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Original Research Article

To Assess the Association Between the Duration of Diabetes Mellitus, Microalbuminuria and Hyperlipidemia with Severity of Diabetic Retinopathy

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Abstract

Aim: The aim of this study to evaluate the correlation of duration of diabetes mellitus, microalbuminuria, hyperlipidemia with severity of diabetic retinopathy. **Methods:** The prospective cross-sectional study which was carried in the Department of Ophthalmology, Nalanda Medical College and Hospital, Patna, Bihar, India from July 2017 to July 2018. Total 220 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 220 subjects of either gender were included in our study, out of which 125 (56.82%) were females and rest were males 95; 43.18%). On ophthalmologic examination we found that only 112 out of 220 diabetics suffered from diabetic retinopathy and the rest 108(49.09%) did not show any signs of diabetic changes in the fundus. Out of 112 patients in the retinopathic group, 57 (25.91%) of them suffered from very mild to moderate NPDR, 32 (14.55%) patients showed signs of severe to very severe NPDR and only 23 (10.45%) had proliferative diabetic retinopathy. statistically significant association was found between the severity of retinopathy and duration of diabetes ($p < 0.001$). Majority of patients (85%) of Grade 0 microalbuminuria (< 2.5 mg/mmol) had no Retinopathy. A statistically significant association between microalbuminuria grade and severity of retinopathy was observed ($p < 0.001$). Out Of 220 patients of diabetes, total cholesterol was found to be desirable (< 200 mg/dl) in only 70 (31.82%) patients. Out of these 70 patients with desirable cholesterol majority (60%) had no retinopathy (Group I), 21.43% had very mild to moderate retinopathy (Group IIA), 12.86% had severe to very severe retinopathy (Group IIB) and 5.71% had proliferative diabetic retinopathy (Group IC). 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 ($p = 009$). **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.

Keywords: Diabetes Mellitus, Diabetic Retinopathy, Microalbuminuria, Hyperlipidaemia.

Introduction

It is estimated that diabetes mellitus affects 4 percent of the world's population, almost half of whom have some degree of diabetic retinopathy at any given time[1,2]. Diabetic retinopathy is a very common, potentially preventable, long-term, microvascular complication of Diabetes Mellitus and a leading cause of visual disability and blindness[3]. It is considered the hallmark of generalized microangiopathy occurring in a diabetic patient. In India the prevalence of diabetic retinopathy in general population is 3.5%, and the prevalence of diabetic retinopathy in the population with diabetes mellitus was 18.0%6. In a population-based study in South India, diabetic retinopathy was detected in 1.78% of the diabetic patients screened[4,5]. While there are multiple risk factors which have been associated with the development and progression of diabetic retinopathy, the duration of the disease and the age of the patient are said to be the strongest predictors. Other risk factors like hypertension, pregnancy, blood glucose level control and presence of nephropathy are shown to have a strong association. Dyslipidemia, microalbuminuria, BMI and smoking are some of the factors whose role as predictors of diabetic retinopathy is not well established[6-7]. Diabetic retinopathy is frequently accompanied by lipid exudation[9]. Elevated serum lipid levels are associated with an increased risk of retinal hard exudate in persons with diabetic retinopathy. Although retinal hard exudate usually accompanies diabetic macular edema, increasing amounts of exudate appear to be independently associated with an increased risk of visual impairment[10]. The elevated lipid levels are also associated with endothelial dysfunction, which appears to play an important role in the pathogenesis of diabetic retinopathy, particularly in relation to the breakdown of blood-retinal barrier.

The association between serum lipid levels and diabetic retinopathy has been investigated in few studies. Some studies show a positive relationship between serum cholesterol and low-density lipoprotein levels and retinal hard exudation. Other studies show serum triglyceride levels as being important in the progression of retinopathy. Certain other studies show no relationship between serum lipid levels and diabetic retinopathy[11].

Material and methods

The prospective cross-sectional study which was carried in the Department of Ophthalmology, Nalanda Medical College and Hospital, Patna, Bihar, India from July 2017 to July 2018.after taking the approval of the protocol review committee and institutional ethics committee.

Methodology

Total 220 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[12]. 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[13].

Lipid profile was also sub graded as- Desirable (< 200); Border line high (200-239); High (≥240)[14].

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 220 subjects of either gender were included in our study, out of which 125 (56.82%) were females and rest were males 95; 43.18%). The male to female ratio was 1.31:1. Majority of the patients lied in the age group of 40-60 years (53.64%) followed by 60-80 years (29.10%) and below 40 years (15.90%), while only 3(1.36%) patients were aged above 80 years (Table 1).

On ophthalmologic examination we found that only 112 out of 220 diabetics suffered from diabetic retinopathy and the rest 108(49.09%) did not show any signs of diabetic changes in the fundus. Out of 112 patients in the retinopathic group, 57 (25.91%) of them suffered from very mild to moderate NPDR, 32 (14.55%) patients showed signs of severe to very severe NPDR and only 23 (10.45%) had proliferative diabetic retinopathy.

A statistically significant association with severity of retinopathy and the age of the patients was observed. None of the 3 patients aged above 80 was suffering from retinopathy. Proportion of Group I (No retinopathy) was higher in younger patients i.e. below 40 (68.57%) and 40-60 (48.31%) as compared to

elderly cases i.e. 60-80 (37.5%) 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	95	43.18
Female	125	56.82
Age group (years)		
Below 40	35	15.90
40-60	118	53.64
60-80	64	29.10
Above 80	3	1.36

Table 2: Correlation of severity of retinopathy with age

Age Group (In Years)	Group I (No Retinopahy) (n=108, 49.09%)		Group Iia (Very Mild to Moderate) (n = 57, 25.91%)		Group Iib (Severe to very Severe) (n = 32, 14.55%)		Group Iic (Proliferative Diabetic Retinopathy) (n = 23, 10.45%)	
	NO.	%	NO.	%	NO.	%	NO.	%
Below 40 (n=35)	24	68.57	5	14.29	6	17.14	0	0
40-60 (n=118)	57	48.31	36	30.51	13	11.02	12	10.17
60-80 (n=64)	24	37.5	16	25	13	20.31	11	17.19
Above 80 (n=3)	3	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 (67.78%) as compared to patients with duration 10-20 years (52%), 20-40 years (8.57%) and > 40 years (25%). 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 (85%) 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 = 108)		Group Iia (Very Mild to Moderate) (n = 57)		Group Iib (Severe to very Severe) (n = 32)		Group Iic (Proliferative Diabetic Retinopathy) (n = 23)	
	NO.	%	NO.	%	NO.	%	NO.	%
<10 years (n= 90)	61	67.78	14	15.56	10	0.90	5	5.56
10-20 years (n= 75)	39	52	13	17.33	12	16	11	14.67
20-40 years (n=35)	3	8.57	15	42.86	10	28.57	7	20
>40 years (n=20)	5	25	15	75	0	0	0	0

Table 4: Correlation of Retinopathy and Microalbuminuria.

Micro-Albuminuria Grade	Group I (No Retinopathy) (n=108)		Group IIA (Very mild to moderate) (n=57)		Group IIB (Severe To Very Severe) (n=32)		Group IIC (Proliferative Diabetic Retinopathy) (n=23)	
	No.	%	No.	%	No.	%	No.	%
Grade 0(n=80)	68	85	10	12.5	2	2.5	0	0
Grade I(n=70) (2.5-12.5 mg/mmol)	35	50	27	38.57	8	11.43	0	0
Grade II (n=45) (>12.5-25 mg/mmol)	5	11.11	19	42.22	10	22.22	11	14.44
Grade III (n=25) (>25 mg/mmol)	0	0	1	4	12	48	12	48

Out Of 220 patients of diabetes, total cholesterol was found to be desirable (< 200 mg/dl) in only 70 (31.82%) patients. Out of these 70 patients with desirable cholesterol majority (60%) had no retinopathy (Group I), 21.43% had very mild to moderate retinopathy (Group IIA), 12.86% had severe to very severe retinopathy (Group IIB) and 5.71% had proliferative diabetic retinopathy (Group IC).

A total of 117 (53.18%) patients had borderline total cholesterol level and of these 117 patients. 55 (47 %) had no retinopathy (Group I). 31 (26.49%) had very mild to moderate retinopathy (Group IIA). 17 (14.53%) had severe to very severe retinopathy and 14 (11.97%) had proliferative retinopathy.

Total cholesterol was found to be high (240 mg/dl) in 33 (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=108)		Group IIA (Very mild to moderate) (n=57)		Group IIB (severe to Very-severe) (n=32)		Group IIC (Proliferative Diabetic Retinopathy) (n=23)	
	NO	%	No	%	No	%	NO	%
Desirable (<200)(n=70)	42	60	15	21.43	9	12.86	4	5.71
Borderline high (200-239) (n=117)	55	47.0	31	26.49	17	14.53	14	11.97
High (>=240) (n=33)	11	33.33	11	33.33	6	18.18	5	15.15

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 = 0.663). 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 = 009).

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 = 0.026).

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 = 0.63) (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 = 0.204) (Table 7).

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

S.Chol. level	No Retinopathy (N=108)		Very mild-moderate (N=57)		Severe-very severeNDPR (N=32)		Proliferative Diabetic Retinopathy (N=23)		Statistically significant	
	No	%	No	%	No	%	No	%	X2	P
Microalbuminuria Grade 0 (n=80)										
Desirable (n=30)	23	76.67	5	16.67	2	6.67	0	0	2.87	0.663
Borderline High (n=40)	32	80	7	17.5	1	2.5	0	0		
High (n=10)	10	100	0	0	0	0	0	0		

Microalbuminuria Grade 1 (N=70)										
Desirable(n=20)	13	65	5	25	2	10	0	0	12.87	0.009
Borderline High (n=40)	17	43.24	20	50	3	7.5	0	0		
High (n=10)	5	50	4	40	1	10	0	0		
Microalbuminuria Grade II (N=45)										
Desirable(n=20)	5	25	6	30	6	30	3	15	15.72	0.026
Borderline High (n=15)	3	20	5	33.33	3	20	4	26.67		
High (n=10)	0	0	5	50	2	20	3	30		
Microalbuminuria Grade III (N=25)										
Desirable(n=8)	0	0	0	0	3	37.5	5	62.5	0.323	0.63
Borderline High (n=11)	0	0	0	0	6	54.55	5	45.45		
High (n=6)	0	0	0	0	3	50	3	50		

Table 7: Multivariate analysis for retinopathy.

	B	**S.E.**	**Wald**	**df**	**Sig.**	**Exp(B)**
Duration of diabetes (>20 years)	3.872	0.434	75.698	1	<0.001	35.631
Microalbuminuria	2.688	0.492	40.76	1	<0.001	21.23
HbA1c	2.46	0.354	47.268	1	<0.001	10.613
Total Cholesterol (High or Borderline high)	0.392	0.349	1.336	1	0.204	1.36
Constant	-2.561	0.375	68.212	1	<0.001	0.05
(B= β constant, SE= standard error, df= Degree of Freedom)						

Discussion

It is believed that the Indian population generally has an unusually efficient glucose metabolism. But with westernisation and the associated weight increase and sedentary lifestyle, the former advantage is lost, and incidence of diabetes has increased. Paralleling this high prevalence of diabetes is a concern that the complications of diabetes, mainly diabetic retinopathy is increasing[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 complication 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 220 subjects of either gender were included in our study, out of which 125 (56.82%) were females and rest were males 95; 43.18%). The male to female ratio was 1.31:1. Majority of the patients lied in the age group of 40-60 years (53.64%)[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, out of 112 patients in the retinopathic group, 57 (25.91%) of them suffered from very mild to moderate NPDR, 32 (14.55%) patients showed signs of severe to very severe NPDR and only 23 (10.45%) 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 microaneurysms and pericyte 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].

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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