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Rom J Diabetes Nutr Metab Dis. **22**(2):159-165
doi: 10.1515/rjdnmd-2015-0020

RISK FACTORS FOR DIABETIC RETINOPATHY PROGRESSION

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received: April 30, 2015 *accepted*: May 22, 2015
available online: June 15, 2015

Abstract

Background and Aims. *There is no unanimous opinion regarding the risk factors associated with progression of diabetic retinopathy (DR). We have done a retrospective analysis of risk factors and clinical features associated with DR progression.* **Material and Methods.** *This analysis included consecutive patients with moderate non-proliferative or severe retinopathy between December 1, 2013 and May 31, 2014 who had at least two eye examinations before that period. We have collected demographic, clinical and lab data.* **Results.** *51.28% of patients were diagnosed with moderate non-proliferative diabetic retinopathy (NPDR), 24.68% with severe NPDR and 21.05% with proliferative diabetic retinopathy. In 82.16% of cases, DR had progressed. The risk factor correlated with DR progression in the whole group was anemia; hypertension, anemia and diabetes duration were risk factors in type 1 and smoking status at diabetes diagnosis in type 2 diabetes. Total cholesterol, triglycerides, diabetes control and presence of diabetic renal disease were positively but not statistically significant correlated with DR progression.* **Conclusions.** *In our study the risk factors correlated with DR progression were hypertension, anemia and diabetes duration in type 1, respectively smoking at diabetes diagnosis in type 2 diabetes. Glycemic goals were achieved in a small number of patients.*

key words: *diabetes mellitus, diabetic retinopathy, risk factors, HbA1c, hypertension.*

Background and Aims

Diabetic retinopathy (DR) is a common complication caused by multiple biochemical abnormalities of the underlying metabolic disease. For decades, it has remained the primary cause of blindness in adults of working age in developed countries. It is one of the most frequent microvascular complications in persons with diabetes. The relative risk of developing retinopathy is higher in a person with type 1 diabetes (T1DM) than with type 2 diabetes (T2DM) [1]. A recent meta-analysis confirmed that persons with T1DM were more prone to retinopathy development and that disease duration, metabolic control and blood pressure were the major risk factors. Smoking and male sex have been identified as additional risk factors for any retinopathy in a large European study of T1DM patients [2].

The diagnosis is based on the alterations of the retinal blood vessels, usually indicating

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abnormalities of the blood–retinal barrier and increased vascular leakage, but the neuroglial elements appear equally vulnerable to the diabetic condition. Control of blood glucose, blood pressure and timely identification of coincident renal disease are important to prevent progression to vision-threatening stages. Guidelines give specific indications for laser photocoagulation, in particular when euglycemia is no longer effective in preventing progression to advanced stages [3].

While the incidence of DR appears to decline due to evidence-based changes in diabetes management, the predicted increase in patients affected in particular by T2DM may outweigh the positive trend [3].

The aim of this study was to assess the risk factors and clinical features associated with DR progression in our out-patient clinic.

Material and Methods

At study entry, clinical data was collected from the records of patients submitted to periodic eye examination done with a retinophotograph (Carl Zeiss Meditec AG), in the Cluj Napoca Diabetes Center and whose medical records showed at least two previous eye examinations. The medical charts were analyzed between the 1st of December 2013 and the 31st of May 2014. During this period of time, 93 patients were diagnosed with moderate non-proliferative diabetic retinopathy (NPDR), severe NPDR or proliferative diabetic retinopathy (PDR). Persons who were not registered at the Cluj Napoca Diabetes Center were excluded from this clinical evaluation. Subjects who didn`t follow regular medical checks in the diabetes out-patient clinic or those with incomplete biochemical analysis results were also excluded. In the end, 79 patients were included in this evaluation. This study was approved by the ethical committee of Cluj-Napoca County Clinical Emergency Hospital.

Information about the onset and treatment of diabetes, the onset and management of retinopathy were collected from the medical charts. The following risk factors were investigated: diabetes control assessed by measurements of HbA1c levels, total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides (TG), lipid-lowering therapy, the presence of hypertension, diabetic renal disease, anemia and smoker status.

Statistical analysis We used the Microsoft Excel statistical analysis package to process the data. Continuous variables with normal distribution were presented as mean and standard deviation – SD (in brackets). Categorical variables were presented as number of patients and percentage. We used the correlation test included in Microsoft Excel statistical analysis package to calculate Pearson's correlation coefficients (*r*-values). The results were interpreted using Dancey and Reidy's categorization. Here, *r*-value of ±1 is interpreted as a perfect correlation, *r*-values between ±0.7 to ±0.9 are interpreted as strong correlations, *r*-values in the range ±0.4 to ±0.6 are categorized as moderate correlations, *r*-values between ±0.1 to ±0.3 are weak correlations and an *r*-value of 0 is zero correlation, implying there is no correlation.

Results

A total of 79 participants were enrolled in this study, 84.81% of them had T2DM and 53.16% were female (Table 1). The mean age at time of T2DM diagnosis was 47.09±12.97 years, with an average duration of diabetes of 16.27±9.17 years at the inclusion in this study. At diagnosis of diabetic retinopathy the mean age of participants was 57.71±11.02 years and the mean duration of diabetes was 11.03±7.84 years. On the follow-up period, the vast majority of patients (51.28%) were diagnosed with moderate NPDR, 24.68% with severe NPDR and

21.05% with PDR (Table 2). In 82.16% of participants the DR had progressed since the last examinations.

The mean HbA1c value of participants was 9.22%±2.4%, the mean total cholesterol level was 196.6±52.3 mg/dl, the mean HDL-cholesterol level was 48.1±13.9 mg/dl and mean triglycerides level was 176.1±114.7 mg/dl. At the time of this evaluation, 59.52% of participants were already diagnosed with diabetic renal disease and just 19.15% had anemia (defined as hemoglobin lower than 12 g/dl or hematocrit below 37%). The smoker status in patients was recorded at diagnosis of diabetes (16.67% of subjects were smokers). We should mention that any changes towards participants smoking behavior was not pursued further.

We analyzed the frequency of achieving glycemic targets indicated by the guidelines. Only 10% of the total number of patients included in this evaluation had an HbA1c <7% and 25% of them had an HbA1c <7.5%. At the assessment of lipid profile, 32.43% of patients had a cholesterol level under 175 mg/dl, 70.49% and 56.16% had normal value of HDL-cholesterol, respectively of triglycerides. The majority of participants in this study received statin therapy (75.51%), 14.29% of the patients were on a combined lipid-lowering therapy and 10.2% of patients on fibrate therapy.

Table 1. Demographic and clinical characteristics of patients according to type of diabetes.

	Total	T1DM	T2DM
Patients	79	12	67
Gender (Women %)	42 (53.16 %)	3 (25.0 %)	39 (58.2 %)
Age at time of T2DM diagnosis (mean age ± SD)	47.09±12.97	25.5±10.48	51.02 ±8.88
Duration of diabetes (mean age±SD)	16.27 ±9.17	27.67 ±9.25	14.22 ±7.51
Age at time of diabetic retinopathy's diagnosis (mean age±SD)	57.71 ±11.02	45.83 ±8.38	59.94 ±9.98
Time from diabetes diagnosis to DR diagnosis (mean age±SD)	11.03 ±7.84	20.33 ±8.23	9.28 ±6.40
Mean current HbA1c % (±SD)	9.22 ±2.4	9.48 ±1.61	9.16 ±2.53
Diabetic renal disease (%)	59.52	60.00	59.38
Total Cholesterol, mg/dl (mean ±SD)	196.61 ±52.30	198.92 ±40.81	196.16 ±54.23
HDL, mg/dl (mean ±SD)	48.11 ±13.96	58.60 ±19.16	45.54 ±10.92
TG, mg/dl (mean ±SD)	176.14 ±114.78	104.42 ±34.97	190.25 ±119.64
Smokers (%)	16.67	66.67	9.52
Anemia (%)	19.15	27.27	16.67
Hypertension (%)	82.28	50	88.06
Current HbA1c <7 %	10%	0%	11.63%
Current HbA1c <7.5 %	25%	18.18%	25.58%
Total Cholesterol <175 mg/dl	32.43%	33.33%	32.26%
HDL >40 mg/dl	70.49%	91.67%	65.31%
TG <150 mg/dl	56.16%	91.67%	49.18%
Statin (%)	75.51	100	70.00
Fibrate (%)	10.20	0	12.50
Statin + fibrate (%)	14.29	0	17.50

Table 2. Staging of diabetic retinopathy.

	Total	T1DM	T2DM
Moderate NPDR (%)	51,28%	50,00%	51,52%
Severe NPDR (%)	24,68%	8,33%	27,69%
PDR (%)	21,05%	33,33%	18,75%

Diabetic retinopathy in patients with T1DM presents several differences compared to patients with T2DM. To support this argument, we analyzed the risk factors separately, in the T1DM group, respectively in the T2DM group. The mean age at time of T1DM diagnosis was 25.5±10.48 years; at the time of T2DM diagnosis was 51.02±8.88 years. The average duration of diabetes in patients with T1DM was 27.67 years in comparison with patients with T2DM (average duration of diabetes was 14.22 years). Diabetic retinopathy was diagnosed after 20.33 years with diabetes in patients with T1DM and after 9.28 years in patients with T2DM.

As shown in Table 2, there were no significant differences regarding the frequency of moderate NPDR between the two groups. Severe NPDR was more frequent in the T2DM group (27.69% vs. 8.33%) and PDR was more frequent in the T1DM group (33.33% vs. 18.75%).

Both groups had a poor glycemic control; the T1DM group had a mean value of HbA1c of 9.48% and 9.16% in the T2DM group. Regarding the diabetic renal disease, 60% of the patients with T1DM had renal disease, respectively 59.38% of the patients with T2DM. The lipid profile (HDL-cholesterol and triglyceride levels) brought differences between the two groups: 91.67% of the patients with T1DM achieved lipid targets for both HDL cholesterol and triglycerides (they used only statin based therapy). In the T2DM group only 49.18% had triglycerides levels under 150 mg/dl (17.5% used a combined statin/fibrate therapy, 12.5% used a fibrate based therapy).

Smoking at diabetes diagnosis was more frequent among T1DM patients (66.67% compared to 9.52%), also anemia (27.27% compared to 16.67%). Hypertension instead was more frequent among T2DM patients (88.06% compared to 50%).

The optimal glycemic target (HbA1c<7%) was achieved by 11.63% of participants with T2DM, but none of the subjects with T1DM reached it. Given the existence of diabetic chronic complications and the duration of diabetes, we considered that achieving an HbA1c<7.5% is an acceptable objective (18.18% of the subjects with T1DM, respectively 25.58% of the subjects with T2DM reached this target).

Analyzing the data of the whole group, we found a moderate positive correlation between anemia (r=0.42) and progression of diabetic retinopathy, respectively a weak correlation for smoking status at diabetes diagnosis (r=0.32), presence of hypertension (r=0.22), duration of diabetes (r=0.15) and progression of diabetic retinopathy. A strong correlation with diabetic retinopathy progression was observed for hypertension (r=0.75) and a moderate correlation for anemia (r=0.54) and diabetes duration (r=0.44) in patients with T1DM. In the T2DM group, smoking at diabetes diagnosis (r=0.54) correlated moderately with DR progression. The other correlations made (total cholesterol, triglycerides, diabetes control and coexistence of diabetic renal disease) were not statistically significant.

Discussions

In the management of DR, special attention is needed for the modifiable risk factors – such

as the glycemic control, hypertension, and lipids. Better glycemic control reduces risks of microvascular complications. Improved HbA1c levels result in benefit of reducing progression of DR in both T1DM and T2DM and also offer long-lasting protective effect due to metabolic memory [4]. Prospective randomized trials demonstrated the role of near-normal glycemia in prevention and/or delaying the onset and progression of retinopathy. In this study, the mean HbA1c value was 9.22% and only 25% of patients achieved an adequate glycemic control (below 7.5%).

The significance of glycemic control as a major risk factor for DR was emphasized in all guidelines through the acknowledgement of the landmark studies, the Diabetes Control and Complications Trial (DCCT) in T1DM and the United Kingdom Prospective Diabetes Study (UKPDS) in T2DM. The results of DCCT demonstrated that over a 6.5-year follow-up, intensive glycemic control compared with conventional treatment was associated with reduction in any DR by 76% and progression of DR by 54%. Similarly, in the UKPDS, the investigators demonstrated that intensive treatment reduced the development of any DR by 25%, furthermore, this was associated with a 29% reduction in progression to requirement of laser photocoagulation in the intensive group compared with conventional treatment [5]. Furthermore, improved control of hypertension in the UKPDS reduced progression of diabetic retinopathy by 34% [6]. In this study, the risk of microvascular complications in T2DM was shown to be associated independently and additively with hyperglycemia and hypertension, with risk reductions of 37% per 1% decrement in HbA1C and 11% per 10 mm Hg decrease in systolic blood pressure [6,7].

A better blood pressure control in diabetic patients reduces progression of DR; hence, a personalized blood pressure target should be set, which is adjusted for the severity of retinopathy. Antihypertensive medication with renin–angiotensin system blockade has a preventive effect on DR in T1DM and protective therapeutic effect on progression of retinopathy in T2DM [4].

In our study, 50% of patients with T1DM and 88.06% of patients with T2DM were diagnosed with hypertension. This high prevalence of hypertension constrains us to follow guideline recommendations regarding proper management of hypertension.

Patients with combined dyslipidemia, but not familial hypercholesterolemia, have an increased incidence of retinal abnormalities. This suggests that elevated cholesterol and triglycerides may be implicated in the development of retinovascular lesions occurring in diabetic retinopathy (for example, haemorrhage and cotton-wool spots) [8]. Evidence from observational studies has also supported a link between serum lipids and diabetic eye disease. Elevated total and low-density lipoprotein (LDL) cholesterol levels, and triglycerides were associated with progression of retinopathy, proliferative retinopathy, and the development of macular edema while negative association with HDL cholesterol was observed [9].

Lipid lowering may be another approach to reduce DR endpoints, particularly for macula edema and exudation. The possibility of an effect of statins has been investigated over the last 10 years with early encouraging results in small studies of macular edema and exudates. Recent data suggests that statins have modest protective effect but fenofibrate may have additional beneficial effect independent of lipid levels [10].

Two recent studies have found that addition of fenofibrate either to treatment naïve or to

statin-treated T2DM patients reduces the risk of diabetic macular edema, for laser treatment, or for progression of retinopathy. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, the protective effect was independent from lipid lowering. In the FIELD study, fenofibrate (200 mg/day) reduced the requirements for laser therapy and prevented disease progression in patients with pre-existing DR [10,11]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study, fenofibrate (160 mg daily) associated with simvastatin resulted in a 40% reduction in the odds of retinopathy progressing over 4 years, compared with simvastatin alone. It seems that fenofibrate is effective in preventing progression of established DR in T2DM and should be considered for patients with pre-proliferative diabetic retinopathy and/or diabetic maculopathy, particularly in those with macular edema requiring laser [7].

Lipid deposition in diabetic macular edema is more likely to occur in T2DM patients with hyperlipidemia while lipid variations within the normal range are associated with retinopathy development in T1DM [3]. The same findings were observed also in our study: 91.67% of patients with T1DM had HDL cholesterol and TG levels in target, but only 49.18% of patients with T2DM had triglycerides levels below 150mg/dl. In this evaluation, fenofibrate was administered in a small proportion: 14.29% of patients received combined therapy (statin and fibrate) and 10.2% only fibrates.

At the end of the ACCORD Eye study, the rates of progression of diabetic retinopathy were significantly reduced in the intensive glycemic control group (HbA1c<6%) and in the fenofibrate group (simvastatin 20 or 40 mg daily with the addition of fenofibrate 160 mg/day). A surprising result of the study was the failure to demonstrate a significant effect of intensive blood pressure control (SBP<120 mmHg) on the progression of retinopathy [7]. It is possible that the median systolic pressure of 133 mm Hg in the non-intensive treatment group was an effective level for preventing progression or that the duration of follow-up was insufficient [11].

We should mention that our study has several limitations. During the period of our study (1st of December 2013 - the 31st of May 2014) we included 93 patients with DR, but only 79 patients were eligible for our statistical analysis. 14 patients were excluded because of inadherence to regular medical checks or lack of biochemical results. Given the relative small number of subjects (12 patients with T1DM and 67 patients with T2DM), we couldn`t elaborate decisive conclusions. Our findings should be carefully interpreted due to the small sample size and unidentified risks of bias.

Conclusions

Available evidence suggests that achievement of recommended targets for HbA1c and blood pressure ameliorates but does not eliminate the risk of diabetic retinopathy, suggesting the need to target other potential risk factors that may be involved in the pathogenesis of diabetic retinopathy. It is therefore vital that other therapeutic targets are considered for potential benefit in the treatment and prevention of diabetic retinopathy.

In this study, patients with T1DM had longer disease duration, and retinopathy was diagnosed after a longer evolution of diabetes, compared to patients with T2DM. Surprisingly, glycemic goals were achieved in a small number of patients in both groups. In our study the only risk factor moderately correlated with DR progression in the whole group was anemia. Smoking status at diabetes diagnosis was associated with retinopathy progression in

patients with T2DM, and hypertension, anemia and diabetes duration in patients with T1DM.

The therapeutic approach of all ophthalmologists, diabetologists, and general practitioners seeing patients with DR should be that good control of blood glucose, blood pressure, and plasma lipids represent essential components of modern medical management. Patients should be given appropriate advice not only at the time of diagnosis of diabetes, but also as soon as retinopathy is first diagnosed. Better outcomes follow good glycemic control early in the course of the diabetes, but it is rarely too late to show benefit from improved control.

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