Original Article

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Association of Microalbuminuria with the Severity of Diabetic Retinopathy in Patients with type II Diabetes Mellitus

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A B S T R A C T

Objective: To evaluate the association of microalbuminuria with the severity of diabetic retinopathy.

Methodology: This is a cross-sectional study that was conducted at Combined Military Hospital Lahore from Dec 2019 to Dec 2020. All Patients having type II diabetes mellitus fulfilling the inclusion and exclusion criteria were selected for this study. All patients underwent complete ocular examination including fundoscopy to grade the stage of diabetic retinopathy using the ETDRS chart. To assess the extent of microalbuminuria, a urine albumin to creatinine ratio was carried out using the urine spot test and classified as mild, moderate and severe according to KIDGO 2012 clinical practice guidelines.

Results: Out of 300 patients 104 (34.6%) had some stage of diabetic retinopathy. Microalbuminuria was present in all (104) patients with diabetic retinopathy and in 55 (28.06%) patients with no diabetic retinopathy. The severity of microalbuminuria correlates with the advancement in stages of retinopathy with a p value < 0.001 as the number of patients with moderate and severe microalbuminuria had higher stages of diabetic retinopathy. None of the patients with very mild diabetic retinopathy had moderately or severely increased microalbuminuria whereas 88% of patients with advanced diabetic retinopathy had moderately increased microalbuminuria and 4% had severely increased microalbuminuria. Furthermore, 76% of the patients had moderately increased and 12% had severely increased microalbuminuria in patients >7 HbA1c and only 28% of patients had moderately increased microalbuminuria and none had severely increased microalbuminuria in patients with ≤ 7 HbA1c.

Conclusion: This study showed that the degree of microalbuminuria increases with each higher stage of diabetic retinopathy.

Keywords: Urine albumin creatinine ratio, Diabetic retinopathy, Fundoscopy, Microalbuminuria.

Introduction

Diabetes Mellitus is a metabolic disorder that results in high blood glucose levels which could be due to insufficient production of insulin or because cells are resistant to the effects of insulin.[1] The International Diabetes Federation (IDF) Atlas of 2017 puts Pakistan at 10 of 221 countries of the world, with 7.5 million cases of diabetes in the age group of 20-79 years, and at number 18 out of 21 countries for having a prevalence of 6.9% in this age group.[2]

Diabetes mellitus affects major and minor blood vessels and longer duration results in an increased risk of involvement of multiple organs like eyes, kidneys, brain and heart.[3] Many factors are contributory towards the progression of complications which include poor glycemic control, microalbuminuria, hypertension, pregnancy, and hyperlipidemia.[4] Diabetic retinopathy

(DR) and diabetic nephropathy are main sources of social and economic burden to patients with diabetes mellitus and to the healthcare system due to the risk of blindness and end stage kidney disease.

Diabetic retinopathy is the most common cause of visual loss in patients with diabetes mellitus.[5,6] A pooled meta-analysis including 35 studies from 1980 to 2008 estimated worldwide prevalence of any diabetic retinopathy and proliferative diabetic retinopathy (PDR) among patients to be 35.4% and 7.5%, respectively.[7] Hyperglycemia leads to retinal vascular changes that result in vascular leakage and non-perfusion of the retina.[8] Features of diabetic retinopathy include, retinal hemorrhages, exudates, macular edema, cotton wool spots, microvascular abnormalities, vitreous hemorrhages and even tractional retinal detachment in advanced cases.[9] Diabetic retinopathy can be classified into various stages according to early treatment diabetic retinopathy study.[10] Stages of diabetic retinopathy can be determined on fundus examination with direct or indirect ophthalmoscopy.[11] Every stage can correspond to duration of diabetes, Hb1Ac levels and microalbuminuria.

Diabetes is one of the leading causes of chronic kidney disease and 40% of the patients will eventually develop diabetic nephropathy.[12] Pathogenesis of diabetic nephropathy is the same as retinopathy. It is characterized by microalbuminuria and nodular glomerular sclerosis. Increased endothelial permeability allows excessive albumin to escape into the glomerular infiltrate. [12] Albuminuria is the most frequently used marker for assessing the development of kidney disease. Over 50% of cases can be missed if albuminuria is not tested thus making it the very important marker for diagnosis and early detection of chronic kidney disease. Development of nephropathy can be determined by measuring the urine albumin to creatinine ratio and it can be classified into mild (3mg/mmol), moderate (3-30mg/mmol) and severe (>30mg/mmol). Urine albumin creatinine ratio has the advantage of increased sensitivity and quantification of results.[13]

Our study was designed to find out the association of end organ damage in terms of microalbuminuria and severity of diabetic retinopathy giving due consideration to few independent values like duration of disease and HbA1c levels.

Methodology

This Cross sectional study was conducted in Combined Military Hospital Lahore from Dec 2019 to Dec 2020. The study design was approved by the ethical review committee (265/2021). Informed written consent was taken from all patients participating in the study and patients were selected through random sampling. Inclusion criteria was all patients presenting to the Eye Department Combined Military Hospital Lahore with type II diabetes mellitus in the age range of 35-75 years. Exclusion criteria included patients having type I diabetes mellitus, gestational diabetes, and those with posterior segment pathology other than diabetic retinopathy.

We evaluated 300 patients with type II diabetes mellitus.[14] Sample size was calculated by WHO sample size calculator using population prevalence proportion of type II diabetes mellitus as 16.9%.[14] Patients reported to Combined Military hospital Lahore with a decrease in vision along with type II diabetes mellitus and for routine fundus examination for diabetic changes. All patients underwent eye examination including best corrected visual acuity, anterior segment examination and fundus examination using Slit Lamp Examination using 90 D lens.. The stage of diabetic retinopathy was determined in each patient using the early treatment diabetic retinopathy chart.[15] Diabetic retinopathy was divided into Very Mild Non Proliferative Diabetic Retinopathy (NPDR), Mild NPDR, Moderate NPDR, Severe NPDR, Very Severe NPDR, Proliferative Diabetic Retinopathy (PDR) and High Risk PDR. Duration of diabetes, HbA1c level and urine albumin to creatinine ratio was determined in each patient.

Microalbuminuria was measured as urine albumin to creatinine ratio in a spot urine sample. It was categorized as mildly increased 3mg/mmol, moderately increased 3-30mg/mmol and severely increased equal to or >30 mg/mmol according to KDIGO 2012 clinical practice guidelines.[15] Grade of retinopathy was determined and microalbuminuria for that grade was calculated. Association of the severity of diabetic retinopathy and microalbuminuria was thus seen in all the patients.

We used the SPSS v23 (SPSS Inc., Chicago, IL, USA) for all analyses. The tables were produced using Microsoft Excel (Microsoft Corp., Redmond, WA, USA). A chi-square test was used to evaluate the severity of microalbuminuria with each stage of diabetic retinopathy. A p value of ≤ 0.05 was considered significant.

Results

A total number of patients examined for diabetic retinopathy were 300. 196 patients did not have diabetic retinopathy. Among the 104 patients who had diabetic retinopathy 11 had very mild NPDR, 17 had mild NPDR, 28 had moderate NPDR, 7 had severe NPDR, 35 patients had PDR and 03 had high risk PDR.

Table I shows that as the severity of diabetic retinopathy increases, the percentage of patients having moderately and severely increased microalbuminuria increases, p value < 0.001 (1.0861E-14). All the patients 100% (n=11) with very mild NPDR had mildly increased microalbuminuria. 58.82% (n=7) had moderately increased and 41.17% (n=10) had mild increased microalbuminuria in patients with mild NPDR. 7.14% (n=2) of patients had mildly increased, 78.57% (n=22) had moderately increased and 14.2% (n=4) had severely increased microalbuminuria in patients with moderate NPDR. All the patients 100% (n=7) had moderately increased microalbuminuria in patients with very severe NPDR. 88% (n=31) of the patients had moderately increased and 11% (n=4) had severely increased microalbuminuria in patients having PDR. All the patients 100% (n=3) had moderately increased microalbuminuria in patients with high risk PDR. Thus it is seen that the severity of microalbuminuria increases with advanced stages of diabetic retinopathy. In 196 patients with no diabetic retinopathy 28.06% (n=55) patients had mildly increased microalbuminuria. Rest had normal range of microalbuminuria.

It was also seen that the longer the duration of diabetes mellitus, the more number of patients had advanced disease of retinopathy p value <0.001(5.67 E-11).

None of the patients with less than 05 years of diabetes mellitus have very severe NPDR, PDR or high risk PDR whereas amongst the people with > 05 years of type II diabetes mellitus, 3.7% had very severe NPDR, 43% had PDR and 3.7% had high risk PDR.

Microalbuminuria was also related to glycemic control. Patients with HbA1c value >7 had higher degrees of microalbuminuria p value <0.001(6.0857E-7). (Table III)

Table III: Microalbuminuria-HbA1c.

Microalbuminuria	HbA1c		Total	p-value
	≤ 7	>7		
Mildly increased	10	10	20	< 0.001
Moderately increased	4	69	73	< 0.001
Severely increased	0	11	11	< 0.001
Total	14	90	104	< 0.001

Discussion

It was seen in our study that an increase in the severity of microalbuminuria was significantly associated with an advanced stage of diabetic retinopathy, poor glycemic control, and longer duration of type II diabetes mellitus p value (<0.001). Poor glycemic control results in glycated end products causing microvascular and macrovascular abnormalities leading to leakage and ischemia in end organs.[5] Retinal microvasculature changes result in hemorrhages, exudates, macular edema, ischemia, vitreous hemorrhage and tractional retinal detachment in advanced cases.[5] The pathogenesis of microvasculature damage in kidneys is the same, resulting in leakage of

Table I: Retinopathy-Microalbuminuria

Grades of Retinopathy	Microalbuminuria			Total	P-value
	Mildly increased	Moderately increased	Severely increased		
Very mild NPDR	11 (100%)	0	0	11	< 0.001
Mild NPDR	7 (58.82%)	10 (41.17%)	0	17	< 0.001
Moderate NPDR	2 (7.14%)	22 (78.57%)	4 (14.28%)	28	< 0.001
Severe NPDR	0	7 (100%)	0	7	< 0.001
Very severe NPDR	0	0	3 (100%)	3	< 0.001
PDR	0	31 (88%)	4(11%)	35	< 0.001
High Risk PDR	0	3 (100%)	0	3	< 0.001
Total	20	73	11	104	< 0.001

Table II: Duration Retinopathy

Duration	Retinopathy							Total	p-value
	Very mild NPDR	Mild NPDR	Moderate NPDR	Severe NPDR	Very Severe NPDR	PDR	High risk PDR		
< 5 years	11	8	4	0	0	0	0	23	<0.001
>5 years	0	9	24	7	3	35	3	81	<0.001
Total	11	17	28	7	3	35	3	104	<0.001

proteins, especially albumin and is one of the earliest signs of start of diabetic nephropathy.[12] This study clearly shows that the severity of both entities is very closely related and one should expect a greater degree of renal damage in patients with advanced diabetic retinopathy.

The result of this study is comparable to previous many international studies. Park HC et al showed that patients with proliferative diabetic retinopathy most commonly presented with renal involvement showing increased levels of microalbuminuria.[16] Ashrit P et al concluded that poor glycemic control, long duration of type II diabetes resulted in an advanced stage of diabetic retinopathy and also increased level of microalbuminuria with each stage.[17] It also showed that the mean microalbuminuria in mg/day increased from 141.62±10.04 in grade 1 diabetic retinopathy to 278.56±11.26 in grade 4 diabetic retinopathy.[17] The study termed microalbuminuria as a reliable marker for the risk of onset and progression of proliferative diabetic retinopathy.[17] Cui J et al also concluded that higher albumin levels is a risk factor for the severity of diabetic retinopathy and can be used for early detection.[18] Another study by Goudinho SJ et al revealed that the percentage of people having microalbuminuria in very mild NPDR was 42.10% which increased to 85.70% in very severe NPDR and 90.90 % in PDR.[19] Rajalakshmi R et al showed that patients with NPDR and PDR had higher levels of albuminuria than those without DR.[20] This study also observed that severely increased levels of microalbuminuria increased the risk of progression to sight threatening diabetic retinopathy. [20]

In our study, the duration of type II diabetes mellitus was higher in patients with advanced stages of diabetic retinopathy. For every 5 years' duration of diabetes mellitus, the risk of diabetic retinopathy increases 1.89 times.[21] Goyal B et al termed duration of diabetes mellitus, microalbuminuria and glycosylated hemoglobin as independent risk factors for diabetes mellitus.[22] Cho A et al revealed that longer duration of diabetes and albuminuria were associated with progression of no DR to NPDR.[23]

The results of many local studies are comparable with the results of this study. Ahmad T et al concluded that microalbuminuria was present in 31.56% of the patients and was an initial sign of diabetic retinopathy along with many other signs.[24] Our study showed that microalbuminuria with diabetic retinopathy was present in 34.6% of the patients. In another study by Mian LS et al it was seen that advanced stage of retinopathy was present in patients with severe chronic kidney disease and as the stage of diabetic retinopathy increased from no DR to NPDR and then to PDR and advanced diabetic disease percentage of patients having severe chronic kidney disease increased from 56.25% to 69.75% and then to 81.81% but this association did not reach a statistical significance.[25]

Our study showed that there is a statistically significant correlation between the increased level of urinary albumin and the severity of diabetic retinopathy and thus all patients with diabetic retinopathy should be monitored and evaluated for signs for diabetic nephropathy for early detection and a multidisciplinary management approach should be kept in mind for such patients to prevent further complications.

Conclusion

Our study results confirmed a close association between microalbuminuria and the severity of type II diabetic retinopathy. Biochemical parameters such as urine for albumin creatinine ratio and HbA1c can serve as helpful tools in the early detection of retinal and renal complication and can reduce irreversible damage in long term. Patients should be counselled about good glycemic control, diet, exercise and adopt healthy lifestyle modification to reduce the chances and complications of diabetic retinopathy.

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