ORIGINAL ARTICLE

The Role of Small Dense LDL Cholesterol and Ischemia Modified Albumin in Patients with Hyperlipidemia

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ABSTRACT

Background: The analysis of lipid profiles is a crucial step for cardiovascular risk evaluation, prevention, and therapeutic management. Small dense LDL (sdLDL) is one of the distinct subfractions of LDL and is established to have pro-atherogenic properties. Ischemia-modified albumin (IMA) is an early biomarker arising as a result of oxidative stress and ischemia. **Objective:** This study aimed to determine serum levels of sdLDL and IMA in patients with hyperlipidemia. **Methods:** Seventy-four patients with hyperlipidemia and 35 healthy controls were included. sdLDL was determined by the heparin-magnesium precipitation method. IMA was measured quantified manually with the colorimetric method. The patient group was divided into three groups: HyperTG (n=11), HyperLDL (n=38), and combined hyperlipidemia (n=25). **Results**: Median serum sdLDL and IMA levels were higher in patients with hyperlipidemia than healthy participants (both, $p<0.001$). Elevated sdLDL levels were observed in the HyperLDL group compared to the HyperTG group and the combined hyperlipidemia group ($p<0.001$). Cut-off values for the detection of patients with hyperlipidemia were >70 mg/dL for sdLDL and >0.7 AU for IMA, and both parameters showed considerably high levels of sensitivity and specificity. Multiple logistic regression analysis revealed that high sdLDL ($p=0.042$) and high IMA ($p<0.001$) were independently associated with hyperlipidemia after adjusting for age and sex. **Conclusion**: Serum sdLDL and IMA levels could be used as biomarkers for dyslipidemia-associated diseases. Further studies with larger sample size are needed to validate the impact of sdLDL on the pathogenesis of atherogenesis, and its value in the diagnosis and prognosis hyperlipidemia.

KEY WORDS: Small dense LDL, Lipoprotein, Ischemia modified albumin, IMA, Atherosclerosis.

Introduction

Atherosclerosis is a chronic inflammatory condition primarily involving the inner wall of large- and medium-sized arteries.[1] Although the exact cause of atherosclerosis has not been fully elucidated and is thought to be multifactorial, dyslipidemia is the one of the major causal risk factors for its development and progression.[2,3] Based on the conclusive role of low-density lipoproteins (LDL) in atherogenesis, reduction of LDL-cholesterol (LDL-C) is a principal therapeutic target in atherosclerosis.[4]

The LDL particles are main plasma lipid carriers in humans that vary in size, density, functional behavior, electrical charge, physicochemical structure, and atherogenic properties.[5] In fact, recent results suggest that the "quality" rather than just the "quantity" of LDL has a direct impact on cardiovascular risk and atherogenesis.[6] Small dense LDL (sdLDL) particles are one of the distinct subfractions of LDL and have several pro-atherogenic properties, involving higher degree of arterial wall retention, reduced receptor-mediated uptake, prolonged half-life in plasma, elevated proteoglycan binding and lower resistance to oxidation, suggesting that it is a significantly better biomarker than plasma LDL-C in determining the risk of atherogenesis.[1]

Access this article online

Quick Response Code:

Website: www.jmsh.ac.in

Doi: 10.46347/jmsh.v9i1.22.433

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Briefly, LDL particles with a diameter less than 25.5 nm and a density greater than 1.034 kg/L are defined as being sdLDL.[7] Few studies have examined circulating sdLDL values in subjects with different types of dyslipidemia to date, and their results are inconclusive.[8,9]

Ischemia modified albumin (IMA) is a novel early biomarker for ischemia and atherosclerosis-related disease and is raised by transient alteration of the N-terminal region of albumin under the effects of conditions causing higher oxidative stress and ischemia, including obesity, hyperlipidemia and diabetes mellitus.[10] Therefore, considering the significance of IMA as a sensitive indicator in the diagnosis of cardiovascular diseases and the link between hypercholesterolemia, oxidative stress and atherosclerosis, we aimed to examine the changes in serum sdLDL and IMA values in patients with different kind of dyslipidemia, including hypertriglyceridemia, hyperlipoproteinemia, and combined hyperlipidemia.

Material and Methods

This study was conducted between August 2019 and December 2019 in the Department of Internal Medicine of Ufuk University Faculty of Medicine, Ankara, Turkey. Seventy-four patients with hyperlipidemia and 35 healthy control participants were included in the study. All research procedures were evaluated and accepted by the Research Ethics Committee of Ufuk University Faculty of Medicine (date and no: 11.11.2019/1) and were conducted in agreement with the ethical standards specified in the Declaration of Helsinki. Written and verbal informed consent was obtained from all participants prior to their participation in this study.

Diagnosis and patient groups

Hyperlipidemia was defined as a serum fasting triglyceride level of >150 mg/dL and/or LDL-C level of >140 mg/dL.[11] The cases were selected among the patients who applied to our outpatient clinic. Patients with acute or chronic infections, malignancy, chronic inflammatory conditions, obesity, those within pregnancy or within 1 year postpartum, medical conditions that could affect lipid metabolism, such as diabetes mellitus, impaired glucose tolerance, chronic renal disease, thyroid disorders, cardiovascular disease were excluded from the study. None of the participants were administered lipid-lowering therapy (drug usage or physical activity) known to affect food intake and/or lipid metabolism. None of the participants adhered to any special diet. The control group comprised healthy individuals without known lipid disorders or a history of chronic or metabolic disease or any medication use. Demographic characteristics including age, sex and current medication were obtained from patient files.

Patients were categorized into four groups: (i) the control group; (ii) the HyperTG group, with subjects who had TG of ≥150 mg/dL and LDL-C of <140 mg/dL; (iii) the hyperLDL group, with patients who had TG of <150 mg/dL and LDL-C of >140 mg/dL; (iv) the combined hyperlipidemia group, with subjects whose LDL-C and TG were higher than 140 and 150 mg/dL, respectively.

Biochemical analyses

Blood samples were drawn from the antecubital vein after 12 hours of fasting and were centrifuged at 3000 rpm for 10 min to separate the serum. Serum TG, total cholesterol and high density lipoprotein-cholesterol (HDL) were measured with photometric methods on an Abbott Architect c8000 analyzer with original kits (Abbott Laboratories, Abbott Park, IL, USA). Serum LDL-C levels were calculated using the Friedewald formula (LDL-C = Total cholesterol - HDL-C - TG/5).[12] The sdLDL concentrations were determined via the heparin-magnesium precipitation method in accordance with the method by Hirano et al.[13] The method consists of two steps. First, lipoproteins with a density less than 1.044 g/mL are precipitated using heparin-magnesium, and then, LDL cholesterol is quantified from the supernatant.

Serum IMA was quantified by the standard manual colorimetric method based on biochemical properties of albumin to bind exogenous cobalt, as previously described by Bar-or et al.[14] For the detection of serum IMA, analyses were performed in a spectrophotometer (Human Humalyzer 2000, Germany) at 470 nm and the results were given as absorbance units (AU).

Statistical analysis

All analyses were performed on IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA), and statistical significance was set at $p < 0.05$. Histogram and Q-Q plots were used to check normality of distribution in quantitative data. Since normal distribution was not identified in the great majority of parameters, quantitative data are given as median (1st quartile – 3rd quartile). Frequency and

percentage (n, %) were used for categorical variables. Quantitative comparisons were performed with the Mann-Whitney U test or the Kruskal-Wallis test, depending on the number of groups being compared. Following >2-group comparisons, pairwise corrections were performed with the Bonferroni correction. Categorical variable distributions in groups were compared with appropriate chi-square tests (Pearson, Yate's correction, Fisher's exact). Receiver operating characteristics (ROC) curve analysis (with area under curve, AUC) was performed to evaluate the discriminative performance of measurements in the identification of hyperlipidemia and healthy controls. Multiple logistic regression analysis was performed to determine the association between measurements and hyperlipidemia after adjusting for age and sex.

Results

A total of 109 participants (96 males and 112 females) were enrolled and categorized into the four groups: controls (n = 35), the HyperTG group (n = 11), the HyperLDL group (n = 38), and the combined hyperlipidemia group (n=25). Of note, controls were found to be significantly younger than the patient group (p = 0.001). The median serum sdLDL levels were found to be high in patients with hyperlipidemia than healthy participants [83.85 (63 - 109.8) mg/dL vs. 52 (46 - 63) mg/dL] (p < 0.001). The median serum level of IMA was significantly higher in the patient group [0.950 (0.728 - 1.406) AU] compared to that of the control group [0.327 (0.247 - 0.426) AU] (p < 0.001). The demographic and laboratory features of participants according to patient and control groups are shown in Table 1.

The levels of sdLDL were significantly higher in the HyperLDL group [105.35 (89.9 - 124.6) mg/dL] compared to the HyperTG group [42.2 (37.9 - 80.6) mg/dL] and the combined hyperlipidemia group [72.0 (57.1 - 87.0) mg/dL] (p < 0.001, Table 2). No differences were found between hyperlipidemia subgroups in terms of IMA levels (p = 0.794,Table 2).

The ROC curve analysis results for IMA and sdLDL are summarized in Table 3 and Figure 1. ROC curve analysis showed that >70 mg/dL of sdLDL was the best cut-off value for the prediction of hyperlipidemia, with sensitivity and specificity values of 68.9% and 94.3%, respectively (AUC: 0.819). The optimum cut-off point of >0.7U for IMA revealed a sensitivity of 79.7% and a specificity of 100% for diagnosing hyperlipidemia (AUC: 0.965).

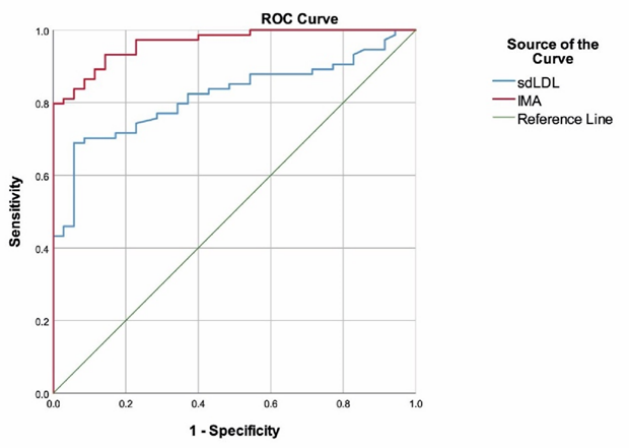

Figure 1: ROC curves of themeasurements to discriminate patients with hyperlipidemia and healthy controls. sdLDL: small dense low-density lipoprotein-cholesterol, IMA: ischemiamodified albumin, ROC: Receiver operating characteristics

Multiple logistic regression revealed that high sdLDL (p = 0.042) and high IMA (p < 0.001) were independently associated with hyperlipidemia after adjusting for age and sex (Table 4).

Discussion

This study aimed to determine circulating levels of sdLDL and IMA in patients with hyperlipidemia. We demonstrated significantly higher sdLDL and IMA levels in the overall hyperlipidemia group compared to healthy individuals. Elevated sdLDL levels were observed in the HyperLDL group compared to the HyperTG group and the combined hyperlipidemia group. Cut-off values of sdLDL >70 mg/dL and IMA >0.7 AU showed respectable sensitivity and specificity percentages to detect hyperlipidemia. Having high sdLDL and high IMA independently increased the likelihood of hyperlipidemia diagnosis after adjusting for age and sex, as demonstrated by multivariable logistic regression.

Dyslipidemia is an imbalance of lipids that can result from organic or inorganic causes, leading to cardiovascular diseases with severe complications, diabetes mellitus, obesity, pancreatitis, fat-soluble vitamin deficiencies, or overall health decline.[15] Dyslipidemia is an expanding field of research, with recent studies providing insight into molecular mechanisms and genetic background, indicating their role in the development and progression of atherosclerosis. This has led to increased interest to investigate new diagnostic and/or prognostic

Table 1: Demographic and laboratory characteristics of the participantswith regard to groups

	Groups			
	Controls (n=35)	**Patients (n=74)**	**Total (n=109)**	**p value**
Age	37 (24 - 54)	54.5 (41 - 65)	51.5 (31 - 63)	0.001
Sex				
Male	8 (22.9%)	29 (39.2%)	37 (33.9%)	0.143
Female	27 (77.1%)	45 (60.8%)	72 (66.1%)	
sdLDL, mg/dL	52 (46 - 63)	83.85 (63 - 109.8)	68.9 (52 - 100)	<0.001
IMA, AU	0.327 (0.247 - 0.426)	0.950 (0.728 - 1.406)	0.729 (0.425 - 1.107)	<0.001

sdLDL: small dense low-densitylipoprotein-cholesterol, IMA: ischemia modified albumin, AU: Absorbanceunits. Data are given as median (1stquartile - 3rd quartile) for continuous variables according to normality ofdistribution and as frequency (percentage) for categorical variables

Table 2: Laboratory measurementswith regard to hyperlipidemia subgroups

	Hyperlipidemia			
	HyperTG (n=11)	**HyperLDL (n=38)**	**Combined HL (n=25)**	p value
sdLDL, mg/dL	42.2 (37.9 - 80.6) [a]	105.35 (89.9 - 124.6) [b]	72.0 (57.1 - 87.0) [a]	<0.001
IMA, AU	1.025 (0.542 - 1.445)	0.960 (0.728 - 1.406)	0.874 (0.729 - 1.306)	0.794

sdLDL: small dense low-density lipoprotein-cholesterol, IMA: ischemia modified albumin, AU: Absorbance units, HyperTG: Hypertriglyceridemia, HyperLDL: Hyper-LDL-cholesterolemia, Combined HL: Combined hyperlipidemia. Data are given as median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. Same letters denote the lack of statistically significant difference between groups

Table 3: Performance of measurements to discriminate patients with hyperlipidemia and healthy controls

	sdLDL, mg/dL	**IMA, AU**
Cut-off	≥ 70	≥ 0.7
Sensitivity	68.9%	79.7%
Specificity	94.3%	100.0%
Accuracy	77.1%	86.2%
PPV	96.2%	100.0%
NPV	58.9%	70.0%
AUC (95.0% CI)	0.819 (0.741 - 0.897)	0.965 (0.936 - 0.993)
p value	<0.001	<0.001

sdLDL: small dense low-densitylipoprotein-cholesterol, IMA: ischemia modified albumin, AU: Absorbance units,PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area underROC curve, CI: Confidence intervals

tools.[16] The analysis of lipid profile is a crucial step in cardiovascular risk evaluation, prevention and therapeutic management. Traditionally, the role of LDL in atherogenesis has been revealed only in terms of cholesterol transport and accumulation in the vascular intima, but atherosclerosis is now recognized as an inflammatory disease associated with endothelial damage triggered by the interaction of multiple risk factors, including oxidative stress and dyslipidemia.[17] In addition, oxidative stress and dyslipidemia function synergistically in maintaining inflammatory processes during the progression of atherosclerosis.[18] Their combined effects are manifested primarily by alterations in structure and function of lipoproteins, thus further influencing their role in atherogenesis.

Table 4: Significant variables independently associated with hyperlipidemia, multiple logistic regression analysis

	β coefficient	Standard Error	p	Exp(β)	95.0% CI for Exp(β)	
Age	0.031	0.033	0.350	1.031	0.967	1.099
Sex, female	-3.999	1.602	0.013	0.018	0.001	0.424
sdLDL	0.068	0.033	0.042	1.070	1.002	1.143
IMA	14.094	4.020	<0.001	1321790.344	500.246	3492539565.805
Constant	-10.196	3.042	0.001			

sdLDL: small dense low-densitylipoprotein-cholesterol, IMA: ischemia modified albumin, CI: Confidence Interval, Nagelkerke R2=0.876

Circulating LDL particles are highly heterogeneous in their size, density, and composition, resulting in differences with regard to various subclasses[3] such as sdLDL,[7] which are a subclass of LDL characterized by absence of cholesterol and cholesterol esters, reduction in phospholipid content, while triglycerides remain unchanged[19]. The sdLDL particle is generated by very low density lipoproteins (VLDL) in TG-rich conditions; whereas, at low TG levels, VLDL particles are converted to intermediate-density lipoprotein (IDL) and large LDL subclasses.[20] Taylan et al. demonstrated in a study with 54 controls and 154 dyslipidemic patients that elevated sdLDL is associated with high levels of TG and low levels of HDL-C in plasma.[8] They also found higher sdLDL levels in patients with hypercholesterolemia or hypertriglyceridemia compared to controls, with highest concentrations among those with combined hyperlipidemia.[8] Similarly, we found lower median serum sdLDL levels in the HyperTG group compared to controls. This may be due to the small sample size of the HyperTG group in our study. In addition, we noticed that after precipitation of samples with Hirano's method, the supernatant was not clear in some patient samples. Hirano et al. mentioned the requirement to modify the method using a filter for HyperTG serum to control this turbidity, and our experience also supports this suggestion.[21]

Recent studies have reported that sdLDL can infiltrate the arterial wall at a greater degree, thus inducing atherosclerosis. Ikezaki et al. showed in the Prospective Framingham Offspring study of 3094 subjects without atherosclerotic cardiovascular disease (ASCVD) that 20.2% of these subjects developed ASCVD over 16 years of follow-up and that sdLDL, direct LDL-C and lipoprotein (a) contributed significantly to ASCVD risk (multivariable analysis), indicating the critical effects of sdLDL.[22] Liou et al. revealed a positive relationship between sdLDL particle or sdLDL-C levels and coronary heart disease in a systematic review and meta-analysis including 21 studies with a total of 30628 subjects and 5693 incident cases of coronary heart disease.[5] sdLDL is recognized as a risk factor for coronary vascular disease by the National Cholesterol Education Program.[23] Pauciullo et al., in their study including 137 patients with familial combined hyperlipidemia (FCHL) and 133 controls, showed that elevated serum sdLDL levels were markers of FCHL, and also, that increased sdLDL in patients with FCHL was independently associated with cardiovascular disease.[9]

There are few studies examining the role of sdLDL and IMA in different types of dyslipidemia. Duarte et al. demonstrated increased IMA levels in hypercholesterolemia patients and observed a significant relationship between IMA levels and total cholesterol, LDL-C, oxidized LDL, oxidized LDL antibodies and HS-CRP levels, suggesting that the formation of IMA might be associated with atheromatous plaque development.[24] This finding again demonstrates the importance of investigating sdLDL and IMA in patients with dyslipidemia. As expected, we found both markers to be significantly higher in patients with hyperlipidemia compared to the control group. We also demonstrated that increased sdLDL and IMA were independently associated with hyperlipidemia after adjusting for age and sex. Our results provide supportive evidence to the hypothesis that IMA and sdLDL are involved in the pathogenesis of dyslipidemia. This also indicates that elevation in sdLDL and IMA may affect the development and progression of atherosclerosis processes in dyslipidemia patients through cellular and molecular interactions between lipid mediator, oxidative stress biomarkers and, immune and inflammatory cells. Our results also suggest that serum levels of sdLDL and IMA could be used as a diagnostic tool and

therapeutic target for dyslipidemia.

The first limitation of our study was relatively small sample size and the conduct of the study in a single center. Second, previous studies have shown that the measurement of sdLDL and IMA is dependent on genetic and environmental factors, and these differences may affect laboratory analysis.[25,26] Third, we utilized the heparin-magnesium precipitation procedure to evaluate sdLDL level, which is not the gold standard, and therefore future studies may benefit from utilizing more accurate methods. Finally, we were unable to obtain extensive clinical and demographic information of patients, including their cardiovascular risk status. This prevented the examination of links between our results and these parameters.

Conclusion

Our study demonstrated that sdLDL and IMA may play an important role in the pathogenesis of dyslipidemia and related conditions, and that serum sdLDL and IMA levels can be used as a biomarker to detect or follow-up dyslipidemia-associated diseases. Further studies with larger sample sizes are needed to validate the impact of sdLDL on lipid metabolism in the pathogenesis of atherogenesis, and also, its potential value as a therapeutic target in atherogenesis.

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How to cite this article: Kalay S, Candar T. The Role of Small Dense LDL Cholesterol and Ischemia Modified Albumin in Patients with Hyperlipidemia. J Med Sci Health 2023; 9(1):43-49

Date of submission: 03.10.2022
Date of review: 27.10.2022
Date of acceptance: 19.12.2022
Date of publication: 08.03.2023