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RESEARCH ARTICLE

Oxidized low-density lipoprotein as an inflammatory marker in the cardiovascular disease

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ABSTRACT

Background: Cardiovascular disease (CVD) is the leading cause of death in the world. Inflammation is a systemic body response aimed to decrease the toxicity of harmful agents and repair damaged tissue. Significantly, production of pro-oxidant is increased at sites of inflammation, suggesting that focal inflammation significantly contributes to the initiation of oxidized low-density lipoprotein (OxLDL) oxidation at early stages of plaque formation. OxLDL thought to promote atherosclerosis through involved inflammatory and immunologic mechanisms that lead to lipid dysregulation and foam cell formation. **Aims and Objective:** The objective of the study was to investigate the role of inflammation in the progression of CVD using OxLDL as a marker. **Materials and Methods:** The study was conducted in at MES Medical College Hospital, Kerala, written informed consent was obtained from all the volunteers recruited for this study. Persons having dyslipidemia were included as a test population, age, and sex-matched healthy subjects who attended the medical camp were included as a control population. **Results:** A Pearson product - moment correlation was run to determine the relationship between OxLDL and high sensitive C reactive protein values. There was a strong, positive correlation between the two, which was statistically significant. The present study shows that circulating OxLDL is a sensitive marker of CAD that is correlated with other risk factors of CAD, further suggests that OxLDL may indeed play a causative role in coronary atherosclerosis. **Conclusion:** Markers of oxidative stress, such as OxLDL particles, are under investigation as possible biomarkers of CVD risk.

KEY WORDS: Cardiovascular Disease; Inflammation; Oxidative Stress; Oxidised Low-density Lipoprotein; High Sensitive C reactive Protein

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the world.[1] The world health organization has projected that CVD will become the most significant cause of morbidity and mortality in the world by the year 2025. CVD is due to structural or functional abnormality of the heart, or of the blood vessels supplying the heart, which impairs its, healthy functioning. Arteriosclerosis, coronary artery disease, heart valve disease, arrhythmia, heart failure, hypertension, orthostatic hypotension, shock, endocarditis vascular, a disease of the aorta and its branches, disorders of the peripheral vascular system, and congenital heart disease are few of them. Risk factors that have an unpretentious association with the CVD thought to explain 50% of the burden. Interaction among the risk factors can augment the risk of disease. Additional risk factors have been proposed that help explain the enduring CVD burden.[2]

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Inflammation is a systemic body response aimed to decrease the toxicity of harmful agents and repair damaged tissue.[3] Not many studies are carried out to assess the inflammatory

mass events accelerating the cardiovascular risk events. A vital feature of the inflammatory response involves activation of phagocytic cells involved in host defense, which fabricate an oxidative rapture of reactive oxygen, chlorine, and nitrogen species, with subsequent formation of a highly prooxidative environment to conflict invading pathogens. Local and systemic infections, arterial wall injury, and excessive holding of low-density lipoprotein (LDL) may all potentiate activation of macrophages in the arterial wall, thereby triggering desirable production of pro-oxidant species.[4] As a result, oxidation of proteoglycan bound LDL may occur in the extracellular space of the arterial intima.

The imbalance between circulating levels of cholesterol transported in high-density lipoprotein (HDL) relative to that in Apolipoprotein B (Apo B)-containing particles is intimately associated with induction of both endothelial dysfunction and oxidative stress in the arterial wall, which is, in turn, closely related to inflammation.[5] As a result, dyslipidemia, oxidative stress, and inflammation are closely interrelated in the development of atherosclerosis. The preferential retention of LDL in the arterial wall makes this lipoprotein a significant substrate for oxidation by pro-oxidant produced by arterial wall cells.[6] Accordingly, reactive oxygen, chlorine and nitrogen species, and lipid-derived free radicals are major pro-oxidant involved in the formation of OxLDL *in vivo*. Significantly, production of both chlorine- and nitrogen-containing prooxidant is increased at sites of inflammation, indicating that focal inflammation is significantly presenting to the initiation of LDL oxidation at early stages of plaque formation. Agreeing with the mantle of oxidative stress and oxidative modification of LDL in atherosclerosis, directly the most robust and integrative marker of oxidative stress *in vivo* in and plasma levels of OxLDL represent strong and independent risk factors for CHD.[7]

OxLDL particles exhibit multiple atherogenic properties, which include uptake and accumulation in macrophages, as well as pro-inflammatory, immunogenic, apoptotic, and cytotoxic activities.[8] In contrast to unmodified LDL, OxLDL is taken up through macrophage scavenger receptor (SRA) pathways that are not downregulated by excess ligand and lead to the formation of cholesterol-loaded foam cells, essential components of atherosclerotic plaques. The pro-inflammatory activities of OxLDL include chemo attractant deed on circulating monocytes, initiation of the expression of adhesion molecules on endothelial cells, the furtherance of monocyte differentiation into macrophages,[9] the consecration of the production and release of pro-inflammatory cytokines and chemokine from macrophages, and inhibition of macrophage motility.

OxLDL is thought to promote atherosclerosis through involved inflammatory and immunologic mechanisms that lead to lipid dysregulation and foam cell formation.[10] It is has been reported that the *in vitro* addition of acetyl groups to LDL (acetylation), generates a modified LDL which can induce cholesterol accumulation in macrophages, indeed, and acetylated.

LDL is incorporated by SRA, which in contrast to the normal LDL receptor, are not "down-regulated," hence, they induce a sizeable intracellular lipid accumulation. Thus, acetylated LDL increases the formation of foam cells. Atherosclerosis is a persistent inflammatory disease of the arterial wall that culminates with the athermanous plaque formation.[11] At present, there is a consensus that oxidation of LDL in the endothelial wall is an early event in atherosclerosis, according to the oxidative hypothesis.

In the present study, an effort was made to evaluate of progression of CVD in patients with dyslipidemia, applying inflammatory markers such as high sensitive C reactive protein (hs-CRP) and OxLDL, after observing cardiovascular risk events by established markers such as total cholesterol (TC), LDL, HDL, and triglycerides (TG). The aforesaid inflammatory markers help to monitor inflammatory events in cardiovascular progression, thereby contributing to the prediction of onset of cardiovascular risk events.

MATERIALS AND METHODS

The study was conducted at MES Medical College Hospital, Kerala, after getting approval from the Institutional Ethical Committee. Written informed consent was obtained from all the volunteers recruited for this study. A total of 60 cases were enrolled in the study, grouped in to test population (30) and control population (30). Persons having dyslipidemia were included as a test population, age, and sex-matched healthy subjects who attended the medical camp were included as a control population. Subjects with infectious disease, cancer, autoimmune disorders, and other terminal diseases were excluded from the study. The demographic parameters such as age, height, body weight, sex, and body mass index of both the groups were noted and recorded. Blood pressure (BP) was recorded separately before the blood collection procedure to avoid the BP fluctuations due to apprehension.

Blood was collected in fasting state from both the control and test group as per clinical laboratory standard institution guidelines. A fully automated analyzer had used to analyze the biochemical parameters such as TC, TG, HDL, LDL, OxLDL, hs-CRP, and Apo-A1 and Apo-B.

RESULTS

There is a significant increase in the OxLDL of the test group, and the significance is $P < 0.01$. LDL undergoes oxidation and OxLDL deposited into the arteries; leading to atherosclerosis. There is a significant increase in the hs-CRP of the test group, and the significance is $P < 0.01$. High hs-CRP also serves

Table 1: Statistics (t-test) of inflammatory markers

Test variable	Group	Mean±SD	t-test statistic	Significant value (P-value)
OxLDL	Control	60.8788±12.18544	10.708	0.000<0.01
	Experimental	87.5938±7.22835		
hs-CRP	Control	0.6612±0.33489	8.800	0.000<0.01
	Experimental	2.0897±0.86840		

SD: Standard deviation, Ox-LDL: Oxidized low-density lipoprotein, hs-CRP: High sensitive C reactive protein

as an inflammatory marker. The above result proves the magnitude of inflammatory changes in CVD [Table 1].

Table 2 shows that there is no statistically significant linear relationship between the different variables and OxLDL values in the control group. The direction of the relationship is positive between the variables except for TC, HDL, and Apo B_1 and Apo A_1 ratio, meaning that these variables tend to increase together, i.e. greater OxLDL value is associated with more significant of these variables. However, for TC, HDL, and Apo B_1 and Apo A_1 ratio, and OxLDL is decreasing with the increase of these values; they are negatively correlated.

Table 3 shows that there is no statistically significant linear relationship between the different variables and hs-CRP values in the control group. The direction of the relationship is positive between the variables except for SBP LDL, TG, and Apo A_1 and Apo B_1 meaning that these variables tend to increase together, i.e. the greater hs-CRP value is associated with more significant of these variables. However, for exceptional variables, hs-CRP is decreasing with the increase of these values; they are negatively correlated.

A Pearson product - moment correlation was run to determine the relationship between Ox-LDL and hs-CRP values. There was a strong, positive correlation between the two, which was statistically significant ($r = 0.628$, $n = 65$, $P = 0.000$) Table 4.

Table 2: Correlation analysis of OxLDL with markers of dyslipidemia

Parameters	Pearson correlation coefficient	Significant value
SBP	0.178	0.323
DBP	0.097	0.592
TC	−0.056	0.756
LDL	0.150	0.403
HDL	−0.190	0.289
TG	0.273	0.125
Apo A_1	0.063	0.728
Apo B_1	−0.135	0.454

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TC: Total cholesterol, TG: Triglycerides, Apolipoprotein A_1: Apo A_1, Apolipoprotein B_1: Apo B_1, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, Ox-LDL: Oxidized low-density lipoprotein

Table 3: Correlation analysis of hs-CRP with markers of dyslipidemia

Parameters	Pearson correlation coefficient	Significant value
SBP	−0.096	0.594
DBP	0.166	0.356
TC	0.138	0.445
LDL	−0.204	0.254
HDL	0.032	0.861
TG	−0.111	0.540
Apo A_1	−0.237	0.184
Apo B_1	−0.230	0.197

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TC: Total cholesterol, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG: Triglycerides, hs-CRP: High sensitive C reactive protein

DISCUSSION

The present study helps to earn the information about the role of inflammatory markers such as OxLDL and hs-CRP in the progression of CVD in patients with dyslipidemia. The elevated level of OxLDL suggests the augmented inflammatory events in dyslipidemia patients, which can be positively correlated with the progression of CVD.

CVD is the leading seed of mortality in many economically developed nations judging for about 30% of all deaths, and its occurrence is still higher. Ongoing research aims to explore and fend off the early development of cardiovascular risk factors such as atherosclerosis, hypertension, dyslipidemia, chronic inflammation, and insulin resistance. As stated in the present-day approximates of the World Health Organization, approximately one-third of all deaths[12] (16.7 million people) around the globe resulted from CVD. The incidence of CVD can be prevented or minimized to a large extent if the risk factors identified in the early stage.

Atherosclerosis is at the helm of for more morbidity and mortality than any other degenerative disease. Its clinical expression in the form of myocardial infarction, stroke, and the peripheral vascular disease accounts for about 50% of all deaths in developed countries. The study of Ross, atherosclerosis is the principal cause of CVD in Western

Table 4: Correlation analysis of Ox-LDL and hs-CRP

Test variables	Pearson correlation coefficient	Significant value
Ox-LDL	0.628	0.000
Hs-CRP		

Hs-CRP: Oxidized low-density lipoprotein, hs-CRP: High sensitive C reactive protein

populations. Various studies suggested that increased level of OxLDL and hs-CRP can induce progression of inflammation that may lead to CVD.[13] The dyslipidemia persons are selected as test population and age, and sex-matched healthy peoples constituted control population. The study found a significant increase in OxLDL, hs-CRP, and Apo B/Apo-A1 ratio. Oxidized LDL, as modified LDLs, is thought to play critical roles in the progression of atherosclerosis. The modification of LDL by oxidation alters its fundamental properties, becomes incorporated into macrophages by SRAs and modulates the gene expression involved in the cellular function of endothelial cells and smooth muscle cells in the vessel walls. Increasing evidence of atherosclerosis as an inflammatory disease raised the possibility of detection of circulating markers in the serum: Increased levels of CRP and cytokines. In this context, the detection and quantification of circulating OxLDL might reflect the severity and phases of atherosclerosis the present study shows that circulating Ox-LDL is a sensitive marker of CAD that is correlated with other risk factors of CAD, further suggests that Ox-LDL may indeed play a causative role in coronary atherosclerosis.

In the current study, the TC, LDL cholesterol, and TG levels were significantly higher in the test population. In this study, the HDL level was significantly lower in the test group, and the findings are similar. The apolipoprotein-A1 is a lipoprotein present in HDL cholesterol; the present study found that Apo-A1 level was significantly lower in the test group. Decreased Apo-A1 in the test population is an indication of increased cardiovascular risk in dyslipidemia patient. It has been known for years that inflammation plays a significant role in the development of CVDs.[14] Assessment of hs-CRP level is often performed to assess the risk of future heart disease. In the study, the level of hs-CRP in the test population was significantly higher when compared to the control population. The elevated hs-CRP level in the test population indicates an increased inflammation and cardiovascular risk in patients with dyslipidemia.

CONCLUSION

The present study evaluates and correlates OxLDL, lipid profile, and hs-CRP in the progression of CVD. The excessive formation of reactive oxygen species creates an environment of oxidative stress that has been associated with hypertension and atherosclerosis. Markers of oxidative stress, such as OxLDL particles, are under investigation as possible biomarkers of CVD risk.

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