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HbA1c variability and long-term glycemic control are linked to diabetic retinopathy and glomerular filtration rate in patients with type 1 diabetes and multiethnic background

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ABSTRACT

Aim: To evaluate the associations between HbA1c variability and long-term glycemic control with microvascular complications in type 1 diabetes (T1D) patients and multiethnic background.
Methods: T1D adults with ≥ 10 years of follow-up and ≥ 2 HbA1c measurements were included. Glycemic variability was evaluated by the standard deviation (HbA1c-SD), and coefficient of variation (HbA1c-CV), and glycemic control by mean HbA1c over 10 years. Diabetic retinopathy (DR), increased urinary albumin excretion rate (UAER) and reduced glomerular filtration rate (eGFR) were diagnosed. Cardiac autonomic neuropathy (CAN) was diagnosed by cardiac reflex tests. Associations between glycemic parameters with complications were assessed by multivariate logistic regressions.
Results: 220 patients were included. Simultaneously adjusted for each other, mean HbA1c was independently associated with DR (OR: 2.82; 95%CI: 1.45-5.50), increased UAER (OR: 1.97; 95%CI: 1.14-3.09) and CAN (OR: 4.42; 95%CI: 1.45-13.51); whereas HbA1c-CV was independently associated with DR (OR: 8.93; 95%CI: 1.86-42.87) and reduced eGFR (OR: 7.02; 95%CI: 1.47-35.55).
Conclusions: Long-term glycemic control was associated with DR, increased UAER and CAN, while glycemic variability was additionally associated with DR and impaired renal function; suggesting that both good and stable glycemic status might be important to prevent microvascular complications in T1D patients and multiethnic background.

1. Introduction

Type 1 diabetes (T1D) is a chronic disease caused by selective and progressive destruction of the insulin-producing pancreatic beta cells, which results in insulin deficiency and hyperglycemia.[1] The Diabetes Control and Complications Trial (DCCT) has demonstrated the relationship between sustained hyperglycemia and microvascular complications. Patients who received intensive insulin therapy and achieved mean glycated haemoglobin (HbA1c) of 7.2% (55 mmol/mol) developed fewer complications such as diabetic retinopathy (DR), increased urinary albumin excretion rate (UAER) and peripheral neuropathy (PN) than those who received conventional therapy and had a mean HbA1c of 9.1% (76 mmol/mol).[2] After the end of the trial, intensive treatment was offered to all participants and they continued to be followed during the observational cohort Epidemiology Diabetes Intervention Complications (EDIC). During EDIC, patients in both previous groups achieved similar mean HbA1c ~8% (64 mmol/mol). However, after 18 years of follow-up the group that had previously received intensive treatment in the DCCT persisted with lower rates of DR (89.7% vs. 95.3%), diabetic kidney disease (DKD) (18.5% vs 24.9%) and cardiovascular autonomic neuropathy (CAN) (27.8% vs 35.7%).[3]

The DCCT/EDIC and other interventional studies have convincingly demonstrated the importance of near normal glycemic control to prevent long-term microvascular complications. However, even with similar mean HbA1c levels, individuals can vary in their glycemic excursions. It is known that glucose oscillations are linked to oxidative stress, a

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Table 1
General characteristics of the whole study group and divided according to the presence or absence of any microvascular complication after 10 years of follow-up.

	N° of patients evaluated	All patients	With complications ($n = 67$)	Without complications ($n = 153$)	p-Value
Epidemiological data					
Sex (female)	220	60%	66%	58%	0.296
Age (yrs)	220	29.6 ± 10.1	32.9 ± 11	28.1 ± 9.3	0.001
Ethnicity (Caucasian/non-Caucasian[a])	220	60.7%/39.3%	56%/44%	63%/37%	0.551
T1D data					
Age at diagnosis (yrs)	220	10.7 ± 8.2	12.9 ± 8.8	9.7 ± 7.7	0.003
T1D duration (yrs)	220	18.2 ± 6.8	19 ± 7.2	17.9 ± 6.6	0.173
Diagnoses (Polis/DKA/Others[b])	220	41%/31%/28%	42%/27%/31%	41%/33%/26%	0.390
N° of A1c/patient/year	220	2.8 ± 0.9	2.8 ± 0.9	2.8 ± 0.8	0.211
N° of complications evaluated	220	1.9 ± 0.8	2.0 ± 0.8	1.8 ± 0.7	0.089
Mean HbA1c (%)	220	8.3 ± 1.5	9.1 ± 1.6	8.0 ± 1.4	<0.001
Mean HbA1c (mmol/mol)		67	76	64	
Adjusted HbA1c-SD (%)	220	1.24 ± 0.88	1.53 ± 1.16	1.11 ± 0.69	0.001
HbA1c-CV	220	1.38 ± 0.63	1.58 ± 0.76	1.29 ± 0.56	0.014
Insulin dosage (units/kg)	97	1.02 ± 0.41	0.98 ± 0.46	1.04 ± 0.38	0.345
Carbohydrate counting	110	66.4%	59%	70%	0.263
Comorbidities/drugs					
Body mass index (kg/m^2)	159	25.5 ± 4.17	25.8 ± 4.6	25.3 ± 4.0	0.564
Hypertension	173	22.5%	43%	13%	<0.001
Use of ACEIs/ARBs	168	28%	43%	19%	0.001
LDL-cholesterol (mg/dl)	149	100.4 ± 36.5	109.6 ± 49.0	96.9 ± 29.8	0.177
Use of statins	153	25.5%	40%	18%	0.002
Current smoking	113	8.8%	18%	5%	0.064

Abbreviations: DKA, diabetic ketoacidosis; CV, coefficient of variation; ACEIs, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers.
[a] Non-Caucasian: African-Brazilians, Mulattos, Asians, Indigenous.
[b] Others: casual exam, unknown.

mechanism involved in the development of microvascular complications.[4,5] Hence, some recent studies suggest that glucose variability may be an additional risk factor for the development of these complications.[6,7]

Glucose variability can be interpreted as the intraday or interday glucose variation[7] or as the long-term visit-to-visit variation of HbA1c measurements, which can be assessed by their standard deviation (SD) or coefficient of variation (CV).[6] The interday and intraday glucose variability can be evaluated by multiple capillary blood glucose measurements or by continuous glucose monitoring. The SD or CV of HbA1c along a certain period of time has been used as a measurement of long-term glycemic variability. Virk et al. demonstrated that a greater HbA1c variability over a mean follow-up of 8.1 years was associated with a greater risk of DR, nephropathy and CAN in Australian patients with T1D.[8] The association between DR and glucose variability had also been reported in previous studies.[9,10] A post-hoc analysis from the DCCT cohort has also shown that patients with greater HbA1c variability had higher increased UAER and cardiovascular disease.[11]

Most studies that have evaluated the link between long-term glycemic control, glycemic variability and diabetic chronic complications were performed in Caucasians. It is still not known if ethnicity can influence the risk of development or progression of chronic complications in patients with T1D, but differences in vascular endothelial growth factor (VEGF) polymorphisms, end-stage renal disease and diabetic neuropathy have been shown in different ethnic groups.[12,13] A variation in the glycation of haemoglobin has also been reported in different ethnic groups.[14] Therefore, studies in patients of different ethnicities are crucial. The aim of this study was to evaluate the associations between the long-term glycemic control and the SD of HbA1c during 10 years of follow up with the development of DR, increased UAER, impaired renal function and CAN in patients with T1D from the Brazilian population, which has a multiethnic background.

2. Subjects

Patients with ≥10 years of T1D duration and follow-up and >17 years of age who had at least 2 measurements of HbA1c in the last 10 years were included. All patients were followed-up in a Hospital, which has a specialized outpatient clinic for T1D care and management.

3. Materials and methods

3.1. Study design

A retrospective cohort study was conducted using data from a tertiary-care University Hospital. The study protocol was approved by the local Ethics Committee (Institutional Review Board, protocol 088766/2014) and an informed written consent was obtained from all patients.

3.2. Glycemic evaluation

All measurements of HbA1c were performed with NGSP certified methods: High Performance Liquid Chromatography (reference range: 5.7–6.4% or 39–46 mmol/mol) or affinity chromatography (reference range: 4.3–6.1% or 23–43 mmol/mol). Their coefficient of variation was <2% (provided by manufacturer's kit and local laboratories; Biorad USA and Trinity Biotech USA). The results of all HbA1c measurements available were used to calculate the mean HbA1c and HbA1c variability over 10 years. To assess HbA1c variability, two parameters were calculated. As the number of individual measurements (n) could influence the SD of HbA1c, the first parameter was the SD adjusted (HbA1c-SDa) for the number of measurements (n): HbA1c-SDa $=$ SD/$\sqrt{[n/(n-1)]}$.[15] The second parameter was the CV of HbA1c (HbA1c-CV), which normalizes the HbA1c-SD for the mean HbA1c level: HbA1c-CV $=$ HbA1c-SD/[0.1 $\times$ m-HbA1c].[8]

3.3. Data source

The clinical, laboratory, and epidemiological data were obtained by the review of the medical charts. The microvascular complications were assessed between 2014 and 2015. DR was assessed by fundoscopy performed by a single experienced retinal specialist, according to the international classification published in 2013.[16] Increased UAER was evaluated either on a single urine sample (it was considered abnormally

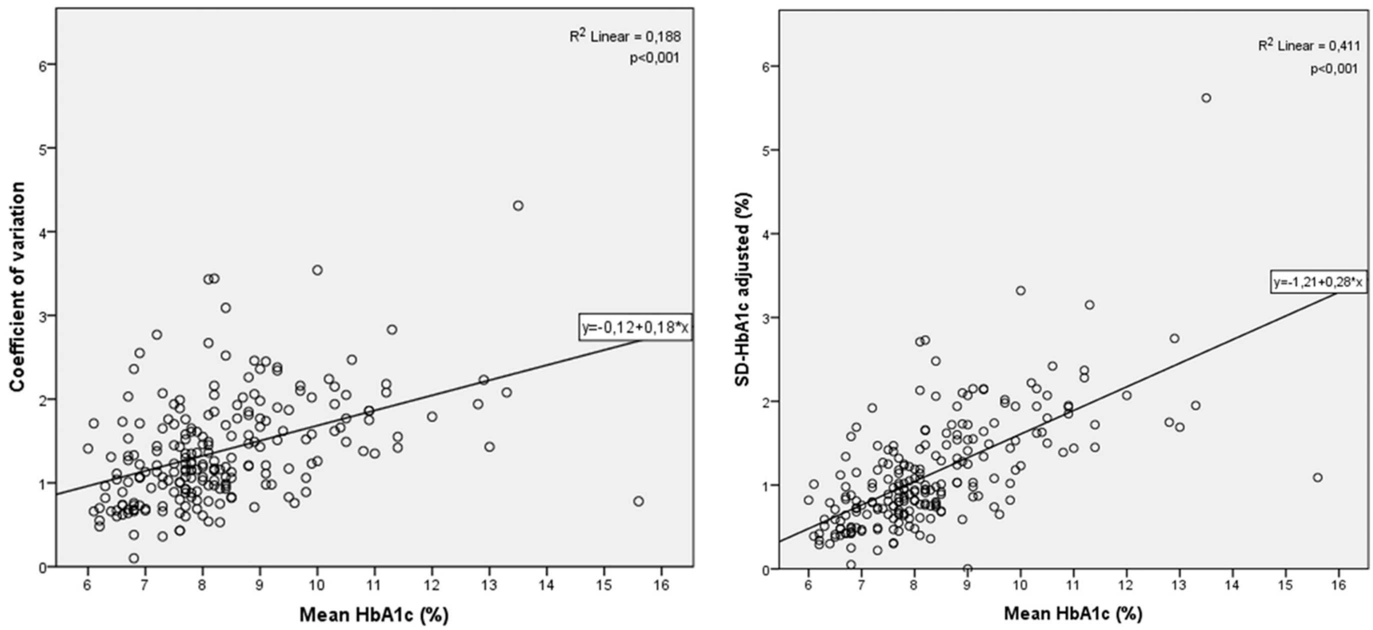

Fig. 1. Scatter plots between mean HbA1c and the two glycemic variability parameters (CV, left panel; SD-HbA1c adjusted, right panel).

increased if albuminuria ≥17 mg/L or urinary albumin-to-creatinine ratio ≥ 30 mg/g) or on 24-hour urine collection (considered increased if ≥30 mg/24 h). The estimated glomerular filtration rate (eGFR), calculated by the CKD-EPI equation, was considered reduced if <60 mL/min/1.73 m.[2] CAN was investigated using cardiovascular autonomic reflex tests that assessed the R-R variation during paced breathing and the Valsalva maneuver, obtained from analysis of 10-minute continuous electrocardiogram recordings using the VNS-Rhythm (Software Poly-Spectrum analysis, Neurosoft Ltd. 5, Ivanovo, Russia), and by postural changes in blood pressure.[17] The ECG was analyzed by a mathematical algorithm (fast Fourier transform) and expressed in a diagram of oscillation amplitude (HR variations per second) versus frequency (Hz). CAN was defined if RR variation in ≥1 of these testes were abnormal or if there was a decrease of >20 mmHg in systolic pressure or >10 mmHg in diastolic pressure after standing for 3 min.[18]

3.4. Statistical analysis

Continuous variables were described as means and SDs and categorical variables as proportions. Bivariate comparisons of baseline characteristics between patients with and without any microvascular complication were performed by Chi-squared or Fisher exact tests, and by *t*-tests or Mann-Whitney tests, where appropriate. Specific comparisons of mean HbA1c and HbA1c variability parameters between patients with and without each microvascular complication (DR, increased UAER, reduced eGFR, and CAN) were undertaken by Mann-Whitney tests. Finally, the independent associations between mean HbA1c and the two HbA1c variability parameters with the presence of each microvascular complication were assessed by multivariate logistic regressions, with each microvascular complication as the dependent variable. First, mean HbA1c and each HbA1c variability parameter were entered into separated models, adjusted for age, sex, T1D duration, presence of hypertension and mean LDL-cholesterol levels (Model 1). Then, each HbA1c variability parameter was entered simultaneously with mean HbA1c, adjusted for the same background covariates (Models 2 and 3). Results of multivariate analyses were presented as odds ratios (ORs) with their respective 95% confidence intervals (CIs). Statistics were performed with SPSS package version 19.0 (SPSS Inc., Chicago, IL, USA), and a 2-tailed probability value <0.05 was considered significant.

4. Results

4.1. Characteristics of the study group

Patient's characteristics are presented in Table 1. In this study, 598 complications from 220 patients were included in the analysis. Patients had a mean of 17 $\pm$ 7 HbA1c measurements during 10 years, which corresponds to a mean of 2.8 HbA1c measurements per patient per year.

The majority (54.9%) of the patients were using human insulin (NPH) as basal insulin while 37.5% used long-acting insulin analogs and 7.6% used continuous system of insulin infusion (CSII). For bolus injections, short-acting insulin analogues were used in 66.4% of the cases and regular insulin in 43.6%.

DR, increased UAER, reduced eGFR and CAN were found in 18%, 20%, 7% and 33% of the patients studied for each complication, respectively. Patients with any of the complications were older, had diabetes diagnosed at an older age, and exhibited higher prevalence of hypertension than those without microvascular complications. These patients were also more likely to use either angiotensin-converting-enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) and statins than those without complications.

Haematologic parameters were within normal range in all patients, except for two cases of iron deficiency anemia and three cases of pernicious anemia, all under treatment. Thalassemia minor and sickle cell trait were reported in one case each.

The exclusion of these cases did not interfere in the results. We have excluded one outlier of the analysis to avoid possible interference of these reported conditions.

4.2. Glycemic control during 10 years of follow-up, glycemic variability and diabetic chronic microvascular complications

Mean HbA1c and glycemic variabilities exhibited a moderate correlation. The correlation between CV with mean-HbA1c and SD-adjusted with mean-HbA1c were $R = 0.433$ ($p < 0.001$) and 0.655 ($p < 0.001$), respectively. Otherwise, it did not implicate collinearity. These data are shown in Fig. 1. Supplementary Fig. 1 shows the correlation between CV with mean-HbA1c and SD-adjusted with mean-HbA1c for each method. Mean HbA1c values ranged from 8 to 9% over 10 years, as shown in Fig. 2.

Mean HbA1c and the two HbA1c variability parameters were higher in patients with any of the complications than in those without complications (Table 1). In bivariate analyses, these differences were also observed for each of the evaluated microvascular complications, as shown in Table 2, except for HbA1c variability in relation to increased albuminuria. Table 3 presents the independent associations of mean HbA1c and HbA1c variability parameters with each microvascular complication. Separated from each other (Model 1), both mean HbA1c and each HbA1c variability parameter were associated with each microvascular complication, independent of age, sex, diabetes duration, presence of hypertension and mean LDL-cholesterol levels, except for HbA1c variability parameters in relation to increased UAER and for mean HbA1c in relation to reduced eGFR. Otherwise, when adjusted simultaneously for mean HbA1c and HbA1c variability (Models 2 and 3), the HbA1c variability parameters were only independently associated with DR and reduced eGFR occurrence; whereas mean HbA1c levels remained associated with DR, CAN and increased UAER, but not with reduced eGFR.

5. Discussion

This study evaluated patients with long-standing T1D aiming to identify the relationships between glycemic control and glycemic variability parameters during 10 years of follow-up with the development of specific microvascular complications (DR, increased UAER, impaired renal function and CAN) in patients from the Brazilian multiethnic population. We demonstrated that long-term glycemic control, as reflected by mean HbA1c levels, was independently associated with DR, CAN and increased albuminuria development, but not with renal function deterioration. Otherwise, long-term visit-to-visit glycemic variability, measured by the SDa or by the CV of HbA1c over 10 years, was independently associated with DR and impaired renal function, but not with CAN and increased albuminuria. Notably, both mean HbA1c and HbA1c variability contributed for the increased risk of DR development. This suggests that glycemic variability, beyond the traditional glycemic control parameter of mean HbA1c, may be used for improving risk prediction of developing microvascular complications, particularly DR and renal function deterioration, in multiethnic patients with T1D.

We have shown associations between long-term glycemic control and chronic complications in individuals of this multiethnic population. Similar associations had been reported in other populations such as Caucasians[19–21] and Asians,[22] but information on other ethnic groups are still lacking. Brazilian population is very diverse and comprises individuals of multiple ethnic backgrounds and racial admixture, especially Caucasoids and Afro-descendants. According to Moura et al., the Brazilian population is estimated to be of approximately 201 million and, in the Latin America context, Brazil has the 5th high European contribution, the 12th for the African component and the 10th for the Amerindian ancestry.[23] It is considered one of the most admixed populations in the world and former genetic studies indicate that a significant proportion of Brazilian patients with T1DM and T2DM within each ethnic group (Caucasoids, Afro-descendants or Amerindians) has genes compatible with other ethnicities.[24] In addition, Gomes et al., has founded that T1DM patients presented a higher percentage of European genomic ancestry than the healthy population.[25]

This study was the first to identify the association between mean HbA1c levels measured over 10 years and microvascular complications in such multiethnic population

We have also identified independent associations between HbA1c variability during a 10-year follow-up and DR and renal function deterioration development. Kilpatrick et al. have shown similar results in the DCCT cohort. However their study group comprised mostly Caucasians (96% of the cases) and their disease duration was shorter than in our study.[26] The Finish Diabetic Nephropathy (FinnDiane) Study demonstrated not only an association between the glycemic variability and DR and progression of renal dysfunction, but also with increased UAER.[27] Although the FinnDiane was a shorter study with a median follow-up of 5.7 years, the larger sample size might have contributed to the difference in these results.[9] Moreover, we analyzed only one urine sample, which could represent a bias to evaluate the association between UAER and HbA1c variability. Virk et al. also reported an association between HbA1c and all the former reported diabetic complications, as well as with CAN.[8] This study used different methods for CAN evaluation (only spectral analysis vs. Ewing tests + spectral analysis in ours), and included a larger number of patients of younger age and shorter disease duration, which might have contributed to the difference in the results.

Some mechanisms have been implicated into the association between HbA1c variability and diabetic complications. Glycemic variability and fluctuations in blood glucose might induce oxidative stress, secretion of inflammatory cytokines and endothelial damage. These abnormalities are implicated in the pathogenesis of diabetic complications.[4,5] Another probable reason linking HbA1c variation with complications is the possible worsening in DR observed after the rapid improvement of glycemic control in patients with T1D.[28] Similarly, in kidneys, homeostatic variations may also be detrimental and

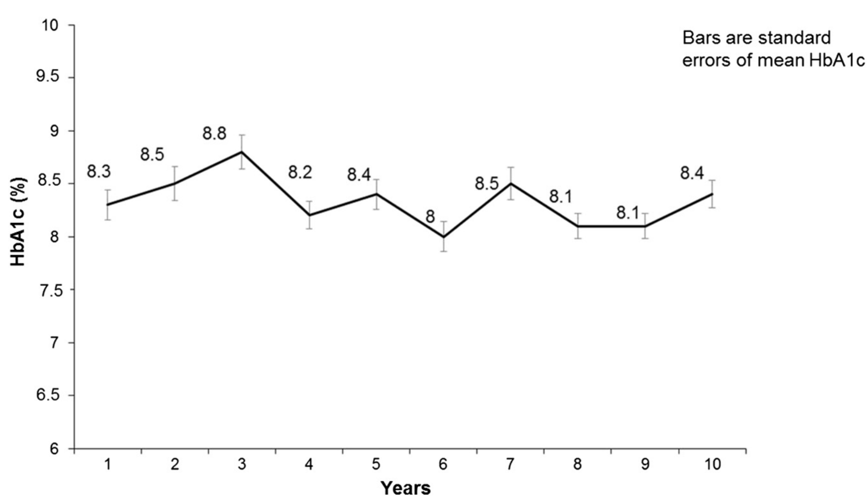

Fig. 2. Mean HbA1c levels during the whole follow-up period.

Table 2
Parameters of glycemic control (mean of HbA1c over 10 years, SD and CV of HbA1c) in patients with and without each diabetic microvascular complication.

Microvascular complication		Mean HbA1c (% mmol/mol)	p-Value	HbA1c-SDa (%)	p-Value	HbA1c-CV (%)	p-Value
DR	Absent ($n = 137$)	8.0 ± 1.4 64	<0.001	1.1 ± 0.5	0.012	1.3 ± 0.6	0.122
	Present ($n = 30$)	9.5 ± 1.9 80		1.5 ± 1.0		1.6 ± 0.9	
Albuminuria	Normal ($n = 131$)	8.0 ± 1.2 64	0.002	1.1 ± 0.6	0.421	1.4 ± 0.6	0.602
	Increased ($n = 32$)	9.0 ± 1.6 75		1.3 ± 0.7		1.5 ± 0.6	
eGFR	Normal ($n = 151$)	8.4 ± 1.6 68	0.008	1.1 ± 0.6	0.05	1.4 ± 0.6	0.127
	Reduced ($n = 11$)	9.7 ± 2.0 83		1.8 ± 1.0		1.8 ± 1.0	
CAN	Absent ($n = 54$)	7.7 ± 1.1 61	<0.001	0.9 ± 0.5	0.001	1.2 ± 0.6	0.100
	Present ($n = 26$)	9.0 ± 1.4 75		1.5 ± 1.0		1.7 ± 1.1	

Abbreviations: DR, Diabetic Retinopathy; eGFR, estimated glomerular filtration rate; CAN, cardiac autonomic neuropathy; HbA1c-SD, standard deviation of HbA1c; HbA1c-CV, coefficient of variation of HbA1c.

induce the secretion of growth factors such IGF-1 and VEGF.[29,30] Alternatively, excessive glycemic variability might represent poor treatment adherence and self-management patient compliance, worse quality of life and lack of social support, and frequent infective complications.[31] On the other hand, it may be argued that increased glycemic variability merely represents poor diabetic control, as HbA1c variability and mean HbA1c levels are correlated. Indeed, this fact have been described in previous most studies that analyzed the association between HbA1c variability and diabetic chronic complications, except that performed by Herman et al. with >35.000 patients in a large German/Austrian multicentre survey.[10] However, it should be noted that the associations between HbA1c variability parameters and microvascular complications demonstrated here were further adjusted for mean HbA1c levels (Table 3, Models 2 and 3), as similarly performed in other previous studies.[3,31,32] Furthermore, the HbA1c-CV itself is normalized for mean HbA1c.

This study has some limitations. First, retinography was not registered for DR diagnosis, but fundoscopy was performed by a specialized ophthalmologist. Second, statins, ACEi and ARBs were used more frequently in patients with chronic complications than in others.[33,34] However, the lack of use of these medications would not be able to favor our results, but only reflect the use of these medications according to the current guidelines. Therefore, this limitation would be expected for all real-life studies. Third, it was a retrospective observational cohort study, hence no cause-and-effect relationships, neither physiopathological inferences, can be made. Furthermore, the possibility of residual confounding due to unmeasured or unknown factors cannot be ruled out. Fourth, we have used only one urine sample to measure UAER. Although the collection of three samples would be ideal, several publications have reported a similar limitation.[15,35,36] Finally, the limited sample size, particularly for CAN evaluation, should be taken into account. The strength of the present study was the analyses of the impact of glycemic variability in chronic complications using a regression model including the most important risk factors for these complications, such as hypertension and serum lipid levels. Only few studies included hypertension as a covariate in this kind of multivariate analysis.

Furthermore, we performed a long and robust evaluation of a significant number of patients with T1D from a multiethnic population which makes this analysis particularly interesting. The impact of glycemic variability in chronic complications in regression model including the most important risk factors for these complications, such as hypertension and serum lipid levels. Only few studies included hypertension as a covariate in this kind of multivariate analysis.[31]

Table 3
Associations between glycemic control parameters measured over 10 years and occurrence of diabetic microvascular complications.

Factors and outcomes	Model 1		Model 2		Model 3	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Retinopathy						
MeanHbA1c	2.35 (1.30–4.24)	0.005	2.15(1.19–3.87)	0.011	2.82 (1.45–5.50)	0.002
HbA1c-SDa	9.83 (2.37–40.84)	0.002	8.30 (1.72–39.96)	0.008	–	–
HbA1c-CV	5.24 (1.60–17.10)	0.006	–	–	8.93 (1.86–42.87)	0.006
Albuminuria						
MeanHbA1c	1.52 (0.99–2.34)	0.055	2.42 (1.20–4.88)	0.013	1.97 (1.14–3.39)	0.015
HbA1c-SDa	0.95 (0.33–2.81)	0.938	0.20 (0.03–1.26)	0.086	–	–
HbA1c-CV	0.60 (0.19–1.90)	0.387	–	–	0.24 (0.05–1.19)	0.081
eGFR < 60						
MeanHbA1c	1.27 (0.72–2.23)	0.417	0.48 (0.14–1.70)	0.257	0.67(0.23–1.90)	0.449
HbA1c-SDa	3.30 (0.99–10.98)	0.051	7.52 (1.05–54.11)	0.045	–	–
HbA1c-CV	5.20 (1.30–20.79)	0.020	–	–	7.02 (1.47–33.55)	0.015
CAN						
MeanHbA1c	4.20 (1.60–10.98)	0.004	3.79 (1.22–11.76)	0.021	4.42 (1.45–13.51)	0.009
HbA1c-SDa	7.87 (1.68–37.04)	0.009	3.89 (0.77–19.60)	0.101	–	–
HbA1c-CV	3.89 (0.99–15.38)	0.052	–	–	0.34 (0.75–11.2)	0.120

Values are odds ratios and 95% confidence intervals, estimated by multivariate logistic regressions.
Model 1 is each glycemic parameter separately adjusted for age, sex, T1D duration, presence of hypertension, and mean LDL-cholesterol levels.
Model 2 is mean HbA1c and HbA1c-SDa entered simultaneously, adjusted for the same covariates of Model 1.
Model 3 is mean HbA1c and HbA1c-CV entered simultaneously, adjusted for the same covariates of Model 1.
Abbreviations: HbA1c-SDa, standard-deviation adjusted of HbA1c; HbA1c-CV, coefficient of variation of HbA1c; eGFR < 60, estimated glomerular filtration rate below 60 mL/min/1.73 m^2.

6. Conclusions

A long-term glycemic control during a 10-year follow-up was linked to DR, increased UAER, and CAN in patients with T1D and multiethnic background. HbA1c variability was associated to DR and renal function deterioration in these individuals. These results highlight the concept that not only a good, but also a stable glycemic control along the course of T1D are important factors to prevent microvascular complications development and progression.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2019.05.022.

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