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SHORT COMMUNICATION

HbA_{1c} and mean blood glucose show stronger associations with cardiovascular disease risk factors than do postprandial glycaemia or glucose variability in persons with diabetes: the A1C-Derived Average Glucose (ADAG) study

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Abstract
Aims Increased glucose excursions and postprandial hyperglycaemia have been suggested as unique risk factors for cardiovascular disease (CVD) and mortality in patients with diabetes mellitus. Much of the evidence is based on a single 2 h glucose value after oral glucose tolerance testing in epidemiological studies. We examined the association between various indices of glycaemia measured during everyday activities and metabolic CVD risk factors in the A1C-Derived Average Glucose (ADAG) study.

Methods Participants (268 with type 1 diabetes, 159 with type 2 diabetes) completed 16 weeks of intensive continuous glucose monitoring (CGM) and self-monitoring of blood glucose (SMBG). From these data, common indices of postprandial glycaemia, overall hyperglycaemia, glucose variability and HbA_{1c} were derived. The associations between glycaemic indices and known CVD risk factors (lipids, high-sensitivity C-reactive protein and blood pressure) were explored in linear regression models.
Results For both diabetes types, the overall strongest associations with CVD risk factors were seen for the measures of average glycaemia (mean blood glucose and HbA_{1c}). Associations between self-monitored postprandial and fasting glucose and CVD risk factors were weaker, but significant. Measurements of blood glucose variability showed non-significant associations. Overall, calculations based on CGM were not more informative than those based on frequent SMBG.
Conclusions/interpretation Mean glycaemia and HbA_{1c} show consistent and stronger associations with CVD risk factors than fasting glucose or postprandial glucose levels or measures of glucose variability in patients with diabetes.

The Electronic supplementary material (ESM) contains a list of members of the ADAG Study Group

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Keywords ADAG study · CVD risk · Glucose monitoring · Glucose variability · HbA_{1c} · Postprandial glycaemia · *z* score

Abbreviations

ADAG	A1C-Derived Average Glucose study
BG	Blood glucose
CGM	Continuous glucose monitoring

CVD	Cardiovascular disease
hs-CRP	High-sensitivity C-reactive protein
PPG	Postprandial glucose concentration
SMBG	Self-monitored blood glucose concentration

Introduction

The role of postprandial hyperglycaemia and glucose variability in relation to the risk of cardiovascular disease (CVD) is heavily debated [1–4]. Treatment regimens and guidelines have increasingly focused on the control of postprandial glucose concentration (PPG) as an additional target beyond average glucose (HbA_{1c}) control. Much of the evidence is based on single glucose concentration values after oral glucose tolerance testing [5, 6]. Direct evidence for an additional effect of controlling PPG excursions, over and above an effect on reduced average glucose levels, on relevant diabetic endpoints is limited.

The objective of this study was to examine the association between different indices of glycaemia, monitored intensively during daily life activities, and CVD risk factors in the A1C-Derived Average Glucose (ADAG) study.

Methods

The ADAG study (2006–2008) defined the mathematical relationship between HbA_{1c} and average glucose levels, and included 268 individuals with type 1 diabetes mellitus and 159 with type 2 diabetes mellitus. A full description of the ADAG study has been published previously [7]. The study was approved by the human studies committees at the participating institutions and informed consent was obtained from all participants.

Continuous glucose monitoring (CGM) (Medtronic Minimed, Northridge, CA, USA) was performed at baseline and three times at 4 week intervals during the 12 week study period. Monitoring lasted at least 48 h, during which glucose levels were assessed every 5 min. Furthermore, participants performed an eight-point profile of self-monitored blood glucose (SMBG) (preprandial, 90 min postprandial, bedtime and 03:00 hours) with a Hemocue Glucose 201 Plus meter (Hemocue, Angelholm, Sweden) during the days of CGM. During the weeks when CGM was not performed, participants performed a seven-point SMBG (preprandial, postprandial and bedtime) (OneTouch Ultra; Lifescan, Milpitas, CA, USA) for at least 3 days per week. All BG values stated are plasma equivalents.

The average BG concentration and SD were calculated based on CGM data and the seven-point SMBG (Lifescan) data. A combined average BG was calculated from CGM and SMBG [7].

Two validated indices of intraday glucose variability were calculated based on CGM: the mean amplitude of glycaemic excursions (MAGE) and the continuous overlapping net glycaemic action (CONGA) [8, 9].

As an indicator of overall hyperglycaemia, the area under the CGM curve (AUC) above levels of 7.8 or 11.1 mmol/l (140 or 200 mg/dl) was calculated for the first 24 h of each CGM monitoring period. Also, a postprandial AUC was calculated for periods of 2 h after meals (without thresholds), and a postprandial increment was calculated from the preprandial glucose level to the highest peak within 2 h after meals. Pre- and postprandial measurements from SMBG (HemoCue) were used to calculate mean pre- and postprandial BG, as well as pre- and post-breakfast, lunch and dinner values. The pre-breakfast BG was used as fasting BG. All indices based on CGM were calculated after exclusion of the initial 2 h of monitoring, considered to be the unstable calibration period.

HbA_{1c} samples were analysed by DCCT-aligned assays; the mean value at the end of the 12 week study period was used [7]. Samples for lipids and high-sensitivity C-reactive protein (hs-CRP) analyses were obtained at baseline (not necessarily fasting) and analysed by validated methods at a central laboratory (for details, see Electronic supplementary material [ESM] Methods).

The associations of the calculated glycaemic indices with the CVD risk factors were explored in separate linear regression models adjusted for sex, age, smoking and diabetes type. To facilitate comparison of associations, glycaemic variables were standardised by the study population SD. Each regression estimate represents the change in the individual CVD risk factor per population SD change in the explanatory variable. Non-standardised estimates are given as examples in clinically relevant units.

In order to assess the combined cardiovascular risk, a summed z score was calculated. CVD risk factors were standardised (based on the distribution within each diabetes type), and combined within the groups of lipids, blood pressure, inflammation and anthropometrics (for details, see ESM Methods). The z score was used as an additional outcome variable in regression analyses with and without stratification by diabetes type. The stratified estimates were tested for interaction.

Results

Glucose monitoring was completed by 427 participants with diabetes, leading to approximately 2,700 glucose values per participant. We excluded one participant (type 1 diabetes mellitus) due to erroneous pre- and postprandial Hemocue measurements.

Characteristics of the study population are summarised in ESM Table 1.

When examining the associations between different glycaemic indices and known CVD risk factors, HbA_{1c} and mean BG consistently showed statistically significant associations with the different risk factors with a larger magnitude than most of the associations of the self-monitored PPG measurements (ESM Table 2). PPG based on CGM, fasting BG and overall hyperglycaemia also showed statistically significant associations with CVD risk factors, albeit at a lower level. Indices of glucose variability and postprandial increment did not show significant associations. A similar pattern of associations was present for the various lipid measures, blood pressure and hs-CRP. Adjustment for antihypertensive treatment or lipid lowering medication, or exclusion of all participants with these treatments, did not substantially alter the results.

Overall, the indices based on CGM were not more informative than those based on frequent SMBG.

Higher levels of HbA_{1c} were associated with higher systolic blood pressure (2.2 mmHg per percentage unit HbA_{1c}), higher total cholesterol (0.1 mmol/l per percentage unit HbA_{1c}), higher hs-CRP (0.39 mg/ml per percentage unit HbA_{1c}) and lower HDL-cholesterol (0.04 mmol/l per percentage unit HbA_{1c}) (ESM Table 3)

The associations of the different glycaemic indices with the combined CVD *z* score are illustrated in Fig. 1. Both for the total group (in grey) and for the two diabetes types (in black), the strongest associations were seen with the measures of average glycaemia (mean BG and HbA_{1c}) and with the mean of all self-monitored postprandial BG values. The difference between estimates for the two diabetes types was not statistically significant (*p* values between 0.15 and 0.92). The associations of the variability indices with the CVD *z* score were not statistically significant.

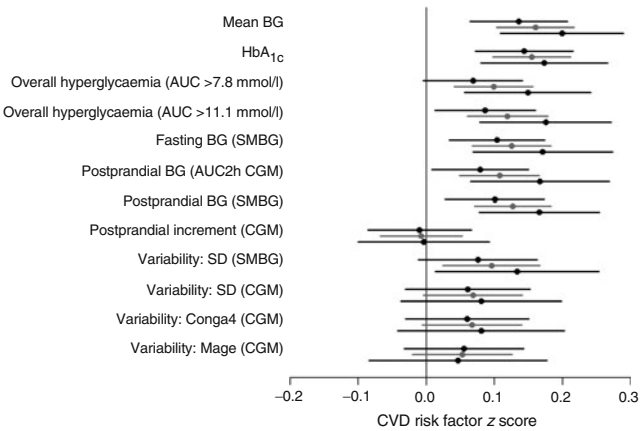

Fig. 1 Standardised associations between different glycaemic indices and the *z* score derived from the CVD risk factors (associations per 1 population SD with 95% CI). Upper and lower black bars are for patients with type 1 and type 2 diabetes mellitus, respectively; middle grey bars are for both groups together (controlling for diabetes type). Postprandial BG (AUC 2hpp CGM), area under the continuous glucose monitoring curve 2 h postprandially; $CONGA_4$, continuous overlapping net glycaemic action (n=4 h); MAGE, mean amplitude of glycaemic excursions

Discussion

We found that average glucose and HbA_{1c} showed the strongest associations with CVD risk factors among a wide set of indicators of glycaemia and variability. Indices of glycaemic variability showed no significant associations with CVD risk factors.

Elevated postprandial glucose levels and/or glucose variability have been suggested to increase the risk of CVD beyond their effect on overall hyperglycaemia. Only a few studies have tested this hypothesis directly or compared the effect with that of overall glucose exposure (HbA_{1c}) and shown postprandial glucose levels and/or glucose variability to be independent mechanisms. One single-blind randomised trial comparing the effects of two insulin secretagogues with different effects on PPG found that control of postprandial hyperglycaemia led to a reduction in carotid intima–media thickness in patients with type 2 diabetes compared with the control group [1]. Therapy with lower PPG levels was associated with significant reductions in the concentrations of the inflammatory markers IL6 and hs-CRP. However, a recent randomised clinical trial in patients with type 2 diabetes mellitus and CVD did not support an added benefit of targeting control of PPG for subsequent CVD events [4]. In our study, glucose variability and postprandial hyperglycaemia did not have a stronger association with known metabolic CVD risk factors than measures of average glucose. This suggests that the impact of PPG on cardiovascular risk is likely to be captured by the assessment of average blood glucose or HbA_{1c}.

Several of the epidemiological studies demonstrating an association between post-OGTT hyperglycaemia and increased CVD and mortality did not take an average glucose measurement (for example HbA_{1c}) into account [2, 5].

In type 1 diabetes mellitus, glucose variability has not been shown to be associated with the development of complications. In the DCCT, BG variability (from seven-point profiles) did not appear to be a factor in the development of microvascular complications, and pre- and postprandial glucose values contributed equally to small-vessel complications [10].

The strength of this study is the analysis of glycaemia under real-life circumstances in a large number of individuals with diabetes. Intensive glucose monitoring using several methods allowed us to compare several approaches for defining PPG, and provided sufficient measurements to reliably assess the different features of glycaemia.

The main limitation of the study is its cross-sectional character. While it has a very high resolution, glucose monitoring is short term and our outcomes are CVD risk factors rather than actual CVD events. Therefore, although we cannot reach direct conclusions regarding the impact of postprandial glucose levels or glucose variability on CVD endpoints, our results show that, if such an effect exists, it is likely to be mediated through mechanisms other than those examined in our study. The CVD risk factors we chose are well-validated risk factors for CVD (lipids, blood pressure and hs-CRP). Treatment to lower these CVD risk factors might have confounded our findings.

The participants had stable HbA_{1c} at baseline (defined as a <1 percentage unit change in HbA_{1c} during the 6 months prior to the study), and were relatively stable during the study. We may therefore have limited the range of glucose variability as seen in a diabetic population. However, high levels of glucose variability were seen among our individuals despite stable HbA_{1c} levels.

Our results do not support a unique role of postprandial hyperglycaemia in CVD. Monitoring PPG and glucose variability may be important in adjusting treatment to achieve target mean glycaemia and to avoid daily excursions, but our results suggest that interventions to reduce the risk of CVD are best aimed at controlling mean glucose and HbA_{1c}.

We conclude that mean glycaemia and HbA_{1c} show stronger and consistent associations with CVD risk factors than fasting glucose and most measures of postprandial glucose and glucose variability. The previously observed associations between glucose variability and postprandial hyperglycaemia (often OGTT-based) and CVD events cannot be explained by an association with CVD risk factors.

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Duality of interest R. J. Heine is employed by and owns stocks of Eli Lilly. K. Borch-Johnsen is head of the Steno Diabetes Center, a hospital integrated in the Danish National Healthcare Service but owned by Novo Nordisk. K. Borch-Johnsen holds shares in Novo Nordisk. The other authors have no duality of interest associated with this manuscript.

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