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A study on oxidized-LDL cholesterol in normolipidemic retinal vein occlusion

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ABSTRACT

Background: Oxidized low-density lipoprotein (ox-LDL) has been implicated in atherosclerotic cardiovascular disease. Arteriolosclerosis is an important causative factor for retinal vein occlusion (RVO). Till, date there is dearth of literature on ox-LDL and RVO. **Aims and Objectives:** The objectives of this study were to see whether ox-LDL cholesterol is an independent risk factor in RVO with normal lipid profile. **Materials and Methods:** Lipid profiles and ox-LDL levels were assayed in 122 adult unilateral RVO cases and 142 age and sex matched controls in this 1 year old case–control study. **Results:** ox-LDL cholesterol levels were significantly elevated in RVO cases than controls (54.5 ± 6.1 in cases vs. 36.6 ± 5.6 in controls, $P < 0.01$), although serum lipid profiles were normal in both cases and controls. **Conclusion:** The ox-LDL-induced atherosclerosis may be responsible for the retinal venous occlusion in absence of other risk factors. Hence, screening for ox-LDL in RVO patients should be worth considering especially in patients with normal lipid profiles.

Key words: Oxidized-LDL cholesterol; LDL cholesterol; Retinal vein occlusion

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INTRODUCTION

Oxidized low-density lipoprotein (ox-LDL) is a modified form of LDL. Each LDL is made up of approximately 600 molecules of free cholesterol, 700 molecules of phospholipids, 185 molecules of triglycerides, 1600 molecules of cholesterol ester, and an apolipoprotein B-100 (apoB-100) protein with 4536 amino acids.[1] Both the lipid and the protein components of LDL particles can be oxidized to form fatty acid fragments and oxidized phospholipids. Fatty acid fragments are converted to aldehyde, which can interact with the lysine residue of apoB-100 to form new epitopes which inhibit the ability of LDL to bind to the LDL-receptors (Liver, adrenal cortex, etc) assigned for their metabolism.[2] Rather ox-LDL will be taken up by macrophages converting themselves to form cholesterol filled foam cells which generate inflammation of the arterial wall causing atherosclerosis.[3]

The second most common retinal vascular disorder after diabetic retinopathy is retinal vein occlusion (RVO) with prevalence ranging from 0.7% to 1.6%.[4] Two most common forms of RVO are central RVO (CRVO) and branch RVO (BRVO).[5] Glaucoma, diabetes, hypertension, dyslipidemia,[6] hypercoagulability,[7] hyperhomocysteinemia,[8] and antiphospholipid syndrome[9] have been associated with RVO, although the basic pathology of the disease is localized atherosclerosis.

Aims and objectives

Till date there is dearth of literature on oxidized low-density lipoprotein and RVO. Therefore, the objective of this study was done to see whether oxidized-LDL cholesterol

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is an independent risk factor in retinal vein occlusion with normal lipid profile.

MATERIALS AND METHODS

This observational case–control study included consecutive, unrelated 122 adult patients, with a diagnosis of acute unilateral RVO (within 1 month from onset) in the absence of any other local and systemic disease. It was conducted in a medical college, Kolkata, for a period of 1 year after obtaining the inform consent from all the study populations, in accordance with the Declaration of Helsinki. The approval was taken from the Institutional Ethics Committee before the study. One hundred and forty-two age- and sex-matched control subjects were the persons who accompanied the patients attending the outpatient department. Sample size was calculated using the formula: $n=\{Z_{1-\alpha/2}\sqrt{[2\,p2\,(1-p2)]}+Z_{1-\beta}\sqrt{[p1(1-p1)+p2\,(1-p2)]}\}^2/(p1-p2)$.[2] [p1: Anticipated probability of exposure for cases. p2: Anticipated probability of exposure for controls. Anticipated odds ratio: $OR=[p1/(1-p1)]/[p2/(1-p2)]$. $Z_{1-\alpha/2}$: Value of normal deviate at considered level of confidence (two sided). $Z_{1-\beta}$: Value of normal deviate at considered power of study]. Family history, social status, and dietary habits, including other habits such as smoking, alcohol intake, history of systemic diseases, thromboembolic diseases, other ocular diseases, and drug history was completed by all the study participants. Patients with atherosclerotic risk factors (such as hypertension, diabetes mellitus, cardiovascular disease, high LDL cholesterol, low high-density lipoprotein (HDL) cholesterol, and high homocysteine), raised intraocular tension, renal disease, liver disease, hematologic and coagulation abnormalities and on anti-oxidants, statins, and fenofibrates therapy were excluded from the study. Visual acuity, relative afferent pupillary defect, and fundus examination were used for the clinical diagnosis of acute unilateral RVO (within 1 month from onset).

Measurement of circulating ox-LDL was done by precipitation method.[10] Total cholesterol (Cholesterol oxidase-peroxidase method), triglyceride (Glycerophosphate oxidase-peroxidase method), HDL cholesterol (Direct method), and LDL cholesterol (Direct method) were measured by enzymatic assays.[11-13]

Other biochemical tests fasting plasma glucose, homocysteine, liver function test (ALT, AST, total bilirubin, direct bilirubin, total protein, and albumin), kidney function test (Urea and creatinine), tests for hematologic (TC, DC, ESR, and Hb), and coagulation defects (CT, BT, and PT) were performed. RA factor, anti-nuclear antibody, was also measured to exclude autoimmune diseases.

Statistical analysis

Data were presented with mean and standard deviation using SPSS software with $P \leq 0.05$ is considered significant.

RESULTS

There were 64 males and 58 females as RVO cases and 73 males and 69 females as controls. Age of the RVO cases and controls were 48.2±8.1 years and 45.7±7.5 years, respectively (Table 1). Among the cases, 30 had unilateral CRVO and 92 had unilateral BRVO. ox-LDL cholesterol levels were significantly elevated in RVO cases than controls (54.5±6.1 in cases vs. 36.6±5.6 in controls, P<0.01), although serum lipid profiles were normal in both cases and controls (Table 2).

DISCUSSION

There were no significant changes in the age (48.2±8.1 years in cases and 45.7±7.5 years in controls, P>0.5) and sex (64 males and 58 females in cases and 73 males and 69 females in controls) profiles in study populations, although males were having slightly higher prevalence in our study (Table 1). Total cholesterol levels were within the normal range in both RVO cases and controls with no statistical significance (157.5±6.9 mg/dL vs. 151.3±6.7 mg/dL, P>0.5). Triglyceride levels were also normal in both RVO cases and controls (67.9±10.3 mg/dL vs. 63.7±11.3 mg/dL, P>0.5). HDL cholesterol levels were within the normal range in both RVO cases and controls with no statistical significance (40.3±2.5 mg/dL vs. 41.9±2.9 mg/dL, P>0.5). LDL cholesterol levels were also

Table 1: Comparison of age and sex profiles between RVO cases and controls

Parameters	Controls	Cases	P-value
Age (years)	45.7±7.5	48.2±8.1	>0.5
Sex (Male/Female)	73/69	64/58	

RVO: Retinal vein occlusion

Table 2: Comparison of Oxidized-LDL cholesterol and serum lipid profiles in between RVO cases and controls

Parameters	Cases	Control	P-value
Total cholesterol (mg/dL)	157.5±6.9	151.3±6.7	>0.5
HDL-cholesterol (mg/dL)	40.3±2.5	41.9±2.9	>0.5
LDL-cholesterol (mg/dL)	85.6±6.9	81.2±7.1	>0.5
VLDL-cholesterol (mg/dL)	13.8±2.4	12.7±3.1	>0.5
TG (mg/dL)	67.9±10.3	63.7±11.3	>0.5
Oxidized-LDL cholesterol (mol/L)	54.5±6.1	36.6±5.6	P<0.01

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG: Triglycerides, RVO: Retinal vein occlusion

normal in both RVO cases and controls (85.6±6.9 mg/dL vs. 81.2±7.1 mg/dL, P>0.5).

Meisinger et al., have shown that ox-LDL has been implicated in atherosclerosis induced acute coronary heart disease events in apparently healthy, middle-aged men from the general population by causing arterial vessel wall inflammation.[14] Other mechanisms of atherogenesis by ox-LDL were endothelial injury, expression of adhesion molecules, and leukocyte recruitment and retention, as well as thrombus formation.[15-17] Gao and Liu have shown the association between circulating ox-LDL and atherosclerotic cardiovascular disease.[18] Trpkovic et al., have identified the role of ox-LDL as a biomarker of cardiovascular diseases.[19] A pilot study with only seven patients (4 RVO) suggested for the 1st time that OX-LDL may be elevated in retinal vascular disease.[20] Although the traditional lipid profiles of cases and controls were of no significance, ox-LDL-Cholesterol level was elevated significantly in our study for RVO cases in comparison to controls (54.5±6.1 in cases vs. 36.6±5.6 in controls, P<0.01) (Table 2).

A retinal arteriole and its corresponding vein share a common adventitial sheath. Thickening of the arteriole appears to compress the vein. This causes secondary changes, including venous endothelial cell loss, thrombus formation, and potential occlusion.[6] The present study showed that ox-LDL level was raised significantly in patients of RVO compared to controls, even though the lipid profiles parameters were same in both groups.

Limitations of the study

Correlations of ox-LDL cholesterol with traditional lipid parameters were not done in this study.

CONCLUSION

The ox-LDL-induced atherosclerosis may be responsible for the retinal venous occlusion in absence of other risk factors in this study. Hence, screening for ox-LDL in RVO patients should be worth considering especially in patients with normal lipid profiles.

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Authors' Contributions:
KDL- Definition of intellectual content, Literature survey, Prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **KDL, AKG, UKB-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **KDL, AKG, UKB-** Design of study, statistical Analysis and Interpretation; **KDL, AKG, UKB-** Review Manuscript; **KDL-** Review Manuscript; **KDL, UKB-** Literature survey and preparation of Figures; **KDL-** Coordination and Manuscript revision.

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