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Risk Factors and Severity of Diabetic Retinopathy in Maramureş

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Abstract:
Aims: We looked for the factors which can be adjust in order to reduce the frequency and severity of diabetic retinopathy in Maramureş County, Romania.
Methods: We done a cross-sectional study of 1269 persons with diabetes mellitus registered in the healthcare system in Maramureş. The signs of diabetic retinopathy were ascertained from retinal digital photographs. We analyzed different parameters: demographics (age, gender, smoking status, alcohol use, living areas, socioeconomic status); physical measurements (body mass index BMI, abdominal circumference); laboratory measurements (glycemic control, lipid profile, the degree of proteinuria) diabetes characteristics (duration, type, other complications) and characteristics of comorbid diseases.
Results: The total number of patients with retinopathy was 246. From these 94 (38.2%) have mild non proliferative diabetic retinopathy (NPDR) 78 (31.7%) have moderate NPDR, 52 (21.1%) have severe NPDR and 22 (9.0%) have proliferative diabetic retinopathy (PDR). Among our patients 3.2% had maculopathy (0.6% mild, 0.6% moderate and 2.0% severe). The risk factors associated with severity of retinopahy were: diabetes duration (p=0.000), HbA1c (p=0.005), presence of nephropathy (p=0.004), presence of polineuropathy (p=0.002). Risk factors associated with severity of maculopathy was presence of nephropathy (p=0.000).
Conclusions: A positive correlation between diabetes duration and diabetes control and severity of retinopathy was found. Severity of retinopathy was higher in the presence of nephropathy and polineuropathy. Severity of maculopathy was higher in the presence of nefropathy.

Keywords: Diabetes; Retinopathy; Severity; Risk factors.

Introduction

There is an enormous increase in the worldwide prevalence of diabetes. It was estimated that more than 250 people around the world have diabetes and it is expected to rise to 380 million within 20 years [1]. An individual's risk is defined by the presence of both genetic and environmental factors. The diabetic retinopathy is the most frequent complication of this burden "epidemic disease".

UKPDS [2], a landmark study in type 2 diabetes, and similar DCCT [3], a remarkable study in type 1 diabetes established the importance of blood glucose control and blood pressure control in reducing the risk of diabetic retinopathy. This established that for a 1% decrement in HbA1c a 31% lower reduction of retinopathy [3]. Similar findings came from Steno-2 Study [4]. Lipid-lowering agents are widely associated in this disease [5]. While hard exudates and macular oedema are often associated with high lipid levels, lipid-lowering agents may be a therapeutic option for the treatment of this complication [6]. Any improvement in management of this disease has a major contribution in reduction of microvascular complications.

Therefore we looked for the factors which can be adjust in order to reduce the frequency and severity of diabetic retinopathy. There are few data about our patients, the patient in Maramureş County, the northeast part of Romania.

Material and Method

All individuals with diabetes registered in the county diabetes register in the region of Maramures at the end of the year 2007 were included in the study. We analysed retrospective the hospital documents, individual records and any other medical notes. All individuals gave oral informed consent for to use their dates. The study followed the recommendations of the Declaration of Helsinki.

Baseline variables

Variables: age, gender, cigarette smoking (present or absent), alcohol consumption (never, occasionally, chronic), areas (urban or rural), socioeconomic status (good, medium, poor) were obtained from the hospital records or any other medical notes.

Diabetes and its complications data (as type, duration, medications, complications (peripheral neuropathy- presence or absence; autonomic neuropathy - presence or absence, diabetic nephropathy - presence or absence; peripheral vascular disease - presence or absence)) were obtained from the hospital records.

Concomitant disease: presence or absence of hypertension and other cardiovascular diseases (heart attacks, cerebrovascular disease, rheumatic heart disease, congenital heart disease, heart failure), hyperlipidemia, any other concomitant disease were obtained from the hospital records (steatohepatitis, hypothyroidism, hyperthyroidism, rheumatic disease etc).

Physical measurement: height without shoes (in m), weight in light clothing (in kg) and waist circumference (in cm). Body mass index (BMI) was calculated: weight(kg)/height^2 (m^2). Laboratory measurements: Glycosylated hemoglobin (HbA1c) (%) (normal < 7%), total cholesterol (mg/dl) â(normal < 180 mg/dl), HDL-cholesterol (mg/dl) (normal HDL > 40 mg/dl in men and >50 mg/dl in women) , triglycerides (mg/dl) (normal < 150mg/dl) from fasting blood samples measured in local laboratories. Total cholesterol was measured by an enzymatic colorimetric cholesterolesterase method, triglycerides were measured by an enzymatic colorimetric glycerophosphatoxidase method and HDL was measured by direct enzymatic determination (analyser ACCENT 300).

Kidney function was assessed by calculating the estimated Glomerular Filtration Rate (GFR) using Modification of Diet in Renal Disease (MDRD). Study equation GFR (mL/min/1.73m2)=175 × (serum creatinine) - 1.154 × (Age) - 0.203 × (0.742 if female) × (1.212 if African American) [7]. We measured the degree of proteinuria and estimate diabetic nephropathy: microalbuminuria (urinary albumin excretion rate of 30-300 mg/24) for incipient nephropathy and macroalbuminuria (urinary albumin excretion more than 300 mg/24 h). It was used colorimetric methods by pyrogallol (analyser ACCENT 300).

Retinal digital photography (auto fundus camera Nidek AFC-210, CE marked) was performed at the end of the examination after medical dilatation of the pupil. We used Standard Internal Fixation, with three positions, the center of the captured image being selected among the macula, the papilla and the midpoint between the macula and papilla. Each of the six digital photographs was graded by greatest degree in any field for the macula and retina separately. Overall retinopathy and maculopathy levels were assessed based on the International Clinical Diabetic Retinopathy and Diabetic Macula Edema Disease Severity Scale [8] for each patient based on the grading score of the worse eye: none, non proliferative diabetic retinopathy (NPDR) (mild, moderate, severe) and proliferative diabetic retinopathy (PDR). In addition, the presence and severity of maculopathy (none, mild, moderate or severe) was identified and recorded. In some unclear or severe situations, we referred the patients to an ophthalmologist for further evaluation and treatment.

Inclusion Criteria: pacients with diabetes mellitus registered in Diabetes Center from Maramureş County. We excluded patients with history of laser treatment, patients with cataract or other

diseases which may affect the quality of digital photography, patients with severe mental diseases, patients whose medical records didn't contain all the dates describe above.

Statistics

The ordered multinomial logit model was used in order to evaluate the possibility of having diabetic retinopathy in relation to the risk factors: diabetes type, diabetes duration, HbA1c, cholesterol, triglycerides, HDL, nephropathy, polineuropathy, peripheral vascular disease hyperlipidemia, cardiovascular disease, hypertension, BMI, abdominal circumference, alcohol, smoke, age, gender, medium, socioeconomic conditions. For these estimations, we used STATA software package version 9.1.

Results

From a total of 12917 registered patients with diabetes only 1269 were available for analysis (the rest were excluded because we did not have all the dates for analyses as mentioned above). The sample was representative, the prevalence of the retinopathy having a confidence interval of $\pm 2.1\%$ for a 0.05 *p*-value. The results of the logit model in analysis of risk factors for diabetic retinopathy is presented in Table 1 and for maculopathy in Table 2.

Table 1. Risk factors for diabetic retinopathy types

	Diabetic retinopathy type (ordered multinomial logit model)	
	coef.	*p*-value
Diabetes type	-0.033272	0.935
Diabetes duration	0.101247	0.000***
HbA1c	0.117456	0.005***
Cholesterol	-0.000688	0.724
Triglycerides	-0.001066	0.135
HDL	0.008627	0.113
Nephropathy	0.829131	0.004***
Hyperlipidemia	-0.033934	0.718
Cardiovascular disease	-0.397895	0.053*
Hipertension	0.350344	0.065
BMI	-0.058148	0.009***
Abdominal circumferince	0.016371	0.077
Alchool	-0.026031	0.845
Smoke	-0.019123	0.930
Age	-0.000014	0.999
Gender	0.110966	0.512
Medium	0.291435	0.070*
Socioeconomic conditions	0.046626	0.693
Polineuropathy	0.644894	0.002***
Peripheral vascular disease	-0.784258	0.296

N=1269, Pseudo $R^2 = 0.0692$

LR $\chi^2(20)=141.80$ ($p<0.001$)

*significant at 10%, **significant at 5%, ***significant at 1%

The total number of patients with retinopathy was 246. From these 94 (38.2%) have mild NPDR, 78 (31.7%) have moderate NPDR, 52 (21.1%) have severe NPDR and 22 (9.0%) have PDR. Among our patients 3.2% had maculopathy (0.6% mild, 0.6% moderate and 2.0% severe). The prevalence of retinopathy in relation with diabetes duration was presented in Table 3.

Regarding maculopathy in relation with diabetes duration we found the results presented in Table 4.

The prevalence disbtribution of retinopathy in relation with HBA1c is presented in Table 5.

Table 2. Risk factors for diabetic maculopathy types

	Diabetic maculopathy type (ordered multinomial logit model)	
	coef.	*p*-value
Diabetes type	0.087442	0.912
Diabetes duration	0.061536	0.022**
HbA1c	0.225284	0.011**
Cholesterol	0.011612	0.008***
Triglycerides	-0.004936	0.050***
HDL	0.004647	0.709
Nefropathy	1.956632	0.000***
Hiperlipidemia	-0.423629	0.332
Cardiovascular diseases	-0.304823	0.506
Hipertension	0.270929	0.541
BMI	-0.058140	0.301
Abdominal circumferince	-0.011453	0.592
Alchool	0.492044	0.097*
Smoke	-0.086044	0.861
Age	0.016946	0.420
Gender	-0.183224	0.629
Medium	0.388188	0.295
Socioeconomic conditions	0.191850	0.465
Polineuropathy	0.893494	0.029**
Peripheral vascular disease	-40.996200	0.999

N=1269, Pseudo R^2 = 0.1456

LR χ^2 (20)=62.81 (p<0.001)

*significant at 10%, **significant at 5%, ***significant at 1%

Table 3. The prevalence of retinopathy in relation with diabetes duration (%)

		Retinopathy type (%)				
		NPDR mild	NPDR moderate	NPDR severe	PDR	Total
Diabetes duration (years)	below 5	4.6	3.9	3.0	0.9	12.4
	from 5 to 10	9.7	6.4	4.3	1.8	22.2
	from 10 to 15	11.5	14.2	7.1	4.4	37.2
	over 15	22.2	30.6	11.1	6.3	70.2

Table 4. The prevalence of maculopathy in relation with diabetes duration (%)

		Maculopathy type (%)			
		mild	moderate	Severe	total
Diabetes duration (years)	below 5	0.65	0.79	1.57	3.01
	from 5 to 10	0.61	0.61	1.82	3.04
	from 10 to 15	0.88	0.00	2.65	3.53
	over 15	0.00	0.00	4.76	4.76

Table 5. The prevalence of retinopathy in relation with HBA1c

HbA1c (values %)	DR type (%)				
	NPDR mild	NPDR moderate	NPDR severe	PDR	DR total
under 7	5.4	4.5	2.9	1.0	13.8
from 7 to 9	8.2	7.6	5.3	1.9	23.0
over 9	11.9	7.9	5.1	3.4	28.3

Discussion

In a population-based cohort followed after WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy, among US adults after 4-14 years' diabetes duration during the period 1990-2002, the authors also observed less severe retinopathy than expected, with a very low prevalence of moderate–severe nonproliferative retinopathy (10 percent) and only one person with treated or proliferative retinopathy by 14 years' duration. In contrast, at the baseline evaluation in WESDR, moderate–severe nonproliferative retinopathy was found in 35 percent of persons and proliferative retinopathy in 25 percent of persons at 13–14 years' duration [9]. Again, the more recent population-based studies in Sweden and Finland reported lower levels of advanced nonproliferative or preproliferative retinopathy, ranging from approximately 2 percent to 5 percent [10,11]. In these countries the improvement in treatment was the principal argument for these decreasing in prevalence and severity.

In a comparative study between France, Italy, Spain, and United Kingdom the authors find that the proportion of diagnosed DR ranged from 10.3% (95% CI [6.7%-14.0%]) in Spain to 19.6% (95% CI = [16.0%-23.1%]) in the United Kingdom and consistently across countries, mild NPDR was the most common severity level of diagnosed DR. PDR ranged from 19.7% (France) to 31.5% (UK). Diabetic macular edema was reported in approximately 10% of patients [12].

In our region the prevalence of moderate and severe DR was higher but the prevalence of PDR was lower. In our region the most prevalent disease is also mild NPDR. We can debate about the fact that in our country there is no screening program for DR. There are many patients who did not ask for medical advice or did not respect their treatment or even refused to go to specialists in diabetes. There are few ophthalmologists trained in diabetic retinopathy and unfortunately they are only in universities.

Glycosylated hemoglobin was also strongly related to the risk of retinopathy, and the association was stronger at longer durations. For a 1 percent increase in mean glycosylated hemoglobin level, at 4 years, the hazard of retinopathy increased by 14%, and at 7 and 9 years, the hazards increased by 44% and 42%, respectively [9].

In Chennai Urban Rural Epidemiology Study, ordinal logistic regression analysis 1715 subjects showed that male gender ($P = 0.041$), duration of diabetes ($P < 0.0001$), glycated haemoglobin (HbA(1c); $P < 0.0001$), macroalbuminuria ($P = 0.0002$) and insulin therapy ($P = 0.0001$) were significantly associated with severity of DR [13]. We also recognize that HbA1c is associated with severity of DR.

A study done in Spain with 208 patients find that patients with long standing diabetes have a high risk to develop diabetic maculopathy, but other closely-related risk factors are hypertension, hyperglycemia, lipids, tobacco smoking and renal status [14]. In a small study with only 38 patients the author noticed that patients with diabetic maculopathy had significantly higher values of total lipids, triglycerides, total cholesterol. There were no statistically significant differences for HDL [15]. Interesting in another study the authors find that the regression of hard exudates was most likely due to the aggressive lipid lowering [16]. In our study we have a small number of patients with diabetic maculopathy and the relation between maculopathy and cholesterol and triglycerides is uncertain. We need much more patients with maculopathy for significant and interpretable dates.

Conclusions

A positive correlation between diabetes duration and diabetes control and severity of retinopathy was found. Severity of retinopathy was higher in the presence of nephropathy and polineuropathy. Severity of maculopathy was higher in the presence of nefropathy.

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