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Glycaemic variability is associated with coronary artery calcium in men with Type 1 diabetes: the Coronary Artery Calcification in Type 1 Diabetes study

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Abstract

Aims—We investigated coronary artery calcium in association with glucose levels and variability measured using continuous glucose monitoring in adults with Type 1 diabetes in the Coronary Artery Calcification in Type 1 Diabetes study.

Methods—Coronary artery calcium was measured by electron beam tomography. The presence of any coronary artery calcium was analysed with respect to glucose levels [mean$_T$ (mean glucose), % of values < 3.9 mmol/l, > 10 mmol/l and either < 3.9 or > 10 mmol/l] and glycaemic variability [SD$_T$ (SD of all glucose values); SD$_{dm}$ (SD of the daily mean glucose levels) and SD$_{hh:mm}$ (glucose SD for a specified time of day, over all days)] using 3–5 days of continuous glucose monitoring from 75 subjects (45 women, 30 men), age 42 ± 9 years (mean ± SD) and diabetes duration of 29 ± 8 years using logistic regression.

Results—We observed significant associations between coronary artery calcium and mean$_T$ (OR = 4.4, 95% CI 1.1–18.6), % of values > 10 mmol/l (OR = 5.5, 95% CI 1.3–22.6), % of measures < 3.9 or > 10 mmol/l (OR = 5.7, 95% CI 1.3–24.9), SD$_T$ (OR = 4.7, 95% CI 1.1–19.7), SD$_{dm}$ (OR = 6.0, 95% CI 1.2–30.4) and SD$_{hh:mm}$ (OR = 4.0, 95% CI 1.1–15.4), among men, but none of these variables were associated with the presence of coronary artery calcium in women.

Conclusions—We report the novel finding that subclinical atherosclerosis is associated with glucose levels and variability in men with Type 1 diabetes. The relationship of coronary artery calcium and glucose variability in Type 1 diabetes, and potential gender differences in this association, deserve further study.

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Competing interests

SG received funding from DexCom Inc., San Diego, CA for studies of the use of new continuous glucose monitoring sensors and the number of days that sensors may be worn continuously. He received no funding from DexCom for the present study and has not shared this manuscript or information about this study with DexCom. He has also received Honoraria for giving lectures for DexCom, MiniMed and Abbott. He reports no equity interest in any of these companies. DR has served as a consultant to DexCom Inc., San Diego, CA on matters related to the methodology for characterizing glycaemic variability using continuous glucose monitoring data. He received no funding from DexCom in regard to the present study and has not shared this manuscript or information about this study with DexCom.

Keywords

continuous glucose monitoring; coronary artery disease; Type 1 diabetes

Introduction

Coronary artery disease is the major cause of mortality and morbidity in Type 1 diabetes and modifications of traditional coronary artery disease risk factors have had a limited impact (1). The incidence of coronary artery disease is approximately 1–2% per year among young adults with Type 1 diabetes (2;3). By the age of 45 years, more than 70% of men and 50% of women with Type 1 diabetes develop coronary artery calcification (4;5).

The Coronary Artery Calcification in Type 1 Diabetes (CACTI) study has followed a cohort of patients with Type 1 diabetes and age-matched control subjects for progression of coronary artery calcification measured by electron beam tomography since 2000. Coronary artery calcification score correlates with plaque burden and coronary angiography (6) and predicts coronary events independently of other risk factors (7). The role of chronic mean glucose elevation in development of macrovascular complications of Type 1 diabetes has been questioned by studies in relatively poorly controlled patients followed until they develop clinical coronary artery disease endpoints (2). In contrast, the CACTI study demonstrated a greater progression of coronary artery calcification in patients with elevated HbA_{1c} (8). The Epidemiology of Diabetes Interventions and Complications study followed the participants in the Diabetes Control and Complications Trial and showed that standard treatment (mean HbA_{1c} = 9%) was associated with coronary artery disease events (9) and coronary artery calcification (10). Studies from Stockholm (11) and Oslo (12) provide additional evidence for a role of chronic hyperglycaemia in acceleration of atherosclerosis in patients with Type 1 diabetes.

HbA_{1c} estimates average blood glucose but gives no information regarding glycaemic variability. Postprandial hyperglycaemia is a strong predictor of cardiovascular risk (13); hence, it is reasonable to hypothesize that glycaemic variability might be a risk factor for coronary artery disease.

Continuous glucose monitoring (14;15) allows for the measurement of glucose excursions and variability during the entire 24-h day. Continuous glucose monitoring use can identify adverse patterns not evident by self-monitored blood glucose or HbA_{1c} (16–18). To examine the possible role of glycaemic variability in accelerated atherosclerosis, we analysed the relationship between coronary artery calcification and measures of glucose variability obtained from continuous glucose monitoring in patients with Type 1 diabetes in the CACTI study.

Patients and methods

Study participants

Inclusion criteria for the CACTI study have been previously described in detail (4): age 19–56 years; no history of coronary artery disease; receiving insulin therapy currently and within 1 year of diagnosis; diagnosis before age 30 years and/or with a clinical course consistent with Type 1 diabetes; and long-standing Type 1 diabetes (mean duration was 23 years). We present data from subjects who underwent continuous glucose monitoring close to the CACTI 6-year follow-up exam.

Data were obtained from two groups of subjects. The first group (n = 41, 20 female) wore a masked continuous glucose monitor (Medtronic MiniMed Gold System; Medtronic, Minneapolis, MN, USA) during the 3 days prior to participating in a hyperinsulinaemic–euglycaemic clamp substudy (‘clamp‘ group). Inclusion criteria included: $HbA_{1c} \leq 9.5\%$, albumin excretion rate < 200 μg/min and triglycerides < 4.52 mmol/l. A second group of subjects (n = 34, 25 women) utilized real-time continuous glucose monitoring as part of their diabetes management [14 used Medtronic MiniMed Guardian® (Medtronic), 20 used the Dexcom SEVEN system (Dexcom, San Diego, CA, USA)]. Continuous glucose monitoring data were obtained from downloads of the sensor data during clinical visits. Reasons for continuous glucose monitoring use were reported as hypoglycaemia (n = 10), hyperglycaemia (n = 6), erratic blood glucose levels (n = 11), pregnancy planning (n = 3) and not noted (n = 4). Records were available for up to 200 days, but we chose to use the continuous glucose monitoring data of the first 5 days in order to obtain a period of time more closely comparable with that for the ‘clamp’ group. In this ’clinic‘ group, patients received education regarding use of the continuous glucose monitor and were instructed not to make adjustments to their insulin doses during the first week of use. Accordingly, the initial 5 days of data should be closely comparable with the masked data obtained from the ‘clamp’ group. We examined these two groups of subjects in order to evaluate associations between coronary artery calcification and continuous glucose monitoring in different settings. We evaluated associations with coronary artery calcification and continuous glucose monitoring variables separately in the two groups, and an interaction term was examined for the group and each continuous glucose monitoring variable to ensure that the relationship of continuous glucose monitoring variables with coronary artery calcification did not differ by group. No interactions were found between group status and any of the continuous glucose monitoring variables. Consequently, the two groups were combined for analysis, and a variable indicating the group was included in the models.

Measures of glycaemic control and variability calculated from the continuous glucose monitoring glucose time series

Evaluation of glycaemic levels (glucose control)

Glycaemic levels (glucose control) were evaluated by:

- **i.** the overall mean glucose ($mean_T$), the average of all glucose values;
- **ii.** the percentage of values outside of the target range (< 3.9 or > 10 mmol/l);
- **iii.** hypoglycaemia, the percentage of glucose values < 3.9 mmol/l;
- **iv.** hyperglycaemia, the percentage of glucose values > 10 mmol/l (19).

Glycaemic variability within days

- **i.** Overall standard deviation ($_{SD}T$), the standard deviation of all glucose values.
- **ii.** $_{SD}hh{:}mm$ is the standard deviation for the average glucose for any time of day using the mean glucose (over days) for a specified time of day (20;21).

Glycaemic variability between days

- **i.** $_{SD}dm$ is the standard deviation of the mean glucose for each day.

Additional details of these measures of glycaemic variability and the relations among these measures have been published (20;21).

In addition to the continuous glucose monitoring variables, HbA_{1c} was measured in both groups as a longer-term measure of glycaemic control. HbA_{1c} was measured both at the time of the 6-year follow-up examination and within 2 months of the continuous glucose

monitoring recording. HbA_{1c} at the 6-year follow-up examination and for the 'clamp' study group was measured using high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA, USA), in the University of Colorado Hospital Clinical Laboratory, while HbA_{1c} for the 'Clinic' group was measured using a DCA-2000 analyser.

Coronary artery calcium

Coronary artery calcium was measured twice using electron beam tomography without contrast. Two sets of scans were acquired within 5 min and averaged, as previously described (22). Images were electrocardiographically triggered at 80% of the R-R interval and 30–40 contiguous 3-mm slices were acquired. Coronary artery calcification scores were log transformed after adding 1 (to allow for log transformation of zero scores) and geometric means were calculated.

Cardiovascular risk factors

Height, weight and waist and hip circumferences were measured. Resting systolic blood pressure and fifth-phase diastolic blood pressure were measured three times while the patients were seated, following a 5-min rest, and the second and third measurements were averaged. Total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides were measured after 12-h fasting.

Statistical analysis

Variables were examined for normality and non-normally distributed variables were log transformed for analysis. Differences in risk factors between men and women in the clamp and clinic groups were examined using unpaired Student's *t*-tests. A χ^2-test for goodness of fit was used to determine if categorical risk factors differed between subjects in the 'clamp' and 'clinic' groups and by sex.

Correlations between coronary artery calcification score (geometric mean), HbA_{1c} and measurements of glycaemic variability and glucose level were examined using Pearson correlation coefficients. The relationship between presence of coronary artery calcification (0 vs. any coronary artery calcification) and continuous glucose monitoring variables were analysed by multivariate logistic regression.

All participants provided informed consent and the study protocol was approved by the Colorado Multiple Institutional Review Board.

Results

Clinical characteristics

Women in the 'clinic' group were younger than women in the 'clamp' group and had a shorter duration of diabetes than men in the 'clinic' group (Table 1). There were no differences in HbA_{1c}, insulin dose, BMI or coronary artery calcification score (geometric mean) by either group or sex, while coronary artery calcification prevalence was significantly lower in women in the 'clinic' group than men in the 'clinic' group. Men in the 'clinic' group exhibited a higher mean glucose ($mean_T$), less hypoglycaemia and a greater percentage of glucose values > 10 mmol/l than men in the 'clamp' group. Women in the 'clinic' group also had less frequent hypoglycaemia than women in the 'clamp' group. In the 'clamp' group, the difference between self-monitored blood glucose measurements and continuous glucose monitoring sensor values (bias), was 0.078 mg/dl, and the mean absolute relative difference of self-monitoring blood glucose and continuous glucose monitoring glucose values was 18.0% on day 1, 12.2% on day 2 and 12.5% on day 3.

Correlation coefficients between HbA_{1c} at the time of the continuous glucose monitoring and glucose levels and measures of glycaemic variability from continuous glucose monitoring were examined. HbA_{1c} was significantly correlated with $mean_T$ in both the 'clinic' and 'clamp' groups ($r = 0.48$ and 0.32, respectively, $P < 0.05$ for both), whereas HbA_{1c} was only correlated with % of values > 10 mmol/L ($r = 0.52$, $P < 0.05$) in the 'clinic' group. HbA_{1c} was not correlated with measures of glycaemic variability (SD_T, SD_{dm} or $SD_{hh:mm}$) in either group.

Relationship of glucose levels and glycaemic variability to coronary artery calcification

We examined the relationship between presence of coronary artery calcification (0 vs. any coronary artery calcification) and glucose levels and variability using logistic regression. We found no significant differences in coronary artery calcification scores or prevalence between the 'clamp' and the 'clinic' groups and so the two groups were combined for the analysis. A variable for group status was included in the models and an interaction term was examined for group and each continuous glucose monitoring variable. Each continuous glucose monitoring variable was entered into a model individually, adjusted for age, diabetes duration, menopause status for women, number of days between the continuous glucose monitoring recording and the coronary artery calcification score measurement, sex and patient group ('clamp' or 'clinic'). Duration of diabetes was significantly associated with the presence of coronary artery calcification (OR = 1.16, 95% CI 1.04–1.29, $P = 0.007$), but there were no significant relationships between presence of coronary artery calcification and age, female sex, group, menopausal status or days between continuous glucose monitoring and coronary artery calcification measurement..

The logistic regression analysis (Table 2) demonstrated significant associations between presence of any coronary artery calcification and $mean_T$, percentage of glucose values out of target range (< 3.9 or > 10 mmol/l), percentage of glucose values > 10 mmol/l, SD_T, SD_{dm} and $SD_{hh:mm}$ among men. We observed significant interactions by sex at $P < 0.05$ for the associations between presence of coronary artery calcification and percentage of values out of target range (< 3.9 or > 10 mmol/l), % of values > 10 mmol/l and SD_{dm}. Interaction terms for study group were not statistically significant for any of the variables examined except for percentage of values out of target range, where the OR between presence of coronary artery calcification was stronger in men in the 'clinic' group (OR = 29.1, 95% CI 3.7–228) than in the men in the 'clamp' group (OR = 3.9, 95% CI 0.9–16.5). There was no association between presence of coronary artery calcification in women in the 'clinic' group (OR = 1.5, 95% CI 0.6–4.3), but there was a protective association in women in the 'clamp' group (OR = 0.2, 95% CI 0.1–0.8).

To examine whether associations between coronary artery calcification and glycaemic variability were independent of glycaemic control, we then modelled the presence of coronary artery calcification associated with glycaemic variability (SD_T, SD_{dm} and $SD_{hh:mm}$) adjusted for HbA_{1c}, in addition to the other covariates. Among men, $mean_T$ (OR = 4.7, 95% CI 1.1–20.5), percentage of values out of target range (OR = 5.4, 95% CI 1.1–23.3), percentage of values > 10 mmol/l (OR = 5.6, 95% CI 1.4–23.0), SD_T (OR = 4.8, 95% CI 1.2–19.9), SD_{dm} (OR = 6.5, 95% CI 1.2–35.4) and $SD_{h:\ mm}$ (OR = 4.3, 95% CI 1.1–17.2) were significantly associated with the presence of coronary artery calcification. When further adjusted for the $mean_T$, SD_{dm} remained significantly associated in men (OR = 6.4, 95% CI 1.1–37.4). None of the continuous glucose monitoring variables were associated with the presence of coronary artery calcification in women when adjusted for HbA_{1c} or when further adjustment was made for $mean_T$.

Correlations between log-transformed coronary artery calcification scores were then examined by sex to evaluate whether the associations found between presence of coronary

artery calcification were also present when the extent of coronary artery calcification was considered. In men, significant correlations were found between log coronary artery calcification score and percentage of values out of target range ($r = 0.41$, $P = 0.03$), percentage of values > 10 mmol/l ($r = 0.47$, $P = 0.01$) and SD_{dm} ($r = 0.48$, $P = 0.009$). None of the correlations were significant among women.

Discussion

We examined associations between continuous glucose monitoring data and presence of coronary artery calcification in two groups of patients, representing two common uses of continuous glucose monitoring: real-time use in clinical management and masked use in a research study setting. The patients in the 'clinic' group experienced more hyperglycaemia and less hypoglycaemia than the 'clamp' study group patients. We believe that this is attributable to selection by physicians of patients with hyperglycaemia/erratic blood glucose levels for the use of continuous glucose monitoring in clinical management and the use of real-time continuous glucose monitoring, respectively. Despite these differences in glycaemic patterns as revealed by continuous glucose monitoring, the patients did not differ in terms of HbA_{1c} or total daily insulin dose from 'clamp' study participants.

Glucose levels during continuous glucose monitoring were measured by $mean_T$ and % of values > 10 mmol/l, while glycaemic variability was measured by SD_T, SD_{dm} and $SD_{hh:mm}$. $Mean_T$ was modestly correlated with HbA_{1c} in both groups, but none of the parameters of glycaemic variability were correlated with HbA_{1c}. There could be several reasons for a modest association between HbA_{1c} and $mean_T$ Participants in the 'clamp' group may have had difficulty adjusting their insulin or they may have been more careful with blood glucose testing and insulin adjustment during the 3-day study diet period. This hypothesis is consistent with the observation that the relationship between HbA_{1c} and $mean_T$ was stronger in the 'clinic' group than in the 'clamp' group. While the continuous glucose monitoring data were masked for the 'clamp' study group and the subjects in the 'clinic' group had been instructed not to change their insulin regimen during the first week of use, it is possible that individuals changed their behaviour because of use of the continuous glucose monitoring. Further, the relationship between HbA_{1c} and mean plasma glucose has been shown to differ based on level of glucose control and treatment intensity (23).

We previously reported a sevenfold greater progression of coronary artery calcification during a 3-year follow-up in patients in the CACTI study with HbA_{1c} in the highest quartile, compared with those with lower HbA_{1c} (8). However, in the present study of a small subset of the cohort, no association was found between HbA_{1c} or HbA_{1c} quartile (data not shown) and cross-sectional presence of coronary artery calcification. An association between mean blood glucose values collected seven times per day and cardiovascular events had been reported previously in the Diabetes Control and Complications Trial, but no association was found with HbA_{1c} (24), suggesting that there may be a stronger association between frequently collected blood glucose values and their variability and cardiovascular outcomes than with HbA_{1c}. Glucose variability, as measured by seven daily blood glucoses, was not, however, associated with long-term risk of microvascular complications in the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications study cohort (25).

This is the first study reporting the relation between coronary artery calcification and glycaemic variability measured by continuous glucose monitoring. Our data are consistent with a study in subjects with Type 2 diabetes who underwent eu-insulinaemic–hyperglycaemic clamps where glucose was infused in increasing or oscillating concentrations. Oscillating glucose had more severe deleterious effects than constant high

glucose on endothelial function and oxidative stress, which are believed to be associated with coronary artery disease risk (26).

We found sex differences regarding the association of chronic hyperglycaemia and glycaemic variability (SD_T, SD_{dm} and $SD_{hh:mm}$) with coronary artery calcification, with a significant association only in men. We had not anticipated this sex difference, as, in contrast to the general population, female sex is generally not regarded as a protective factor for coronary artery disease in Type 1 diabetes (4). Glycaemic variability may cause oxidative stress, leading to atherosclerosis (27). Young healthy men have greater levels of oxidative stress than pre-menopausal women (28) and oestrogen may protect against oxidative stress (29), perhaps protecting pre-menopausal women with Type 1 diabetes against this mechanism of increased atherosclerosis.

The present study has limitations. In this study, we report the relationships between continuous glucose monitoring and coronary artery calcification score in a subset of 75 out of 543 CACTI study participants with Type 1 diabetes who completed a 6-year follow-up examination, who may not be a representative sample. However, there were no significant differences in coronary artery disease risk factors between subjects in the 'clamp' group and the remaining CACTI cohort, while the 'clinic' group was younger and had lower systolic blood pressure. Subjects in the 'clamp' group used the continuous glucose monitoring 3 days prior to a clamp study, during which they were provided a standardized diet of 30% fat, 15% protein and 55% carbohydrate and were requested to avoid exercise. Otherwise, they were 'free living' during the 3-day continuous glucose monitoring recording and they were instructed to manage their insulin regimen based on the carbohydrate content of the diet. The continuous glucose monitoring data obtained under these conditions and during this type of dietary management may differ from the patient's typical glycaemic patterns. Accordingly, we also examined continuous glucose monitoring in a second group of subjects (the 'clinic' group). Subjects included in the 'clinic' group might have used the continuous glucose monitoring on their own personal initiative or based on the advice of their physicians. These factors could have influenced patient selection. Real-time continuous glucose monitoring has been shown to improve glycaemic control and reduce HbA_{1c} in adult populations (18). To reduce this potential bias, we chose to analyse data from the initial 5 days of continuous glucose monitoring recording, a period during which patients had been asked to make no changes to their insulin dose or regimen (learning phase). Further bias may have been introduced because of the larger proportion of women than men who had continuous glucose monitoring in the 'clinic' group, as some women may have used continuous glucose monitoring to improve glycaemic control prior to pregnancy and this may explain why the women in this group were younger and had less coronary artery calcification.

Continuous glucose monitoring data from 3 to 5 days were utilized in the present study and may not be representative of the patient's overall long-term metabolic control. Nevertheless, mean glucose and percentage of values > 10 mmol/l were correlated with HbA_{1c}. The continuous glucose monitoring data were obtained close to the most recent CACTI study visit and, in several cases, were recorded after the coronary artery calcification measurement. Accordingly, the present study does not demonstrate causality. Coronary artery calcification may not be as predictive of cardiovascular events in women as in men (30) and so the sex difference observed may be attributable to limitations of coronary artery calcification as a marker of atherosclerosis in women.

The present data indicate that glucose levels and several measurements of glycaemic variability were consistently associated with coronary artery calcification among men. These findings indicate that more detailed long-term study is warranted for effects of glucose

variability on presence and progression of coronary artery calcification and coronary artery disease events in patients with Type 1 diabetes.

Abbreviation

CACTI Coronary Artery Calcification in Type 1 Diabetes

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Table 1

Characteristics of study population by group and sex

	Clamp group		Clinic group	
	Men (*n* = 21)	**Women (*n* = 20)**	**Men (*n* = 9)**	**Women (*n* = 25)**
Age (years)	46 ± 9	44 ± 10	42 ± 10	38 ± 8*
Post-menopausal (%)	—	25	—	8
Duration of diabetes (years)	29 ± 7	29 ± 9	33 ± 10	27 ± 8‡
HbA_{1c}, % (mmol/mol))				
at 6-year examination	7.8 (62) ± 1.1	7.7 (61) ± 1.0	7.4 (57) ± 1.0	7.7 (61) ± 0.9
at time of CGM	7.5 (58) ± 1.0	7.6 (60) ± 0.9	7.3 (56) ± 1.1	7.2 (55) ± 0.8
Insulin dose (units/kg/day)	0.65 ± 0.20	0.57 ± 0.20	0.64 ± 0.22	0.58 ± 0.18
BMI (kg/m^2)	27.2 ± 3.6	25.7 ± 4.0	27.6 ± 3.2	26.4 ± 6.2
Waist circumference (cm)	94.3 ± 9.4	81.9 ± 11.1§	97.6 ± 10.5	80.5 ± 12.2§
Systolic blood pressure (mmHg)	120 ± 10	112 ± 11§	115 ± 12	11 ± 8
Diastolic blood pressure (mmHg)	80 ± 6	73 ± 8§	72 ± 11	72 ± 6
Total cholesterol (mmol/l)	4.50 ± 0.73	4.02 ± 0.83	3.39 ± 0.39†	4.35 ± 0.78‡
LDL cholesterol (mmol/l)	2.59 ± 0.67	2.02 ± 0.67§	1.58 ± 0.26†	2.31 ± 0.75‡
HDL cholesterol mmol/l)	1.53 ± 0.41	1.66 ± 0.44	1.40 ± 0.34	1.66 ± 0.44
Triglycerides (mmol/l)	1.84 ± 0.78	1.74 ± 0.75	2.12 ± 1.22	1.87 ± 1.09
% with CAC	71%	60%	67%	28%*
CAC score (geometric mean)	5.5 ± 7.9	4.8 ± 7.5	24.2 ± 21.3	2.2 ± 5.5
$Mean_T$ (mmol/l)	7.52 ± 1.22	7.93 ± 1.73	9.23 ±1.56*	8.87 ± 1.65
% of values < 3.9 mmol/l	16.2 ± 9.3	14.3 ± 14.2	3.6 ± 3.1†	4.4 ± 4.3*
% of values > 10 mmol/l	22.3 ± 12.7	27.2 ± 15.0	35.5 ± 15.8*	32.7 ± 17.6
% of values out of target range (< 3.9 or > 10 mmol/l)	38.5 ± 15.1	41.5 ± 14.0	39.1 ± 15.8	37.0 ± 16.7
SD_T (mmol/l)	3.6 ± 1.1	3.4 ± 1.2	3.4 ± 1.0	3.3 ± 0.9
SD_{dm} (mmol/l)	1.4 ± 0.9	1.9 ± 0.8	1.8 ± 0.9	1.4 ± 1.1
$SD_{hh:mm}$ (mmol/l)¶	2.4 ± 1.1	2.5 ± 1.2	2.5 ± 1.3	2.2 ± 0.8

Reported are means ± SD or geometric mean (SD).

*$P < 0.05$ for difference by group within sex.

† $P < 0.001$ for difference by group within sex.

‡ $P < 0.05$ for difference by sex within group.

§ $P < 0.001$ for difference by sex within group.

¶ As the SD*hh:mm* is related to the number of days of CGM recorded, for this variable 3 days of CGM were used in both groups.

CAC, coronary artery calcification; CGM, continuous glucose monitoring.

Table 2

Standardized ORs and 95% CI for association of continuous glucose monitoring data and presence of coronary artery calcification (0 vs. any) by sex for both groups (’clamp‘ and ’clinic‘) combined

	Men (*n* = 30)	***P*-value for men**	**Women (*n* = 45)**	***P*-value for women**	***P*-value for interaction by sex**
$Mean_T$ (per 1.65 mmol/l)	4.4 (1.1–18.6)	0.04	1.4 (0.6–2.9)	0.31	0.13
% of values out of target range (< 3.9 or > 10 mmol/l)	5.7 (1.3–24.9)	0.02	0.7 (0.3–1.5)	0.42	0.02
% below 3.9 mmol/l	0.9 (0.3–2.6)	0.78	0.5 (0.2–1.1)	0.08	0.42
% above 10 mmol/l	5.5 (1.3–22.6)	0.02	1.1 (0.5–2.4)	0.55	0.049
SD_T (per 1.05 mmol/l)	4.7 (1.1–19.7)	0.03	1.0 (0.5–2.2)	0.76	0.068
SD_{dm} (per 0.80 mmol/l)	6.0 (1.2–30.4)	0.03	0.6 (0.3–1.5)	0.32	0.017
$SD_{hh:mm}$ (per 1.05 mmol/l)*	4.0 (1.1–15.4)	0.043	1.0 (0.5–2.0)	0.97	0.067
HbA_{1c} at 6-year examination (per 0.99%)	1.3 (0.6–3.2)	0.52	1.0 (0.5–2.3)	0.90	0.66

Standardized ORs (per SD change) and 95% CI are presented.

Each variable was tested in a separate model, adjusted for age, diabetes duration, number of days between CGM recording and CAC measure, group (‘clamp’ vs. ‘clinic’) and interaction term by sex.

*As the $SD_{hh:mm}$ is related to the number of days of CGM recorded, for this variable 3 days of CGM were used in both groups.

CAC, coronary artery calcification; CGM, continuous glucose monitoring; SD_T, SD of all glucose values; SD_{dm}, SD of the daily mean glucose levels; $SD_{hh:mm}$, glucose SD for a specified time of day, over all days.