

Severe Forms of Retinopathy Predict the Presence of Subclinical Atherosclerosis in Type 1 Diabetes Subjects

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Abstract

Background: In patients with type 2 diabetes, the presence of retinopathy is associated with increased cardiovascular disease, regardless of known risk factors for vascular disease.

Objective: To investigate the association of diabetic retinopathy (DR) and its grades with the presence of subclinical coronary atherosclerosis in patients with type 1 diabetes.

Methods: A cross-sectional study was conducted with 150 type 1 diabetes individuals asymptomatic for coronary artery disease. They underwent to clinical evaluation for microvascular complications and evaluation for the presence of coronary artery calcification (CAC).

Results: Severe forms of DR (severe non-proliferative DR and proliferative DR) were associated with CAC (OR: 3.98 95% CI 1.13-13.9, $p = 0.03$), regardless of known risk factors for cardiovascular disease (age, A1C, hypertension, dyslipidemia and male gender).

Conclusion: Patients with severe forms of DR are at risk for the presence of coronary artery disease regardless of traditional cardiovascular risk factors. (Arq Bras Cardiol 2011;97(4):346-349)

Keywords: Type 1 diabetes, diabetic retinopathy, coronary artery calcification.

Introduction

Retinal vascular changes are associated with hypertension and diabetes and can predict clinical cardiovascular events and deaths in both middle-aged and elderly populations¹⁻⁴. In recent years, there has been an increasing recognition that microvascular disease plays an important role in the pathogenesis of coronary heart disease⁵⁻⁸. In patients with type 2 diabetes (T2D), the presence of retinopathy is associated with increased coronary heart disease (CHD) and risk of heart failure, regardless of known risk factors for cardiovascular disease^{9,10}.

In the Multi-Ethnic Study of Atherosclerosis the presence of retinal changes was associated with increased odds of having moderate-to-severe coronary artery calcification. This association was significant in both sexes regardless of the presence of hypertension and diabetes¹¹.

Subclinical atherosclerosis has been associated with presence of diabetic retinopathy (DR) in a small sample of type 1 diabetes (T1D) individuals¹². However, there is no evidence that grade of DR is associated with atherosclerosis. This study aimed at

investigating the relation between severe forms of DR and the presence of subclinical atherosclerosis in the coronary vessels of patients with T1D, assessed by coronary artery calcification (CAC).

Methods

A cross-sectional study was conducted with 150 T1D individuals asymptomatic for coronary artery disease and with no history of CHD attending the Endocrine Division's outpatient clinic at Hospital de Clínicas de Porto Alegre. The Ethics Committee of the hospital approved the project, and written informed consent was obtained from all patients.

Patients underwent an interview and clinical examination to record demographic and anthropometric data, as previously described¹³. Retinopathy was assessed by direct and indirect ophthalmoscopy after mydriasis, by the same ophthalmologist (JFE). Patients were classified according to the Global Diabetic Retinopathy Group¹⁴. For the purpose of this study, patients classified as without DR, with mild or moderate non-proliferative DR (NPDR) were grouped, and those with severe NPDR or proliferative DR were included in the severe DR group. The presence of diabetic nephropathy (DN) was defined according to the urinary albumin excretion rate (UAER) measured in two 24-h sterile urine collections 3 months apart. Patients with microalbuminuria (UAER ≥ 20 and ≤ 200 $\mu\text{g}/\text{min}$) and macroalbuminuria (UAER > 200 $\mu\text{g}/\text{min}$) were analyzed as a group with DN.

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UAER was measured by immunoturbidimetry (Microal; Ames-Bayer, Tarrytown, NY) (intra- and interassay coefficient variation of 4.5 and 11%, respectively) and A1c test was measured by a high-performance liquid chromatography system (reference range 4-6%; Merck-Hitachi 9100). HbA1c was measured by a high-performance liquid chromatography system (reference range 4-6%; Merck-Hitachi 9100), lipid profile was measured by a colorimetric method and glomerular filtration rate (GFR) was estimated with the Modification of Diet in Renal Disease Study formula¹⁵: $186 \times [\text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times (0.742, \text{ if female}) \times (1.210, \text{ if of African ethnicity})]$.

CAC was measured using a multidetector computed tomography system that acquired 64 simultaneous 2.5-mm slices for each cardiac cycle with prospective ECG-triggered scan acquisition at 60% of the RR interval in a sequential scan mode (Somatom Sensation 64 Cardiac, Siemens Medical Solutions, Forchheim, Germany).

Statistical analysis

Student's t-test or χ^2 tests were used to compare clinical and laboratory data. Data were expressed as mean \pm S.D., except for UAER, triglycerides and eGDR, which were log-

transformed and expressed as geometric mean and range. Multiple logistic regression analyses were performed with the presence of CAC as dependent variables; independent variables were the following: A_{1c} test, age, presence of hypertension, HDL and LDL cholesterol and DR. Variables were included in the model by biological importance and from univariate analysis. SPSS 16.0 (SPSS Inc, Chicago, IL) was used for these analyses.

Results

Clinical and laboratory characteristics are displayed in Table 1. Patients with CAC (n = 59) were older, had longer duration of diabetes, higher systolic blood pressure levels, were more frequently hypertensive and had DR more often than patients without CAC. Glycemic control was not different, but had a borderline tendency to be worse in individuals with CAC. There were no differences according to lipid profile, insulin dose, and current smoking, GFR or UAER level. Anti-hypertensive medication was taken more frequently by patients with CAC than by individuals without CAC (61 % vs. 27% for angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, p <0.0001, 20% vs. 7% for

Table 1 - Characteristics according to the status of coronary artery calcification

	Presence of CAC n = 59	Absence of CAC n = 91	p
Men (%)	60.4	56.7	0.67
Age (years)	48 \pm 8	37 \pm 9	<0.0001
Diabetes duration (years)	24 \pm 11	16 \pm 8	<0.0001
Ethnicity (white) (%)	92	87	0.46
Current smoking (%)	30%	16%	0.08
Waist circumference (cm)			
Men	88 \pm 10	88 \pm 8	0.94
Women	85 \pm 10	80 \pm 8	0.06
BMI (kg/m ²)	25 \pm 3	25 \pm 3	0.85
Systolic BP (mm Hg)	127 \pm 15	122 \pm 15	0.03
Diastolic BP (mm Hg)	76 \pm 9	77 \pm 9	0.61
Hypertension (%)	67	26	<0.0001
Insulin dose/kg (U/kg)	0.7 \pm 0.3	0.7 \pm 0.2	0.60
A1c (%)	8.8 \pm 2.0	8.2 \pm 1.5	0.07
Total cholesterol (mg/dl)	175 \pm 36	180 \pm 44	0.58
HDL cholesterol (mg/dl)	59 \pm 18	58 \pm 15	0.92
LDL cholesterol (mg/dl)	99 \pm 32	103 \pm 40	0.58
Triglycerides (mg/dl)	227 (37-475)	204 (30-706)	0.12
UAER (μ g/min)	3.0 (0.92-1.145)	3.56 (3.50-1.251)	0.22
GFR (ml/min per 1.73m ²)	89.00	99.26	0.09
Any degree of diabetic retinopathy (%)	74	45	0.002
Presence of severe diabetic retinopathy (%)	46	18.6	0.003

CAC - coronary artery calcification; BMI - body mass index; BP - blood pressure; GFR - glomerular filtration rate was estimated with the Modification of Diet in Renal Disease Study formula; UAER - urinary albumin excretion rate.

beta blockers, $p = 0.03$, 46 % vs. 14 %, $p < 0.0001$ for thiazide diuretics and no difference 4.4 % vs. 3.5% for calcium channel blockers, $p = 0.78$). A total of 26% of individuals with CAC were on statin therapy vs. 15% of individuals without CAC, $p = 0.05$.

Among patients with CAC and any grade of DR, 46% had proliferative DR or severe NPDR ($n = 27$) versus 18.6% ($n = 17$) those individuals with any grade of DR and absence of CAC ($p = 0.003$).

To evaluate the association between DR and presence of CAC, we evaluated the severe forms of DR and their association with subclinical atherosclerosis through a logistic regression model, including severe DR (severe NPDR and proliferative DR) as a primary explanatory variable. In this model, severe DR was associated with the presence of CAC, regardless of known risk factors for the presence of CAC (age, A1C, hypertension, HDL cholesterol, LDL cholesterol and male gender). Only glycemic control and severe forms of DR were associated with subclinical atherosclerosis [odds ratio (OR) 1.44 95% CI 1.02-2.02, $p = 0.04$ and OR: 3.98 95% CI 1.13-13.9, $p = 0.03$ respectively]. There was a correlation between age and duration of diabetes, ($r = 0.5$, $p < 0.0001$). Therefore, age was included in the model because it has a very well known association with CAC.

Worthy of note, patients with severe DR were more frequently hypertensive (66 % vs. 26%, $p < 0.0001$), had higher UAER [8.35 $\mu\text{g}/\text{min}$ (0.9-435) vs. 21.3 $\mu\text{g}/\text{min}$ (4-1251), $p = 0.002$], longer diabetes duration (26 ± 9 years vs. 15 ± 8 years, $p < 0.0001$), and higher calcium score [0.0 HU (0-637) vs. 2.90 (0-1490), $p < 0.0001$] than patients with others forms of DR. When we evaluated the groups according to each individual cardiovascular risk factors, we observed that patients with CAC had higher prevalence of hypertension (67% vs. 26%, $p < .0001$) than individuals with no CAC and there was no difference as for the prevalence of dyslipidemia (28% vs. 16%, $p = 0.05$ and smoking (30% vs. 16%, $p = 0.08$).

Discussion

These results reveal a significant association between coronary subclinical atherosclerosis and the presence of more severe forms of DR in patients with T1D. This association contributes to a better understanding of the increased risk of death and cardiovascular events in patients with diabetic microvascular complications¹⁻⁴.

DR and cardiovascular disease have the same risk factors, including hypertension and hyperglycemia¹⁶. Consequently, the association of DR and coronary atherosclerosis is very

reasonable. Thereby, severe forms of DR could represent long periods of uncontrolled metabolic disease and this may also favor cardiovascular atherosclerosis. We can hypothesize that severe DR could precede cardiovascular events. But only long term prospective studies will clarify this aspect. In fact, retinopathy and retinal arterioles with a small caliber have been associated with a higher incidence of coronary artery disease in T1D individuals¹⁷.

This information reinforces the pathway between micro- and macrovascular complications in T1D and our findings support the hypothesis that microvascular changes precede macrovascular events. Before the vascular event, the DR is related to subclinical atherosclerosis.

However, this was a cross-sectional study with a limited number of patients. Consequently, we cannot establish an accurate relation of cause and effect from this data. This is a limitation of our study and one should consider this when these data are taken into account.

Patients with severe forms of DR, besides being at risk of becoming blind¹⁴ are at risk of presence of CAC, a powerful predictor of clinical coronary artery disease¹⁷ and should be better evaluated for the presence of CHD regardless of traditional cardiovascular risk factors. Further prospective studies and meta-analyses are needed to characterize this relationship and to define the DR as a marker of cardiovascular risk.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

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