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Microalbuminuria and Other Risk Factors in Diabetic Retinopathy

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Abstract

The objective of this paper was to study positivity of microalbuminuria and other risk factors in DM type II and their relation to DR. An analytic study was done among 300 selected cases of Type 2 DM in one year. The grading of the severity of DR was done using ETDRS protocol. Tests for hemoglobin, fasting blood sugars, micro-albuminuria, glycated hemoglobin (HbA1c) and lipid profile were done. 137 (45.67%) cases of DM found to have DR [22(7.33%) mild NPDR, 43 (14.33%) moderate NPDR, 30(10%) severe NPDR and 42 (14%) PDR]. 61(20.33%) cases of DR have microalbuminuria [50% (21/42) cases of PDR, 66.67% (20/30 cases) in severe NPDR cases, 34.89% (15/43 cases) in moderate NPDR and 13.64% (3/22 cases) in mild NPDR cases]. Duration of DM, hypertriglyceridemia, cholesterol had positive relation with DR. Levels of HDL, LDL and hemoglobin had no relation with DR although the occurrence of low HDL, high LDL, hypertension and anemia had relation with DR. Occurrence and progression of DR is associated with uncontrolled DM, long duration of DM, dyslipidemia, anemia and hypertension. Microalbuminuria is a contributing factor in the degree of retinopathy.

***Keywords**: Diabetic retinopathy, diabetes mellitus, microalbuminuria, risk factors*

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INTRODUCTION

Diabetes mellitus type 2 is one of the common metabolic disorders. The global prevalence of diabetes is estimated to increase from 4% in 1995 to 5.4% in 2025 [1].

Diabetic retinopathy (DR) is the most terrible complication and the leading cause of new cases of legal blindness among working-age individuals. In India, prevalence of DR is estimated to be 23.5% [1]. Retinopathy and nephropathy (DN) are both related to endothelial dysfunction mediated microvascular complications of DM [1].

DN is an important cause of morbidity and mortality and is now among the most common causes of end-stage renal disease. However there is an early phase of DR when there is a rise in urinary excretion of albumin, i.e., microalbuminuria. Various studies reported relationship between microalbuminuria or proteinuria with retinopathy [2–4]. Up to the stage of microalbuminuria, DR can be reversed or prevented from further progression. The sensitive marker for the detection of DN is to estimate excretion of microalbumin in urine; and for the detection of DR, to have a fundus evaluation after pupillary dilatation [5]. The purpose of this study was to evaluate positivity of microalbuminuria and other risk factors in DM Type II and their relation to DR.

MATERIAL AND METHODS

This was a hospital-based analytic study done in upgraded department of Ophthalmology at a tertiary center in north India. In the study, 300 selected cases of Type 2 diabetes mellitus (defined according to ADA 2007) [6], who visited retina clinic during the period of September 2011 to September 2012, were included after taking informed consent. Cases of DM who had pregnancy, accelerated hypertension, active systemic infection, coexisting ocular disorders like uveitis, opaque/hazy media, retinal disorders like retinal vein/artery occlusions, retinitis

pigmentosa, vitreoretinal degenerations and dystrophies, high myopia and recent ocular surgeries (< 6 months) including vitreo-retinal surgery for causes other than DR, neovascular glaucoma or neovascularization of iris or disease (other than diabetes) than can cause microalbuminuria, e.g., myocardial infarction, acute pancreatitis, burn, inflammatory bowel disease, congestive heart failure, chronic obstructive pulmonary disease, malignancy were excluded from the study.

Complete history regarding duration of disease, previous photocoagulation and medication taken and detailed physical and ophthalmologic evaluation was done for every subject. Best-corrected visual acuity (BCVA) for distance according to ETDRS protocol and for near using Jaeger's chart were calculated. The optic disc, macula and the retinal background were evaluated using indirect ophthalmoscopy and slit-lamp biomicroscopy with 78 diopter (D) lens. Laboratory investigation – ECG, hemoglobin, fasting and 2 h postprandial blood sugars, micro-albuminuria, urine complete examination, glycated hemoglobin (HbA1c) and lipid profile – were done.

The grading of the severity of DR and diagnosis of CSME was done using ETDRS protocol [7]. Clinitek 100 (made by Bayer Corporation-Elkhart, IN 46515, USA) was used to measure microalbuminuria. The device shows the ratio of albumin to creatinine in mg/g. If the ratio is < 30 mg/g, the patient is normoalbuminuric. Ratios of 30–300 mg/g are indicative of microalbuminuria and > 300 mg/g reveals macroalbuminuria. Plasma glucose was measured by glucose oxidase technique on an automated analyzer. Glycated Hb (HbA1c) was measured by a chromatography analyzer. Plasma lipoproteins were measured with glucose oxidase technique on automated analyzer. Dyslipidemia was defined using NCEP ATP III guidelines as total cholesterol > 200 mg/dL and/or high density lipoprotein (HDL) cholesterol < 40 mg/dL and/or low density lipoprotein (LDL) cholesterol > 100 mg/dL and/or triglycerides > 150 mg/dL [8]. HbA1c > 7% is considered abnormal [7]. Hypertension was defined as a blood pressure measurement of above 140/90 mmHg in the right upper limb supine position or when the patient was on antihypertensive drugs [9].

Statistical Analysis

Chi-square test and student t-test were used to find the significance among various parameters. The odd ratio was used to find the strength of relationship. $P < 0.05$ was taken as statistically significant.

RESULTS

This study was conducted among 300 DM patients who had male:female ratio 1.24:1, mean age 60.68 ± 9.43 years (range 40–90 years), mean duration of diabetic 75.38 ± 63.88 months and 40 (13.33%) DM cases were taking insulin. DR was found in 137 (45.67%) cases of DM [22 (7.33%) mild NPDR, 43 (14.33%) moderate NPDR, 30(10%) severe NPDR and 42 (14%) PDR]. Sixty-one cases of DR have microalbuminuria. The positivity of microalbuminuria in PDR was 50% (21/42 cases), 66.67% (20/30 cases) in severe NPDR cases, 34.89% (15/43 cases) in moderate NPDR and 13.64% (3/22 cases) in mild NPDR.

DISCUSSION

In this study, 45.67% positivity of DR was found among 300 DM cases. The mean duration of DM was found to be highly significant statistically when compared among normal retina with DR cases. So, as duration of DM increases, the risk and severity of DR also increases. Duration of DM also shows positive association in previous studies [10–13].

Statistically significant difference for BMI was not found between normal and mild NPDR, moderate NPDR, severe NPDR or PDR groups ($P > 0.05$). BMI had no relation with DR. In another study, when patients with normal and abnormal glucose metabolism were followed for 9.4 years, BMI was found not to be associated with the development of any degree of retinopathy [14]. Also, in a population-based study, BMI was not related to progression of DR [15]. But in some studies, BMI was found to be associated with DR [10, 12, 13].

Table 1: *Positivity of Risk Factors of DR in DM Cases.*

Risk factor		Normal	DR	Total	P	Retinopathy			
						NPDR			PDR
						Mild	Moderate	Severe	
		163(54.33)	137(45.67)	300(100)		22(7.33)	43(14.33)	30(10.00)	42(14.00)
Duration of DM (years)	< 8	156(52)	56(18.67)	212(70.67)	< 0.05	16(5.33)	17(5.67)	11(3.67)	12(4)
	≥ 8	7(2.33)	81(27.00)	88(29.33)		6(2.00)	26(8.67)	19(6.33)	30(10)
BMI	Normal	65(21.67)	49(16.33)	114(38.00)	> 0.05	9(3.00)	15(5.00)	9(3.00)	16(5.33)
	Over weight	76(25.33)	74(24.67)	150(50.00)		12(4.00)	23(7.67)	17(5.67)	22(7.33)
	Obese	22(7.33)	14(4.67)	36(12.00)		1(0.33)	5(1.67)	4(1.33)	4(1.33)
TG	Normal	140 (46.67)	87(29)	227(75.67)	< 0.05	11(3.67)	27(9.00)	19(6.33)	30 (10.00)
	High	23(7.67)	50(16.67)	73(24.33)		11(3.67)	16(5.33)	11(3.67)	12(4.00)
TC	Normal	143(47.67)	111(37)	254(84.67)	< 0.05	17(5.67)	34(11.33)	25(8.33)	30(10.00)
	High	20(6.67)	26(8.67)	46(15.33)		5(1.67)	9(3.00)	5(1.67)	12(4.00)
HDL	Normal	150(50.00)	123(41)	273(91.00)	< 0.05	17(5.67)	38(12.67)	24(8.00)	37(12.67)
	Low	13(4.33)	14(4.67)	27(9.00)		5(1.67)	5(1.67)	6(2.00)	5(1.33)
LDL	Normal	89 (29.67)	63(21)	152(50.67)	< 0.05	12(4.00)	25(8.33)	13 (4.33)	13(4.33)
	High	74 (24.67)	74(24.67)	148 (49.33)		10(3.33)	18(6.00)	17(5.67)	29(9.67)
HbA1c (%)	Normal	129(43.00)	52(17.33)	181(60.33)	< 0.05	13(4.33)	17(5.67)	7(2.33)	15(5.00)
	High	34(11.33)	85(28.33)	119(39.67)		9(3.00)	26(8.67)	23(7.67	27(9.00)
Hb (g/dL)	Normal	91(30.33)	70(23.33)	161(53.67)	> 0.05	10(3.33)	23(7.67)	15(5.00)	22(7.33)
	Anemia	72(24.00)	67(22.33)	139(46.33)		12(4.00)	20(6.67)	15(5.00)	20(6.67)
HTN	Present	54(18.00)	53(17.67)	107(35.67)	> 0.05	7(2.33)	15(5.00)	13(4.33)	22(7.33
	Absent	109(36.33)	84(28.00)	193(64.33)		15(5.00)	28(9.33)	17(5.67)	20(6.67)
Albuminuria	Normal	161(53.67)	73(24.33)	234(78.00)	< 0.05	19(6.33)	24(8.00)	10(3.33)	20(6.67)
	Micro-albuminuria	2(0.66)	59(19.67)	61(20.33)		3(1.00)	15(5.00)	20(6.67)	21(7.00)

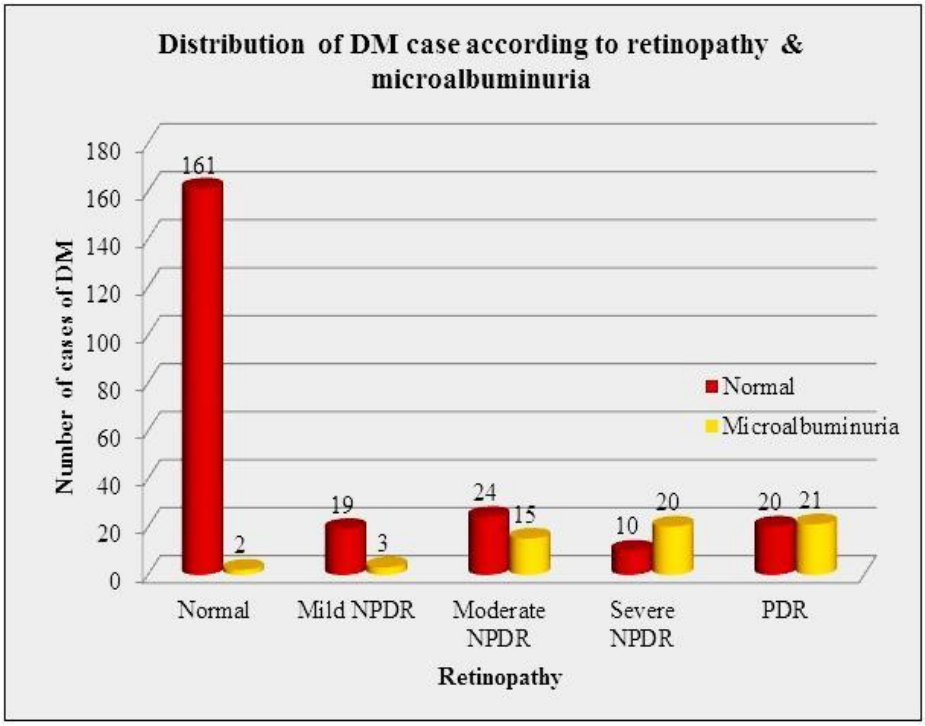

Table 2: *Type of Diabetic Retinopathy and Mean ± SD of Risk Factor.*

Risk factor	Retinopathy					P
	Normal (163)	Mild NPDR (22)	Moderate NPDR (43)	Severe NPDR (30)	PDR (42)	
Duration of DM (years)	36.12 ± 35.79	88.36 ± 45.57	127.25 ± 67.04	130.80 ± 58.41	128.28 ± 46.21	< 0.01
BMI (kg/m^2)	24.10 ± 2.80	23.84 ± 2.03	24.52 ± 3.17	24.60 ± 2.63	23.98 ± 2.56	> 0.05
TG (mg/dL)	122.23 ± 34.60	153.09 ± 44.06	146.98 ± 50.13	146.03 ± 57.38	134.16 ± 64.84	< 0.05
TC (mg/dL)	161.71 ± 37.46	157.41 ± 24.56	169.30 ± 34.07	172.03 ± 33.66	180.50 ± 55.35	< 0.05
HDL (mg/dL)	44.35 ± 4.28	42.22 ± 6.90	44.72 ± 5.09	44.67 ± 4.44	44.38 ± 4.90	> 0.05
LDL (mg/dL)	102.16 ± 27.44	95.54 ± 26.34	97.32 ± 27.90	111.00 ± 31.09	116.31 ± 38.59	> 0.05
HbA1c (%)	6.52 ± 0.85	6.67 ± 0.81	7.63 ± 1.36	7.97 ± 1.22	7.50 ± 1.32	< 0.05
Hb (g/dL)	11.55 ± 1.84	10.84 ± 2.01	11.46 ± 1.73	11.27 ± 1.71	11.23 ± 2.07	> 0.05
HTN (%)	33.13%	31.82%	34.88%	43.33%	52.28%	> 0.05

In a landmark study, Dornan *et al.* [16] first showed the association of LDL-cholesterol in subjects with DR. Klein *et al.* [17] reported an association of serum cholesterol with severity of hard exudates in macula. This was further substantiated by Miccoli *et al.* [18]. Data from the ETDRS [18] and Leiden *et al.* [19] have also demonstrated the association of total cholesterol and LDL-cholesterol with the onset as well as severity of retinal hard exudates [18]. This was consistent with the authors' findings of an association between serum triglyceride, total cholesterol, LDL-cholesterol and HDL cholesterol with DR. Hove *et al.* [20] found no association between DR and triglycerides, total cholesterol and HDL-cholesterol in an unselected population of Type 2 diabetic patients from Denmark. Also, some studies reported that while total serum cholesterol, LDL-cholesterol and HDL-cholesterol were related to PDR, serum triglycerides showed no association [21, 22]. Sachdev [23] also reported serum cholesterol, LDL and TG as independent risk factors for retinal hard exudates formation in Type 2 diabetic north Indian patients.

The mechanisms by which high serum lipids cause the development and progression of DR are not fully understood. It has been postulated that an increase in blood viscosity and alterations in the fibrinolytic system occur in hyperlipidemia and lead to the formation of hard exudates. Also, incorporation of triglycerides into the cell membrane may lead to changes in membrane fluidity and leakage of plasma constituents in the retina. This results in hemorrhage and edema in the retina. Also, high lipid levels are known to cause endothelial dysfunction through a local inflammatory response, with subsequent release of cytokines and growth factors, hypoxia, increase in LDL oxidation, etc. In animal models, it has been shown that endothelial dysfunction in diabetic vasculature results in blood–retinal barrier breakdown [24].

Though statistically significant difference for HbA1C levels was not found between normal and mild NPDR and moderate NPDR groups ($P > 0.05$) in this study but the difference in HbA1c levels was statistically significant among normal and severe NPDR, normal and PDR groups ($P < 0.001$). The probable explanation for this observation is that HbA1c has somewhat less role in initiation of the retinopathy than its progression. Previous studies also found poor glycemic control as a risk factor for proliferative DR [25–28].
In the current study, although anemia is more common in DR but hemoglobin levels had no effect on severity of DR. Mohan [10] reported anemia to be a significant risk factor for occurrence of DR. In this study, the authors found that as the severity of DR increases, occurrence of hypertension also increases. But they failed to find any significant difference between hypertensive and normotensive cases of DR UKPDS [26] and Boelter [12] did not reveal any relation between the progression of retinopathy and blood pressure levels in patients who already presented DR at baseline.

Albuminuria and Diabetic Retinopathy
Current study showed that as severity of DR

increases, the positivity of microalbuminuria also increases. Previous studies [10, 12, 13] also showed microalbuminuria as a contributing factor in the degree of retinopathy and this can be explained by the common mechanism involved in tissue damage. An independent association between microalbuminuria and NPDR was observed in a study from Cameroon by Sobngwi *et al.* [29]. Singh *et al.* [30] found that increasing albuminuria was significantly associated with PDR. In these previous studies, albuminuria has been considered as a predictor of diabetic retinopathy. These findings support the suggestion that both DR and nephropathy progress in a parallel way. These findings stress on the need for close monitoring for DR in patients with microalbuminuria to prevent irreversible visual loss.

Table 3: *Association between Types of Diabetic Retinopathy and Risk Factors.*

Diabetic retinopathy	Duration of DM (years)	BMI (kg/m^2)	TG	TC	HDL	LDL	HbA1c (%)	Hb (g/dL)
Normal v/s mild NPDR	P < 001 HS	P > 05 NS	P < 0.01 Sig	P > 05 NS	P >> 05 NS	P > 05 NS	P > 05 NS	P > 05 NS
Normal v/s mod NPDR	P < 001 HS	P > 05 NS	P < 0.01 Sig	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS
Normal v/s Severe NPDR	P < 001 HS	P > 05 NS	P < 0.01 Sig	P > 05 NS	P > 05 NS	P > 05 NS	P < 001 HS	P > 05 NS
Normal v/s PDR	P < 001 HS	P > 05 NS	P<.05 Sig	P<.05 Sig	P > 05 NS	P > 05 NS	P<.001 HS	P > 05 NS
Mod NPDR v/s PDR	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS	P<.05 Sig	P > 05 NS	P > 05 NS
Mild NPDR v/s Mod NPDR	P < 01 Sig	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS	P < 001 HS	P > 05 NS
Mild NPDR v/s Severe NPDR	P < 01 Sig	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS	P < 001 HS	P > 05 NS
Mild NPDR v/s PDR	P < 01 Sig	P > 05 NS	P > 05 NS	P < 05 Sig	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS
Mod NPDR v/s Severe NPDR	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS	P < 05 Sig	P < 001 HS	P > 05 NS
Severe NPDR v/s PDR	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS	P > 05 NS

Table 4: *Association between CSME and Microalbuminuria.*

CSME	Microalbuminuria		Total	P
	Present	Absent		
Yes	31 (13.22)	29 (41.69)	60 (44.07)	> 0.05
No	1 (7.46)	1 (37.63)	2 (55.93)	
Total	32 (20.68)	30 (79.32)	62 (100.00)	

The authors did not find significant association between CSME and microalbuminuria (P > 0.05). Manaviat [13] and Mohan [10] showed positive relation between CSME and microalbuminuria.

LIMITATIONS

The limitation of the present study was the self-reported diabetic population and so the possibility of a selection bias. A possible limitation of the present study was the inclusion of individuals from tertiary care centers, favoring the selection of patients with more severe forms of diabetes and its complications. Another limitation of the present study was DR grading that was based on indirect ophthalmoscopy and not on fundus photography grading.

CONCLUSIONS

DR is a common complication of DM. Occurrence and progression of DR is associated with uncontrolled DM, long duration of DM, dyslipidemia, anemia and hypertension. Microalbuminuria is a contributing factor in the degree of

retinopathy. This study stresses on the need for close monitoring of DR in patients with microalbuminuria to prevent irreversible visual loss.

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