Original article

Retinopathy in type 2 diabetic patients with microalbuminuria

Reddy SC[1], Khin YM[2], Nurjahan MI[3], Ramli A[4]
[1]Department of Ophthalmology, Faculty of Medicine, International Medical University Clinical School, Seremban, Negeri Sembilan, Malaysia
[2] Department of Internal Medicine, Faculty of Medicine, International Medical University Clinical School, Seremban, Negeri Sembilan, Malaysia
[3]Department of Family Medicine, Faculty of Medicine, International Medical University Clinical School, Seremban, Negeri Sembilan, Malaysia
[4]Klinik Kesihatan (government health clinic), Seremban, Negeri Sembilan, Malaysia

Abstract

Objective: To determine the prevalence of retinopathy in type 2 diabetic patients with micoalbuminuria and to evaluate the association of risk factors with prevalence of retinopathy in these patients. **Material and methods**: A fundus examination of 137 patients suffering from type 2 diabetes mellitus with microalbuminuria was done, with direct ophthalmoscope/ binocular indirect ophthalmoscope after dilating the pupils with 1 % tropicamide eye drops. Retinal changes were graded as no retinopathy, non-proliferative retinopathy, proliferative retinopathy and maculopathy. The association of the duration of diabetes, control of diabetes, hypertension, hyperlipidemia, smoking, obesity and peripheral neuropathy was assessed with the prevalence of retinopathy in these patents. **Results**: The mean age of the patients was 58 years (range 35 - 79 years); 62 % were females, and 49.6 % were Chinese. Diabetic retinopathy was seen in 36.5 % of the patients — non proliferative in 29.2 %, proliferative in 7.3 % and maculopathy in 5.1 % of patients. A longer duration of diabetes ($p = 0.002$), poor control of diabetes ($p = 0.002$), presence of hypertension ($p = 0.03$), and presence of peripheral neuropathy ($p = 0.001$) were significantly associated with the prevalence of retinopathy; while hyperlipidemia ($p = 0.29$), smoking ($p = 0.43$) and obesity ($p = 0.43$) were not associated with retinopathy. **Conclusion**: Retinopathy was seen in 36.5 % of type 2 diabetic patients with microalbuminuria; 7.3 % had proliferative retinopathy and 5.1 % maculopathy (both sight threatening changes). All diabetic patients with microalbuminuria should be screened for retinopathy so that treatment can be instituted in the required patients to prevent ocular morbidity/ blindness.

Key-words: diabetis mellitus, microalbuminuria, retinopathy, peripheral neuropathy

Introduction

Microalbuminuria has been reported to be a strong predictor for diabetic retinopathy, clinically significant macular edema and hard exudates formation in type 2 diabetic patients (Ajoy Mohan et al, 2011). Many studies have reported microalbuminuria (MA) to be a reliable marker of retinopathy in diabetic patients; and significantly related to proliferative retinopathy (Manaviat et al, 2004; Lunetta et al, 1998; Boelter et al, 2006) and

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Correspondence address: Dr. S. Chandrasekhara Reddy, Professor & Head Department of Ophthalmology, UCSI School of Medicine Bukit Khor, 21600 Marang, Terengganu, Malaysia
Tel: +6013-6244532, Fax: +609-6281885
Email: profscreddy@gmail.com

background retinopathy (Wirta et al, 1999) in these patients. Presence of MA is a well known indicator of incipient nephropathy and it progresses to overt proteinuria in type 2 diabetes mellitus (Mogensen 1984) . Diabetic nephropathy is a clinical syndrome characterized by persistant albuminuria , progressive decline in the glomerular filtration rate and elevated arterial blood pressure (Batuman, 2011) .

Retinopathy, nephropathy and peripheral neuropathy are the common microvasular complications seen in diabetic patients. It takes many years for microvascular complications to develop in diabetes mellitus. It is believed that when microalbuminuria (incipient nephropathy) is already present, there are more chances for occurrence of retinopathy and/or peripheral neuropathy in these patients. Retinopathy in type 2 diabetes mellitus patients has been reported to vary from 48.6% (Shriwas et al, 1966) to 51.6% (Tajunisah et al, 2006) in Malaysia. In both these studies, there is no mention whether the patients had microalbuminuria or not. The pubmed search revealed the prevalence of retinopathy in type 2 diabetics with microalbuminuria to be varying from 10.1% (Al-Maskari and El-Sadig, 2007),

19.5% (Lunetta et al, 1998), 40.3% (Kim et al, 2004) to 43.3% (Manaviat et al, 2004). There is no report available on retinopathy in diabetic patients with microalbuminuria from Malaysia. Therefore, this study was undertaken to determine the prevalence of retinopathy in type 2 diabetic patients with microalbuminuria , and to evaluate the association of risk factors with prevalence of retinopathy in these patients.

Material and methods

This cross sectional study was carried out on diabetic patients with positive microalbuminuria who were attending Klinik Kesihatan Seremban over a period of two years (September 2006 - August 2008). All the patients had type 2 diabetes mellitus. Inclusion criteria: (i) diabetis mellitus diagnosed according to WHO guile lines, 2006. (ii) urine sample positive for MA, which was measured using Clinitek 100 kit (Bayer corporation-Elkhart, IN, USA). The device shows the ratio of albumin to creatinine in mg/g. If the ratio was less than 30, the patient was normoalbuminuric; ratios between 30-300 were indicative of MA; and ratio above 300 revealed macroalbuminuria. When two out of three urine samples showed MA, it was considered as positive for microalbuminuria. Exclusion criteria: (i) pregnancy, (ii) opaque/hazy media not allowing to see the fundus, (iii) retinal diseases like central retinal vein occlusion without diabetic retinopathy changes.

After completing the questionnaire on socio demographic details, duration of diabetes, current treatment, history of smoking, heart disease, peripheral neuropathy, any visual problems and earlier eye check up; blood pressure measurement with mercury sphygmomanometer was done, and estimation of body mass index were done after taking height and weight. The reports of recent laboratory investigations (glycosylated haemoglobin-HbA1C, lipid profile, renal profile) were noted from the case records. Hypertension was taken as blood pressure reading of $\geq$ 140/90 mm Hg during the previous/ current examination. Based on HbA1C reading, control of diabetes was taken as good:6.5 % or less and poor: > 6.5 %. Hyperlipidemia was considered when the reading of triglycerides was >1.7 mmol/L or total cholesterol was >4.5 mmol/ L or low density cholesterol was >2.6 mmol/L. Obesity classification was based on Academy of Medicine Malaysian guidelines, 2004: obesity: $\geq$ 27.5 kg/m^2. Smokers were defined as those who have history of smoking more than ten cigarettes per day in the past one month.

The clinical examination of patients for peripheral neuropathy or any other complications was done by the physician. Then, the fundus examination was done by the ophthalmologist in the health clinic itself, with direct ophthalmoscope/binocular indirect ophthalmoscope, after dilating both pupils with 1% tropicamide eye drops. The retinal changes were categorized into no retinopathy, non proliferative retinopathy (presence of microaneurysms, haemorrhages, hard exudates and cotton wool

spots), proliferative retinopathy (non proliferative retinopathy + new vessel formation on/around the disc-NVD or elsewhere in the retina-NVE), and maculopathy (presence of hard exudates, haemorrhages and/or edema in the macula with any of the above retinal findings). When the findings in both eyes fell into different categories, categorization of the patient was based on the eye with more severe type of retinopathy.

The association of risk factors (duration and control of diabetes, hypertension, hyperlipidemia, smoking, obesity, peripheral neuropathy) were evaluated with prevalence of retinopathy. The data were entered in a proforma and analysed using SPSS programme. Pearson chi square test, Fisher's exact test and one-way analysis of varience (ANOVA) test were performed to test the association of risk factors with prevalence of retinopathy. P value of <0.05 was considered as statistically significant. This study was approved by Ethics committee of International Medical University.

Results

A total of 137 patients with type 2 diabetes mellitus who had positive microalbuminuria (incipient nephropathy) were examined. Females (62%) were more than males. Half of the patients (49.6%) were Chinese. The mean age of patients was 58 years (range 39-79 years). The mean duration of diabetes was 9.5 years (range 5- 37 years). Control of diabetes was poor in 75.9% of patients. Hypertension was present in 69.3% of patients. Peripheral neuropathy was present in 19.7% of patients (Table 1).

Table 1: Demographic data and the percentage of risk factors in type 2 diabetic patients with microalbuminuria (n=137).

Parameter	Number	Percentage
Gender		
Male	52	38.0%
Female	85	62.0%
Race		
Malay	23	16.8%
Chinese	68	49.6%
Indian	46	33.6%
Age		
31-40 years	6	4.4%
41-50 years	23	16.8%
51-60 years	58	42.3%
61-70 years	35	25.5%
71-80 year	15	10.9%
Duration of diabetes		
1-10 years	89	64.9%
11-20 years	34	24.8%
21-30 years	11	8.0%
31-40 years	3	2.2%
Control of diabetes (HbA1C)		
Good	33	24.1%
Poor	104	75.9%
Hypertension		
Present	95	69.3%
Absent	42	30.7%
Hyperlipidemia		
Present	52	38%
Absent	85	62%
h/o Smoking		
Present	8	5.8%
Absent	129	94.2%
Obesity		
Present	81	59.1%
Absent	56	40.9%
Peripheral neuropathy		
Present	27	19.7%
Absent	110	80.3%

Retinopathy of any form was present in 50 (36.5%) patients (Table 2). Patients who had any form of diabetic retinopathy changes were referred to eye clinic, Hospital Seremban for management and further follow up and treatment.

Table 2: Different grades of retinopathy in type 2 diabetic patients with microalbuminuria (n=137).

Retinal changes	No.	Percentage
No retinopathy	87	63.5%
Retinopathy present	50	36.5%
Non proliferative retinopathy	40	29.2%
Proliferative retinopathy	10	7.3%
Maculopathy	17	5.1%

History of ischemic heart disease was present in 10 patients in our study; seven of them did not have

any retinopathy, one had non proliferative retinopathy and two had proliferative retinopathy. Out of 137 patients examined, some had the following eye conditions in one or both eyes: pseudophakia-13, cataract-6, open angle glaucoma-2, astroid hyalitis-3, age related macular degenetaion-2, hypertensive retinopathy (grade I or II) changes in 8 patients. In 2 patients pan retinal photocoagulation was done in both eyes. All of them gave history of taking treatment already from the eye clinic, Hospital Seremban.

Longer duration of diabetes (p=0.002), poor control of diabetes (p=0.002), presence of hypertension (p=0.03), and presence of peripheral neuropathy (p=0.001) were significantly associated with retinopathy in these patients. However, gender (p=0.52), race (p=0.73), hyperlipidemia (p=0.29), smoking (p=0.43) and obesity (p=0.43) were not significantly associated with retinopathy in our study (Table 3).

Table 3: Association of various risk factors with prevalence of retinopathy in type 2 diabetic patients with microalbuminuria (n=137).

Parameter	No DR	NPDR	PDR	P value
Duration of diabetes				
1-10 years (89)	67	20	2	0.002
11-20 years (34)	16	12	6	
21-30 years (11)	3	7	1	
31-40 years (3)	1	1	1	
Control of diabetes(HbA1C)				
Good (33)	28	5	0	0.02
Poor (104)	59	35	10	
Hypertension				
Present (95)	64	23	8	0.03
Absent (42)	23	17	2	
Hyperlipidemia				
Present (52)	28	19	5	0.29
Absent (85)	59	21	5	
h/o Smoking				
Present (8)	4	4	0	0.43
Absent (129)	83	36	10	
Obesity				
Present (81)	50	24	7	0.43
Absent (56)	37	16	3	
Peripheral neuropathy				
Present (27)	7	16	4	0.001
Absent (110)	80	24	6	

No DR= no diabetic retinopathy, NPDR=non proliferative diabetic retinopathy, PDR= proliferative diabetic retinopathy

Discussion

Diabetic retinopathy (DR) is one of the leading causes of blindness in the world that increases the chances of loosing vision about 25 times higher compared to normal individuals (Taylor, 1996). The prevalence of retinopathy in diabetics with microalbuminuria in our study was 36.5% which is much higher than the prevalence reported by Al-maskari & El-Sadig (2007) and Lunetta et al (1998); and slightly lower than the prevalence reported by Manaviat et al (2004) and Kim et al (2004), (Table 4).

Table 4: Prevalence of retinopathy in diabetic patients with microalbuminuria

Author	Country	No.of diabetics examined	No. of patients with MA	No. of patients with retinopathy and percentage
Al-Maskari & El-Sadig	UAE	513	276	28 (10.1%)
Lunetta et al	Italy	230	76	39 (19.5%)
Manaviat et al	Iran	590	143	62 (43.3%)
Kim et al	South Korea	231	231	93 (40.3%)
PRESENT STUDY	Malaysia	137	137	50 (36.5%)

MA= microalbuminuria, UAE=United Arab Emirates

Microalbuminuria is frequently associated with hypertension, dislipidemia, obesity, and insulin resistance in patients with type 2 diabetes (Groop et al, 1993). Earlier studies by Parving et al, 1992; Fioretto et al, 1996 showed that all patients with proteinuria/microalbuminuria and concurrent diabetic retinopathy have evidence of diabetic nephropathy. Tzeng et al (2001) and Chandy et al (2008) have reported a significant relationship between diabetic nephropathy and diabetic retinopathy.

Boelter et al (2006) in a cross sectional study on 1214 type 2 diabetic patients (after excluding the patients with macroalbuminuria and on dialysis) reported that MA was significantly (p=0.002) associated with proliferative diabetic retinopathy. They suggested that patients with proliferative diabetic retinopathy may have more often renal involvement and all such patients must undergo an evaluation of renal function including urinary albumin measurements. In another study of 125 type 2 diabetic patients, Wirta et al(1999) reported that subjects with MA had more frequently background retinopathy than their counterparts with a normal urinary albumin excretion rate (p=0.026). In our study, non proliferative retinopathy was seen in 29.2%, and proliferative in 7.3% of diabetic patients with microalbuminuria.

Poor control of diabetes (hyperglycemia) and hypertension were significantly associated with diabetic retinopathy in the present study, while hyperlipidemia was not significantly associated with retinopathy (Table 3). Spencer et al (2004) reported that hyperlipidemia and hyperglycemia act synergistically in inducing renal injury. Therefore, adequate control of these two factors is vital in patients with diabetic retinopathy, to slow down the progression of nephropathy.

Peripheral neuropathy was seen in 27 (19.7%) patients in our study; and it was significantly associated with diabetic retinopathy. Among these 27 patients, non proliferative retinopathy was seen in 16 and proliferative retinopathy in 4 patients (Table 3). In a study of 201 patients of type 2 diabetis mellitus, Phoksunthorn and Thatsnarong (2007) have reported history of peripheral neuropathy in 34% of patients and stated that history of peripheral neuropathy had a significant relationship with retinopathy in these patients. Abdollahi et al (2007) have reported that a severe diabetic retinopathy is associated with diabetic neuropathy and sated that diabetic neuropathy might be used as a tell tale sign of diabetic retinopathy, necessitating more intensive ophthalmic care in longstanding diabetic patients.

Conclusion

In our study more than one-third (36.5%) of type 2 diabetic patients with microalbuminuria had retinopathy; 7.3% had proliferative retinopathy and 5.1% maculopathy (both sight threatening changes). Since retinopathy and nephropathy are significantly related to each other in type 2 diabetic patients, all diabetic patients with microalbuminuria should be screened for retinopathy so that treatment can be instituted in the required patients to prevent ocular morbidity/blindness.

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