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TO EVALUATE THE CHARACTERISTICS OF DIABETIC MACULAR OEDEMA IN FUNDUS FLUORESCEIN ANGIOGRAPHY ALONG WITH VARIOUS BIOCHEMICAL PARAMETERS

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ABSTRACT

Introduction: To study the correlation between biochemical parameters like blood sugar, HbA1c, serum creatinine and lipid profile and diabetic macular oedema (DME) changes as seen on fundus fluorescein angiography (FFA).

Materials & Methods: An observational, analytical, cross-sectional and hospital-based study where diabetic patients attending the Department of Ophthalmology at army hospital in central India were studied for the characteristics of diabetic macular oedema and its association with various biochemical parameters and systemic co-morbidity.

Results: Non proliferative diabetic retinopathy was seen in 66% patients and Proliferative diabetic retinopathy (PDR) in 34% patients. All patients had clinically significant macular oedema on FFA of which 56% had focal DME and 44% had diffuse DME. Central macular thickness (CMT) >300µm was seen in 74% of all cases. 36% of patients had hypertension as the most common comorbidity. 72% had HbA1c level >6.5% of which 84.21% patients were with CMT >300µm. Serum creatinine >1.2mg/dl was seen in 26% of total patients of DME, more in diffuse type (40.90%) patient. 71% of focal type and 95% of diffuse had elevated fasting blood sugar level (FBS). 89% patients with CMT >300µm were found have elevated FBS level. 82% patients of diffuse DME and CMT >300µm had postprandial blood sugar (PPBS) >150mg/dl. 86% of all PDR patients had elevated PPBS. Serum cholesterol level was high in 77% patients of diffuse DME and in 11% patients of focal DME. Serum LDL and VLDL level was not significantly associated with the severity of DME.

Conclusions: PDR is more common in patients who have elevated PPBS. Elevated HbA1c, raised fasting and postprandial blood sugar levels are an independent single risk factor for DME and reduction of HbA1c levels with tight glycaemic control decreases the rates of DME. Elevated serum creatinine and cholesterol levels could be risk factors particularly for diffuse DME.

KEYWORDS : Diabetes mellitus, Diabetic retinopathy, Diabetic macular oedema, Biochemical parameters.

INTRODUCTION

India is the "diabetes capital of the world", where every 5th diabetic is an Indian. Diabetic retinopathy (DR) is one of the most common microangiopathy affecting the retinal precapillary arterioles, capillaries and venules.[1] Diabetic retinopathy accounts for 3% blindness in India and is a major cause of visual impairment worldwide among the people in working age and is a leading cause of visual loss in older patients.[2]

Diabetic macular oedema (DME) is the major cause of vision loss in people with diabetic retinopathy. DME occurs when blood vessels in the retina of patients with diabetes begin to leak fluid and protein in macular area and causes it to thicken and swell. People with diabetes have 10 percent risk of developing the condition during lifetime.

In diabetes, increased flux of glucose and free fatty acids is associated with mitochondrial reactive oxygen species overproduction and, as a consequence, increased oxidative stress. Studies in the past have shown that Glycaemic control in form of blood sugar level and Glycosylated Haemoglobin (HbA1c) levels could be correlated with the severity of Diabetic Retinopathy. Many studies have shown that a strong association exists between dyslipidemia and increased risk of macrovascular disease. However, the association of dyslipidemia with the pathogenesis of DR remains unclear, though it is thought to be a risk factor for its development. In the Early Treatment of Diabetic Retinopathy Study (ETDRS); dyslipidemia, especially elevated triglycerides and LDL cholesterol, was found to be associated with increased risk of forming hard (lipid) exudates which are often found in the macular region. The purpose of this study is to determine the correlation between biochemical parameters like blood sugar, HbA1c and lipid profile and diabetic macular oedema changes as seen on fundus fluorescein angiography (FFA).

MATERIALS AND METHODS

Study Design: This is an observational, analytical, cross-sectional and hospital-based study.

Study population: All known diabetes or newly diagnosed diabetic adult attending the Department of Ophthalmology at army tertiary care hospital in central India during the study period from 01 Jan 2018 to 31 Dec 2019 were randomly selected on the basis of inclusion & exclusion criteria.

Inclusion Criteria:

1.Patients with either pre-existing or newly diagnosed type-2 diabetes mellitus with DR changes, without any medical or surgical intervention in the eye for DR.

Exclusion Criteria:

1. Patient without any DR changes,
2. Patients with pre- existing non diabetic maculopathy, myopic degenerations and other retinal degenerations.
3. Patients who have undergone laser photocoagulation therapy.
4. Patient's eye having mature cataract or dense cataract where fundus view is not possible.
5. Patients having non diabetic renal disorders, Sickle cell disease, Glucose 6 phosphate dehydrogenase deficiency, Vitamin B12 & folate deficiency.

Study Procedure: The consent form was explained to each participant and consent was obtained. Patients were examined & investigated and data was entered in the study proforma as per the history, examination, investigations & hospital records of the patient. In history taking, the duration of diabetes, family h/o diabetes, h/o hypertension, cardiovascular diseases or any other systemic disorders, drug history for treatment for Diabetes, Hypertension, Dyslipidemia along with duration, any ocular complaints with durations and any previous ocular surgery were recorded. All patients were investigated for HbA1c, Lipid profile and Serum creatinine, blood sugar fasting and post prandial and blood urea.

All the patients were examined for visual acuity, anterior and posterior segment examination, intraocular pressure and gonioscopy. The dilated fundus examination for evidence of DR using slit-lamp biomicroscopy and indirect ophthalmoscopy was performed. The macular area was specifically examined with a +78 D lens to document any pathology. FFA was done to see the characteristic of diabetic macular oedema. Optical coherence tomography (OCT) time domain type was done to grade macular oedema. Clinical grading of DR was done as per International Clinical Disease Severity Scale For DR[3]. Clinically significant macular oedema (CSME) was defined upon slit lamp biomicroscopy as per ETDRS group.[4]

Diagnosis of Diabetes: Diabetes was diagnosed based on the past

medical history, drug treatment for diabetes, and/or using the American Diabetes Association (ADA) criteria.[5]

Comorbidities: Comorbidity was defined as the simultaneous occurrence of one or more disease or disorders independently, like Hypertension, dyslipidemia, BPH etc. or a complication of diabetes like nephropathy, diabetic foot etc. taken as per history and drug treatment.

Data Analysis: Descriptive and inferential statistical analysis has been carried out in the present study. Significance was assessed at p <0.05 level of significance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. The Statistical software SPSS 15.0 was used for data analysis.

RESULTS

A total of 200 patients all were having DME with type 2 diabetes mellitus were enrolled in study. 36 (18%) patients were in 40-50 years age group, 64 (32%) patients were in 51-60 years age group, 72 (36%) patients were in 61-70 years age group and 28 (14%) patients were in age group > 70 years. More than half (56%) of patients were male while 44% patients were female. On FFA all patients had CSME of which diffuse DME (including 8 cases of ischaemic maculopathy) was seen in 88 (44%) patients and focal DME in 112 (56%) patients. HbA1c level was elevated > 6.5% in 144 (72%) patients and in 56 (28%) is < 6.5% which is normal. Elevated serum creatinine > 1.2mg/dl was present in 52 (26%) patients. On the other hand 148 (74%) patients had normal serum creatinine level <1.2mg/dl. All 112 patients of focal DME and all 88 patients of diffuse DME had normal VLDL level (<30mg/dl). In this study hypertension was the most common comorbidity associated in 36% of total patients. The table 1 is showing different features of DR in relation to various biochemical markers.

Table 1: Different Features Of DR In Relation To Various Biochemical Markers

Characteristics	NPDR	PDR	Focal DME	Diffuse DME	CMT<300 µm	CMT>300 µm
Total	66% (n=132)	34% (n=68)	56% (n=112)	44% (n=88)	26% (n=52)	74%(n=148)
Sex	M - 58% F - 42%	M - 55% F - 45%	M - 57.10% F - 42.90%	M - 54.50% F - 45.50%	M - 56% F - 44%	M - 54.5% F - 44.5%
HbA1c < 6.5%	35%	15%	36%	18.20%	61%	15.79%
HbA1c > 6.5%	65%	85%	64%	81.80%	39%	84.21%
Fisher's exact test value & p value	0.0017; significant at p< .05		0.0065; significant at p< .05		<0.00001; significant at p< .05	
Serum Creatinine <1.2mg/dl	80%	60%	85.70%	59.10%	83%	58%
Serum Creatinine >1.2mg/dl	20%	40%	14.30%	40.90%	17%	42%
Fisher's exact test value & p value	0.0032; significant at p< .05		0; significant at p< .05		0.0002; significant at p< .05	
FBS <110mg/dl	24%	6%	29%	5%	38%	11%
FBS >110mg/dl	76%	94%	71%	95%	62%	89%
Fisher's exact test value & p value	0.0009; significant at p< .05		<0.00001; significant at p< .05		0; significant at p< .05	
PPBS <150mg/dl	88%	14%	89%	18%	92%	18%
PPBS >150mg/dl	12%	86%	11%	82%	8%	82%
Fisher's exact test value & p value	<0.00001; significant at p< .05		<0.00001; significant at p< .05		<0.00001; significant at p< .05	
Serum Cholesterol <200mg/dl	76%	29%	89%	23%	85%	25%
Serum Cholesterol >200mg/dl	24%	71%	11%	77%	15%	75%
Fisher's exact test value & p value	<0.00001; significant at p< .05		<0.00001; significant at p< .05		<0.00001; significant at p< .05	
Serum LDL<100mg/dl	94%	88%	96%	91%	92%	92%
Serum LDL>100mg/dl	6%	12%	4%	9%	8%	8%
Fisher's exact test value & p value	0.1759; not significant at p< .05		0.1357; not significant at p< .05		1.0; not significant at p< .05	

DR – Diabetic retinopathy; NPDR – Non proliferative diabetic retinopathy; PDR – Proliferative diabetic retinopathy; DME – Diabetic macular oedema; CMT – Central macular thickness; Hb1Ac – Glycosylated Haemoglobin; FBS – Fasting blood sugar; PPBS – Postprandial blood sugar; M – Male; F – Female

DISCUSSION

The study found on FFA two types of DME, diffuse (44%), focal (56%). Findings of both OCT and FFA imply that diabetic macular edema is a disease of diverse manifestations and its treatment should be decided according to the subtypes of macular oedema. The interpretation of clinically significant diabetic macular oedema based on OCT and FFA findings would help to select an appropriate treatment plan for the diverse manifestations of DME.

HbA1c was statistically significantly associated with DME (p value=0.0065). Similar findings were noted in a study done in Brazil (p value = 0.001).[6] Elevated HbA1c level is a single independent important risk factor for DME. In addition, patients with normal HbA1c (<6.5%) CMT of < 300µm was present in 61% and >300µm was present in 15.79%. On the other hand, in patients with elevated HbA1c (>6.5%) CMT of <300µm was present in 39% and >300µm was in 84.21%. Therefore elevated HbA1c level could be a risk factor for increased CMT in DME. A study done by Agarwal et al found that the prevalence of DR was 36.4% with HbA1c levels more than 10%.[7] In CURES, HbA1c was significantly (P <0.0001) associated with severity of DR.[8] Raman et al found that suboptimal glycemic control (High HbA1c) was detrimental (P = 0.016) for the development of DR.[9] Thus HbA1c is a good indicator of microvascular complications of DM.[10] Chou T. H et al.[11] found that patients with HbA1c of 8% or above had macular thickness in Type 2 DM and there was a significant correlation between younger age shorter duration and macular thickness.

In diffuse, elevated serum creatinine was seen in 40.90% patients and 59.10% patient had normal serum creatinine level (<1.2mg/dl) which has shown that elevated serum creatinine level is associated more in diffuse type of edema therefore elevated serum creatinine is risk factor for diffuse DME. Diabetic nephropathy is usually first manifested as an increase in urinary albumin excretion (microalbuminuria), which progresses to overt albuminuria and then to renal failure.[12,13,14] It is also a reliable indicator of retinopathy in diabetics[15], however we could not perform the test in this study because of non-availability of the test in our laboratory.

Elevated fasting blood sugar was significantly associated with focal as well as diffuse type of DME (p value <0.00001). Therefore uncontrolled and elevated fasting blood sugar is an independent single risk factor for focal as well as diffuse type of DME. Elevated FBS level is an independent risk factor for increased CMT in macular oedema focal as well as diffuse oedema. FBS level is an important risk factor for both NPDR and PDR. PDR was strongly associated with elevated FBS level (p value=0.0009). Similarly postprandial blood sugar may be a risk factor for DME, particularly diffuse type and for increased CMT in DME(p value <0.00001).

NPDR was seen in 66% of patients, of which 76% patients had normal serum cholesterol level (<200mg/d) and 24% patients had elevated serum cholesterol level. While in PDR 71% of patients had elevated serum cholesterol level and 29% patients had normal serum cholesterol level. This is again indicating that elevated serum cholesterol level is an important risk factor for PDR and severity of DR (p value <0.00001). In diffuse macular oedema 77% patients had elevated serum cholesterol and only 23% patients had normal serum cholesterol <200mg/dl which is again suggestive of elevated serum cholesterol level being an independent factor for diffuse DME. Rema et al found that mean cholesterol, triglyceride and non-HDL (high density lipoprotein) levels were higher in patients with DR as compared to those without DR, but only high level of triglyceride was independently associated with DR.[16] Larsson et al found an association between higher levels of serum total cholesterol, declining ratios of HDL/total cholesterol and more severe retinopathy in diabetes mellitus type.[17] Elevated serum cholesterol level is significantly more with CMT >300µm (p value <0.00001) which again indicates that elevated serum cholesterol could be a risk factor for increased central macular thickness in DME. A study conducted by Cetin EN et al[18] concluded that serum lipid levels were not significantly associated with the severity of DR or existence of DME despite the significant correlation between the mean blood glucose, HbA1c and total cholesterol.

Elevated Serum LDL level was not significantly associated with macular oedema (p value=0.1357), increased CMT (p value=1.0) and with severity of DR (p value =0.1759). The serum level of VLDL was normal in all cases hence is not associated with severity of DR and type of macular oedema. In literature, the relationship between serum lipids and diabetic retinopathy has been quite variable. Miljanovic reported no association between lipid profile and progression of DR or PDR.[14] In another study, there was no association between DR and lipid profile, but CSME was found to be associated with serum lipids.[15] However a study done by Ozer et al could not show a correlation between serum lipid levels and macular oedema in diabetic patients.[19] Possible explanation for discrepancy of association of lipid profile and DR and DME may be the effect of ethnicity specific risk factors. Such risk factors may include differential susceptibility to conventional risk factors, insulin resistance, truncal obesity and genetic susceptibility.[20]

In this study Hypertension (HTN) was the most common comorbidity associated in 36% of total patients. HTN was found as a comorbidity ranging from 30% to 55% in other studies among DR patients.[21,22] Klein et al found an association of HTN with long term incidence and progression of DR, but there is no clinical evidence that HTN control prevents the incidence and progression of retinopathy in those with type 1 diabetes mellitus. The data for people with type 2 diabetes mellitus is inconsistent.[23]

CONCLUSION

PDR and CMT >300µm is more common in patients who have elevated PPBS. Elevated HbA1c, raised fasting and postprandial blood sugar levels are an independent single risk factor for DME and reduction of HbA1c levels with tight glycemic control decreases the rates of DME. Elevated serum creatinine and cholesterol levels could be risk factors particularly for diffuse DME. Serum LDL, VLDL level was not significantly associated with the severity of DME. Hypertension is most common comorbidity in our study and is a possible risk factor for DME.

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