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Glycemic Variability and Its Impact on Quality of Life in Adults With Type 1 Diabetes

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Abstract

Background: There is evidence suggesting that glycemic variability reduces quality of life (QoL) in people with type 2 diabetes, but this association has not been explored in type 1 diabetes. We aimed to assess whether glycemic variability has an impact on QoL in adults with established type 1 diabetes using multiple daily injections (MDI) of insulin or continuous subcutaneous insulin infusion (CSII).

Methods: Participants wore a blinded continuous glucose monitor for up to 5 days and completed the diabetes quality of life (DQOL) questionnaire. Glycemic variability measures were calculated using the EasyGV version 9.0 software. A correlation analysis was performed to assess whether there was a relationship between glycemic variability and measures of QoL.

Results: In all, 57 participants with type 1 diabetes (51% male, 65% on CSII, 35% on MDI, mean [SD] age 41 [13] years, duration of diabetes 21 [12] years, HbA1c 63 [12] mmol/mol [7.9% (1.1)], body mass index 25.2 [4.0] kg/m^2) were included in the analysis. No significant associations between glycemic variability and DQOL total or subscale scores were demonstrated. The glycemic variability was significantly higher for MDI participants compared to CSII participants ($P < .05$ for all glycemic variability measures), but no significant difference in QoL between the 2 treatment modality groups was observed.

Conclusions: Treatment with CSII is associated with lower glycemic variability compared to MDI. Despite this, and contrary to findings in type 2 diabetes, this study did not find an association between glycemic variability and QoL in adults with relatively well-controlled type 1 diabetes, irrespective of whether they are on MDI or CSII.

Keywords

continuous glucose monitoring; glycemic variability; type 1 diabetes; quality of life

Quality of life (QoL) is recognized as an important health outcome in diabetes and other long-term conditions.[1] People with type 1 diabetes have reduced QoL when compared to the non-diabetic population and sustained improvements in QoL are a key goal of diabetes self-management.[2,3] The determinants associated with health-related QoL in people with diabetes have been investigated and are multifold with lower income, increased age and body mass index (BMI), smoking status, and coexisting diabetes-related complications among the determining factors.[4] Psychosocial factors such as depression are stronger predictors of poor health outcomes, including hospitalization and death, for people with diabetes, than other factors such as metabolic control, weight, and complications.[5]

Optimal glycemic control, however, when not accompanied by significant hypoglycemia and treatment burden, has been shown to have a positive association with QoL.[6] In addition to the positive effect of metabolic control, there is evidence that educational interventions can improve QoL in type 1 diabetes.[7,8]

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Glycemic variability is characterized by glucose excursions in either direction and can be measured as intra- or interday variability. Over the last decade there has been increased interest in the role of glycemic variability as a contributory factor in the pathogenesis of macro- and microvascular complications in diabetes. However, the importance of glycemic variability remains uncertain. In vitro and in vivo data suggest that glucose fluctuations are associated with oxidative stress and endothelial dysfunction,[9-11] but there are studies that contradict these findings in people with type 1 diabetes.[12,13] Reference ranges for measures of glycemic variability in a nondiabetes multiethnic population have been described providing baseline values to benchmark diabetes populations.[14]

Despite anecdotal reports that glucose fluctuations are distressing for people with diabetes, the impact of glycemic variability on QoL has not been extensively explored. One study suggests that negative mood and impaired cognitive function 1 hour after breakfast and evening meal are significantly correlated with the rate of glucose rise regardless of insulin regimen in participants with type 2 diabetes.[15] A further study correlating QoL with variability showed that the glycemic variability measures, 24 hour standard deviation (SD) and continuous overall net glycemic action (CONGA), were significantly associated with health-related QoL in 23 women with type 2 diabetes.[16]

In type 1 diabetes, there is less literature on the association between glycemic variability and QoL. Hermanns et al investigated the effect of actual glucose levels and glycemic variability on mood in 36 participants with type 1 diabetes and showed that higher glucose levels were associated with negative mood; however no significant association was found between mood ratings and glucose variability. The glucose variability measures (coefficient of variation and absolute change in glucose) used in that study were calculated using continuous glucose monitoring (CGM) data from short 60-minute periods preceding each mood rating completed by the participants.[17] With this methodology only intermittent snapshots of glycemic variability are analyzed which may not accurately reflect global glycemic variability, making the lack of association with mood interpretable only during short periods.

The current study aimed to establish whether there is an association between increased glycemic variability and overall QoL and whether the 2 measures differ between type 1 diabetes participants on multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII).

Methods

This study forms part of and includes participants from 2 separate diabetes technology studies composed of (1) a closed-loop insulin delivery study in type 1 diabetes and (2) a glycemic variability study in type 1 diabetes. Approval by the regional ethics committee was obtained. Adult participants with type 1 diabetes were recruited from the diabetes clinics at Imperial College Healthcare NHS Trust in London. Inclusion criteria were age > 18 years, duration of diabetes > 1 year, treatment with MDI of insulin or CSII. Exclusion criteria were recurrent severe hypoglycemia (defined as needing third-party assistance), pregnancy or planning pregnancy, breastfeeding, active malignancy (defined as being on treatment or palliation), or being under investigation for malignancy. Informed written consent was obtained from each participant and screening performed.

Each participant included in the study wore a blinded retrospective continuous glucose monitor (Sof Sensor or Enlite sensor, Medtronic, Northridge, CA) for up to 5 days at home and was instructed to do at least 2 finger-prick capillary blood measurements per day for calibration purposes, maintain a food diary and complete the validated diabetes quality of life (DQOL) questionnaire.[18] The Hba1c and DQOL questionnaire were performed at the beginning of the CGM period. During this period, participants were allowed to continue "normal activities of daily living" and were blinded to the CGM readings so that these would not affect their regular, daily diabetes management practices; their only awareness of fluctuations in their glucose levels was then that provided by routine fingerprick glucose measurements.

In this analysis we explored the primary hypothesis that increased glycemic variability would be associated with lower QoL. Secondary hypotheses were that CSII would be associated with less glycemic variability and higher QoL than MDI.

Statistical Analysis

Twelve different glycemic variability measures (SD, CONGA, lability index [LI], J-Index, low blood glucose index [LBGI], high blood glucose index [HBGI], glycemic risk assessment in diabetes equation [GRADE], mean of daily differences [MODD], mean amplitude of glucose excursions [MAGE], average daily risk ratio [ADRR], M-value, mean absolute glucose [MAG]) were calculated using the EasyGV version 9.0 software.[19] In addition the coefficient of variation (CV) was calculated. The entire CGM period was included in the analysis. Most of the glycemic variability indices assess intraday variability (CV, SD, CONGA, LI, J-Index, LBGI, HBGI, GRADE, MAGE, M-value, MAG), whereas the others evaluate interday variability (MODD, ADRR).

The standard scoring system was used for analysis of the DQOL questionnaires including DQOL subscales (satisfaction, impact, worry: social/vocational, worry: diabetes-related). Parametric statistical tests were used throughout and log or square root transformation was applied to the data if necessary to normalize distributions (as indicated by the asterisk or dagger, respectively, in tables). A Pearson correlation analysis was performed to identify any significant associations between glycemic variability and QoL, and similarly between glucose measures (mean, HbA1c, percentage time

Table 1. Participant Baseline Characteristics and Glucose Measures.

Characteristic	All subjects, N = 57	MDI group 35%, n = 20	CSII group 65%, n = 37	*P* value
Age	41 (13)	43 (17)	40 (11.2)	.3
Sex women (%)	49	50	49	.9‡
Duration of diabetes (years)	21 (12)	21 (14)	21(11)	.9
HbA1c (mmol/mol) (%)	63 (12)	69 (14)	60 (9)	<.01
	7.9 (1.1)	8.5 (1.3)	7.6 (0.8)	
BMI (kg/m^2)	25.1 (4.0)	25.8 (3.3)	24.9 (4.3)	.4
TC/HDL ratio	2.78 (0.6)	2.9 (0.7)	2.7 (0.5)	.1
Glucose measures from CGM data				
Mean glucose (mg/dl)	158 (34)	175 (43)	151(25)	.01
% time in hypoglycemia <70 mg/dl, median (IQR)	3.2 (0.5-9.6)	8.2 (0.1-14.0)	2.3 (0.7-7.4)	.1
% time in range 70-180 mg/dl	60.7 (20.8)	44.0 (17.4)	69.9 (16.4)	<.01
% time in hyperglycemia >180 mg/dl	32.7 (20.8)	45.5 (21.3)	25.5 (16.8)	<.01

The results are shown as mean (SD), unless otherwise stated.
‡Chi-square test.

in hypo-, eu-, and hyperglycemia). A subanalysis was also done to evaluate any correlation between glycemic variability/glucose measures and QoL in men and women as separate cohorts. Multiple regression analyses were then performed to minimize any effect that the potential confounding factors: modality of treatment, HbA1c, age, gender, duration of diabetes, and BMI might be having on univariate associations between QoL and glycemic variability/glucose measures. Unpaired *t* tests were performed to compare QoL scores and glycemic variability measures between subjects on MDI and CSII. Nonnormally distributed variables are summarized as median and interquartile ranges, otherwise the outcome measure is presented as mean and SD. All *P* values below .05 were considered statistically significant. Data were analyzed using Stata/SE version 13.1

Results

Sixty potential participants were screened, of whom 3 did not fit the inclusion criteria and were therefore excluded. A total of 57 adult participants with type 1 diabetes were included in the final analysis of whom 20 were on MDI and 37 on CSII (of which 2 participants were on sensor-augmented pump). The participant baseline characteristics are outlined in Table 1. Two (5.4%) of the CSII participants had a previous history of depression/anxiety, but neither were on antidepressant medication at the time of inclusion in the study. Five (13.5%) of the CSII participants' weekly alcohol consumption was above the recommended limit (>21 units/week for men, >14 units/week for women). None of the participants had a history of other substance abuse. Mean HbA1c was significantly higher in the MDI group compared to the CSII. All the other participant characteristics were comparable between the 2 subgroups. Table 1 also shows the mean sensor glucose and percentage time spent in glucose target range (70-180 mg/dl), hypoglycemia (<70 mg/dl), and hyperglycemia (>180 mg/dl) derived from the CGM data. A mean (SD) of 3.2 (1.5) days of CGM data was collected across the study population.

Primary Outcomes

No significant correlations between glucose or glycemic variability measures and total DQOL scores were apparent in the overall study population as outlined in Table 2. The correlation analysis of glycemic variability measures and DQOL subscale scores (satisfaction, impact, worry: social/vocational, worry: diabetes-related) also showed no significant correlation (all *P* values > .05). Multiple regression analysis, taking into account treatment modality, HbA1c, age, gender, duration of diabetes, and BMI, confirmed the lack of association between glycemic variability and QoL. Analysis of the MDI and CSII subgroups separately confirmed that the lack of association between glycemic variability and QoL was irrespective of treatment modality. A correlation analysis of glycemic variability and QoL in men and women separately did not show any association between glycemic variability and QoL in either gender group (all R^2 values were < .3 with corresponding *P* values > .05).

Secondary Outcomes

Glycemic variability was significantly higher for those participants on MDI compared to the CSII group for all glycemic variability measures (Table 3). Further analysis identified a significant, but weak (all R^2 values were below .3) association between HbA1c and some glycemic variability measures (SD, CONGA, J-Index, HBGI, GRADE, MODD, MAGE, M-value), but not for others (CV, Li, LBGI, ADRR, MAG). The dependency of the higher glycemic variability in the MDI group on long-term glycemia, as expressed by Hba1c concentration, was explored in multivariable analyses with, successively, each of the 8 glycemic variability (GV)

Table 2. Association Between Glycemic Variability/Glucose Measures and QoL.

	DQOL total score, all subjects (N = 57)		DQOL total score, MDI subjects (n = 20)		DQOL total score, CSII subjects (n = 37)	
Glycemic variability measures	R^2	*P* value	R^2	*P* value	R^2	*P* value
CV*	.001	.8	.04	.4	.003	.7
SD†	.003	.7	.059	.3	.003	.7
CONGA	.004	.6	.032	.4	.0	.9
Li†	.007	.5	.08	.2	.001	.8
J-INDEX†	.003	.6	.045	.3	.001	.8
LBGI†	.00	.9	.021	.5	.037	.2
HBGI†	.001	.7	.028	.4	.00	.9
GRADE*	.005	.5	.001	.9	.007	.6
MODD	.009	.4	.046	.3	.01	.5
MAGE	.002	.7	.051	.3	.0	.9
ADRR	.01	.4	.144	.1	.0	.9
M-value*	.000	.9	.001	.9	.00	.9
MAG†	.001	.8	.033	.4	.002	.8
Glucose measures						
Mean glucose	.004	.6	.036	.4	.0	.9
HbA1c*	.01	.4	.12	.1	.011	.5
% time in hypoglycemia <70 mg/dl	.016	.3	.076	.2	.005	.6
% time in range 70-180 mg/dl	.006	.5	.039	.4	.0	.9
% time in hyperglycemia >180 mg/dl	.0	.9	.0	.8	.0	.8

*Log transformation.
†Square root transformation.

Table 3. Glycemic Variability With MDI Compared to CSII.

Glycemic variability measures	MDI, n = 20	CSII, n = 37	*P* value
CV*	39.0 (33.4-46.8)	31.3 (28.2-37.7)	.03
SD†	3.5 (3.0-4.7)	2.8 (2.1-3.5)	.006
CONGA	8.6 (2.3)	7.5 (1.4)	.02
Li†	7.2 (4.3-10.8)	4.0 (2.1-4.6)	.002
J-Index†	64.4 (41.8-78.0)	41.6 (28.3-52.5)	.006
LBGI†	6.7 (2.6-11.3)	2.8 (1.8-5.4)	.01
HBGI†	14.5 (10.2-20.4)	9.0 (5.1-11.5)	.001
GRADE*	9.8 (5.4-15.4)	5.8 (3.1-7.4)	<.001
MODD	4.2 (0.5)	3.5 (0.9)	<.001
MAGE	8.6 (1.9)	5.2 (1.9)	<.001
ADRR	30.7 (8.4)	22.2 (8.3)	<.001
M-value*	21.3 (13.0-34.7)	8.0 (4.3-13.0)	<.001
MAG†	3.2 (2.3-4.1)	2.0 (1.5-2.7)	.006

The results are shown as mean (SD) or as median (IQR) when transformation of the data has been applied for nonnormally distributed variables.
*Log transformation.
†Square root transformation.

measures that correlated significantly with HbA1c as dependent variable. For 3 of the measures, SD, MODD, and MAGE, MDI group positively and significantly predicted GV whereas HbA1c ceased to be a significant predictor. For 3 other measures, HGBI, GRADE, and M-value, both MDI group and HbA1c were significant positive predictors. For 2 measures, CONGA and J-Index, group ceased to be a significant predictor but HbA1c remained significant. Therefore, for 6 of the 8 GV measures that related to HbA1c, the higher GV in the MDI group was not accounted for by higher HbA1c. There was no significant difference in QoL or subscale QoL between the 2 treatment modality groups. Moreover, HbA1c did not correlate with QoL (R^2 = .01, *P* value = .4) in the overall study population. In the

subanalysis of women and men separately an association between HbA1c and QoL was apparent in the cohort of women on MDI (R^2 = .55, P value = .01).

A formal power calculation was not undertaken at the outset of this work. However, with 57 participants, a correlation coefficient of .25 or more would have been detected as significant at $P < .05$. Therefore, if glucose variability explained 6.3% (0.25 squared) or more of the variation in QoL, the study would have detected that as significant. With regard to detecting differences in glucose variability between MDI and CSII groups, with 20 in 1 group and 37 in the other, a 0.9 SD difference in means would have been detected as significant at $P < .05$ with 90% power. In post hoc evaluation of data presented in Table 3, the observed differences in mean for all measures of glucose variability except CONGA were greater than 0.9 SD, indicating that the study was adequately powered for those measures. CONGA differed by 0.6 SD between MDI and CSII groups, which means that although the difference between the groups in CONGA was detected as significant, this was only at 59% power.

Discussion

This study was a preliminary investigation into the relationship between GV and diabetes-specific QoL in participants with relatively well-controlled type 1 diabetes. There is conflicting evidence regarding the role of GV in the pathogenesis of diabetes-related complications and limited literature is available on whether GV affects QoL in people with diabetes.

Our study results suggest that neither overall glucose, measured by mean and HbA1c, nor GV impacts overall or subscale QoL in adults with type 1 diabetes, irrespective of whether they are on MDI or CSII. These findings contradict existing, albeit limited, evidence in type 2 diabetes where an association between GV and QoL has been demonstrated.[15,16] The results are also surprising given the anecdotal reports of the impact that glucose fluctuations from low to high have on motivation and mood. The lack of association noted may, in part, reflect a selected population taking part in a diabetes technology study and may also reveal weaknesses in the DQOL scale. Our study population, especially those on CSII, were generally well-controlled based on HbA1c and percentage time within target range (70-180 mg/dl) compared to previous studies[6] that have looked at associations of glycemic control and QoL and may therefore not be completely representative of the general type 1 diabetes population. Of note, we also excluded participants with recurrent severe hypoglycemia. Recurrent severe hypoglycemia will be very likely to adversely affect QoL. Inclusion of affected individuals in our analysis might then have biased the results in favor of positive findings and obscured more subtle effects associated with more representative GV. Ideally we would have undertaken separate analyses in people affected and unaffected by severe hypoglycemia and this is important further work. DQOL was initially validated and used in the Diabetes Control and Complications Trial study but has fixed domains which may not be applicable to everyone tested. One of the challenges in evaluating the association between QoL and GV is that QoL is a generally stable parameter whereas GV is inherently more variable with intra- and inter-day fluctuations. Thus it could be that subtle changes in mood or worries triggered by the GV were not detected, since the DQOL was only completed once prior to the CGM period. Measuring GV based on several days of CGM data will provide an average of the GV for that period, hence a longer CGM duration provides a better assessment of long-term GV. Limitations of our study include timing of the DQOL questionnaire in relation to the GV assessment and the relatively short CGM duration. The advantage of using blinded CGM rather than real-time open CGM is that it allows a pure assessment of GV without participant interference (extra bolus corrections) and hypo- and hyperglycemia alarms which may have an independent affect on QoL.

The HbA1c was higher in the MDI group than the CSII group, and one might expect a higher HbA1c to equate to higher GV.[20] Eight GV measures were positively correlated with HbA1c and their higher values in the MDI group could, therefore, have been accounted for by the higher long-term glycemia (as expressed by HbA1c) in that group. However, of these 8 measures, multivariable analysis suggested that only 2 (CONGA and J-Index) were higher in the MDI group on account of the group's higher HbA1c, the other 6 measures of GV being higher in the MDI group independently of HbA1c. The maximum variance in any GV measure accounted for by HbA1c was 25%. There was, therefore, appreciable variance that was not explained and we may assume that it is this residual variance that accounts for the differences in the multivariable analysis findings for the different GV measures. The most we would conclude on the basis of these observations is that differences in GV between the groups might, to some extent, be accounted for by long-term glycemia, as expressed by HbA1c, but mostly the difference in GV appeared independent.

As expected we found that GV was higher in participants on MDI than in participants on CSII, but no significant difference in QoL was observed between these subgroups. It has previously been shown that people with type 1 diabetes treated by CSII have a better QoL compared to MDI,[21-23] but our findings contrast with this despite the risk of hypoglycemia, (measured by LBGI) being significantly higher in the MDI group. There is a well-established association between hypoglycemia and increased anxiety and worry,[24,25] which is not apparent in our population. There are several factors that could have contributed to this, not least the potential insensitivity of the measure, the self-selecting participant group and the short duration of the study period. In the United Kingdom, CSII treatment has to be justified by clinical reasons such as recurrent hypoglycemia and suboptimal glycemic control. Therefore, it cannot be excluded that people with CSII have a more complicated course of diabetes and lower QoL. Similarly people with good QoL

on MDI may opt to remain on MDI despite suboptimal glycemic control. These factors may explain why no difference in QoL was observed between the CSII the MDI groups.

There remains uncertainty about the role of GV in diabetes management, but improved accuracy and reliability of CGM devices has created opportunities to investigate this further. Several statistical measures of GV exist, but there is no consensus as to which is the "best measure," and hence comparing data from published GV studies is challenging. Although we refer to GV measurements in general, it is important to remember that whilst some GV metrics evaluate actual variability of glycemia (SD, CONGA, LI, MAGE, MAG), others measure quality of glycemic control (J-Index, GRADE, M-value) and glycemic risk (HBGI, LBGI and ADRR), all of which reflect GV even if they are not a direct measure per se. As with GV, there is no "gold standard" for assessing QoL in participants with type 1 diabetes. Several tools assess either QoL or aspects of QoL such as psychosocial functioning, but confusion exists as to the best measure for clinical research. Tools such as DQOL, the Diabetes Treatment Satisfaction Questionnaire, and the Diabetes Attitudes Wishes and Needs Questionnaire are available, but poor implementation, poor process evaluation, and the use of different methods in different studies make comparisons difficult.

Conclusions

While it is limited by short duration and small numbers, this is the largest study of GV and QoL to date. Our post hoc exploratory analysis with 1 assessment did not reveal any associations between correlated measures of GV and QoL in people with type 1 diabetes. Given the anecdotal reports in clinical practice that the glucose fluctuations some people with diabetes experience are distressing this is perhaps surprising and contrasts with previous studies in type 2 diabetes. A larger prospective study over a longer period with repeated mixed measures is needed to confirm these findings. Achieving and maintaining optimal QoL is an important aspect of type 1 diabetes management, but whether the reduction of GV is a justified intervention target remains unclear.

Abbreviations

ADRR, average daily risk ratio; BMI, body mass index; CGM, continuous glucose monitoring; CONGA, continuous overall net glycemic action; CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; DQOL, diabetes quality of life; GRADE, glycemic risk assessment in diabetes equation; GV, glycemic variability; HBGI, high blood glucose index; J-Index,; LBGI, low blood glucose index; Li, lability index; MAG, mean absolute glucose; MAGE, mean amplitude of glucose excursions; MDI, multiple daily injections; MODD, mean of daily differences; M-value,; QoL, quality of life; SD, standard deviation.

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