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Original research article

An association analysis of diabetes mellitus duration microalbuminuria and hyperlipidemia with diabetic retinopathy: prospective cross-sectional study

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Abstract

Aim: To evaluate the association of duration of diabetes mellitus, microalbuminuria, hyperlipidemia with diabetic retinopathy.

Methods: The prospective cross-sectional study which was carried in the Department of Ophthalmology, Patna Medical College and Hospital, Patna, Bihar, India for 1 year. Total 200 patients were included in this study. For the study, type II DM is defined as a fasting plasma glucose of more than or equal to 126 mg/dl or 2-hour post glucose load plasma glucose of more than or equal to 200 mg/dl or a random plasma glucose of more than or equal to 200 mg/dl in the presence of symptoms of hyperglycemia. All the biochemical assessments were done using an Auto analyzer.

Results: A total of 200 subjects of either gender were included in our study, out of which 110 (55%) were females and rest were males (90; 45%). Majority of the patients lied in the age group of 40-60 years (55%). Out of 100 patients in the retinopathic group, 50 (25%) of them suffered from very mild to moderate NPDR, 30 (15%) patients showed signs of severe to very severe NPDR and only 20 (10%) had proliferative diabetic retinopathy. Proportion of Group I (No retinopathy) was higher in younger patients i.e. below 40 (73.33%) and 40-60 (49.09%) as compared to elderly cases i.e. 60-80 (37.93%) and this difference was found to be statistically significant ($p < 0.001$). It was found that proportion of Group I (non-retinopathy) patients was higher in patients with duration of diabetes < 10 years (70%) as compared to patients with duration 10-20 years (51.43%), 20-40 years (6.67%) and > 40 years (30%). Majority of patients with duration of diabetes 20-40 years and > 40 years belonged to Group IIA (very mild to moderate retinopathy). Majority of patients (86.49%) of Grade 0 microalbuminuria (< 2.5 mg/mmol) had no Retinopathy. Out Of 200 patients of diabetes, total cholesterol was found to be desirable (< 200 mg/dl) in only 60 (30%) patients.

Conclusion: Duration of diabetes and microalbuminuria has been found to be the independent risk factors for diabetic retinopathy, but serum cholesterol levels did not show an independent role in our study.

Key words: Diabetes Mellitus; Diabetic Retinopathy; Microalbuminuria; Hyperlipidaemia

Introduction

Diabetes mellitus is a syndrome in which there is a combination of irregular metabolism, insulin resistance or insulin secretion, or insufficient secretion for compensation of hyperglycemia.[1] Diabetes is one of the leading causes of mortality and morbidity in the world and is the sixth chief reason for mortality in the USA. The USA has over 71,000 deaths annually.[2] The vast majority of patients with diabetes fall into two broad categories: absolute

insulin deficiency and insulin secretion, characterized by type 2 diabetes, insufficient type of growth compensation and the presence of insulin resistance. In addition to the two main types, pregnancy and pancreatic disorders, endocrinopathies and drugs, etc are also the causes.[3] Prolonged hyperglycemia promotes glucose reactions with components of the artery wall, resulting in an increase in glycation end products.[4] These products are cross-linked with collagen, which increases the stiffness of the arteries supporting atherosclerosis in the presence of high density lipoproteins (LDL) and cholesterol. In this way, high blood sugar leads to endothelial damage that occurs as microvascular or macrovascular damage. A diabetic patient is sensitive to many complications that cause morbidity and early mortality. Diabetic complications pose a huge burden to healthcare, as poor glycemic control in diabetic patients is also directly related to increased overall healthcare costs. The microvascular disease also has a significant impact on the lives of type II diabetic patients. Diabetic retinopathy is the most serious of the various complications of diabetes.[5,6] The incidence of diabetic retinopathy is 21% to 60%, respectively, in people with diabetes below five years and at least 15 years. Proliferative retinopathy ranges from 1.2% to 67% in people with diabetes for less than a decade and for 35 or more years. The incidence of blindness was 16% in patients with DM. Retinopathy after ten years of diabetes is associated with longer hemoglobin glycine and proteinuria, increase diastolic pressure and infertility in males.[7] Renal diseases linked with type II diabetes mellitus is the major cause of end-stage renal disease in the world. In the USA, the incidence of renal diseases linked with diabetes mellitus has augmented by 150% over the last ten years. The 1st clinical indication of renal dysfunction in diabetic patients is usually microalbuminuria, which progresses between two to five percent annually.[8,9] Microalbuminuria rarely reversible in type II diabetes, but in its place, 20 to 40 percent of patients exceed proteinuria. In 10 to 50 percent of CKD patients and proteinuria finally need transplantation or dialysis. 40 to 50 percent of diabetic patients with microalbuminuria sooner or later die of cardiovascular anomalies; this ratio is 3 times greater from cardiac causes, with diabetes, but without signs of renal disease. In cases of renal disease and diabetes mellitus, decreasing blood pressure and reduced albumin in urine are operative in declining the risk of myocardial infarction, end-stage renal disease, stroke and heart failure. Angiotensin II antagonists and ACE inhibitors supposed to be the utmost beneficial antihypertensive agents. Calcium channel blockers other than dihydropyridine also reduce urine albumin and the advancement of kidney disease, and the grouping of calcium channel blockers and dihydropyridine other than ACE inhibitor treatment is even more effective.[10]

Material and methods

The prospective cross-sectional study which was carried in the Department of Ophthalmology, Patna Medical College and Hospital, Patna, Bihar, India for 1 year, after taking the approval of the protocol review committee and institutional ethics committee.

Methodology

Total 200 patients were included in this study. For the study, type II DM is defined as a fasting plasma glucose of more than or equal to 126 mg/dl or 2-hour post glucose load plasma glucose of more than or equal to 200 mg/dl or a random plasma glucose of more than or equal to 200 mg/dl in the presence of symptoms of hyperglycemia. All the Patients with acute or chronic renal failure, Opaque/hazy ocular media preventing fundus visualization, Co-existing ocular disorders likely to mask the findings of diabetic retinopathy, Patients with presence of any of the confounding factors, like fever, active systemic infections, exercise, high protein intake, accelerated hypertension, congestive heart failure, patients not willing to participate in the study were excluded from the study.

Thorough ocular evaluation was done on all selected patients both clinically as well as with the help of diagnostic instruments. Both Uncorrected and best corrected visual acuity was recorded using a Snellen's chart. Anterior segment evaluation was done using slit lamp examination to look for any other ocular disease or ocular surgery.Amsler Grid Examination was also performed. The intraocular pressure was measured using an applanation tonometer.
Fundus examination was performed by Direct Ophthalmoscopy, Indirect Ophthalmoscopy and +90D lenses. Optical coherence tomography was performed using Cirrus 500 machine manufactured by Carl-Zeiss, Germany to measure the macular thickness, and Fundus Fluorescein Angiography by using Carl Zeiss fundus camera. Diabetic retinopathy was graded as per the ETDRS guidelines.
The biochemical evaluation was done by obtaining 2 ml of blood sample from the patient in a sterile vial and sent to the Department of Biochemistry. All the biochemical assessments were done using an Auto analyzer. All the patients were advised to undergo biochemical investigations for Blood sugar (fasting/pp), HbA1c taken as HbA1c: Good Control: = 7.0%: grade1, Fair control: 7.1-8.5%: grade 2; poor control: > 8.5%: grade3.[11] Urinary albumin to creatinine ratio in a random spot collection of urine and Lipid profile.
For the purpose of this study microalbuminuria was further sub graded as-Grade 0: < 2.5mg/mmol; Grade I: 2.5-12.5mg/mmol; Grade II: > 12.5-25mg/mmol and Grade III: > 25mg/mmol for men and Grade 0: < 3.5mg/mmol; Grade I: 3.5-12.5mg/mmol; Grade II: > 12.5-25mg/mmol and Grade III: > 25mg/mmol for women.[12]
Lipid profile was also sub graded as- Desirable (< 200); Border line high (200-239); High (≥240).[13]

Statistical analysis
The data was analyzed using SPSS software version 20. Categorical data chi-square test was used whereas continuous data was analyzed using ANOVA and student "t-test". Multivariate assessment was done using logistic regression. The confidence level of the study was kept at 95% and hence a "p" value of less than 0.05 indicated a statically significant association.

Results
A total of 200 subjects of either gender were included in our study, out of which 110 (55%) were females and rest were males (90; 45%). The male to female ratio was 1.22:1. Majority of the patients lied in the age group of 40-60 years (55%) followed by 60-80 years (29%) and below 40 years (15%), while only 2(1%) patients were aged above 80 years (Table 1).
On ophthalmologic examination we found that only 100 out of 200 diabetics suffered from diabetic retinopathy and the rest 100 (50%) did not show any signs of diabetic changes in the fundus. Out of 100 patients in the retinopathic group, 50 (25%) of them suffered from very mild to moderate NPDR, 30 (15%) patients showed signs of severe to very severe NPDR and only 20 (10%) had proliferative diabetic retinopathy.
A statistically significant association with severity of retinopathy and the age of the patients was observed. None of the 2 patients aged above 80 was suffering from retinopathy. Proportion of Group I (No retinopathy) was higher in younger patients i.e. below 40 (73.33%) and 40-60 (49.09%) as compared to elderly cases i.e. 60-80 (37.93%) and this difference was found to be statistically significant ($p < 0.001$).(Table 2).

Table 1: Sex and Age distribution.

Parameter	No. of Cases	Percentage
Gender		
Male	90	45
Female	110	55

Age group (years)		
Below 40	30	15
40-60	110	55
60-80	58	29
Above 80	2	1

Table 2: Correlation of severity of retinopathy with age.

Age Group (In Years)	**Group I (No Retinopathy) (n=100, 50%)**		**Group Iia (Very Mild to Moderate) (n = 50, 25%)**		**Group Iib (Severe to very Severe) (n = 30, 15%)**		**Group Iic (Proliferative Diabetic Retinopathy) (n = 20, 10%)**	
	NO.	**%**	**NO.**	**%**	**NO.**	**%**	**NO.**	**%**
Below 40 (n=30)	22	73.33	4	13.33	4	13.33	0	0
40-60 (n=110)	54	49.09	32	29.09	14	12.73	10	9.09
60-80 (n=58)	22	37.93	14	24.14	12	20.69	10	17.24
Above 80 (n=2)	2	100	0	0	0	0	0	0

Another statistically significant association was found between the severity of retinopathy and duration of diabetes ($p < 0.001$). It was found that proportion of Group I (non-retinopathy) patients was higher in patients with duration of diabetes < 10 years (70%) as compared to patients with duration 10-20 years (51.43%), 20-40 years (6.67%) and > 40 years (30%). Majority of patients with duration of diabetes 20-40 years and > 40 years belonged to Group IIA. (Very mild to moderate retinopathy) (Table 3).

Majority of patients (86.49%) of Grade 0 microalbuminuria (< 2.5 mg/mmol) had no Retinopathy. It was found that higher the level of microalbuminuria more is the severity of retinopathy. Proportion of Severe to very severe retinopathy and proliferative diabetic retinopathy were higher in higher grade of microalbuminuria (Grade II and Grade III). A statistically significant association between microalbuminuria grade and severity of retinopathy was observed ($p < 0.001$) (Table 4).

Table 3: Correlation of severity of retinopathy and duration of diabetes mellitus.

Duration Of Diabetes (Years)	**Group I (No Retinopathy) (n = 100)**		**Group Iia (Very Mild to Moderate) (n = 50)**		**Group Iib (Severe to very Severe) (n = 30)**		**Group Iic (Proliferative Diabetic Retinopathy) (n = 20)**	
	NO.	**%**	**NO.**	**%**	**NO.**	**%**	**NO.**	**%**
<10 years (n= 80)	56	70	12	15	8	10	4	5
10-20 years (n= 70)	36	51.43	11	15.71	13	18.57	10	14.28
20-40 years (n=30)	2	6.67	13	43.33	9	30	6	20
>40 years (n=20)	6	30	14	70	0	0	0	0

Table 4: Correlation of Retinopathy and Microalbuminuria

Micro-Albuminuria Grade	Group I (No Retinopathy) (n=100)		Group IIA (Very mild to moderate) (n=50)		Group IIB (Severe To Very Severe) (n=30)		Group IIC (Proliferative Diabetic Retinopathy) (n=20)	
	No.	%	No.	%	No.	%	No.	%
Grade 0(n=74)	64	86.49	8	10.81	2	2.70	0	0
Grade I(n=67) (2.5-12.5 mg/mmol)	32	47.76	26	38.81	9	13.43	0	0
Grade II (n=38) (>12.5-25 mg/mmol)	4	10.53	15	39.47	9	23.68	10	26.32
Grade III (n=21) (>25 mg/mmol)	0	0	1	4.76	10	47.67	10	47.67

Out Of 200 patients of diabetes, total cholesterol was found to be desirable (< 200 mg/dl) in only 60 (30%) patients. Out of these 60 patients with desirable cholesterol majority (60%) had no retinopathy (Group I), 21.67% had very mild to moderate retinopathy (Group IIA), 13.33% had severe to very severe retinopathy (Group IIB) and 5% had proliferative diabetic retinopathy (Group IC).

A total of 110 (55%) patients had borderline total cholesterol level and of these 110 patients. 52 (47.27%) had no retinopathy (Group I). 30 (27.27%) had very mild to moderate retinopathy (Group IIA). 16 (14.55%) had severe to very severe retinopathy and 12 (10.90%) had proliferative retinopathy.

Total cholesterol was found to be high (240 mg/dl) in 30 (15%) patients. Prevalence of retinopathy was 60%, in patients having high total cholesterol levels. Proportional difference in severity of retinopathy in patients with different total cholesterol levels was found to be statistically significant (p = 0.001) (Table 5).

Table 5: Correlation of Severity of Retinopathy and Total cholesterol.

Total cholesterol Level	Group I (No Retinopathy) (n=100)		Group IIA (Very mild to moderate) (n=50)		Group IIB (severe to Very-severe) (n=30)		Group IIC (Proliferative Diabetic Retinopathy) (n=20)	
	NO	%	No	%	No	%	NO	%
Desirable (<200)(n=60)	36	60	13	21.67	8	13.33	3	5
Borderline high (200-239) (n=110)	52	47.27	30	27.27	16	14.55	12	10.90
High (>=240) (n=30)	12	40	7	23.33	6	20	5	16.67

On doing a trivariate analysis between severity of retinopathy, microalbuminuria and serum cholesterol levels, it was observed that in microalbuminuria grade 0, difference in prevalence of retinopathy in patients with different serum cholesterol levels was not found to be statistically significant (p = 0.612). In microalbuminuria grade l, prevalence of retinopathy in

patients having desirable cholesterol levels was lower as compared to those having borderline or high cholesterol levels and this difference was found to be statistically significant (p = 007).

In microalbuminuria grade II, proportional differences in grades of retinopathy and serum cholesterol levels were observed and these differences were found to be statistically significant (p = 0.021).

In microalbuminuria grade Ill. majority of patients were suffering from very mild-moderate retinopathy and no statistically significant association between retinopathy and serum cholesterol levels was found (p = 0.748) (Table 6).

Multivariate analysis revealed a statistically significant association of Diabetic retinopathy with HbA1c values. High grade Microalbuminuria (Grade II and III Duration of diabetes >20 years). Association between retinopathy and high total cholesterol levels (Borderline high and high) was not found (p = 0.221) (Table 7).

Table 6: Trivariate analysis of severity of Retinopathy, Microalbuminuria and S. Cholesterol

S.Chol. level	No Retinopathy (N=100)		Very mild-moderate (N=50)		Severe-very severe NDPR (N=30)		Proliferative Diabetic Retinopathy (N=20)		Statistically significant	
	No	%	No	%	No	%	No	%	X2	P
Microalbuminuria Grade 0 (n=74)										
Desirable (n=27)	22	81.48	4	14.81	1	3.70	0	0	2.56	0.612
Borderline High (n=38)	31	81.58	6	15.79	1	2.63	0	0		
High (n=9)	9	100	0	0	0	0	0	0		
Microalbuminuria Grade 1 (N=67)										
Desirable(n=20)	12	60	6	30	2	10	0	0	13.74	0.007
Borderline High (n=37)	16	43.24	19	51.35	2	5.41	0	0		
High (n=10)	3	30	5	50	2	20	0	0		
Microalbuminuria Grade II (N=38)										
Desirable(n=18)	1	5.56	7	38.89	8	4.44	2	11.11	14.22	0.021
Borderline High (n=12)	2	16.67	4	33.33	3	25	3	25		
High (n=8)	0	0	3	37.5	2	25	3	37.5		
Microalbuminuria Grade III (N=21)										
Desirable(n=6)	0	0	0	0	4	66.67	2	33.33	0.373	0.748
Borderline High (n=10)	0	0	0	0	6	60	4	40		
High (n=5)	0	0	0	0	3	60	2	40		

Table 7: Multivariate analysis for retinopathy.

	B	S.E.	Wald	df	Sig.	Exp(B)
Duration of diabetes (>20 years)	3.642	0.414	76.978	1	<0.001	34.631
Microalbuminuria	2.888	0.472	39.86	1	<0.001	20.23
HbA1c	2.36	0.334	48.528	1	<0.001	9.613
Total Cholesterol (High or Borderline high)	0.382	0.319	1.511	1	0.204	1.58
Constant	-2.721	0.335	66.872	1	<0.001	0.05
(B= β constant, SE= standard error, df= Degree of Freedom)						

Discussion

Diabetes has become a global epidemic affecting children, adolescents, and adults. According to the World Health Organization, approximately 150 million people worldwide currently have type 2 DM (formerly called adult- onset diabetes): The number of people with type 2 DM is estimated to double by 2030.[14] Diabetes is a disease that is strongly associated with both microvascular and macrovascular complications, including retinopathy, nephropathy and neuropathy (microvascular) and ischemic heart disease, peripheral vascular disease, and cerebrovascular disease (macrovascular), resulting in organ and tissue damage in approximately one third to one half of people with diabetes Among different microvascular complications, diabetic retinopathy is the most common.[15]

Microalbuminuria is a nephrotic disorder which if remains untreated progresses to proteinuria and overt diabetic nephropathy. It has been reported that as many as 7% of patients with type 2 diabetes already have microalbuminuria at the time they are diagnosed with diabetes.[16] Thus microalbuminuria is a microvascular complications that is often accompanied with the diagnosis of type 2 diabetes and in effect may have a crucial role in determining the future course of disease and per se complications associated with it.

A total of 200 subjects of either gender were included in our study, out of which 110 (55%) were females and rest were males (90; 45%). Majority of the patients lied in the age group of 40-60 years (55%).[17] Contrary to the profile of patients in present series, Chung et al.[18] (2011) had majority of male patients (54%) with a mean age of 64.9 ± 10.8 years in the study population, thus, showing the patients in their series to be older than in present study. Similarly a study done on Indian population by us in 2016 showed that prevalence of diabetic retinopathy is significantly higher in men (68.5%) than in women and in those who were 50-70years of age (75.5%).[19] Manaviat et al[20] (2004) had majority of females (58.64%) and mean age of patients comparable to that in present study (54.9 +/- 10.2 years). He et al[21] (2012) had majority of male patients (57%) with mean age of 59.69+/-12.28 years. These findings indicate that gender and age of patients with diabetes and microalbuminuria might vary and is a study characteristic rather than being a population characteristic.

Fundus examination findings positive for retinopathy were observed in 198 (44.59%) cases. Thus, prevalence of diabetic retinopathy in type II diabetic cases with microalbuminuria as observed in present study was 44.59%.[17]

In the present study, majority of diabetic retinopathy patients had very mild to moderate non-proliferative diabetic retinopathy (50%) followed by severe to very severe non-proliferative diabetic retinopathy (30%), Only 20 (20%) cases had proliferative diabetic retinopathy. In different cross- Sectional studies, prevalence of different grades of retinopathy have been shown to be of similar order with prevalence of lower grades of retinopathy being higher as compared to higher grades or proliferative retinopathy.[15,17,22-25]

Retinopathy, a progressive disorder, assumes greater severity if remains undiagnosed and untreated[26,27] hence late stages (i.e. severe to very severe NPDR and proliferative diabetic retinopathy) are diagnosed at advanced stages of diabetes. The findings in most of the

studies[22-25] support the rate of proliferative diabetic retinopathy to be lower as compared to non-proliferative diabetic retinopathy.

We also investigated the role of duration of diabetes on causation of diabetic retinopathy among microalbuminuria patients and found that this logical relationship was working perfectly. It was observed that in general, prevalence as well as severity of diabetic retinopathy increased significantly with increasing duration of diabetes. This finding eventually correlates well with the observations of other clinical studies[16,28-30] as well as population studies[31] which have laid emphasis that early onset of diabetes (≈ longer duration of diabetes) poses increased risk for diabetic retinopathy in general and that in patients with microalbuminuria in particular. We also conducted a study in past in which we found that albuminuria was significantly higher in our patients with diabetic retinopathy than in those without retinopathy.[32] Owing to sustained hyperglycemia in diabetic patients, longer duration of diabetes causes microvascular complications that include diabetic retinopathy. Hyperglycemia leads to no enzymatic formation of advanced glycosylated end products (AGEs). In experimental studies, AGES have been found to be associated with formation of micro aneurysms and pericytes loss.[33] Longer duration of diabetes might have a role in promoting AGEs production and hence could result in increased risk of microvascular complications in general and diabetic retinopathy in particular.

Present study shows a significant association between total cholesterol levels and severity as well as prevalence of diabetic retinopathy ($p < 0.001$). Hyperlipidemia is regarded as one of the major factors responsible for diabetic retinopathy apart from hyperglycemia and hypertension.[14] A significant association between retinal hard exudate secretion and elevated serum lipid levels has also been reported.[34,35] However, some studies have rejected this relationship[36] but they are limited in number.

On multivariate analysis, we found that duration of diabetes, microalbuminuria and HbA1c levels were independent significant predictors of diabetic retinopathy, but serum cholesterol levels did not show an independent role. These findings suggest that hyperlipidemia has a limited role which is often confounded and that is the reason that in some studies, the role of lipid levels as predictor of diabetic retinopathy and its severity remains unexplained.

CONCLUSION

Duration of diabetes and microalbuminuria have been found to be the independent risk factors for diabetic retinopathy, but serum cholesterol levels did not show an independent role in our study.

Our study was limited by time and limited subjects; hence a better understanding of this relationship could be gathered with the help of longitudinal clinical trials among new onset type 2 diabetic patients.

Conclusion

Duration of diabetes and microalbuminuria have been found to be the independent risk factors for diabetic retinopathy, but serum cholesterol levels did not show an independent role in our study. The findings in present study endorsed the view that microalbuminuria poses a risk for diabetic retinopathy which is affected by duration of diabetes, level of glycemic control and lipid levels.

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