Lipoproteins in Diabetic Maculopathy


1Department of Biochemistry, 2Department of Ophthalmology, SRM Medical College Hospital & Research Center, Kattankulathur, Kancheepuram District - 603 203.

Available Online: 2nd September, 2015

Abstract
Diabetic maculopathy, defined as retinopathy within one disc diameter of the centre of the macula, is a major cause of vision loss in diabetes. Cross-sectional studies suggest that higher serum lipid levels are found in patient in patients with macular exudates and prospective studies have shown an increased risk of exudative maculopathy if baseline cholesterol is higher. Therefore in this study we have analysed the status of lipoprotein and lipoprotein (a) in a group of subject with Diabetic maculopathy. This study was carried out on patients with type 2 Diabetes Mellitus attending the Ophthalmology outpatient department of SRM Medical College Hospital and Research Centre in Kattankulathur. 30 diabetic patients with diabetic maculopathy formed the study group. 30 diabetic patients without diabetic maculopathy formed the control group. The mean levels of Lp (a), Total cholesterol and LDL-C in the diabetic maculopathy group showed a statistically significant elevation compared to the control group. The statistically significant difference was also observed in the levels of HDL-C between the two groups. The mean levels of triglycerides did not differ significantly between the two groups. Lipoprotein in the circulation may have an indirect, yet important, role in the development of diabetic retinal complications due to Blood Retinal Barrier (BRB) impairment and lipoprotein extravasation.

Key Words: Diabetes Mellitus, Diabetic maculopathy, Lipoprotein, Lipoprotein (a).

INTRODUCTION
Diabetic retinopathy is the most common microvascular complication in diabetes mellitus which can produce severe loss of vision1,2. Diabetic maculopathy, defined as retinopathy within one disc diameter of the centre of the macula, is a major cause of vision loss in diabetes mellitus3.

Diabetic maculopathy is a common complication of diabetes mellitus, characterised by macular oedema and frequently accompanied by lipid exudation4. Factors associated with the development of maculopathy are mostly unknown5-7. Several previous reports have suggested that poor metabolic control might be involved in haemodynamic changes of retinal circulation, and thereby lead to maculopathy8. Cross-sectional studies suggest that higher serum lipid levels are found in patients with macular exudates and prospective studies have shown an increased risk of exudative maculopathy if baseline cholesterol is higher4.

Lp(a) is a LDL like molecule which may attenuate the generation of plasmin and reduces fibrinolytic activity in blood circulation9,10. Elevated Lp(a) levels may play a causative role in Diabetic Retinopathy by damaging the microcirculation11. Blood retinal barrier (BRB) becomes deficient in diabetes, allowing extravasation of lipoproteins which then become modified (i.e. oxidized and/or glycated) in tissue, rendering them toxic towards nearby retinal cells. BRB impairment may be caused by many common, intermittent metabolic stresses that are present in diabetes, such as high and fluctuating glucose, free fatty acids, oxidative stress and osmotic stress12-16. Therefore in this study we have analysed the status of lipoproteins and lipoprotein (a) in a group of subjects with Diabetic Maculopathy.

MATERIALS AND METHODS
This study was carried out on patients with type 2 Diabetic Mellitus attending the Ophthalmology outpatient department at SRM Medical College Hospital and Research Centre in Kattankulathur. The protocol of the study was approved by the Institutional ethics Committee of SRM Medical College Hospital and Research Centre and informed written consent was taken from all subjects. We enrolled 60 diabetic patients. The exclusion criteria were (1) Cataract; (2) glaucoma; (3) females taking oral contraceptive pills or hormone replacement therapy; (4) familial hypercholesterolemia; (5) hypothyroidism; (6) patients with chronic liver disease; (7) patients with kidney disease. Assessment of DR was performed by ophthalmoscopy through dilated pupils by an ophthalmologist. Clinically significant diabetic maculopathy was defined as the presence of retinal thickening at or within 500 μm of the centre of the macula17. 30 diabetic patients with diabetic maculopathy formed the study group. 30 diabetic patients without diabetic maculopathy formed the control group.

Venous blood samples were drawn from patients and all examinations were performed after an overnight fast. The samples were allowed to clot, and serum was separated by
Table:1 Comparison of mean ±SD of the measured biochemical parameters between the control group and patients with Diabetic Maculopathy.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n=30)</th>
<th>Patients (n=30)</th>
<th>'p' value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a) (mg/dl)</td>
<td>25.169±15.679</td>
<td>52.262±31.04</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total cholesterol(mg/dl)</td>
<td>214.4±9.3</td>
<td>244.72±54.28</td>
<td>0.0038</td>
</tr>
<tr>
<td>Triglycerides(mg/dl)</td>
<td>150.7±14.4</td>
<td>183.57±93.9</td>
<td>0.0631</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>111.4±41.5</td>
<td>140.3±40.6</td>
<td>0.0007</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>47.3±14.3</td>
<td>41.6±6.4</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Values are expressed in mean ±standard deviation. The values are statistically significant if the ‘p’ value is less than 0.05.

RESULTS

The study included 30 diabetic patients with diabetic maculopathy and 30 diabetic patients without diabetic maculopathy as the control group. The mean levels of Lp(a). Total cholesterol and LDL-C in the diabetic maculopathy group showed a statistically significant elevation compared to the control group. A statistically significant difference was also observed in the levels of HDL - C between the two groups. The mean level of triglycerides did not differ significantly between the two groups.

DISCUSSION

MACULAR ODEMA is thought to be caused principally by breakdown of the inner blood-retinal barrier. A number of cross-sectional studies suggest that serum lipids may have a causative role in the development of macular exudates4. An elevation in cholesterol has been shown in studies of exudative maculopathy in type 1 diabetes18. A direct toxic effect of LDL on retinal capillary pericytes has also been demonstrated and this toxic effect can be enhanced by LDL glycation or oxidation. In other small cross-sectional studies, lipoprotein (a) has been suggested as a risk factor for maculopathy19,20. The presence of elevated levels of total cholesterol, LDL cholesterol, Lp (a) and reduced levels of HDL cholesterol in patients with diabetic maculopathy in our study may indicate the role of lipids in the development of diabetic maculopathy.

The role of circulating lipoproteins in DR depends on the integrity of BRB. Normally, plasma LDL does not cause retinal damage, but plasma oxLDL (mostly mildly modified) may contribute to the initial BRB impairment. Once the BRB becomes leaky, even in a short period, LDL can extravasate, aggregate and become progressively modified by oxidation and glycation in the extracellular milieu, resulting in generalized damages to all retinal cell types in proximity21. Jeremy et al21 have reported the presence of lipoprotein extravasation in all diabetic patients with the extent correlating with the severity of retinopathy. In the Early Treatment Diabetic Retinopathy Study (ETDRS), serum lipid levels were measured in 2709 patients and those with elevated total or LDL cholesterol levels at baseline were twice as likely to have retinal hard exudates as those with normal levels22.

In the Atherosclerosis Risk In Communities study the presence of retinal hard exudates was correlated with LDL cholesterol and lipoprotein (a)23. The retinal pigment epithelium (RPE) is a metabolically active tissue. Oxidized lipids are taken up by the base of RPE cells24. These particles accumulate in the inner collagenous layer and is a critical event and a prominent histopathological marker in age related macular degeneration (AMD)25.

Although some studies have shown a relationship between elevated Lp(a) levels and active retinopathy in patients with type 1 diabetes mellitus, a large prospective study failed to demonstrate this association26-29. In other small cross-sectional studies, lipoprotein (a) has been suggested as a risk factor for maculopathy39,20, although this finding is refuted on examination of a small subset of the WESDR population40.

Lipoproteins in the circulation may have an indirect, yet important, role in the development of diabetic retinal complications due to BRB impairment and lipoprotein extravasation21. A number of studies have shown that lipid lowering therapy may reduce macular exudates, but numbers in these trials are small. Larger studies using more defined populations are required to better understand the relationship between Lp(a) concentrations and retinopathy in patients with type 2 diabetes mellitus27.

REFERENCES

3. Henriksson M, Tyrberg M, Heijl A, Janson L. Incidence of blindness and visual impairment in
4. TA Chowdhury D Hopkins P M Dodson and G C Vafidis. The role of serum lipids in exudative diabetic maculopathy: is there a place for lipid lowering therapy? 2002; Eye 16: 689–693