Association of glycemic variability and the anti-glycemic medication effect score in adults with type 2 diabetes

Pennie J Taylor*[1,2,3], Kylie Lange[2], Campbell H Thompson[2], Wittert Gary[2,3] & Grant D Brinkworth[4]

ABSTRACT

While evidence implicates glycemic variability (GV) as an independent risk factor for type 2 diabetes (T2D) complications, individual characteristics and factors that determine and influence GV remain unclear. This study explored associations between GV and individual characteristics including age, body fat, diabetes duration, physical activity, gender, glycated haemoglobin (HbA1c) with a focus on anti-glycemic medication use. An observational, cross-sectional investigation was conducted as a secondary analysis on baseline data of 95 participants (age: 35-65 y; Body Mass Index (BMI): 26-45 kg/m^2) with T2D (HbA1c ≥ 7.0% and/or using diabetes medication) who participated in a Randomised Control Trial. Three glycemic variability indices were calculated using interstitial glucose level readings (mean of 5-mins) over a 48 h period, collected by continuous blood glucose monitoring. Multiple linear regressions were used to examine the association between the participant characteristics of interest and the GV indices. There were significant positive associations between all GV indices and anti-glycemic medication use (all; P<0.004). Similarly, significant positive associations between all GV indices and HbA1c (all; P<0.001) were observed. However, associations between HbA1c and all GV indices plateaued above an HbA1c of 8%. Finally, there were no observable associations between the GV indices and any other characteristics. From a range of patient characteristics, only the characteristic of a greater anti-glycemic medication score was significantly associated with greater GV in overweight or obese individuals with T2D. These data suggest clinical targets for optimal glycemic management may require greater consideration of the impact of pharmacotherapy on GV.

Introduction

Glycemic variability (GV), the amplitude, frequency and duration of glycemic fluctuations around mean blood glucose [1,2] is emerging as an independent risk factor of type 2 diabetes related macro- and microvascular complications [3-9]. Consequently, strategies to reduce GV are becoming recognised as an important treatment target in T2D management. These strategies involve lifestyle adjustment and often medication as well [2,10-12]. However, there is limited understanding and characterisation of individual and modifiable factors that may influence GV. This limits the development of effective targeted therapeutic strategies that consider all the factors that influence GV in individuals with T2D. The aim of this study was to explore associations between characteristics of overweight or obese individuals with T2D, most importantly their pharmacotherapy, and their GV.

[1]*Commonwealth Scientific and Industrial Research Organisation - Health and Biosecurity, Adelaide, Australia*

[2]*Discipline of Medicine, Adelaide Medical School, University of Adelaide, Adelaide, Australia*

[3]*Nutrition and Metabolism, South Australian Health and Medical Research Institute (SAHRMI), Adelaide, Australia*

[4]*Commonwealth Scientific and Industrial Research Organisation - Health and Biosecurity, Sydney, Australia*

**Author for correspondence: Pennie.Taylor@csiro.au*

KEYWORDS
- type 2 diabetes
- glycemic variability
- risk factor
- medication

Methods

Study outline

This was an observational, cross-sectional study conducted as a secondary analysis of the baseline data of 95 participants who participated in a diet and lifestyle intervention trial (ACTRN12612000369820) [13]. Participants with established T2D under the care of a general practitioner and/or endocrinologist were recruited from the community in Adelaide, Australia. Participants were aged between 35-68yrs with T2D (HbA1c ≥ 7.0% and/or using diabetes medication), and with a body mass index (BMI) of 26 to 45 kg/m^2. Exclusion criteria included smoking, type 1 diabetes, renal, hepatic, respiratory, gastrointestinal or cardiovascular disease; history of malignancy or any significant endocrinopathy (other than stable treated thyroid disease); pregnancy/lactation; history of or current eating disorder [13]. All study participants provided written informed consent and the study was approved by the CSIRO Human Research Ethics Committee.

Covariates and medication effect score

The participant characteristics identified to have an established and/or potential influence upon GV and to be included in the analysis models based on cohort size were: 1. age; 2. duration of diabetes; 3. HbA1c measured by a certified laboratory (SA Pathology; Adelaide, Australia); 4. percentage of body fat determined by whole-body dual-energy X-ray absorptiometry (DEXA; Lunar Prodigy; General Electric Corporation, Madison, Wisconsin); 5. time spent in sedentary and moderate/vigorous activity assessed using data from seven consecutive days of triaxial accelerometry (GT3X+model; ActiGraph, Pensacola, Florida), with pre-defined validity cutoffs [14] and 6. diabetes medication as measured by the anti-glycemic medication effect score (MeS). The MeS provides an overall assessment of the utilisation of anti-glycemic agents based on type and dose of agent, with a higher score corresponding to higher anti-glycemic medication use [13,15]. The calculation includes determining the prescribed dose of each anti-glycemic drug for each patient as a percentage of the maximum recommended daily dose of that drug. If the maximum daily dose of metformin is 3000 mg and the daily dose utilised is 500 mg, the percentage of maximum daily dose is 16.7%. This percentage , for each medication, is then multiplied by an adjustment factor: for metformin (biguanides) and sulfonylureas the adjustment factor is 1.5; for insulin 2.5. In this example, the subject on this dose of metformin alone has a MeS of 0.25. For a patient taking more than one anti-glycemic medication, each medication's prescribed/maximum daily dose is multiplied by the respective adjustment factor and the outcomes summed to generate the final MeS [15].

Glycemic variability assessment

Blood glucose profiles were collected at 5-minute intervals over a 48 h period, using an interstitial glucose sensor and the iPro 2 continuous glucose monitoring device (Medtronic, North Ryde, Australia). Glycemic variability measures were computed and included the mean amplitude of glycemic excursions (MAGE, average of blood glucose excursions exceeding 1 SD of the mean blood glucose value), and continuous overall net glycemic action (CONGA-2 and CONGA-4, SD of differences between observed blood glucose reading and an observed blood glucose level (n) hours prior (i.e. 2 or 4 hours apart, respectively)) [16].

Data analysis

Multiple linear regressions were used to examine the association between the participant characteristics including age, duration of diabetes, HbA1c, percentage of body fat, time spent in sedentary and moderate/vigorous activity and diabetes medication and each GV outcome. All GV outcomes were computed by automated algorithm and log transformed (ln) prior to analysis [17]. Covariates to be included were specified a priori, based on clinical justifications. A quadratic term for HbA1c was also included to account for non-linearity. Normality, heteroscedasticity and collinearity assumptions were assessed for each model and were met. Statistical significance was assessed at $P<0.05$. Analyses were conducted using SPSS Statistics 25 (IBM Corp, 2017).

Results

A total of 95 participants were included in the multiple regression analysis for this study. An additional 20 participants had been recruited for participation in the initial lifestyle intervention but were excluded from this analysis due to the unavailability of diabetes duration data. Participants' characteristics are presented in **TABLE 1**. **TABLE 2** presents relationships between GV outcomes and patient characteristics. There were significant positive

Table 1. Baseline characteristics of participants (n=95)	
Characteristics	**Mean (± SD)**
Demographics	
Age (years)	58.3 ± 6.8
Gender (n)	95 (55 Male, 40 Female)
Duration of T2D (years)	6.7 ± 5.9
Diabetes Medication	
Diabetes Medication Effect Score (MeS)	1.2 ± 1.1
Sulfonylureas (n [%])	28 [30]
Metformin (n [%])	40 [42]
GLP 1 agonists (n [%])	2 [2]
DPP4 inhibitors (n [%])	2 [2]
Thiazolidinedione's (n [%])	6 [6]
Insulin (n [%])	10 [11]
Other (n [%])	3 [4]
Nil Medication (Lifestyle Control Only) (n [%])	1 [1]
Anti-hypertensive Medication [n (%)]	88 (92%)
Body Composition	
Weight (kg)	101.8 ± 15.7
BMI (kg/m^2)	34.5 ± 4.4
Waist Circumference (cm)	112.0 ± 10.8
Total Body Fat (%)	39.8 ± 7.4
Glycemic Control	
Glycated Hemoglobin (% HbA1c)	7.3 ± 1.1 (n27>8%)
Fasting Glucose (mmol/L)	8.1 ± 2.1
MAGE (mmol/L)	5.1 ± 1.7
CONGA –2 (mmol/L)	2.4 ± 0.8
CONGA-4 (mmol/L)	2.9 ± 1.0
Physical Activity	
Time Spent in Sedentary behavior (%)	87.5 ± 3.7
Time Spent in Moderate to vigorous intensity activity (%)	3.5 ± 1.4

Standard Deviation. Data is mean ± SD, unless otherwise stated Abbreviations: MeS: anti-glycemic Medication Effect Score; GLP-1 agonists, Glucagon-like peptite-1 agonist; DPP-4 inhibitors, Dipeptidyl-peptidase-4 inhibitors, BMI: Body Mass Index; SD, MAGE: Mean Amplitude of Glycemic Excursions; CONGA-2: Continuous Overall Net Glycemic Action of observations 2 hour apart; CONGA-4: Continuous Overall Net Glycemic Action of observations 4 hour apart'.

Table 2. Adjusted Multiple Regression Output (unstandardized regression coefficients)			
	Glycemic Variability Indices		
Characteristics	**MAGE (ln (mmol/L))**	**CONGA 2 (ln (mmol/L))**	**CONGA 4 (ln (mmol/L))**
Age (yrs)	b= 0.006 (P=0.230)	b= 0.001 (P=0.820)	b= 0.003 (P=0.536)
Female gender	b= 0.061 (P=0.494)	b= 0.115 (P=0.153)	b= -0.091 (P=0335)
Body fat (%)	b= -0.006 (P=0.344)	b= -0.009 (P=0.111)	b= -0.009 (P=0.192)
HbA1c (%)	b= 2.018 (P <0.001)	b= 2.157 (P<0.001)	b= 2.069 (P<0.001)
HbA1c squared	b= -0.119 (P <0.001)	b= -0.130 (P<0.001)	b= -0.123(P<0.001)
MeS (arbitrary units)	b= 0.113 (P=0.003)	b= 0.115 (P=0.001)	b= 0.115(P=0.004)
Diabetes Duration (yrs)	b = -0.002 (P=0.756)	b= -0.003 (P=0.646)	b= -0.004 (P=0.596)
Time Spent Sedentary Activity (%)	b= -0.019 (P=0.169)	b= -0.021 (P=0.088)	b= -0.019 (P=0.196)
Time Spent Mod/Vig Activity (%)	b= -0.032 (P=0.398)	b= -0.021 (P=0.525)	b= -0.023 (P=0.558)

Significance p<0.05

Abbreviations. HbA1c%, Glycated Hemoglobin; MeS: anti-Glycemic Medication Effect Score; MAGE: Mean Amplitude of Glycemic Excursions; Conga 2: Continuous Overall Net Glycemic Action 2-Standard Deviations of the difference in blood glucose readings 2 hours apart (Score); Conga 4, Continuous Overall Net Glycemic Action 3-Standard Deviations of the difference in blood glucose readings 3 hours apart (Score).

associations between HbA1c and all GV indices (all P<0.001), which plateaued above an HbA1c of 8%, and between MeS and all GV indices (all P<0.004). There were no statistically significant associations between GV indices and any of the other characteristics in the model.

Discussion

After controlling for individual characteristics, results revealed a significant, independent positive association between GV and the anti-glycemic MeS. Beyond the expected, positive associations between HbA1c and all GV indices [18], there were no observable associations of GV indices with any of the other characteristics included in the model. Hyperglycaemia (as measured by HbA1c) is an important contributor to the incidence of microvascular and macrovascular complications in T2D [4,18]. In contrast, a growing body of evidence suggests that high GV is an important determinant of vascular damage and reflects sub-optimal diabetes control [4,5,19-23]. The positive associations between GV and the anti-glycemic MeS suggests that a higher use of anti-glycemic medication is not associated with any decrease in GV. Similarly, a previous study, conducted in T2D patients on mixed insulin with concomitant anti-glycemic medication, observed short and occasional prolonged episodes of hypoglycemia in individuals with low mean blood glucose levels and wide fluctuations in blood glucose values in patients taking higher insulin doses [7]. This study also reported no correlation between HbA1c and time spent in hypoglycemia. This suggests that a glycemic profile with smaller GV should be a target when designing an intervention to optimise glycemic control over and above lowering HbA1c concentrations [7]. These findings have important clinical implications, suggesting close attention should be considered when prescribing anti-glycemic medication and dosing regimes. These drugs may affect GV in addition to any effect they have on HbA1c. In a separate line of evidence, a recent cross-over study demonstrated that participation in moderate intensity exercise over a 3-day period reduced GV in individuals with T2D [24]. No association between GV and either time spent in sedentary activity or in moderate/vigorous activity was observed in the present study. The exact reason for this discrepancy remains unclear. It is possible that medication use has a stronger association with GV than any of the other variables considered in the model, at least in patients with T2D.

■ Study limitations

This is the first study investigating associations between GV and individual characteristics in T2D that includes diabetes medication usage yet several limitations exist. Firstly, this was a secondary analysis of baseline data that consisted of a heterogeneous population treated with a variety of treatment strategies for diabetes management. Those stategies included oral anti-glycemic medications and insulin in addition to concomitant medications including anti-hypertensives. This limits the ability to explore specific associations by medication type. Secondly, whilst the anti-glycemic MeS is useful in clinical research to assess global changes in medication over time, it has not yet been established in clinical practice. At this point it is impossible to decipher the relationship between GV and specific medication types and dosages. Finally, the study sample examined was relatively small, with well controlled diabetes. Inclusion of potential cofounding variables was limited. Consequently, the present findings may not be generalizable to the wider population and larger studies examining more diverse populations considering the confounding effects of diet, caloric intake, kidney and renal disease should be conducted to describe these relationships more comprehesively. It is also important to acknowledge that the cross-sectional design of this study does not provide evidence of cause-and-effect. Future interventional studies should be conducted to understand the direct effect of changing medication dosage and type on GV, including HbA1c. It will also be necessary to conduct longitudinal studies in controlled *vs* poorly controlled individuals investigating the effects on GV of differing types and changes of dose of medication over time on. This will inform clinical practice guidelines and appropriate prescription of medications with greater consideration of GV control.

Conclusion

From a range of patient characteristics, only the characteristic of a greater anti-glycemic medication score was significantly associated with greater GV in overweight or obese individuals with T2D. These findings suggest that clinical targets for optimal glycemic management should consider the impact of pharmacotherapy upon GV because more medication may not translate

to lower GV.

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