Original Research Article

Influence of serum lipids on clinically significant macular edema in type 2 diabetic retinopathy cases

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A R T I C L E  I N F O

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A B S T R A C T

Background: Diabetic retinopathy (DR), a paramount microvascular complication of diabetes mellitus (DM), has a significant impact on the world’s health system. Up to 30 percent of patients with clinically significant macular oedema (CSME) will develop moderate visual loss. Other than diabetes, several systemic factors like dyslipidemia play an important role in the pathogenesis of DME. Thus, addressing these additional risk factors, in addition to adequate control of blood glucose helps to prevent and reverse maculopathy to some extent, thereby preserving their vision.

Materials and Methods: This study was done on 150 patients with type 2 diabetes mellitus, presenting to the outpatient department of ophthalmology of a tertiary care hospital, with CSME in either or both eye(s). A detailed history of each of these patients was taken and a comprehensive ophthalmic evaluation of anterior and posterior segments was done. Following Biochemical tests were carried out: 1. fasting blood glucose and post prandial blood glucose, 2. fasting lipid profile (serum total cholesterol, serum triglycerides, LDL-cholesterol, HDL-cholesterol, and VLDL-cholesterol). Dyslipidaemia was defined by using national cholesterol education program-adult treatment panel III (NCEP ATP III) guidelines. Accordingly, dyslipidemia was identified, when at least one of the Fasting lipid profile parameters crossed the desirable range.

Statistical Analysis: Data obtained from Diabetic Retinopathy cases was analysed using chi-square test.

Results: A total of 150 patients of either gender, between the age groups 30-70 years, were enrolled into the study after applying inclusion and exclusion criterias. Dyslipidemia was present in 101/150 (67.3%) patients. LDL-cholesterol level was significantly high, whereas Total Cholesterol, Triglycerides and VLDL showed borderline high values. Further, the occurrence of CSME showed a statistically significant correlation with LDL in majority of patients.

Conclusions: We found a positive correlation between altered lipid profile and the development of CSME. Therefore, early detection of dyslipemic changes, and appropriate intervention to control serum lipid levels might have a significant role in preventing moderate visual loss due to CSME, in Diabetic Retinopathy cases.

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1 Introduction

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia.1 Chronic hyperglycaemia and other metabolic disturbances of DM lead to significant long-term ocular tissue damage as well as other systemic dysfunction like renal, vascular and nervous system damage.2 The prevalence of diabetes and its related complications are
rising all over the globe in alarming rate, thus leading to increased morbidity and mortality. Visual impairment in DM is mainly attributed to retinopathy and macular edema.\(^3\) WHO projects that DM will be the 7th prime cause of death by 2030.\(^4\) Diabetic retinopathy caused 1.9% of moderate to severe visual impairment worldwide and 2.6% of blindness in 2010. Studies suggest that prevalence of retinopathy in persons with diabetes is 35%.\(^5,6\)

Early diagnosis, intensive evaluation and consistent long term follow up of DM patients, for their risk factors and/or complications are essential for effective care, which can help to preserve the vision and significantly lower the risk of blindness.

CSME, as defined by the ETDRS study is “thickening of the retina at / within 500 \(\mu\)m of the centre of the macula (or) hard exudates at / within 500 \(\mu\)m of the centre of macula, if associated with thickening of the adjacent retina or one or more zones of retinal thickening, 1 disc area or larger, any part of which is within 1 disc diameter of the centre of the macula”.\(^7,8\) CSME is a common occurrence in many cases of diabetic retinopathy. Up to 75,000 new cases of diabetic macular edema develop each year,\(^9\) and about 30% of patients with clinically significant macular edema develop moderate visual loss.\(^9\) CSME is the commonest cause of moderate visual loss in diabetic retinopathy cases.\(^10\) Presence of CSME may identify individuals, who require subsequent detection and treatment of associated cardiovascular disease(s).\(^11\) From previous studies, certain risk factors for CSME have been identified, such as: elderly age group, increased duration of diabetes, high values of serum total cholesterol / LDL / Fasting blood glucose / HbA1c / serum creatinine, high blood pressure, tobacco smoking, high levels of proteinuria and microalbuminuria.\(^1,12\)

Studies show that lipid-lowering drugs preserve vision and decreases the risk of hard exudates in clinically-significant macular edema in diabetics with an abnormal lipid profile.\(^10\) Once diabetic maculopathy occurs, the prognosis of visual outcome is poor in majority of patients due to irreversibility of effects of diabetes on retina. Hence, there is a need to find out the prevalence and the effect of dyslipidaemia, on the development of CSME, which if addressed adequately and timely, may reduce the incidence of Diabetic maculopathy and its associated visual loss in future.

2. Materials and Methods

This study included 150 patients with type 2 diabetes mellitus, who presented themselves to the outpatient department of ophthalmology in a tertiary care hospital, and who were detected to have CSME in either / both eye(s).

With prior informed consent for the study, a detailed history of each patient was taken and a comprehensive ophthalmic evaluation of anterior and posterior segments was done. Under aseptic precautions, blood samples were collected from anterior cubital vein and following tests were carried out:

1. Fasting Blood Glucose and Post Prandial Blood Glucose
2. Fasting Lipid profile (Serum Total Cholesterol, Serum Triglycerides, LDL-Cholesterol, HDL-Cholesterol, and VLDL-Cholesterol)

Dyslipidaemia was defined by using National Cholesterol Education Program–Adult Treatment Panel III (NCEP ATP III) guidelines. Accordingly, dyslipidaemia was identified, when at least one of the Fasting lipid profile parameters crossed the desirable range.

2.1. Statistical analysis

Data obtained from Diabetic Retinopathy cases was analysed using chi-square test, in relation to CSME.

2.2. Inclusion criteria

Type 2 Diabetes Mellitus patients, of either gender, presenting with CSME.

2.3. Exclusion criteria

1. Patient with hazy media which impair visualization of fundus.
2. Patient on lipid lowering drugs.
3. Type 1 diabetes mellitus patients.

All patients with Type 2 DM were subjected to complete ocular examination by assessing visual acuity with Snellen’s chart, slit lamp examination, intraocular pressure with rebound tonometry. Fundus examination was conducted with direct ophthalmoscope, Indirect Ophthalmoscope (IDO), and slit lamp biomicroscopy using +90 D lens. After fundus examination, only patients having CSME in either / both eyes were recruited for further study. OCT (Optical Coherence Tomography) was done in some patients to quantify and find out the type of macular edema. FFA (Fundus Fluorescein Angiography) was done in few patients to plan the treatment. In all these study subjects, aseptically collected venous blood was used for estimating fasting lipid profile, fasting blood glucose and Post Prandial blood glucose. Further, lipid profile values were correlated with the occurrence / incidence of CSME in these patients.

According to ATP III criteria, derangement of one or more lipid profile parameters above the desirable range was considered as dyslipidaemia.

BCVA (Best Corrected Visual acuity) was classified as follows:
2.4. Classification of deterioration of vision

3. Results

An observational correlation clinical study with 150 patients were undertaken to analyse the influence of serum lipids on the development of CSME in type 2 DR patients.

3.1. Age distribution

Majority of patients included in this study were in the age group 61-70 years (58%) (Table / Figure 1). Mean age of patients was 58.07 ± 6.95.

![Age wise distribution of Study Participants](image1)

3.1.1. Gender distribution

Out of 150 patients, 96 (64%) were males and 54 (36%) were females.

3.1.2. Laterality of CSME

96 (64%) in the study had unilateral CSME, while only 54 (36%) had bilateral CSME.

3.1.3. BCVA distribution of patients studied

The BCVA (considering the BCVA of worst eye) in the study group of 150 patients:

None had BCVA of 6/6, 3 (2%) had mild visual impairment, majority 99 (66%) had moderate visual impairment and 48 (32%) had severe visual impairment.

3.1.4. BCVA distribution in relation to Incidence of Dyslipidemia

Lipid profile was normal in 3 (2%) patients with mild visual impairment and none had dyslipidemia. In moderate visual impairment, 64% were normal and 36% had dyslipidemia. In severe visual impairment, 32% were normal and 68% had dyslipidemia.

![Gender distribution](image2)

![Laterality of CSME](image3)

![BCVA distribution of patients](image4)
loss, 60(40%) patients had dyslipidemia whereas 39 (26%) had normal lipid profile. In severe visual loss, 41(27.33%) patients had dyslipidemia whereas only 7 (4.67%) patients had normal lipid profile. P value (<0.0005) shows there is a significant association between dyslipidemia and BCVA

Table 1: BCVA distribution in relation to Incidence of Dyslipidemia

| BCVA            | Incidence of Dyslipidemia | Total (n=150) | P value |
|-----------------|---------------------------|---------------|---------|
|                 | Presence of Dyslipidemia  | (n=101)       |         |
| 6/6 (Normal)    | 0 (0%)                    | 0 (0%)        |         |
| 6/9 - 6/12 (Mild visual impairment) | 0 (0%) | 3 (2%) | 3 | 0.0005 |
| 6/18 - 6/36 (Moderate visual impairment) | 60 (40%) | 39 (26%) | 99 |
| > 6/60 (Severe visual impairment) | 41 (27.33%) | 7 (4.67%) | 48 |
| Total           | 101 (67.33)              | 49 (32.67)    | 150     |

3.1.5. Distribution of Severity of DR

Severity of diabetic retinopathy in the study group (according to worst eye) is presented below. Majority of patients had mild NPDR 57(38%) and 44(29.4%) had moderate NPDR. Severe NPDR was present in 23(15.3%). Early PDR was present in 16(10.6%) and High Risk PDR was present in 10(6.7%).

Table 2: Distribution of Severity of Diabetic Retinopathy in relation to Dyslipidemia

| Fundus  | Incidence of Dyslipidemia | Presence of Dyslipidemia(n =101) | Absence of Dyslipidemia(n =49) | P value |
|---------|---------------------------|----------------------------------|--------------------------------|---------|
| Mild NPDR | 31(20.67%)                | 26(17.34%)                       | 2(1.33%)                       | <0.001  |
| Moderate NPDR | 26(17.33%)                | 18(12%)                          |                                |         |
| Severe NPDR | 21(14%)                   | 2(1.33%)                         |                                |         |
| Early PDR | 13(8.67%)                 | 3(2%)                            |                                |         |
| High Risk PDR | 10(6.66%)                 | 0(0%)                            |                                |         |
| Total    | 101(67.33%)               | 49(32.67%)                       |                                |         |

3.1.6. Distribution of severity of diabetic retinopathy in relation to dyslipidemia

The occurrence of dyslipidemia was very significantly higher at all stages of Diabetic Retinopathy, with a p-value of < 0.001

3.1.7. Glucose parameters distribution

40% patients had FBS between 100-140 mg/dl and 60% patients were above 140mg/dl with mean value of 156.22±37.21. 1.3% patients had PPBS less than 140mg/dl, 7.3% had 140-200mg/dl and 91.3% had above 200mg/dl with mean value of 277.69±68.23.

Fig. 6: FBS parameters distribution

3.1.8. Inference on distribution of patients studied

Out of 150 patients, 101 (67.33%) had altered lipid profile with 95% confidence interval of 59.48-74.32, and 49(32.67%) had normal lipid profile with 95% confidence interval of 25.68-40.52. This shows that there is significant correlation between altered lipid profile and development of CSME.
Fig. 7: Table 3: Inference on distribution of patients studied

| Inference            | No. of patients | %    | 95% CI (Confidence Interval) |
|----------------------|-----------------|------|-----------------------------|
| Absent Dyslipidemia  | 49              | 32.67| 25.68 - 40.52               |
| Present Dyslipidemia | 101             | 67.33| 59.48 - 74.32               |
| Total                | 150             | 100.0| —                           |

4. Discussion

Diabetes Mellitus is the most common metabolic disorder globally. Diabetes induced systemic complications are influential on individuals as well as on the society, since they affect diabetic patients in the most important and useful years of their productivity in the community. Diabetic retinopathy is the most common microvascular complication of diabetes, which can lead to severe visual loss. Independent of diabetic retinopathy, severe visual impairment among diabetes mellitus patients may also be caused by diabetic maculopathy. Several previous studies have suggested that abnormal serum lipid levels, are important risk factors for the development of CSME.

Majority of patients in this study were between 61-70 years (Mean ± SD: 58.07±6.95). This supports the fact that CSME becomes more evident as the age advances. Prakash GS et al in their study found that the mean age of the patients in the study group (with CSME) was 57.02 ± 9.75. Study conducted by Seyed Ahmad et al found that the mean age of CSME patients as 53.22± with the range of 18-77 years.

The present study included 96 (64%) males and 54 (36%) females. In this study, it was found that CSME was common in male gender. However, Asensio-Sanchez VM et al in their study reported 60% women and 40% men with CSME, and Ong Ming Jew et al in their study reported 42% males and 58% females with CSME.

In the present study patients with unilateral CSME [96(64%)] were more, compared to patients with bilateral CSME [54(36%)]. Arulanandham A et al in their study found 22 unilateral and 15 bilateral cases of CSME among 37 subjects. This shows the importance of early detection and treatment for risk factors of CSME, so that the risk of vision loss in the other eye due to CSME can be reduced by timely intervention.

BCVA of patients in the study showed that majority (66%) of the patients with CSME had moderate visual loss, which supports the fact that CSME is the most common cause of moderate visual loss in diabetes, which is also revealed by Narang S et al in their study on. Prakash GS et al., in their study. In our study, incidence of dyslipidaemia in CSME patients was significantly associated with moderate visual loss than with mild or severe form with significant p value of < 0.0005.

In the present study, the severity of diabetic retinopathy (according to worst eye), found to have majority of patients with mild NPDR (38%), followed by moderate NPDR (29.4%). Severe NPDR was seen in 15.3% patients, early PDR was seen in 10.6% patients and High Risk PDR was seen in 6.7% patients. Rajiv Raman et al in their study have found 6.3% mild NPDR, 25% moderate NPDR, 50% severe NPDR and 18.8% PDR among CSME patients.

In this study, it was found that mean FBS and PPBS were 156.22 ± 37.21 and 277.69 ± 68.23 respectively, which is higher than the normal values of FBS and PPBS. In the study done by Rajiv Raman et al, the mean fasting plasma glucose was found to be 217.94 ±80.42. This supports the fact that hyperglycaemia is one of the risk factors for development of CSME. High blood glucose levels for a long period of time can cause alterations in pericytes and basic membrane, contributing to endothelial barrier dysfunction.

In the present study, 68(45.34%) patients had high cholesterol, 50(33.4%) patients had high triglycerides, 101(67.33%) had high LDL, 51(34%) patients had high VLDL and 24(16%) patients had low HDL. Sachdev N et al, in their study have shown that 44.45% had raised LDL and 51.67% had raised cholesterol.

Our findings of an association between abnormal LDL and CSME is similar to the previous reports, which have specifically proved this results. In conclusion, in the present study of CSME patients, 49(32.67%) had no dyslipidaemia with 95% confidence interval of 25.68-40.52 and 101(67.33%) had dyslipidaemia with 95% confidence interval of 59.48-74.32. This shows that dyslipidaemia is
significantly associated with development of CSME.

Several mechanisms discussed in earlier report regarding association of serum lipids and CSME, include the direct involvement of serum lipids in endothelial dysfunction, leading to exudation of serum lipids and lipoproteins to intercellular space in the retina. Finally the present study has shown that serum lipids, especially LDL, was largely associated with CSME(67.3%), but not with the severity of DR, suggesting a differential impact of dyslipidemia in the pathogenesis of DR and CSME, similar to the fact said by Rebab Benarous et al. \(^{20} \) in their study.

5. Conclusion

Increasing number of individuals with diabetes mellitus globally, suggests that diabetic retinopathy and diabetic macular edema will continue to be the major contributors for visual impairment and associated functional impairment in the coming years. At any stage of diabetic retinopathy, macula can be affected by CSME, leading to sudden and debilitating impact on the visual acuity.

This study has shown that CSME is more common in the elderly age group of 61-70 years with male gender predilection. Most of the patients were presented with unilateral CSME. We found mild NPDR patients were more in number compared to other types of retinopathy, which was also true for incidence of dyslipidemia. This study also showed Mean FBS and PPBS levels above normal limit. In this study serum LDL, showed significant association (67.35%) with CSME. Serum mean value of cholesterol and triglycerides have shown borderline high values. Similar studies like ETDRS also have shown similar correlation of serum LDL to CSME and associated visual loss in such patients. Considering the BCVA of the worst eye, majority of the patients had moderate visual loss, which was also true for incidence of dyslipidemia. In conclusion, out of 150 patients, 101(67.33%) had dyslipidemia with 95% of confidence interval of 59.48-74.32, which shows positive correlation between the dyslipidemia and the development of the CSME. Control of the abnormalities in serum lipids is important in preserving visual function because dyslipidemia has been identified as a risk factor for both development and progression of CSME.

Thus, periodic screening and timely intervening the dyslipidemia in diabetic patients definitely makes major differences in terms of visual loss and lifestyle of individual.

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7. Conflicts of Interest

All contributing authors declare no conflicts of interest.

8. Source of Funding

None.

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