PREVALENCE OF DIABETIC RETINOPATHY IN NEWLY DIAGNOSED TYPE 2 DIABETIC PATIENTS IN ISFAHAN, IRAN

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Abstract

Background. Retinopathy is a common complication of diabetes and strongly related to the duration of the disease and the quality of its management. Despite this relationship, some studies have reported the prevalence of diabetic retinopathy at diagnosis to be 5-30%.

Aim. To investigate the prevalence of retinopathy in patients with newly diagnosed type 2 diabetes and its relation to some association factors in Isfahan, Iran.

Methods. During 2001-2004, all newly diagnosed type 2 diabetics (n= 710) attending Isfahan Endocrine and Metabolism Research Center, were enrolled, by consecutive patient selection. Everybody accepted our invitation. The patients were examined by an internist and then by an ophthalmologist for retinopathy. Fasting plasma glucose, glycosylated hemoglobin, lipid profile, and 24-hour urinary albumin and creatinine concentrations were measured.

Results. Of 710 patients, 286 were male. Mean age of the patients was 48.8(9.8) years (31-72 years) and median of diabetes duration was 6 months (0.5-12 months), respectively. Nine percent of patients (CI95%: 7-11) [(9.8% of men (CI95%: 6-13) and 8.5% of women (CI95%: 6-11)] had retinopathy (Odds ratio= 0.85, CI95%: 0.51-1.43, P= 0.5). In the final analysis using logistic regression test, body mass index (OR= 0.9, CI 95%: 0.8-1, P= 0.01), diastolic hypertension (OR= 3.9, CI 95%: 1.33-11.7, P= 0.01) and 24-hour urinary albumin concentration (OR= 1.005, CI 95%: 1-1.01, P= 0.01) were identified as association factors for retinopathy.

Conclusions. Retinopathy was moderately prevalent in our patients.

Key words: prevalence, diabetes mellitus type 2, diabetic retinopathy, association factors.

INTRODUCTION

Retinopathy is an important complication of diabetes and the most important cause of blindness in the active population group (1). Retinopathy is strongly

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correlated with the duration of diabetes. In the Wisconsin epidemiologic study III (2), the prevalence of diabetic retinopathy was 15.2% at the time of diagnosis, 28.8% in diabetics with less than 5 years duration of disease, and 77.8% in those with 15 years of diabetes duration. The prevalence of retinopathy in patients with newly diagnosed diabetes has been reported with a wide range, from 5% to more than 30% in different studies (3-6). Several investigations have implicated some risk factors such as uncontrolled glycemia, hypertension, hyperlipidemia, albuminuria, and smoking in the development of retinopathy (7-10). The severity and progression of diabetic retinopathy is also shown to be more aggressive in those patients with retinopathy at the time of diagnosis (11,12).

This study was conducted to investigate the prevalence of retinopathy and its relationship with the above mentioned association factors in the population of newly diagnosed type 2 diabetes in Isfahan, a centrally located city in Iran.

PATIENTS AND METHODS

This cross-sectional study was conducted on 710 consecutive patients with newly diagnosed type 2 diabetes presenting to Isfahan Endocrine and Metabolism Research Center (IEMRC) in 2001-2004. All patients accepted our invitation. Newly diagnosed type 2 diabetics defined as patients with diagnosis of diabetes, which has been done within one year of the study. Diagnosis of diabetes was made according to the American diabetes association (ADA) criteria, using fasting plasma glucose (FPG) measurement, or glucose tolerance test (GTT) (13).

Demographic data and information about date of diabetes diagnosis and smoking were obtained. Height and weight were measured barefoot and in light clothing, by an internist working at IEMRC. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m). Patients with BMI less than 25 kg/m^2, between 25-29.9 kg/m^2, and BMI 30 kg/m^2 were considered as normal, overweight, and obese, respectively (14). Blood pressure was measured on the right arm, in sitting position after 15 minutes of rest using a standard mercury sphygmomanometer. The mean of two readings, five minutes apart, was recorded as the patient's blood pressure. Systolic blood pressure 130 mmHg or diastolic blood pressure 80 mmHg was considered as hypertension according to ADA criteria (15). Patients who were on antihypertensive medications were also considered to be hypertensive. In all patients FPG, 2-hour postprandial plasma glucose (2hpp), glycosylated hemoglobin (HbA1C), plasma lipid profile, and 24-hour urinary albumin and creatinine concentrations were measured. Plasma glucose was measured with the glucose oxidase method. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride were measured using Pars Azmun and Chem Enzyme kits. Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula (16).

HbA1C was measured using a DSS machine via the ion exchange

chromatography method. Direct and indirect ophthalmoscopy was performed after pupil dilation by an ophthalmologist to examine the patients for retinopathy. Retinopathy was classified as follows: *a) mild retinopathy*: any sign of microaneurysm, punctate or linear retinal hemorrhage or hard exudate, b) *moderate to severe retinopathy*: the above findings together with cotton-wool spots, venous beading, and microvascular lesions in the retina; the latter types have been described in the results as nonproliferative or background retinopathy; c) *proliferative retinopathy*: neovascular and fibrous tissue formation in the retina, intravitreal or preretinal hemorrhage, d) *maculopathy*: macular edema or ischemic maculopathy. Patients with corneal opacity, advanced cataract, or history of retinal lesions were excluded. 24-hour urinary albumin was measured with an autoanalyzer using Randox kits. 24-hour urinary albumin levels less than 30 mg, 30-300 mg, and more than 300 mg were considered as normal, microalbuminuria and macroalbuminuria (American Diabetes Association, 2003). Urinary samples were assayed for albuminuria when there was no evidence of infection or hematuria in urinalysis and the specific gravity of the sample was greater than 1015. When the 24-hour urinary albumin concentration was more than 30 mg, another sample would be taken and analyzed at least two months later. The presence of more than 30 mg of albumin in the second sample would confirm abnormal urinary albumin excretion.

Smoking was defined according to WHO protocols. In this study, smokers were defined as individuals who regularly smoked at least one cigarette daily (daily smokers) (14).

Statistical analysis

Quantitative data with normal distribution were compared using Student's t-test and expressed as mean and standard deviation (SD). Those data which were not normally distributed were analyzed by Mann-Whitney test and expressed as median (range). It was included the comparison between males and females and those with and without retinopathy. Qualitative variables were compared using Chi-square test. Covariates entered in logistic regression test were age, sex, body mass index, systolic hypertension, diastolic hypertension, fasting plasma glucose, 2hpp, $HbA_{1C,}$ cholesterol, triglyceride (TG), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, 24 hour urinary albumin (its logarithmic form) and albuminuria to determine their relationship with retinopathy. As the distribution of 24 hour urinary albumin concentration was not normally distributed, we entered its logarithmic form to logistic regression test. Data were analyzed using SPSS software version 10. P-values less than 0.05 were considered statistically significant. This study was approved by the Research Ethics Committee of IEMRC and informed consent was obtained from all participants.

RESULTS

Of 710 studied patients, 286 (40.3%) were male and 424 (59.7%) were female.

Table 1. Mean (SD) or median (range) or number (%) of characteristics of patients with newly diagnosed type 2 diabetes

	All (n=710)	Male (n=286)	Female (n=424)	P value
Duration of diabetes(median, range) (months)	6 (0.5-12)	6 (0.5-12)	6 (0.5-12)	0.1
Body mass index (kg/m2)	28.6 (4.5)	27.3 (3.8)	29.5 (4.7)	0.001
Fasting plasma glucose (mmol/L)	10.5 (2.7)	11.1(3.3)	10.1 (3.2)	0.001
2-hour postprandial glucose (mmol/L)	14.1 (3.1)	14.9 (4.3)	13.5 (4.1)	0.001
$HbA1_C$ (%)	9.5 (2.3)	9.9 (2.3)	9.3 (2.2)	0.001
Total cholesterol (mmol/L)	5.9 (0.8)	5.7 (1.5)	6.1 (1.3)	0.001
Low-density lipoprotein cholesterol (mmol/L)	3.3 (0.9)	3.2 (0.9)	3.5 (0.9)	0.001
High-density lipoprotein cholesterol (mmol/L)	1.1 (0.2)	1.0 (0.2)	1.2 (0.2)	0.001
Triglycerides (mmol/L)	2.8 (0.9)	2.9 (1.9)	2.7 (1.4)	0.2
Systolic blood pressure (mm Hg)	124 (16.2)	122 (15.4)	125 (16.7)	0.004
Diastolic blood pressure (mm Hg)	73 (13.6)	72 (12.9)	75 (13.7)	0.004
24-hour urinary albumin (mg)	58 (9-400)	74(12-400)	50(9-382)	0.001
Retinopathy (n (%))	64 (9%)	28 (9.8%)	36 (8.5%)	0.5

The patients had a mean age of 48.8(9.8) years [49.9(9.8) years in men and 47(9.7) years in women], with no statistically significant difference between the two groups. Median (range) duration of diabetes was 6 (0.5-12) months. Table 1 shows the characteristics of the patients.

The prevalence of retinopathy was 9% in all patients (CI 95%: 7-11) [(9.8% of men (CI95%: 6-13) and 8.5% of women (CI 95%: 6-11)] (Odds ratio= 0.85, CI95%: 0.51-1.43, P= 0.5). Fifty-three patients (7.5%) had mild retinopathy and 11 patients (1.5%) had moderate to severe retinopathy; both were considered as having background retinopathy in the final analysis. We observed no cases of macular edema and/or proliferative diabetic retinopathy. HbA_{1c} in males was higher than in females (Table 1).

Patients with and without retinopathy were not different in mean of FPG, 2hpp, HBA_{1C}, and cholesterol, TG, HDL-c and LDL-c. However, mean age, BMI, systolic and diastolic blood pressure and median of 24-hour urinary albumin in patients with retinopathy were higher than in those without (Table 2). Median duration of diabetes was not different in patients with [8(0.5-12) months] and without [6(0.5-12) months] retinopathy.

The prevalence of retinopathy increased with the decrease in BMI and the presence of hypertension. Final analysis was performed using logistic regression. After matching for other covariates mentioned in the method section, the independent retinopathy-related variables were BMI (OR= 0.9, CI 95%: 0.8-1, P= 0.01), diastolic hypertension (OR= 3.9, CI 95%: 1.33-11.7, P= 0.01) and 24 hour

Table 2. Comparison of mean (SD) or median (range) of quantitative variables studied in patients with newly diagnosed type 2 diabetes with and without retinopathy

	Without retinopathy (n= 646)	With retinopathy (n= 64)	P value
Age (years)	48.6(9.7)	51.9(10.9)	0.01
Body mass index (kg/m^2)	28.8(4.5)	26.7(3.8)	0.0001
Fasting plasma glucose (mmol/L)	10.4(3.3)	11.1(3.1)	0.1
2-hour postprandial glucose (mmol/L)	14.0(4.2)	14.8(4.1)	0.1
$HbA1_C$ (%)	9.5(2.3)	9.9(2)	0.1
Total cholesterol (mmol/L)	5.9(1.3)	6.2(1.5)	0.06
Low-density lipoprotein cholesterol (mmol/L)	3.3(0.9)	3.6(0.8)	0.07
High-density lipoprotein cholesterol (mmol/L)	1.1(0.2)	1.1(0.2)	0.7
Triglycerides (mmol/L)	2.8(1.6)	2.9(1.6)	0.7
Systolic blood pressure (mm Hg)	123.2(15.8)	130.6(18.4)	0.0001
Diastolic blood pressure (mm Hg)	72.8(13.2)	79.3(13.9)	0.0001
24-hour urinary albumin (mg)	56 (9-400)	103 (12-400)	0.001

urinary albumin concentration (OR= 1.005, CI 95%: 1-1.01, P= 0.01). Using multiple logistic regression analysis, to adjust for FPG, 2hpp glucose and HbA_{1c}, we found that BMI was an independent associated risk variable for retinopathy. P-values were 0.335, 0.336 and 0.36, respectively, for the above mentioned variables.

DISCUSSION

In this study, the prevalence of retinopathy in patients with less than 1 year duration of diabetes was 9%. In our study, about 60% of patients are females. Women in all parts of our society stick more to their treatment than men. It is not exclusive to diabetes. It can explain why women are included in the study more, while the method of sampling was consecutive to patient selection.

Hypertension and albuminuria were the important determinants of retinopathy. Studies in different parts of the world have reported a different prevalence of retinopathy in patients with newly diagnosed type 2 diabetes.

The prevalence of retinopathy at the time of diagnosis of diabetes was reported at 21% and 28.3% in the studies conducted in China (17) and Taiwan (18), respectively. Two studies in India reported prevalence of 6.7% and 7.3% and a study in Australia and another in the US reported prevalence rates of 6.2% and 10.2%, respectively (19-22). In the UKPDS study (8), which used advanced methods such as photography in conjunction with ophthalmoscopy, 39% of males

and 35% of females with type 2 diabetes had microaneurysm in at least one eye; 8% of men and 4% of women had cotton wool spots or microvascular lesions.

The prevalence of retinopathy in diabetic patients with a duration of diabetes more than 12 years was 40.7% in Isfahan, Iran (23). The low prevalence of retinopathy observed in the current study compared with some previous reports may be due to racial, demographic factors. However, the methods of detecting retinopathy and diagnosing diabetes used in different studies may be the most important reasons. For example, the prevalence of retinopathy detected by photography in conjunction with ophthalmoscopy reported in UKPDS study was rather high (8). The differences between findings of those studies, which have reported a higher prevalence of retinopathy, using a similar method of detection, are most likely due to longstanding undiagnosed diabetes.

In a study, the presence of diabetes was reported 4-7 years before its diagnosis (24). In another study in Hong Kong, which was conducted about prevalence of retinopathy on newly diagnosed type 2 diabetes since 1990 till 1994, increasing retinopathy prevalence was reported to be 14.8%, 13%, 24.5%, 32.3% and 35.4%, in consecutive years. However, it decreased to 8.2% and 7.4% in the following two years (1995-1996) (25). This decrease may be attributed to increased public awareness, and better and earlier diagnosis of diabetes. The prevalence of retinopathy in this study was lower than in China and Taiwan (17,18).

In our study, a higher prevalence of retinopathy was observed in patients with lower BMI, and final analysis revealed a statistically significant reverse relationship between BMI and retinopathy. The relationship between retinopathy and BMI has been reported as controversial in a different population study. In a study in the United Arab Emirates, there was no statistically associated relationship between retinopathy and BMI (26). In another study in Thailand, the prevalence of retinopathy was increased with a higher body weight, and poor metabolic control and hypertension. The authors concluded that obesity affects retinopathy indirectly *via* its effect on metabolic control (27).

Just the opposite of what was reported in Thailand, there was an inverse relationship between retinopathy and BMI in the research reported by Nguyen and colleagues in Australia, similar to the present study (28). This relation was still observed after adjusting for fasting plasma glucose. Nguyen et al. concluded that BMI represents the insulin secretory function regardless of the glycemic status (28). We used multiple logistic regression analysis, adjusting for fasting plasma glucose, 2hpp glucose and HbA1c. Body mass index was an independent associated risk variable for retinopathy. It is concluded that the effect of BMI on retinopathy is independent of glycemic status.

Our study was performed on newly diagnosed type 2 diabetics. Physicians and people are aware of obesity as a risk factor of diabetes. It is supposed that people with higher BMI are screened for diabetes more frequently. However, people with lower BMI will be diagnosed late when they are symptomatic, and complications of diabetes, such as retinopathy, have already developed. Researchers have

highlighted the increased prevalence of diabetic retinopathy in patients with poor glycemic control (8, 29, 30). In this study, we observed no difference in FPG, 2hpp, and HbA_{1C} between the patients with, and those without retinopathy.

Hypertension is a common finding in type 2 diabetic patients. In "Hypertension in Diabetes Study" (HDS), 38% of patients were hypertensive (31). Some studies have referred to hypertension as the underlying etiology of retinopathy and maculopathy (32). In our study diastolic hypertension was the only strong independent retinopathy-related variable. Some studies have reported the relationship between hyperlipidemia and the prevalence of microvascular complications, including retinopathy; they have also related increased serum cholesterol to the formation of cotton wool spots (33-35). In the present study, total cholesterol, LDL and triglyceride levels were not significantly different in patients with from those without retinopathy.

Usually, microvascular complications develop concurrently throughout the body. Several studies have reported an association between retinopathy and abnormal albumin excretion (36-38). In this study, increased albumin excretion was one of the determinants of retinopathy. Some patients in this study were on antihypertensive and hyperlipidemic medication prior to the diagnosis of diabetes; hence these findings may have been underestimated. Likewise, as diet therapy and glucose-lowering medications had already been started for some patients, plasma glucose and HbA1C levels might have been controlled better. However, the relationship between retinopathy and glycemic control status may be obscured. In our study, the retina was examined by direct and indirect ophthalmoscopy after pupil dilation by an ophthalmologist. There are some limitations by using this simple way to define the existence or severity of retinopathy. When the pupil was not fully dilated, the retinal lesion at the periphery may not be detected and the reproducibility or accuracy of a single examiner would be challenged.

In conclusion, retinopathy is moderately prevalent in our patients with newly diagnosed type 2 diabetes and has a correlation with diastolic hypertension.

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