Risk factors for eye complications in patients with diabetes mellitus: development and progression

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عوامل اختطار المضاعفات العينية في السكّريين: ظهورها وتفاقمها

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خلاصة: أجريت دراسة متعددة المراكز على حالات وشواهد من أجل التعرُّف على عوامل الاختطار التي قد تؤثر في ظهور اعتلال الشبكية السكّري وفي تفاقمه، وقياس تلك العوامل كمياً. فتمت مقارنة بين 200 من السكّريين المصابين باعتلال غير تكاثري بالشبكية، وبين 400 من السكّريين الذين ليست لديهم أية مضاعفات عينية، وذلك من حيث ظهور اعتلال الشبكية السكري. كما تمت مقارنتهم بمئتين من السكّريين الذين لديهم مضاعفات عينية كبرى، من أجل دراسة تفاقم المضاعفات العينية السكرية. ولقد أظهرت النتائج أن بالإمكان اتقاء تفاقم مضاعفات العين السكرية، نظراً لأن سائر المتغيرات المؤثرة بدرجة كبيرة في عملية تفاقم المضاعفات يمكن تجنُّبها، باستثناء نمط الداء السكري.

ABSTRACT A multicentre case-control study was conducted to identify and quantify risk factors that may influence the development and progression of diabetic retinopathy. A total of 200 diabetic patients with nonproliferative retinopathy were compared with 400 diabetic patients without any eye complications with regard to the development of diabetic retinopathy. They were also compared with 200 diabetic patients with major eye complications to study the progression of diabetic eye complications. Results showed that the progression of diabetic eye complications was preventable since all the variables significantly affecting the process of progression, except type of diabetes, were avoidable.

Facteurs de risque de complications oculaires chez des patients atteints de diabète sucré: apparition et progression

RESUME Une étude cas-témoins multicentre a été réalisée pour identifier et quantifier les facteurs de risque qui peuvent influencer l'apparition et la progression de la rétinopathie diabétique. Au total, 200 diabétiques ayant une rétinopathie non proliférante ont été comparés avec 400 diabétiques n'ayant aucune complication oculaire associée à l'apparition de la rétinopathie diabétique. Ils ont également été comparés avec 200 diabétiques ayant des complications oculaires majeures afin d'étudier la progression des complications oculaires liées au diabète. Les résultats ont montré que la progression des complications oculaires diabétiques pouvait être évitée puisque toutes les variables affectant le processus de progression de manière significative, à l'exception du type de diabète, étaient évitables.

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Introduction

Diabetic retinopathy is recognized as one of the most prevalent complications of both type 1 and type 2 diabetes [*1*]. It is one of the leading causes of blindness in economically advanced countries [*2*].

Retinopathy syndromes are generally categorized as simple (nonproliferative) or proliferative. Simple retinopathy may impair vision if the lesions extend into the macular region, and may lead to serious loss of vision. Proliferative retinopathy, which is the most serious complication of diabetic ophthalmology, carries a high risk of blindness [*3*].

Epidemiological data have shown that the natural history of retinopathy is similar in both types; however, the prevalence is higher and the severity greater in people with type 1 than in those with type 2 diabetes [*4*]. The prevalence of diabetic retinopathy shows wide variations between countries. In type 1, it ranges from 14% (India) to 80% (Finland) and in type 2 it ranges from 17% in Switzerland to 52% in the United Kingdom [*5*].

Generally, development of diabetic complications is linked to metabolic control, which is determined by a variety of factors [*6,7*]. Diabetic retinopathy, in turn, may be influenced by a number of factors, including those related to the interaction between patients and health care systems. Problems related to accessibility of care, patient satisfaction, or coordination among the different health professionals involved in the care of diabetic patients can have a major impact on the accessibility of medical recommendations [*8,9*]. Factors such as age, co-morbidity, socioeconomic status and social support are equally important in determining a good compliance and adequate self-care [*10,11*].

Study of the incidence and progression of diabetic retinopathy and associated risk factors is important in the prevention of its development and the visual impairment caused by this complication [*12*]. To decrease the burden of diabetic retinopathy, it is necessary to identify factors which are most relevant in defining the risk profile of diabetic patients who are more liable to have diabetic eye complications, particularly those factors that can be considered avoidable because they are related to patient and/or doctor practices and attitudes.

Subjects and methods

This study was carried out between February and September 1998 as a case–control study in 14 outpatient clinics and diabetic centres representing health insurance companies, medical care organizations, and governmental and university hospitals in Alexandria, Egypt.

Patient identification and accrual

Patients were selected from different health sectors proportionate to the total number of diabetic patients served by these sectors. Two days per week were chosen for recruitment of patients. To avoid any imbalance in the selection of cases and controls from many different sources, which could affect the risk estimate, the same ratio of cases to controls was kept in the different outpatient clinics and diabetic centres. The purpose of the study was explained to selected patients and they all gave their informed consent to participate.

The first comparison was to assess the development of diabetic retinopathy in patients who had had type 1 or type 2 diabetes mellitus for at least 5 years with nonproliferative retinopathy. Patients were considered eligible as controls if they had had

type 1 or type 2 diabetes for at least 5 years and had never been affected by any diabetic eye complications.

The second comparison was aimed at studying the progression of diabetic retinopathy. Patients with type 1 or type 2 diabetes of at least 5 years were included as cases if they had proliferative retinopathy, maculopathy or had developed blindness within the previous 12 months. Patients with simple retinopathy recruited in the first part of the study were considered as controls in this comparison.

Measurements

Trained physicians in the chosen structures collected data by interviewing patients and by reviewing the patient medical records. All patients enrolled in the study had a 15-minute interview. Clinical data were obtained by revising medical records, including patient ophthalmic reports. Questions focused on sociodemographic data (age, sex, marital status, education and occupation), clinical data (type and duration of diabetes, co-morbidity and presence of other diabetic complications) and health-care characteristics (accessibility of clinic, self-care, social support, regularity and frequency of educational interventions received). In order to ensure uniformity of data measuring methods that relied on clinical judgement, all participating physicians were trained on data collection and the questionnaire was thoroughly tested for clarity before it was accepted.

The clinical data collected referred to each patient's current situation as well as their ability to access health services and health habits for a period of up to 5 years prior is the study. This was a period of time presumably before the development of eye complications, which was necessary in order to test the effect of these events as exposure factors.

A full ophthalmic examination, including visual acuity, anterior segment and fundus examination with fluorescein angiography, was performed to verify the ophthalmic reports of the patients. Diabetic retinopathy was classified according to a modified early treatment diabetic retinopathy study [*13*]. Patients were considered as having simple, proliferative retinopathy or blindness if one or both eyes were affected. Patients were classified as having type 1 diabetes if their age at diagnosis was < 30 years and insulin was used continuously from the time of diagnosis. Patients were considered as having type 2 diabetes if their age at diagnosis was > 30 years. Hypertension was considered uncontrolled by treatment on the basis of clinical judgement and confirmed by the presence of systolic blood pressure values ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg in the patient's records [*14*]. Similarly, patients were classified as having diabetic neuropathy on the basis of the presence of clinical symptoms and signs. A patient was considered as having symptomatic nephropathy if he or she had undergone dialysis or had had a serum creatinine level of 3 mg/dL or more. The glycaemic state of each patient referred to the last values of fasting blood glucose in the past 12 months and it was considered adequate if the arithmetic mean of these values was ≤ 5.6 mmol/L. Major limb complications included foot ulcers, claudication, gangrene, persistent ischaemic rest pain or amputation. Co-morbidity included conditions that had already been present prior to the diagnosis of diabetes (angina pectoris, hypertension, renal disease, endocrine dysfunction, dyslipidaemia and liver diseases). In the classification according to employment status, considered an indicator of socioeconomic status, a husband's employment was considered for housewives, while the last employment was considered for retired patients.

Sample size estimation

It was assumed that a hypothetical risk factor with a 33% prevalence in the ill patients and a 20% prevalence in the control population was associated with a relative risk of developing two or more complications. Considering a case–control ratio of 1:2, $\alpha = 0.05$ and $1 - \beta = 0.95$, the number of cases with nonproliferative retinopathy required for the first comparison of the study is 142. The actual sample of 200 cases thus allows for a reliable detection of risk factors with a lower prevalence in the control group or presenting a weaker association with the outcome of interest. For the second comparison, 200 cases with proliferative retinopathy were needed assuming a case–control ratio of 1:1 [*15*].

Statistical analysis

Analysis was initially carried out based on a series of univariate comparisons. In order to control simultaneously for the possible confounding effect of the variables, multiple logistic regression was used for the final analysis [*16*]. Both in univariate and multivariate analyses, the association between exposures and outcome was expressed in terms of odds ratios (OR) together with their 95% confidence intervals (95% CI).

All the explanatory variables included in the logistic model were categorized into two or more levels (R = reference category): age (years): < 50 (R), 50–70, > 70; sex: male (R), female; marital status: married (R), single, divorced/widowed; education: higher (R), secondary/preparatory, primary, read and write/illiterate; occupation: professional/managerial (R), technical/clerical, skilled worker/artisan, unskilled worker; type of diabetes: type 2 (R), type 1, type 2 insulin treated; duration of diabetes (years): < 10 (R), 10–20, > 20; glycaemic state: within normal (R), above normal; co-morbidity: no (R), yes controlled, yes uncontrolled; hypertension: no (R), yes controlled, yes uncontrolled; diabetic neuropathy: no (R), yes; major complications of lower limbs: no (R), yes; diabetic nephropathy: no (R), yes; health insured: yes (R), no; need of help to reach health-care facility: no (R), yes; self-monitoring of glycaemia: yes (R), no; regular follow-up visits: yes (R), no; compliance with diet recommendation: yes (R), no; frequency of educational interventions: regular (R), occasional, never; smoking: no (R), ex-smoker, current. Analysis was performed using *SPSS* 6.1.1.

Results

A total of 200 diabetic patients with nonproliferative retinopathy were compared with 400 control patients with no eye complications. They were also compared with 200 diabetic patients with major eye complications. The clinical, sociodemographic and health-care related characteristics associated with the development and progression of eye complications, together with the results of the univariate analyses are reported in Tables 1 to 3.

The results of the final analysis using multiple logistic regression are summarized in Table 4, from which the following results could be detected.

Development of diabetic eye complications

No significant association could be detected between the development of eye complications and age, sex, marital status, occupation or level of education.

The type of diabetes was associated with the development of eye complications. Patients with type 1 had an increased risk as compared to type 2 diabetic patients (OR =

3.6, CI: 1.7–7.2), while those with type 2 insulin-treated had the same probability. Patients with diabetes of 10–20 years had a 90% increased risk of developing eye complications (OR = 1.9, CI: 1.4–2.5), and those with diabetes lasting more than 20 years had a 70% higher risk (OR = 1.7, CI: 1.1–3.7) than patients with diabetes of less than 10 years. Patients who showed poor glycaemic control were at a 20% higher risk (OR = 1.2, CI: 1.1–1.5). The presence of uncontrolled hypertension was also significantly associated with an increased risk of eye complications (OR = 1.6, CI: 1.2–2.2). Patients suffering from symptomatic diabetic neuropathy or nephropathy were more likely to develop eye complications (OR = 2.0, CI: 1.3–3.1 and OR = 2.9, CI: 1.8–5.2). Co-morbidity or diabetic lower limb complications were not independently associated with the outcome.

Table 1 **Sociodemographic characteristics of 200 diabetic patients with nonproliferative retinopathy (NPR), 200 diabetic patients with proliferative retinopathy (PR) and 400 diabetic patients without eye complications**

Sociodemographic characteristic	Without eye complications		NPR		PR		OR (95% CI)	
	No.	%	No.	%	No.	%	Without eye complications versus NPR	NPR versus PR
Age (years)								
< 50[R]	109	27.2	41	20.5	40	20.0	1	1
50–70	199	49.8	99	49.5	98	49.0	1.3(0.8–2.1)	1.1(1.0–1.8)
> 70	92	23.0	60	30.0	62	31.0	1.7(1.0–2.9)	1.1(0.6–1.9)
Sex								
Male[R]	205	51.5	94	47.0	91	45.5	1	1
Female	195	48.5	106	53.0	109	54.5	1.2(0.8–1.2)	1.1(0.7–1.6)
Marital status								
Married[R]	278	69.5	140	70.0	123	61.5	1	1
Single	14	3.5	7	3.5	8	4.0	1.0(0.7–1.5)	1.3(0.4–4.1)
Divorced/widowed	108	27.0	53	26.5	69	34.5	1.0(0.7–1.5)	1.5(1.0–2.3)
Education								
Higher[R]	64	16.0	31	15.5	18	9.0	1	1
Secondary/preparatory	112	28.0	55	27.5	45	22.5	1.0(0.6–1.8)	1.4(0.7–3.0)
Primary	36	9.0	22	11.0	22	11.0	1.3(0.6–2.6)	1.7(0.7–4.3)
Illiterate/read and write	188	47.0	92	46.0	115	57.5	1.1(0.6–1.7)	2.2(1.1–4.3)
Occupation								
Professional/managerial[R]	45	11.2	21	10.5	19	9.5	1	1
Technical/clerical	60	15.0	31	15.5	32	16.0	1.1(0.5–2.3)	1.2(0.5–2.7)
Skilled worker/artisan	170	42.5	84	42.0	86	43.0	1.1(0.6–2.0)	1.1(0.5–2.4)
Unskilled worker	125	31.3	64	32.0	63	31.5	1.1(0.6–2.1)	1.0(0.5–2.4)

[R] = reference category
OR = odds ratio
CI = confidence interval

No significant association could be detected between being health insured, accessibility of the health facility, educational intervention, self-monitoring of blood glucose, regularity of follow-up visits, compliance with diet recommendations and smoking, and the development of retinopathy.

Table 2 **Clinical characteristics of 200 diabetic patients with nonproliferative retinopathy (NPR), 200 diabetic patients with proliferative retinopathy (PR) and 400 diabetic patients without eye complications**

Clinical characteristic	Without eye complications		NPR		PR		OR (95% CI)	
	No.	%	No.	%	No.	%	Without eye complications versus NPR	NPR versus PR
Type of diabetes								
Type 2[R]	269	67.3	64	32.0	40	20.0	1	1
Type 1	32	8.0	27	13.5	48	24.0	3.6(1.9–6.6)	2.8(1.5–5.5)
Type 2-insulin treated	99	24.7	109	54.5	112	56.0	4.6(3.1–6.9)	1.4(1.0–2.7)
Duration of diabetes (years)								
< 10[R]	222	55.5	54	27.0	44	22.0	1	1
10–20	110	27.5	104	52.0	99	49.5	3.9(2.6–5.9)	1.2(0.7–2.0)
> 20	68	17.0	42	21.0	57	28.5	3.1(2.9–5.2)	1.4(0.6–2.4)
Glycaemic state								
Within normal range[R]	232	58.0	96	48.0	73	36.5	1	1
Abnormal	168	42.0	104	52.0	127	63.5	1.5(1.1–2.1)	1.6(1.1–2.4)
Co-morbidity								
No[R]	240	60.0	110	55.0	109	54.5	1	1
Yes, controlled	108	27.0	60	30.0	58	29.0	1.2(0.8–1.8)	1.0(0.6–1.6)
Yes, uncontrolled	52	13.0	30	15.0	33	16.5	1.3(0.7–2.1)	1.1(0.6–2.0)
Hypertension								
No[R]	249	62.5	111	55.5	96	48.0	1	1
Yes, controlled	128	32.0	64	32.0	61	30.5	1.1(0.8–1.7)	1.1(0.7–1.8)
Yes, uncontrolled	23	5.5	25	12.5	43	21.5	2.4(1.3–4.7)	2.2(1.1–3.6)
Diabetic neuropathy								
No[R]	330	82.5	129	64.5	106	53.0	1	1
Yes	70	17.5	71	35.5	94	47.0	2.6(1.7–3.9)	1.6(1.1–2.5)
Diabetic lower limb complication								
No[R]	352	88.0	157	78.5	164	82.0	1	1
Yes	48	12.0	43	21.5	36	18.0	2.0(1.3–3.3)	0.8(0.5–1.4)
Diabetic nephropathy								
No[R]	384	96.0	169	84.5	168	84.0	1	1
Yes	16	4.0	31	15.5	32	16.0	4.4(2.3–8.7)	1.0(0.6–1.8)

[R] = reference category
OR = odds ratio
CI = confidence interval

Progression of diabetic eye complications

Widowed or divorced patients had a 10% higher risk of progression of eye complications as opposed to married patients (OR = 1.1, CI: 1.1–1.3). Illiteracy was also associated with higher probability of progression of retinopathy as opposed to those with higher education (OR = 2.7, CI: 1.2–6.6). No significant association was found between age, sex or occupation and the outcome.

Patients with type 1 diabetes had an increased probability of progression of nonproliferative retinopathy to proliferative retinopathy (OR = 2.3, CI: 1.3–3.9). The presence of hypertension, especially if it was uncontrolled, was significantly asso-

Table 3 **Pattern of care and patient practice of 200 diabetic patients with nonproliferative retinopathy (NPR), 200 diabetic patients with proliferative retinopathy (PR) and 400 diabetic patients without eye complications**

Pattern of care and patient practice	Without eye complications		NPR		PR		OR (95% CI)	
	No.	%	No.	%	No.	%	Without eye complications versus NPR	NPR versus PR
Health insured								
Yes[R]	276	69.0	131	65.5	108	54.0	1	1
No	124	31.0	69	34.5	92	46.0	1.2(0.8–1.7)	1.6(1.1–2.5)
Need help to reach health-care facility								
No[R]	381	95.2	182	91.0	163	81.5	1	1
Yes	19	4.8	18	9.0	37	18.5	2.0(1.0–4.1)	2.3(1.2–4.4)
Self-monitored blood glucose								
Yes[R]	23	5.8	13	6.5	9	4.5	1	1
No	377	94.2	187	93.5	191	95.5	1.1(0.9–2.3)	1.4(0.5–3.7)
Regular follow-up visits								
Yes[R]	330	82.5	161	80.5	157	78.5	1	1
No	70	17.5	39	19.5	43	21.5	1.1(0.7–1.8)	1.1(0.7–1.9)
Compliance with diet recommendations								
Yes[R]	257	64.3	126	63.0	123	61.5	1	1
No	143	35.7	74	37.0	77	38.5	1.1(0.7–1.5)	0.1(0.7–1.6)
Frequency of educational intervention								
Regular[R]	76	19.0	34	17.0	32	16.0	1	1
Occasional	165	41.2	86	43.0	89	44.5	1.2(0.7–1.9)	1.1(0.6–2.0)
Never	159	39.8	80	40.0	79	39.5	1.1(0.7–1.9)	1.1(0.6–1.9)
Smoking								
No[R]	241	60.2	118	59.0	130	65.0	1	1
Ex-smoker	60	15.0	33	16.5	26	13.0	1.1(0.7–1.9)	0.7(0.4–1.3)
Current	99	24.8	49	24.5	44	22.0	1.0(0.7–1.6)	0.8(0.5–1.4)

[R] = reference category
OR = odds ratio
CI = confidence interval

Table 4 **Factors affecting the development and progression of diabetic eye complications: results of multivariate logistic regression analysis**

Variable	OR (95% CI)	Variable	OR (95% CI)
Nonproliferative retinopathy versus no eye complications		**Proliferative versus nonproliferative retinopathy**	
Type of diabetes		*Marital status*	
Type 2[R]	1	Married[R]	1
Type 1	3.6(1.7–7.2)	Single	1.1(0.7–2.1)
Type 2, insulin treated	1.1(0.5–1.7)	Divorced/widowed	1.1(1.1–1.3)
Duration of diabetes (years)		*Education*	
< 10[R]	1	Higher[R]	1
10–20	1.9(1.4–2.5)	Secondary/preparatory	1.0(0.6–1.6)
> 20	1.7(1.1–3.7)	Primary	1.3(0.8–2.2)
Glycaemic state		Illiterate/read and write	2.7(1.2–6.6)
Within normal range[R]	1	*Type of diabetes*	
Abnormal	1.2(1.1–1.5)	Type 2[R]	1
Hypertension		Type 1	2.3(1.3–3.9)
No[R]	1	Type 2, insulin treated	1.3(0.8–2.1)
Yes, controlled	1.1(0.8–1.4)	*Hypertension*	
Yes, uncontrolled	1.6(1.2–2.2)	No[R]	1
Diabetic neuropathy		Yes, controlled	1.3(0.9–2.6)
No[R]	1	Yes, uncontrolled	1.9(1.3–2.8)
Yes	2.0(1.3–3.1)	*Glycaemic state*	
Diabetic nephropathy		Within normal range[R]	1
No[R]	1	Abnormal	1.2(1.1–2.5)
Yes	2.9(1.8–5.2)	*Health insurance*	
		Yes[R]	1
		No	1.2(1.1–2.5)
		Diabetic neuropathy	
		No[R]	1
		Yes	1.8(1.3–2.9)
		Help needed to reach health care facility	
		No[R]	1
		Yes	1.9(1.2–2.7)

[R] = reference category
Variables included in the model: age, sex, marital status, education, occupation, type of diabetes, duration of diabetes in years, glycaemic state, co-morbidity, hypertension, diabetic neuropathy, major complications of lower limb, diabetic nephropathy, health insured, help needed to reach health care facility, self-monitoring of blood glucose, regular follow-up visits, compliance with diet recommendations, frequency of educational interventions and smoking
OR = odds ratio
CI = confidence interval

ciated with an increased risk of progression of eye complications (OR = 1.9, CI: 1.3–2.8). Patients suffering from diabetic neuropathy were more likely to develop severe eye complications (OR = 1.8, CI: 1.3–2.9). Patients with an uncontrolled glycaemic state had a 20% greater risk (OR = 1.2, CI: 1.1–2.5). Duration of diabetes, symptomatic diabetic nephropathy as well as the presence of co-morbid conditions were not independently associated with the outcome.

Non-health-insured patients were at a 20% higher risk of progression of eye complications (OR = 1.2, CI: 1.1–2.5), while those who needed help to reach the health facility showed an 80% higher risk than those who did not need help (OR = 1.9, CI: 1.2–2.7). No association emerged between the regularity of follow-up, regulation of diet, health education intervention or self-monitoring of blood glucose and progression of diabetic eye complications. Also, analysis of health habits showed that no significant effect of smoking could be detected.

Discussion

To our knowledge, our study, aimed at identifying the risk factors for the development and progression of diabetic retinopathy, is one of the largest case–control studies conducted in Egypt so far. It was designed to investigate the relative importance of both clinical and care-related factors affecting diabetic eye complications. The focus on the problem of avoidability, and thus on the quality of care-related issues required the involvement of a large number of patients, reflecting different practice styles. Furthermore, patients were enrolled from most health care sectors in Alexandria, making the results more generalized.

Our data showed that several factors relating to personal characteristics, clinical variables and the delivery of care played an important role in the development and/or progression of diabetic retinopathy. Of the personal factors, marital status and level of education were found to be indicators of the progression of diabetic eye complications. Widowed or divorced patients were at a higher risk than married patients. This indicates the importance of family support in the management of chronic diseases [*17,18*]. Progression of diabetic retinopathy was more likely in illiterate patients than in well educated patients. This reflects the importance of education and health awareness as vital factors in avoiding the progression of complications.

Among the clinical variables, diabetes type and duration were the strongest predictors of the development of eye complications, but duration of diabetes could not be proved to be an indicator of progression of retinopathy. Higher risk was reported in patients with type 1 diabetes than those with type 2. The same findings have been reported by others [*18*]. In fact, patients with all types of diabetes are susceptible to microvascular complications, including retinopathy, but microangiopathic changes usually do not occur without long-standing hyperglycaemia, which is present in type 1 diabetes. Also, patients with type 2 diabetes are older at diagnosis and usually die of macrovascular diseases before microvascular diseases become advanced [*19*]. The effect of duration of diabetes on retinopathy is observed in type 1 diabetes mellitus where retinopathy is usually seen 5–6 years after the development of diabetes. However, type 2 patients do not infrequently present with retinopathy [*20*]. The greater risk in type 1 is probably closely related to the duration of diabetes.

Glycaemic control was found to be a protective factor in the development and progression of diabetic eye complications. This finding has been reported in many studies on type 1 [*7,22*] and type 2 [*23–25*] diabetes. In our study, the role of glycaemic control emerged, although the association was weak. While it was decided to include metabolic control among the covariates, it should be emphasized that, because of the retrospective nature of the study, the levels of fasting blood glucose during the past year could have a poor correlation with the metabolic control before the complication developed. In a recent study, duration of diabetes and level of glycaemia were the most important factors associated with diabetic retinopathy [*23*], although in another study, a strong relationship between glycosylated haemoglobin and retinopathy remained after controlling for duration of diabetes [*25*]. Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) suggest that poor glycaemic control is associated with increased risk of incidence and progression of diabetic microvascular complications, independent of the type of diabetes [*26*].

Inadequately controlled hypertension was associated with a greater risk of the development and progression of eye complications. Hypertension and diabetes are interrelated diseases and, generally, diabetic patients who have hypertension are more likely to develop both macrovascular and microvascular complications [*27*]. The association between retinopathy and elevated blood pressure has been found in many studies [*26,28*]. The results of WESDR demonstrated that systolic blood pressure was a predictor of the incidence of retinopathy and that diastolic blood pressure was a predictor of the progression of retinopathy in type 1 diabetes mellitus, although no association between blood pressure and retinopathy could be detected in type 2 diabetes mellitus [*29*].

Peripheral neuropathy emerged as a risk factor for both the development and progression of retinopathy. A significant association was also found between the development of retinopathy and diabetic nephropathy. Associations of chronic diabetic complications have been observed in many studies especially in type 1 diabetes mellitus [*21,30,31*]. This finding can be explained by the hypothesis that poor glycaemic control is a risk factor for all microvascular complications [*32*]. In type 2 diabetes mellitus, this association has not been clearly established, although in a recent study an association between progression of retinopathy and proteinuria has been reported [*24*].

Health insurance health care systems emerged as a protective factor against the progression of diabetic eye complications, hence the need for such systems to cover all diabetic patients. In fact, non-health-insured participants represented the more disadvantaged part of the population with a much higher proportion of low educational/low social class participants. In the health insurance system, record-keeping is much better organized, there is a well defined policy of follow-up visits and all care is available for free. Patients have to attend follow-up visits regularly to obtain drugs even if they are not compliant with the examination. Specialties are well defined and referrals from general practitioners to specialists are organized according to settled rules.

The importance of patient autonomy is supported by our finding that there was an increased risk of progression of retinopathy in those who needed help reaching the health facility. Poor compliance with the visit scheduling was not confirmed to be a risk factor in our study. Also no association

emerged between adequate compliance and diet recommendations.

The probability of the development and progression of retinopathy was not related to any particular feature of the health educational intervention. The crucial role of patient education has certainly been underestimated in our study and many patients may have received information on specific aspects of diabetes care only after the development of the complication.

Although many studies have reported a strong relationship between smoking and microvascular complication [*33,34*], in our study, smoking was not a risk factor for either the development or progression of diabetic retinopathy. This lack of association has also been reported in many other studies [*18,35,36*]. The lack of association may be due to the fact that patients who smoke are usually free of complications and they stop smoking only after their appearance.

It is acknowledged that, as in any case–control study, it is impossible to draw any conclusion about the causal relationship between the variables investigated and the outcome of interest. Nevertheless, the large sample size and wide coverage of the population balance this limitation. Furthermore our results confirm those obtained from prospective studies [*21–31*].

Conclusions

The study helped to identify factors likely to be related to a serious diabetic complication and to differentiate avoidable from unavoidable factors. Among the former, control of hypertension, glycaemic control, family support and general availability of a health insurance system were the most effective tools for reducing the incidence of diabetic retinopathy and its progression. The study also underlines the need for setting priorities for patients with type 1 diabetes mellitus as they are more likely to develop diabetic retinopathy.

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