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To Study the Significance of Oxidized Low-Density Lipoprotein in Coronary Atherosclerotic Heart Disease In Indian Population.

Ashok Kumar[1], Arundhati[2]

[1]H.O.D. And Consultant Cardiologist, Mahavir Vatsalya Aspatal, L.C.T. Ghat, Patna 800001, Bihar, India.
[2]Consultant Pathologist, Mahavir Cancer Sansthan and Research Institute, Patna, India.

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ABSTRACT

Background: Traditional risk factors for coronary artery diseases are not very specific in identifying coronary artery disease (CAD). LDL cholesterol is a proven risk factor for developing coronary artery disease (CAD). However Indian populations with established CAD often have lipid levels within normal range. Oxidized LDL is seen as a sensitive marker for CAD, so it might be a better predictor of coronary atherosclerosis than standard lipid profile and traditional risk factors. **Objectives:** The proposed study was therefore designed to analyze the levels of oxidized LDL level in Indian patients undergoing coronary angiography and to study its value in predicting the occurrence and extent of CAD in this patient population. **Methods:** This cross-sectional study included patients undergoing diagnostic coronary angiography and on the basis of presence or absence of CAD, was grouped as normal or CAD group. Conventional risk factors (i.e. age, sex, diabetes mellitus, hypertension, smoking, total cholesterol and HDL cholesterol) were analyzed in all subjects as per institutional protocol. Levels of ox-LDL were measured in a monoclonal antibody 4E6 based competition ELISA. **Results:** A total of 211 patients were included in the study of which 151 had disease on angiography (angiographically proven coronary artery disease) and 60 subjects had normal coronary angiogram (free of coronary artery disease). There was no significant difference in traditional lipid parameters and traditional risk factors between patients with and without CAD, and a significant difference was noted with respect to oxidized LDL in subjects with CAD (104.6±7.9 U/l) compared to subjects without CAD (79.4±3.9U/l, p<0.001). On ROC analysis at cutoff value 84 U/l, sensitivity and specificity of oxidized LDL was 97.4% and 90% respectively for detection of CAD. **Conclusion:** we conclude, that plasma oxidized-LDL is a very sensitive marker of CAD in Indian population even in near normal lipid profile or patients treated with statin and addition of oxidized-LDL to the established risk factors may improve CAD risk prediction.

Keywords: Body Mass Index, Coronary Artery Disease, Diabetes Mellitus, Low Density Lipoprotein.

INTRODUCTION

Most common cause of death worldwide is coronary artery disease (CAD). In developed countries the disease afflicts mainly aged population (>70 years), whereas in a developing country like India major brunt of the disease comes upon middle aged and even younger population and 52% of coronary artery disease death occur in people younger than 70 year of age.[1]

Name & Address of Corresponding Author
Dr. Arundhati
Consultant Pathologist,
Mahavir Cancer Sansthan and Research Institute,
Patna, India.

Traditional risk factor for coronary artery disease includes advancing age, family history of premature CAD, sex, hypertension, diabetes mellitus, dyslipidemia, sedentary life style and smoking. Of these factors dyslipidemia is a major modifiable risk factor.[2] Amongst the lipid components low density lipoprotein (LDL) and high density lipoprotein have a key role in formation and inhibition of atherosclerosis. LDL cholesterol is an important risk factor for developing coronary heart disease, though in Asian Indian as compared to their western counterpart didn't show deranged total lipid in patients of CAD.[3,4] Indians have several fold greater risk of having CAD than western population,[5] however the prevalence of classical risk factors such as total cholesterol, LDL Cholesterol, hypertension and smoking are not higher as compared to the western population, suggesting contribution of additional unidentified risk factors.[6] Invitro it has been proven that LDL oxidation is inhibited by HDL. Human paroxonase (PON-1) is a calcium dependent HDL associated ester hydrolase enzyme which has been associated with protective effect of HDL by retarding the oxidation of LDL and preventing the generation of lipid peroxides. Other LDL associated enzymes include platelet activating factor acetyl hydrolase and lecithin: cholesterol acyl transferase which prevents LDL oxidation by checking lipid peroxide synthesis. Amongst the above mentioned these

enzymes PON-1, genetic polymorphism has also been associated CAD.

Oxidized form of LDL is central to the whole event of atherosclerosis and its complication. Goldstein reported the role of modified LDL in foam cell transformation from macrophage and paving the way for atherosclerosis.[7] Thus oxidative modification hypothesis is the main mechanism for atherosclerosis.[8] Oxidized LDL upregulates the expression of LOX-1 on endothelial cells, promotes growth and migration of smooth muscle cells, monocytes/ macrophages and fibroblasts. it stimulates endothelial activation, inflammation, recruitment activation and migration of monocytes through endothelial gaps to sub endothelial regions.[9] Monocytes differentiation into macrophage, which takes up oxidized LDL via receptor SR-A1, SR- A2 and LOX-1 and make fatty streaks, the earliest form of atherosclerosis. It stimulates collagen formation in fibroblast and activates platelets.[10-12] Unstable plaques are filled with LDL, and oxidized LDL levels correlates positively in acute coronary syndrome and its level of severity.[13]

MATERIALS AND METHODS

This cross-sectional observational study was conducted in Departments of Cardiology. A total of 151 consecutive patients suspected or proven CAD undergoing coronary angiography at our institute were included, which confirmed to the institutional ethical guidelines and grouped on the basis of presence or absence of CAD. Adult patient from 18 – 65 years of age group irrespective of risk factor status were enrolled. Patients with history of cancer, terminal illness and pregnancy were excluded. Detailed history, clinical information and other routine clinical laboratory tests were done in all patients as per the institutional protocol. Fasting blood samples from all these patients are collected after 12 hours of fasting on the day of coronary angiography. Coronary Angiography was performed in the standard manner in all patients through either radial or femoral artery access. Angiographic CAD is defined as even presence of plaque or any amount of stenosis in any of the major epicardial coronary arteries, and the severity of disease analysed based on number of vessels involved. The test results were compared with the angiographic severity of the disease with respect to number of vessels involved. Group 1 includes subjects with normal coronaries and group II includes subjects with coronary artery disease. Conventional risk factors (i.e. age, sex, diabetes mellitus, hypertension, smoking, total cholesterol and HDL cholesterol) were analyzed in all subjects. Blood samples of these patients were collected in between September 2013 to February 2014 irrespective of last acute event or statin therapy and were analyzed within 30 days of collection. An informed consent was taken from all the subjects who agreed to participate in the study.

Hypercholesterolemia is considered when the patient had total cholesterol level ≥240mg/dl and/or LDL cholesterol level ≥130mg/dl or were treated with cholesterol lowering statins or fibrates. Dyslipidemic patients had HDL cholesterol level <35mg/dl or fasting triglyceride levels > 150mg/dl, irrespective of the LDL cholesterol levels. Smokers and former smokers were separated on the basis of blood sampling within or beyond one month of any amount of cigarette consumed. All those persons were considered hypertensive if they were on antihypertensive or their systolic pressure were ≥140mm Hg or diastolic ≥90mm Hg. All Subjects included in the study with diabetes were having type 2 diabetes.

Sampling

Fasting venous blood samples were collected in EDTA vaccutainers. These samples were centrifuged for 15 minutes at 3000 g at room temp within 1 hour of collection, aliquoted immediately and store at -30 ^{O}C. Repeated freeze-thaw cycles was avoided.

Assays

For estimation of plasma oxidized-LDL levels human oxidized low density lipoprotein ELISA kit, used for the assay was from Mercodia and ELISA was performed as per the instructions provided by the manufacturer. Briefly, Plasma oxidized LDL concentrations were measured by using monoclonal antibody 4E6, which specifically binds to an epitopes in the apolipoprotein B-100 (apo B-100) moiety of oxidized LDL. Mercodia Oxidized LDL ELISA is a solid phase two-site enzyme immunoassay based on the sandwich technique, in which two monoclonal antibodies are directed against separate antigenic determinants on the oxidized apolipoprotein B molecule. Oxidized LDL in the sample reacts with anti-oxidized LDL antibodies bound to microtitration wells and peroxidase conjugated anti-oxidized LDL antibodies in the solution. Result is expressed in U/L and measurement ranges from 8 - 150 U/l and is specific for human oxidized LDL. Grossly lipemic, icteric or haemolyzed samples do not interfere in the assay. Total cholesterol, HDL cholesterol and and triglyceride levels were measured by Boehringer-Mannheim enzymatic method and LDL levels were calculated by Friedewald formula.

Statistical Analysis

All the data were analysed using SPSS 20 statistical software (SPSS Inc., Chicago, Illinois, USA). All data are expressed as mean ± standard deviation. Student t-test was used to compare means between groups, and the chi-square test was used to compare proportions between groups. The Pearson correlation was used to analyse the correlations between CAD with oxidized LDL and other risk factors; p value less than 0.05 was considered statistically

significant. Linear regression analysis was performed to determine the influence of various cardiovascular risk factors on levels of circulating oxidized LDL in subjects without clinical evidence of CAD.

RESULTS

The demographics and clinical features of the patient population are summarized in [Table 1]. A total of 211 patients were included in the study, of which 151 had significant disease on angiography (angiographically proven coronary artery disease) and 60 subjects had normal coronary angiogram (free of coronary artery disease). The mean age was 55.7±9.5 years (51.5±10.5 years for control with normal coronaries, 57.4±9.1years for CAD group, which is significant; p <0.01). Among the total CAD patients 25.5% were females. Diabetes was present in 36%, hypertension in 49%, history of smoking in 14.2%, and 29.3% were tobacco chewers (33.7% in CAD group and 18.3% in non CAD group; p= 0.03). The mean BMI of study population was 25.2±3.8 (23.9±3.5 in CAD and 24.9±4.5 in non CAD group; p= 0.9). There was no significant difference amongst patients with CAD and those without, in terms of various risk factors, like age, diabetes status, BMI, current smoking, tobacco chewing and hypertension. There was no statistically significant difference in terms of various parameters like total cholesterol, HDL cholesterol, total cholesterol/HDL ratio, dyslipidemia, diabetes, smoking, BMI, serum creatinine and blood glucose level. There were significant difference in term of age, sex, hypertension, tobacco chewing and oxidized LDL between CAD and non CAD groups.

Dyslipidemia was present in 65.3% of study population mainly due to low HDL and high triglyceride level not due to raised LDL which is a prime target to be achieved according to international guidelines. There was no significant difference in dyslipidemia in CAD and non CAD group. The mean total cholesterol level was 132.0 ± 33.4 mg/dl, mean LDL was 71.6±27.5 mg/dl. The mean HDL cholesterol (33.0±11.4mg/dl) was below recommended range. The mean oxidized LDL was 97.4±13.4 U/l, and patient with CAD showed marked elevation of oxidized LDL compared with control subject (104.6±3.5 U/l in CAD and 79.4±3.9 U/l, p <0.001).

[Table 2] summarizes CAD risk factor distribution in different subgroup of CAD patients according to the disease severity. There were 48, 42 and 61 patients with single vessel disease (SVD), double vessel disease (DVD) and triple vessel disease respectively. Level of oxidized LDL were 99.1±6.8 U/l for patients with single vessel disease, 104.6±7.8U/l for patients with double vessel disease, 108±5.7 U/l for patients with triple vessel disease.

On analyzing the factors, predicting the significant coronary artery disease using the univariate logistic regression analysis [Table 3] age [OR1.07(95%CI 1.03-1.10), p=<0.01], gender (male) [OR 0.27(95% CI 0.14-0.51),p=0.01], hypertension [OR 0.45 (95% CI 0.26-0.9), p=0.02] and oxidized LDL [OR 1.86(95% CI 1.36 -2.5), p=<0.01] were found to be significant predictors while BMI, DM, dyslipidemia, tobacco chewing and smoking were not found to be significant predictors of CAD.

In multivariate analysis [Table 4], age [OR1.15 (95%CI 1.03-1.28), p=0.01] and oxidized LDL [OR 2.15 (95% CI 1.36 -3.37), p=<0.001] were the strongest predictors of CAD. [Figure 1] shows rise of oxidized LDL level according to the disease severity such as single, double and triple vessel disease. On oneway ANOVA analysis level of oxidized LDL was very much significantly different between each groups as shown in [Table 5], but it was non-significant between double vessel and triple vessel disease on non-parametric analysis as shown in [Figure 2]. This might be due to non-homogenous distribution of case and control or small sample size.

As shown in the figure 3 of ROC curve at a cut of value of 84 U/l, the assay of Oxidized LDL showed a sensitivity of 97.4% and specificity of 90% with area under curve is 0.994.

Table 1: Demographic characteristics among CAD and non CAD groups.

Parameter	Total (n=211)	CAD group (n=151)	Non CAD (n=60)	P value
Age (years)	55.7±9.5	57.4±9.1	51.5±10.5	<0.01
Females (%)	54(25.5)	27(17.8)	27(45)	<0.01
BMI (Kg/m^2)	25.2±3.8	23.9±3.5	24.9±4.5	0.90(NS)
Hypertension (%)	104(49)	82(54.3)	22(36.6)	0.02
DM (%)	76(36)	58(38.4)	18(30)	0.25(NS)
Smoker (%)	30(14.2)	22(14.5)	8(13.3)	0.82(NS)
Tobacco (%)	62(29.3)	51(33.7)	11(18.3)	0.03
Dyslipidemia (%)	138(65.4)	98(64.9)	40(66.6)	0.80(NS)
TCh (mg/dl)	132.0±33.4	130.1±32.4	136.9±35.7	0.18(NS)
HDL (mg/dl)	33.0±11.4	33.4±12.3	32.0±8.8	0.40(NS)
LDL (mg/dl)	71.6±27.5	69.3±28.3	77.3±24.7	0.04
Ratio (T.Ch/ HDL)	4.3±1.7	4.2±1.2	4.7±2.5	0.06(NS)
Creatinine(mg/dl)	1.1±0.4	1.1±0.4	1.1±0.5	0.60(NS)
Glucose (mg/dl)	123.2±78.7	125.4±78.7	117.5±78.9	0.05(NS)
Oxidised LDL(mg/dl)	97.4±13.4	104±7.9	79.4±3.9	<0.001

Table 2: Distribution of CAD risk factors among patients with normal coronaries, singe vessel disease and double vessel and triple vessel disease.

Parameter	Normal (n=60)	SVD(n=48)	DVD(n=42)	TVD(n=61)	P
Female gender (%)	27(45)	6(12.5)	11(26)	10(16)	<0.01
Age(years)	51.5±10.5	56.4±10.5	57.2±9.2	58.4±7.9	0.01
BMI(kg/m2)	24.9±4.5	23.5±3.9	24.9±3.1	23.6±3.3	0.09(NS)
Hypertension (%)	22(36.7)	21(43.7)	26(62)	35(57.4)	0.03
Diabetes (%)	18(30)	12(25)	20(47.6)	26(42.6)	0.07(NS)
Smoking (%)	8(13.3)	9(18.7)	4(9.5)	9(14.7)	0.65(NS)
Tobacco chewing (%)	11(18.3)	21(43.7)	11(26.1)	19(31)	0.03
Dyslipidemia (%)	40(66.6)	31(64.5)	28(66.6)	39(63.9)	0.98(NS)
Tch	139±35.7	128.9±33.1	124±35.7	135±28.9	0.22(NS)
HDL	32±8.8	34.5±14.1	31.1±7.2	34.1±13.6	0.39(NS)
LDL	77.3±24.7	69.5±28.2	67.4±29.3	70.6±28.1	0.27(NS)
T.Ch/HDL	4.6±2.5	4.01±1.0	4.4±1.2	4.3±1.3	0.21(NS)
Ox. LDL	79.4±3.9	99.1±6.8	104.6±7.8	108±5.7	<0.01
Glucose	117.5±78.9	108.2±47.9	131.7±90.1	135.0±88.4	0.28(NS)
S. Creat	1.1±0.5	1.1±0.3	1.1±0.2	1.1±0.5	0.79(NS)

Table 3: Univariate regression analysis for predicting CAD.

Parameter	Odd ratio (±95% CI)	P – value
Age	1.07(1.03-1.1)	<0.01
Sex	0.27(0.14-0.51)	<0.01
hypertension	0.45(0.26-0.9)	0.02
BMI	0.94(0.86-1.01)	0.09 (NS)
Diabetes mellitus	0.69(0.36-1.31)	0.25(NS)
smoking	0.9(0.38-2.2)	0.8(NS)
tobacco	0.9(0.38-2.2)	0.82(NS)
dyslipidemia	1.08(0.58-2.04)	0.8(NS)
T.Ch(total cholesterol)	0.99(0.98-1.04)	0.18(NS)
HDL	1.01(0.98-1.0)	0.41(NS)
LDL	0.99(0.98-1.0)	0.06(NS)
HDL/T.Ch	0.85(0.7-1.03)	0.09(NS)
OXD. LDL	1.86(1.36-2.5)	<0.01

Table 4: Multivariate regression analysis for predicting CAD.

Variables	odd ratio (±95% CI)	P value
Age	1.15(1.03-1.28)	0.01
Sex	0.79(0.05-13.9)	0.87(NS)
Hypertension	0.87(0.69-1.11)	0.27(NS)
Oxidized LDL	2.15(1.36-3.37)	<0.001

Table 5: Oneway ANOVA, POST HOC ANALYSIS between groups.

Multiple Comparisons

Dependent Variable: oxidised LDL
Bonferroni

(I) ANGIO	(J) ANGIO	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Normal	Svd	-19.75125*	1.17917	.000	-22.8924	-16.6101
	Dvd	-25.23429*	1.22507	.000	-28.4977	-21.9709
	Tvd	-29.54951*	1.10717	.000	-32.4988	-26.6002
Svd	Normal	19.75125*	1.17917	.000	16.6101	22.8924
	Dvd	-5.48304*	1.28658	.000	-8.9103	-2.0558
	Tvd	-9.79826*	1.17487	.000	-12.9279	-6.6686
Dvd	Normal	25.23429*	1.22507	.000	21.9709	28.4977
	Svd	5.48304*	1.28658	.000	2.0558	8.9103
	Tvd	-4.31522*	1.22093	.003	-7.5676	-1.0628
Tvd	Normal	29.54951*	1.10717	.000	26.6002	32.4988
	Svd	9.79826*	1.17487	.000	6.6686	12.9279
	Dvd	4.31522*	1.22093	.003	1.0628	7.5676

*. The mean difference is significant at the 0.05 level.

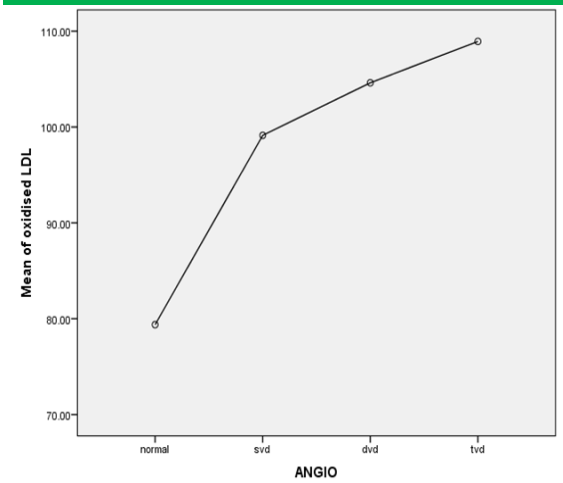
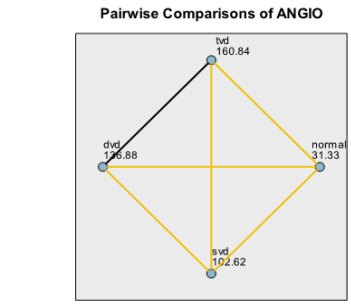


Figure 1: Showing level of oxidized LDL according to severity of disease.



Each node shows the sample average rank of ANGIO.

Sample1-Sample2	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj.Sig.
normal-svd	-71.292	11.823	-6.030	.000	.000
normal-dvd	-105.548	12.283	-8.593	.000	.000
normal-tvd	-129.503	11.101	-11.666	.000	.000
svd-dvd	-34.256	12.899	-2.656	.008	.047
svd-tvd	-58.211	11.779	-4.942	.000	.000
dvd-tvd	-23.955	12.241	-1.957	.050	.302

Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same.
Asymptotic significances (2-sided tests) are displayed. The significance level is .05.

Figure 2: Kruskal-wallis nonparametric analysis.

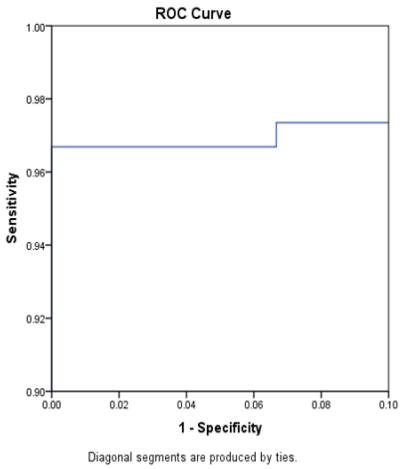


Figure 3: ROC curve.

Area Under the Curve				
Test Result Variable(s): oxidized LDL				
Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.994	.003	.000	.989	1.000

DISCUSSION

In our study plasma oxidized LDL level is used to determine CAD patients and correlated with the extent and severity of the disease. Coronary Artery Stenosis is an occlusive disease of the vasculature, commonly caused by atheromatous plaque and enhanced platelet activity, most critically affecting the coronary vasculature. The mean age of this disease occurrence in western world (60.0± 9.1 years) and Japan (59.8±0.9 years) is almost half decade higher as compared to the mean age of this disease in Indian population (55.7±9.5 years).[14,15]

Age, sex, hypertension and oxidized LDL were significantly associated with CAD in univariate analysis, however in multivariate analysis only age and oxidized LDL came out significantly associated.

In this study no significant positive correlation could be established between CAD and factors like Diabetes Mellitus, BMI, Smoking and tobacco chewing. Inoue et al, in their study found that HDL cholesterol level was lower in multi vessel CAD group than controls however this study not reflect any significant positive correlation with dyslipidemia and CAD.[16]

Toshima et al in their study showed that oxidized LDL levels didn't differ significantly between 1-vessel, 2-vessel, 3-vessel disease.[15] Contrary to this, the current study reflects that patient with CAD showed significant difference in oxidized LDL level between 1 – vessel, 2- vessel, 3- vessel disease as per one way ANOVA [Table 5], where as in non-parametric analysis it was non-significant between 2-vessel and 3-vessel disease [Figure 2].

The first and foremost limitation of our study is its small sample size. For Coronary stenosis assessment IVUS is more sensitive method was not used in our study so relationship between plaque load and plasma oxidized level couldn't be estimated. No attempt was made to establish any relationship between homocysteine, LPa, and hsCRP with plasma oxidized LDL.

ROC curve at a cut of value of 84 U/l, the assay of Oxidized LDL showed a sensitivity of 97.4% and specificity of 90% with area under curve is 0.994. Holvoet et al also demonstrated in their study that oxidized LDL was increased in patient with coronary heart disease and sensitivity was 76% and similarly

Toshima et al in their study showed a sensitivity and specificity of 78 and 72% respectively.[14,15]
Thus we can conclude that plasma oxidized LDL level is a sensitive marker of CAD and its severity.

Study limitations

The study included small number of patients and the proportion of patients with normal coronaries constituting only 28.44% of study population. This could be possibly because only patients with high clinical probability of CAD with multiple risk factors underwent invasive coronary angiography. The insignificant difference in traditional CAD risk factors suggests heterogeneity in the study population. The study population does not represent the risk factor pattern in general population.

CONCLUSION

In Indian population with established CAD, it is not uncommon to find serum lipid levels within in acceptable range. Addition of oxidized LDL to routine lipid panel find additional benefit in diagnosis and risk stratification even on patient with statin therapy or with near normal lipid profile. Oxidized LDL also shows significant association with incremental severity of CAD. Oxidized LDL levels >84 U/l were significantly associated with CAD in Indian population.

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