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SMALL DENSE LOW DENSITY LIPO-PROTEIN AND CORONARY ARTERY DISEASE: A STUDY IN A TERTIARY CARE CENTRE IN EASTERN INDIA.

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INTRODUCTION

Ischaemic heart disease (IHD) is projected to be the most important cause of mortality worldwide by 2020.[1] The prevalence of coronary artery disease (CAD) is very high in the population residing in the South East Asian countries, particularly, among the male sex.[2,3] The major independent risk factors for CAD are advancing age, elevated blood pressure, elevated serum total and LDL cholesterol levels, low serum HDL cholesterol level, diabetes mellitus, and cigarette smoking. While the importance of low-density lipoprotein (LDL) cholesterol in the development of atherosclerosis cannot be over-emphasised, recent research activity has shifted the focus on the heterogeneity of LDL particles, particularly with regard to differences in lipoprotein composition, size and metabolism.[4] Of these, the biochemical characteristics of small dense LDL (sd-LDL) appear to be of paramount importance in the pathogenesis of CAD. Sadly, there appears to be a dearth of studies co-relating sd-LDL and CAD in this part of the country. Therefore, it was deemed worthwhile to undertake a study to estimate the levels of sd-LDL in patients presenting with acute coronary syndrome (ACS) attending a tertiary care hospital in Eastern India.

AIMS AND OBJECTIVES

1. To see the titres of sd-LDL in patients of acute coronary syndrome. (ACS)
2. To identify whether elevated sd-LDL titre is a potential risk factor in acute coronary syndrome.
3. To compare and co-relate the sd LDL in diabetic and non-diabetic patients presenting with ACS.

MATERIALS AND METHODS

This observational descriptive study was undertaken in the Department of Cardiology, Institute of Cardiovascular sciences, R.G. Kar Medical College. Among 100 randomly selected patients of ACS attending the emergency, 50 patients were designated as cases and 50 as controls. ACS was diagnosed on the basis of history (typical chest pain), clinical examination, elevated cardiac biomarkers, electrocardiographic abnormalities and echocardiographic findings and those patients were included in the study. Patients with a past history of ACS or those who have previously received treatment for ACS, e.g. post CABG etc and those who are on antihyperlipidaemic drugs and those who denied of informed consent were excluded from the study.

Blood samples drawn from these patients were investigated for complete blood count, fasting blood glucose and post-prandial blood glucose, liver function tests, urea, creatinine and lipid profile, sd-LDL, Creatinine kinase-MB and Troponin-T. Titres of sd-LDL were measured in serum by spectrophotometry before initiation of treatment. The data thus accumulated was statistically analysed by using statistical package of social science SPSS version 20.

RESULTS AND ANALYSIS

The results thus obtained from statistical analysis of the data are elaborated below in the form of tables and charts.

TABLE 1: Table showing statistical distribution of all the parameters in cases and controls

		CASES	CONTROLS	p VALUE
TOTAL COUNT	MEAN±SD	7103.60±1257	7088.40±1190	0.951
	MEDIAN	6900	7300	
	RANGE	4900-10400	4800-9600	

LDL	MEAN±SD	121.90±19.46	69.66±14.01	0.001
	MEDIAN	127	66	
	RANGE	88-178	56-120	
HDL	MEAN±SD	38.20±4.076	38.82±5.05	0.501
	MEDIAN	38	38	
	RANGE	30-48	31-55	
TG	MEAN±SD	206.44±24.247	145.50±19.279	0.001
	MEDIAN	200	145	
	RANGE	111-260	105-195	
TOTAL CHOLESTEROL	MEAN±SD	201.54±21.517	138.26±17.461	0.001
	MEDIAN	203	133	
	RANGE	159-260	110-195	
CK MB	MEAN±SD	459.86±70.90	101.64±35.180	0.001
	MEDIAN	465.50	92.50	
	RANGE	339-600	56-200	
sd LDL	MEAN±SD	78.80±17.364	30.92±9.969	0.001
	MEDIAN	79	28	
	RANGE	43-144	14-62	

TABLE 2: Distribution of study subjects by sdLDL values with diabetes in cases and controls.

		Sd LDL	**CASE**		**CONTROL**		**p VALUE**
			Number (No)	**%**	**No.**	**%**	
DIABETES	No	25-75	7	63.6%	21	100.0%	0.003
		76-125	4	36.4%	0	.0%	
	Yes	25-75	16	41.0%	29	100.0%	0.001
		76-125	22	56.4%	0	.0%	
		126-200	1	2.6%	0	.0%	

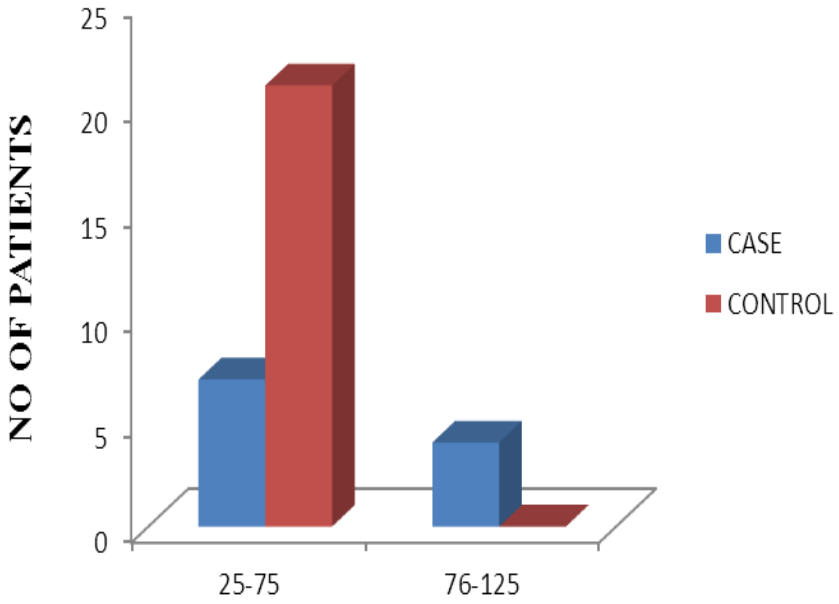

Fig 1: bar diagram showing sd-LDL values in cases and controls without diabetes.

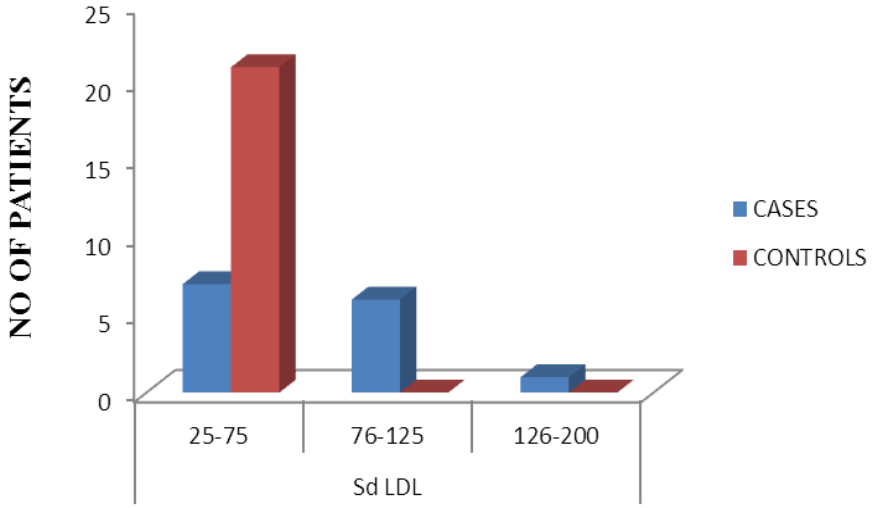

Figure 2: Sd LDL levels in cases and controls with diabetes

The correlation of sd LDL with diabetes is shown in the table 2 and figures 1 and 2.

TABLE 3: Distribution of study subjects by sd LDL values with HDL in cases and controls

		sd LDL(ng/dl)	ARM				p VALUE
			CASE		CONTROL		
			Count	N %	Count	N %	
HDL	A	25-75	17	42.5%	32	100.0%	0.001
		76-125	22	55.0%	0	.0%	
		126-200	1	2.5%	0	.0%	
	B	25-75	6	60.0%	16	100.0%	0.006
		76-125	4	40.0%	0	.0%	
	C	25-75	0	.0%	2	100.0%	--

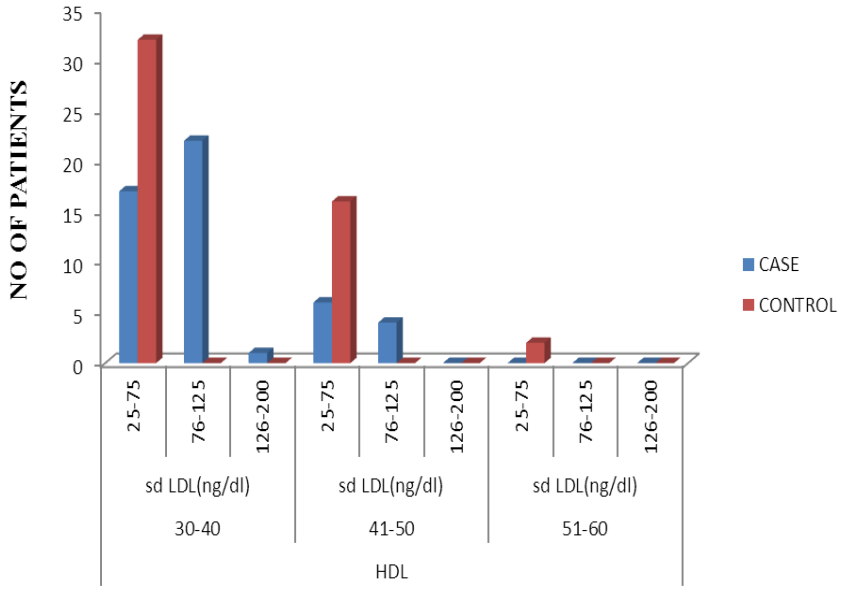

Figure 3: showing co-relation between sd-LDL and HDL among cases and controls.

The correlation between sd LDL and HDL is depicted in table 3 and figure 3. In the HDL grade A (30-40), among the cases, there are 17 patients in sd LDL grade A (25-75) and 22 patients in sd LDL grade B (76-125) and 1 patient in the grade C (126-200). In the HDL grade B (41-50), among the cases, there are 6 patients in sd LDL grade A (25-75), 4 patients in sd LDL grade B (76-125). In the HDL grade C (51-60), among the cases, there are no patients any sd LDL grades.

In the HDL grade A (30-40), among the controls, there are 32 patients in sd LDL grade A (25-75) and no patients in sd LDL grade B and grade C. In the HDL grade B (41-50), among the controls, there are 16 patients in sd LDL grade A (25-75), no patients in sd LDL grade B and grade C. In the HDL grade C (51-60), among the controls, there are 2 patients in grade A and no patients in grade B and C.

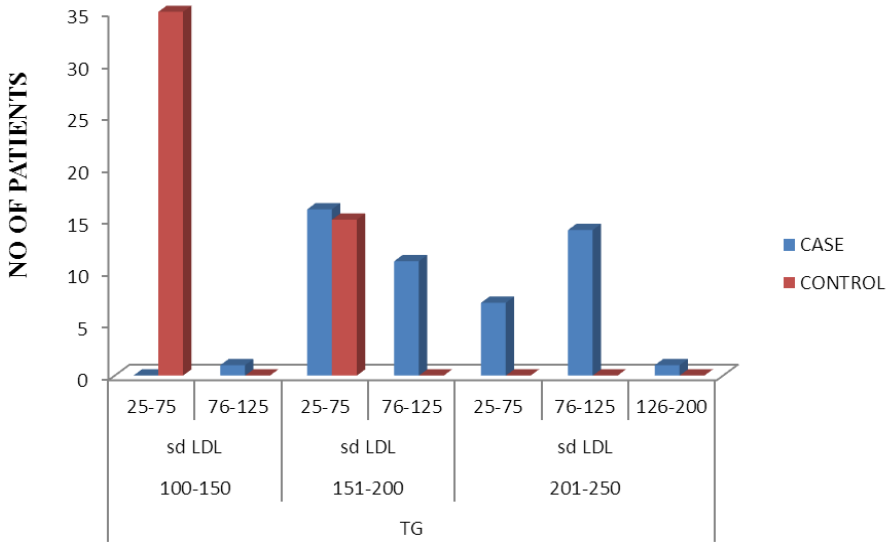

Figure: 4 Correlation between sd-LDL and`TG in study subjects

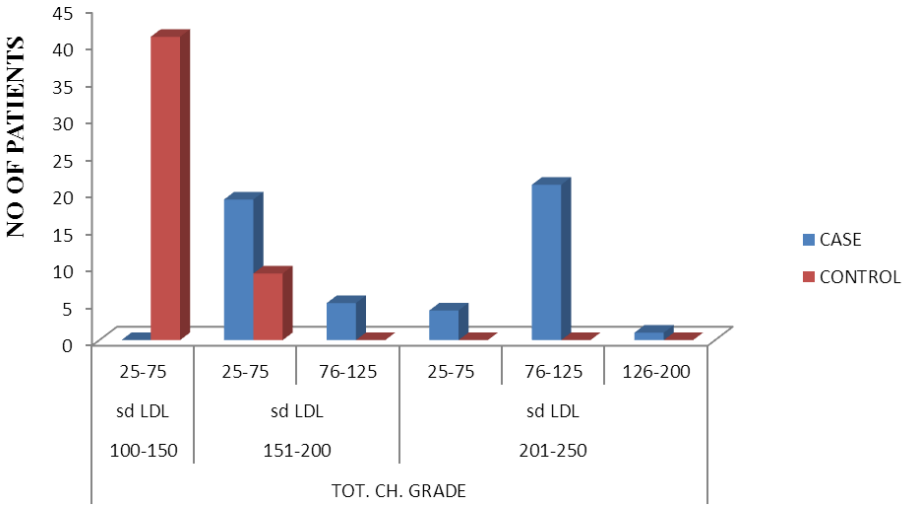

Fig 5: bar diagram showing the co-relation between sdLdL and TG in cases and controls.

The results of the statistical analysis have been described above in the form of tables and charts. The implications of the results will be dealt with in the discussion.

DISCUSSION

The present study was carried out with 50 patients as subjects and 50 patients as controls. Non-ACS patients were considered as controls and ACS patients as cases, provided they met the inclusion and the exclusion criteria. The mean sd LDL in the case and control groups

are 78.80 ± 17.364 and 30.92 ± 9.969 respectively, the difference being statistically significant (**p value 0.001**). Subsequently, correlation was calculated with sd -LDL and other parameters of lipid profile, namely HDL, triglycerides and total cholesterol. The correlation between HDL and sd LDL is statistically significant (**p value 0.001)**. Triglycerides correlated significantly (**p value 0.001**) with sd LDL while total cholesterol did not (**p value 0.137**). In this study diabetes also correlated significantly (**p value 0.001**) with sd LDL.

As previously mentioned, IHD is predicted to be most important cause of mortality particularly in the south-east Asian countries in near future. An unfavourable lipid profile remains one of the foremost risk factors and therefore therapeutic intervention is aimed at management of dyslipidaemia. The therapeutic modulation of distinct LDL subspecies is also of great benefit in reducing the risk of cardiovascular events.[5,6,7] The shape of LDL curve in humans shows a bimodal (rather than a normal) distribution, and can be separated into two phenotypes that differ in size, density, physicochemical composition, metabolic behaviour and atherogenicity. These phenotypes have been called 'pattern A' (larger, more buoyant LDL) and 'pattern B' (smaller, denser LDL).[8,9] There are several proposed biochemical and cellular mechanisms related to the sd-LDL atherogenicity. For example, sd-LDL may reside in the plasma longer, may not bind the LDL receptor as well, or may bind the scavenger receptor more avidly, be more susceptible to oxidation, have fewer antioxidants in its core, enter the arterial wall more easily maybe due to greater transendothelial transport,[10] and bind to the glycosaminoglycans in the arterial wall more readily.[11] The sialic acid content of LDL plays a determinant role in the in vitro association of LDL with the polyanionic proteoglycans and has been found to be less in subjects with phenotype B in several studies. The cellular mechanisms include: an sd-LDL promotion of endothelial cell dysfunction, induction of greater PAI-1 (plasminogen activator inhibitor-1) production in endothelial cells, an increase in thromboxane secretion in endothelial cells and an increase in arterial smooth muscle intracellular calcium.

Oxidative susceptibility increases and antioxidant concentrations decrease with decreasing LDL size.[12] The altered properties of the surface lipid layer associated with a reduced content of free cholesterol.[13] and increased content of polyunsaturated fatty acid[14] might also contribute to the enhanced oxidative susceptibility of small dense LDL. It is perhaps on these grounds that, a predominance of small, dense LDL has been accepted as an emerging cardiovascular risk factor by the National Cholesterol Education Program Adult Treatment Panel III. Recently, the Coordinating Committee of the National Cholesterol Education Program stated that very high-risk patients may benefit from more aggressive therapeutic approaches. Screening for the presence of small, dense LDL in patients with coronary or non-coronary forms of atherosclerosis may identify those with even higher vascular risk and assist in the targeting of appropriate treatment. CAD progression is significantly greater in patients with a predominance of small, dense LDL and arteriographic benefit is concentrated in patients with a predominance of small, dense LDL who receive treatment that tends to lower it. These studies included the Stanford Coronary Risk Intervention Project, the Familial Atherosclerosis Treatment Study (FATS), the St Thomas Atherosclerosis Regression Study (STARS) and the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial.[15,16,17]

SUMMARY AND CONCLUSION

Though there are a large number of studies dealing with the situation of CAD in South East Asia, this is actually one of the very few studies depicting the real scenario in this part of the country. In this study, we found that sd-LDL significantly co-related with HDL, diabetes and triglycerides but not so with total cholesterol. High triglyceride levels, low HDL and diabetes are associated with increased sd LDL levels. Based on the study results, it is clearly evident that sd-LDL is a potential risk factor for ACS. The sd-LDL, as a percentage of total LDL, was higher in the ACS group than the non-ACS group. Although the sample size was very small in this study, the results obtained from this study are largely in agreement with those from landmark studies. The sd-LDL, because of its physicochemical properties, plays an important role in coronary atherosclerosis and so therapeutic targeting of sd-LDL is rational. Here on a parting note, it may be mentioned that sd-LDL also serves as a good co-relate of non-coronary atherosclerosis as well and for which well designed studies are also lacking.

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