ORIGINAL ARTICLE

Association between glucose variability as assessed by continuous glucose monitoring (CGM) and diabetic retinopathy in type 1 and type 2 diabetes

Giovanni Sartore · Nino Cristiano Chilelli ·
Silvia Burlina · Annunziata Lapolla

Abstract There is a growing debate in the literature on whether glucose variability contributes, as well as high HbA1c levels and longstanding diabetes, to the onset and progression of diabetic retinopathy (DR) in patients with diabetes types 1 (DM1) and 2 (DM2). Few data, obtained only by self-monitoring of blood glucose, support this hypothesis. We used continuous glucose monitoring (CGM) to investigate the association between DR and glucose variability parameters (SD, CONGA 2, MAGE), acute hyperglycemia (HBGI) and chronic exposure to glucose (AG and AUC tot). We studied 68 patients from 19 to 69 years old, 35 with DM1 and 33 with DM2. The prevalence of retinopathy was 43 % in DM 1 patients and 39 % in DM 2 patients. The values of all indicators were obtained by CGM for 72 h. DR was diagnosed on direct or indirect ophthalmoscopic examination, after inducing mydriasis with tropicamide. HbA1c was measured at the baseline and 6 weeks after CGM to test the stability of the patients' glycemic control. Univariate analysis showed a close association between DR and duration of diabetes (OR 1.11; 1.04–1.19), intensive insulin therapy (OR 5.6, CI 1.14–27.30), SD (OR 1.03; CI 1.01–1.06) and CONGA 2 (OR 1.02; CI 1.00–1.04)—both indicators of variability and HBGI (OR 1.1, CI 1.01–1.18)—a parameter reflecting acute hyperglycemia. There was no significant correlation with HbA1c ($p = 0.070$). Multivariate regression analysis showed that disease duration is the parameter most significantly correlating with DR (OR 1.05; 1.01–1.15). These results reinforce the evidence that longstanding disease is the factor most closely associated with DR. Our data also suggest, however, that glucose variability—regardless of HbA1c—may also have a role as a risk factor for DR, particularly in the case of acute fluctuations (as represented by CONGA 2 and SD) and acute hyperglycemia (as represented by HBGI).

Keywords Glucose variability · Diabetic retinopathy · Continuous glucose monitoring (CGM) · Type 1 diabetes · Type 2 diabetes

Introduction

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes, and one of the leading causes of poor visual acuity and blindness in many developed countries [1]. The Wisconsin Epidemiological Study on Diabetic Retinopathy (WESDR) reported an overall 10-year incidence of retinopathy of 74 % among diabetic patients, while 20 % of them (be they type 1 [DM1] or type 2 [DM2] diabetics) developed macular edema during a 10-year follow-up [2].

In a recent in-depth review published in The Lancet, Cheung et al. [3] included exposure to sustained hyperglycemia, longstanding diabetes, poor blood pressure control and certain ethnic origins among the well-established risk factors for DR. The pathological role of chronic hyperglycemia has been established by large-scale prospective studies, that is, the Diabetes Control and Complications Trial (DCCT) [4] for DM1 and the United Kingdom Prospective Diabetes Study (UKPDS) [5] for DM2. These two landmark trials showed a close relationship between HbA1c and the risk of DR progressing. On

G. Sartore · N. C. Chilelli (✉) · S. Burlina · A. Lapolla
Department of Medicine, University of Padova,
Via Giustiniani n 2, 35128 Padua, Italy
e-mail: ninocristiano.chilelli@studenti.unipd.it

the other hand, further analysis of the DCCT data showed that, although intensive therapy reduced the risk of DR progressing by 73 % compared to standard treatment, high HbA1c levels and longstanding diabetes explained only 11 % of the variation in the risk of retinopathy [6], giving the impression that other factors may contribute to the overall risk of DR progression.

Aiming to explain the so-called glycemic memory or legacy effect, Brownlee et al. [7, 8] looked into the epigenetic changes caused by the production of mitochondrial superoxide as a possible mechanism adding to vascular damage. Such a pathological cascade would be triggered by the short-term hyperglycemic spikes typical of patients with a high glucose variability. A number of studies consequently posed the question of whether glucose variability, irrespective of HbA1c, could confer an additional risk for the development of microvascular diabetic complications [9], but its role remains controversial, especially in DM1 [10].

Analyses on the relationship between glucose variability and DR have focused mainly on further analyzing the DCCT findings or data from the self-monitoring of blood glucose (SMBG) [9]. Current continuous glucose monitoring (CGM) systems are capable of grasping the direction and magnitude of short-lived changes in glucose levels and can therefore assess glucose variability more accurately than SMBG measurements [11].

To date, no studies have examined the association between glucose variability (as expressed by CGM readings) and DR in patients with DM1 or DM2.

The aim of this work was therefore to establish whether high glucose variability, as measured by CGM, is associated with an increased risk of DR, regardless of patients' HbA1c levels and other established risk factors.

Materials and methods

Patients

Data were obtained on 35 DM1 and 33 DM2 patients (37 women and 31 men, aged 19 to 69 years) attending the Diabetology and Dietetics Service in Padua (Italy). These patients had already been recruited for the A1c-derived average glucose (ADAG) trial [12], and additional data were reported in our previous publication [13].

The patients had to have a stable glycemic control (as demonstrated by two HbA1c readings differing by no more than 1 %) during the 6 months prior to the start of the study.

Duration of diabetes was defined as the known years of disease as at the time of recruitment. Patients' body mass index (BMI) was calculated by dividing their weight in

kilograms by the square of their height in meters. Patients with DM2 were treated with oral hypoglycemic agents or insulin (always using a basal bolus regimen for the latter). Macroangiopathy was assessed from clinical history (specified from charts) of myocardial infarction, angina pectoris, coronary artery surgery, angioplasty and peripheral vascular disease (brain and lower extremities). Microalbuminuria was defined as a urinary albumin excretion level between 30 and 299 mg/g creatinine on at least two of three occasions; macroalbuminuria was defined as a urinary albumin excretion level ≥ 300 mg/g creatinine on at least two of three occasions.

The study was approved by our local human studies committees and has been performed in accordance with the ethical standards of Declaration of Helsinki. Informed consent was obtained from all participants.

Glucose variability measurements and laboratory tests

Glucose variability indicators were calculated from CGM (Medtronic MiniMed) data, disregarding the first 2 h of the monitoring session, which served as the initial instrument calibration period. Data were analyzed retrospectively, and patients were blinded to their glucose values. For the Medtronic MiniMed, previous medical publications have indicated median relative absolute differences (RAD) of 11 % between paired CGM findings and reference serum glucose values, which is lower than with the first-generation CGM equipment [14]. All CGM sessions were completed correctly, with 100 % of the data available for statistical analysis.

The monitoring periods lasted at least 72 h and glucose levels were recorded every 5 min, obtaining a total of ~ 800 measurements per patient. Using these data, indicators were calculated with complex formulas designed specifically for CGM data [15]. We considered average glucose (AG) as an indicator of metabolic control [16]. Short-lived glucose variability was assessed by measuring the standard deviation of the blood glucose rate of change (SD-BG ROC), the mean amplitude of glucose excursions (MAGE) and the continuous overlapping net glycemic action calculated every 2 h during the monitoring period (CONGA 2). We also considered the HBGI (high blood glucose index) for the purposes of assessing the hyperglycemic risk.

The MAGE was calculated as the arithmetic mean of the differences between consecutive glycemic peaks and nadirs, only considering changes in the glycemic values of more than 1 SD [17]. The CONGA is the SD of the glycemic differences recorded between a specific point on the CGM profile and a point n hours previously (where $n = 1,2,3,4,\ldots$) [18]. The HBGI and SD-BG ROC were calculated using complex formulas designed specifically to obtain these indicators from CGM data [19].

As for HbA1c levels, four different DCCT-aligned assays were performed according to the ADAG protocol, that is, one high-performance liquid chromatography assay, two immunoassays and one affinity assay (all as approved by the National Glycohemoglobin Study Program), and the mean HbA1c level was considered [12].

Ophthalmic examinations

Patients were examined by the same ophthalmologist, who knew nothing of the patients' metabolic control. The fundus was examined using direct and indirect ophthalmoscopy after inducing pupillary dilation, then two-field stereoscopic retinal photographs (50°) were taken according to a standard protocol [20]. Retinal lesions were classified as mild, moderate or severe nonproliferative DR, the key lesions being at least two microaneurysms and/or dot hemorrhages in each eye (mild); venous dilations and/or beading (moderate); and more than 20 microaneurysms and/or dot hemorrhages in four quadrants or venous beading in two quadrants or intraretinal microvascular abnormalities in one quadrant (severe). Proliferative diabetic retinopathy was defined as neovascularization of the optic disk or elsewhere, preretinal hemorrhage, or vitreous hemorrhage [21].

Statistical analysis

Descriptive statistics are given as means and standard deviations. Normality of distribution was tested by calculating skew and kurtosis values. In this cross-sectional study, two logistic regression analyses were performed to assess the impact of different risk factors on DR: In the univariate analysis, a model was constructed using duration of disease, type of therapy, HbA1c levels and glucose variability indicators as independent variables. Since variability indicators correlate closely with one another and with SD-BG ROC [16], a collinearity analysis had to be performed, after which only SD-BG ROC and CONGA 2 remained statistically significant. Based on said univariate and collinearity analyses, a multivariate logistic regression analysis was conducted to identify independent risk factors for DR. The small size of our sample made it impossible to conduct the statistical analysis separately for DM1 and DM2 patients.

Statistical significance was assumed for a $p < 0.05$. Other statistics were obtained using the unpaired t test. The statistical analyses were completed with the Stata/SE 11.0 software for Windows (StataCorp LP, Texas, USA).

Results

Table 1 shows the baseline clinical characteristics of the 68 DM1 and DM2 patients who underwent CGM. By

Table 1 Clinical features of DM1 and DM2 patients in relation to the baseline presence/absence of retinopathy ($n = 68$)

	Retinopathy ($n = 28$)	No retinopathy ($n = 40$)	p value
Age (years)	49.3 ± 12.6	48.1 ± 14.7	n.s.
Gender (% male)	53.6 %	55.1 %	n.s.
Duration of diabetes (years)	19.1 ± 9.2	12.1 ± 7.7	0.02
BMI (kg/m^2)	27.9 ± 4.2	26.5 ± 4.9	n.s.
Insulin treatment (%)	75.0 %	30.0 %	0.05
Mean HbA1c (%)	8.3 ± 1.2	7.9 ± 1.8	0.06
Hypertension (%)	39.9 %	30.0 %	n.s.
Hypercholesterolemia (%)	44 %	42 %	n.s.

BMI body mass index

Statistical significance for $p < 0.05$

comparison with patients with no retinopathy, those with DR had longer-standing diabetes, they were more frequently on insulin therapy, and they had a worse glycemic control, though the difference in mean HbA1c levels was not statistically significant ($p = 0.06$). No differences were observed between the two groups (with and without DR) as regards the prevalence of hypertension and hypercholesterolemia.

The clinical features of the DM1 and DM2 patients are briefly compared in Table 2: DM2 patients were older and had a higher BMI, while the two groups' HbA1c values did not differ statistically. All the glucose variability indicators considered were significantly higher in DM1 patients (all p values < 0.0001), who carried a more than twofold risk of severe hyperglycemia by comparison with DM2 patients, as shown by comparing the HBGI. None of the patients had history of coronary hearth disease. The two groups were comparable with regard to micro–macroangiopathy.

In particular, the prevalence of DR was 43 % among the DM1 patients and 39 % for the DM2 group (p value n.s.), findings comparable with the prevalence of DR recorded in clinically matched diabetic populations recently studied in two large trials [22, 23]. Almost 90 % of the pathological fundus examinations revealed a nonproliferative DR in patients with both types of diabetes, which was mild in 40 %, moderate in 35 % and severe in 5 % (data not shown).

Univariate analysis (Table 3) showed a significant association between DR and duration of diabetes (OR 1.1; CI 1.04–1.19), insulin treatment (OR 5.6; CI 1.14–27.30), AG (OR 1.02; CI 1.00–1.02), SD-BG ROC (OR 1.03; CI 1.01–1.06), CONGA 2 (OR 1.02; CI 1.00–1.04) and HBGI (OR 1.1; CI 1.01–1.18), whereas no significant association emerged with MAGE, and the association with HbA1c only reached borderline significance. After an appropriate collinearity analysis between the glucose variability indicators and AG, multivariate regression analysis (Table 3)

Table 2 Comparison in clinical characteristics between 35 type 1 (DM1) and 33 type 2 (DM2) diabetic patients enrolled in the study

	DM1 (n = 35)	DM2 (n = 33)	p value
Age (years)	39 ± 11	58 ± 9	0.001
Gender (M/F)	17/18	16/17	n.s.
Duration of disease (years)	16 ± 9	17 ± 8	n.s.
BMI (kg/m^2)	25.1 ± 2.6	31.0 ± 5.7	0.001
Prevalence of macroangiopathy (n)	6 (17 %)	8 (24 %)	n.s.
Prevalence of micro/macroalbuminuria (n)	4/2 (11/6 %)	5/1 (15/3 %)	n.s.
Prevalence of retinopathy (n)	15 (43 %)	13 (39 %)	n.s.
Mean HbA1c (%)	8.4 ± 1.6	7.8 ± 1.5	n.s.
MAGE	1.17 ± 0.58	0.68 ± 0.33	<0.001
SD-BG ROC (mg/dl)	61.34 ± 20.64	35.71 ± 15.17	<0.001
CONGA 2 (mg/dl)	68.92 ± 28.54	41.18 ± 15.89	<0.001
HBGI	10.75 ± 8.25	4.72 ± 5.20	<0.001

BMI body mass index, *MAGE* mean amplitude of glucose excursion, *SD-BG ROC* standard deviation of blood glucose rate of change, *CONGA 2* continuous overlapping net glycemic action (2-h intervals), *HBGI* high blood glycemic index

Statistical significance for $p < 0.05$

Table 3 Risk of retinopathy in 35 type 1 and 33 type 2 diabetic patients, by logistic regression (cross-sectional analysis)

Parameters	Univariate analysis OR (95 % CI)	p value	Multivariate analysis OR (95 % CI)	p value
Duration of diabetes (years)	1.11 (1.04–1.19)	0.002*	1.05 (1.01–1.15)	0.010*
DM 1 (%)	0.68 (0.26–1.79)	0.434	–	–
Insulin treatment (%)	5.6 (1.14–27.30)	0.034*	2.76 (0.44–17.35)	0.279
SD-BG ROC (mg/dl)	1.03 (1.01–1.06)	0.012*	1.03 (0.98–1.08)	0.271
CONGA 2 (mg/dl)	1.02 (1.00–1.04)	0.035*	0.99 (0.95–1.03)	0.640
MAGE (mg/dl)	1.74 (0.69–4.40)	0.240	–	–
HBGI	1.10 (1.01–1.18)	0.034*	–	–
AG (mg/dl)	1.02 (1.00–1.03)	0.020*	–	–
HbA1c (%)	1.37 (0.98–1.90)	0.070	–	–

Results are given as odds ratios and 95 % confidence intervals (OR; 95 % CI)

Analysis corrected for hypertension and hypercholesterolemia

SD-BG ROC standard deviation of blood glucose rate of change, *CONGA 2* continuous overlapping net glycemic action (2-h intervals), *MAGE* mean amplitude of glucose excursion, *HBGI* high blood glycemic index, *AG* average glucose, *DM1* type 1 diabetes mellitus

* Statistical significance for $p < 0.05$

showed that duration of diabetes was the only parameter independently associated with a higher risk of DR in our population.

Discussion

The aim of this cross-sectional study was to analyze the association between glucose variability (as assessed by 72-h CGM) and DR in patients with diabetes mellitus.

Our findings confirm that the duration of the disease is the most relevant risk factor for the onset and progression of DR, as Hammes et al. [22] recently reported. Glucose variability also seemed to have a role in the prevalence of

DR, but its significance was lost in multivariate analysis. This finding supports the recent growing interest in studying the effect of glucose variability on the onset of micro- and macrovascular diabetic complications.

While a high glucose variability in DM1 is due mainly to the lack of basal insulin secretion by the beta cells and to intensive insulin therapy [24], glucose fluctuations in DM2 have recently been linked to a much more complex mechanism. The glucotoxicity and lipotoxicity that often precede sustained hyperglycemia can damage early beta cell function [25]. A CGM study by Kohnert et al. [26] on DM2 patients showed that this early beta cell dysfunction develops into a high glucose variability. By triggering oxidative stress, short-lived hyperglycemic spikes can

contribute to the progression of DR in both DM1 and DM2 patients, irrespective of any sustained hyperglycemia [7]. So, although HbA1c is the strongest marker of DR risk, it is probably not a comprehensive predictor of DR progression [27]. Consistently with this hypothesis, the HbA1c values in our study only showed a borderline association with DR, even though patients with retinopathy generally had a worse glycemic control. On the other hand, the lack of any association between glucose variability and DR in the multivariate model could be attributable to the high percentage of patients on insulin therapy in our sample. As neatly explained by Monnier et al. [28], exogenous insulin may exert an inhibitory effect on the activation of the pathways involved in oxidative stress, dampening the effect of this co-responsible key factor underlying microvascular injury.

All studies on glucose variability and DR in search of a cause–effect relationship have been based on data from seven-point SMBG profiles [29] or standard deviations obtained from periodic measurements of fasting or postprandial plasma glucose [30, 31].

It has now been fairly well established that seven-point glucose profiles do not fully reflect real changes in diabetic patients' blood glucose levels; measuring glucose variability with CGM has proved more accurate [32, 33].

To our knowledge, this is the first study to have examined the association between CGM-assessed glucose variability and the risk of DR. Among the dozens of possible indicators, we chose those capable of specifically describing rapid blood glucose fluctuations and short-lived hyperglycemic spikes, some of which have been strongly and positively correlated with biochemical markers of oxidative stress [34], while others accurately define and quantify the time course of hypo–hyperglycemic fluctuations, especially for hyperglycemic spikes [19].

As mentioned earlier, the very good accuracy of the CGM device used in this study adds to the clinical validity of our results, which can theoretically be extended to a much larger population because our patients had already been included in the ADAG database and consequently followed a standardized multicenter protocol.

The most obvious limitation of this study is the cross-sectional statistical analysis, which does not allow for any assessment of the temporal/causal sequence of events (though this was not the initial aim of the study). Then there is the small sample size, which may also explain the borderline correlation between HbA1c and the prevalence of DR.

Another possible limitation concerns the heterogeneity of the patients involved (cases of DM1 and DM2), but while these diseases are distinct from the pathophysiological and clinical viewpoints, when it comes to glucose variability, they share the same mechanisms of hyperglycemia-induced mitochondrial superoxide production, leading to the epigenetic changes hypothesized to explain the "glycemic memory" phenomenon [35].

In conclusion, despite the above limitations, the present work confirms the pivotal role of the duration of diabetes in determining the progression of DR. We also showed, however, that glucose variability (as expressed by CGM-derived indicators of short-lived glucose fluctuations) is an important part of glycemic control in relation to the prevalence of DR in both DM1 and DM2. Longitudinal trials on large samples of patients, using appropriate measurements of glucose variability obtainable with CGM systems, will be crucially important in future to obtain a definitive picture of the HbA1c-independent role of glucose variability in the onset and progression of DR.

Conflict of interest   None.

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