PREVALENCE OF DIABETIC RETINOPATHY IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

JORGE F. ESTEVES1, CAROLINE K. KRAMER2, MIRELA JOBIM DE AZEVEDO3, ANDRESSA P. STOLZ4, MURILDO F. ROGgia4, ANDRÉA LARANGEIRA4, SUELLA A. MIOZZO5, CAROLINA ROSA5, JOSE HUMBERTO LAMBERT5, MIRIAM PEcis5, TICIANA C. RODRIGUES3, LUIS HENRIQUE SANTOS CANANI2

Trabalho realizado no Serviço de Oftalmologia, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brasil, Serviço de Endocrinologia, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brasil, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS

INTRODUCTION

Diabetic retinopathy (DR) is the most frequent microvascular complication of diabetes mellitus (DM), resulting in blindness for over 10,000 people with DM every year4 and is the leading cause of legal blindness5. In type 1 DM, the overall prevalence of DR after eleven years of follow-up is 66.6%, and almost all patients have some degree of DR after 20 years of DM4, 5. Further, severe forms of the disease leading to visual impairment occur in 50% of type 1 DM patients2.

The main risk factors for the development and progress of DR are persistent hyperglycemia, DM duration and high blood pressure levels6-11. However, there is an important individual variability in incidence of DR among diabetic patients. The question often asked is why some patients under good metabolic control develop DR while others remain free of this complication, despite poorly controlled DM12. This may be due to different genetic backgrounds.

The aims of the present study were to describe prevalence of DR and its risk factors in type 1 DM outpatients from a general hospital in Southern Brazil.

METHODS

Research design

This is a cross-sectional study that described baseline characteristics of a prospective cohort study of outpatients with type 1 DM from July 2003 to December 2007.

1. Professor assistente do Departamento de Oftalmologia da Universidade Federal do Rio Grande do Sul, Porto Alegre, RS
3. Professora adjunta do Departamento de Medicina Interna da Universidade Federal do Rio Grande do Sul, Porto Alegre, RS
4. Médica residente do Serviço de Oftalmologia do Hospital de Clínicas de Porto Alegre, Porto Alegre, RS
5. Estudante de medicina - Estudante de Medicina da Universidade Federal do Rio Grande do Sul, Porto Alegre, RS
6. Bolsista de Pós-doutorado do CNPq
7. Médica do Serviço de Endocrinologia do Hospital de Clínicas de Porto Alegre, Porto Alegre, RS
8. Professor adjunto do Departamento de Medicina Interna da Universidade Federal do Rio Grande do Sul, Porto Alegre, RS
Subjects

Patients with type 1 DM attending the Hospital de Clínicas de Porto Alegre, Brazil, in the Endocrine Clinic and referred to the Ophthalmology Clinic for routine eye examination were included. The criteria for referral were patients more than 18 years of age with a diagnosis of type 1 DM for five years or more. Definition of type 1 DM was based on the presence of DM, diagnosed before 30 years of age, at least one episode of diabetic ketoacidosis and/or cetonemia and need for insulin therapy within 1 year of DM diagnosis.

Eye examination and classification of retinopathy

Eye examination included, in addition to fundoscopy, visual acuity test (logMAR notation), refraction, tonometry and biomicroscopy of the anterior segment.

DR was graded at the time of ophthalmologic assessment by fundoscopy through dilated pupils by the same researcher (JFE) and severity was established using the scale developed by the Global Diabetic Retinopathy Group. The first level was “absent DR”, with no fundus abnormalities; the second was “mild non proliferative diabetic retinopathy (NPDR)”, microaneurysms only; the third, “moderate NPDR”, included more than just microaneurysms, but less than severe NPDR; the fourth, “severe NPDR”, included any of the following: >20 intra-retinal hemorrhages in each of the 4 quadrants, definite venous beading in 2+ quadrants, prominent intra-retinal microvascular abnormalities in 1+ quadrant, and no signs of proliferative DR; and the fifth level, “proliferative DR” (PDR), which includes eyes with one or more of the following: definite neovascularization or vitreous pre-retinal hemorrhage.

Classification of patient DR was based on the most severe degree of retinopathy in the worst affected eye. We have previously described an excellent agreement of DR classification (95.3%) carried out by different trained ophthalmologists from our group. Therefore, in the present study only a single observer, not aware of the patients’ clinical data, classified all the subjects.

According to the DR classification, three groups were defined for further analysis: 1- absent DR; 2- mild and moderate NPDR (mild/moderate NPDR) and 3- severe non proliferative and proliferative DR (advanced DR group).

Macular edema was evaluated upon dilated eyes, using slit-lamp biomicroscopy in a subset of patients. Clinically significant macular edema (CSME) was defined as one or more of the following: any retinal thickening within 500mm of the center of the macula, with or without loss of retinal transparency; hard exudates associated with retinal thickening within 500mm of the center of the macula; or one disc area of thickening within one disc diameter of the center of the macula.

Clinical evaluation

Risk factors for DR were recorded at the time of ophthalmologic examination and included age, age at onset of DM, DM duration, ethnicity (self reported), smoking habit, body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP). All patients answered a brief standard questionnaire and underwent physical examination and laboratory tests. They were weighed wearing light outdoor clothes without shoes and height was recorded. BMI was calculated as weight (kilograms)/height2 (meters). Waist circumference was measured on a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest. Sitting blood pressure was measured twice on the right arm to the nearest 2mm Hg after a 10 minute rest using a standard mercury sphygmomanometer (phases I and V of Korotkoff sounds). Subjects who smoked one or more cigarettes daily were classified as current smokers. Those who had smoked in the past and stopped for more than one year were classified as former smokers.

Statistical analysis

In univariate analysis the Chi-square test and the one-way analysis of variance (ANOVA) followed by post-hoc Bonferroni test on residual analyses were used. Multinomial multivariate regression was performed with DR as the dependent variable (absent DR, mild/moderate NPDR and advanced DR) and all variables associated with the presence of DR in the univariate analysis were included as independent variables. P value < 0.05 was considered significant. Continuous variables were presented as mean ± standard deviation. Variables with a non normal distribution (albuminuria and triglycerides) were presented as median (range). Categorical data were presented as absolute numbers and percentages.
Results

Sample description

A total of 437 patients were evaluated (50.3% males, 82.4% whites). Mean age at ophthalmologic examination was 26.8 ± 7.8 years and at diagnosis of DM was 12.9 ± 7.1 years. Duration of DM was 14.4 ± 7.3 years. Overall prevalence of any DR was 44.4% (n = 194). Sixty-six patients (15.1%) had mild NPDR, 18 patients (4.2%) moderate NPDR, 13 (3.0%) patients severe NPDR, and 97 patients (22.2%) were diagnosed with PDR. Patients with mild and moderate NDPR were grouped as mild/moderate (n=84), and patients with severe NPDR and PDR were grouped as advanced DR (n = 110).

Demographic, anthropometric and smoking habit data

Clinical and laboratory features of type 1 DM patients grouped according to the degree of DR are shown in Table 1. Patients with absent DR had a shorter duration of DM and were younger than the patients with mild/moderate NPDR and advanced DR. Duration of DM was not different between patients with mild/moderate NPDR and advanced DR. Onset of DM occurred earlier for patients without DR when compared to patients with mild/moderate NPDR and advanced DR. Gender proportion, ethnic group and anthropometric indices did not differ among groups. Neither general obesity (BMI) nor central obesity (waist circumference) was linked to DR.

Current or past smoking history was associated with DR (P < 0.001). There was a progressive increase in the frequency of smokers/former smokers among those with absent DR, mild/moderate DR and advanced DR (P for trend <0.001).

Blood pressure and glycemic control

Patients with mild/moderate NPDR and advanced DR had higher SBP than patients without DR (Table 1). The DBP levels were higher in the group with advanced DR than in patients without DR, but DBP was not different between those without DR and with mild/moderate NPDR. There was a progressive increase in the prevalence of arterial hypertension from those without DR to mild/moderate NPDR and advanced DR (21.0% vs. 38.1 vs. 56.4%; P <0.001).

There was no difference in FPG values among the three groups (178.7 ± 102.2 vs. 189.5 ± 118.8 vs. 170.8 ± 100.2 mg/dl, P = 0.520). The A1C test was higher among those with mild/moderate NPDR and advanced DR when compared to those without DR.

Figure 1 shows the frequency of advanced DR according to SBP and A1C test quartiles. Prevalence of advanced DR was 8.2% in patients in the lower A1C test and SBP quartiles. Even in patients with the best metabolic control (A1C test <7.2%), prevalence of advanced DR increased with the increase of blood pressure quartiles, reaching 28% in those of the upper SBP quartile (>130 mm Hg). The same pattern was observed for the A1C quartiles in those with low SBP (<110 mm Hg). Those in the

Table 1 - Clinical and laboratory characteristics of patients grouped according to the stages of diabetic retinopathy

<table>
<thead>
<tr>
<th>Diabetic Retinopathy</th>
<th>Absent N = 243</th>
<th>Mild/moderate NPDR N = 84</th>
<th>Advanced DR N = 110</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.0 ± 7.7</td>
<td>28.8 ± 7.3</td>
<td>32.5 ± 5.8</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Age at diagnosis of DM (years)</td>
<td>12.0 ± 7.3</td>
<td>14.0 ± 5.5</td>
<td>14.7 ± 7.8</td>
<td>0.146</td>
</tr>
<tr>
<td>DM duration (years)</td>
<td>13.2 ± 7.2</td>
<td>15.8 ± 6.0</td>
<td>17.7 ± 8.1</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Male gender - n (%)</td>
<td>129 (53.1)</td>
<td>46 (54.8)</td>
<td>45 (40.9)</td>
<td>0.070</td>
</tr>
<tr>
<td>White - n (%)</td>
<td>201 (82.7)</td>
<td>63 (75.0)</td>
<td>96 (87.3)</td>
<td>0.081</td>
</tr>
<tr>
<td>Smoking habit n (%)</td>
<td>41 (16.9)</td>
<td>20 (23.8)</td>
<td>40 (36.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>23.0 ± 5.0</td>
<td>23.7 ± 4.6</td>
<td>23.3 ± 6.0</td>
<td>0.741</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>83.2 ± 8.7</td>
<td>84.9 ± 9.5</td>
<td>83.9 ± 8.6</td>
<td>0.770</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>116.3 ± 13.7</td>
<td>125.4 ± 17.6</td>
<td>134.3 ± 24.0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>75.2 ± 9.9</td>
<td>79.1 ± 10.7</td>
<td>83.9 ± 15.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Arterial hypertension - n (%)</td>
<td>21.20</td>
<td>38.36</td>
<td>56.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>178.7 ± 102.2</td>
<td>189.5 ± 118.8</td>
<td>170.8 ±100.2</td>
<td>0.522</td>
</tr>
<tr>
<td>A1C test (%)</td>
<td>8.90 ± 5.26</td>
<td>9.45 ± 2.39</td>
<td>8.84 ± 1.98</td>
<td>0.561</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>171.1 ± 39.7</td>
<td>181.2 ± 49.6</td>
<td>190.9 ± 45.1</td>
<td>0.002**</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>56.3 ± 16.19</td>
<td>56.3 ± 15.9</td>
<td>58.6 ± 18.9</td>
<td>0.590</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>96.4 ± 29.4</td>
<td>104.9 ± 39.6</td>
<td>107.1 ± 42.7</td>
<td>0.060</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>68 (22-900)</td>
<td>84 (31-534)</td>
<td>97 (33-507)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.07 ± 1.09</td>
<td>1.28 ± 1.34</td>
<td>2.23 ± 2.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated GFR (ml/min/1.73 m2)</td>
<td>109.0 ± 34.11</td>
<td>92.5 ± 37.00</td>
<td>66.4 ± 34.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Urinary albumin excretion (mg/l)</td>
<td>7.64 (0.1-903)</td>
<td>8.25 (0.1-7110)</td>
<td>72.67 (0.1-9477)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normo/Micro-/Macro-ESRD (%)</td>
<td>78.97/14.87/6.14</td>
<td>65.33/21.33/13.34</td>
<td>25.33/28.0/46.67</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data expressed as mean (± standard deviation), median [range] or number of cases (%).

NPDR= non proliferative diabetic retinopathy

* absent DR vs. NPDR and advanced DR, ** absent DR vs. advanced DR Advanced DR vs. absent and NPDR. Current and former smokers
upper quartiles for A1C test and SBP had the highest prevalence of severe DR (41%).

**Lipid profile**

Patients with advanced DR had higher values of total cholesterol, LDL cholesterol and triglycerides than patients without DR. There were no differences in the levels of HDL cholesterol values among groups.

**Renal function**

Patients with advanced-DH had higher serum creatinine values than patients with mild/moderate NPDR and without DR. Estimated GFR was also lower among patients with advanced DR than among those with mild/moderate NPDR or without DR.

There was a progressive increase in UAE according to the degree of retinal involvement, lower among those patients without DR and higher among those with advanced DR. To establish an index of magnitude, subjects were divided according to the UAE into normo, micro or macroalbuminurics. Subjects with ESRD were included in the macroalbuminuric group. Microalbuminuria increases the chance of advanced DR by 4.8 times (95% CI 2.5-9.4, P <0.001), but not the mild/moderate forms (OR 1.75, 95%CI 0.9 - 3.5, P = 0.320). Macroalbuminuria was associated with both, mild/moderate NPDR (OR 2.6, 95%CI 1.1-6.3, P =0.020) and advanced DR (OR 23.3, 95%CI 11.0 - 50. 1, P <0.001).

**Macular edema**

In the subset of 223 patients in whom the presence of CSME was evaluated, 21 patients (9.4%) presented CSME, and this frequency increased with the severity of DR: 16.4% in advanced DR, 9.6% in mild/moderate NPDR, and 4.7% in the group without DR (P = 0.020). Current smoking was also associated with CSME (OR 3.19, 95%CI 1.24-8.2, P = 0.012). There was a progressive increase in the frequency of CSME according to renal status: normo 5.4%, micro 11.4%, and macroalbuminuria 22.2% (P for trend 0.005). CSME was not associated with gender, ethnicity, blood pressure levels, lipid profile, serum creatinine or metabolic control.

**Multivariate analysis**

**Mild/moderate non proliferative diabetic retinopathy**

Mild/moderate NPDR was associated with most variables, except for total cholesterol, and smoking. SBP, A1C test, microalbuminuria (log transformed), DM duration, total cholesterol and smoking (current or past) were included in the initial multivariate logistic regression model. For each increase in one year of DM duration, in one mmHg in SBP or in one point in A1C test, there was an increased chance of presenting mild/moderate NPDR of 6%, 2% and 2% (P <0.005), respectively.

Other models were constructed substituting SBP for DBP or arterial hypertension, or substituting total cholesterol for tryglycerides (log transformed), or degree of albuminuria for stages of diabetic nephropathy (norm, micro or macroalbuminuria) or serum creatinine. The inclusion of arterial hypertension instead of SBP showed an OR of 3.12 (95%CI 1.06-9.40). Neither DBP nor triglycerides were associated with mild/moderate NPDR. When microalbuminuria was replaced by serum creatinine, the OR for mild/moderate NPDR was 1.76 (95% CI 1.03-3.48).

**Advanced diabetic retinopathy**

Advanced DR was associated to all variables with the exception of total cholesterol and A1C test. Each increase in one year of DM duration or in one mmHg in SBP was associated with an increase in the odds of advanced DR of 4% (95% CI 1.3-7.8, P <0.05). Smoking increased chances for advanced DR by 2.75 times (OR 95%CI 1.15-6.60). Hypertension was associated with an OR of 2.48 (95% CI 1.13-5.40) for advanced DR. Presence of diabetic nephropathy (DN) (micro- or macroalbuminuria) was associated with an OR of 8.53 (95% CI 3.81-18.05). When serum creatinine was used in the model instead of microalbuminuria it was also associated with advanced DR (OR 2.64 - 95% CI 1.40-5.01).

The five major independent risk factors for advanced DR were dichotomized into present or absent (arterial hypertension, DN and smoking) or above or below the median value (A1C test - 8.7% and DM duration - 17 years). Forty-two of the patients (9.6%) had no risk factors, 131 patients (30%) had one, 139 patients (31.8%) two, 49 (11.4%) three, 50 (11.4%) four, and only 7 patients (1.6%) had all five risk factors. The prevalence of advanced DR increased with the number of risk factors (Figure 2). However, even in the presence of four or five risk factors, about 40% of the subjects were free of the most severe degree of DR (proliferative form).

**Discussion**

In this study, DR was present in a high percentage of this sample of type 1 DM patients and it was associated with the main traditional risk factors, namely glycemic control, blood pressure and DM duration. On the other hand, glycemic control was not associated with advanced DR in multivariate analyses. This may suggest that for more severe forms of DR, glycemic control does not play a major role as observed for systolic blood pressure. An alternative explanation is that absence of association could reflect improvement of glycemic control that results from medical advice, once diagnosis of this severe microvascular chronic
A similar association in patients with type 2 DM 16. Concordance associated only with more severe forms of DN. We have shown type 1 DM patients 24. In the present study, microalbuminuria was association of incipient DN and DR was previously described in severe forms of DR could reflect the major role of genetic factors Finally, unmarked influence of A1C test levels in patients with dl) of our patients studied, probably related to their young age. This aspect is reinforced by a high magnitude of OR for almost all DR risk factors in advanced DR stages of diabetic eye disease. This aspect is this was not observed in the present study for any DR. This could associations since there were only 22 patients with CSME. This would also preclude performing a multivariate analysis to identify the independence of the associations found.

**CONCLUSION**

In conclusion, prevalence of 44.4% of any DR in type 1 DM patients attending a general hospital shows that this condition continues to be a major public health problem despite current knowledge about advanced DR. Furthermore, prevalence of 24% of advanced DR stages is a warning sign. Those with a long DM duration, positive smoking, elevated blood pressure, poor metabolic control and albuminuria are at highest risk of presenting advanced DR forms. Finally, CSME should be suspected in presence of smoking or any degree of DN.

**ACKNOWLEDGEMENTS**

Grant Support: Research supported by grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundo de Incentivo a Pesquisa e Eventos (Fipe) - Hospital de Clínicas de Porto Alegre, LHC was the recipient of a postdoctoral (ProDoc) grant from Fundação de Coordenação de Aperfeiçoamento de Pessoal de Ensino Superior (Fundação CAPES) and MP was the recipient of a posdoctoral grant from CNPq.

**Conflict of interest:** none

**RESUMO**

**PREVALENÇA DE RETINOPATIA DIABÉTICA EM PACIENTES COM DIABETES MELLITUS TIPO 1**

**Objetivos.** Determinar a prevalência de RD e seus fatores de risco em pacientes com DM tipo 1 atendidos em um hospital geral.

**Métodos.** Foi realizado um estudo transversal com 437 pacientes (50,3% homens, 82,4% brancos). RD foi agrupada em: 1) ausente; 2) não proliferativa leve e moderada (RDNP leve/moderada); 3) não proliferativa grave e RD proliferativa (RD avançada). Edema de mácula clinicamente significativo (EMCS) também foi registrado.

**Resultados.** Qualquer grau de RD esteve presente em 44,4% dos pacientes. Na análise multivariada, duração do DM, pressão arterial sistólica e teste A1C foram associados com a RD leve/moderada (P<0,005). RD avançada foi associada com duração do DM, pressão arterial sistólica (PAS), fumo (razão de chances (RC) 2,75, IC 95% 1,15-6,60) e micro- ou macroalbuminúria (RC 8,53, IC 95% 3,81-18,05). EMCS esteve presente em 21 (9,4%) dos pacientes associado ao fumo, aumentando com a gravidade da RD (16,4% RD avançada; 9,6% RD leve/modera, e 4,7% no grupo sem RD; P = 0,020).

---

**Table**

<table>
<thead>
<tr>
<th>Number of Risk Factors</th>
<th>Prevalence of advanced diabetic retinopathy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I</td>
<td>10</td>
</tr>
<tr>
<td>II</td>
<td>20</td>
</tr>
<tr>
<td>III</td>
<td>40</td>
</tr>
<tr>
<td>IV</td>
<td>60</td>
</tr>
<tr>
<td>V</td>
<td>100</td>
</tr>
</tbody>
</table>

High values of LDL cholesterol and total cholesterol-HDL cholesterol ratio have been suggested to increase by two and fourfold the risk of CSME, respectively. In type 1 DM patients, old age at diagnosis of DM, male gender and higher A1C test levels significantly increase the risk of clinically significant macular edema. We did not find an association between demographic data, blood pressure, lipid profile or metabolic control indices and CSME. This could be due to the low power to detect these associations since there were only 22 patients with CSME. This would also preclude performing a multivariate analysis to identify the independence of the associations found.
References


Artigo recebido: 13/06/08
Aceito para publicação: 13/09/08