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Epidemiological study of diabetic retinopathy in a primary care setting in Hong Kong

一項在香港基層護理環境進行的糖尿病視網膜病變的流行病學研究

Objectives. To estimate the prevalence and risk factors of diabetic retinopathy in type 2 diabetic patients, and to investigate the difference in retinopathy progression in patients with normal fundi or established retinopathy at baseline and the risk factors implicated in the progression.
Design. Retrospective community-based study.
Setting. Ten primary care clinics in Hong Kong.
Patients. Type 2 diabetic patients; subsidiary analysis included subjects with more than one screening event.
Main outcome measures. Patient demographics, baseline prevalence, and risk factors of diabetic retinopathy; progression of retinopathy in patients with normal fundi and established retinopathy at baseline, and the associated risk factors.
Results. A total of 6165 patients were recruited from January 1998 to May 2004. Primary analysis included 4423 patients with good-quality retinal photographs. The mean age of the patients was 60.36 years (standard deviation, 10.80 years; range, 28-94 years), the mean duration of diabetes was 4.71 years (standard deviation, 4.67 years; range, 0.1-40.6 years), and the mean level of glycated haemoglobin was 7.47% (standard deviation, 1.44%). The prevalence of retinopathy at baseline was 28.4%. Subsidiary analysis showed progression to sight-threatening retinopathy was more common in the group with baseline retinopathy than that without (7.9% vs 0.7%), and occurred at a faster rate (mean, 1.5 [range, 0.5-3.0] vs 2.0 [1.0-4.2] years). Logistic regression revealed that the level of glycated haemoglobin was positively associated with both the onset (P<0.001) and progression of retinopathy (P=0.03).
Conclusion. Optimal glycaemic control is important for reducing sight-threatening retinopathy. Close observation is required for patients with established retinopathy as progression occurs more rapidly.

Key words:
Diabetic retinopathy;
Disease progression;
Prevalence;
Primary health care;
Risk factors

關鍵詞：
糖尿病視網膜病變；
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目的：估算二型糖尿病病人患上糖尿病視網膜病變的普遍程度和危險因素，並調查正常眼底的病人與在基準點時便被確診為視網膜病變的病人，在視網膜病變惡化時的不同之處，以及影響到病情惡化的危險因素。
設計：回顧式社區研究。
安排：香港十間基層護理診所。
患者：二型糖尿病病人，並對接受過多於一次篩查的病人進行輔助分析。
主要結果測量：病人的人口統計數據、基準點的流行、糖尿病視網膜病變的危險因素、正常眼底的病人與在基準點時便被確診為視網膜病變的病人的視網膜病變情況，以及相關的危險因素。
結果：由 1998 年 1 月至 2004 年 5 月期間，共有 6165 名病人參與這研究。

初步分析有4423名病人有清晰的視網膜照像，他們平均年齡為60.36歲（介乎28至94歲，標準差10.8歲），平均糖尿病患病期為4.71年（介乎0.1至40.6年，標準差4.67年），而糖化血色素平均值為7.47%（標準差1.44%）。在基準點有視網膜病變的病人佔28.4%。輔助分析顯示，基準點視網膜病變的病人比其他病人，更常出現視網膜病變危害視力（分別佔7.9%和0.7%），並且更早發病（基準點組別介乎0.5至3.0年，平均為1.5年；非基準點組別介乎1.0至4.2年，平均為2.0年）。統計學的邏輯迴歸顯示，糖化血色素的水平，與視網膜病變的發病（P<0.001）和惡化（P=0.03）呈正比關係。

結論：將血糖控制在理想水平，對減低危害視力的視網膜病變十分重要，而在基準點時便被確診為視網膜病變的病人更須密切留意病情，因為這類病人的視網膜病變惡化較為迅速。

Introduction

Diabetes mellitus is a major public health concern that has a significant socio-economic impact. The prevalence of diabetes in the working population of Hong Kong has doubled over the past 10 years. It was estimated to be 9.8% in the 2000 Hong Kong Cardiovascular Risk Factor study.[1] In elderly subjects, the prevalence was even higher (>20%).[2] The long-term systemic complications of diabetes are devastating. They are major causes of morbidity and mortality, significantly impair the quality of life of patients and contribute a significant health cost to society.[3]

Retinopathy, a complication of diabetes, has been a recent focus of attention because of its potential treatability with laser photocoagulation when detected early.[4-9] Screening for diabetic retinopathy has been advocated internationally to reduce unnecessary vision loss in patients and costs to the community.[10-15] Numerous studies have supported the use of retinal photography as the preferred method of screening.[16-21] Several countries have reported their incidence and progression of diabetic retinopathy using fundus photography. The incidence ranged from 22% to 79% and the rate of progression ranged from 29% to 69%.[22-24] All studies nonetheless consistently demonstrated the importance of glycaemic control in the development and progression of diabetic retinopathy.

In our clinic, screening for diabetic retinopathy commenced in 1998 using a digital retinal camera and local epidemiological data—which had been previously lacking particularly in a primary care setting—were collected. This information is vital when planning screening services, projecting costs, and developing causal inferences, especially in the light of an escalating prevalence of diabetes mellitus in the community. This paper examined the prevalence and risk factors of diabetic retinopathy in type 2 diabetic patients in a community setting. It also investigated the difference in retinopathy progression in patients with normal fundi or established retinopathy at baseline, and the risk factors implicated in the progression. The rate of progression in different groups of patients may be helpful when devising a more risk-stratified and cost-effective screening programme.

Methods

Patients

Retinal screening for diabetic patients with retinal photography began at the Ngau Tau Kok Family Medicine Training Centre in 1998. Type 2 diabetic patients were recruited from this training centre and nine other primary care clinics that included five general out-patient clinics, one elderly health centre in the East Kowloon Region, and the three civil servant clinics in Wanchai, Chai Wan, and Yaumatei. Doctors in these centres were encouraged to refer all type 2 diabetic patients currently being regularly followed up to the screening programme. Exclusion criteria included a history of glaucoma, patients already receiving ophthalmologic care, and refusal to participate. All patients with high-quality retinal photographs within the study period (January 1998 to May 2004) were included for primary data analysis. Subsidiary data analysis was restricted to patients with two or more screening events.

Procedure

Demographic data and clinical information for all patients were collected from the standardised referral form and included age and sex of patient, duration of diabetes, type of diabetic treatment (diet control, oral hypoglycaemic agent or insulin), updated glycated haemoglobin (HbA_{1c}) within 1 year, visual acuity by Snellen's chart, smoking status, hypertension, and presence of other eye pathology such as cataract and previous eye laser treatment. Hypertension was defined as three or more consecutive office blood pressure measurements of higher than 140/90 mm Hg or being prescribed anti-hypertensive medication. Smoking status was categorised as never or ever smoked.

Table 1. Baseline characteristics of 4423 patients at entry

Characteristic	Patients*
Sex†	
Male	2078 (47.2)
Female	2322 (52.8)
Mean age (SD, range) [years]	60.36 (10.80, 28-94)
Smoking status	
Never smoked	3481 (78.7)
Ever smoked	942 (21.3)
Mean glycated haemoglobin (SD, range) [%]	7.47 (1.44, 5-15)
Hypertension	
No	1822 (41.2)
Yes	2601 (58.8)
Mean duration of diabetes mellitus (SD, range) [years]	4.71 (4.67, 0.1-40.6)
Treatment type	
Diet	1106 (25.0)
Oral hypoglycaemic agent	3317 (75.0)
Mean duration of retinal screening (SD, range) [years]	1.91 (0.88, 0.5-4.5)

* Data are expressed as the number of patients with percentage in brackets, except otherwise stated
† Data were missing for 23 patients

Table 2. Grading of diabetic retinopathy of patients at entry

Retinopathy grading*	No. of patients, n=4423	Percent	Cumulative percent
Normal	3169	71.6	71.6
Minimal NPDR	575	13.0	84.6
Mild NPDR	425	9.6	94.2
Moderate NPDR	169	3.8	98.0
Severe NPDR	61	1.4	99.4
Early PDR	23	0.5	99.9
High-risk PDR	1	0.0	99.9†

* NPDR denotes non-proliferative diabetic retinopathy, and PDR proliferative diabetic retinopathy
† Cumulative percent is not equal to 100 because of rounding

After obtaining informed consent from each patient, a non-mydriatic fundus photograph of each eye was taken using the Canon CR-45UAF camera with 45°C single field. Retinal images were interpreted by a group of qualified family physicians, specially trained in the interpretation of retinal photographs. For doubtful cases, arbitration was obtained from an ophthalmologist. The grading of retinopathy was defined according to the modified Airlie House classification adopted by the Early Treatment Diabetic Retinopathy Study[25]—(i) normal, (ii) minimal non-proliferative diabetic retinopathy, (iii) mild non-proliferative diabetic retinopathy, (iv) moderate non-proliferative diabetic retinopathy, (v) severe non-proliferative diabetic retinopathy, (vi) early proliferative diabetic retinopathy, and (vii) high-risk proliferative diabetic retinopathy.

Patients with sight-threatening retinopathy, defined as moderate non-proliferative diabetic retinopathy or worse, were referred to an ophthalmologist for subsequent follow-up or treatment. Those with milder involvement were re-screened 1 year later using the same method. Levels of disease for the worse eye for each patient were presented.

'Onset of new retinopathy' was diagnosed in patients who had no diabetic retinopathy at entry to the study but had developed retinopathy in subsequent examinations. 'Progression of established retinopathy' was defined as an increase in the retinopathy grading of one step or more in subsequent examinations compared with baseline retinopathy grading. If there was more than one follow-up examination, the last retinal grading was used in the analysis.

Statistical analysis

The explanatory variables included in the analysis were chosen on the basis of clinical relevance and previous literature findings.[22] These included age, sex, smoking status, history of hypertension, duration of diabetes, treatment type, and HbA_{1c}.

Data analysis was performed with the Statistical Package for the Social Sciences (Windows version 10.0; SPSS Inc, Chicago [IL], United States). Descriptive information for each of the explanatory variables was derived. Univariate association of the variables with retinopathy was assessed using the Mann-Whitney test for continuous variables and Chi squared test for categorical variables. Logistic regression with explanatory variables selected by the forward conditional method was applied to adjust for confounding factors. A P value of less than 0.05 was considered significant.

Results

There were 6165 patients registered in the screening programme from January 1998 to May 2004. Patients with unqualified retinal photographs or an under-visualised retina were excluded from analysis. The primary analysis recruited 4423 patients with high-quality retinal photographs. The baseline characteristics of these patients are shown in Table 1. They had a mean age of 60.36 years (standard deviation [SD], 10.80 years; range, 28-94 years). There were slightly more female subjects (52.8%) than male (47.2%). Mean duration of diabetes was 4.71 years (SD, 4.67 years; range, 0.1-40.6 years), and the mean level of

Table 3. Association of risk factors with baseline retinopathy

Risk factor	Patients with no baseline retinopathy	Patients with established retinopathy	P value
Mean age (years)	59.2	61.8	<0.001
Sex			
Male	49.0%	42.9%	
Female	51.0%	57.1%	<0.001
Smoking status			
Never smoked	79.3%	77.1%	
Ever smoked	20.7%	22.9%	0.11
Hypertension			
No	41.9%	39.2%	
Yes	58.1%	60.8%	0.09
Treatment type			
Diet	30.3%	11.4%	
Oral hypoglycaemic agent	69.7%	88.6%	<0.001
Mean glycated haemoglobin (%)	7.36	7.94	<0.001
Mean duration of diabetes mellitus (years)	4.0	6.3	<0.001

HbA_{1c} was 7.47% (SD, 1.44%). Three quarters of patients required oral hypoglycaemic medication. Hypertension was present in over half (58.8%) of the patients. Most (78.7%) patients had never smoked. With regard to the history of retinal screening, the mean duration of screening was 1.91 years (SD, 0.88 years; range 0.5-4.5 years); 41.7% of subjects were screened twice or more.

The prevalence of diabetic retinopathy in our study population was 28.4%. The retinal grading of the subjects at baseline is shown in Table 2. Proliferative diabetic retinopathy was present in 24 (0.5%) patients at entry. Univariate analysis for the association of risk factors with baseline retinopathy revealed that subjects with established retinopathy at baseline were significantly older (P<0.001), had a longer history of diabetes (P<0.001), and higher HbA_{1c} (P<0.001). Female subjects were more likely to have retinopathy at entry (P<0.001) [Table 3]. After adjusting for the confounding effects between variables in the logistic regression model, the duration of diabetes and poor glycaemic control were the only risk factors significantly associated with the baseline development of retinopathy (P<0.001). Nonetheless, the predictive power of the regression model was rather low with the value of R^2 equal to 0.068 only.

Incidence of new retinopathy and progression of established retinopathy

A total of 1844 patients were included in this analysis—patients who had qualified retinal photographs from at least two retinal screenings, and a full data set for the risk factors under consideration. The retinopathy grading of these subjects is shown in Table 4. Worsening diabetic retinopathy over the study period occurred in 276 (15.0%) of 1844 patients. Of the 1350 patients with no retinopathy at entry, 186 (13.8%) subsequently developed 'new retinopathy' on further screening(s), but only nine (0.7%) were sufficiently sight-threatening to warrant ophthalmologist referral. Of the 494 patients with established retinopathy at entry, 90 (18.2%) progressed in severity by one step or more, and when compared with patients with no retinopathy at entry, a much greater proportion of them (7.9%, n=39) were sight-threatening retinopathy.

Table 4. Grading of diabetic retinopathy of patients in subsidiary analysis

Retinopathy grading*	No. of patients, n=1844	Percent	Cumulative percent
Normal	1350	73.2	73.2
Minimal NPDR	291	15.8	89.0
Mild NPDR	169	9.2	98.2
Moderate NPDR	24	1.3	99.5
Severe NPDR	5	0.3	99.8
Early PDR	5	0.3	100.1†

* NPDR denotes non-proliferative diabetic retinopathy, and PDR proliferative diabetic retinopathy

† Cumulative percent is not equal to 100 because of rounding

Evaluation of risk factors associated with onset of new retinopathy and progression of established retinopathy

Both the univariate analysis and multiple logistic regression analysis revealed consistent results. Glycated haemoglobin was positively associated with the onset of new retinopathy (P<0.001). Likewise, patients with progression of established retinopathy had higher HbA_{1c} (P=0.03), although the effect was less steep. Duration of diabetes was significantly associated with development of new retinopathy (P<0.001), but there was no relation between progression of retinopathy

Table 5. Association of risk factors with onset of new retinopathy

Risk factor	Patients with no development of retinopathy	Patients with new development of retinopathy	P value
Mean age (years)	58.5	60.4	0.06
Sex			
Male	48.1%	50.0%	0.64
Female	51.9%	50.0%	
Smoking status			
Never smoked	79.6%	75.0%	
Ever smoked	20.4%	25.0%	0.17
Hypertension			
No	43.6%	44.6%	0.80
Yes	56.4%	55.4%	
Treatment type			
Diet	32.3%	16.7%	
Oral hypoglycaemic agent	67.7%	83.3%	<0.001
Mean glycated haemoglobin (%)	7.30	7.65	<0.001
Mean duration of diabetes mellitus (years)	3.70	5.00	<0.001

Table 6. Association of risk factors with progression of established retinopathy

Risk factor	Patients without progression	Patients with progression	P value
Mean age (years)	61.0	62.6	0.20
Sex			
Male	42.0%	36.0%	
Female	58.0%	64.0%	0.26
Smoking status			
Never smoked	79.0%	77.8%	
Ever smoked	21.0%	22.2%	0.80
Hypertension			
No	39.0%	51.1%	
Yes	61.0%	48.9%	0.03
Treatment type			
Diet	14.5%	6.7%	
Oral hypoglycaemic agent	85.5%	93.3%	0.05
Mean glycated haemoglobin (%)	7.52	7.85	0.03
Mean duration of diabetes mellitus (years)	5.91	6.61	0.19

and duration of diabetes (P=0.19). Hypertension had no effect on new retinopathy although significantly fewer patients with progressed retinopathy were hypertensive (P=0.03). The inverse relationship of hypertension with progression of retinopathy was also demonstrated in logistic regression analysis (P=0.006) [Tables 5 and 6].

Rate of retinopathy development and progression

In the 'normal-at-baseline' patients, 0.7% (9/1350) had developed moderate non-proliferative diabetic retinopathy or worse at the last assessment. The mean time for development was 1.99 years (range, 0.99-4.23 years). For the 'established-at-baseline' patients, a higher proportion of them (39/494, 7.9%) had advanced to that referral grading on subsequent screening(s) and the progression was more rapid (mean, 1.46 years; range, 0.5-2.97 years).

Discussion

Diabetic retinopathy is the leading cause of blindness in developed countries in spite of the availability of effective treatment with laser photocoagulation.[26] Early detection of the condition and timely intervention are the keys to successful management. Screening has been recommended worldwide as a standard procedure to decrease the threat of blindness.[10-12] Our retinopathy screening programme started in 1998. We worked closely with ophthalmologists on the interpretation of fundoscopy data and referral criteria. We also studied the epidemiology of diabetic retinopathy in Hong Kong. In addition to reporting the prevalence and risk factors of diabetic retinopathy locally, we also studied the incidence and progression of retinopathy in the cohort of patients with type 2 diabetes followed from baseline to further screening visit(s). Of the

patients included in the final analysis, most (91.6%) had been screened 2 to 3 times within the study period.

At baseline, 28.4% of the subjects had diabetic retinopathy that was sight-threatening in 5.7%. Subsequent screening(s) of patients with established retinopathy revealed that 18.2% had progressed at least one step in severity and 7.9% had advanced to sight-threatening retinopathy. On the contrary, a lower proportion (13.8%) of patients with normal fundi at diagnosis subsequently developed retinopathy and in only 0.7% was it sight-threatening.

The prevalence of diabetic retinopathy in our study population was lower than that reported in the United Kingdom Prospective Diabetes Study (UKPDS[23]) [37%] and Pima Indians[24] (31.8%). The exclusion of patients under ophthalmologic care from statistical analysis might have underestimated the prevalence. Nonetheless most of these patients were followed up for reasons other than diabetic retinopathy, for example, cataract. The prevalence might not be significantly different between these two groups of patients.

The incidence of retinopathy progression was comparable with a previous study on Pima Indians (18.3%[24]) that also suggested the greater tendency of progression in previously established retinopathy than previously normal fundi. Similarly, the Wisconsin Epidemiologic Study[22] confirmed that the risk of proliferative retinopathy increased with more severe retinopathy grading at baseline.

Many epidemiological studies have demonstrated that glycaemic control played an important role in the development of microvascular complications.[27] We also showed a positive relation of a higher HbA_{1c} with onset and progression of retinopathy. The UKPDS[23] demonstrated that strict control of blood glucose reduced the need for photocoagulation and improved microvascular disease and retinopathy outcomes. A number of therapeutic trials further demonstrated that a difference of HbA_{1c} between a median of 7.9% in conventional therapy and 7.0% in intensive therapy resulted in a risk reduction of 21% for progression of retinopathy at 12 years.[28,29] Guidelines should emphasise the necessity for effective therapeutic intervention to achieve an optimal level of HbA_{1c}.

Somewhat counter-intuitively, this study showed that hypertension was inversely related to the progression of established retinopathy. The finding was at variance with much of the published epidemiology of diabetic retinopathy. Previous studies have demonstrated the importance of blood pressure control in diabetic retinopathy.[30,31] The UKPDS also reported a pronounced decrease in microvascular end points with tight blood pressure control.[32,33] The differences in findings may be related to the small sample size in our progression group that may consequently have given rise to statistical error. With the continuation of our screening programme, and accumulating data from patients undergoing further screening events, more valid conclusions will become clear for the population in Hong Kong.

In line with another large epidemiological study,[34] smoking in this study was not associated with either development or progression of retinopathy.

Considering the rate of progression, our 'normal-at-baseline' patients developed sight-threatening retinopathy at a mean duration of 2 years; while the 'established-at-baseline' patients took a shorter time (approximately 1.5 years) to progress to the same grading. As expected and demonstrated by other major studies, a more severe retinopathy grading at baseline is associated with a faster progression.[22,35] These data may have implications when determining a more appropriate screening interval and thus more cost-effective screening programme that best suits the needs of patients in Hong Kong. With more data from patients in future, it will be possible to be more specific.

Conclusion

Diabetic retinopathy is prevalent in Hong Kong. Optimal glycaemic control improves the visual outcome for diabetic patients and an effective screening programme is vital if retinopathy is to be detected early on and timely treatment is initiated. More aggressive interventions are required for those with established retinopathy at baseline.

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