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Research Article

PREVALENCE OF SMALL DENSE LDL IN TYPE 2 DIABETES MELLITUS AND ITS CORRELATION WITH INFLAMMATORY MARKERS: A COMPREHENSIVE STUDY

ANUSH N[1]*, SUKHDEEP KUMAR[2]*, RIJU MATHEW[3], PRANAV KUMAR PRABHAKAR[4]

[1,2]Department of Medical Laboratory Sciences, School of Allied Medical Science, Lovely Professional University, Phagwara, Punjab, India. [3]Department of Biochemistry, Believers Church Medical College and Hospital, Thiruvalla, Kerala, India. [4]Department of Biotechnology, School of Engineering and Technology, Nagaland University, Kohima Nagaland, India.
*Corresponding author: Sukhdeep Kumar; Email: sukhdeep.28616@lpu.co.in

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ABSTRACT

Objectives: This research pursues to determine the incidence of elevated levels of small dense low-density lipoprotein (sdLDL) in Type 2 diabetes mellitus patients and study its association with inflammatory biomarkers, including high-sensitivity C-reactive protein (hsCRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), and red cell distribution width (RDW).

Methods: The study involved 158 participants, comprising both diabetic and non-diabetic individuals, recruited from a tertiary care facility. Blood samples underwent analysis for sdLDL levels using a two-step enzymatic technique. Inflammatory markers were estimated using nephelometry and chemiluminescent immunoassays. The Statistical package for the social sciences was employed for statistical analysis to establish relationships and significance levels.

Results: Diabetic subjects demonstrated particularly higher sdLDL levels than non-diabetic controls ($p<0.001$). A robust positive correlation was identified between sdLDL and hs-CRP, Lp-PLA2, and RDW, suggesting a connection between sdLDL and systemic inflammation. Regression analysis further substantiated that elevated inflammatory marker levels were linked to increased sdLDL concentrations.

Conclusion: The outcomes underline the crucial role of sdLDL in diabetic dyslipidemia and its strong relationship to inflammation. Estimation of sdLDL levels along with inflammatory biomarkers may improve cardiovascular risk assessment in diabetic patients. Therapeutic interventions, including lipid-lowering and anti-inflammatory approaches, could possibly reduce sdLDL-induced atherosclerosis.

Keywords: Diabetes, Dyslipidemia, Inflammation, Small dense low-density lipoprotein, Type 2 diabetes mellitus, Cardiovascular.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is becoming a growing concern for people around the globe. The health risks are significant, and the number of patients is expected to reach 700 million by 2045. The primary regulatory factor in the biochemical pathway of diabetes is insulin. A disproportionate amount of this hormone causes a variety of physical abnormalities and collateral damage in the body [1]. The relationship between T2DM and cardiovascular disease (CVD) needs to be investigated in-depth and low-density lipoprotein (LDL) particles which are related to the pathogenesis of CVD. Small dense LDL (sdLDL) is more susceptible to penetrating the endothelium and arterial wall. Elevated small-dense LDL levels have been shown to predict insulin resistance, abnormal glucose metabolism, and increased CVD events [2]. This finding prompted the investigation of the prevalence of sdLDL in patients with T2DM, as it had not received comprehensive attention before. The purpose of this study is to shed light on the emergence of sdLDL as a major pathological factor of the link between T2DM and vascular diseases.

Background and rationale

The incidence of T2DM is increasing globally due to a combination of factors such as sedentary lifestyles, obesity, and rapid urbanization. T2DM portends an increased burden of other underlying conditions and relatively rapid development of obesity and insulin resistance progress to T2DM. Patients with T2DM have an increased risk of atherosclerotic CVD compared to the general population. The proportion of sdLDL is higher in patients with diabetes and hypertriglyceridemia. sdLDL is more simply oxidized, and oxidized lipids are more likely to cause inflammation. Monocyte-mediated oxidized LDL is transformed into a foam cell and is the beginning of arteriosclerosis. Experimental and epidemiological studies also suggest that inflammation is linked to atherosclerosis, even in the pre-diabetic stage. Several studies show that the proportion of sdLDL particles and changes in this proportion predict changes in carotid intima-media thickness and insulin resistance [3]. Beyond this, they are closely associated with other determinants of an adverse metabolic status.

Importance of sdLDL and inflammatory biomarkers in diabetes

LDL Cholesterol, well known as bad cholesterol, can be further classified according to size into three categories: Large buoyant refers to the larger particles, while "small dense" refers to the smaller, denser LDL particles; "intermediate" describes a middle-sized LDL particle that falls between the large buoyant and small dense categories. Until recently, sdLDL had been less commonly studied and was mostly overlooked. They carry most of the circulating cholesterol and are mainly responsible for the risk of coronary artery disease (CAD) [2]. Conversely, small, dense LDL particles are much denser and can penetrate the arterial wall almost without modification, leading to atherosclerosis. This finding prompted the investigation of the prevalence of sdLDL in patients with T2DM, as it had not received comprehensive attention before [4].

sdLDL particles have been shown to correlate significantly with parameters closely associated with those of metabolic syndrome and insulin resistance. More significant increases in sdLDL are observed with the higher magnitude of weight gain. Consequently, sdLDL particles could represent a "connecting link" between components

of the metabolic syndrome and the accelerated progression of atherosclerotic disease [5]. Most notably, sdLDL particles were shown to strongly predict both increases in carotid intima-media thickness as well as changes in insulin sensitivity during a long-term follow-up [2]. These results are consistent with the hypothesis that sdLDL particles might represent a "causal link" between diabetes, atherosclerosis, and CHD. In this context, assessment of sdLDL particles in plasma may be helpful in the identification of Type 2 diabetes patients with increased cardiovascular risk [6].

Inflammatory markers in diabetes and atherosclerosis

Chronic low-grade inflammation and atherosclerosis are both significantly involved in the pathogenesis of T2DM, and an increase in inflammatory markers related to diabetic dyslipidemia has been demonstrated to be a significant risk factor for atherogenesis in diabetes. The increased small-dense LDL levels, as are found in those with Type 2 diabetes, may also be present in obesity without diabetes [7]. Although traditional cardiovascular risk factors are always predictors of CVD in the general population, recently, systemic inflammation assessed by biomarkers has been reported to be a considerable predictor of CVD for both non-diabetic and diabetic subjects. In addition, inflammation is significantly involved in the disturbance of glucose metabolism, and many proinflammatory markers are related to insulin resistance or β-cell dysfunction. Elevated concentrations of sdLDL-cholesterol (sdLDL-C) have been positively associated with inflammatory and thrombotic markers such as high-sensitivity C-reactive protein (hs-CRP) and PAI-1, even in non-diabetic adults. These findings suggest that sdLDL-C contributes to early atherogenesis and metabolic dysregulation before the onset of diabetes [8]. Furthermore, inflammatory mechanisms in diabetes and obesity play an essential role in the development from diabetes to atherosclerosis, suggesting the importance of exploring inflammatory markers for the prevention of CVD and for the management of diabetes [9].

hs-CRP

CRP is an acute-phase reactant produced by the liver in response to inflammation. While often used as a clinical tool to confirm infection or monitor disease activity, elevated levels of hs-CRP have been additionally established to signify systemic inflammatory status, thereby deeming it a reliable marker of inflammation. Different studies observe a strong positive correlation connecting hs-CRP with an amplified risk for CVD among T2DM patients, which signifying its utility as a prognostic tool [10,11]. Mechanistically, inflammation is suggested to hasten atherogenesis, which in turn impairs glucose metabolism and leads to the development of T2DM. However, as a paradoxical observation, any degree of inflammation within diabetic patients has been shown to raise the levels of sdLDL, complicating the interpretation of hs-CRP as a mediator of inflammation and lipid metabolism.

Lipoprotein-associated phospholipase A2 (Lp-PLA2)

sdLDL particles have detrimental effects on lipid metabolism in macrophages, such as increases in proinflammatory cytokines and atherosclerosis development. Lp-PLA2 is a calcium-independent serine lipase responsible for the hydrolysis of the oxidized phospholipids in LDL, yielding proinflammatory products. Since atherosclerosis is a chronic inflammatory condition, and LDL cholesterol is modified by oxidation or time, Lp-PLA2 has a predictive capability beyond the standard lipid-based parameters. A number of studies have investigated the mass distribution and the relationship of Lp-PLA2-phospholipids with LDL-C size in T2DM. *Post hoc* analysis found that Lp-PLA2 activity was associated with sdLDL-C. It was found that over the 8 years of follow-up (year 2–8), Lp-PLA2 mass became significantly and positively associated with sdLDL-C [12].

Red cell distribution width (RDW)

RDW is a measure of heterogeneity in the dimensions of circulating RBCs. It is thought to reflect impaired erythropoiesis or inadequate erythropoietin production. In recent years, it has been shown that RDW levels increase in patients with T2DM compared to the general population. In addition, elevated levels of sdLDL particles have been associated with increased inflammatory markers such as CRP and interleukin-6 (IL-6). This suggests that the pathophysiological mechanisms underlying T2DM may involve a complex interplay between lipid metabolism and inflammatory processes. This relationship underscores the need for further research to elucidate the specific pathways through which sdLDL particles may exacerbate inflammatory responses in diabetic patients.

Besides, growing attention has also been paid to the association between RDW and cardiovascular events. RDW levels have been shown to be increased in patients with heart failure, CAD, and stroke [13-15]. Furthermore, elevated RDW levels have been found to be independently associated with a more significant number of future cardiovascular events.

METHODS

Selection and grouping of subjects

A total of 173 patients were recruited from the Outpatient Division of a tertiary care hospital in Kerala, India, after obtaining informed consent and Institutional Ethical Review Board clearance. Sixteen were subsequently excluded based on inclusion/exclusion criteria related to age or disease status. This resulted in a total of 158 participants, comprising 83 males and 75 females.

The inclusion norms for this study include several factors. Primarily, individuals must be aged 45–65 and willing to take part by providing informed consent. In addition, participants must be non-smokers and non-alcoholics. Moreover, persons currently not taking lipid-lowering or anti-inflammatory medicines are eligible to be included in the study. These criteria were put forward to protect the reliability and significance of the findings by picking a standardized sample population. The exclusion criteria for this study outline specific conditions that render individuals ineligible for participation. Individuals diagnosed with cardiovascular, liver, or renal diseases are excluded from the study. In addition, individuals with infectious diseases, inflammation, or drug reactions are not considered eligible for inclusion.

Laboratory assessments

The patients were divided into two clusters: Diabetic and non-diabetic. The diagnosis of T2DM depends on evaluating blood glucose levels and Hemoglobin A1c (HbA1c) concentrations. Patients were defined as T2DM if their fasting blood glucose exceeded 126 mg/dL if their postprandial blood sugar was on or have crossed 200 mg/dL, or if they were on therapy with hypoglycemic medicines. A quantitative technique by Randox UK determined small, sdLDL-C levels. This is a two-step technique where chylomicrons and other lipoproteins are removed by utilizing a surfactant and sphingomyelinase. Subsequently, cholesterol, specifically from sdLDL-C, is freed using a surfactant, quantitated colorimetrically thereafter. Supplementary laboratory examinations, including his CRP and Lp-PLA2, were done using nephelometry and chemiluminescent immunoassay, respectively, and RDW data were taken from the hematology Analyzer.

Table 1: Distribution of gender

Gender	Frequency (%)
Male	83 (52.5)
Female	75 (47.5)

Table 2: Comparison of study variables between groups

Study variable	Group		p-value
	Diabetic group #109	Non-diabetic group #49	
sdLDL	45.311±11.53	32.102±6.32	<0.001*
sdLDL/LDL ratio	0.340±0.05	0.290±0.053	<0.001*

*Using Independent sample t-test. sdLDL: Small dense low-density lipoprotein

Statistical analysis

IBM the Statistical Package for the Social Sciences version 20.00 was used to study the statistical data (Chicago, USA). The mean and standard deviation were used to express continuous variables. Numbers and percentages were used to denote categorical factors like gender. To determine whether each continuous parameter is

Table 3: Correlation of study variables with sd LDL among DM patients

Study variables	Correlation coefficient with sdLDL	p-value
hs-CRP	0.426	<0.001*
Lp-PLA2	0.475	<0.001*
RDW	0.389	<0.001*

LDL: Low-density lipoprotein, hs-CRP: High-sensitivity C-reactive protein, Lp-PLA2: Lipoprotein-associated phospholipase A2, RDW: Red cell distribution width, sdLDL: Small dense low-density lipoprotein, DM: Diabetes mellitus

Table 4: Correlation of study variables with sd LDL among controls

Study variables	Correlation coefficient with sd LDL	p-value
hs-CRP	0.619	<0.001*
Lp-PLA2	0.165	0.257
RDW	0.120	0.413

hs-CRP: High-sensitivity C-reactive protein, Lp-PLA2: Lipoprotein-associated phospholipase, RDW: Red cell distribution width

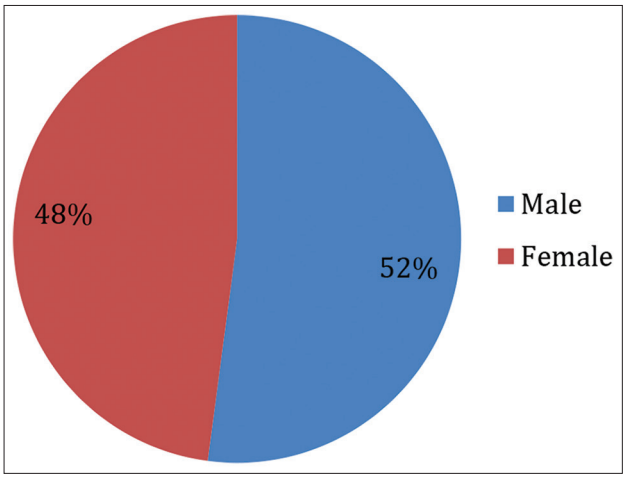

Fig. 1: Gender distribution among participants

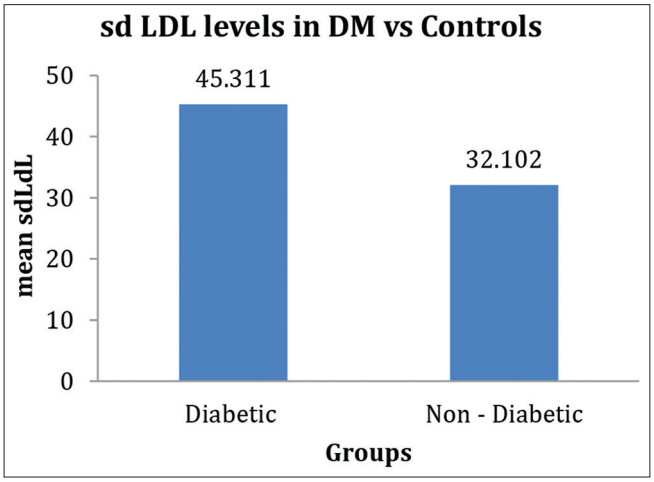

Fig. 2: Prevalence of small dense low-density lipoprotein across study groups
Mean±SD-45.311±11.53 versus 32.102±6.32

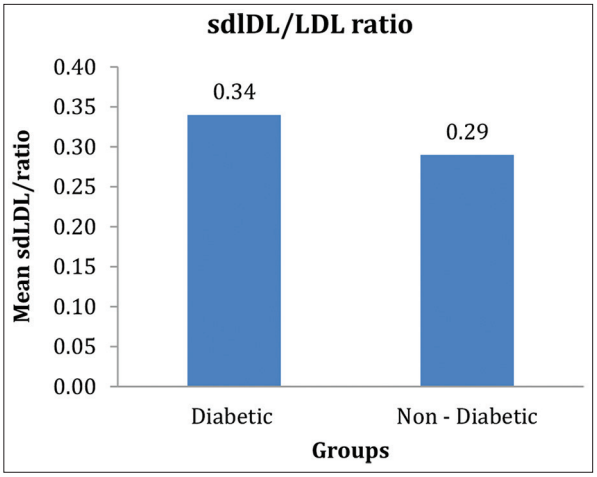

Fig. 3: Ratio of small dense low-density lipoprotein to low-density lipoprotein-cholesterol

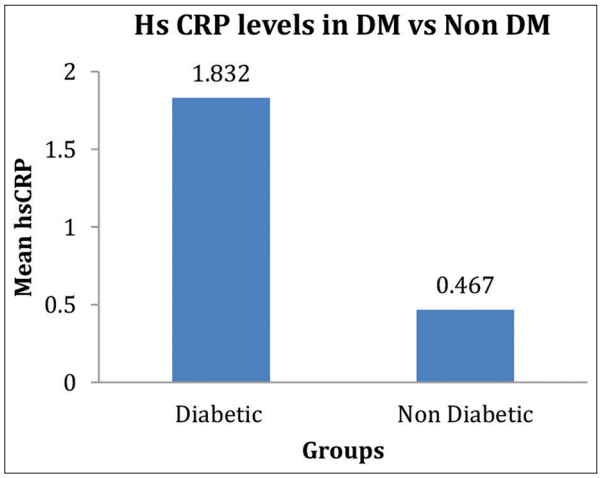

Fig. 4: High-sensitivity C-reactive protein levels across groups
Mean±SD-1.832±1.006 versus 0.467±0.566

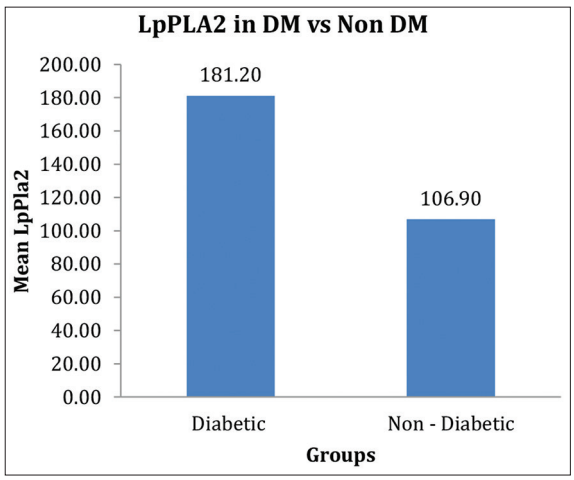

Fig. 5: Lipoprotein-associated phospholipase A2 concentrations in diabetes mellitus versus non-diabetes mellitus
Mean±SD-181.2±66.65 versus 106.9±29.7

statistically significant between groups, the Mann–Whitney U test for skewed data or the Independent Sample t-test for standard data. The Pearson correlation coefficient was calculated for normal data, and the Spearman rank correlation was calculated for skewed data to determine the link between all continuous parameters and sdLDL. The linear regression t-test was used to determine the significance of the results. For statistically significant variables, the univariate and multivariate linear regression equations were established. A statistically significant outcome was defined as a $p<0.05$.

The prevalence of sdLDL particles in individuals with T2DM has become an important focus of research, mainly due to their association with various inflammatory markers that may exacerbate cardiovascular risk.

RESULTS AND DISCUSSION

The mean age of the participants is recorded at 55.3±6.4 years, indicating a relatively mature demographic, and the gender distribution is somewhat equal, with 52% of participants being Males and 48% being Females in Table 1 (Fig. 1). Table 2 presents comprehensive data on a total of 158 patients, with 109 individuals identified as having diabetes mellitus, while the remaining 49 participants are classified as non-diabetic. Among these patients, the age range falls between 45 and 65 years. The study explored the incidence of sdLDL in both diabetic and non-diabetic patients, alongside a thorough examination of the association between inflammatory markers, which include RDW, Lp-PLA2, and hs-CRP. The findings offer valuable insight into the intricate relationship between sdLDL levels and inflammatory markers, also revealing statistically significant differences in sdLDL levels between the two groups of participants.

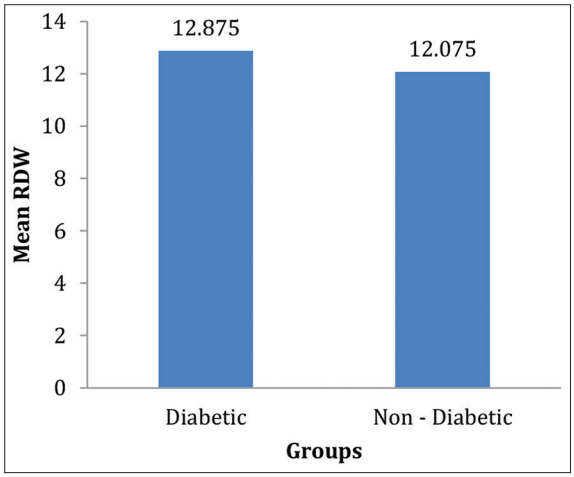

Fig. 6: Red cell distribution width among study subjects Mean±SD-12.875±0.573 versus 12.07±0.442

Comparison sd LDL between groups with and without diabetes

In contrast to the non-diabetic control group, where average sdLDL levels were considerably lower, the diabetes group's sdLDL levels were found to be significantly higher, being measured at 45.311±11.53 compared to 32.102±6.32 for the control group, with a statistically significant difference indicated by $p<0.001$. Moreover, the sdLDL/LDL ratio was observed to be more pronounced in the diabetes group, with values of 0.340±0.05 versus 0.290±0.053, again resulting in a $p<0.001$ which underlines the significance of the result in Table 2 (Figs. 2 and 3). These critical findings are in alignment with previous studies that have shown a strong association between diabetes and an increased prevalence of sdLDL particles. This particular subclass of LDL is recognized to be more atherogenic due to its smaller size, a factor that contributes to a greater susceptibility to oxidation processes. In addition, sdLDL particles are known to be retained more efficiently within the arterial walls, exacerbating the risk of plaque formation [16]. Given this altered and unfavorable lipid profile, it is concerning that diabetic patients may find themselves at a heightened risk for developing CVD, making it imperative that further attention is directed toward managing lipid levels in this population.

sdLDL level and inflammatory markers in T2DM

There was a significant positive connection between sdLDL and all three inflammatory markers in the diabetic group: SdLDL is a significant influence in the occurrence of systemic low-grade inflammation,

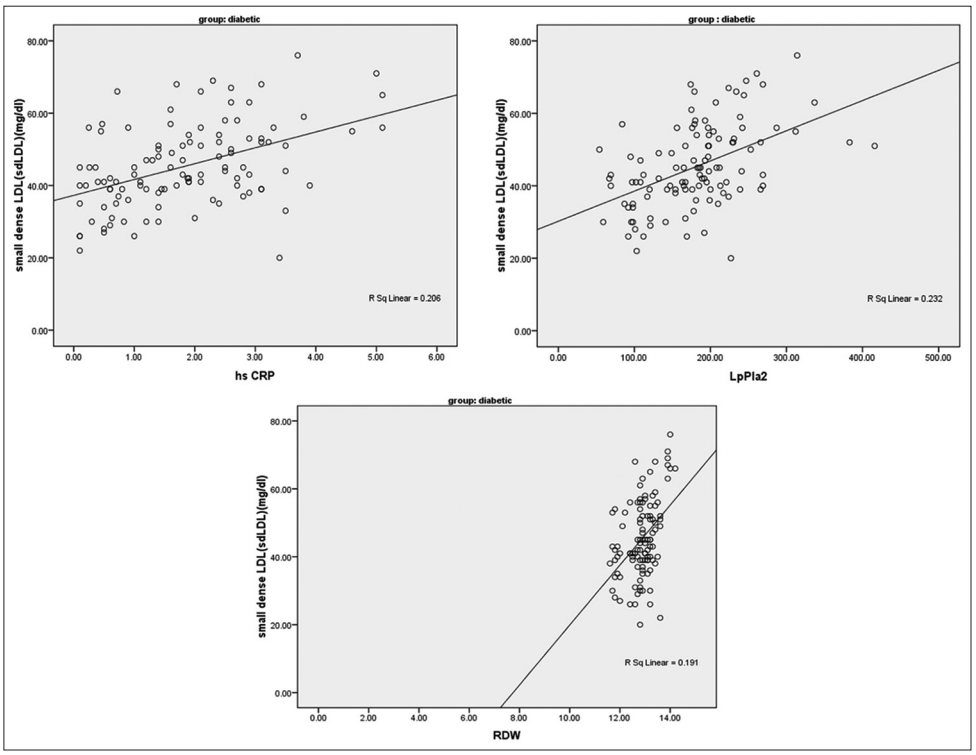

Fig. 7: Correlation of the inflammatory markers in the diabetic group

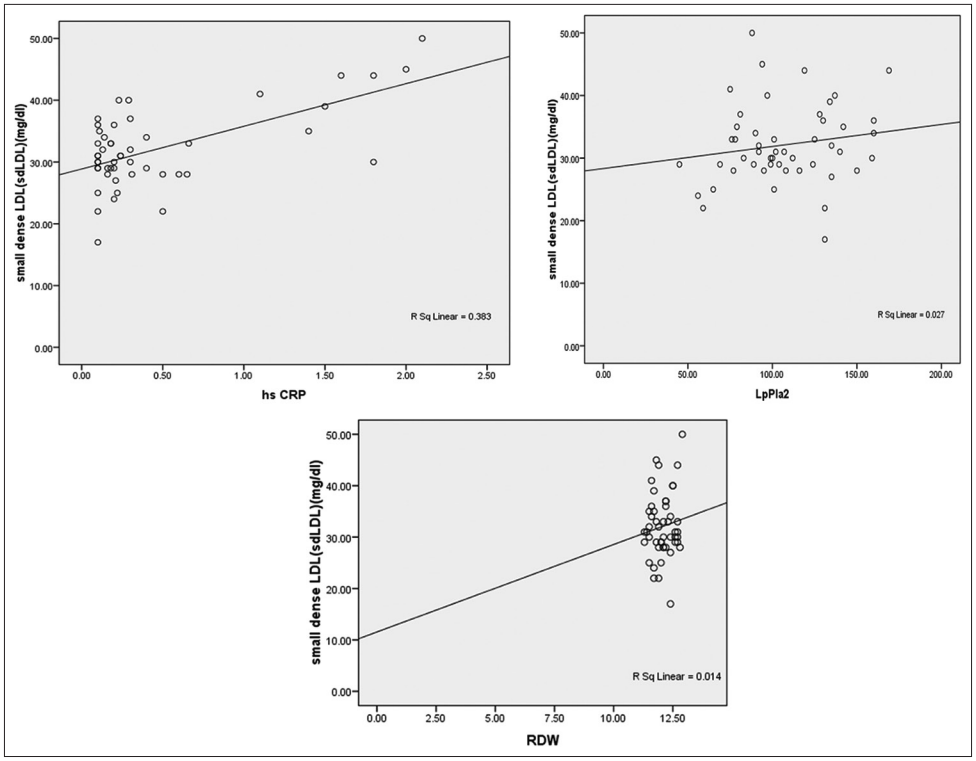

Fig. 8: Correlation of the inflammatory markers in the diabetic group

as seen by the positive correlation between sdLDL and hsCRP in Table 3 (Figs. 4-7). Their correlation with sdLDL supports the notion that chronic inflammation in diabetes may exacerbate atherogenic lipid changes [17]. Similarly, sdLDL was significantly associated with Lp-PLA2, an enzyme that hydrolyzes oxidized phospholipids and is a sign of inflammation in the blood vessels. This finding raises the possibility that endothelial dysfunction and sdLDL in diabetics are related molecularly.

Furthermore, a significant correlation was found between sdLDL and RDW, a recently created measure of inflammation and oxidative stress. This suggests a possible link between vascular inflammation and lipid metabolism and the alterations in red blood cell shape and heterogeneity commonly observed in metabolic disorders.

sdLDL and inflammatory marker association in non-diabetic patients

In the study focusing on individuals without diabetes, only hsCRP exhibited a notable positive correlation with sdLDL, with a correlation coefficient of r=0.619 and a p<0.001, indicating strong statistical significance in Table 4. Conversely, other inflammatory markers such as RDW and Lp-PLA2 did not demonstrate any meaningful associations with sdLDL, as evidenced by their correlation coefficients of r=0.120 (p=0.413) and r=0.165 (p=0.257), respectively, which suggest a lack of significant relationship (Fig. 8). On the other hand, the impact of sd LDL on other inflammation-related indicators-specifically Lp-PLA2 and RDW-appears to be considerably greater among individuals diagnosed with diabetes. This observation holds true even though sdLDL contributes to the inflammatory response, as measured by hs-CRP, in individuals who do not have the disease [18,19]. The absence of significant correlations between sdLDL and Lp-PLA2 or RDW in non-diabetic individuals hints strongly that factors such as insulin resistance and hyperglycemia likely play crucial roles in influencing these markers' functions within lipid metabolism. In T2DM, the presence of LDL phenotype B (sdLDL dominant) is linked with higher levels of inflammatory markers like IL-6, tumor necrosis factor alpha, and hs-CRP. This proinflammatory profile persists despite good glycemic control, indicating sdLDL's independent role in inflammation and cardiovascular risk [20]. This idea is further supported by regression analysis, which highlighted the anticipated connections between inflammatory markers and sdLDL levels in patients who have diabetes. Specifically, univariate regression models revealed that an increase in levels of hs-CRP, Lp-PLA2, and RDW corresponded to a rise in sdLDL levels, reinforcing the understanding of the interconnectedness between these variables in a diabetic context.

CONCLUSION

This research finds the higher prevalence of sdLDL in diabetic patients and its close relationship with inflammatory markers. It seems that higher levels of sdLDL contribute to low-grade inflammation and, as a result, enhance the risk of CVD in diabetic patients. The evident disparity of sdLDL levels among diabetic and non-diabetic subjects implies that metabolic derangements associated with diabetes amplify lipid disturbances through inflammatory mechanisms. A most striking finding is the strong correlation between sdLDL and hs-CRP in both populations, highlighting the global role of inflammation in sdLDL metabolism. These observations suggest the promise of therapeutic intervention that addresses both sdLDL and inflammation for the treatment of diabetes. Recent advancements using shear horizontal surface acoustic wave technology allows for rapid and precise quantification of sdLDL-C. This innovation enhances the feasibility of incorporating sdLDL-C testing in clinical practice for early cardiovascular risk assessment in T2DM and pre-diabetic individuals [21]. The focus of future studies should be to assess the efficacy of anti-inflammatory therapy on lowering sdLDL levels and improving cardiovascular endpoints. Nanotechnology may one day be used to treat diabetes in a personalized and efficient manner. Better treatment results and fewer complications from diabetes could result from this [22]. In total, the intricate interaction between sdLDL, inflammation, and diabetes needs to be further studied to inform focused treatment strategies.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this research article.

AUTHORS' CONTRIBUTIONS

Anush N: Conceptualization, methodology design, data collection, statistical analysis, manuscript drafting. Sukhdeep Kumar: Supervision, validation of methodology, critical revision of manuscript for intellectual content. Riju Mathew: Laboratory analysis of biochemical markers, data interpretation, literature review. Pranav Kumar Prabhakar: Data curation, visualization, final proofreading, and reference management. All authors have read and approved the final version of the manuscript.

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