Risk factors for diabetic retinopathy in Kuwaiti type 2 diabetic patients

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ABSTRACT

Objective: To determine the risk factors associated with diabetic retinopathy in Kuwaiti subjects with type 2 diabetes.

Methods: Kuwaiti subjects with type 2 diabetes (n=165) attending the Diabetic Clinic at Al-Sabah Hospital, Kuwait between October 2000 and March 2005 were screened for diabetic retinopathy.

Results: Any diabetic retinopathy was found in 40% while 20.6% had sight threatening retinopathy. Mild NPDR was present in 21.2%, moderate to severe non-proliferative diabetic retinopathy (NPDR) in 7.9%, and proliferative diabetic retinopathy (PDR) in 3.0%. Maculopathy was present in 10.3% and 7.9% of the patients were photocoagulated. Compared to those without retinopathy, diabetic patients with any retinopathy were significantly older (51.7 ± 10.3 versus 47.2 ± 9.5 years; p<0.005), had longer duration of diabetes $(13.1 \pm 6.3 \text{ versus } 4.7 \text{ cm})$ \pm 5.4 years; p<0.0001), higher systolic blood pressure (142.9 \pm 23.0 versus 130.3 \pm 20.2; *p*<0.0001) and poor glycemic control (Hemoglobin A1c = 10.1 ± 2.4 versus 8.9 ± 2.3 ; *p*<0.005). The prevalence of hypertension and nephropathy was significantly higher in patients with any retinopathy than those without retinopathy (70.8% versus 49.5%; p<0.01 and 64.4% versus 30.8%; p<0.0001) respectively. Longer duration of diabetes and presence of nephropathy was the most significant independent factors associated with any retinopathy and sight-threatening retinopathy. Treatment with sulphonylurea or insulin, and poor glycemic control were other significant independent factors associated with any retinopathy.

Conclusion: Longer duration of diabetes, presence of nephropathy, glycemic control and mode of treatment were the most significant independent risk factors of diabetic retinopathy. However, a population-based study is warranted to identify the risk factors, as well as the prevalence of diabetic retinopathy.

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iabetic retinopathy remains a major cause of blindness in the world.¹ In type 2 diabetes, 21% of patients have retinopathy at the time of first diagnosis of diabetes and >60% of patients have retinopathy during the first 2 decades of disease.² Screening and treatment of diabetic retinopathy is one of the most cost-effective health procedure.³ Screening strategies depend on the rates of appearance and progression of diabetic retinopathy and on risk factors such as poor glucose control, proteinuria, high blood pressure and serum lipids that alter the rate.⁴ Visual loss and blindness can be reduced by modifying or controlling the risk factors including laser therapy.⁵⁻⁸ Laser therapy is usually successful if applied optimally whereas the therapy benefit falls sharply if the therapy is applied too late.⁹ Therefore, screening programs have been recommended in order to optimize the timing of laser therapy in diabetic retinopathy.¹⁰ Screening for diabetic retinopathy using 2-field retinal photography with 35-mm film processing is found to be an effective method.¹¹ In Kuwait, type 2 diabetes is a major health problem, affecting 14.8% Kuwaiti adult population aged 20 years and older. National data on prevalence of diabetic retinopathy, risk factors predisposing to development of retinopathy and the severity of visual impairment due to the disease in the Kuwaiti population is lacking. Therefore, this study was conducted.

Methods. Kuwaiti subjects with type 2 diabetes (n=165) attending the Diabetic Clinic at Al-Sabah Hospital, Kuwait between October 2000 and March 2005 were screened for diabetic retinopathy. Retinopathy levels were assessed by 2-field fundus photography per eye after pupillary dilation using non-mydriatic Retinal Camera (CR5-45NM, Canon) in 128 subjects and digital camera (IMAGE net 2000 LITE, Topcon) in 37 subjects. Two retinal photographs of each eye were made (nasal and

temporal fields). Retinopathy was categorized from fundus photography as no diabetic retinopathy, mild non-proliferative diabetic retinopathy (NPDR), and moderate to severe NPDR, and proliferative diabetic retinopathy (PDR). Maculopathy was defined as hard exudates within one disc diameter of the center of the macula. Sight-threatening retinopathy was defined as any of the following: moderate to severe NPDR, PDR, photocoagulated, or maculopathy. The retinopathy level was based on the most severe degree of retinopathy in the worst eye. Patients with corneal opacities or cataract (n=5) were excluded from the study. Table 1 demonstrates categories of diabetic retinopathy.

Other data collected included age, gender, duration of diabetes, diagnosis of hypertension, smoking status, body mass index (BMI), blood pressure, HbA1c, serum cholesterol and triglycerides, and urinary albumin. Diagnosis of hypertension was based on pre-existing history of hypertension or systolic BP \geq 140mm Hg and/ or diastolic BP \geq 90 mm Hg on physical examination. BMI (kg/m²) was calculated from weight and height measurements. Hemoglobin A1c [HbA1c] was performed using turbid metric inhibition immunoassay (Roche HB1c II kit); glycemic control was diagnosed as good, acceptable, or poor when HbA1c % was <7.0, 7.0-8.0, and >8.0 respectively. Serum cholesterol and triglycerides were measured by the enzymatic method using Dade Dimension. Urinary albumin concentrations were measured by urinary albumin creatinine ratio (U-ACCR) or 24-hour collection. Normal value for U-ACCR was <1.5 mg/mmol and <20

Table 1 - Categories of diabetic retinopa
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Category	Clinical findings
Mild NPDR	Microaneurysms Blot hemorrhages Hard exudates
Moderate to severe NPDR	Cotton wool spots Venous abnormalities (loops, beading, and reduplication) Intraretinal microvascular abnormalities Extensive intraretinal hemorrhages and microaneurysms
Proliferative DR	New vessels on disc or elsewhere on retina Preretinal and vitreous hemorrhage Fibrovascular proliferation Retinal detachment Rubeosis iridis and neovascular glaucoma
Maculopathy	Hard exudates within one disc diameter of the centre of the macula
NPDR - non-p DR	roliferative diabetic retinopathy, - diabetic retinopathy

mg for 24-hour collection. Nephropathy was defined as positive if U-ACCR was \geq 1.5 mg/mmol and/or 24 hour collection was \geq 20 mg on 2 occasions.

Data management and analysis were conducted using the SPSS program. Continuous variables are presented as means \pm SD, whereas categorical variables are presented as numbers and percentages. The χ^2 test was used to test for differences in proportions between categorical variables while analysis of variance (ANOVA) was used to compare between means. A *p*-value of <0.05 was considered to be statistically significant. Multiple logistic regression analysis was performed to determine independent effects of risk factors on diabetic retinopathy.

 Table 2 - Characteristics of Kuwaiti subjects with type 2 diabetes screened for diabetic retinopathy.

Characteristic	n	(%)			
Gender					
Male	56	(33.9)			
Female	109	(66.1)			
Age (years)					
<u>≤</u> 40	33	(20.0)			
41-50	64	(38.8)			
51-60	46	(27.9)			
>60	22	(13.3)			
Duration (years)					
<5	70	(42.5)			
5-10	40	(24.2)			
>10	55	(33.3)			
Diabetes treatment					
Diet only	33	(20.0)			
Metformin	14	(8.5)			
Sulphonylurea	44	(26.7)			
Combination oral antihyperglycemic agents	26	(15.8)			
Insulin only	30	(18.2)			
insuin + orai antinypergiycemic agent(s)	10	(10.9)			
Current smoker					
No	140	(87.0)			
Yes	21	(13.0)			
Hypertension					
No	69	(42.1)			
Yes	95	(57.9)			
Systolic blood pressure (mmHg)	135.3 ± 22.2				
Diastolic blood pressure (mmHg)	81.2 ± 10.4				
Body mass index (kg/m ²)	33.4 ± 7.5				
Nephropathy					
No	84	(56.0)			
Yes	66	(44.0)			
HbA1c%	9.4 ± 2.4				
Total cholesterol (mmol/l)	5.7 ± 1.1				
Triglycerides (mmol/l)	1.9 ± 1.2				
Data are means ± SD or n (%)					

Results. There were 56 (33.9%) men and 109 (66.1%) women, with a mean age of 48.99 ± 10.08 years and a mean duration of 8.03 ± 7.04 years. Of the patients, 13.0% had history of smoking, 57.9% had hypertension, and 44.0% had nephropathy. Of the 165 patients, 20% were being treated by diet only, 8.5% by metformin, 26.7% by sulphonylurea, 15.8% by combination oral therapy, 18.2% by insulin only, and 10.9% by combination insulin/oral therapy. Mean systolic and diastolic blood pressure was 135.3 \pm 22.2 and 81.2 \pm 10.4 mm Hg respectively. Mean HbA1c % was 9.4 \pm 2.4 and mean BMI was 33.4 \pm 7.5. Mean total cholesterol and triglyceride level was 5.7 \pm 1.1 and 1.9 \pm 1.2 mmol/l respectively (Table 2).

Diabetic retinopathy and associated risk factors. Any diabetic retinopathy was found in 40% while 20.6% had sight threatening retinopathy. Mild NPDR was present in 21.2%, moderate to severe NPDR in 7.9%, and PDR in 3.0%. Maculopathy was present in 10.3% and 7.9% of the patients were photocoagulated. Presence of any diabetic retinopathy by personal and clinical characteristics is presented in Table 3. Diabetic patients with any retinopathy were significantly older $(51.7 \pm 10.3 \text{ versus } 47.2 \pm 9.5 \text{ years}; p < 0.005)$, and had longer duration of diabetes $(13.1 \pm 6.3 \text{ versus } 4.7 \pm 5.4 \text{ })$ years; p < 0.0001). The prevalence of any retinopathy increased significantly with increasing age (p < 0.05, using χ^2 test for linear trend) and increasing duration of diabetes (p<0.0001, using χ^2 test for linear trend) than patients without retinopathy. The risk for diabetic retinopathy has increased from 8.6% in patients who had diabetes <5 years to 45.0% in patients who had diabetes for 5-10 years to 76.4% in patients who had diabetes longer than 10 years. Of the newly diagnosed patients (n=25), 16% had any diabetic retinopathy and 8% sight-threatening retinopathy. The prevalence of any retinopathy was higher among those treated with sulphonylurea, insulin only, and combination of oral/insulin therapy compared with those treated with diet only, metformin, or oral combination therapy, (p < 0.0001) (Table 3). The prevalence of any retinopathy was significantly higher in hypertensive compared to normotensive patients (p<0.01) and in patients with nephropathy compared to those without nephropathy (p < 0.0001). In addition, the prevalence of hypertension and nephropathy was significantly higher in patients with any retinopathy than those without retinopathy (70.8% versus 49.5%; *p*<0.01 and 64.4% versus 30.8%; p < 0.0001, respectively). Patients with any retinopathy had higher systolic blood pressure $(142.9 \pm 23.0 \text{ versus})$ 130.3 ± 20.2 ; p<0.0001), and poor glycemic control compared to those without retinopathy (HbA1c % = 10.1 ± 2.4 versus 8.9 ± 2.3 ; *p*<0.005). Sight-threatening retinopathy was also significantly associated with the

same factors except for hypertension. There were no significant differences regarding gender, smoking, BMI, diastolic blood pressure, and serum lipids in patients with or without diabetic retinopathy.

Multiple logistic regression analysis was performed to determine independent effects of associated risk factors on diabetic retinopathy. The results showed that longer duration of diabetes and the presence of nephropathy

Table 3 - Personal and clinical characteristics of diabetic patients with and without any retinopathy.

Characteristic	No retinopathy	Any retinopathy	P value		
Gender			NS		
Male	60.7	39.3			
Female	59.6	40.4			
Age (vears)			< 0.05		
<40	72.7	27.3			
41-50	65.6	34.4			
51-60	54.3	45.7			
>60	36.4	63.6			
Duration (years)			< 0.0001		
<5	91.4	8.6			
5-10	55.0	45.0			
>10	23.6	76.4			
Diabetes treatment			< 0.0001		
Diet only	97.0	3.0			
Metformin	92.9	7.1			
Sulphonylurea	47.7	52.3			
Combination oral	76.9	23.1			
antihyperglycemic agents					
Insulin only	23.3	76.7			
Insulin + oral antihyperglycemic agent(s)	33.3	66.7			
Current smoker			NS		
No	59.3	40.7			
Yes	61.9	38.1			
Hypertension			< 0.01		
No	72.5	27.5			
Yes	51.6	48.4			
Systolic blood pressure	142.9 ± 23.0	130.3 ± 20.2	< 0.0001		
Diastolic blood pressure (mm Hg)	82.7 ± 11.9	80.2 ± 9.3	NS		
Body mass index (kg/m ²)	32.9 ± 8.6	33.6 ± 6.8	NS		
Nephropathy			< 0.0001		
No	75.0	25.0			
Yes	42.4	57.6			
HbA1c%			< 0.005		
<7	77.8	22.2			
7-8	78.1	21.9			
>8	50.5	49.5			
Total cholesterol (mmol/l)	5.8 ± 1.3	5.7 ± 1.5	NS		
Triglycerides (mmol/l)	1.9 ± 1.5	1.9 ± 1.1	NS		
Data are expressed as number and (%) and mean ± SD					

were the most significant independent factors associated with any diabetic retinopathy and sight-threatening retinopathy. Treatment with sulphonylurea or insulin, and poor glycemic control were other significant independent factors associated with any diabetic retinopathy.

Discussion. Kuwait is a small oil-producing developing country. Socio-economic development and changes in lifestyle have been accompanied by the emergence of diabetes as a major health problem, posing a great impact on the health care system.¹² Diabetes is a multisystem disease in which each system has significant influence on another. Thus, identification and management of the associated risk factors may have a positive impact on the progression of diabetic retinopathy. We found that the most independent significant factors associated with diabetic retinopathy were duration of diabetes and nephropathy. Our study showed that duration of diabetes was the most important independent risk factor associated with diabetic retinopathy. This is consistent with previous studies.^{13,14} In the present study, the risk for diabetic retinopathy has increased from 8.6% in patients who had diabetes <5 years, to 45.0% in patients who had diabetes for 5-10 years, to 76.4% in patients who had diabetes longer than 10 years. Of the newly diagnosed patients, 16% had any diabetic retinopathy and 8% had sight-threatening diabetic retinopathy. Klein et al¹⁵ reported, that up to 3% of newly diagnosed type 2 diabetics aged above 30 years have a sight-threatening diabetic retinopathy.¹⁵ These data are important for planning screening programs for type 2 diabetes and also indicates the importance of screening for diabetic retinopathy at the time of diagnosis. As expected, diabetic retinopathy and nephropathy were strongly associated. This supports what is currently known.^{16,17} In the present study, nephropathy was present in 64.4% of patients with diabetic retinopathy. The WHO multinational study of vascular disease in diabetes has shown that increased urinary albumin excretion is significantly associated with retinopathy.¹⁸ In addition, visual impairment was strongly associated with proteinuria.¹⁹ Therefore, based on these data, detection of diabetic retinopathy in patients with nephropathy should be strongly recommended in any screening program for diabetic retinopathy. In addition, clinical studies carried out on angiotensin converting enzyme inhibitors suggest that they may decrease retinopathy progression in diabetic patients.^{20,21} In our study, modifiable risk factors had significant association with diabetic retinopathy but they were no longer significant when adjusted for in the multiple logistic regression model. These include poor glycemic control and systolic blood pressure. The relationship of hyperglycemia to the

development and progression of diabetic retinopathy is well documented.^{14,22,23} The UKPDS study has shown that for every 10% decrease in HbA1c, there was a 24% reduction in the risk of development of diabetic retinopathy.24 The association of hypertension with retinopathy is also clearly shown. Data from UKPD Study has shown that the development of diabetic retinopathy is strongly associated with high blood pressure in type 2 diabetes.¹⁴ Okudaira et al²⁵ have found that diastolic blood pressure is a significant predictor of progression from background diabetic retinopathy to proliferative diabetic retinopathy in type 2 diabetes. Our study did not show any association between serum lipid levels and retinopathy. Whereas, the ETDRS showed an association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy.7 The Wisconsin epidemiologic study also found a significant association between hard exudates and elevated cholesterol levels in insulin-using patients.²⁶ Our study did not show a relationship between obesity, gender, smoking and diabetic retinopathy. This finding is consistent with other studies.²⁷⁻²⁹ The association of diabetic retinopathy with not smoking is an intriguing issue. The relationship of cigarette smoking to retinopathy is less well defined than that with other microvascular complications of diabetes and studies were less consistent regarding the development of diabetic retinopathy and smoking. The UKPDS have shown that development and progression of diabetic retinopathy in type 2 diabetes were strongly associated with not smoking.¹⁴ Moss et al³⁰ reported a similar result.³⁰ Whereas, EURODIAB and other studies have found that cigarette smoking is an important factor for the development of diabetic retinopathy in type 1 diabetes.³¹⁻³³ Muhlhauser et al³⁴ suggested that this inconsistency of data could be attributed to the different statistical methods used in the clinical and epidemiological research.³⁴

In conclusion, longer duration of diabetes, presence of nephropathy, glycemic control and mode of treatment (insulin and/or sulphonylurea) were the most significant independent risk factors of diabetic retinopathy. Presence of hypertension and higher systolic blood pressure had no significant independent association with retinopathy when other covariates were considered. No significant association was observed with gender, smoking, BMI, diastolic blood pressure or serum lipids. However, a population-based study is warranted to identify the risk factors, as well as the prevalence of diabetic retinopathy, with efforts to improve detection and treatment.

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