glycaemic control in people with type 3c diabetes mellitus.¹⁹ As a result, the role of CGM in type 3c diabetes mellitus is yet to be established. Addressing this gap in knowledge could potentially guide and enhance management to improve glycaemic control in this population. Therefore, this study aims to (i) assess and describe GV in people with various forms of type 3c diabetes mellitus and (ii) compare GV and other CGM variables between people with type 1 diabetes mellitus, type 2 diabetes mellitus and type 3c diabetes mellitus.

We hypothesise that GV in participants with type 3c diabetes mellitus will be similar or higher to that in type 1 diabetes mellitus, and greater than those with type 2 diabetes mellitus. In addition, among participants with type 3c diabetes mellitus, we hypothesise that those who require pancreatic enzyme supplementation would display higher GV than those who are not on supplementation.

2 | METHODOLOGY

2.1 | Study design and participants

This was an open label, prospective observational study conducted at the Prince of Wales Hospital, Sydney,

Australia between May 2020 and May 2021. The study was approved by the South Eastern Sydney Local Health District Human Research Ethic Committee (SESLHD HREC, 2020/ETH011963). Informed consent was obtained from all participants.

Individuals aged 18 years or older with a diagnosis of either type 1, 2 or 3c diabetes mellitus were included in the study. Participants who had 2 weeks of flash glucose monitoring available, with at least 70% data recorded within the 2-week period being assessed were included. Exclusion criteria were women who were pregnant or lactating at time of study, use of glucocorticoids and individuals who were classified as having latent autoimmune diabetes in adults. The diagnosis of diabetes type was gathered from documentation in the hospital's medical database, as confirmed by the treating endocrinologist.

2.2 | Experimental procedure and CGM variables

Clinical history and demographic data of participants were extracted from the hospital's electronic medical record database. Data on diabetes duration, insulin dosing, pancreatic enzyme supplementation, estimated glomerular filtration rate (eGFR), chronic diabetic complications including neuropathy, retinopathy and macrovascular complications, HbA_{1c} values, paired glucose and non-fasting C-peptide values, glutamic acid decarboxylase and anti-insulin antibodies were acquired. Data on chronic diabetic complications were gathered based on documentation in the medical record. A value of 91 was used for tabulation for participants with eGFR >90 ml/min/1.73 m². Where C-peptide values were reported as <0.10 nmol/L, a value of 0.09 nmol/L was imputed.

Participants were provided with a factory calibrated flash glucose monitoring device (FreeStyle Libre, Abbott, Australia), that recorded 14 days of data. Participants were provided with the same CGM device and scanner, and all received the same education. All participants were able to contact the diabetes educator if any assistance was required. Key CGM variables studied were as follows: mean glucose, GV, TIR, time below range (TBR), time above range (TAR) and number of hypoglycaemic events; all of which were derived from the Libreview ambulatory glucose report (AGP).²⁰

GV is expressed as a %CV, as provided in the CGM report. Stable GV is defined as %CV <36%, while unstable GV is defined as %CV >36%.⁸ TIR refers to the amount of time that the measured glucose levels fall within the target range. The target range of 3.9–10 mmol/L has been considered acceptable for glycaemic management in clinical practice in the Advanced Technologies

and Treatments for Diabetes (ATTD) consensus statements.⁸ Following the same recommendations, TAR is further classified into level 1 'high' (10.1–13.9 mmol/L) and level 2 'very high' (>13.9 mmol/L). Similarly, TBR can be subdivided into level 1 'low' (3.0–3.9 mmol/L) and level 2 'very low' (<3.0 mmol/L) according to the International Hypoglycaemia Study Group definitions.²¹ Time in ranges (TIR, TAR and TBR) were expressed as a percentage of readings per day in this study. One episode of hypoglycaemia was defined as having a blood glucose level <3.9 mmol/L for more than 15 min.

2.3 | Outcomes

The primary outcome was difference in GV, as measured by %CV, against the accepted range of 36% in type 3c diabetes mellitus. The secondary outcome was difference in GV between type 1 diabetes mellitus, type 2 diabetes mellitus and type 3c diabetes mellitus participants. Another secondary end-point was comparing GV within the type 3c diabetes mellitus cohort, between participants who were either on, or not on pancreatic enzyme supplementation. Further subgroup analyses were performed to study the relationship between GV and C-peptide in type 3c diabetes mellitus group, and the relationship between GV and duration of diabetes in participants with type 1 diabetes mellitus and type 2 diabetes mellitus.

2.4 | Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp.). Data were presented as % (*n*/*N*) for categorical variables. Histograms were visually inspected to determine normality of data. Continuous variables that were normally distributed were reported as mean and standard deviation (SD), whereas skewed variables were presented as median and interquartile range (IQR). Missing data were omitted in the analysis, and the results were produced using the respective total number of values obtained and presented as *n* = *x*, where *x* is the total number of values included for analysis.

Between-group comparisons were done to explore how the groups differed in their baseline characteristics and CGM data. Continuous variables were assessed by a one-way analysis of variance (ANOVA) model or Kruskal–Wallis test depending on normality of data, and either the chi-square test or Fisher's exact test for categorical variables. A one-sample *t*-test was used to describe GV in type 3c diabetes mellitus as compared to standard ranges described in the ATTD consensus.¹² Group differences in GV were also evaluated using

a one-way ANOVA model, with further post hoc testing performed to determine the association. An independent *t*-test was used to compare differences in GV in type 3c diabetes mellitus participants who either had or did not have pancreatic enzyme supplementation.

A univariate linear regression model was constructed in the subgroup analysis to determine the correlation between GV and C-peptide levels in participants with type 3c diabetes mellitus. Linear regression models were used to assess the relationship between duration of diabetes and GV in the combined type 1 diabetes mellitus and type 2 diabetes mellitus cohort. *p* values of <0.05 were considered to be statistically significant.

In a previous study, Monnier et al. reported the difference in medians between people with type 2 diabetes mellitus on basal insulin compared to people with type 1 diabetes mellitus for GV as 7.5 (IQR 8).²² Therefore, we estimated we would need to study 19 people with type 2 diabetes mellitus and 19 with type 1 diabetes mellitus to be able to reject the null hypothesis that the mean GV of the type 1 diabetes mellitus and type 2 diabetes mellitus groups are equal with power 0.8.

3 | RESULTS

A total of 128 participants were selected during the initial screening process. In all, 40 participants had insufficient or missing data, 2 participants who were pregnant during time of study and 4 participants who were classified as LADA were excluded from the final analysis. Overall, 41 participants with type 1 diabetes mellitus, 20 with type 2 diabetes mellitus and 21 with type 3c diabetes mellitus were included in the final study (Figure 1). The aetiologies of type 3c diabetes mellitus participants include recurrent or chronic pancreatitis ($n = 7$), of which three participants had alcohol consumption higher than the recommended guidelines by the National Health and Medical Research Council, two with hypertriglyceridemia, one with chemotherapy-related pancreatitis and one with idiopathic pancreatitis; pancreatic cancer without any prior surgical management ($n = 2$); pancreatic surgical procedures including Whipple's procedure, total or distal pancreatectomy ($n = 10$); CF ($n = 1$); and thalassaemia ($n = 1$). Five of the participants had pre-existing type 2 diabetes mellitus.

3.1 | Participant characteristics

Baseline clinical characteristics of study participants are summarised in Table 1. Mean age of type 3c diabetes mellitus participants was slightly lower than type 2 diabetes

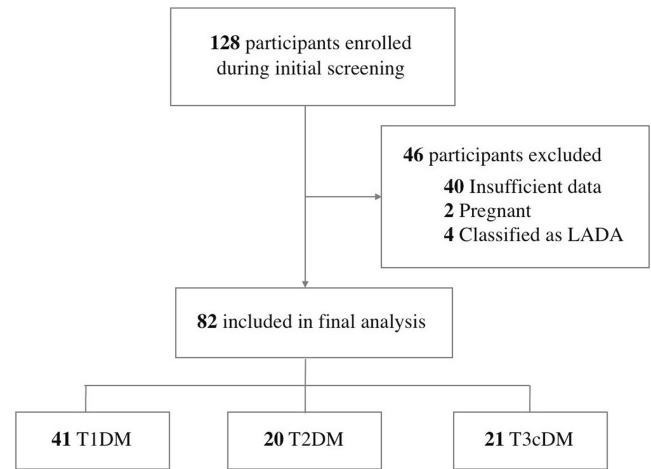


FIGURE 1 Screening and inclusion of study participants. LADA, latent autoimmune diabetes in adults; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; T3cDM, type 3c diabetes mellitus.

mellitus participants but higher than type 1 diabetes mellitus participants (mean (SD): 58 (18) vs. 63 (13) vs. 44 (19), $p < 0.001$). Type 3c diabetes mellitus participants had significantly shorter duration of diabetes as compared to participants with type 1 diabetes mellitus and type 2 diabetes mellitus (median (IQR): 4 (2–15) vs. 15 (6–26) vs. 21 (13–30), $p = 0.002$). BMI was lowest in the type 3c diabetes mellitus group (25.9 [5.9], $p = 0.025$). There was no significant difference in mean HbA_{1c} values between the three groups ($p = 0.749, 0.764$). C-peptide values were obtained from all 21 participants in the type 3c diabetes mellitus group, but only in 13 of 41 and 8 of 20 participants in the type 1 diabetes mellitus and type 2 diabetes mellitus cohorts, respectively. C-peptide levels were similar between type 3c diabetes mellitus and type 2 diabetes mellitus participants (0.40 (0.09–0.95) vs. 0.42 (0.28–0.89), $p = 0.618$), but type 3c diabetes mellitus participants had a significantly higher C-peptide level than type 1 diabetes mellitus participants (0.40 (0.09–0.95) vs. 0.09 (0.05–0.31), $p = 0.021$). Consequently, the type 3c diabetes mellitus cohort had higher C-peptide: glucose ratios than the type 1 diabetes mellitus group (3.3 (1.0–7.5) vs. 1.0 (0.4–1.8), $p = 0.011$).

3.2 | Glycaemic parameters

Results of glycaemic outcomes obtained from participants' CGM report are shown in Table 2. Overall, participants with type 3c diabetes mellitus had the lowest GV and least TIR among the three groups. Mean glucose levels and estimated HbA_{1c} levels were highest in participants with type 3c diabetes mellitus, followed by those with type 1 diabetes mellitus and type 2 diabetes mellitus. Percentage

TABLE 1 Demographic and clinical characteristics of study participants

	Group			p value
	Type 1 diabetes mellitus (n = 41)	Type 2 diabetes mellitus (n = 20)	Type 3c diabetes mellitus (n = 21)	
Age, years	44 (19)	63 (13)	58 (18)	<0.001
Ethnicity				0.034
European	97.6 (40/41)	100 (20/20)	76.2 (16/21)	
Asian, including Indian subcontinent	2.4 (1/41)	0 (0/20)	23.8 (5/21)	
Duration of diabetes, median (IQR), years	15 (6–26)	21 (13–30) n = 19	4 (2–15)	0.002
Sex				0.664
Men	48.8 (20/41)	60.0 (12/20)	57.1 (12/21)	
Women	51.2 (21/41)	40.0 (8/12)	42.9 (9/21)	
BMI, kg/m ²	26.2 (6.1) n = 40	28.9 (4.7)	25.9 (5.9)	0.025
HbA _{1c} , mmol/mol	68 (23)	70 (11) n = 19	72 (18)	0.764
HbA _{1c} , %	8.4 (2.1)	8.6 (1.1) n = 19	8.7 (1.6)	0.749
Insulin therapy	100 (41/41)	100 (20/20)	100 (21/21)	
Insulin regimen				
Basal alone	2.43 (1/41)	20.0 (4/20)	9.5 (2/21)	
Basal-bolus	82.9 (34/41)	60.0 (12/20)	81.0 (17/21)	
Premixed insulin	0.0 (0/41)	15.0 (3/20)	9.5 (2/21)	
Insulin pumps	12.2 (5/41)	5.0 (1/20)	0.0 (0/21)	
Insulin dosage				
Total daily dose, median (IQR), units	38.0 (27.3–50.8) n = 40	51.0 (26.8–61.0)	37.0 (23.0–65.0)	0.489
Total daily dose, median (IQR), units/kg	0.5 (0.4–0.7) n = 40	0.6 (0.3–0.8)	0.5 (0.3–1.0)	0.113
Total basal dose, median (IQR), units	19.0 (13.9–28.5)	27.0 (17.6–37.8)	19.0 (16.0–33.1)	0.185
Total bolus dose, median (IQR), units	16.8 (12.0–24.0) n = 40	17.0 (7.7–30.0)	18.0 (6.5–30.0)	0.938
Pancreatic supplementation	0 (0/41)	0 (0/20)	47.4 (9/19)	
Any diabetic complications				
Retinopathy	24.4 (10/41)	20.0 (4/20)	14.3 (3/21)	0.727
Neuropathy	2.4 (1/41)	25.0 (5/20)	9.5 (2/21)	0.003
Macrovascular complications	4.9 (2/41)	30.0 (6/20)	4.8 (1/21)	0.057
Estimated GFR, median (IQR), mL/min/1.73 m ²	91 (80–91) n = 36	75 (45–91)	91 (85–91)	0.010
C-peptide level, median (IQR), nmol/L	0.09 (0.05–0.31) n = 13	0.42 (0.28–0.89) n = 9	0.40 (0.09–0.95)	0.029
Paired glucose, median (IQR), mmol/L	13.0 (8.2–20.3) n = 13	9.0 (7.7–24.9) n = 9	11.9 (7.1–17.1)	0.751
C-peptide to glucose ratio, median (IQR)	1.0 (0.4–1.8) n = 13	3.9 (2.0–7.3) n = 9	3.3 (1.0–7.5)	0.009

Note: Continuous data presented as mean (SD) unless stated otherwise, and % (n/N) for categorical variables. All laboratory results taken within a year from CGM data; HbA_{1c} values taken within 3 months from CGM data with the exception of 8 participants in the type 1 diabetes mellitus group, 2 in the type 2 diabetes mellitus group and 3 in the type 3c diabetes mellitus group. Concurrent haemoglobin levels were in reference ranges except for one type 3c diabetes mellitus participant with thalassaemia.

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; IQR, interquartile range; SD, standard deviation.

TABLE 2 Glycaemic parameters obtained from CGM

	Group			p value
	Type 1 diabetes mellitus (n = 41)	Type 2 diabetes mellitus (n = 20)	Type 3c diabetes mellitus (n = 21)	
Sensor activity, median (IQR), %	92 (79–97)	80 (59–92) n = 18	90 (75–98) n = 18	0.096
Mean glucose, mmol/L	9.6 (2.6)	9.1 (1.9)	11.6 (3.8)	0.012
Glucose management indicator [eHbA _{1c}], %	7.4 (1.1) n = 40	7.2 (0.8) n = 17	8.2 (1.7) n = 20	0.025
Glycaemic variability, %CV	38.6 (8.5)	33.5 (5.9)	31.2 (6.7)	0.001
Time in range, %	55 (22)	63 (18)	43 (29)	0.026
Times above range, %				
High (10.1–13.9 mmol/L)	21 (10)	24 (11)	26 (13)	0.211
Very high (>13.9 mmol/L), median (IQR)	13 (1–30)	6 (1–16)	21 (8–43)	0.058
Time below range, %				
Low (3.0–3.9 mmol/L), median (IQR)	3 (1–6)	1 (0–3)	0 (0–1)	<0.001
Very low (<3.0 mmol/L), median (IQR)	1 (0–4)	0 (0–1)	0 (0–0)	0.002
Hypoglycaemic episodes (<3.9 mmol/L for >15 min), median (IQR)	7 (4–12)	2 (1–6) n = 16	1 (0–3) n = 17	<0.001

Note: Data presented as mean (SD) unless stated otherwise.

Abbreviations: CGM, continuous glucose monitoring; eHbA_{1c}, estimated HbA_{1c}; IQR, interquartile range; SD, standard deviation; %CV, percentage coefficient of variation.

of TAR in the ‘high’ level was similar across all groups, but the type 3c diabetes mellitus cohort had more time spent in the ‘very high’ level. Time spent in ‘very low’ was similar and non-significant across groups.

3.3 | Analyses of primary and secondary outcomes

3.3.1 | Primary outcome

GV of type 3c diabetes mellitus participants (mean (SD): 31.2 (6.75)) was found to be lower than the accepted threshold value of 36%, with a statistically significant difference of 4.78 (95% CI, 1.71 to 7.85, $t(20) = -3.247$, $p = 0.004$).

3.3.2 | Secondary outcomes

There was strong evidence ($F[2,79] = 7.498$, $p = 0.001$) of an association between GV and type of diabetes. Post-hoc pairwise comparisons using the Tukey HSD test showed evidence that the type 3c diabetes mellitus group had

significantly lower GV than the type 1 diabetes mellitus group ($p = 0.001$, diff = -7.36 , 95% CI, -12.20 to -2.52). However, there was no evidence of a significant difference between the type 3c diabetes mellitus and type 2 diabetes mellitus groups ($p = 0.602$, diff = -2.271 , 95% CI, -7.90 to 3.36).

In type 3c diabetes mellitus participants, there was no significant difference ($t[16.39] = 0.442$, $p = 0.664$) in GV for participants on pancreatic enzyme supplementation (30.5 [3.92]) and those who were not on supplementation (31.7 [8.42]).

3.4 | Regression analyses

3.4.1 | GV and C-peptide level

There was a non-significant inverse relationship between GV and C-peptide levels in the type 3c diabetes mellitus group. Results ($t = -1.267$, $p = 0.22$, $R^2 = 7.8\%$) showed that GV decreases as C-peptide level increases ($\beta = -3.385$, 95% CI, -8.98 to 2.21). We performed further analysis using the same variables, but excluding participants who had a total pancreatectomy ($n = 3$). However,

this did not alter the results ($t = -1.534$, $p = 0.144$, $R^2 = 12.8\%$).

3.4.2 | GV and duration of diabetes

GV and duration of diabetes were significantly correlated in the type 1 diabetes mellitus and type 2 diabetes mellitus cohorts combined ($t = 2.094$, $p = 0.041$, $R^2 = 7.0\%$). Higher GV was associated with a longer duration of diabetes ($\beta = 0.163$, 95% CI, 0.007 to 0.381) (Figure 2).

4 | DISCUSSION

While participants with type 3c diabetes mellitus had the highest HbA_{1c} values, they had the lowest GV amongst the three groups. In contrast, in type 1 diabetes mellitus and type 2 diabetes mellitus, higher HbA_{1c} readings are associated with higher GV.²³ GV in type 3c diabetes mellitus participants was considered as 'stable' according to the ATTD clinical target. People with type 3c diabetes mellitus have been assumed to have 'brittle' diabetes, due to the loss of glucagon-secreting alpha cells and the subsequent lack of counter-regulatory mechanisms to hypoglycaemia.¹⁸ However, our results give new insight into glycaemic patterns in type 3c diabetes mellitus, and provides reassurance that people with type 3c diabetes mellitus are not more prone to labile blood glucose levels. Furthermore, our study data highlight the limitations of HbA_{1c} as a method of assessing optimal glycaemic control. Participants across all three cohorts had similar mean baseline HbA_{1c}, yet they had significantly varying degrees of GV.

A previous study showed that people with fibrocalculus pancreatic diabetes, a form of type 3c diabetes mellitus, had a greater degree of GV than people with type

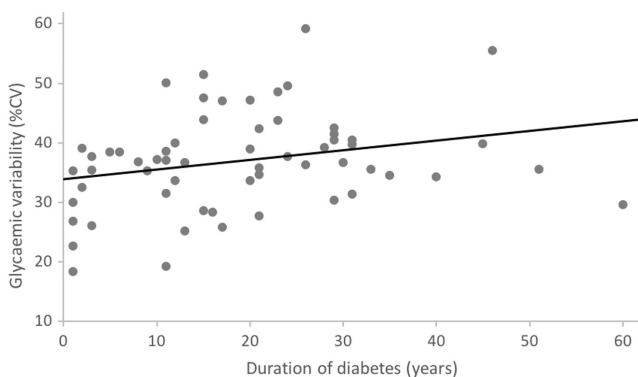


FIGURE 2 Scatterplot of duration of diabetes versus glycaemic variability in the combined type 1 and 2 diabetes cohorts, $r = 0.265$, $p = 0.041$.

2 diabetes mellitus.¹⁸ Another recent study by Juel and colleagues that compared glycaemic control between participants with longstanding type 1 diabetes mellitus and participants with diabetes secondary to total pancreatectomy showed that those with type 3c diabetes mellitus displayed greater fluctuations in blood glucose compared to people with type 1 diabetes mellitus.¹⁹ People with type 3c diabetes mellitus may be more malnourished due to PEI, and it is expected that they would have a lower lean body mass compared to other groups. This would mean that there are less sites for insulin-dependent uptake of glucose.²⁴ Our study showed higher blood glucose levels in participants with type 3c diabetes mellitus, but not higher GV.

Our cohort of type 3c diabetes mellitus participants were comparably older than the cohort with type 1 diabetes mellitus. Due to possible concerns about increased fragility, clinicians may be reluctant to treat these patients intensively by increasing the insulin dose for fear of increased hypoglycaemic episodes. As a result, type 3c diabetes mellitus participants had higher fluctuating blood glucose levels. However, this group of type 3c diabetes mellitus participants had normal mean BMIs and less macrovascular complications compared to the type 1 diabetes mellitus and type 2 diabetes mellitus groups. These data contradict clinicians' perception of the frailty of people with type 3c diabetes mellitus, and is a possible learning point for future diabetes management in this cohort.

Based on the pathophysiology behind type 1 diabetes mellitus and type 3c diabetes mellitus, we expected to see similar levels of GV and hypoglycaemic events in these groups. However, the type 1 diabetes mellitus cohort displayed higher GV, and had higher frequency of hypoglycaemic episodes. Our study found that type 1 diabetes mellitus participants had significantly lower levels of insulin secretion as compared to type 3c diabetes mellitus participants, as seen from lower C-peptide values. Lower C-peptide values have been associated with greater levels of GV and poorer glycaemic control.²⁵ Previous studies have reported that any amount of residual β -cell function resulting in preserved C-peptide secretion was associated with lower HbA_{1c} and less GV.²⁶ However, there has not been an accepted consensus on what level of C-peptide secretion is associated with meaningful clinical outcomes.²⁵⁻²⁷

In the subgroup analysis, our study found that rather than a continuous inverse relationship between C-peptide levels and GV in type 3c diabetes mellitus participants, there was a possibility of a threshold effect. Consistent with previous studies, we found that lower C-peptide levels, which indicate greater β -cell dysfunction, was associated with higher GV.^{28,29} Although the relationship was non-significant, the trend towards a higher GV under a

certain C-peptide level seemed apparent. Jeyam et al. have suggested that C-peptide association with glycaemic variables and diabetic complications demonstrated a trend of a threshold effect.³⁰ Based on the expectation that participants who had a total pancreatectomy are more likely to have lower C-peptide values and could therefore potentially skew data, we removed these participants and conducted the same analyses. However, this did not alter our results.

We expected type 3c diabetes mellitus participants who were on pancreatic enzyme replacement therapy (PERT) to have higher GV than those who were not on supplementation. Those with more severe pancreatic damage would typically have higher GV due to the larger extent of damage, and these people are likely to receive PERT. However, our participants who were on PERT displayed lower GV. This could be explained by the effectiveness of PERT in increasing incretin response, which improves glycaemic control.¹ In contrast, there could be participants with unrecognised subclinical PEI, resulting in higher levels of GV in this cohort.

Strengths of this study were the inclusion study participants across three types of diabetes cohorts, which highlighted certain similarities and differences in glycaemic outcomes across the different groups. Study sample was reasonably sized, and included type 3c diabetes mellitus participants with different aetiologies.

This study has a number of limitations. First, type 3c diabetes mellitus is a heterogeneous group. Our study did not have sufficient numbers across the different aetiologies to compare subgroups. We acknowledge that the aetiology of type 3c diabetes mellitus could be a possible confounding factor that could have an effect on GV. Additionally, our study only looked at a single measure of GV, which was %CV. There is a potential for difference in results when other metrics are used to evaluate GV. Another limitation was adherence to CGM use. Participants with poorer glycaemic control could be less involved in their diabetes management, and hence less compliant when it comes to scanning their readers frequently. For this reason, these participants would have insufficient data to be included in our analysis, which is a potential selection bias. To address these limitations, studies with larger study populations, specific to each aetiology in type 3c diabetes mellitus, are warranted.

In conclusion, people with type 3c diabetes mellitus have higher blood glucose levels but not GV than people with type 1 diabetes mellitus or type 2 diabetes mellitus. The reasons for this observation are still unclear and warrant further investigation. Nonetheless, the use of new technology like CGM is potentially useful in managing and optimising diabetes control in people with type 3c diabetes mellitus.

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CONFLICT OF INTEREST

The authors have nothing to declare.

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