

Original Research Article

Proportion of severity of retinal hard exudates and its association with systemic risk factors

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ABSTRACT

Background: Diabetic macular edema (DME) characterized by deposition of hard exudates in central retina is now the leading cause of visual loss in persons with diabetes mellitus. Several studies have shown association between severity of retinal hard exudates and various components of serum lipid. The aim of this study is to estimate the proportion of severity of retinal hard exudates with risk factors like dyslipidemia, duration of diabetes, hypertension, HbA1c levels and microalbuminuria.

Methods: A hospital based cross sectional study was done involving 242 diabetic retinopathy patients. After dilated fundus examination, severity of retinal hard exudates was graded by photographs with Topcon fundus camera using modified Airline house classification. These grades were divided into three groups. Group 1 (absent or minimal hard exudates) included patients with grade 0, 1 or 2 hard exudates; group 2 (hard exudates present), included patients with grade 3 or 4 hard exudates and group 3 (prominent hard exudates), patients with grade 5 hard exudates. Values of serum lipid profile, HbA1C and urine microalbumin were analysed in association with severity of retinal hard exudates.

Results: Out of the 242 diabetic retinopathy patients, the male female ratio was 1:1 and the mean age was 59.8±7.4 years. There were 12% patients in group one, 52.5% in group two and 35.5% in group three. On univariate analysis, severity of hard exudates was significantly associated with serum cholesterol (p value<0.01), LDL (p value<0.01) triglycerides (p value<0.01), HbA1c (p value<0.01), systemic hypertension (p value<0.01) and urine microalbumin (p value=0.01).

Conclusions: Severity of retinal hard exudates in diabetic retinopathy patients is significantly associated with risk factors like systemic hypertension, dyslipidemia, raised HbA1C levels and urine microalbumin.

Keywords: Hard Exudate, Diabetic macular edema, Dyslipidemia, HbA1c, Microalbuminuria

INTRODUCTION

The prevalence of diabetes mellitus is growing rapidly worldwide and is reaching epidemic proportions. The International diabetes federation (IDF) has projected that the number of people with diabetes in India would rise from 65.1 million in 2013 to 109 million in 2035.¹ Retinopathy is the most common micro vascular complication of diabetes and is one of the leading global causes of preventable blindness. Diabetic macular edema (DME), which can occur at any stage of diabetic

retinopathy, is characterized by increased vascular permeability and the deposition of hard exudates into the extracellular spaces of the retina.² As the density of these hard exudates increases, they tend to migrate towards the foveal centre where their deposition predisposes to development of subfoveal fibrosis leading to irreversible visual loss.

Elevated serum cholesterol at baseline also increased the risk for visual loss by 50% compared with lower serum cholesterol levels. Independent of the accompanying

macular edema, the severity of retinal hard exudates at baseline was associated with decreased visual acuity. Lowering serum lipids has shown a benefit on both proliferative disease and maculopathy besides their lipid lowering effect.³ In addition to serum lipids, there is significant association of microalbuminuria with the occurrence and severity of diabetic retinopathy, occurrence of hard exudate and clinically significant macular edema (CSME) remained strong even after correction for duration of diabetes, one of the most important predictors of DR and other co-morbid conditions.⁴

While correlation between the various components of serum lipids and increased hard exudate formation and CSME has been demonstrated by various studies in Western population and North Indian population, no similar studies has been conducted in Kerala. Hence, the rationale to determine the proportion of severity of retinal hard exudates in patients with diabetic retinopathy and its association with dyslipidemia as the primary objective. Secondary objectives are to study the association of other risk factors like duration of diabetes, presence of associated hypertension, levels of HbA1C, microalbuminuria with severity of retinal hard exudates.

METHODS

A hospital based cross sectional study was done for a period of one year, from January 2017 to January 2018 in Type 2 Diabetic patients with retinopathy who attended the retina clinic of a tertiary care teaching hospital. Eyes with significant media haze, preventing adequate visualization of the fundus to permit grading of hard exudates, advanced diabetic eye disease and patients on lipid lowering agents were excluded from the study. By consecutive sampling a total of 242 patients satisfying the inclusion criteria were included in the study. Study variables included dyslipidemia, age of onset, duration of diabetes, HbA1c levels, microalbuminuria, presence of hypertension and outcome variable measured was severity of retinal hard exudates.

All patients were subjected to detailed ocular examination, including best corrected visual acuity and dilated fundus examination with 1% tropicamide and 10% phenylephrine eyedrops. The severity of retinal hard exudates was graded by colour fundus photograph using Topcon fundus camera. It consisted of comparing stereo photographs in seven standard photographic fields with patients' findings in those same seven photographic fields according to the early treatment for diabetic retinopathy study (ETDRS) standard. The grading of retinal hard exudates was performed by utilizing the modified Airlie House Classification on a central 50° digital fundus photograph.⁵ In diabetic retinopathy patients with hard exudates, both eyes were studied and based on severity score the worse eye with the highest grade of hard exudate was selected for association study. These grades were further divided into three groups of patient severity as follows: group 1 (absent

or minimal hard exudates) included patients with Grade 0, 1 or 2 hard exudates; group 2 (hard exudates present) included patients with grade 3 or 4 hard exudates and group 3 (prominent hard exudates) included patients with grade 5 hard exudates.⁵

Blood pressure was measured with mercury sphygmomanometer applied to the right arm of patient at sitting posture. Two BP measurements were taken 5 minutes apart, and if the two BP measurements differed by more than 10 mm systolic and 5 mm diastolic, a third measurement was taken and the average of two closest readings were taken as the BP value. Hypertension was defined as a self-reported current use of antihypertensive medication or systolic BP \geq 140 mm Hg or diastolic BP \geq 90 mm Hg.⁶

For blood collection and laboratory investigations: 5-10 ml of venous blood was collected from each subject during fasting state for assessment of serum lipid profile and glycated haemoglobin (HbA1c). Serum sample were analysed for total cholesterol, LDL, HDL and serum triglycerides by sending the samples to hospital laboratory. Dyslipidemia was diagnosed according to national cholesterol education programme (NCEP), Adult treatment panel iii (NCEP ATP III).⁷

Microalbuminuria is the presence of a slightly high level of protein in the urine in 24 hours. Urine protein levels of 30 to 300 mg is known as microalbuminuria and it may indicate early kidney disease. For this test urine is collected for a 24-hour period in a container and a sample from it was sent for laboratory spot analysis. Less than 30 mg of urine protein is normal.⁶

Categorical variables were expressed as proportions and quantitative variables were expressed as mean and standard deviation. Statistical test of significance was Chi-square test for categorical variables and students t test for quantitative variables. Analysis of data was done using SPSS Version 22 (statistical package for social sciences, IBM Corp., New York, NY, USA). Ethical clearance was obtained from Institutional ethics committee and informed consent was obtained from the participants. Confidentiality was ensured and maintained throughout the study. The study conforms to the guidelines of the Declaration of Helsinki.

RESULTS

The study included 242 patients (484 eyes) with diabetic retinopathy. Percentage distribution of the sample according to gender showed equal male: female ratio of 1:1.

Percentage distribution of the sample according to age showed 12% in <50 years, 45% in 51-60 years, 36.4% in 61-70 years and 6.6% in >70 years. Mean age was 59.8 \pm 7.4 years with highest being 86 and lowest 36 years. Percentage distribution of the sample according to

duration of diabetes showed 42.6 % in <10 years age group, 31.4% in 10-15 years group and 26% in >15 years group. Mean duration of diabetes mellitus in the sample population was 12.7±5.4 years.

Grade 2 or less hard exudates were present in 29 (12%) patients and were included in group 1. Hard exudates of grade 3 and 4 were seen in 127 (52.5%) and were included

in group 2. Grade 5 hard exudates were in group 3 and included 86 (35.5%) cases.

Comparison of gender based on maximum grade of hard exudates showed no significance in the study group (P value=0.354). On univariate analysis there is significant association between the severity of hard exudates and duration of diabetes mellitus. (p<0.01) (Table 1).

Table 1: Comparison of duration of diabetes based on maximum grade of hard exudates.

Duration of diabetes	Grade 1		Grade 2		Grade 3		χ ²	P
	Count	Percent	Count	Percent	Count	Percent		
<10	24	82.7	59	46.5	20	23.3	36.38	p<0.01
10-15	4	13.8	41	32.3	31	36.0		
>15	1	3.5	27	21.2	35	40.7		

Table 2: Comparison of serum lipid profile parameters based on maximum grade of hard exudates.

Serum Lipid Profile		Group 1		Group 2		Group 3		Tests of significance	
		Count	Percent	Count	Percent	Count	Percent	χ ² *	P†
Cholesterol	Normal	29	100	41	32.3	1	1.2	103.31	p<0.1
	High	0.0	0.0	86	67.7	85	98.8		
Triglycerides	Normal	26	89.6	34	26.7	1	1.2	90.43	p<0.01
	High	3	10.4	93	73.3	85	98.8		
LDL‡	Normal	27	93	26	20.5	0	0.0	110.23	p<0.01
	High	2	7	101	79.5	86	100		
HDL§	Normal	29	100	119	93.7	52	60.5	46.41	p<0.01
	Low	0	0.0	8	6.3	34	39.5		

§ High density lipoprotein * Chi squared test, ‡ Low density lipoprotein † Probability value

Table 3: Comparison of other parameters: associated hypertension, HbA1c and urine microalbumin based on maximum grade of hard exudates.

Other parameters		Group 1		Group 2		Group 3		χ ² *	P†
		Count	Percent	Count	Percent	Count	Percent		
Hyper Tension	Normal	1	3.5	71	55.9	77	89.5	71.55	p<0.01
	High	28	96.5	56	44.1	9	10.5		
Serum HbA1c	Normal	25	86.2	24	18.9	3	3.5	89.02	p<0.01
	High	4	13.8	103	81.1	83	96.5		
Urine micro albumin	Normal	28	96.5	26	20.5	2	2.3	109.33	p<0.01

There is increasing grade of hard exudates with increase in serum lipid profile. On univariate analysis there is significant association between maximum grade of retinal hard exudates and serum cholesterol levels, abnormal triglycerides, LDL levels and low HDL levels (p<0.01) (Table 2).

The mean HbA1c was 7.56%. The association of raised HbA1c with increasing grade of hard exudates was statistically significant. The mean value of urine microalbumin is 230.36 mg. Associated hypertension was present in 38.4% patients. Among the hypertensives 86%

were on regular antihypertensive treatment. The association of hypertension with increasing grade of hard exudates was found to be statistically significant. (p<0.01). The comparison of parameters like associated hypertension, HbA1c and urine microalbumin based on maximum grade of hard exudates is shown in Table 3.

DISCUSSION

In this study out of 242 patients 121 were males and 121 were females. Mean age group of the patients were 59.8±7.4 years. Mean duration of diabetes mellitus was

12.7±5.4 years. In diabetic retinopathy patients with hard exudates, both eyes were studied and single eye with highest grade of hard exudate was selected for association study.

History-based variables that were significantly associated with increased risk of diabetic retinopathy included gender (men at greater risk), use of insulin, longer duration of diabetes (>15 years). Differences in the socioeconomic status did not influence the occurrence of diabetic retinopathy.⁸

In the Chennai urban rural epidemiology study (CURES) Eye Study, the overall prevalence of diabetic retinopathy in the population was 17.6%, which included 20.8% in known diabetic subjects and 5.1% in subjects with newly detected diabetes.⁹ The prevalence of diabetic retinopathy was significantly higher in men than in women and among subjects with proteinuria. Association of longer duration of diabetes mellitus and severity of retinal hard exudates in this study is in agreement with earlier studies conducted in India and abroad.^{10,11} However in a study by Sachdev et al in North Indian population there was no significant association found between duration of diabetes mellitus and severity of retinal hard exudates.¹²

Pradeepa et al in a study from urban South India, identified higher HbA1c levels and longer duration of diabetes as independent risk factors for diabetic macular edema.¹⁰

In a study by Jyothi Idiculla et al, retinal hard exudate formation was found to have statistically significant correlation with the presence of dyslipidemia, increased total cholesterol and LDL levels. However there was no significant association between severity of retinal hard exudates and Serum triglycerides or HDL levels.¹³

Kabita et al aimed to determine the relationship between serum lipid profile and the severity of diabetic macular edema. They found that, Total cholesterol, LDL, VLDL, and Cholesterol: HDL ratio is a significant risk factor and is associated with diabetic macular edema. However, on correlating the increasing lipid components with foveal thickness on OCT, this study could not appreciate any definite pattern of linear relation between lipid components and macular edema severity.¹⁴

ETDRS study showed that patients with elevated total serum cholesterol levels or serum low-density lipoprotein cholesterol levels at baseline were twice as likely to have retinal hard exudates as patients with normal levels. These patients were also at higher risk of developing hard exudate during the course of the study. The risk of losing visual acuity was associated with the extent of hard exudate even after adjusting for the extent of macular edema.¹⁵

In this study we have found a significant association between elevated serum lipids and severity of retinal hard exudates. This study finds concurrence with previous

studies regarding association of serum lipids and severity of retinal hard exudates.^{9,13-15}

This study assumes significance in that strict control of dyslipidemia may reduce retinal hard exudate formation and prevent development of clinically significant macular edema and impairment of vision in diabetic patients. However, no correlation was found between serum lipid levels and macular edema severity in some studies.¹⁶⁻¹⁸

This study showed a significant association between high HbA1c level and severity of retinal hard exudates ($p<0.01$). Acan et al evaluated prevalence and systemic risk factors of diabetic macular edema in Turkish population and found that prevalence of DME was associated with male gender, diabetes duration, HbA1c $\geq 7.0\%$, insulin usage, alcohol consumption, low HDL-C levels, nephropathy, neuropathy, severity of DR, and previous cataract surgery.^{12,19} Previous Studies done in India also showed a significant association between higher HbA1C and severity of retinal hard exudates.^{5,21} However study by Sasaki et al didn't find significant association between high HbA1c and retinal hard exudates.^{22,23}

Further analysis showed that for every 5-year increase in the duration of diabetes, the risk for diabetic retinopathy increased 1.89-fold. For every 2% elevation of glycated hemoglobin (HbA1c), the risk for diabetic retinopathy increased by a factor of 1.710.

There was significant association between severity of retinal hard exudates and hypertension ($p<0.01$) similar to a study done in North India but several other studies showed no such correlation.^{12,24,25} Our study also found a significant association between urine albumin excretion rate and retinal hard exudates in type 2 diabetic retinopathy patients similar to other studies.^{16,26}

This study assumes significance in that strict control of dyslipidemia may reduce retinal hard exudate formation and prevent development of clinically significant macular edema and impairment of vision in diabetic patients.

Recent studies have shown that lipid lowering agents reduces retinal hard exudates formation and lipid lowering agents may also causes regression of retinal hard exudates. In addition to lipid lowering treatment, control of other risk factors like systemic hypertension and hyperglycemia and management of urine microalbuminuria may also prevent retinal hard exudates formation and diabetic macular edema.

CONCLUSION

Increased duration of diabetes mellitus is a risk factor for retinal hard exudates formation. Elevated serum cholesterol, LDL, triglycerides and low HDL levels were significantly associated with severity of retinal hard exudates in type 2 diabetic patients. In addition to

dyslipidemia, risk factors like hypertension, microalbuminuria and poor glycemic control are also significantly associated with severity of retinal hard exudates. There was no significant association between age, gender and severity of retinal hard exudates. Screening for dyslipidemia is indicated in diabetic retinopathy patients with hard exudates formation.

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