Original Article

CHARACTERIZATION OF PATIENTS WITH TYPE 1 DIABETES MELLITUS IN SOUTHERN BRAZIL: CHRONIC COMPLICATIONS AND ASSOCIATED FACTORS

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ABSTRACT

Objective. To evaluate the prevalence of chronic vascular complications and associated factors in patients with type 1 diabetes mellitus (DM).

Methods. Cross-sectional study with type 1 DM patients seen in the Endocrinology Division of the Hospital de Clínicas de Porto Alegre. Patients were evaluated for presence of chronic vascular complications.

Results. We evaluated 573 patients, mean age of 33 years. The presence of diabetic retinopathy (DR) was observed in 43.3%. Diabetes duration [OR: 1.07, CI95%: 1.03 to 1.11, P <0.001], presence of diabetic nephropathy (DN) [OR: 3.40; CI95%: 1.89 to 6.13, P <0.001] and hypertension (HPT) [OR: 2.12, CI95%: 1.16 to 3.87, P = 0.014] were associated with DR. The DN was present in 34.5% and was associated with HPT [OR: 1.93, CI95%: 1.16 to 3.21, P = 0.001] and total cholesterol [OR: 1.0, CI95%: 1.0-1.01, P = 0.05]. Seven patients had macrovascular disease. Only 22% achieved an HbA1c of <7.0%. HPT prevalence was 33%, and 48% had blood pressure levels <130/80 mmHg and 45% of the patients had LDL values > 100 mg/dl.

Conclusion. We observed a high prevalence of microvascular complications and HPT. The duration of DM, HPT and presence of DN were associated with DR. HPT and dyslipidemia were associated with DN. Most patients did not meet the desired glycaemic control, blood pressure and lipid targets. Greater efforts are needed to intensify the pressure and metabolic control of patients with type 1 DM.

Key words: Type 1 Diabetes *Mellitus*. Diabetes complications. Diabetic angiopathies.

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Introduction

Patients with type 1 diabetes mellitus (DM) represent 10% of the DM patients.[1] However, DM's micro and microvascular complications present high prevalence in this group of patients. There are few data on the prevalence of chronic complications in Brazilian type 1 DM patients, and the studies represent a limited number of patients.[2-4]

Hyperglycemia and hypertension are the main risk factors for the development of DM's chronic complications.[5-7] Lipid profile is also considered a risk factor for microvascular complications,[8] in addition to its traditional association with macrovascular complications, as seen in the population with no DM.[9,10] From these observations, especially based on clinical trials,[5,7,11,12] values considered to be optimum were determined (treatment targets) for glycaemic and pressure control, and lipid profile of the DM patients.[13,16] Despite the importance of these factors, little information is available on the percentage of patients who can achieve these targets in Brazil. An assessment study on the lipid profile in type 1 DM showed that more than half the patients evaluated were off the values considered optimum for total cholesterol and LDL cholesterol,[17] reflecting the difficulty

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of meeting the treatment targets established for these patients.

The objective of this study was to evaluate the presence of micro and macrovascular complications and possible associated factors in type 1 DM ambulatory patients.

Methods

Patients

A cross-sectional study with 573 type 1 DM patients over 16 years of age, seen in the Diabetes ambulatory of the Endocrinology Service of the Hospital de Clínicas de Porto Alegre from 1998 to 2008, was conducted. The diagnostic criterion used for type 1 DM was essentially clinical: age when diagnosed lower than 40 years, previous episode of diabetic ketoacidosis or ketonuria documented, and obligatory use of insulin for life maintenance. All the patients started to use insulin in less than 1 year before the DM diagnosis, as well as presented at least ketonuria in the time of the DM diagnostic. The study protocol was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre and all the patients signed an informed consent term.

Clinical Evaluation

Patients were submitted to standardized clinical evaluation, as previously described,[18] emphasizing micro and macrovascular complications. The patients have classified themselves as Caucasian and not Caucasian. Summing up, diabetic retinopathy (DR) was evaluated by direct and indirect ophthalmoscopy after mydriasis by an ophthalmologist, and the severity was classified using the *Global Diabetic Retinopathy Group* scale.[19] Patients were classified as: 'absence of DR', 'mild non-proliferative DR' (NPDR), 'moderate NPDR', 'severe DR', and proliferative DR' (PDR). For the analyses the patients were divided in two groups: absence of DR and presence of any degree of DR.

Renal function was assessed by measuring urinary albumin excretion (UAE) and the glomerular filtering rate (GFR) estimated through the *Modificated Diet Renal Disease* (MDRD) formula: 186 x [serum creatinine$^{-1.154}$ x age$^{-0.203}$ x (0.742, if female) x (1.210, if black ancestry)].[20] The presence of diabetic nephropathy (DN) was defined by the UAE measured in sterile urine, minuted in 24 hours, in at least two occasions with a six months interval. The patients were classified in normoalbuminuric (<20 μg/min), microalbuminuric (UAE 20 to 200 μg/min) and macroalbuminuric (UAE ≥200 μg/min) or in renal substitution program. The diagnosis of coronary artery disease (CAD) was established according to the presence of documented history of acute myocardial infarction (EGC abnormalities [Codes in Minnesota: pattern Q and QS (1-1 to 1-3); linkage S-T (J) and segment depression (4-1 to 4-4); wave T(5-1 to 503), and complete block of the left branch (7-1)],[21] and perfusion abnormalities in myocardial cintilography during rest (fix) and after infusion of dipiridamol (variable), angina, or myocardial infarction determined through the World Health Organization (WHO)[21] or myocardial revascularization. An electrocardiogram during rest was done in all the patients. A treadmill test and myocardial cintilography were done only in the presence of compatible symptoms with ischemic cardiopathy or in patients with high risk for cardiovascular disease (CVD) [> 40 years, HPT, smoking, DN, dislypedimia, and/or previous history of (CVD)].[13] The presence of possible peripheral arterial disease (PAD) was defined by the WHO's questionnaire[21] and/or absence of arterial pulses in the clinical exam.

Weight and height measure were done in an anthropometric scale with no shoes on and light clothes. The body mass index (BMI) was calculated by the ratio weight (kg)/height (m) squared. The waist circumference (medial point between the last rib and the iliac crest, with a non-extensible tape measure, parallel to the floor) and hip (at the femur great tochanter level) were measured, and the waist/hip index was calculated, being considered as abnormal (abdominal obesity) >0.90 to men, and >0.85 to women.

To assess blood pressure (BP), two measures with the aneroid sphygmomanometer were done, with a one minute-interval, with the patient sitting down after five minutes of rest, using an adequate mitten to the arm's diameter, in the Korotkoff phases I and V, with the readings being made as closer as the 2 mm mark in the scale.

The following parameters were adopted as targets for desirable glycaemic, pressure, and lipid control: HbA1c <7.0%, BP office measurement <130/80 mmHg and LDLc <100 mg/dl.

Laboratory evaluation

The measure for HbA1c was done by high performance liquid chromatography in a Merck-Hitachi 9100 device by column method with cations exchange with reference value <6.0% (DCCT).' The glucose was measured by the glucose-peroxidase colorimetric enzymatic method – Biodiagnóstica kit. Serum creatinine was measured through the Jaffé method, and the lipid profile by the colorimetric enzymatic method. The LDL cholesterol was calculated using the Friedewald equation. Albuminuria was measured by immunoturbidimetry with commercial kit (Microalb; Ames-Bayer, Tarrytown, NY, USA). In our laboratory, using urine samples with 30 and 100 mg/L concentrations, the intra and intertrial variance coefficient was inferior to 6% to both tests.[22]

Statistic analysis

The T Student's test was used for the continuous variables, and the Chi square test was used for categorical variables. The non-parametric variables (triglycerides and UAE) suffered a logarithmic transformation for the statistic analysis. The continuous variables were presented as average ± standard deviation, excepting triglycerides and UAE, which were expressed as median and interquartile range (P25-P75%). The categorical variables were expressed as number of cases and percentage of patients affected. Multiple logistic regression models were performed with the presence of DR and DN as dependent variables. The independent variables were chosen according to their biological importance and the univariate analysis' result. The significance level adopted was 5%, and the statistic program used was SPSS 16.

Results

Clinical characteristics

573 patients with type 1 DM were evaluated, whose clinical and laboratory data were described in Table 1. Most of them were Caucasian (81%), male (50.5%), with average age of 33 ± 13 years (16-72 years), average DM duration, 16 ± 19 years (1-67 years) with onset at 17 ± 9 years (1-35 years). Average

time of follow up due to data collection was 9 ± 5 years (1-20 years). Age of DM diagnosis was 17 ± 9 years (1-39 years). Average BMI 23.6 ± 6.5 kg/m^2, waist/hip ratio for men 0.85 ± 0.07 and 0.79 ± 0.06 for women. Hypertension was present in 33% of the patients in the whole group, use of angiotensin II-converting enzyme receptor inhibitor or blockers was observed in 29% of the patients. The use of aspirin and statin were 18.6% and 12%, respectively.

Microvascular chronic complications

The presence of any DR was observed in 43.3% of the patients. Around 25% of them presented severe grades of DR: severe NPDR (3%) and proliferative DR (22.7%). The other part of the group was divided in light NPDR (15%) and moderate NPDR (4.1%). The presence of DN (micro, macroalbuminuria and dialysis) was observed in 34.5% of the evaluated patients. Microalbuminuria was present in 18.8%, macroalbuminuria in 13.3% and 10.5% of the patients were going through hemodialysis.

Table 2 describes the clinical and laboratory characteristics according to the DR presence. Patients with any degree of DR had more DM duration, were older, presented a higher prevalence of smoking and HPT, and had a more favorable lipid profile, higher values of UAE and lower values of eGFR than those without DR. The association of possible risk factors for DR was evaluated through multiple logistic regression analysis with the presence of any degree of DR as dependent variable. The DM duration [Odds ratio (OR): 1.07; CI95% 1.03-1.11; P < 0.001], presence of DN [OR 3.40; CI95% 1.89-6.13; P <0.001] and presence of HPT [OR: 2.12; CI95% 1.16-3.87; P = 0.014] were the variables associated with the presence of DR, adjusted to HbA1c [OR: 0.98; CI95% 0.93 – 1.04; P: 0.715], total cholesterol [OR:1.0; CI95% 0.99-1.01; P = 0.287] and presence of smoking [OR: 1.43; CI95% 0.97-2.09; P = 0.066]. When the UAE was replaced with eGFR in the same model, it was observed that only eGFR remained associated with the DR [OR: 0.97; CI95% 0.95-0.98; P = 0.001].

Table 3 describes the clinical and laboratory characteristics according to DN presence. Patients with any degree of DN had more DM duration, were older and hypertensive, with a worse lipid profile and lower eGFR when compared to patients without DN. Among the 138 patients classified as DN sufferers, 75 patients (54%) had microalbuminuria and 53 (38%) were macroalbuminuric. Ten patients (25%) were undergoing a dialysis program. In a multiple logistic regression analysis, considering the presence of DN as dependent variable, the presence of HPT [OR: 1.93; CI95% (1.16-3.21); P = 0.001] and total cholesterol [OR: 1.0; CI 95% (1.0-1.01); P = 0.05] were associated with the presence of DN. This model was adjusted for DM duration [OR: 1.02; CI 95% (0.99-1.04); P = 0.14] and HbA1c [OR: 0.99; CI 95% (0.95-1.04): P = 0.84]. When in the logistic regression model the cholesterol values were replaced by the triglycerides values, the results were similar: presence of HPT [OR: 1.81; CI95% (1.07-3.06); P = 0.027], triglycerides [OR: 1.0; CI 95% (1.0-1.01); P < 0.001], DM duration [OR: 1.0; CI 95% (0.99-1.05); P = 0.11], and HbA1c [OR: 0.98; CI95% (0.93-1.03): P = 0.58].

Table 1 – Clinical and laboratory characteristics of the 573 type 1 DM patients

Characteristic	
Age (years)	33 ± 13 (range:16-72)
Male n (%)	289 (50.5)
DM duration (years)	16 ± 9 (range: 1-67)
DM onset age (years)	17 ± 9 (range: 1-35)
Ethnic group (Caucasian) (n%)	460 (81)
BMI (kg/m2)	23.6 ± 6.5
Insulin dosage (U/kg)	0.72 ± 0.28
Ratio waist/hip	
Men	0.85 ± 0.07
Women	0.79 ± 0.06
Systolic blood pressure (mmHg)	122.5 ± 18.7
Diastolic blood pressure (mmHg)	78.0 ± 11.8
Hypertension n (%)	186 (33)
Current smoking n (%)	52 (9.2%)
Total cholesterol (mg/dl)	178 ± 45
HDL cholesterol (mg/dl)	56 ± 16
Triglicerydes (mg/dl)	80 (57-119)
LDL cholesterol (mg/dl)	102 ± 36
Fasting glycaemia (mg/dl)	181 ± 107
HbA_{1c} (%)	9.0 ± 3.9
eGFR (ml/min per 1.73m2)	98 ± 38
ACEi or ARB-II use n (%)	167 (29.2)
Aspirin use n (%)	106 (18.6)
Statin use n (%)	69 (12)

BMI = body mass index, eGFR = estimated glomerular filtration rate, ACEI = converting enzyme inhibitor, ARB-II = angiotensin II receptor blocker. Data expressed as average ± SD, number of patients with the studied characteristic (%) or median (P25-P75%).

Macrovascular chronic complications and cardiovascular risk factors

In relation to macrovascular complications, seven patients presented evidence of CAD: four patients with previous myocardial infarction, one patient with angina, and two patients diagnosed by myocardial cintilography, asymptomatic for CAD. All these patients were using aspirin and statin. Three of them presented PVD, with one being also CAD sufferer.

The proportion of patients with risk factors for CVD was 33% to HPT, 45% with dyslipidemia (LDL > 100 mg/dl), 5%

Table 3. Clinical and laboratory characteristics of type 1 DM patients according to the presence of diabetic nephropathy.

	No DN	DN	P
N	261	138	-
Age (years)	31 ± 12	35 ± 15	0.04
DM duration (years)	15 ± 9.0	18 ± 9.0	0.005
Male	127 (49%)	77 (56%)	0.19
Ethnic group (Caucasian)	208 (80%)	118 (86%)	0.48
Current smoking	21 (8%)	16 (12%)	0.70
Hypertension	62 (24%)	61 (44%)	<0.001
Systolic blood pressure (mmHg)	119 ± 6	136 ± 20	0.002
Diastolic blood pressure (mmHg)	77 ± 11	80 ± 13	0.01
Insulin dosage (U/kg)	0.7 ± 0.3	0.7 ± 0.3	0.20
BMI (kg/m^2)	23 ± 4	23 ± 7	0.15
Fasting glycaemia (mg/dl)	177 ± 101	176 ± 97	0.90
HbA_{1c} (%)	8.8 ± 5.0	9.0 ± 2.3	0.71
Total cholesterol (mg/dl)	171 ± 35	189 ± 58	0.001
HDL cholesterol (mg/dl)	57 ± 15	56 ± 19	0.57
Triglycerides (mg/dl)	68 (54-103)	95 (69-146)	<0.001
LDL cholesterol (mg/dl)	98 ± 29	107 ± 47	0.02
eGFR (ml/min/1.73m^2)	104 ± 32	83 ± 43	0.001
ACEI or ARB-II use	36 (13.7%)	92 (66.5%)	<0.001

BMI = body mass index, eGFR = estimated glomerular filtration rate, ACEI = converting enzyme inhibitor, ARB-II = angiotensin II receptor blocker. Data expressed as average ± SD, number of patients with the studied characteristic (%) or median (P25-P75%).

Table 2. Clinical and laboratory characteristics of type 1 DM patients according to the presence of diabetic retinopathy.

	No DR	DR	P
N	244	197	-
Age (years)	29 ± 14	37 ± 12	<0.001
DM duration (years)	14 ± 9.3	20.0 ± 8.0	<0.001
Male	129 (53%)	100 (51%)	0.66
Ethnic group (Caucasian)	202 (83%)	161 (82%)	0.74
Current smoking	14 (6%)	25 (13%)	0.01
Hypertension	51 (21.5%)	89 (45.5%)	<0.001
Systolic blood pressure (mmHg)	116 ± 13	130 ± 21	<0.001
Diastolic blood pressure (mmHg)	75 ± 10	81 ± 13	<0.001
Insulin dosage (UI/kg)	0.7 ± 0.3	0.7 ± 0.3	0.12
BMI (kg/m^2)	23 ± 5	23 ± 5	0.48
Fasting glycaemia (mg/dl)	178 ± 102	180 ± 109	0.88
HbA_{1c} (%)	8.9 ± 5.2	9.0 ± 2.2	0.62
Total cholesterol (mg/dl)	171 ± 40	188 ± 53	0.001
HDL cholesterol (mg/dl)	56 ± 16	57 ± 17	0.64
Triglycerides (mg/dl)	68 (53-105)	91 (61-124)	0.001
LDL cholesterol (mg/dl)	96 ± 29	107 ± 44	0.01
UAE (μg/min) *	7.40 (5.0-16)	12.25 (6.9-98.6)	<0.001
eGFR (ml/min/1.73m^2)	109 ± 34	79 ± 37	<0.001
ACEI or ARB-II use	32 (13%)	94 (48%)	<0.001

BMI = body mass index, eGFR = estimated glomerular filtration rate, ACEI = converting enzyme inhibitor, ARB-II = angiotensin II receptor blocker. Data expressed as average ± SD, number of patients with the studied characteristic (%) or median (P25-P75%). * patients in dyalisis were excluded.

with general obesity (BMI > 30 kg/m^2) and 28% of abdominal obesity (waist/hip ratio > 0.90 to men and > 0.85 to women).

Glycaemic, blood pressure and lipid control

The average glycaemic control evaluated through HbA1c was 9.0 ± 3.9%. Only 22% of the patients were within the established target for HbA1c (<7.0%). Among hypertensive patients, 68.4% were using angiotensin-converting enzyme inhibitors (ACEI), 4% were using the angiotensin II receptor blocker (ARB-II), 47.7% were using diuretics, 26.6% using beta-blockers, and 7% using inhibitors of calcium channels. Fifty percent of the patients were using combinations of anti-hypertensive medications. From the total amount of patients receiving anti-hypertensive treatment, 48% had the BP within desirable range (<130/80mm/Hg), and among these patients, 53% were using two or more anti-hypertensive medications. The patients using more than one anti-hypertensive drug (n = 94) were older (46 ± 10 years vs. 37 ± 10 years, P <0.001) and had DM for a longer time (24 ± 11 years vs. 19 ± 8 years, P = 0.02) and the same DN proportion (67 x 53% , P = 0.49) when compared to monotherapy patients.

The patients with LDL values >100 mg/dl represented almost half the studied population (45%).

Discussion

In this study it was demonstrated that the prevalence of microvascular chronic complications in type 1 DM patients seen in a University Hospital is high, being DR present in 45% and DN in 34.5% of the patients. In relation to possible risk factors to these complications, the presence of HPT was associated to DR and DN, high values of serum cholesterol, as well as high levels of triglycerides, were associated to DN and the DM duration was associated to DR, with analyses adjusted according to glycaemic control.

In relation to CVD and associated comorbidities, the prevalence of CAD in this population was 1.2%. The main risk factors for CVD were dyslipidemia, HPT, obesity, and abdominal obesity. Although obesity evaluated by the BMI has been detected only in around 5% of the patients, abdominal adiposity was observed in more than 25%, reflecting the importance of body fat distribution as a risk factor also in type 1 DM patients.

The association of DR with the time of disease is well known. After 11 years of DM existence, the prevalence of some degree of DR is around 66.6%,[23] increasing to approximately 100% after 20 years of DM.[24] Recently, a Brazilian group described a prevalence of 21% to DR in a sample of 81 type 1 DM patients.[4] This lower prevalence, when compared to this study, may be explained by the bigger duration of DM in our population. The presence of DN has been associated with DR, as expected, since DN is also a well known risk factor for DR.[25]

The presence of HPT is also a well known risk factor for the presence of DR[24] and our data reinforce this association. We also found an interesting association between eGFR reduction and DR presence. This observation was demonstrated also in a study that assessed type 1 and 2 DM patients.[26]

The observed prevalence of DN in our patients sample is in accordance with what is described in literature and, in this study, DN was associated to the presence of HPT and dyslipidemia. The importance of dyslipidemia as a risk factor for DN is reinforced by the observation that lipids reduction by using antilipemics may preserve the GFR and reduce proteinuria in DM patients.[27]

CVD is the main cause of mortality in type 1 DM patients.[28] In this study, CVD prevalence was extremely low, which is explained by the high number of young patients. The bigger occurrence of mortality due to CAD in type 1 DM patients has been reported since the 1970s.[29] Krolewski et al[30] demonstrated that at 55 years of age the cumulative mortality rate in this population was 30%-40%, if compared to the mortality of 4%-8% in non-diabetic patients described in *Framingham*'s study. It is probable that a higher number of events be detected in the next years in this group of patients, being the evaluation of this outcome one of the main aspects of this cohort's follow up.

Glycaemic control of the patients studied was not ideal, since only 22% of them reached HbA1c levels <7.0%. It is known that a proper metabolic control prevents and hinders the upcoming of microvascular complications.[5] The absence of a significant association between HbA1c and microvascular complications, traditionally recognized, may have occurred due to the homogeneity of the population studied in relation to the poor glycaemic control. Although our patients have been seen by an endocrinologist, nurse, and nutritionist, there was not a specifically structured multidisciplinary group in the occasion to attend exclusively type 1 DM patients. This may be one of the reasons for the higher proportion of patients with improper glycaemic control. In this sense, a Brazilian study that evaluated the intervention of a multidisciplinary team in type 1 DM patients demonstrated that 50% of these patients have reached the established target (HbA1c <7%) after one year in comparison to only 17% of the patients seen only by an endocrinologist.[3] Another important aspect of these patients' care is the socioeconomic problem that hinders their adherence to treatment orientations, whether they are related to diet, therapy, medication or home self-monitoring of capillary glycaemia. Indeed, these difficulties seem to occur also in other regions of the country and other Brazilian authors have observed even higher HbA1c values (around 10%) than the ones seen in this study.[4] Finally, the importance of glycaemic control for the type 1 DM patients has become even more relevant due to recent demonstration that more intensive glycaemic control is associated to the lower CVD development in these patients.[31,32] Besides that, there is an intrinsic relation of glycaemic control to pressure values, verified through the assessment of patients placed, for intensive treatment, in the *Diabetes Control and Complication Trial*.[33] It was demonstrated that the better glycaemic control of type 1 DM patients is capable of preventing HPT.

In this study the best pressure control occurred in patients using combined medications, similarly to what happens with type 2 DM patients, with whom the proper control is obtained only by using multiple anti-hypertensive drugs.[7] Our results differ from what was observed in a study that compared a cohort of type 1 DM patients to non-diabetic hypertensive control subjects.[34] The pressure target (<130/80 mmHg) was reached in 42% of the type 1 DM hypertensive patients and the majority by using only one anti-hypertensive drug. The most probable reason for this difference may be the higher age group of our patients in comparison to the study described.[34]

HPT prevalence in patients studied was 33%, being less than

50% of these patients within desirable BP values (< 130/80 mmHg). In Brazil, another study done with type 1 DM patients has observed an extremely low HPT prevalence, around 0.8%.[35] However, the patients were considerably young, around 17 years old (12-25 year-old patients). In that study, after a follow up of five years the patients who had BP levels in the higher limit within normality (pre-hypertensive) had already presented a bigger chance of developing HPT (RR= 3.2 CI95% 0.8-12.3, P = 0.09).[35] Blood pressure values in pre-HPT levels are also important predictors for microvascular complications. In a prospective cohort of type 1 DM patients, we have demonstrated that BP values in the higher limit within normality were associated to DR development.[18]

In relation to lipid control, we observed that the results were below what was considered an ideal level.

A possible limitation of this study could be the fundamentally clinical criterion adopted for type 1 DM classification, since anti-islet antibodies, anti-GAD, or C peptide measurement were not performed in all the patients. In this sense, the presence of elder patients, as observed in the sample studied, could compromise the accuracy of patients' classification. However, it is little likely that type 2 DM patients were included, since all the patients had ketoacidosis or ketonuria by the time of the diagnosis and used insulin for 1 year before the DM diagnosis.

Despite the fact that current evidence demonstrate that chronic DM complications might be minimized, for a better control of its risk factors, the situation of patients studied is below what is desirable.

Conclusion

In this study we evaluated a Brazilian type 1 DM patients' population attended in a University Hospital and we observed a high prevalence of microvascular complications, as well as HPT. Associations with the following risk factors were verified: DM duration, blood pressure control, and dyslipidemia. Most patients were outside the desired targets of glycaemic, pressure, and lipid control. Greater efforts are needed to intensify metabolic and pressure control in these patients, being important to implement more effective and comprehensive health policies.

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