CLINICAL SIGNIFICANCE OF SMALL DENSE LDL (sd LDL) IN TYPE 2 DIABETIC PATIENTS

Thesis Submitted for the Award of the Degree of

DOCTOR OF PHILOSOPHY

in

Clinical Biochemistry

By

Anush N

Registration Number: 41800042

Supervised By

Dr. Sukhdeep Kumar (28616)
Assistant Professor
Department of Medical Laboratory Sciences
Lovely Professional University

Co-Supervised by

Dr. Riju Mathew
Associate Professor
Department of Biochemistry
Believers Church Medical College
Thiruvalla, Kerala

LOVELY PROFESSIONAL UNIVERSITY
2026

DECLARATION

I, hereby declared that the presented work in the thesis entitled **"Clinical Significance of Small dense LDL (sd LDL) in Type 2 Diabetic Patients"** in fulfilment of degree of **Doctor of Philosophy (Ph. D.)** is outcome of research work carried out by me under the supervision of Dr Sukhdeep Kumar working as Assistant Professor in the Department of Medical Laboratory Sciences, School of Allied Health Sciences of Lovely Professional University, Punjab, India. In keeping with general practice of reporting scientific observations, due acknowledgements have been made whenever work described here has been based on findings of another investigator. This work has not been submitted in part or full to any other University or Institute for the award of any degree.

(Signature of the scholar)

Name of the scholar: ANUSH N

Registration No .41800042

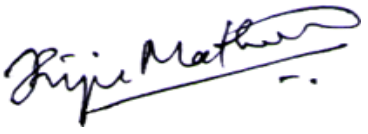
Department/School: Medical Laboratory Sciences, /School of Allied Health Sciences

Lovely Professional University,

Punjab, India

CERTIFICATE

This is to certify that **Mr. ANUSH N** has completed the Ph.D. Biochemistry titled **"Clinical Significance of Small dense LDL (sd LDL) in Type 2 Diabetic Patients"** under my guidance and supervision. To the best of my knowledge, the present work is the result of his original investigation and study. No part of this thesis has ever been submitted for any other degree or diploma. The thesis is fit for the partial fulfillment of the condition for the award of the degree of Ph.D. in Clinical Biochemistry.



Dr. Sukhdeep Kumar

Department of Medical Laboratory Sciences,
School of Allied Health Sciences
Lovely Professional University, Punjab

Dr. Riju Mathew

Associate Professor
Department of Biochemistry
Believers Church Medical
College, Thiruvalla, Kerala

ABSTRACT

Diabetes mellitus (DM), a chronic metabolic ailment, is accompanied with a multitude of complications, many of which are linked to lipid metabolism and systemic inflammation. Among the emerging markers for cardiovascular risk in diabetic patients, small dense low-density lipoprotein (sd LDL) has gained prominence due to its atherogenic potential. Concurrently, inflammatory and oxidative stress markers such as high-sensitivity C-reactive protein (hs-CRP), lipoprotein-associated phospholipase A_2 (Lp-PLA_2), and red cell distribution width (RDW) are also attributed to the pathophysiology of dyslipidemia in diabetes. This study assessed the scientific importance of small dense low-density lipoprotein (sdLDL) and examined its association with inflammatory biomarkers (hs-CRP, Lp-PLA_2) and erythrocytic biomarkers.This assessment compared separate participant groups: non-diabetic individuals, control participants, and patients with diabetes. It also compared people with hypercholesterolemia to those without hypercholesterolemia within these groups.

This study represented a cross-sectional observational analysis conducted at Believers Church Medical College Hospital, Kerala. A total of 211 participants were engaged and divided into four groups: Group 1 (Control, n=49), Group 2 (Metabolic Syndrome without DM, n=53), Group 3 (DM without hypercholesterolemia, n=52), and Group 4 (DM with hypercholesterolemia, n=57). Serum levels of sd LDL, hs-CRP, Lp-PLA_2, RDW, Total cholesterol, and LDL were measured. The sd LDL /LDL-C and sd LDL /Total Cholesterol ratios were calculated. Statistical analyses included correlation studies and regression modelling to evaluate associations between sd LDL and the inflammatory markers.

The highest mean sd LDL levels were observed in Group D (DM with hypercholesterolemia), at 46.8 ± 8.5 mg/dL, lot greater than that of other groups. (p<0.01). But, Group A (controls) had the lowest mean sd LDL levels (18.7 ± 4.2 mg/dL). Similarly, the sd LDL /LDL-C and sd LDL /Total Cholesterol ratios were highest in Group D (0.43 and 0.31, respectively) and lowest in Group A (0.19 and 0.12, respectively), demonstrating that small dense LDL formation is markedly influenced by

both diabetic status and hypercholesterolemia.

Mean hs-CRP levels showed a parallel trend: Group D had a mean hs-CRP of 6.1 ± 1.4mg/L, significantly elevated compared to Group A (1.2 ± 0.5 mg/L). Lp-PLA_2 was also markedly higher in Group D (245 ± 36 ng/mL), compared to Group A (152 ± 28 ng/mL), supporting its role in pro-inflammatory lipid modification pathways. RDW was moderately elevated across all disease groups but was highest in Group D (15.3 ± 1.1%) and Group C (14.9 ± 1.2%), suggesting systemic inflammation and erythrocyte variability in diabetics.

Statistical correlation revealed that sd LDL exhibited a robust positive association with hs-CRP in diabetic groups ($r = 0.69$, $p<0.001$ in Group D). A moderate correlation was observed with Lp-PLA_2 ($r = 0.58$, $p<0.01$). However, the correlation with RDW was weak ($r = 0.19$, $p=0.08$), failing to reach statistical significance. This suggests that while RDW may reflect general inflammatory stress, it does not specifically track lipid-related oxidative processes like hs-CRP or Lp-PLA_2.

Regression analysis inveterate hs-CRP as the strongest independent predictor of sd LDL and sd LDL /TC ratio in individuals with diabetes, making up to 42% of variance ($p<0.001$). Lp-PLA_2 also emerged as a substantial predictor but to a lesser extent (28% of variance). RDW failed to show a significant independent predictive value in multivariate models.

In Group B (MetS without diabetes), sd LDL levels were elevated (32.5 ± 6.4 mg/dL) in contrast to controls, and the levels of hs-CRP were also raised (4.2 ± 1.0 mg/L). However, in this group, there was no significant correlation with Lp-PLA_2 or RDW, and the relationship between sd LDL and hs-CRP was weaker ($r = 0.28$, $p = 0.06$). This indicates that sd LDL elevations in MetS may occur through insulin resistance and transformed lipid metabolism independent of overt systemic inflammation.

In the control group, sd LDL levels, inflammatory markers, and correlations remained low and non-significant. This group served to affirm the baseline physiological ranges

and confirmed that atherogenic lipid profiles are rare in metabolically healthy individuals. Our findings reaffirm the central role of chronic inflammation in driving lipid atherogenicity in diabetes. Elevated hs-CRP and Lp-PLA$_2$ levels reflect ongoing vascular and systemic inflammation which correlate strongly with sd LDL —a key contributor to endothelial dysfunction and atherosclerosis. These relationships were significantly accentuated in patients with both diabetes and hypercholesterolemia, indicating a synergistic effect of dysglycemia and dyslipidemia.

Although RDW is often described as a simple marker of inflammation, our study found only a weak link between RDW and sd LDL.This may reflect the nonspecific character of RDW, which can be affected by anaemia, micronutrient deficiency, erythropoiesis, and renal function, factors that are common in diabetic dyslipidemia but not limited to it. Several studies support the use of RDW in broader cardiovascular risk prediction, but they also indicate that RDW is less specific than lipid-focused markers such as hs-CRP and Lp-PLA$_2$ (Cengiz et al. 2015) and Baye et al. In the non-diabetic MetS group, sd LDL was higher even though there was no clear rise in inflammatory markers. This pattern is consistent with initial dyslipidemia that is likely related to insulin resistance. This points to the importance of identifying MetS early and starting management promptly, even before diabetes develops.

The findings indicate that sd LDL is a clinically relevant and strongly atherogenic lipid fraction in diabetes, particularly when hypercholesterolemia is also present. Of the biomarkers assessed, hs-CRP showed the strongest and most consistent association with sd LDL and the sd LDL/TC ratio in both diabetic and pre-diabetic groups, with Lp-PLA$_2$ showing the next strongest association. Although RDW was elevated, it was a less reliable marker for sd LDL because it can be influenced by a wide range of systemic disruptions. In diabetic patients, measuring sd LDL, hs-CRP, and Lp-PLA$_2$ together can serve as a useful biomarker panel for cardiovascular risk stratification. Taken together, these markers provide a clear overview of lipid-related inflammation and oxidative stress, and they may support early identification of people at higher risk who could benefit from lifestyle changes or drug treatment.

Clinically, adding sd LDL, hs-CRP, and Lp-PLA2 to routine lipid panels may improve cardiovascular risk prediction and support risk assessment in diabetes care. RDW is

easy to obtain and low cost, but it is best treated as a secondary marker and interpreted alongside the patient's clinical findings.Longitudinal studies in the future are needed to confirm how well this biomarker panel predicts outcomes and to set standard cut-off values for use in clinical decisions.

Keywords:

Small dense LDL (sd LDL), hs-CRP, Lp-PLA_2, RDW, Inflammatory markers, Metabolic Syndrome, Atherogenicity, Type 2 Diabetes Mellitus, Dyslipidemia

ACKNOWLEDGEMENT

I am grateful to the Almighty for providing me with the perseverance and resilience necessary to finish this study project. I thank God for giving me opportunity and means to overcome obstacles. Throughout the entire research period, I went through a range of emotions.

I would like to acknowledge my obligation, offer my sincere gratitude, and extend my warmest thanks to my esteemed supervisor, **Dr.Sukhdeep Kumar** from the Department of Medical Laboratory Sciences at Lovely Professional University's School of Allied Medical Science. His insightful guidance, unwavering support, and genuine belief in my potential laid the foundation for my doctoral work. I extend my heartfelt gratitude to my co-supervisor, **Dr. Riju Mathew**, for his generous investment of time, knowledge, and expertise throughout the course of my research. I am truly grateful for his endurance, insightful feedback, and steadfast support at every stage of this journey. I would like to express my profound gratitude to **Dr. Pranav Kumar Prabhakar,** Professor, Department of Biotechnology, Nagaland University, who has been a remarkable mentor and guide in my academic journey. As my first mentor during his tenure at the Department of Medical Laboratory Sciences, Lovely Professional University, Dr. Prabhakar played an instrumental role in shaping my research path.

I would like to take this chance to express my gratefulness to **Dr. Ashok Mittal, the Honorable Chancellor of LPU, Mrs. Rashmi Mittal, the Worthy Pro-Chancellor of LPU, Dr. Jaspal Singh Sandhu, the Honorable Vice Chancellor of LPU, and Dr. Monica Gulati, Registrar and Head of the Faculty of Applied Medical Sciences** for giving me the chance to work at such a respected university.

My sincere gratitude is extended to **Prof. Dr. George Chandy Matteethra**, the Director and CEO of Believers Church Medical College Hospital, and **Fr. Sijo Pandappallil**, Manager of Believers Church Medical College, Thiruvalla, Kerala along with the staff members of the Central Laboratory of BCMCH, Thiruvalla .

I am grateful to **Mr. Gurinder Singh**, Head of the Department of Medical Laboratory Sciences, and the entire faculty of Lovely Professional University's School of Allied Medical Sciences for giving me the environment that I needed to conduct my research and for their encouragement during the journey.

I want to express my gratitude to my wife **Mrs. Jasmin Anush**, who has been the backbone of my journey, for the encouragement, and emotional support both inside and outside of it. I appreciate you being there for me no matter what. I owe my parents more than words can say. I would want to dedicate this thesis to my beloved father **Prof. S Naziruddin Kunju (Late)** and my loving mother **Mrs. Suhra Naziruddin**. My parents who have always been eager to offer any assistance during since my childhood. Their endless sacrifice has enabled me to get to where I am now. I cannot move forward without mention the encouragement rendered by my siblings, **Mr. Aseem N and Mrs. Aneesa Rejims** who stood beside me with the energy I wanted. I will always be grateful to God for providing me with parents and siblings who love me without conditions and who encouraged me to chase my dreams.

I owe a special note of gratitude to my beloved children, **Aakhil** and **Amina**, whose unwavering love, patience, and quiet strength have been my constant source of motivation throughout this journey. Now in their twenties, they have shown incredible understanding and maturity, often putting aside their own needs so I could pursue mine and their presence has been a comforting reminder of what truly matters.

The love and support of my colleagues and friends have also played a significant role in this journey, and I will always cherish it. I am especially thankful to **Mrs. Nisha Joseph**, Principal, SNVHSS Sreekandeswaram, for granting me the time and freedom to pursue my academic work and research. My sincere thanks also go to **Mr. K.K. Rajappan**, former Manager of Sree Narayana Vocational Higher Secondary School, Sreekandeswaram, Cherthala, Kerala for his warm support and encouragement, and to **Mr. K.L. Asokan**, the current Manager, for his kind provision and backing.

Finally, I extend my heartfelt thanks to everyone, named and unnamed, whose support, guidance, or even simple gestures helped me complete my thesis and experimental work, whether directly or indirectly.

TABLE OF CONTENTS

List of Figures

List of Tables

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AUC	Area Under Curve
BMI	Body Mass Index
BCMCH	Believers Church Medical College Hospital
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CI	Confidence Interval
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
cPLA2	Cytosolic Phospholipase A2
DM	Diabetes Mellitus
FBS	Fasting Blood Sugar
FPG	Fasting Plasma Glucose
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein Cholesterol
HF	Heart Failure
hs-CRP	High-Sensitivity C-Reactive Protein
HTN	Hypertension
IEC	Institutional Ethics Committee
IDF	International Diabetes Federation
IGT	Impaired Glucose Tolerance
IFG	Impaired Fasting Glucose
IL-6	Interleukin-6
IR	Insulin Resistance
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein Cholesterol
LMICs	Low- and Middle-Income Countries
Lp-PLA2	Lipoprotein-Associated Phospholipase A2
MetS	Metabolic Syndrome
NCEP-ATP III	National Cholesterol Education Program – Adult Treatment Panel III
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
ROS	Reactive Oxygen Species

sd LDL	Small Dense Low-Density Lipoprotein
sd LDL-C	Small Dense Low-Density Lipoprotein Cholesterol
SD	Standard Deviation
SE	Standard Error
SPSS	Statistical Package for the Social Sciences
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
TG	Triglycerides
TNF-α	Tumor Necrosis Factor-alpha
TyG	Triglyceride–Glucose Index
UKPDS	United Kingdom Prospective Diabetes Study
VLDL	Very Low-Density Lipoprotein
WHO	World Health Organization

CHAPTER-1
INTRODUCTION

1.1 TYPE 2 DIABETES MELLITUS (T2DM)

Diabetes mellitus (DM) is a composite condition with heterogenous origin .It is marked by metabolic disturbances and increased plasma glucose levels. A sustained rise in blood glucose is usually due to reduced synthesis of insulin or reduced insulin action in target cells, which is called insulin resistance.The main forms of diabetes mellitus include type 1 diabetes, type 2 diabetes, and MODY (maturity-onset diabetes of the young).Type 2 diabetes mellitus is the most common form of diabetes, accounting for about 90% of cases worldwide.Type II diabetes mellitus typically starts with insulin resistance and later includes reduced secretion of insulin, which leads to chronic hyperglycemia (Piero et al.).(2014).In 2019, statistics indicated that about 500 million adults were living with diabetes. Current projections estimate that this number will rise to about 700 million by 2045. About 79% of cases are expected to be in developing countries and approximately 4.2 million people die each year.(About Diabetes, 2019). Asia, especially India and China, bears the highest burden of diabetes mellitus (Singh et al.).(2011).

1.1.1. EPIDEMIOLOGY OF DIABETES MELLITUS IN INDIA

India is facing a growing diabetes epidemic, mainly driven by type 2 diabetes mellitus (T2DM). This rise appears to reflect a mix of genetic risk and major shifts in socioeconomic conditions and everyday lifestyle (Jena et al.2023),(Sharma et al.2024)India accounts for nearly one in six people living with diabetes worldwide, and it has the second-highest diabetes prevalence among countries.(Sharma et al.2024).In 2019, an estimated 77 million people in India were affected, which corresponds to an adult prevalence of 8.9%, and estimates suggest that this number will rise to more than 134 million by 2045 (Pradeepa & Mohan, 2021).India carries about 14% of the world's diabetes burden, and roughly 95% of these cases are type 2 diabetes mellitus (Narayan et al.2023).The country also has the highest diabetes-related mortality in Southeast Asia, with more than 1 million deaths reported in 2019.In the study by Kalra

et al., 42.6% of cases occurred in individuals younger than 70 years.(2022).The age-standardized DALY rate for T2DM increased by 39.A 6% increase from 1990 to 2016 suggests a rising burden of early illness and death (Kalra et al.2022).A key issue in diabetes control in India is underdiagnosis: about 57% of people with diabetes do not know they have it, which delays care and raises the risk of complications (Pradeepa & Mohan, 2021).In India, the rising prevalence of diabetes is associated with urbanization and economic growth, alongside shifts toward diets higher in refined carbohydrates and energy-dense foods, lower physical activity, and increasing overweight and obesity, consistent with the country's ongoing nutritional changeover). (Kumar et al., 2021; Mohan et al., 2023).

1.1.2. COMPARATIVE ANALYSIS OF GLOBAL AND INDIAN DIABETES BURDEN

India illustrates that diabetes rates have risen faster in low- and middle-income countries than in high-income countries.(Abhinav et al.2020).Projections indicate that India and China will continue to have the largest numbers of adults living with T2DM worldwide through 2045 (Joseph et al.2022).The global burden of diabetes is large, and India's share is especially a warning one ,because of high rates of early death, rapid changes in disease patterns, and a large number of people who have diabetes but have not been diagnosed (Kalra et al.2022; Pradeepa and Mohan, 2021).Taken together, these comparisons point to a need for prevention that fits local settings, earlier detection, and stronger management approaches, especially in India, to reduce future increases in diabetes-related illness, deaths, and economic burden.

Table 1.1: Diabetes Burden-Global vs Indian

Parameter	Global Scenario	Indian Scenario
No of Patients	463 million (2019) 700–783 million by 2045 (projected)	77 million (2019) 134 million by 2045 (projected)
Global Share	Not Applicable	~14% of the global diabetes population
Morbidity Status	14th leading cause of disability worldwide. Number of disability-adjusted life years (DALYs) linked to it has increased since 1990.	Age-standardized DALY rate increased by about 39.6% (1990–2016), High rise in premature morbidity
Diabetes-related deaths	~4.2 million deaths (2019); About 10% of all global deaths	>1 million diabetes-related deaths (2019)
Premature mortality (<70 years)	Varies by region; highest increases in South and Central Asia	About 42.6% of diabetes-related deaths occur before 70 years of age
Mortality trend	Rising , especially in South Asia and Sub-Saharan Africa	Highest diabetes-related mortality in the South-east Asia
Undiagnosed diabetes	Substantial but varies by country to country	About 57% of remain undetected

1.2 . DYSLIPIDEMIA IN TYPE 2 DIABETES

CVD is a frequent sequela of of type 2 diabetes mellitus and is closely allied with dyslipidemia in diabetics. Long-term hyperglycemia is associated with abnormal lipoprotein profiles and complications affecting kidney function (Guijarro and Kaene, 1994).Lipoproteins differ in their size and density. HDL is generally associated with a lower risk of cardiovascular disease, while LDL contributes to atherosclerosis and is present as two main particle types: large buoyant LDL (lb LDL) and small dense LDL (sd LDL).

1.3 SMALL DENSE LDL (sd LDL): CHARACTERISTICS AND METABOLIC IMPLICATIONS

Small dense LDL (sd LDL) refers to a subset of low-density lipoprotein particles that are smaller in size and higher in density than typical LDL. These particles tend to carry less cholesterol per particle but may be present in larger numbers, which matters when interpreting lipid profiles. sd LDL is often linked to higher triglycerides, lower HDL cholesterol, insulin resistance, and other features of metabolic dysfunction.

Small, dense LDL cholesterol appears to predict cardiovascular disease risk more accurately than total LDL cholesterol. These particles remain in plasma for a longer time, are linked with lower levels of antioxidant vitamins, and are more prone to oxidative damage. Desialylation, which lowers the sialic acid content, and extensive glycation of ApoB in small, dense LDL can increase deposition in the arterial wall, which helps explain why small, dense LDL is strongly atherogenic (Ivanova et al.).(2017)

1.4 ROLE OF sd LDL IN ATHEROSCLEROSIS AND CARDIOVASCULAR RISK

Small, dense LDL can undergo several atherogenic changes and may promote inflammation in the vessel wall. People with high sd LDL-C have a higher risk of cardiovascular disease, even when their LDL-C level is within the normal range.Large cohort studies, for example(e,g.In ARIC), the incidence of CAD was about 51% higher among participants with the highest sd LDL-C levels.In the REAL-CAD clinical trial, statin therapy was associated with lower small dense LDL-C and fewer major cardiac events, with the largest reductions seen among participants who had higher baseline levels.

Small dense LDL-C levels above 50 mg/dL are associated with a higher risk of later cardiac events, even after accounting for age, blood pressure, and diabetes status. Because of its small size, it can enter the arterial wall and become oxidized, which speeds up plaque formation.

1.5 CLINICAL SIGNIFICANCE OF sd LDL IN TYPE 2 DIABETES

Traditional LDL-C has limited predictive value in T2DM, where patients often show high TG and increased sd LDL despite normal LDL-C.

T2DM is associated with hyperglycemia, dyslipidemia, hypertension, and obesity, all of which favor sd LDL formation. sd LDL explains the combined risk of high TG and LDL-C ("atherogenic duo") and is elevated in MetS and insulin resistance, sometimes termed "metabolic LDL".

Insulin resistance promotes hepatic fat accumulation and VLDL overproduction, which converts to sd LDL. sd LDL is also linked to NAFLD and CKD in diabetes. Importantly, sd LDL levels do not always correlate with glycemic control, indicating stronger dependence on lipid metabolism.

Automated assays now enable routine sd LDL measurement, and studies confirm it as a superior ASCVD predictor compared to total LDL-C (Fan et al., 2019).

1.6 NEED FOR THE STUDY

CVD is one of the major reasons of mortality in many countries, with individuals having T2DM being particularly prone. The condition is further exacerbated by the presence of dyslipidemia, which serves as a major contributing factor, making diabetes worse.
Traditional lipid markers are routinely used to assess cardiovascular risk. However, recent studies suggest that small dense LDL (sd LDL) provides a stronger correlation, as it is a more atherogenic lipoprotein fraction, playing a significant part in the progression of AS and CVD. The characteristic feature includes its increased susceptibility to oxidation, prolonged circulation time, and higher arterial wall penetration.
These factors collectively enhance the initiation of plaque formation and promote vascular inflammation, increasing the risk of atherosclerosis. Evidence also suggests that elevated sd LDL levels directly correlate with insulin resistance, yet is not frequently used in practice.

This study evaluates the clinical consequence of sd LDL levels in T2DM and its

association with CVD risk. It aims to determine whether sd LDL could be an independent biomarker for early CV risk assessment in diabetic patients.

Addressing this gap in lipid profiling could enhance routine clinical assessments, as traditional LDL-C measurements do not differentiate between sd LDL and less atherogenic LDL fractions.

Given the exponential global prevalence of DM and its complications, evaluating sd LDL as a potential indicator may provide a more reliable predictive value for CVD than conventional lipid markers. Ultimately, this might make early intervention easier and result in better patient outcomes.

1.7 RESEARCH GAP

Currently, there are no reports available regarding the association between small dense LDL and inflammatory markers like hs-CRP ,Lp-PLA2 and RDW in a study. Earlier methods and calculations for determining sd LDL were not standardized, and the results could not be compared.

The newly introduced homogeneous assay has made the analysis of sd LDL sub-fractions easier and more accurate to the next level. The therapeutic target of sd LDL is established till now.

1.8 AIM OF THE STUDY

This study aimed to evaluate the clinical significance of small dense LDL (sd LDL) in Type 2 diabetic patients, particularly its association with cardiovascular risk and metabolic-implications.

1.9 ETHICAL CONSIDERATIONS

The study started with getting ethical clearance and permission. It was granted by the institutional ethics committee (reg no: ECR/1098/Inst/KL/2018/, vide approval IEC Study No.IEC/2020/06/160 Dated 08/09/2020).

CHAPTER-2

REVIEW OF LITERATURE

2.1 INTRODUCTION

T2DM is a long-term condition affecting metabolism, which leads to serious complications, especially cardiovascular disease. One key factor in this risk is diabetic dyslipidemia, which includes changes in lipid profiles—most notably, an increase in sd LDL. Compared to larger LDL forms, sd LDL particles are potentially hazardous as they are more likely to enter artery walls, get oxidized, and stay longer in circulation. In many diabetic patients, sd LDL levels are high even if total LDL seems normal, which can mask the actual risk. With T2DM cases rising worldwide, sd LDL is gaining importance as an emerging laboratory marker to assess early CV risk assessment in such patients.

The pathophysiology of T2DM involves genetic predisposition and environmental factors. As peripheral tissues lose their sensitivity to insulin, insulin resistance arises, raising plasma glucose levels. Over time, beta-cell function declines, resulting in relative insulin deficiency despite initial compensatory hyperinsulinemia.

Persistent hyperglycemia leads to microvascular complications such as nephropathy, retinopathy, and neuropathy, as well as macrovascular complications including coronary artery disease, stroke, and cardiovascular disease. These complications significantly impair quality of life and escalate healthcare costs.

Management is based on lifestyle modifications—dietary changes, increased physical activity, and weight loss—supplemented by oral hypoglycemic agents and insulin therapy. Patient education and regular monitoring are essential for improving outcomes and mitigating complications.

Maintaining normal blood glucose levels is often difficult because some patients do not take their medications as prescribed, face socioeconomic constraints, and have limited access to health care. Because the disease worsens over time, treatment regimens should be refined and improved in line with new clinical evidence. This challenge is made harder by the large global economic burden linked to diabetes,

which is projected to reach about 1.425 trillion by 2040, which calls for new and cost-effective approaches to management .This calls for an approach that combines pharmacological treatment with public health programs focused on prevention and early diagnosis (Guan et al.2024).Even though many glucose-lowering therapies are available, many patients with type 2 diabetes still do not achieve or sustain target glycemic control (Starr 2022.Treatment outcomes are shaped by taking medication on schedule, socioeconomic conditions, and access to health care services. Because the disease continues to worsen over time, the current treatment plan may need to be strengthened and reviewed for possible changes.(Fang et al.,2018).

Type 2 diabetes mellitus places a heavy strain on health systems worldwide, linked to aging populations, urban growth, unhealthy diets, and low levels of physical activity . In the United States, about 17 million people are affected, and this is a major public health issue linked to disability, death, higher healthcare costs, and lower quality of life.

2.2 ETIOLOGY

Between 1975 and 2014, age-standardized obesity prevalence (BMI ≥30 kg/m²) rose steeply across all regions. Based on current trends, obesity prevalence in 2025 is expected to exceed 21% among women and reach about 18% among men. Estimates suggest that, by 2035, about 592 million people worldwide may be living with diabetes. (Tao et al.2015).

Type 2 diabetes mellitus accounts for about 90–95% of all diabetes cases. It was once seen mainly in wealthier Western countries, but it is now a global public health problem, with rising rates in younger people and in many traditional minority groups. (Pradeepa et al., 2021). However, rising prevalence is largely driven by modifiable factors like being sedentary, poor diet, obesity, smoking, alcohol use, exposure to pollutants, stress, inadequate sleep, and urban environmental influences (Savvopoulos et al., 2025).

Evidence suggests that food and lifestyle modifications, including carbohydrate-restricted or calorie-restricted diets and bariatric surgery, may reverse insulin resistance and T2DM. In the adult population, 8.8% had diabetes in 2015, and projections for

2040 indicate an increase to 10.4 %, which is about 642 million people then. (Ogurtsova et al., 2017).

There is growing awareness of sex and gender differences in the epidemiology and pathophysiology of NCDs, particularly diabetes (Schiebinger et al., 2011).

Research has indicated that more physical exercise both resistance and aerobic exercise —reduces the risk of developing T2DM (Yamada et al., 2014; Ekelund et al., 2009). Yet, metabolic syndrome (MetS) definitions often omit critical variables such as sex, age, and socioeconomic status (Mozumdar et al., 2011).

Obesity, predominantly visceral fat accumulation, is a significant risk factor and is commonly linked with persisitant low-grade inflammation, hepatic steatosis, and insulin resistance (Hajer et al., 2008; Hwang et al., 2007). Several studies report a higher tendency for young women to develop central obesity and insulin resistance under similar dietary exposures (Kautzky-Willer et al., 2016; Barclay et al., 2008).

In India, a growing burden of disease is linked to unhealthy diet, obesity, hypertension, hyperglycemia, and hyperlipidemia, with tobacco use also play an important role (India State-Level Disease Burden Report, 2021; Pradeepa and Mohan, 2021). Prospective trials show that changes in lifestyle, such as moderate weight loss, significantly reduce T2DM incidence by up to 58% in high-risk individuals (Tuomilehto et al., 2004; Delahanty et al., 2014).

Different fiscal, social statuses and environmental factors also back to diabetes risk. A lower socioeconomic background is a s s o c i a t e d with a 40–60% higher relative risk of developing T2DM, mediated partly through higher BMI (Sacerdote et al., 2012; Stringhini et al., 2016). Urbanization, industrialization, and the spread of fast-food culture are key environmental contributors (Pieroni et al., 2014; Kautzky-Willer et al., 2016). T2DM results from the collaboration between genomic and environmental components. Heritability estimates range from 20% to 80%, with a stronger genetic contribution in younger age groups (Meigs et al., 2000; Almgren et al., 2011). More than 500 genetically susceptible loci have been found by genome- wide association studies (GWAS), many of which act through cell-type specific pathways

(Suzuki et al., 2024).

The risk is found increased for those with a genealogy of type 2 diabetes—lifetime risk is about 40% if one parent is affected, rising to 70% if both are (Florez et al., 2003; Ali, 2013). Monozygotic twins show a concordance rate of about 70%, compared to 20–30% in dizygotic twins (Kaprio et al., 1992).

T2DM is a heterogeneous condition; insulin resistance and β- cell dysfunction are both causative factors. Among these, β-cell failure plays a more central role (Kahn, 2003; Laakso et al., 2022). However, treatment approaches still frequently fail to reflect this heterogeneity, stressing the necessity for more custom-made management approaches (Williams et al., 2022). The underlying causes of T2DM are not entirely understood, yet substantial evidence highlights strong correlations with obesity, advancing age, alcohol misuse, and specific ethnic backgrounds with a family history of diabetes (Ssekamatte et al., 2023). Furthermore, individuals of Indian descent are particularly susceptible to insulin resistance and visceral fat deposition, even at similar BMI levels compared to other populations, indicating a significant genetic predisposition and increased risk for T2DM (Himanshu et al., 2020; Joseph et al., 2022). The adoption of unhealthy dietary practices, characterized by high saturated fat and insufficient fiber, also significantly contributes to the development of metabolic disorders including T2DM (Paul et al., 2024).

2.3 METABOLIC SYNDROME AND T2DM

MetS represents many factors, such as dysregulated glucose and lipid levels, abdominal obesity, and hypertension (Huang, 2009). As stated earlier, it is a growing global epidemic with notable socioeconomic impact (Kassi et al., 2011). These disturbances affecting the metabolism notably elevate the risk of CHD, CVD and T2DM (Reaven, 1988).

Poor diet, sedentary lifestyle, obesity, and genetic predisposition are causative factors (Galassi et al 2006). MetS substantially raises the risk for T2DM, coronary artery disease (CAD), and other cardiovascular ailments, and it has been linked to increased

all-cause mortality (Wilson, 2005).

Global obesity rates have increased by twofold since 1980, and over 1.9 billion people are overweight or obese at the moment, including over five crore children under the age of five. (Hotamisligil 2006). The health burden of obesity is immense and growing, with type 2 diabetes being one of its most severe complications (Saltiel and Olefsky 2017).MetS is now recognized as an standalone risk factor for CVD and T2DM but also for cancer and overall mortality (Swinburn et al., 2011). T2DM, in turn, can lead to significant damage to various body systems, especially the kidneys, eyes, heart, and vasculature (Black and Macinko 2008). Individuals with T2DM who also have metabolic syndrome face a compounded risk of complications from each additional MetS component compared to diabetic individuals without the syndrome (Najarian et al., 2006).

Despite public health efforts focusing on diet and physical activity, the burden of T2DM continues to grow, highlighting the limited success of population-wide interventions (Cnop et al 2007). Environmental and neighborhood characteristics are now also being investigated as possible contributors to T2DM risk (Nolan et al., 2011).

Globally, the prevalence of MetS ranges from 7.9% to 43% in men and from 7% to 56% in women (Balkau 2004). This variation depends on several factors, including the diagnostic criteria used, as well as age, gender, ethnicity, and lifestyle (Gui et al.,2017). Rapid urbanization and sedentary lifestyles, along with changes in dietary habits, have been credited for the rising number of cases worldwide (Li et al., 2021).

In 2012, the universal frequency of diabetes among adults was estimated to be about 4%. (Danquah et al.,2012). In urban Ghana, the prevalence of MetS ranges from 23% to 38% based on the NCEP/ATP III guidelines (Nyarko et al., 1997), while T2DM affects at least 6% of the adult population (Nsiah et al., 2015).

In India, the state of Kerala has long been known for strong health care indices, but in recent decades it has seen a marked increase in non-communicable diseases (Thankappan et al.).(2010). Coronary artery disease (CAD) is presently regarded as

the main cause of death in Kerala, responsible for 31% of deaths among men and 18% among women. (Alberti et al 2009). MetS is defined by a constellation of central obesity, glucose intolerance, hyperinsulinemia, high triglycerides, low HDL cholesterol, and hypertension (Regufe et al 2020). Its primary underlying factor is insulin resistance, particularly that associated with obesity, which is primarily brought on by improper diets and inactivity. (Ferrannini 1995; Nsiah et al.,2015).

In 70%–80% of diabetic individuals, MetS either precedes or accompanies the diagnosis of T2DM, and it increases the occurance of CVD and untimely death by about threefold (Lee et al.,2018). Several factors influence the development of MetS, such as regional and urban-rural differences, lifestyle patterns, and socioeconomic and cultural contexts (Kaur 2014). Kerala, for instance, has a diabetes prevalence of 14.8% in the 15–64 age group and shows nearly double the cardiovascular mortality compared to the United States (Srinivasan et al.,2016).

Other risk factors or predictors of MetS include age over 40, smoking, alcohol consumption, obesity, physical inactivity, and a family history of T2DM (Ferrannini 1995). Krishnan et al., 2016 stated that Kerala has highest rates of T2DM and hypertension in India. These same results were also quoted by Sathish et al. in the year 2012.

Several studies have established a strong link between MetS and the risk of developing T2DM (Shin et al.,2013). Therefore, the treatment of MetS involves a multifactorial approach targetted at minimizing the occurrence of T2DM (Grundy et al., 2005). Unfortunately, lifestyle-related risk factors—such as obesity, substance abuse, and physical inactivity—remain challenging to address due to the rapid rise in consumption of adulterated, preservative-laden packaged foods, which are often more appealing than healthier options like green leafy vegetables (Sathish et al., 2012).

2.4 BIOCHEMICAL FACTORS IN T2DM

MetS was conceptualized on many of interrelated risk factors—such as elevated (FPG), atherogenic dyslipidemia, high blood pressure, and abdominal obesity (Simmons et al.,2010). Over time, the term "metabolic syndrome" has gained significance for

its predictive power regarding both CVD and T2DM (Lorenzo et al., 2003).

MetS presentations include elevated triglyceride levels, reduced HDL-C, central obesity, hypertension, and glucose intolerance (Alberti et al.,1998). Guidelines have been developed to manage MetS using readily available clinical markers (Huang 2009). Among these, dyslipidemia, hypertension, and dysregulated glucose metabolism are consistently highlighted. Insulin resistance (IR) and abdominal obesity, however, have drawn more attention recently as central features of the syndrome (Kassi 2011). The presence of MetS is associated with a three- to fivefold increased risk of developing T2DM, which has now become alarmingly prevalent worldwide (Balkau 2004).

Emerging research also emphasizes the biochemical role of inflammation in the pathogenesis of T2DM. Obesity-induced inflammation appears to have a major impact on insulin resistance which leads to diminished insulin secretion, and unsettling general energy balance (Saltiel and Olefsky 2017). Obesity-related inflammation is marked by the low-grade stimulation of immune system that might last for years, often throughout a lifetime (Saltiel and Olefsky 2017).
These are the significance of managing these risk factors and detecting them early in clinical practice and public health settings. (Després & Lemieux 2006).

2.5 LIPID LEVELS AND T2DM

Hypercholesterolemia is a well-established hazard factor for CVD in the general population (Peters et al., 2014). Cardiovascular disease continues to be the primary cause of morbidity and death among these people.T2DM exhibits a risk factor similar to a myocardial infarction—known as "coronary risk equivalent" (Poznyak et al.,2020).

It is important to understand that the management of T2DM is more than glycemic control. Regulation of lipid parameters and blood pressure is essential, primarily to regulate macrovascular outcomes (Geldsetzer et al.,2018). Indian populations, compared to Caucasians, have notably more macrovascular complications even when both groups show similar rates of microvascular complications (Unnikrishnan et al., 2016). Cholesterol metabolism acts as an aggregating cause in the development of the conditions linked to T2DM (Hu et al.,2022; Yousri et al., 2022).
Dyslipidemia manifests early in the course and tends to persist throughout the

progression (Wang et al.,2012). Among lipoproteins, low- density lipoprotein cholesterol (LDL-C) has long been recognised as a chief factor in the progress of atherosclerotic cardiovascular disease (ASCVD) (Festa et al 2005). However, dyslipidemia also involves abnormalities in other lipid components such as high-density lipoprotein cholesterol (HDL-C) and triglycerides (Oh et al., 2019). ASCVD is a major cause of death among diabetic individuals, and managing dyslipidemia is therefore, essential (Lee and Lee ,2023).

Dyslipidemia in type 2 diabetes is characterized by elevated triglyceride levels, reduced HDL-C concentrations, and an increased share of small, dense LDL particles. These factors that accelerate atherosclerosis in type 2 DM patients (Faselis et al., 2020). Hyperlipidemia associated with diabetes substantially increases the risk of developing arteriosclerotic vascular disease. (Rapp et al.,1989), and triglyceride levels, once underestimated, are now recognized as important contributors to vascular risk (Duran et al.,2020; Reiner 2017).

While traditional lipid management has focused on LDL-C and HDL-C, newer studies suggest that residual cardiovascular risk remains even when these markers are inside target ranges. This has led to increasing attention toward triglyceride-rich lipoproteins (TRLs), which are hallmarks of diabetic dyslipidemia and are not fully addressed by statin therapy (Raposeiras-Roubin et al. , 2021; Hagström et al., 2022; Boden et al., 2020). TRLs have also been linked to the onset of diabetes itself (Jialal & Singh 2019).

Molecular lipid studies have confirmed that plasma triglyceride values are closely related to diabetes in high-risk populations. High-fat diets increase hepatic triglyceride synthesis, reduce HDL-C, and accelerate the onset of diabetes (Rabinovich-Nikitin et al.,2019; Sokooti et al., 2021). Importantly, small dense LDL particle concentrations are now recognized as strong predictors of coronary events, irrespective of conventional risk variables (Blake et al., 2002). Besides, TG-related indicators have been related with diabetes independent of insulin resistance, underpinning the vital role of TRLs in advancement of the disease (Gong et al., 2021; Kim et al.,2021).

In T2DM, insulin resistance enhances free fatty acid release via lipolysis, increasing

hepatic secretion of VLDL particles (Hirano 2018). Conversely, type 1 diabetes, which is characterized by a deficiency of insulin, typically leads to hypertriglyceridemia through impaired triglyceride clearance rather than overproduction (Lee & Lee 2023; Wu et al.,2014).

Insulin resistance aids in the formation of small dense LDL particles early in the course of glucose dysregulation, even before overt diabetes develops (Nogueira et al., 2012). Moreover, insulin resistance increases postprandial production of chylomicrons, contributing to hyperlipidemia after meals—although the precise mechanisms remain incompletely understood (Vergès 2022; Strikić et al., 2023).

2.6 PATHOPHYSIOLOGY OF DYSLIPIDEMIA IN T2DM

2.6.1 INSULIN RESISTANCE AND LIPID METABOLISM

MS is defined as a confluence of risk factors that boost the likelihood of type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and coronary heart disease (CHD). Insulin resistance is the primary cause of MS (Reaven ,1988). Poor eating habits, lack of physical activity, obesity, and genetic factors all contribute to this issue (Galassi et al., 2006).

Metabolic syndrome significantly increases the risk of developing T2DM and cardiovascular diseases and is allied with augmented all-cause mortality (Wilson, 2005). The rising global burden of obesity, affecting over 1.9 billion individuals—including more than 50 million children under age 5—has contributed to the doubling of obesity prevalence since 1980 (Hotamisligil,2006). One of its most severe complications is type 2 diabetes (Saltiel & Olefsky ,2017). In general, MS is acknowledged as a separate risk factor for cancer, heart disease, type 2 diabetes, and premature mortality (Swinburn et al., 2011).

T2DM is characterized by persistent hyperglycemia, either fasting or postprandial (Care 2016). In 1988, it was initially identified as a part of the metabolic syndrome. (Patlak 2002). Unlike type 1 diabetes, which involves insulin deficiency, most individuals with T2DM have elevated levels of insulin in both fasting and postprandial states, unless a

beta-cell failure occurs (Reaven, 2005).

Diabetes is often called a “silent disease” due to its sneaky progression without prominent symptoms (Ning et al.,2022). The term "insulin resistance" (IR) explains why glucose levels remain elevated despite the presence of insulin.

2.6.2 ROLE OF HYPERGLYCEMIA IN LIPOPROTEIN ALTERATIONS

Metabolic syndrome was conceptualized based on a cluster of contributing factors, including elevated fasting plasma glucose (FPG), atherogenic dyslipidemia, high blood pressure, and central obesity—conditions strongly predictive of CVD and T2DM (Simmons et al., 2010; Lorenzo et al., 2003). Key features include hypertriglyceridemia, low HDL cholesterol, central(visceral) obesity, and insulin insensitivity (Alberti et al., 1998).

Recent studies emphasize the crucial role of inflammation induced by obesity, which may back insulin resistance, impaired insulin synthesis, and disturbance of energy homeostasis (Saltiel & Olefsky 2017). This inflammation is distinct because it involves a chronic, low-grade activation of the innate immune system, which can persist throughout life and impair metabolic balance.

2.6.3 IMPACT OF OBESITY ON LIPID PROFILE IN DIABETES

Subclinical inflammation and systemic inflammation are often observed in diabetic patients (Herder et al., 2013). Inflammation is also now categorized as a main mediator in the pathogenesis of T2DM (Elimam et al., 2013), and thus T2DM is regarded as a state of low-grade inflammation (Lucci et al., 2020).

Evidence increasingly supports the role of inflammatory developments in T2DM pathology (Kanmani et al., 2019). Elevated inflammatory proteins like C-reactive protein (CRP) are frequently linked to T2DM (Wang et al., 2013).

T2DM and atherosclerosis share this inflammatory foundation, with cardiovascular patients showing heightened inflammatory states (Zhao et al., 2022). The production of CRP may be stimulated by hyperglycemia, adipokines, and free fatty acids—all of which are metabolic stressors commonly seen in T2DM (Mugabo et al., 2010).

2.6.4 INTERCONNECTION OF DYSLIPIDEMIA AND CARDIOVASCULAR RISK

High cholesterol levels are a significant risk factor for cardiovascular disease even in healthy populations and has more pronounced effects in individuals with underlying metabolic disorders like T2DM (Peters et al., 2014). For the people with Type 2 diabetes, cardiovascular disease continues to be the leading cause of death and morbidity and are considered to have a coronary risk equivalent to those with previous myocardial infarction (Poznyak et al., 2020). In the Indian population, the incidence of macrovascular complications is higher than in Caucasians, although microvascular complications remain similar (Unnikrishnan et al., 2016).

Dyslipidemia is a major contributor to ASCVD. Characterized by abnormalities in LDL-C, HDL-C, and triglycerides (Oh et al., 2019). It is a leading cause of death among DM, yet dyslipidemia remains a modifiable risk factor (Lee and Lee et al., 2023). The atherogenic lipid profile typical of T2DM includes increased triglycerides, decreased HDL-C, and a predominance of small dense LDL particles, Faselis et al., 2020).

2.7 CHARACTERISTICS AND METABOLISM OF SMALL DENSE LDL (sd LDL)

2.7.1 BIOCHEMICAL PROPERTIES OF sd LDL

Although T2DM does not present with classic hematological disorders, several hematologic abnormalities have been observed in patients with the condition (Jones 1981). T2DM has been linked with alterations in coagulation systems, red blood cells (RBCs), white blood cells (WBCs), and platelets (PLTs) (Arkew et al., 2021).

Low-density lipoprotein (LDL) particles, the leading plasma lipid carriers, differ in size, density, charge, structure, and atherogenic potential (Liou and Kaptoge 2020). Recent findings suggest that it is not just the amount of LDL but also its properties that influences cardiovascular risk and atherogenesis (Rizzo et al., 2009).

Sd LDL particles are highly atherogenic and thus act as an important CV risk factor as stated earlier (Gerber et al., 2013). Therefore, these raised sd LDL levels are seen as associated to elevated triglycerides. They also show lower HDL-C levels, as

commonly seen in insulin resistance (Fan et al., 2019). When epidemiological studies were conducted, Asian Indian populations reported a higher prevalence of sd LDL (Xia et al., 2015).

2.7.2 DIFFERENCES BETWEEN sd LDL AND LARGE BUOYANT LDL (lb - LDL)

sd LDL and lb LDL differ significantly in size and densities. sd LDL particles are smaller and denser; because of this, they are more prone to oxidation. The arterial wall penetration of these smaller-size particles is also more and thereby directly correlates to contributing atherogenesis. In contrast, lb LDL particles are bigger and less dense. Because of such peculiar characteristics, they are less atherogenic. There exists a strong association between elevated sd LDL/lb LDL ratios and metabolic disorders. In the Thai population study, the ratio was strongly correlated with metabolic syndrome components, suggesting this ratio may serve as an effective marker of metabolic status (Pornpen et al., 2015).

Similarly, the sd LDL/lb LDL ratio was notably higher in pregnant women suffering from gestational diabetes (Chen et al., 2017). Moreover, in individuals with T2DM, this ratio was identified as a standalone risk factor with high predictivity for disease (Cui Wang et al., 2024).

2.7.3 OXIDATION AND GLYCATION OF sd LDL IN DIABETES

The atherogenic potential of LDL is high (Austin et al., 1990). Among them, small dense LDL particles represent a significant danger—they undergo oxidation more readily. These factors increase their chances of greater endothelial permeability, reduced receptor affinity, and enhanced interaction with vascular matrix components (Kotani et al., 2012).

Sd LDL brings several problems to the table: it lingers longer in plasma, slips past normal receptor uptake, sticks more stubbornly to the walls of arteries, binds tightly to proteoglycans, and resists oxidation less than other LDL types. All these traits make sd LDL a major driver of atherosclerosis. (Boren et al., 2020).

However, clinical measurement of sd LDL is hindered by the need for specialized equipment and time-consuming procedures (Srisawasdi et al., 2011). The predominance of sd LDL may also help explain the elevated coronary heart disease (CHD) risk in

diabetic patients with nephropathy (Mattock et al., 1992).

2.8 sd LDL AND ATHEROSCLEROSIS

2.8.1 ROLE OF sd LDL IN PLAQUE FORMATION

Small dense LDL (sd LDL) is increasingly recognized as a key contributor to atherosclerosis, especially in the initial phases of plaque formation. (Liu et al., 2004) found that individuals from familial combined hyperlipidemia families had smaller LDL particle sizes and elevated oxidized LDL (Ox-LDL) levels, significantly correlated with carotid intima-media thickness, indicating subclinical atherosclerosis.

Hirayama et al., 2012 demonstrated that sd LDL is a more substantial risk factor than total LDL-C, particularly in high-risk populations such those with metabolic syndrome and type 2 diabetes. However, the absence of standardized sd LDL separation techniques has limited its clinical utility, although newer homogeneous assays show potential for broader application. Ivanova et al., 2017 further supported sd LDL's atherogenicity, citing its susceptibility to desialylation, glycation, and oxidation, which amplify its inflammatory effects within the vascular system.

2.8.2 ARTERIAL WALL PENETRATION AND OXIDATIVE STRESS

Beyond plaque initiation, sd LDL has a greater capacity to enter the arterial wall and undergo oxidation, triggering chronic vascular inflammation. (Akram et al., 2025) emphasized that reactive oxygen species induce lipid peroxidation, transforming sd LDL into highly reactive forms that interact with endothelial cells and promote atherogenesis. (Tan et al., 1999) found that type 2 diabetes patients had elevated levels of sd LDL (LDL-III) with higher oxidation susceptibility. This oxidative stress was linked to impaired vasodilation, suggesting that sd LDL has a direct influence on endothelial dysfunction and vascular complications in DM.

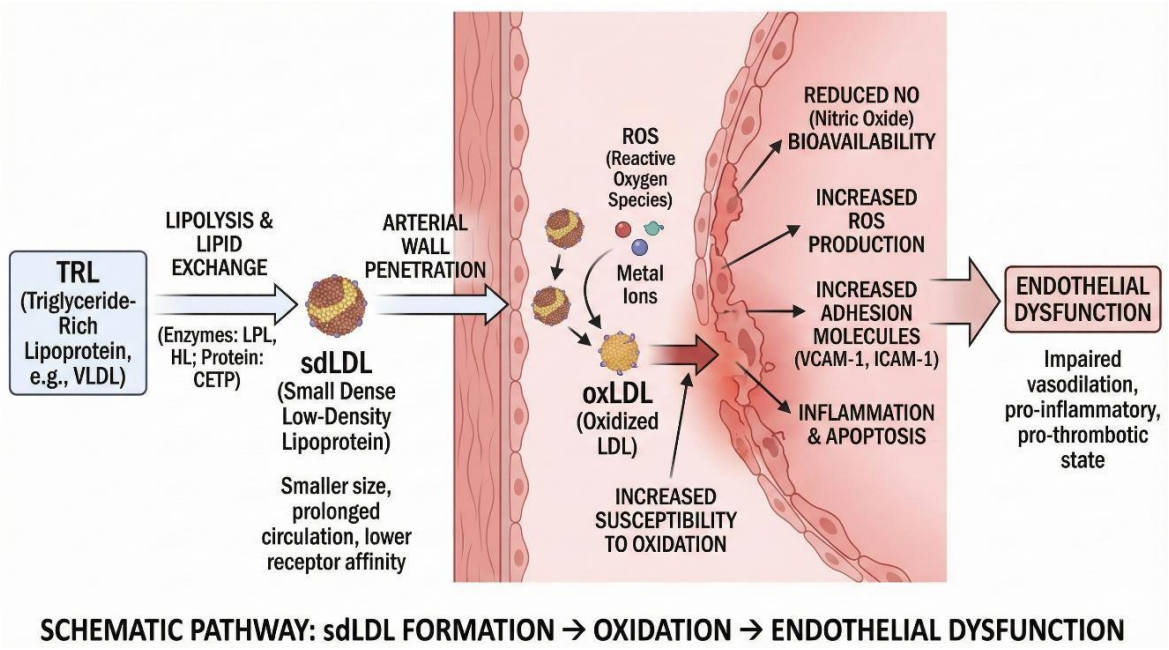


Figure 2.1: Overview of Small Dense LDL Formation, Oxidation, and Endothelial Effects

2.9 sd LDL AS A BIOMARKER FOR CARDIOVASCULAR RISK IN T2DM

2.9.1 CORONARY ARTERY DISEASE (CAD) AND sd LDL

(Amuti et al., 2025) concluded that elevated sd LDL levels were notably related with the plaque development of the coronary arteries in a progressive pattern, especially in diabetic patients with stable CAD, indicating it is an independent contributing factor for atheroma growth. (Farooq et al., 2025) supported this by showing a strong association between sd LDL and coronary artery calcium development, particularly during early atherosclerotic stages. (Zhang and He et al., 2021) observed that among over 6000 ACS patients undergoing PCI, those in the highest sd LDL quartile had nearly double the risk of major adverse cardiovascular events during an 18-month follow-up, independent of LDL-C levels or diabetes status, further reinforcing the predictive value of cardiovascular risk assessment.

2.9.2 RELATIONSHIP BETWEEN sd LDL AND INSULIN RESISTANCE

Yin et al., 2024 confirmed that a higher Atherogenic Index of Plasma (AIP), reflecting elevated sd LDL levels, was strongly linked with increased IR and a higher chance of developing type 2 diabetes, suggesting that sd LDL could contribute to early metabolic derangements. Maithili Karpaga (Selvi et al., 2021) explained the Triglyceride Glucose (TyG) index. This states that high triglyceride levels showed a distinct link with HbA1c

and HOMA-IR. This explains the fact that sd LDL can help to identify insulin resistance in people with diabetes. The study also suggests that sd LDL might be indirectly involved in poor glucose control and could be responsible for both metabolic and cardiac-related problems in T2DM.

2.9.3 CLINICAL VALUE OF sd LDL IN RISK STRATIFICATION

Long term inflammatory process of the body has a crucial role in the development of atherosclerotic diseases, and sd LDL has been implicated in exacerbating this process. Shitara et al., 2019 pointed out that inflammation has a substantial part in causing coronary artery disease (CAD). Esser et al., 2015 found that high CRP levels can predict CVD in people with DM. Ridker et al., 2003 also detailed comparable outcomes in conjugation with other studies and stated that hs-CRP is a strong marker for future heart issues. These results were not accepted by Khera et al., 2005, it differed by stating that hs-CRP levels can change based on age, gender, and obesity. The literature suggests that looking at sd LDL along with hs-CRP could give a better idea of CVD risk in people with T2DM.

2.10 ADVANCEMENTS IN sd LDL QUANTIFICATION

Recent progress in quantifying sd LDL-C has enhanced its clinical relevance as a biomarker for atherosclerotic cardiovascular disease (AS-CVD). Kotani et al., 2021 highlighted sd LDL-C as main contributor to residual CV risk. Homogeneous assay is now a newly developed method that allows rapid and simplified sd LDL-C measurement. Moreover, an increasing assessment of such parameters in clinical settings is observed. In addition to this, an estimation equation derived from standard lipid profiles has shown an even stronger correlation with ASCVD than directly measured sd LDL-C, making it a promising tool for routine use. Still, the lack of a universal gold standard and differences in testing methods make it hard to interpret results consistently, highlighting the need for better standardization and validation.

2.11 ROLE OF OTHER BIOMARKERS IN CARDIOVASCULAR RISK PREDICTION

2.11.1 RED CELL DISTRIBUTION WIDTH (RDW) AND ITS ASSOCIATION WITH CVD

The information linking RDW to an increased risk of mortality has been addressed since the early reports. One of these studies was conducted by Pickup et al., 1997, which assessed the utility of RDW as a follow up marker in cardiac failure patients. RDW is a basic parameter as it is derived from the standard complete blood count (CBC). It is a routine examination and a measure of anisocytosis, the heterogeneity in the size of RBC's in the circulation (Evans and Jehle et al., 1991).

RDW is reported as a percentage and is calculated by dividing the standard deviation of the volume of erythrocytes by the mean corpuscular volume (MCV), then multiplying the result by 100. (Babker et al., 2024). The resulting value is reflected by an automated hematology analyzer. It provides the final inference as a reflection of the range of the red cell size. It has been demonstrated that the RDW can predict overall CV mortality in a variety of high-risk populations as well as the general population on its own (Zalawadiya et al., 2011). Higher RDW levels track closely with more cardiovascular problems in people with heart failure, those recovering from coronary surgeries, and patients with coronary artery disease. (Azul et al 2020). It also is a strong predictor of mortality in conditions such as obesity, malignancies, and chronic kidney diseases (Ridker et al., 1998). Beyond its usual role in diagnosing blood disorders, RDW stands out as a strong predictor of negative cardiovascular outcomes in the general population. (Xanthopoulos et al., 2021). As previously stated, RDW is an independent predictive marker for various health conditions. Thus, its reliability to predict DM is questioned (Montagnana et al., 2012). But research keeps linking high RDW to worse outcomes in coronary artery disease, metabolic syndrome, and heart failure (Patel et al., 2010; Sánchez-Chaparro et al., 2010)

2.11.2 .hs-CRP AND T2DM

Type 2 diabetic patients have been identified to exhibit subclinical inflammation along with nearly all markers of systemic inflammation (Herder et al., 2013). According to current research, inflammation may have a significant role in the onset of this illness (Elimam et al., 2013). According to Luci et al. (2020), type 2 diabetes is in fact regarded

as a condition of low-grade inflammation. More recently, evidence shows that chronic inflammation plays a major role in how atherosclerotic coronary artery disease develops (Shitara et al., 2019). The critical role that inflammation plays in T2DM diseases is supported by mounting evidence (Kanmani et al., 2019). The pathophysiology of type 2 diabetes is associated with low-grade inflammation, which is indicated by increased quantities of inflammatory proteins, like CRP (Wang et al., 2013).

Increased circulating levels of inflammatory markers, such as CRP or hs-CRP and inflammatory cytokines, indicate a systemic and subclinical process (Herder et al., 2013). Because the liver produces CRP as an acute-phase protein, it is a highly responsive indicator of systemic inflammation (Fordetal.,2003). Elevated hs-CRP indicates chronic low-grade inflammation, which may be a contributing factor to the development and presentation of type 2 diabetes (T2DM) (Pradhan et al., 2001). The mechanics are still unclear, though (Mahajan et al. 2009). The common biomarker generated in the liver, CRP, is controlled by adipocyte-derived proinflammatory cytokines, including IL-6 and TNF-α. (Sproston and Ashworth et al., 2018). AS are multifactorial conditions and share a common inflammatory basis. Furthermore, CVD patients exhibit a more prominent inflammatory state (Zhao et al., 2022). Low-grade inflammation has been detected using hs-CRP (Shitara et al., 2019).

But according to Khera et al. (2005), hs-CRP levels differ amongst groups and are impacted by age, gender, and obesity. Several studies report that higher CRP levels are positively associated with a greater vulnerability to contracting type 2 diabetes. (Han et al., 2002; van Woudenbergh et al., 2011). Although the prevalence of type 2 diabetes is 11.6% in urban populations worldwide, some studies do not find the connection after considering various characteristics that support to the ailment, such as obesity and hyperinsulinemia (Thorand et al., 2003).

Besides, Asian Indians are known to have a greater likelihood of metabolic syndrome, cardiovascular disease, and type 2 diabetes (Ramachandran et al., 2008). While high levels of hs-CRP have been found in Indian adolescents and adult expatriates living in India, there is little information available on adult Indians living in India (Mohan et al., 2005; Mahajan et al., 2009).

2.11.3 HbA1c LEVELS IN T2DM

Red blood cells live about three months. Upon measuring glycated hemoglobin (HbA1c) in the blood, you get an overview of a person's average blood glucose over that entire time (Khan et al., 2011). Studies show that long-term swings in blood sugar point to more than a hard day—they're linked to cardiovascular autonomic neuropathy, macrovascular complications, diabetic kidney disease, microvascular problems, and even higher overall mortality in people with diabetes (Wan et al., 2016).

The American Diabetes Association (ADA) proposes Glycated hemoglobin (HbA1c) test to detect diabetes (Vijayakumar et al., 2017). There aren't enough longitudinal research examining the connection between childhood HbA1c and the risk of diabetes (American Diabetes Association, 2010). A1c is now suggested as part of standard care for detecting and managing diabetes, with a focus on type 2 diabetes. (WHO 2012).

Glycemic variability shows up in two main forms: short-term and long-term. Long-term variability tracks how much a person's blood sugar shifts over months and years, usually measured by the changes in their glycated hemoglobin from one clinical visit to another (Cardoso et al., 2018). Short-term variability, on the other hand, captures the ups and downs within or between days, and continuous glucose monitoring picks this up best. More researchers now recognize the value of using HbA1c to diagnose diabetes instead of relying on plasma glucose alone (Bonora & Tuomilehto et al., 2011).

People with prediabetes who have HbA1c levels between 5.7% and 6.4% are more likely to develop diabetes mellitus (DM) (Hare et al., 2012).Strict glycemic control and decreased HbA1c levels will bringdown the chances of diabetic complications; at HbA1c<7%, the prevalence of diabetic retinopathy is reduced by 76%, diabetic nephropathy by 54%, peripheral neuropathy by 60%, and the likelihood of cardiovascular disease by 35% (Nathan et al., 2014). The 2011 WHO Consultation on HbA1c emphasizes the need for studies to determine precise HbA1c cut lines for identifying diabetes and prediabetes in a variety of ethnic groups (WHO 2011).

According to current research, variability in HbA1C readings probably even a more

true indicator than the average HbA1C in type 2 diabetes and is an independent risk factor for complications in type 2 DM patients (Prentice et al., 2016).When evaluating the glycemic spectrum for insulin resistance, the HbA1c readings have shown a little overlap in values among standard glucose tolerance in individuals with type 2 diabetes (Huisman et al., 1958). HbA1c can help predict insulin resistance and serves as a reliable biomarker. (Sherwani et al., 2016). Because of differences in hemoglobin structure, genetics, and glucose metabolism, different ethnic groups have different HbA1c cut-point levels (Nair et al., 2011).

Numerous studies conducted in India and globally, along with a systematic review, have reported inconsistent point cut-point levels for prediabetes (IFG) and diabetes (Rajput et al., 2015). On the other hand, lowering HbA1c levels is associated with a higher risk of hypoglycemia and a higher risk of hypoglycemia prevalence among patients with type 1 and type 2 diabetes (Yu et al., 2016).

In the absence of circumstances that might distort the findings, HbA1c measurement should adhere to international standards (d'Emden et al., 2015). Changes in hemoglobin structure can impact glycation processes. In central India, where hemoglobinopathies are common, perhaps leading to inaccurate HbA1c readings (Gaidhane et al., 2024). The HbA1c range for non-diabetic people is typically 4.0% to 5.6% (ADA 2014). According to Bozkaya et al. (2010), people with prediabetes often have HbA1c levels between 5.7% and 6.4%, whereas people with diabetes have HbA1c levels 6.4% or above. Maintaining a balanced diet and exercise routine, as well as lowering HbA1c readings below 7.0%, are advised for people with diabetes because the disease is linked to a number of comorbidities (Sherwani et al., 2016).

2.11.4 RED CELL DISTRIBUTION WIDTH (RDW) AND T2DM

Even though RDW has been customarily employed in the examination of the etiology of hematological diseases particularly anemia, increasing evidences link raised RDW with poor outcomes in the general population in individuals with coronary artery disease, metabolic syndrome, and heart failure (Patel et al.,2010; Sánchez-Chaparro et al., 2010).

Plenty of research links high RDW levels to more cases of heart disease and increased

mortality among people with heart failure, coronary artery disease, and those undergoing percutaneous cardiac procedures (Azul et al. Diabetes mellitus pushes this risk even higher, speeding up the progression of atherosclerosis and making cardiovascular complications more likely (Babker et al., 2024)

Because type 2 diabetes is associated with changes in blood cell structure, metabolism, and function, red cell distribution width (RDW) has been examined as a marker for identifying the disease and other related conditions (Arkew et al.).(2021). Other hematologic measures, including MCV, hemoglobin, and hematocrit, did not affect the association. (Stratmann & Tschoepe, 2011). One widespread comorbidity and independent associated risk factor for heart failure is diabetes mellitus (DM) (Stratton et al., 2000). In clinical practice, RDW was first employed in conjunction with the mean corpuscular volume (MCV) to distinguish between anemia's causes (Montagnana et al., 2012). It has been suggested that inflammation has a role in diabetes (Pickup et al., 1997). Acute phase reactant levels were shown to be higher in patients with type 2 diabetes who did not have atherosclerosis than in healthy individuals (Nada, 2015). Numerous things can contribute to these changes, including high reactive oxygen species (ROS) levels, which ultimately result in oxidative stress and RBC malfunction (Arkew et al., 2021).

Individuals with type 2 diabetes have been reported to have changed white blood cell parameters (Allahyani et al., 2023). Chances of heart failure increases by 8% for every 1% increase in HbA1c (Braunstein et al., 2003). Furthermore, the prevalence of DM in HF patients ranges from 19 to 31%, and diabetic individuals have an approximately two fold increased risk of HF (Henkel et al., 2008). Nonetheless, there has been inconsistency in the findings regarding altered hematological markers in T2DM patients (Arkew et al., 2021). Amplified oxidative stress and arterial inflammation are symbols of diabetes mellitus (Azul et al., 2020).

2.12 HIGH-SENSITIVITY C-REACTIVE PROTEIN (hs-CRP) AND INFLAMMATION

The general and subclinical inflammatory courses are often marked by elevated levels of inflammatory parameters in circulation, including C-reactive protein (CRP) or high sensitivity CRP (hs-CRP) and inflammatory cytokines (Herder et al., 2013). C- reactive

protein, an acute-phase reactant produced by the liver, is an extremely sensitive marker of systemic inflammation (Ford, 2003).

It is apparent that chronic low-grade inflammation, as demonstrated by elevated hs-CRP, might potentially be a cause underlying the etiology and manifestation of type 2 diabetes (Pradhan et al., 2001). Nevertheless, the precise mechanisms remain unclear (Mahajan et al., 2009).

A highly sensitive assay is used to test hs-CRP. The traditional acute-phase protein is CRP (Elimam et al., 2019). Plasma levels of hs-CRP offer a sensitive indicator of elevated inflammatory activity in the artery wall. The liver makes CRP, a pentameric protein, when the body faces inflammation (Pfützner & Forst 2006).A few studies have found a link between cardiovascular events and high hs-CRP in individuals with type 2 diabetes (Lucci et al., 2020; Świątkiewicz et al., 2021).

Research also shows that higher CRP levels strongly link to an increased risk of developing type 2 diabetes (Han et al., 2002; van Woudenbergh et al., 2011).However, despite controlling for a number of T2DM- causing variables, such as obesity and hyperinsulinemia, some studies do not find this connection (Thorand et al., 2003).

Additionally, Asian Indians are known to have a higher risk of metabolic syndrome, cardiovascular disease, and type 2 diabetes (Ramachandran et al., 2008). While high levels of hs-CRP have been found in Indian adolescents and adult expatriates living in India, there is little information available on adult Indians living in India (Mohan et al., 2005; Mahajan et al., 2009).

2.13 LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 (Lp-PLA2) AND ATHEROGENESIS

Atherosclerosis, retinopathy, peripheral artery disorders, cerebrovascular diseases (strokes), and aneurysms are among the many vascular diseases that are currently affecting a growing number of individuals (Houser et al., 2012). Phospholipase A2 (PLA2) belongs to the lipolytic group of enzymes that hydrolyze the ester bond at the sn-2 location of phospholipids (Murakami &Kudo ,2002).

PLA2s produce lysophospholipids (LPLs) and free fatty acids when the phospholipids are hydrolyzed (Khan et al., 2023). Arachidonic acid (AA) and oleic acid (OA), two

types of free fatty acids, are vital energy sources (Murakami & Kudo 2002). The phospholipase A2 superfamily, sometimes referred to as Group VIIA PLA2, includes human lipoprotein-associated phospholipase A2 (Lp- PLA2), also called plasma platelet-activating factor acetylhydrolase (Dennis et al., 2011).

A number of reviews about the structure, genetic factors, physiological roles, disease consequences, and particular inhibitors of Lp-PLA2 have been published in the last ten years (Sofogianni et al., 2018). Furthermore, Lp-PLA2 was studied as a member of the PAF-Ahs or PLA2 superfamily (Liu et al., 2016). Early research on Lp-PLA2 centered on determining if its activity affected the autoxidation and degradation of low-density lipoprotein (LDL), with discussions beginning in the 1980s.(Steinbrecher et al.,1984; Wang et al., 2023).

The West of Scotland Coronary Prevention Study found the association of Lp-PLA2 with CV condition and consequences, independent of traditional risk factors such as LDL-C (Packard et al., 2000). Moreover, COXs, LOXs, and CYP450 enzymes transform AA into eicosanoids, which act as key players in inflammation and cancer development (Peng et al). Researchers later linked Lp-PLA2 to cardiovascular disease (Wang et al., 2023).

Brilakis et al. (2005) found a correlation between mean Lp-PLA2 levels and fibrinogen ,total cholesterol, HDL, LDL, and creatinine. In addition to CRP, Lp-PLA2 is also acknowledged as an independent indicator of CAD (Wang et al., 2023). Lp-PLA2 is predominantly linked with lipoproteins in human blood, where ~70% binds to LDL and ~30% binds to HDL (Khan et al., 2023). Initially, it was shown to be an enzyme that hydrolyzes the acetyl group at the sn-2 position to create lyso-PAF and acetate, thereby inactivating platelet-activating factor (PAF) (Tjoelker et al., 1995). In contrast to traditional enzymes that are soluble and work on their exact water-soluble substrates, phospholipase A2 enzymes are amphiphilic (Lam et al., 2022). The first 17 residues of the secreted enzyme Lp-PLA2 (Met1 to Ala17) most likely make up a hydrophobic signal peptide (Tjoelker et al., 1995).

According to Burke and Dennis (2009), the endogenous Lp-PLA2 protein has a heterogeneous N-terminus that comprises Ser35, Ile42, or Lys55, and a C-terminus that

contains Asn441 and two putative N-linked glycosylation sites at Asn423 and Asn433. In the aquatic environment, PLA2 enzymes relate with phospholipid assemblies to produce supramolecular structures such liposomes, micelles, and vesicles (Dennis et al., 2011).

These enzymes hydrolyze phospholipids only when docked at the water/lipid interface via interfacial activation (Khan et al., 2023). Additional research revealed that Lp-PLA2 has similar activity toward F2-isoprostanes esterified phospholipids, which contain oxidized fatty acyl chains at the sn-2 position, oxidized PCs (oxPCs), and phosphatidylcholines (PCs) with short acyl chains at the sn-2 position (Stafforini et al., 2006; Davis et al., 2008). Lp-PLA2 is a member of the PLA2 superfamily's Group VII, which is made up of 16 distinct groups and six kinds (Dennis et al., 2011).

Macrophages primarily secrete this enzyme, which circulates in the blood as a complex with LDL and HDL (Tellis et al., 2014). Originally, Because Lp-PLA2 hydrolyzes platelet-activating factor (PAF), it has been called plasma platelet-activating factor acetylhydrolase (pPAF-AH) (Huang et al., 2020). In humans, Lp-PLA2 serves two main purposes: (1) Antioxidant Function: T cells, mast cells, and macrophages within the walls of the arteries release Lp-PLA2 and exists in association with LDL.

Under oxidative stress, Lp- PLA2 hydrolyzes oxidized LDL (Wang et al., 2023). (2) Atherogenic Function – Lp- PLA2 expression increases significantly in macrophages during atherosclerotic lesion formation, hydrolyzing oxidized phospholipids in LDL particles and contributing to plaque instability (Elstad et al.,1989; Noto et al., 2003). Lp-PLA2 is strongly associated with metabolic diseases, CVD, and T2DM, correlating with metabolic syndrome (MetS) (Hatoum et al., 2010).

Since diabetic patients are more prone to CVD (De Stefano et al., 2019Higher Lp-PLA2 levels are associated with an increased risk of cardiovascular disease, according to various epidemiological studies, such as the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS) (Hatoum et al., 2010). Lp-PLA2 is currently acknowledged as a significant cardiovascular biomarker because of its pro-atherogenic and inflammatory characteristics (Cojocaru et al., 2010; De Stefano et al.,

2019).

Regardless of standard coronary heart disease (CHD) risk factors, elevated Lp-PLA2 levels in older persons predict future CHD occurrences (Daniels et al., 2008). While cytosolic calcium-dependent PLA2 (cPLA2) and calcium-independent PLA2 (iPLA2) contribute to inflammation through immune cells, prior research has shown that Lp-PLA2 directly enhances arterial inflammation (Toth et al 2010). Lp-PLA2 is modulated in vascular diseases, obesity, and inflammation, as indicated by recent research (Kinney et al., 2011).

Lp-PLA2 has been authorized by the US FDA as a diagnostic biomarker for the risk of stroke and coronary heart disease (Saenger et al., 2010; Cao et al., 2013; Lp-PLA2 Studies Collaboration 2010).

OBJECTIVES OF THE STUDY

- To assess the relation of sd LDL to hs-CRP, RDW and Lp-PLA2 in Type 2 DM.
- To compare the levels of sd LDL in both diabetic and non-diabetic groups.
- To compare the sd LDL induced inflammatory response of both diabetic and non-diabetic population**.**

CHAPTER-3
MATERIALS AND METHODS

.

3.1 RESEARCH DESIGN AND APPROACH

The study was conducted in both rural and urban regions of Kerala over a period from November 2020 to August 2022.

A well-structured and pre-validated proforma was utilized to collect detailed information from each participant. This included demographic data, clinical history, and relevant biochemical parameters. Anthropometric measurements such as weight and height were recorded for each subject in order to estimate Body Mass Index (BMI) and determine obesity status.

Prior to initiation, ethical clearance was acquired from the institutional ethics committee, and each participant's informed written consent was obtained, in adherence with morally sound research standards.

3.2 STUDY SETTING

The study was conducted at Believers Church Medical College and Hospital, located in Thiruvalla, Kerala, a tertiary care centre that serves both rural and urban populations. The hospital offered the perfect environment for the recruitment and follow-up of participants, confirming approachability to a diverse population base and the accessibility of required laboratory and diagnostic facilities for the meticulous collection of data.

3.3 SAMPLE SIZE

A total of 211 individuals, aged between 45 and 65 years, were recruited for the study. The study population included both male and female participants, ensuring gender representation. Subjects were selected based on predefined criteria for inclusion and exclusion to preserve the uniformity and importance of the study sample.

Participants were categorized into appropriate study groups based on their glycemic status and other metabolic parameters, in accordance with standard diagnostic guidelines. The chosen sample size was considered adequate to provide statistically significant insights into the relationship.

3.4 SELECTION CRITERIA

3.4.1 CRITERIA FOR INCLUSION

- Willing to participate in the study.
- Non-smokers and non-alcoholics.
- No history of cardiovascular disease, liver disease, renal disease, anemia and no recent infection, or inflammation
- Not on anti-inflammatory, lipid-lowering, or any drugs that might affect biochemical measurements

3.4.2 CRITERIA FOR EXCLUSION

Participants will be excluded from the study if they meet any of the following conditions:

- Unwillingness to participate – Individuals who do not provide informed consent.
- Lifestyle factors – Current or past history of smoking or alcoholism
- Medical conditions – Presence of cardiovascular disease, liver disease, renal disease, recent infections, or any acute/chronic inflammatory disorders.
- Medication use – Current use of anti-inflammatory agents, lipid-lowering drugs, or any medications likely to interfere with biochemical measurements.
- Other factors – Any condition or circumstance deemed by the investigator to potentially affect participation, data quality, or study outcomes.

3.5 STUDY GROUPS

Participants were divided into four major groups:

• Group I (Control subjects): MetS and Non-DM individuals recruited randomly from routine laboratory analysis, with no diagnosis of DM or CV disease.

• Group II: Subjects with Metabolic Syndrome but without Overt Diabetes.

•Group III: DM patients without Hypercholesterolemia.

• Group IV: DM patients with Hypercholesterolemia.

3.6 DATA COLLECTION

A comprehensive and structured data collection process was followed for all enrolled participants. The evaluation included subjective and objective assessments to capture relevant clinical, biochemical, and anthropometric parameters. The following components were systematically recorded:

• Demographic Data: Age, sex, height, weight, waist circumference, and other relevant sociodemographic variables.

• Family History: Information regarding any family history of DM, HTN, dyslipidemia, or CV disease was documented.

• Medical H/O and Current Medications: Participants were interviewed regarding past and present illnesses, as well as any medications currently being taken.

• Routine Laboratory Investigations: Blood samples were collected to evaluate fasting plasma glucose, postprandial glucose, lipid profile, and glycated hemoglobin (HbA1c).

• Blood Pressure Measurement: Calibrated sphygmomanometer following standardized protocols.

• Body Mass Index (BMI) Calculation:Body Weight of the subject in kilograms divided by the square of their heights in meters to assess the obesity status.

Based on the collected laboratory findings and anthropometric measurements, participants were categorized into appropriate metabolic subgroups. The classification of MetS and Hypercholesterolemia was performed according to the National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATP III) guidelines. These criteria helped in recognizing persons at increased cardiovascular and metabolic risk.

The diagnosis of DM was made in accordance with the ADA 2019 guidelines, which define diabetes as:

- FPG ≥126 mg/dL in two different samples and/or
- 2-hour post-glucose load or postprandial glucose ≥200 mg/dL in two different and/or
- FPG ≥126 mg/dL and PPBG ≥ 200 mg/dL in the same day
- HbA1c value of ≥6.5%

All measurements were taken by trained healthcare personnel to minimize observer bias, and standardized procedures were followed to ensure the accuracy and reproducibility of results.

3.7 BIOCHEMICAL ASSAY KITS AND INSTRUMENTATION

3.7.1 sd LDL ASSAY KIT AND INSTRUMENTATION

The quantitative estimation of sd LDL-C was carried out by the sLDL-EX "SEIKEN" kit. The assay is based on an enzymatic colorimetric endpoint method, suitable for determining sd LDL-C concentrations in human serum or plasma. The automated biochemistry Analyzer by Sysmex (BX3010) was employed to carry out the assay.

The system was calibrated using Randox sd LDL Calibrators (Cat. No. CH 5050), and internal quality control was ensured using Randox sd LDL Control Levels 1, 2, and 3 (Cat. Nos. LE 5013, LE 5014, LE 5015 respectively). Daily QC was performed as per manufacturer recommendations.

Sample Handling:

- Specimen Type: Human serum
- Collection Time: Morning fasting samples were preferred
- Processing: Samples were centrifuged after complete clotting. In cases using tubes with clot activators, recommended blood volumes were strictly followed to avoid dilution errors.
- Storage: Separated samples were refrigerated at 2–8°C for up to 3 days or stored at -80°C for long-term preservation. Freeze-thaw cycles were limited to a maximum of three.

Reagents:

R1 (19.8 mL) and R2 (8.6 mL) were ready-to-use reagents and remained stable for 28 days when stored at 2–8°C after opening.

Assay Specifications:

Sensitivity - 4 mg/dL
Linearity -100 mg/dL

Precision (CV) - 3.8 %
Correlation with Ultracentrifugation method- (r=0.91)

Quality Control

Randox sd LDL Control level 1 Cat :SKU: LE5013

Instrument Parameters:

Specific analyzer settings (including sample volume, reagent volume, wavelengths, OD limits, dynamic range, calibration method, and QC ranges) were configured as per the kit insert. A dual-wavelength measurement (typically at 600 nm and 700 nm) was used. The method followed was an endpoint with a positive reaction slope, and calibration was typically of type AB, based on the formula Y = AX + B. Dynamic ranges and reagent OD limits were set between -0.1 to 2.0, depending on the analyzer model.

Calibration was performed when a new reagent lot was introduced when results deviated from QC ranges, and according to laboratory quality assurance protocols.

Quality control measures included verifying OD ranges, monitoring reaction slope and temperature, checking for contamination and ensuring equipment calibration, and following manufacturer instructions for panic values and repeat run decision levels when applicable.

3.7.2 HIGH SENSITIVITY C-REACTIVE PROTEIN (hs-CRP) ASSAY

Principle

The assay is based on a latex-enhanced turbidimetric in-vitro immunoassay. CRP in the serum sample binds to anti-CRP antibodies coated on latex particles, causing agglutination.

Reagent Composition

The kit contains prefilled cartridges with the following reagents: Reagent R1 (Well No. 3) – glycine buffer solution, and Reagent R2 (Well No. 4) – latex suspension containing anti-CRP rabbit polyclonal antibodies.

Storage and Stability

Reagents are provided ready-to-use in sealed cartridges and must to be kept between 2 and 8°C, protected from light. Do not freeze. Discard any cartridges showing turbidity or precipitation.

Precautions

Use sterile and dry pipette tips during handling. Ensure reagents are not exposed to light and are before usage, allowed to come to room temperature.

Avoid introducing air bubbles and do not reuse samples. Before loading, wipe the exterior of the cartridge cell to maintain cleanliness and accuracy.

Sample Type

Fresh serum (free of hemolysis).

Interferences

Hemoglobin up to 0.5 g/dL, bilirubin up to 0.03 g/dL, intralipid up to 0.5 g/dL, and rheumatoid factor up to 500 IU/mL did not show any discernible interference.

Test Procedure

Insert the smart card containing calibration data, then load the cartridge and pipette 80 µL of serum into Well No. 6. The analyzer automatically detects the cartridge and runs the assay. Results are displayed and printed upon completion of the analysis.

Reference Range

Less than 1 mg/L indicated low cardiovascular risk, 1.0–2.9 mg/L suggested intermediate risk, and values greater than 3 mg/L were considered high cardiovascular risk.

Performance Characteristics

- Linearity: Up to 10 mg/L

- Sensitivity: 0.15 mg/L
- Precision:
    - Intra-run CV: Sample 1 – 1.38%; Sample 2 – 2.14%
    - Inter-run CV: Sample 1 – 2.84%; Sample 2 – 1.36%
- Accuracy: Measured mean value for Control Level 1 – 5.15 mg/L

Calibration

Preloaded in smart card; no external calibration required unless card expires.

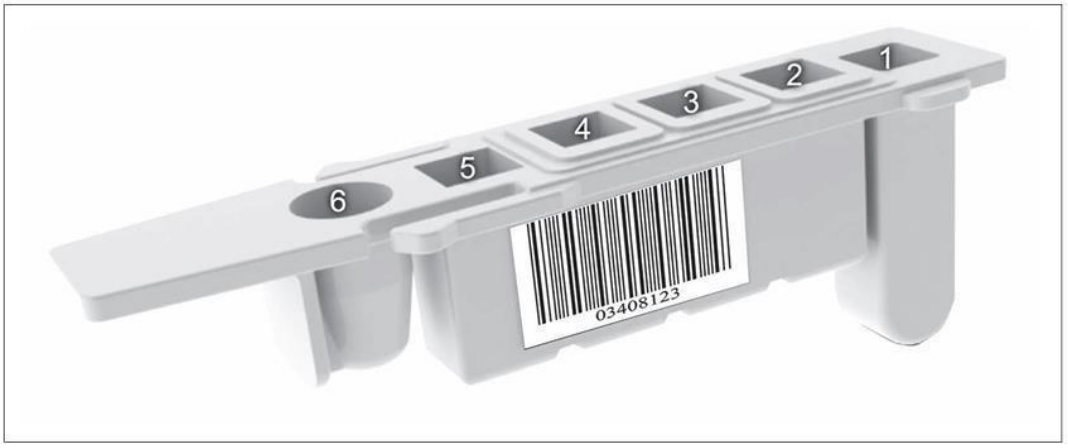


Figure 3.1: hs-CRP Cartridge Image

3.7.3 HBA1c ASSAY

The Afinion™ HbA1c assay is a point-of-care, rapid diagnostic test designed for the quantitative determination of HbA1c levels in human blood. The test uses a small 1.5 µL capillary or venous whole blood sample and provides results within 3 minutes using the Afinion™ 2 Analyzer.

The system utilizes boronate affinity chromatography to measure the proportion of glycated hemoglobin, expressed as a percentage of total hemoglobin. The test is NGSP and IFCC certified and CLIA waived, ensuring both reliability and ease of use in outpatient or clinic settings.

Procedure:

The Afinion™ HbA1c test is designed for quick and convenient use at the point-of-care. The entire process is completed in 3 simple steps:

1. Sample Collection: Collect a capillary or venous whole blood sample using the integrated sampling device.

2. Sample Loading: Insert the sampling device back into the test cartridge.

3. Analysis: After placing the cartridge and closing the lid. The analyzer automatically detects the cartridge and initiates processing.

Performance Specifications:

The Afinion™ HbA1c assay offers a measuring range of 4% to 15% and supports both capillary and venous whole blood samples, requiring only 1.5 µL. Results are available within 3 minutes. For up to three months, the test components remain stable at ambient temperature. No interference is observed from common hemoglobin variants. Ready-to-use dual-level controls are provided with the Afinion™ HbA1c

Analyzer Used:

The Afinion™ 2 Analyzer is a compact device used to process the HbA1c test cartridges. It offers rapid, lab-accurate results at the point-of-care, making it ideal for physician clinics, OPDs, and health centers.

Performance Characteristics

- Linearity: Up to 15 %
- Sensitivity: 4.0 %
- Precision: 1.37 % with the mean of 6.0
- Control used : AFINION™ HbA1c CONTROL KIT 1116975

Figure 3.2: Afinion™ HbA1c Test

3.7.4 ESTIMATION OF RDW

Sample Collection

2–3 mL of venous blood Is collected and transferred in an EDTA anticoagulant tube to prevent clotting. It is then gently mixed to avoid hemolysis. Load the sample into an automated hematology analyzer. The analyzer calculates RDW as part of the Complete Blood Count (CBC) panel.

Measurement Principle

RDW is determined based on the extent of variation in size of red blood cells. The analyzer uses either impedance or optical methods to measure cell volume.

Instrumentation Used

The Yumizen H500 automated hematology analyzers are capable of performing complete blood count (CBC) and leukocyte 5-part differential (DIFF) tests by Horiba ABX SAS. It Provide the results like WBC, NEU# & NEU%, LYM# & LYM%, MON# & MON%, EOS# & EOS%, BAS# & BAS %, LIC# & LIC%, RBC, HGB,

HCT, MCV, MCH, MCHC, RDW-CV, RDW-SD, PLT, MPV, PCT, PDW, P-LCC, P-LCR**.**

Calculation

RDW is expressed as

RDW-CV (%) or RDW-SD (fL).

▪ RDW-CV = (Standard deviation of MCV ÷ Mean Cell Volume) × 100

▪ RDW-SD = Direct measurement of width (in fL) at 20% cell height in histogram.

Performance Characteristics

- Linearity: Not Specified/ Applicable
- Sensitivity: Not Specified/Applicable
- Precision: 0.67 % with the mean of 11.6
- Control used :ABX Difftrol (2N)-Cat No 2062203

Result Interpretation

Normal RDW-CV range: approximately 11.5–14.5%. Elevated RDW indicates higher degree of variation in red cell size (anisocytosis), which is a common finding in anemia, nutrient deficits, or in chronic diseases.

3.7.5 ESTIMATION OF LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 (Lp-PLA2)

Platelet-activating factor acetylhydrolase which is popularly termed as Lp-PLA2 was quantitatively estimated using a sandwich chemiluminescence immunoassay (CLIA) provided by the MAGLUMI® kit (SNIBE, China). The assay was performed on the MAGLUMI series of fully-automated chemiluminescence immunoassay analyzers (MAGLUMI X3).

Principle of the Test

This two-site sandwich immunoassay mixes patient serum with buffer and magnetic beads coated with anti-Lp-PLA2 antibodies. A second ABEI-labeled antibody is added, forming an immunocomplex. After magnetic separation and washing, a chemiluminescent reaction occurs. The light emitted (in RLUs) is directly proportional to the Lp-PLA2 level.

Specimen Collection

Approximately 2–3 mL of venous blood was collected under aseptic precautions in a plain (non-additive) vacutainer. Serum was separated after complete clot formation and centrifugation. Hemolyzed, lipemic, or contaminated samples were excluded.

Sample Volume and Storage

A minimum of 20 µL of serum was required for each assay. Serum samples were either analyzed immediately or stored at 2–8°C for up to 72 hours. For longer durations, samples were stored at –20°C. All stored samples were brought to room temperature and vortexed before analysis.

Calibration and Quality Control

Calibration was done using a 2-point calibration system with a master curve stored via an RFID chip. Internal controls were run in parallel to validate each assay run. Quality control procedures followed the manufacturer's instructions and internal laboratory standards.

Reference Range

Based on the kit literature and a study on 256 healthy individuals in China:

• 90th percentile: <200 ng/mL

• 95th percentile: <250 ng/mL

Each laboratory is advised to establish its own reference range based on the local population.

Performance Characteristics

Precision: Intra-assay CV ranging from 1.58% to 5.84% and inter-assay CV from 0.00% to 4.53%. The limit of blank (LoB) was 1.0 ng/mL, and the limit of detection (LoD) was 2.0 ng/mL. The measuring range was 1.0–1000 ng/mL, with linearity between 2.0 and 1000 ng/mL and 90–110% recovery. No significant interference was observed from common medications (e.g., atorvastatin, clopidogrel, aspirin) or endogenous substances such as triglycerides and all procedures were carried out as per the manufacturer's instructions, and quality control criteria were strictly adhered to during the assay process.

- Precision: 6.1 % with the mean of 257.0
- Control used :LpPLA2 Control-1 by SNIBE

3.8 OTHER LABORATORY INVESTIGATIONS

3.8.1 Blood Glucose Measurement

(Glucose Oxidase-Peroxidase Method - GOD-POD)

Glucose oxidase converts glucose to hydrogen peroxide and gluconic acid. Hydrogen peroxide is then transformed by the peroxidase into water and nascent oxygen which reacts with the chromogens (4-aminoantipyrine and phenol) to form a pink-coloured complex measured at 520 nm.

3.8.2 Lipid Profile Estimations

• Total Cholesterol (Cholesterol Oxidase-End Point Assay):

Cholesterol esters are hydrolyzed by cholesterol esterase, followed by oxidation by cholesterol oxidase, producing cholestenone and hydrogen peroxide. The oxygen from H_2O_2 reacts with 4-aminoantipyrine in the presence of phenol to form a pink-colored complex measured at 505 nm.

• **Triglycerides (GPO-PAP End Point Assay):**

Lipoprotein lipase hydrolyzes triglycerides to produce glycerol and free fatty acids. Glycerol is transformed into glycerol-3-phosphate when ATP and glycerol kinase (GK) are involved. G-3-P is oxidized by glycerol phosphate oxidase (GPO) to yield hydrogen peroxide. The oxidative condensation of 4-chlorophenol and 4-aminophenazone in the presence of peroxidase (POD) creates a pink -coloured complex, which is measured at 505 nm.

• **HDL Cholesterol (Enzymatic Direct Clearance Assay):**

This two-step reaction first eliminates chylomicrons, VLDL-Cholesterol, and LDL-Cholesterol via cholesterol esterase, cholesterol oxidase, and catalase. The second reagent contains a detergent that solubilizes HDL specifically. The solubilized HDL-C reacts with a chromogenic coupler to develop colour, measured at 600 nm.

• **LDL Cholesterol (Enzymatic Direct Clearance Assay):**

This two-step reaction eliminates chylomicron, VLDL-Cholesterol, and HDL-Cholesterol in the first phase. The second reagent uses a detergent to solubilize LDL specifically, which then reacts with enzymes and a chromogenic coupler to form a colour, measured at 600 nm.

3.9 STATISTICAL ANALYSIS

Data was analyzed using IBM SPSS version 20.00(Chicago USA). Continuous variables were expressed as mean and sd. Variables such as gender was expressed in number and percentage. To determine the statistical significance of all continuous parameters between groups, an independent sample t-test for normal data or Mann Whitney U-test for skewed data. To find the relationship between all continuous parameters with sd LDL, Pearson correlation coefficient was computed for normal data or Spearman rank correlation for skewed data and its significance was tested using linear reg t test. Univariate and multivariate linear regression equation was determined for statistically significant variables. A p value of < 0.05 met the normal cutoff for statistical significance.

3.10 ETHICAL CONSIDERATION

The study was started after getting the ethical clearance and permission was granted by the Institutional Ethics Committee "(reg no: ECR/1098/Inst/KL/2018/, vide approval IEC Study No. IEC/2020/06/160 Dated 08/09/2020)." Written informed consent was obtained from both test and control group participants.

Chapter-4

RESULTS

OBSERVATIONS AND RESULTS

According to diabetic and non-diabetic conditions, 211 study subjects were classified into four groups:

- **Group I:** Control subjects without metabolic syndrome and diabetes (n=49).
- **Group II:** Subjects with metabolic syndrome but without diabetes (n=53).
- **Group III:** Diabetics without hypercholesterolemia (n=52).
- **Group IV:** Diabetics with hypercholesterolemia (n=57).

Both male and female subjects within the age range of 45-65 years were included. The average age of study subjects was **54.5±6.4 years**. Biochemical factors and biomarkers were evaluated in each study subject.

Table 4.1: Distribution of study subjects

Study subjects	Number (n=211)	Percentage (%)
Group I	49	23
Group II	53	25
Group III	52	25
Group IV	57	27

Table 4.1 shows the distribution of study subjects across four groups based on their diabetic and metabolic status. The highest proportion of subjects belonged to **Group IV (Diabetics with hypercholesterolemia, 27%)**, while the smallest Group was **Group I**

(Control, 23%) ,while **Group II (With metabolic syndrome but without diabetes)** and **Group III (Diabetics without hypercholesterolemia)** accounted for equal distribution with 25 % each.

Table 4.2: Distribution of study subjects according to gender

Gender	Number	Percentage
Male	110	52%
Female	101	48%

Table 4.2 demonstrated the gender distribution among study subjects, revealing that Among the 211 study subjects, 52% (n=110) were male, and 48% (n=101) were female. This indicates that the proportion of male participants was slightly higher than that of females.

Table 4.3: Distribution of mean sd LDL among study subjects

Group	Sd LDL	p-value
Mets without DM (Mean ± sd) (n=53)	46.60±9.61	<0.001*
Control (n=49)	32.10±6.32	
DM w/o hypercholesterolemia (Mean ± sd) (52)	38.153±7.11	<0.001*
Control (n=49)	32.10±6.32	
DM with hypercholesterolemia (Mean ± sd) (n=57)	51.842±10.93	<0.001*
Control (n=49)	32.10±6.32	
Diabetic group (n=109)	45.311±11.53	<0.001*
Control (n=49)	32.10±6.32	

Table 4.3 presented the **mean small dense LDL (sd LDL) levels** among different study groups. The findings showed that **sd LDL levels were significantly higher in all diabetic and metabolic syndrome groups compared to the control group (p<0.001)**. Among the study groups, the highest mean sd LDL level was observed in the **DM with hypercholesterolemia group (51.84±10.93)**, whereas the **lowest mean sd LDL level was found in the control group (32.10±6.32)**. This suggests that patients with diabetes and hypercholesterolemia had the greatest elevation in sd LDL levels, highlighting a potential association between these conditions and increased sd LDL concentrations.

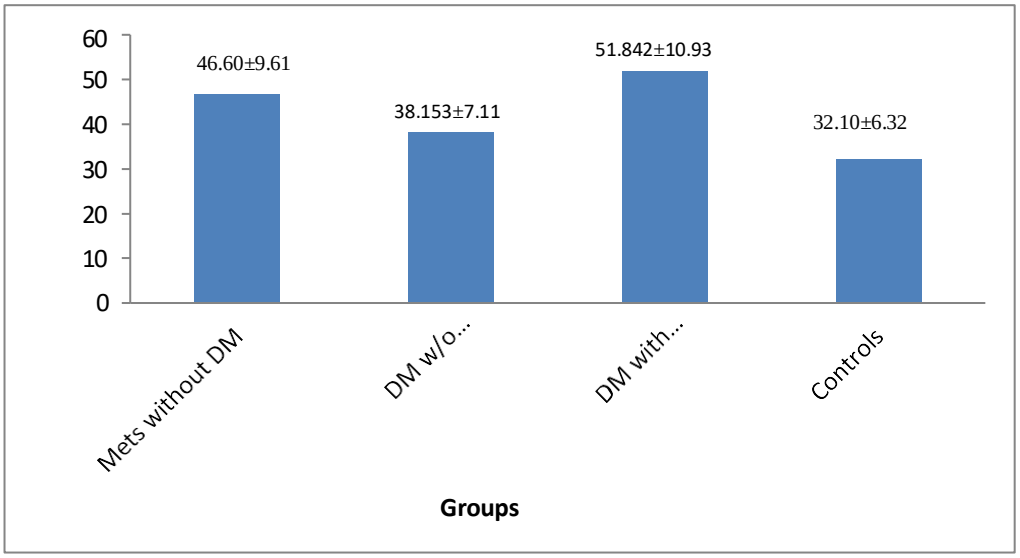


Figure:4.1: Mean sd LDL Levels Among Study Subjects (

Mean sd LDL levels in Controls (n=49), MetS without DM (n=53), DM without hypercholesterolemia (n=52), and DM with hypercholesterolemia (n=57). All test groups > controls (p<0.001).

The **bar graph** provides a visual representation of the observed **mean small dense LDL (sd LDL) levels** among different study groups. The study subjects were categorized into **Mets without DM, DM w/o hypercholesterolemia, DM with hypercholesterolemia, and Control**. Their corresponding **mean sd LDL levels** were **46.60±9.61, 38.153±7.11, 51.842±10.93, and 32.10±6.32**, respectively.

The findings clearly indicate that **sd LDL levels were significantly higher in all test groups compared to the control group**. The highest mean sd LDL level was observed

in the **DM with hypercholesterolemia group (51.842±10.93)**, whereas the lowest was in the **control group (32.10±6.32)**. This suggests a robust association between **diabetes, hypercholesterolemia, and elevated sd LDL levels**, reinforcing the clinical implication of sd LDL in these conditions.

Table 4.4: sd LDL/LDL Ratio Comparison Among Study Groups

Group	**sd LDL**	**p value**
Mets without DM (Mean ± sd) (n=53)	0.331±0.04	<0.001*
Control (n=49)	0.290±0.05	
DM w/o hypercholesterolemia (Mean ± sd) (52)	0.348±0.05	<0.001*
Control (n=49)	0.290±0.05	
DM with hypercholesterolemia (Mean ± sd) (n=57)	0.338±0.054	<0.001*
Control (n=49)	0.290±0.05	
Diabetic group (n=109)	0.340±0.05	<0.001*
Control (n=49)	0.290±0.053	

Table 4.4 illustrated the **comparison of the sd LDL/LDL ratio** across different study groups. The findings indicated that the **sd LDL/LDL ratio was significantly higher in all test groups compared to the control group (p<0.001)**. The **highest ratio** was observed in the **DM without hypercholesterolemia group (0.348±0.05)**, while the **lowest ratio** was in the **control group (0.290±0.05)**.

This suggests that **diabetes and metabolic syndrome contribute to an increased proportion of sd LDL within total LDL cholesterol**, highlighting the potential role of sd LDL in **cardiovascular risk stratification**. The consistently significant p-values reinforce the **clinical relevance** of monitoring sd LDL levels in these patients.

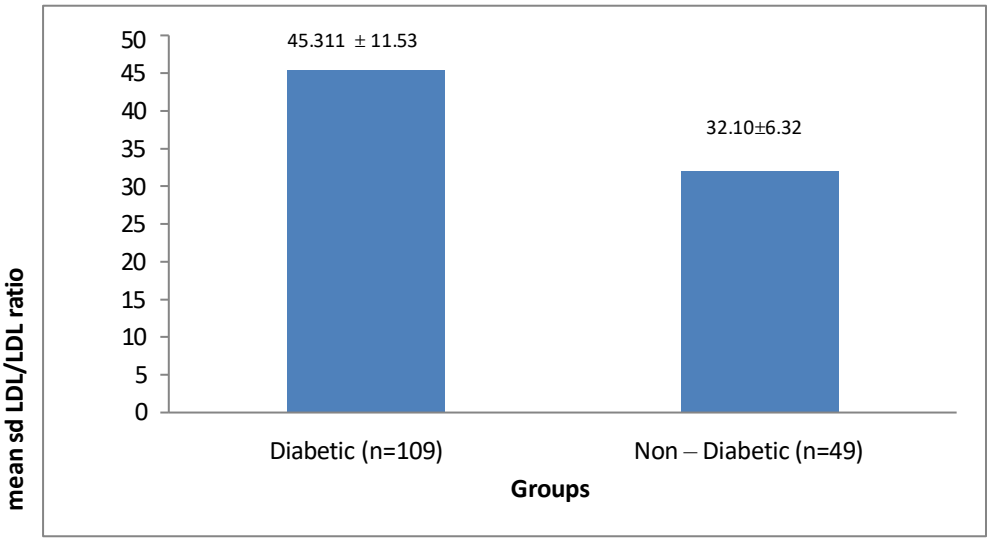


Figure:4.2: Distribution of mean sd LDL among diabetic and non-diabetics group

The bar graph visually represents the **mean sd LDL levels** among **diabetic and non-diabetic subjects**. The **mean sd LDL value in the diabetic group** was **45.311±11.53**, whereas for the **non-diabetic subjects**, it was **32.10±6.32**.

A **statistically significant difference (p<0.001)** was observed between the two groups, as also demonstrated in **Table 4.3 and Figure 4.4**. This indicates that **diabetic individuals had markedly higher sd LDL levels**, reinforcing its potential role in assessing cardiovascular risks associated with diabetes.

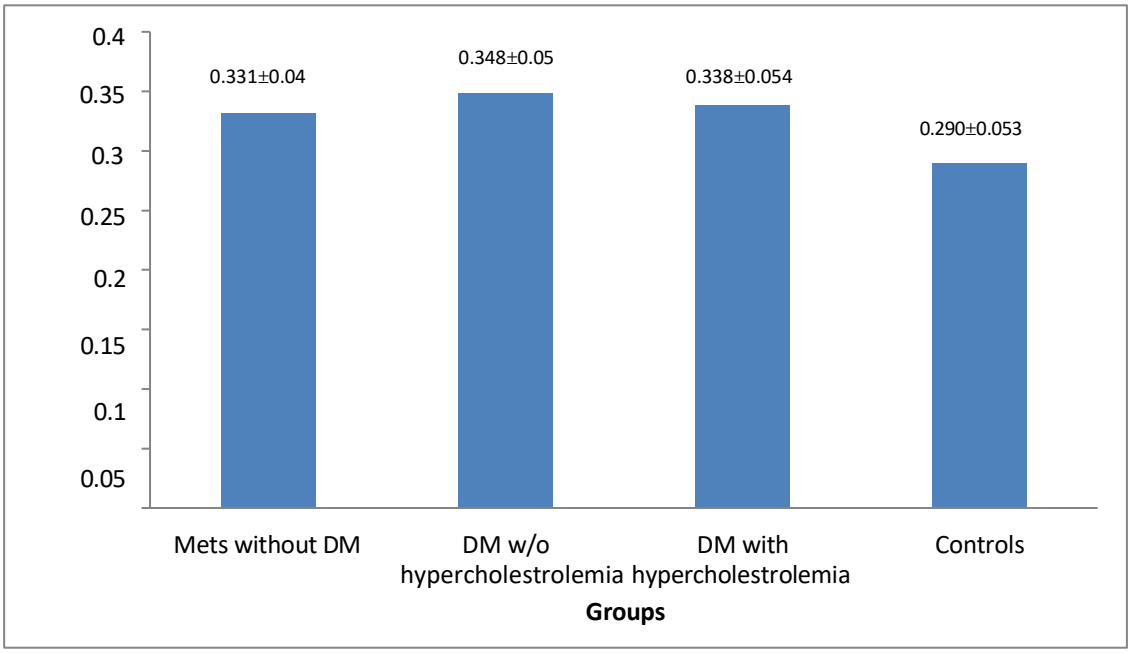


Figure:4.3: Distribution of mean sd LDL/LDL ratio among study subjects

Mean sd LDL levels in Controls (n=49), MetS without DM (n=53), DM without hypercholesterolemia (n=52), and DM with hypercholesterolemia (n=57). Elevated in all metabolic and diabetic groups vs controls (p<0.001).

The **bar graph** represents the **distribution of mean sd LDL/LDL ratio** among different study groups. The **mean sd LDL/LDL ratio** for **Mets without DM** was **0.331±0.04**. For **DM without hypercholesterolemia**, it was **0.348±0.05**. For **DM with hypercholesterolemia**, the ratio was **0.338±0.054**. The **control group** had the lowest mean ratio of **0.290±0.05**.

The analysis with **a t-test indicated that the SD LDL/LDL ratio was markedly elevated in all diabetic and metabolic syndrome patients** compared to the **control group patients**. This suggests a possible correlation between **diabetes, metabolic conditions, and altered sd LDL distribution**, as shown in **Table 3.4 and Figure 3.5**.

Table 4.5: Comparison of sd LDL/cholesterol ratio between groups

Groups	Mean ±sd	p value
Mets w/o DM	0.217±0.022	<0.001**
Controls	0.175±0.034	
DM with hypercholesterolemia	0.222±0.037	<0.001*
Controls	0.175±0.034	
DM w/o hypercholesterolemia	0.206±0.035	<0.001*
Controls	0.175±0.034	
Diabetic	0.214±0.037	<0.001*
Non-Diabetic	0.175±0.034	

*Using Independent sample t test, using Mann Whitney U test

Table 4.5 presents the **sd LDL/cholesterol ratio** across different study groups. The results demonstrated a **statistically significant increase (p<0.001) in all test groups compared to the control group**.

- The **highest mean sd LDL/cholesterol ratio** was observed in **diabetics with hypercholesterolemia (0.222±0.037)**.

- The **diabetic group overall** had a mean ratio of **0.214±0.037**, while the **non-diabetic group** (control) had the **lowest ratio (0.175±0.034)**.
- Among the metabolic syndrome group, the **Mets without DM group** had a mean ratio of **0.217±0.022**, while the **DM without hypercholesterolemia** group had a ratio of **0.206±0.035**.

These findings suggest that **diabetes and hypercholesterolemia are associated with a higher sd LDL/cholesterol ratio**, reinforcing the role of **lipoprotein alterations in metabolic disorders**.

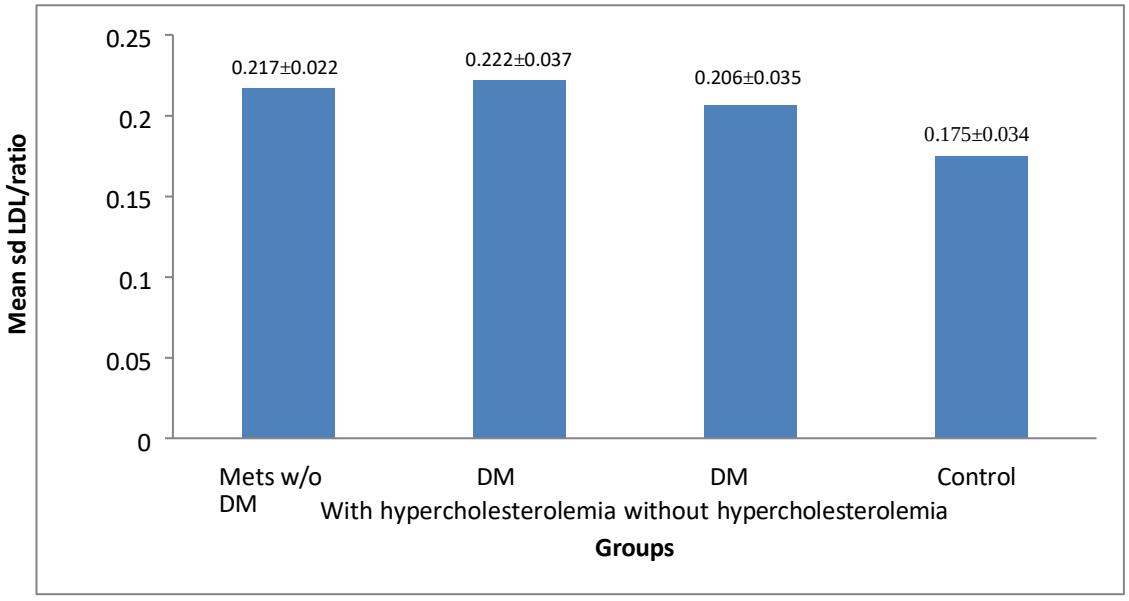


Figure:4.4: Distribution of mean sd LDL/Cholesterol ratio among diabetic and non- diabetics groups

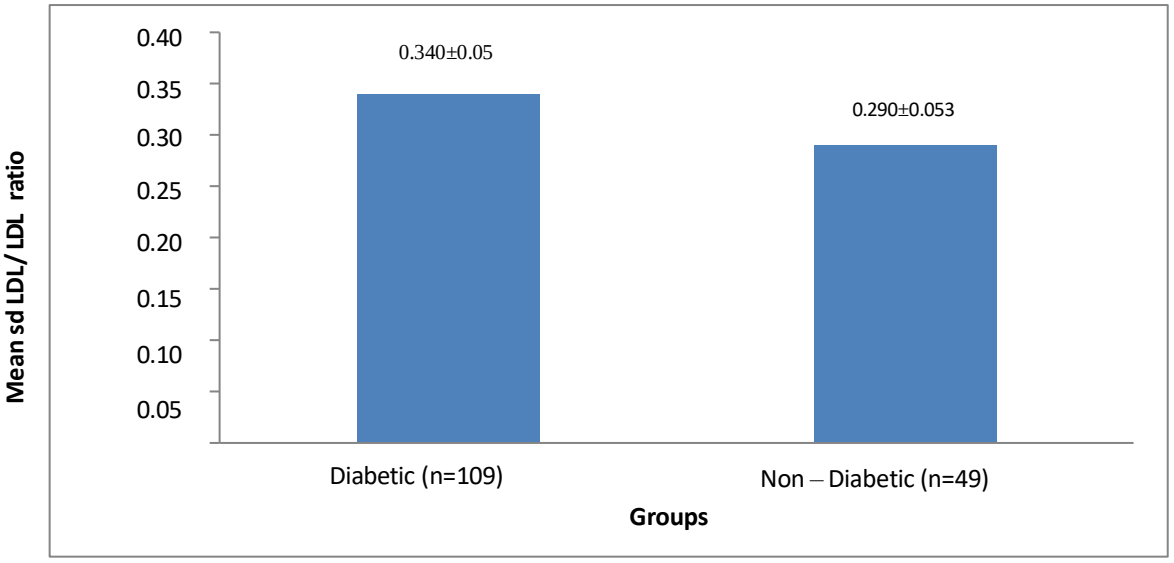


Figure:4.5: Distribution of mean sd LDL/LDL ratio among groups
Highest in DM with hypercholesterolemia; all test groups > controls (p<0.001).

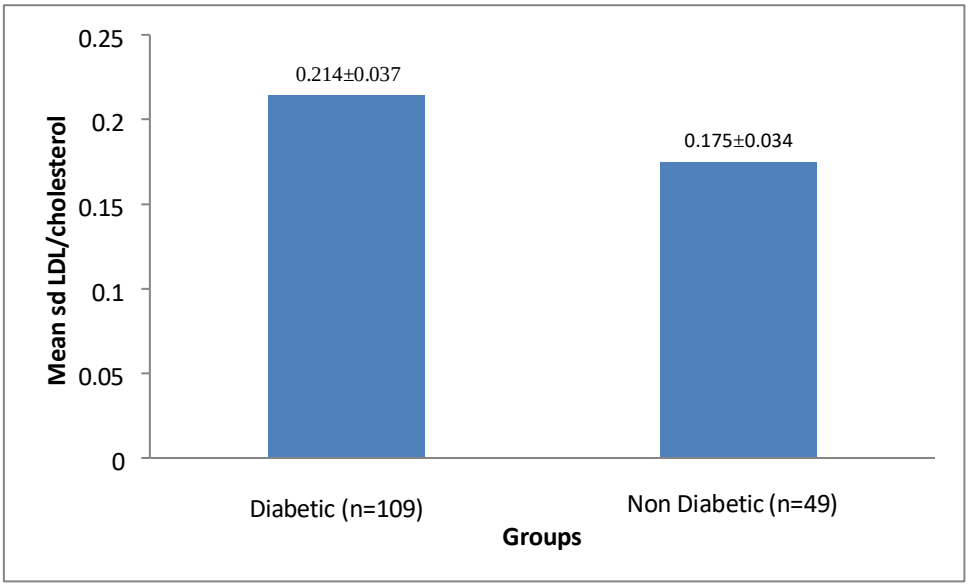


Figure:4.6: Distribution of mean sd LDL/ cholesterol ratio among diabetic and non-diabetics groups (p<0.001).

Figure 4.4 compares the **sd LDL/LDL ratio** between diabetic and non-diabetic groups. The diabetic group had a higher ratio (**0.340±0.05**) than the non-diabetic group (**0.290±0.053**), indicating that diabetics have a greater proportion of small dense LDL in their total LDL, which may support to an elevated risk of cardiovascular complications.

Figure 4.5 shows the **sd LDL/cholesterol ratio** among study groups. The highest ratio was in **DM with hypercholesterolemia (0.222±0.037)**, followed by **Mets without DM (0.217±0.022)** and **DM without hypercholesterolemia (0.206±0.035)**. The diabetic group had a ratio of **0.214±0.037**, while the lowest was in the **non-diabetic group (0.175±0.034)**. This suggests that diabetics and individuals with metabolic syndrome tend to have a higher proportion of sd LDL relative to their total cholesterol, which may indicate an increased risk of atherosclerosis.

Figure 4.6 compares the **sd LDL/cholesterol ratio** between diabetic and non-diabetic groups. Diabetics had a **higher ratio (0.214±0.037)** than non-diabetics (**0.175±0.034**), meaning that diabetics have a greater proportion of small dense LDL in relation to their cholesterol levels, which could lead to developing CVS diseases.

Table 4.6: Comparison of Lp-PLA2 concentration between groups

Groups	Lp-PLA2 (Mean ±sd)	p value
Mets w/o DM	166.6±53.59	
Controls	106 ± 29.70	<0.001*
DM with hypercholesterolemia	196.14±75.68	
Controls	106.90±29.70	<0.001*
DM w/o hypercholesterolemia	164.826±50.94	
Controls	106.898±29.70	<0.001*
Diabetic	181.201±66.65	
Non-Diabetic	106.898±29.70	<0.001*

Table 4.6 presents the **Lp-PLA2 concentration** across different study groups. The levels were notably increased in all test groups compared to the controls. The highest concentration was observed in **diabetics with hypercholesterolemia (196.14±75.68)**, while the lowest was in the **control group (106.90±29.70)**. This suggests that individuals with diabetes and metabolic abnormalities tend to have elevated Lp-PLA2 levels, which may indicate increased vascular inflammation and a higher risk of cardiovascular diseases.

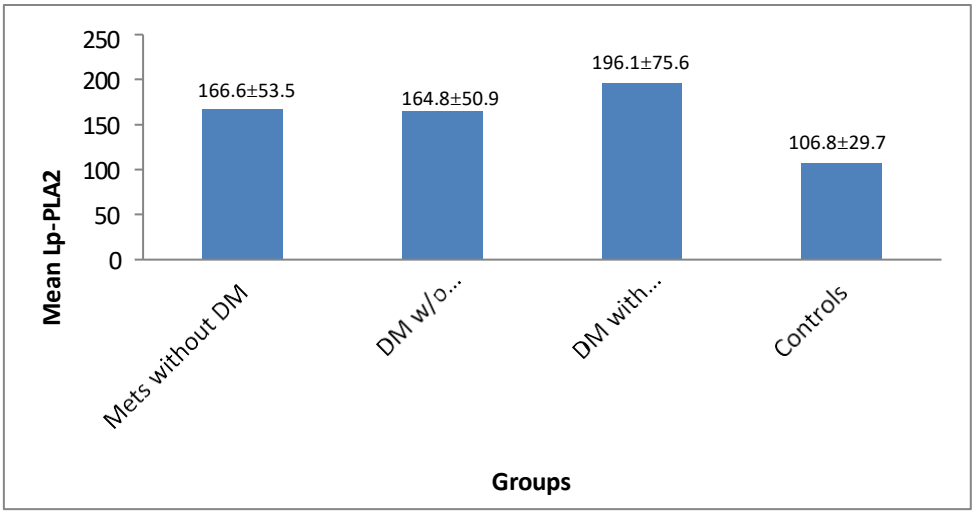


Figure:4.7: Comparison of Lp-PLA2 concentration between group Elevated in all test groups vs controls (p<0.001).

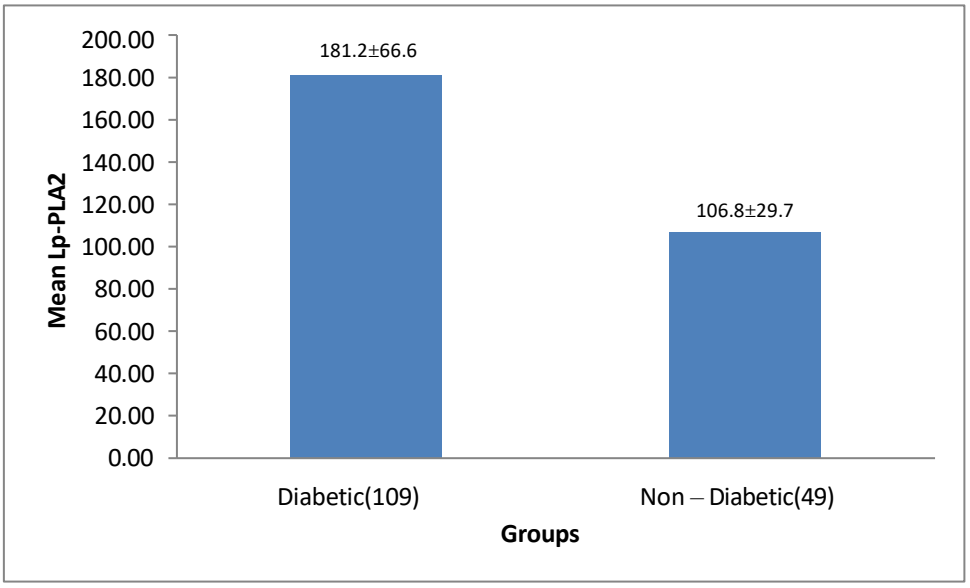


Figure 4.8: Comparison of Lp-PLA2 concentration among diabetes and no-diabetes groups

Figure 4.9 illustrates the Lp-PLA2 concentration across different study groups. The mean Lp-PLA2 levels were 166.6±53.59 in Mets without DM, 196.14±75.68 in diabetics with hypercholesterolemia, and 164.826±50.94 in diabetics without hypercholesterolemia. These values indicate that Lp-PLA2 levels were consistently higher in individuals with diabetes and metabolic disorders compared to controls.

Figure 4.8 compares the Lp-PLA2 concentration between diabetic and non-diabetic groups. The mean Lp-PLA2 level in the diabetic group was 181.201±66.65, whereas in non-diabetic subjects, it was 106.898±29.70. This difference suggests that diabetics had significantly elevated Lp-PLA2 levels, which may be associated with a higher degree of vascular inflammation and an increased risk of atherosclerosis.

Table 4.7: Comparison of hs-CRP concentration between groups

Groups	Mean ±sd	p-value
Mets w/o DM	1.679±0.97	<0.001*
Controls	0.467±0.56	
DM with hypercholesterolemia	2.03±1.29	<0.001*
Controls	0.467±0.56	
DM w/o hypercholesterolemia	1.60±1.035	<0.001*
Controls	0.467±0.56	
Diabetic	1.832±1.19	<0.001*
Non-Diabetic	0.467±0.566	

Table 8 demonstrated the **hs-CRP (high-sensitivity C-reactive protein) concentration** across different study groups. The mean hs-CRP levels were **1.679±0.97** in Mets without DM, **2.03±1.29** in diabetics with hypercholesterolemia, and **1.60±1.035** in diabetics without hypercholesterolemia. The diabetic group had a mean hs-CRP level of **1.832±1.19**, whereas the non-diabetic group had the lowest value of **0.467±0.566**.

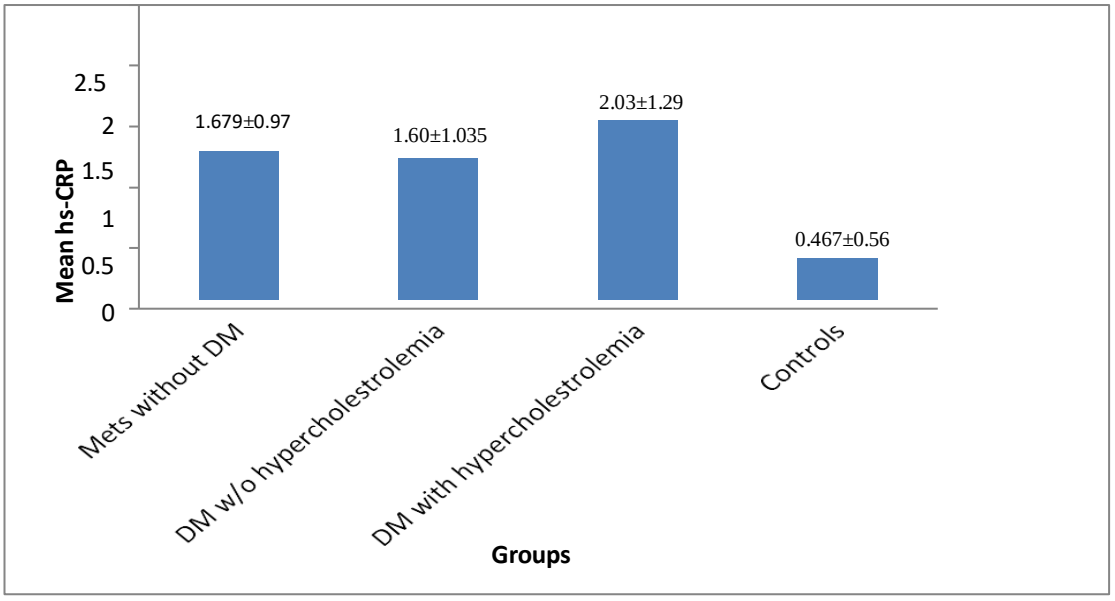


Figure 4.9. hs-CRP concentrations across groups (n=49–57). Higher in metabolic and diabetic groups vs controls (*p*<0.001).

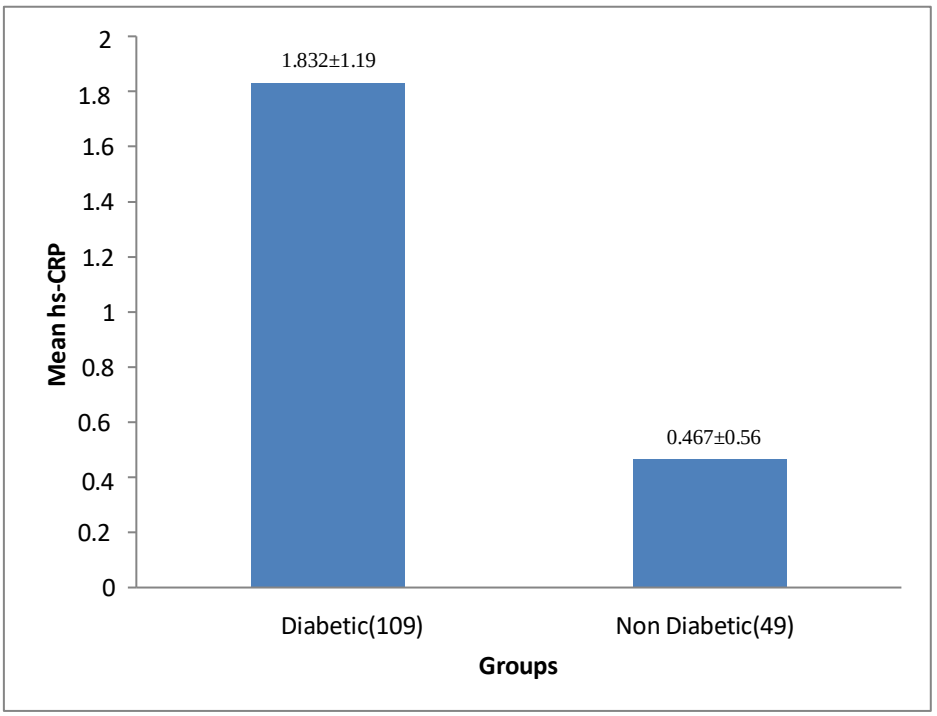


Figure 4.10: Comparison of hs-CRP among Diabetic and non-diabetic groups

The concentration of **hs-CRP (high-sensitivity C-reactive protein)** among the study subjects was analyzed. The **Mets without DM group** had a mean hs-CRP level of **1.679±0.97**. Among diabetic subjects, those with **hypercholesterolemia** showed the highest hs-CRP level (**2.03±1.29**), while those without hypercholesterolemia had a slightly lower level (**1.60±1.035**). The overall **diabetic group** had an hs-CRP level of **1.832±1.19**, whereas the **non-diabetic group** had the lowest level of **0.467±0.566**. These findings highlight that diabetic and metabolic syndrome patient had higher levels of systemic inflammation compared to non-diabetic individuals (**Table 7, Figures 4.11 and 4.12**).

Table 4.8: Comparison of RDW concentration between groups

Groups	Mean ±sd	p-value
Mets w/o DM	12.288±0.42	0.015*
Controls	12.075±0.44	
DM with hypercholesterolemia	13.038±0.566	<0.001*
Controls	12.075±0.44	
DM w/o hypercholesterolemia	12.692±0.529	<0.001**
Controls	12.075±0.44	
Diabetic	12.875±0.57	<0.001**
Non-Diabetic	12.075±0.44	

Table 4.8 compared red cell distribution width (RDW) among study groups. The findings demonstrated that **RDW values were significantly higher in diabetics with and without hypercholesterolemia compared to controls (p<0.001)**. The highest RDW was found in **diabetics with hypercholesterolemia (13.038±0.566)**, while the lowest was recorded in the **control group (12.075±0.44)**.

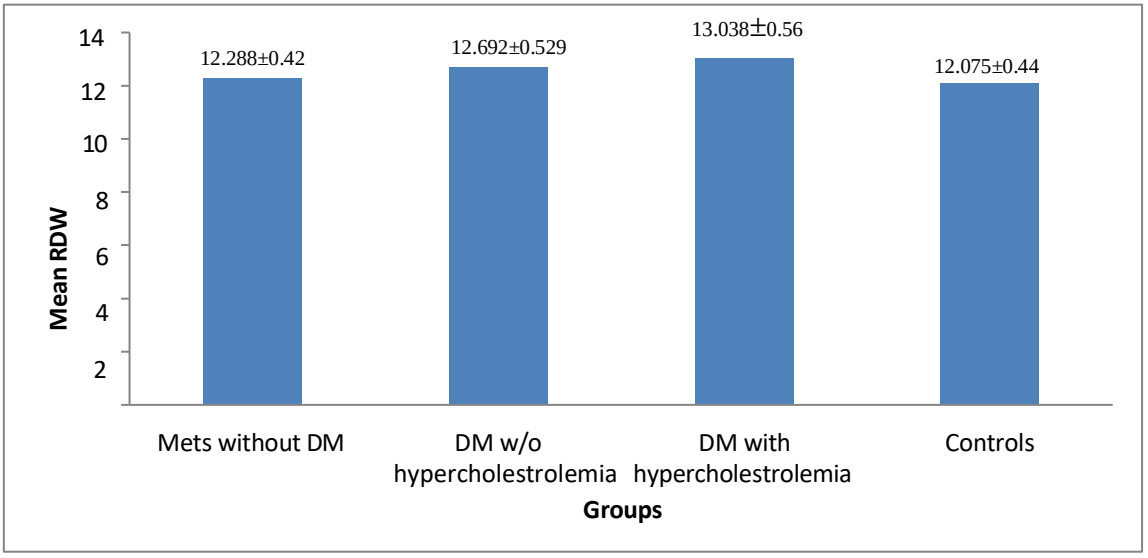


Figure 4.11. RDW across study groups. Increased in diabetic groups, highest in DM with hypercholesterolemia (*p*<0.001).

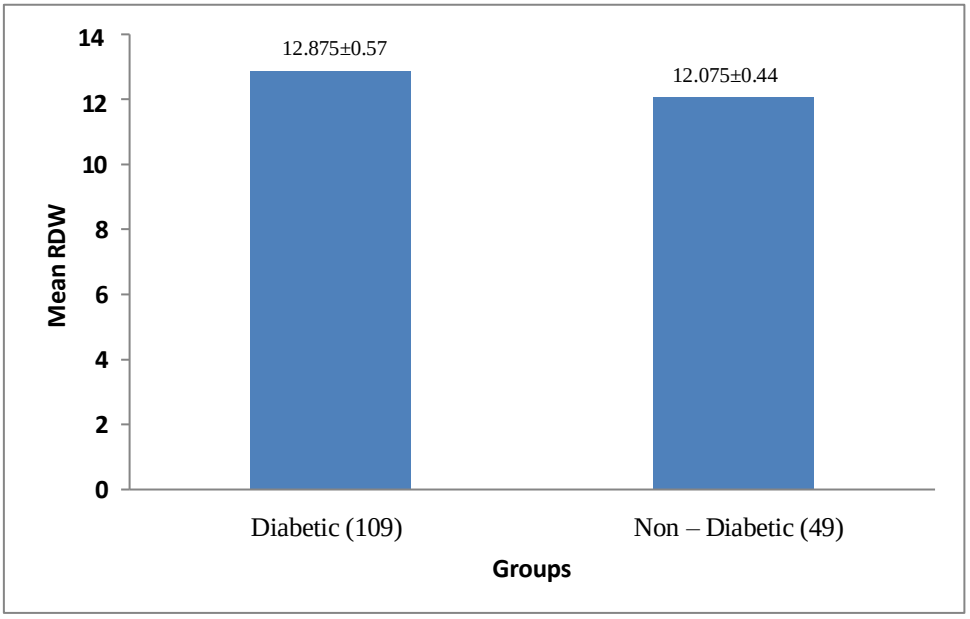


Figure 4.12: Comparison of RDW concentration between groups

Figure 4.11 shows the comparison of RDW concentration across the different study groups. The Mets without DM group recorded a mean RDW of **12.288±0.42**, while DM without hypercholesterolemia showed **12.692±0.529**, and DM with hypercholesterolemia had the highest RDW at **13.038±0.566**. This pattern highlights that RDW increases with the presence of diabetes and hypercholesterolemia.

Figure 4.12 compares RDW concentration between diabetic and non-diabetic groups. The diabetic group had a higher mean RDW value of **12.875±0.57**, whereas the non-diabetic group showed a lower mean of **12.075±0.44**. This directs that persons with diabetes tend to have more variation in red blood cell size than those without diabetes. (Table 8, Figures 4.13 and 4.14).

Table 4.9: Correlation of study variables with sd LDL among Mets W/o DM group

Study variables	Correlation coefficient with sd LDL	p-value
hs-CRP	0.774	<0.001*
Lp-PLA2	0.704	<0.001*
RDW	0.217	0.118

Table 4.9 evaluated the association between study variables and sd LDL levels in subjects with metabolic syndrome but without diabetes. It was observed that hs-CRP (r = 0.774) and Lp-PLA2 (r = 0.704) had a strong positive correlation with sd LDL. This implies that as inflammation markers like hs-CRP and Lp-PLA2 increase, sd LDL levels also tend to rise. In contrast, RDW (r = 0.217) had a weak positive correlation with sd LDL, which was not statistically significant, indicating a limited relationship.

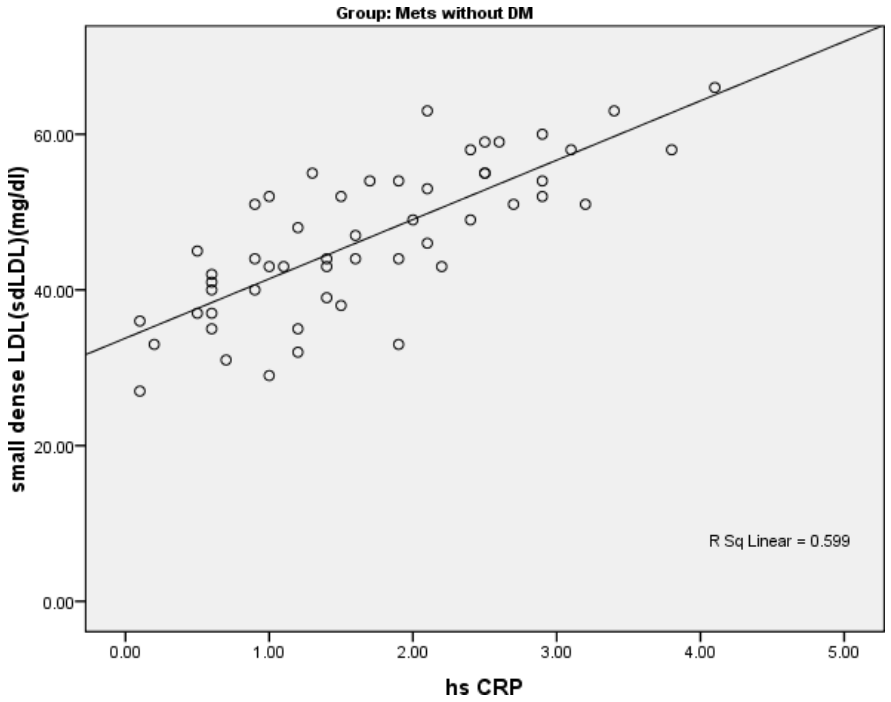


Figure 4.13. hs-CRP vs sd LDL in MetS without DM (n=53): *r*=0.774, *p*<0.001.

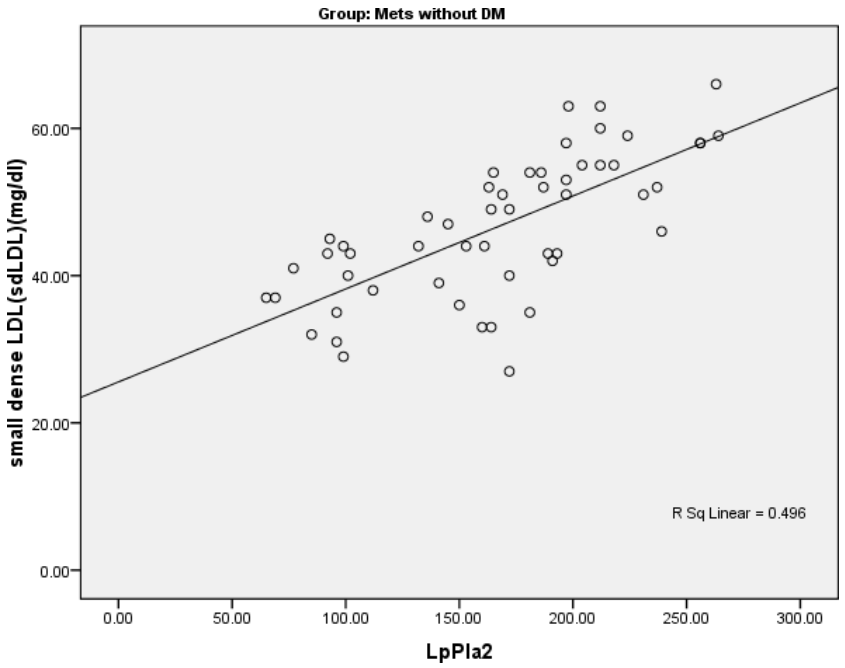


Figure 4.14. **Lp-PLA₂ vs sd LDL in MetS without DM (n=53): *r*=0.704, *p*<0.001.**

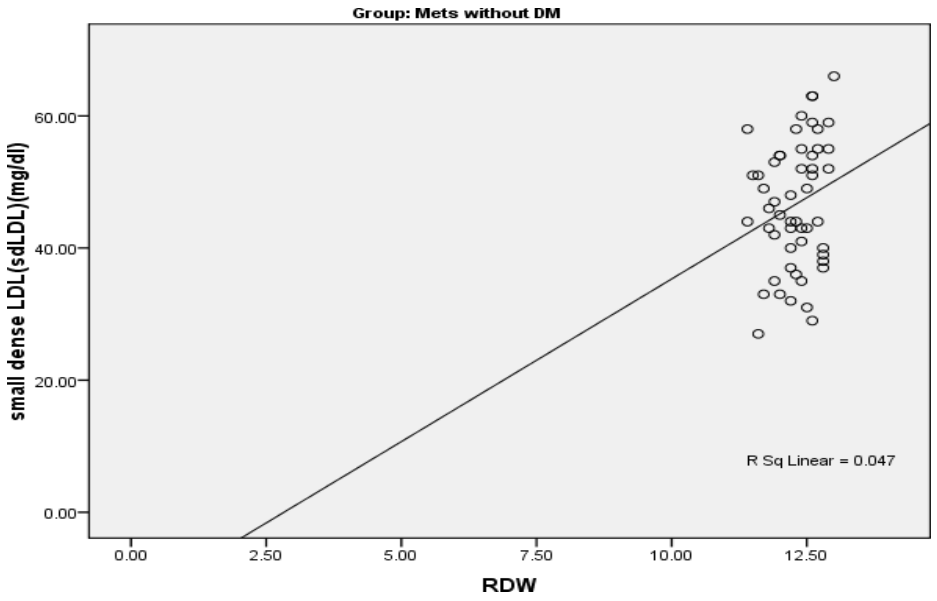


Figure 4.15. RDW vs sd LDL in MetS without DM (n=53): *r*=0.217, *p*=0.118.

Figure 4.13 illustrates the Pearson correlation between **hs-CRP and sd LDL**. The plot shows a strong rising trend, representing that individual with higher hs-CRP levels—an indicator of systemic inflammation—also had elevated levels of sd LDL. This supports the idea that inflammation is closely linked to atherogenic lipid changes in the metabolic syndrome group.

Figure 4.14 presents the Pearson correlation between **Lp-PLA2 and sd LDL**. Similar to hs-CRP, Lp-PLA2 also demonstrated a strong positive association with sd LDL. The graph depicts that as Lp-PLA2, an enzyme related to vascular inflammation, increases, sd LDL concentrations also rise, suggesting a parallel rise in cardiovascular risk.

Figure 4.15 shows the Pearson correlation between **RDW and sd LDL**. In this graph, the data points propose only a mild positive trend, and the scatter is more dispersed. This reflects the weak correlation noted statistically, indicating RDW may not be a reliable marker of sd LDL levels in this group.

Along with the correlation and regression analysis was performed to assess how well hs-CRP and Lp-PLA2 could predict sd LDL levels among study subjects. In **univariate regression**, two distinct equations were derived. The first was **sd LDL = 33.80 + (7.622 × hs-CRP)**, indicating that for each unit rise in hs-CRP, the sd LDL level increased by 7.622 units. This showed a sturdy and straight association between inflammation and sd LDL.

The second univariate equation was **sd LDL = 25.565 + (0.126 × Lp-PLA2)**, suggesting that Lp-PLA2 also contributed to higher sdL DL levels, but to a smaller extent compared to hs-CRP. When both hs-CRP and Lp-PLA2 were analyzed together in a **multivariate regression model**, the equation obtained was **sd LDL = 27.966 + (5.427 × hs-CRP) + (0.057 × Lp-PLA2)**.

This showed that both variables continued to positively influence sd LDL levels, but **hs-CRP had a stronger predictive value than Lp-PLA2**. Overall, the analysis exposed that higher levels of inflammatory markers like hs-CRP and Lp-PLA2 were allied with increased sd LDL, with hs-CRP having a comparatively bigger effect.

Table 4.10: Correlation of study variables with sd LDL among DM w/o hypercholesterolemia

Study variables	Correlation coefficient with sd LDL	p-value
hs-CRP	0.333	0.016*
Lp-Pla2	0.279	0.045*
RDW	0.152	0.286

Table 4.10 presents the correlation of hs-CRP, Lp-PLA2, and RDW with sd LDL in diabetic subjects without hypercholesterolemia. A moderate positive correlation was observed between hs-CRP and sd LDL (r = 0.333) and between Lp-PLA2 and sd LDL (r = 0.279), suggesting that elevated concentrations of these inflammatory markers are linked to higher levels of sd LDL. In contrast, RDW showed only a weak positive correlation (r = 0.152) was not notably significant.

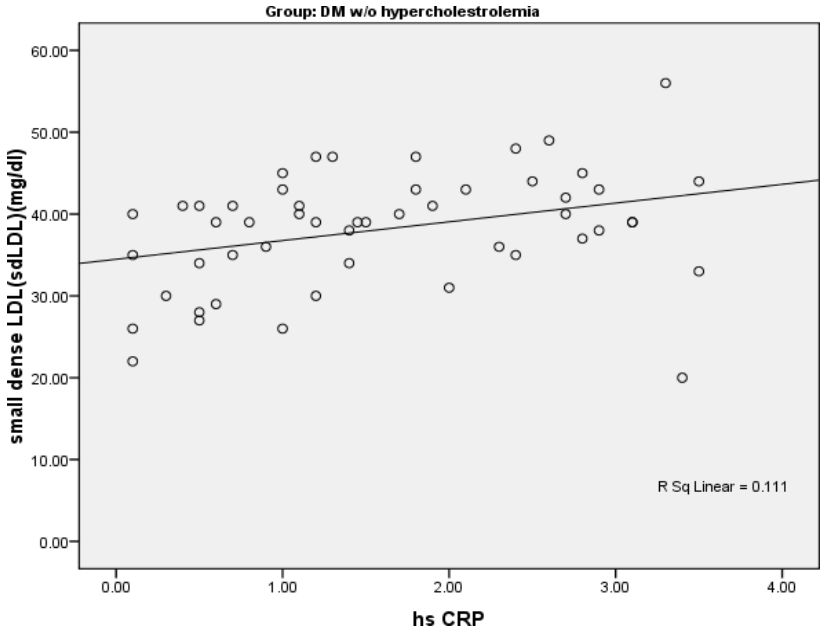


Figure 4.16. hs-CRP vs sd LDL in DM without hypercholesterolemia (n=52): *r*=0.333, *p*=0.016.

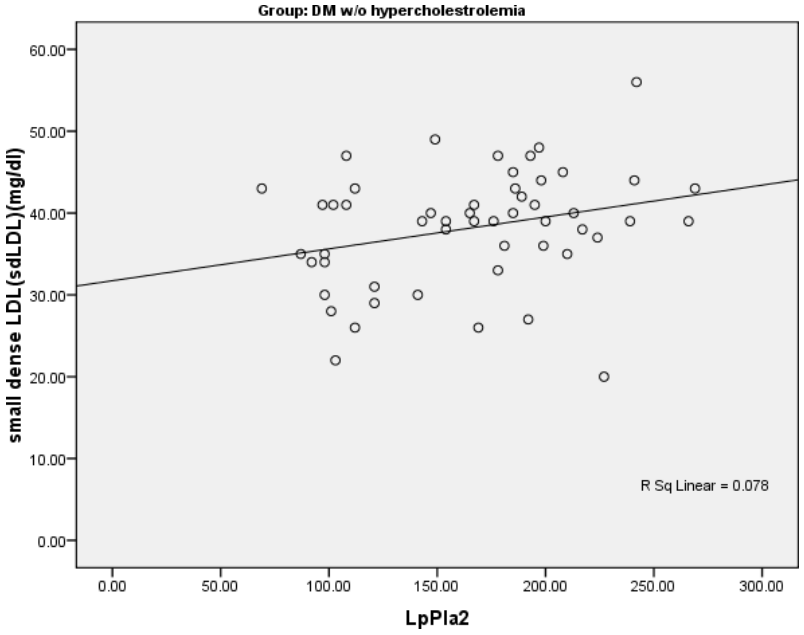


Figure 4.17. Lp-PLA₂ vs sd LDL in DM without hypercholesterolemia (n=52): *r*=0.279, *p*=0.045.

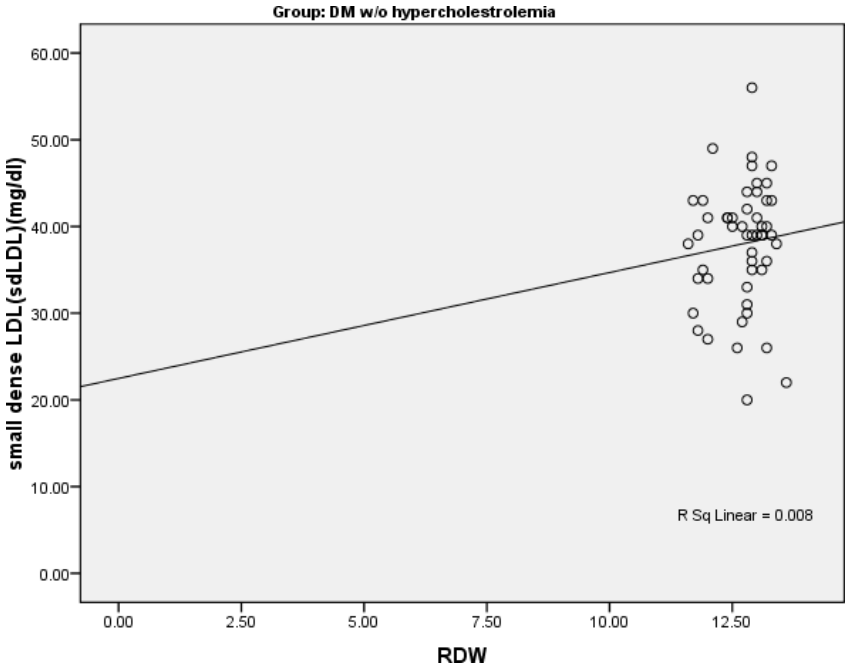


Figure 4.18. RDW vs sd LDL in DM without hypercholesterolemia (n=52): *r*=0.152, *p*=0.286.

Figures 4.16, 4.17, and 4.18 depict the Pearson correlation plots for hs-CRP, Lp-PLA2, and RDW with sd LDL, respectively. Both hs-CRP and Lp-PLA2 showed a moderate upward trend with sd LDL, backup the positive correlation observed. However, the RDW plot displayed a flat pattern, reinforcing the minimal association with sd LDL in this group.

Univariate Regression Equations

The univariate regression analysis demonstrated that sd LDL increased by 2.29 units for every unit increase in hs-CRP, represented by the equation:
sd LDL = 34.479 +(2.290 × hs-CRP).
Similarly, for Lp-PLA2, sd LDL rose by 0.039 units per unit increase, as per the equation: **sd LDL = 31.734 + (0.039 × Lp-PLA2)**.

Multivariate Regression Equation

When hs-CRP and Lp-PLA2 were included together in a multivariate regression model, the equation was: **sd LDL = 33.29 + (1.897 × hs-CRP) + (0.011 × Lp-PLA2)**. This indicates that both variables independently contributed to sd LDL levels, although the unique impact of each was slightly reduced when considered together.

Table 4.11: Correlation of study variables with sd LDL among DM with hypercholesterolemia

Study variables	Correlation coefficient with sd LDL	p-value
hs-CRP	0.488	<0.001*
Lp-Pla2	0.500	<0.001*
RDW	0.474	<0.001*

Table 4.11 assessed the correlation of study variables with sd LDL in diabetics with hypercholesterolemia. The findings revealed that **hs-CRP (r = 0.488, p < 0.001)**, **Lp-PLA2 (r = 0.500, p < 0.001)**, and **RDW (r = 0.474, p < 0.001)** all exhibited significant moderate positive correlations with sd LDL. This suggests that increases in inflammation and red cell distribution are strongly associated with elevated sd LDL levels in this subgroup.

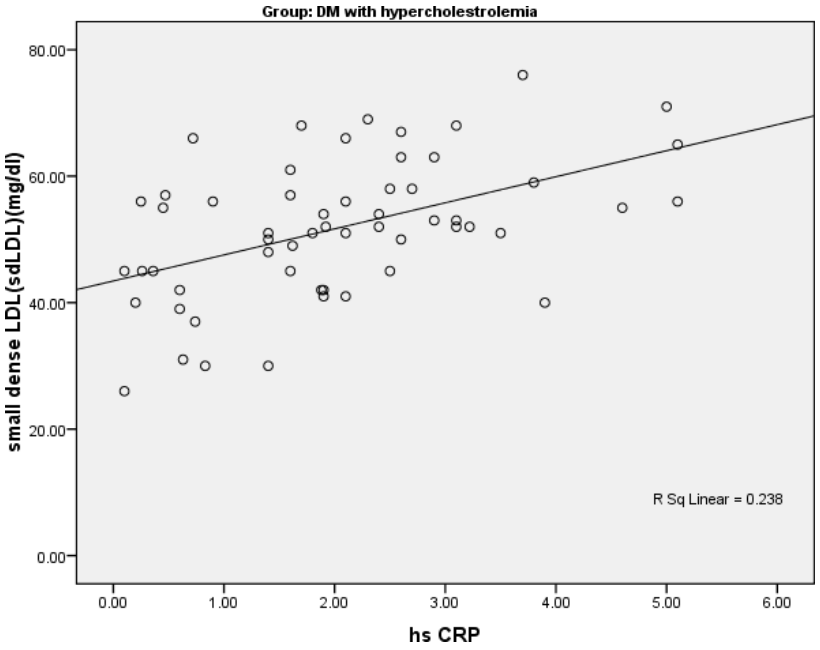


Figure 4.19: Pearson correlation between RDW and sd LDL

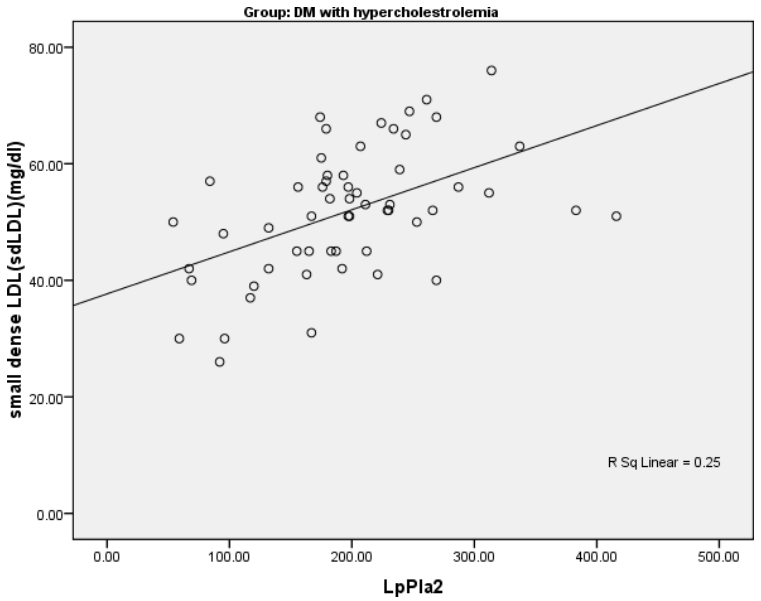


Figure 4.20: Pearson correlation between Lp-PLA2 and sd LDL

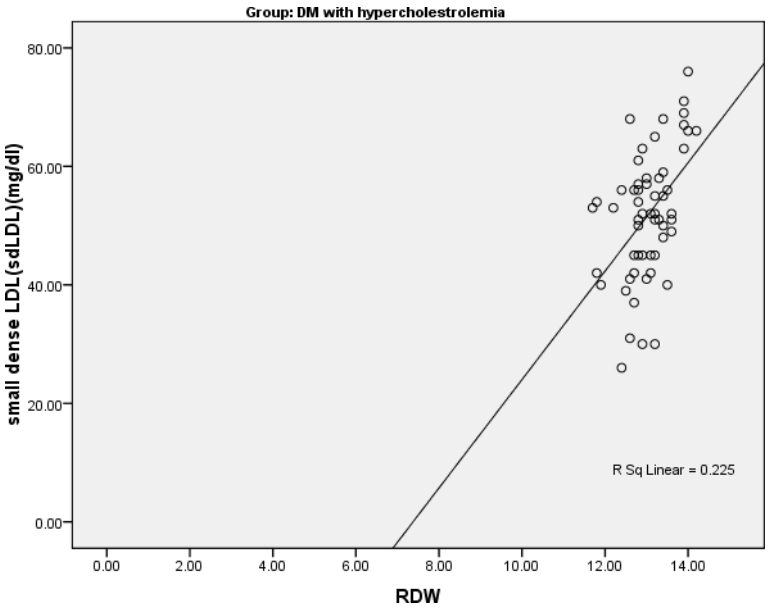


Figure 4.21: Pearson correlation between RDW and sd LDL

Figures 4.19–4.21. Correlations in DM with hypercholesterolemia (n=57): hs-CRP (r=0.488), Lp-PLA₂ (r=0.500), RDW (r=0.474); all p<0.001.

Figures 4.19, 4.20, and 4.21 represent the Pearson correlation plots between hs-CRP, Lp-PLA2, and RDW with sd LDL, respectively. All three variables showed a moderately rising trend, visually supporting the statistical correlation. These plots emphasize how increases in inflammation and red cell variability coincide with higher sd LDL concentrations in diabetics with hypercholesterolemia.

Univariate Regression Equations

The univariate regression models for this group were as follows:

- **sd LDL = 43.438 + (4.121 × hs-CRP)**
- **sd LDL = 37.68 + (0.072 × Lp-PLA2)**
- **sd LDL = -67.516 + (9.154 × RDW)**

These equations display that every variable independently contributes to the prediction of sd LDL, with RDW showing the steepest slope.

Multivariate Regression Equation

When each of the three factors were entered into a multivariate regression model, the resulting equation was:
Sd LDL = -39.481 + (2.161 × hs-CRP) + (0.028 × Lp-PLA2) + (6.248 × RDW).

This indicates that each variable maintained its predictive value for sd LDL even after adjusting for the others, though the effect size was slightly attenuated.

Table 4.12: Correlation of study variables with sd LDL among DM patients

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

Table 4.12 summarized the correlation of study variables with sd LDL among diabetic patients. The results showed a **moderate positive correlation** between sd LDL and **hs-CRP (r = 0.426, p < 0.001)**, **Lp-PLA2 (r = 0.475, p < 0.001)**, and **RDW (r = 0.389, p < 0.001)**. These findings suggest that higher levels of inflammation and altered red cell indices were consistently linked with elevated sd LDL among diabetics.

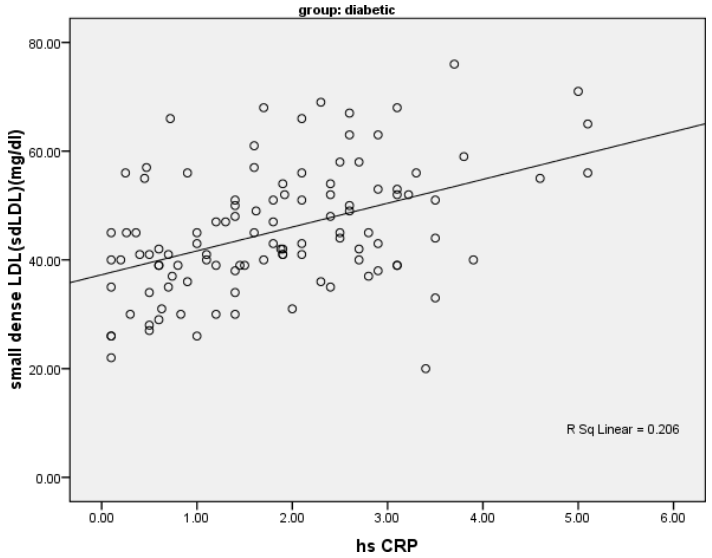


Figure 4.22: Pearson correlation between hs-CRP and sd LDL

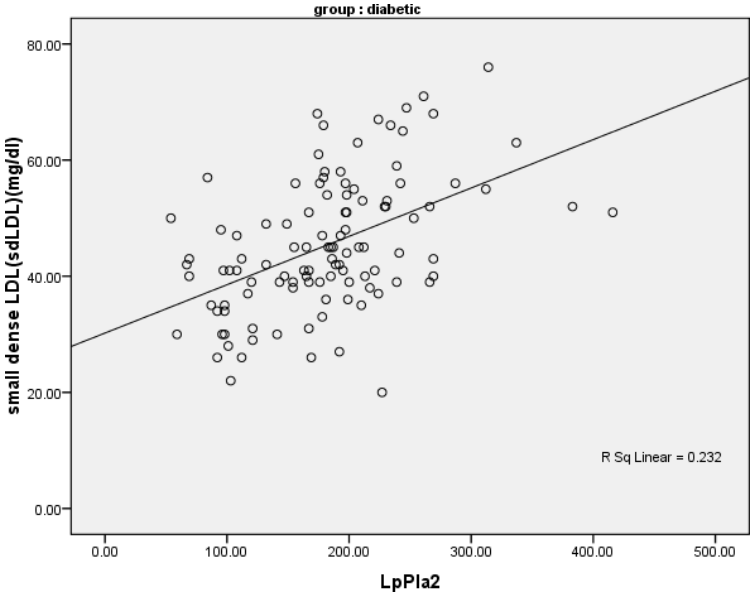


Figure 4.23: Pearson correlation between Lp-PLA2 and sd LDL

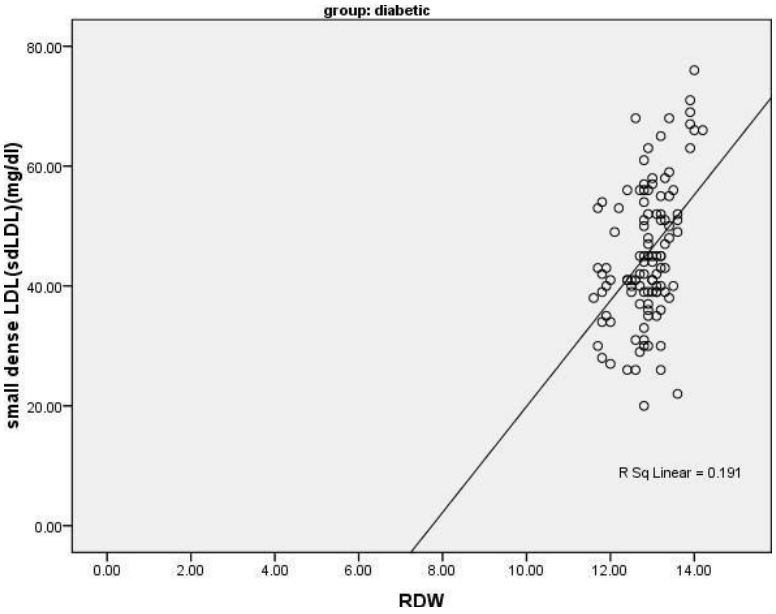


Figure 4.24: Pearson correlation between RDW and sd LDL

Figures 4.22–4.24. Correlations in total diabetics (n=109): hs-CRP (r=0.426), Lp-PLA₂ (r=0.475), RDW (r=0.389); all p<0.001.

Figures 4.22, 4.23, and 4.24 illustrate the Pearson correlation between sd LDL and hs-CRP, Lp-PLA2, and RDW, respectively. Each plot showed an upward trend, visually reinforcing the moderate positive relationship between these variables and sd LDL levels in diabetic individuals. This suggests that as the levels of these markers rise, sd LDL also tends to increase.

Regression Equations

In univariate regression analysis, sd LDL increased by:

- **4.384 units for each unit increase in hs-CRP →**
  sd LDL = 37.27 + (4.384 × hs-CRP)
- **0.083 units per unit rise in Lp-PLA2 →**
  sd LDL = 30.216 + (0.083 × Lp-PLA2)
- **8.832 units for every 1 unit increase in RDW →**
  sd LDL = -68.413 + (8.832 × RDW)

In the multivariate model including all three variables, the equation was: **sd LDL = -35.577 + (2.225 × hs-CRP) + (0.033 × Lp-PLA2) + (5.499 × RDW)** This shows that all three variables remained independent predictors, although with slightly reduced individual contributions when considered together.

Table 4.13: Correlation between inflammatory markers with sd LDL/TC among diabetic patients

Study variables	Correlation coefficient with sd LDL	p value
hs-CRP	0.487	<0.001*
Lp-PlA2	0.436	<0.001*
RDW	0.239	0.013*

Among diabetic patients, the sd LDL/Total cholesterol ratio showed a **moderate positive correlation** with hs-CRP (r = 0.487, p < 0.001) and Lp-PLA₂ (r = 0.436, p < 0.001), both statistically significant. A **weaker yet significant correlation** was noted with RDW (r = 0.239, p = 0.013), illustrating that greater inflammatory marker concentrations are allied with increased sd LDL proportion in total cholesterol.

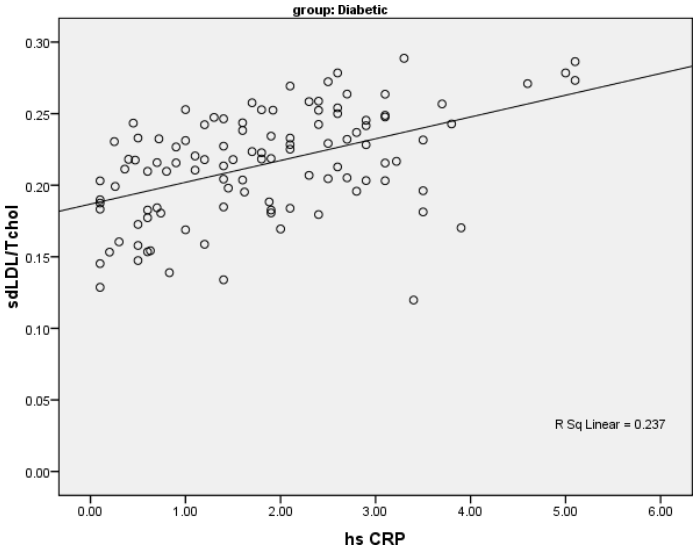


Figure 4.25: Correlation Between hs-CRP and sd LDL/Total Cholesterol Ratio in Diabetic Patients

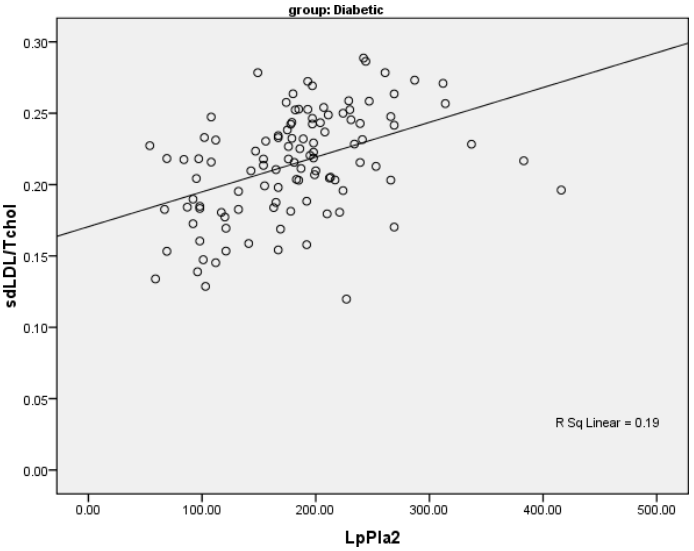


Figure 4.26: Correlation Between Lp-PLA₂ and sd LDL/Total Cholesterol Ratio in Diabetic Patients

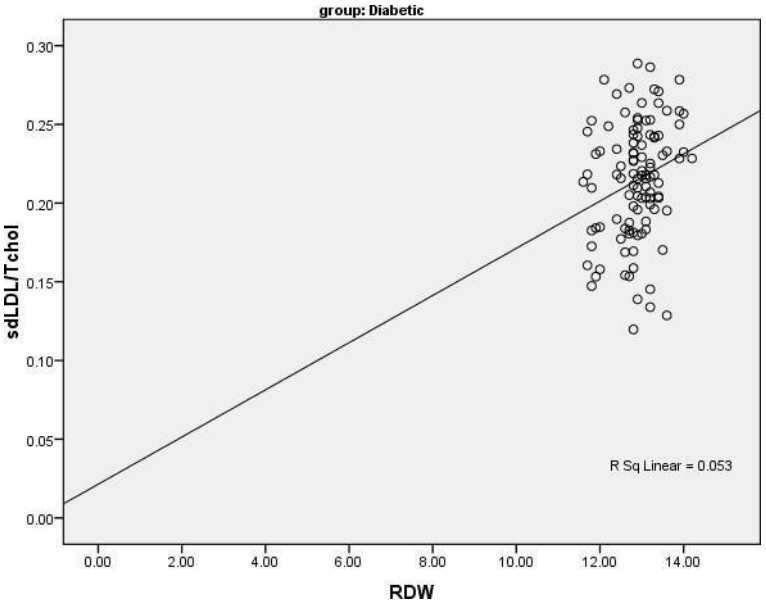


Figure 4.27: Correlation Between RDW and sd LDL/Total Cholesterol Ratio in Diabetic Patients

Figures 4.25–4.27. sd LDL/TC vs markers in diabetics (n=109): hs-CRP (r=0.487, p<0.001); Lp-PLA₂ (r=0.436, p<0.001); RDW (r=0.239, p=0.013).

Among diabetic patients, the sd LDL/total cholesterol (TC) ratio presented a moderate positive association with both hs-CRP ($r = 0.487$, $p < 0.001$) and Lp-PLA$_2$ ($r = 0.436$, $p < 0.001$), indicating a strong association between inflammatory markers and sd LDL levels. The biomarker RDW demonstrated a mild but statistically significant correlation with the sd LDL/TC ratio ($r = 0.239$, $p = 0.013$), suggesting its potential role in assessing atherogenic risk in diabetic individuals.

Univariate regression equations were as follows:

- **sd LDL/TC = 0.187 + (0.015 × hs-CRP)**
- **sd LDL/TC = 0.171 + (0 × Lp-PLA$_2$)**
- **sd LDL/TC = 0.044 + (0.011 × RDW)**

The multivariate regression equation combining all three inflammatory markers was:

sd LDL/TC = 0.151 + (0.011 × hs-CRP) + (0.00 × Lp-PLA$_2$) + (0.002 × RDW)

These models highlight the significant influence of hs-CRP and RDW on sd LDL/TC ratios in diabetic patients.

Table 4.14: Correlation between inflammatory markers with sd LDL/TC among non -diabetic patients

Study variables	Correlation coefficient with sd LDL	p-value
hs-CRP	0.430	0.002*
Lp-Pla2	0.087	0.553
RDW	0.141	0.334

Among non-diabetic patients, the sd LDL/ Total cholesterol (TC) ratio showed a moderate and statistically significant positive correlation with hs-CRP ($r = 0.430$, $p = 0.002$), indicating an association between inflammation and atherogenic lipid levels even in the absence of diabetes. However, Lp-PLA$_2$ ($r = 0.087$, $p = 0.553$) and RDW ($r = 0.141$, $p = 0.334$) did not show any significant correlation with sd LDL/TC, suggesting a weaker or non-contributory role of these markers in non-diabetic individuals.

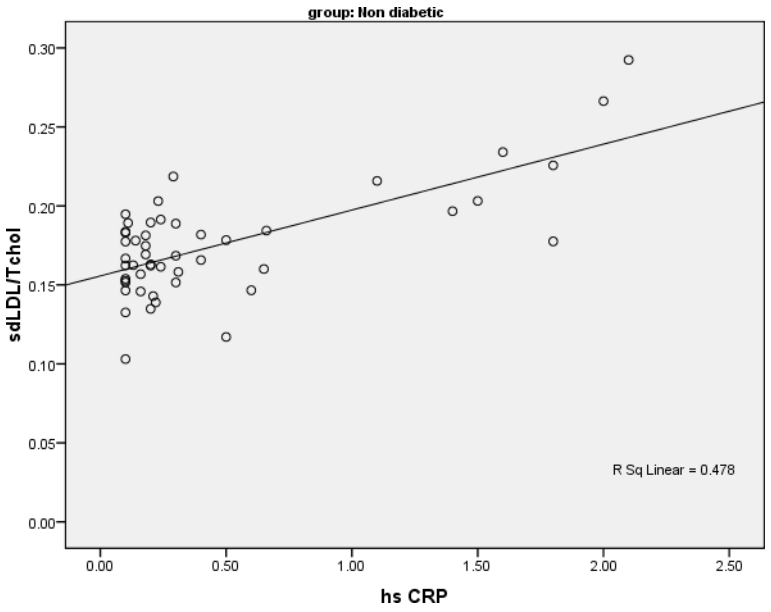


Figure 4.28: Correlation Between hs-CRP and sd LDL/Total Cholesterol Ratio in Non-Diabetic Patients

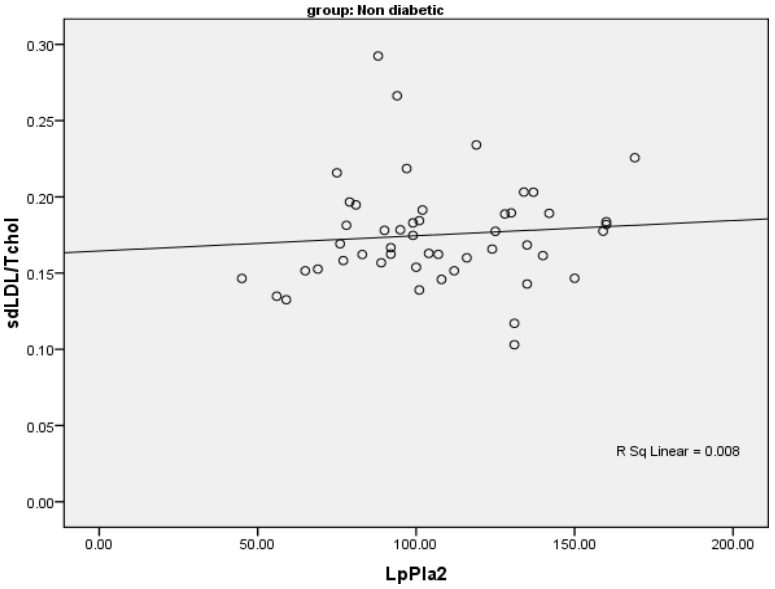


Figure 4.29: Correlation Between Lp-PLA$_2$ and sd LDL/Total Cholesterol Ratio in Non-Diabetic Patients

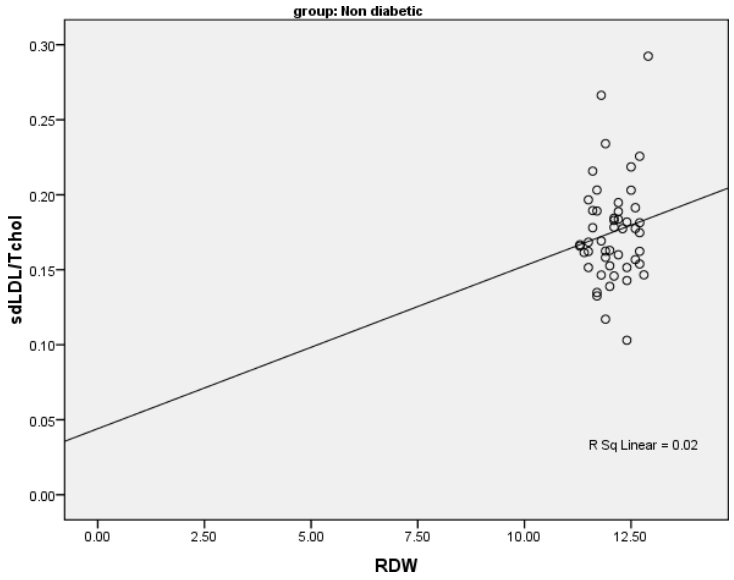


Figure 4.30: Correlation Between RDW and sd LDL/Total Cholesterol Ratio in Non-Diabetic Patients

Figures 4.30–4.32. sd LDL/TC vs markers in non-diabetics (n=102): hs-CRP (*r*=0.430, *p*=0.002); Lp-PLA₂ (*r*=0.087, *p*=0.553); RDW (*r*=0.141, *p*=0.334).

Figures 4.28,4.29,4.30: In non-diabetic patients, sd LDL/Total cholesterol ratio showed a moderate correlation with hs-CRP, indicating a possible link between inflammation and lipid profile. However, correlations with Lp-PLA₂ and RDW were weak and not significant, suggesting limited relevance of these markers in assessing sd LDL in non-diabetics.

Among non-diabetic patients, a statistically significant moderate positive correlation was observed between hs-CRP and sd LDL/TC. However, both Lp-PLA₂ and RDW disclosed no substantial correlation with sd LDL/TC.

The univariate regression equation was:

sd LDL/TC = 0.156 + (0.042 × hs-CRP).

Table 4.15: Comparison of correlation coefficient

Parameters	Z calculated	Z tabled	Decision
hs-CRP	0.414	1.96	$r_1=r_2$
Lp-PLA2	2.15	1.96	$r_1\neq r_2$
RDW	0.579	1.96	$r_1=r_2$

Comparison of correlation coefficients between diabetic and non-diabetic groups showed that the correlation of hs-CRP and RDW with sd LDL/TC was similar across both groups ($Z < 1.96$). However, the correlation coefficient for Lp-PLA$_2$ differed significantly between the two groups ($Z = 2.15 > 1.96$), indicating a group-specific variation in its association with sd LDL/TC.

Table 4.16: 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

Among control subjects, there was a strong and statistically significant positive association found between hs-CRP and sd LDL ($r = 0.619$, $p < 0.001$), suggesting a close association between inflammation and sd LDL even in healthy individuals. In contrast, Lp-PLA$_2$ and RDW showed weak and non-significant correlations with sd LDL, indicating minimal relevance of these markers in the control group.

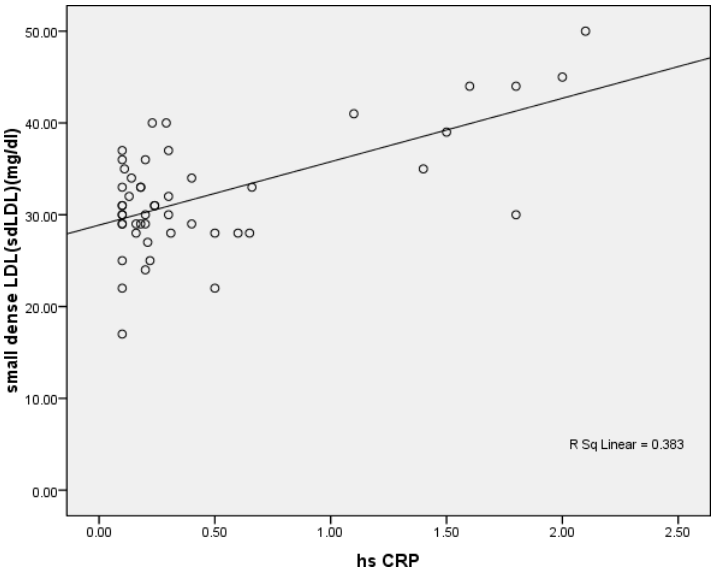


Figure 4.31: Correlation of hs-CRP with sd LDL among Controls (n=49): *r*=0.619, *p*<0.001.

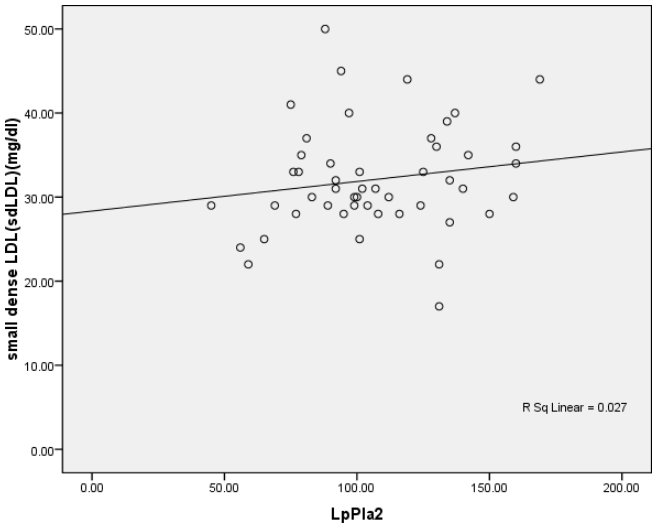


Figure 4.32: Correlation of Lp-PLA₂ with sd LDL among Controls (n=49): *r*=0.165, *p*=0.257.

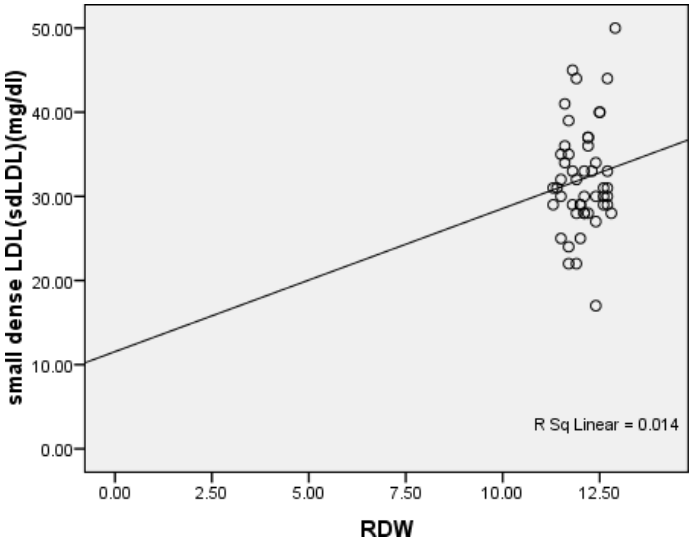


Figure 4.33: Correlation of RDW with sd LDL among Controls (n=49): *r*=0.120, *p*=0.413

In the control group, hs-CRP showed a strong and significant positive correlation with sd LDL, indicating that inflammation may influence sd LDL levels even in metabolically healthy individuals. In contrast, Lp-PLA₂ and RDW showed weak and statistically non-significant correlations, suggesting these markers may not be closely linked to sd LDL in controls. (Fig. 4.33,4.34,4.35)

Among non-diabetic patients, hs-CRP presented a moderate positive association with sd LDL, which was statistically significant, indicating that increases in hs-CRP levels were associated with higher sd LDL values. In contrast, Lp-PLA_2 and RDW did not show significant correlations and had very weak associations with sd LDL levels.

The univariate regression equation was:

sd LDL = 28.876 + (6.907 × hs-CRP)

Table 4.17: Comparison of correlation coefficient

Parameters	Z calculated	Z tabled	Decision
hs-CRP	1.07	1.96	$r_1=r_2$
Lp-PLA2	2.15	1.96	$r_1\neq r_2$
RDW	2.24	1.96	$r_1\neq r_2$

Comparison of correlation coefficients between diabetic and non-diabetic groups showed that the r values for **hs-CRP** were statistically similar across both groups (Z = 1.07 < 1.96). However, the **Lp-PLA_2** and **RDW** correlation coefficients significantly differed between the two groups (Z = 2.15 and 2.24 respectively > 1.96), indicating that these markers may behave differently in diabetic versus non-diabetic individuals in relation to sd LDL.

Chapter-5
DISCUSSION

Small dense low-density lipoprotein (sd LDL) particles are critical components of lipid metabolism. Their distinctive characteristics, in terms of size and density make them an important marker of cardiovascular diseases, dyslipidemia, etc. Since these particles are considered atherogenic and are correlated to insulin resistance understanding their significance in the diabetes is gaining importance. This highlights sd LDL as a mechanistic bridge between metabolic dysregulation and vascular injury rather than a mere lipid subfraction.

On comparing the sd LDL values in the four different categories of our study we observed that mean sd LDL levels are highest in DM patients with hypercholesterolemia compared to patients with metabolic syndrome without DM. Several factors could contribute to this distinction. Increased insulin resistance could be the prime factor. Even though insulin resistance is also associated with metabolic syndrome, it is sustained and more pronounced in diabetes. This suggests that severity and chronicity of insulin resistance, rather than its presence alone, determine sd LDL predominance.

The disrupted lipid metabolism can lead to higher sd LDL levels in diabetic patients. Impaired liver function in them compromises their ability to process triglyceride-rich lipoproteins efficiently which leads to increased VLDL and thereby elevates sd LDL (Watts, G. F., & Chan, D. C, 2011). Chronic Inflammation and Oxidative Stress in Diabetes could be another factor. Increased oxidative stress in diabetes contributes to LDL oxidation, which leads to elevated small dense particles in circulation. This inflammatory response is often more pronounced in diabetes than in metabolic syndrome alone, further increasing the sd LDL levels in diabetic patients (Wang et al.,2012). Thus, our findings support a dual mechanism of sd LDL accumulation — overproduction of triglyceride-rich precursors and oxidative modification.

The poor glycemic control in diabetes could also explain the elevated sd LDL levels. Hyperglycemia accelerates the glycation of lipoproteins. Oxidization of glycated LDL results in sd LDL production which in turn leads to elevated sd LDL levels (Chahil, T.

J., & Ginsberg, H. N.,2006). Pronounced hepatic lipid metabolism impairment is evident in diabetic patients, which may lead to altered lipoprotein remodeling and increased VLDL and sd LDL levels (Adiels M et al.,2008).

A specific lipid profile is often characterized by increased triglycerides, lower HDL cholesterol, and a shift toward more atherogenic, dense LDL particles in diabetic subjects with hypercholesterolemia, while in metabolic syndrome, even though dyslipidemia is common, the degree of lipid abnormalities differ, resulting in less sd LDL accumulation than in diabetes (Verges B ,2015). Elevated levels of circulating VLDL in diabetic patients and impaired clearance together can also be attributed to increased sd LDL levels in diabetes than in metabolic syndrome (Packard, C. J., & Shepherd, J,1997). These observations indicate amplification of the atherogenic lipid triad (↑TG, ↓HDL, ↑sd LDL) in diabetes beyond that seen in MetS.Previous reports affirm our results that the impaired metabolism in diabetes, particularly with concomitant hypercholesterolemia, drives a more profound shift towards a high proportion of sd LDL particles than metabolic syndrome.

We found that small dense LDL (sd LDL) levels were higher in patients with metabolic syndrome (MetS) without diabetes than in diabetic patients who did not have hypercholesterolemia. Metabolic syndrome is characterized by elevated triglycerides, a hallmark of dyslipidemia (Adiels, M. et al.,2008), distinct lipid profile etc. which can increase the sd LDL levels. The stable but slightly elevated glycemic index also contributes to sd LDL levels through VLDL synthesis and remodeling (Després et al., 2008). This indicates triglyceride-driven lipoprotein remodeling may play a more dominant role than glycemia in MetS-related sd LDL formation

Enhanced hepatic lipase activity is often reported in individuals with MetS, which could promote the hydrolysis of triglyceride-rich lipoproteins, leading to an increase in sd LDL formation (Hokanson, J. E., & Austin, M. A, 1996). The potential effects of medication for diabetes could also contribute to our observed result., The lipid-lowering medications, like statins or fibrates, prescribed for diabetic patients, even without hypercholesterolemia, can reduce both LDL-C and sd LDL levels (Otvos, J. D et.al 2006). Also, the pattern of lipoprotein dysregulation in MetS is often more severe. McLaughlin, T.et al.,2005 reported that even in the absence of diabetes, insulin

resistance in MetS promotes a lipid profile with high sd LDL levels due to increased VLDL and triglyceride processing into sd LDL particles. In short, our results suggest that Mets without diabetes show lipid profile favoring higher sd LDL production through altered lipid metabolism, higher triglycerides, and often due to therapeutic interventions aimed to lower VLDL and sd LDL.

Sacks, F.M.and Campos, H.In 2003, it was reported that people with hypercholesterolemia often have higher total LDL cholesterol (LDL-C), and this increase is associated with higher small, dense LDL levels that contribute to the total LDL fraction. Therefore, the absolute levels of sd LDL will be higher in those with hypercholesterolemia, even if the proportion of sd LDL remains consistent.

Also, in hypercholesterolemia, accelerated liver enzyme activity is often observed, evidenced by increased synthesis of lipoproteins like VLDL, which can be eventually transformed into sd LDL (Austin, M. A. et al 1990). This process could be triggered more often in diabetes where an increased output of sd LDL particles could be observed due to insulin resistance which leads to altered hepatic lipid metabolism. Insulin resistance can lead to a dyslipidemic profile characterized by lower HDL-C levels and elevated triglycerides conducive to higher sd LDL production (Krauss, R. M. 2004)). Increased hepatic lipase, along with reduced LDL receptor activity, can lead to impaired clearance of sd LDL, which will prolong the circulation of those particles in patients with hypercholesterolemia (Sniderman et al., 2019). Thus, both increased generation and delayed removal of sd LDL operate simultaneously in diabetic hypercholesterolemia.

The ratio of LDL to HDL cholesterol is commonly used as an indicator of cardiovascular risk. In clinical and research settings, a higher ratio is generally associated with a greater risk of cardiovascular disease.In this study, the LDL/HDL cholesterol ratio was higher in patients with diabetes than in participants without diabetes.This finding is consistent with the typical lipid pattern seen in diabetes, with higher LDL-C and lower HDL-C levels.In people with diabetes, LDL particles tend to be smaller and denser, and this pattern is linked to greater atherogenic potential.The higher ratio likely indicates both an increase in LDL levels and a shift in particle profile toward small, dense LDL.

At the same time, glycation and oxidative stress can reduce both the amount and function of HDL particles, which limits their role in cholesterol efflux and in maintaining endothelial health.In diabetic subjects, higher LDL alongside lower HDL increases the LDL/HDL ratio, which is consistent with a more atherogenic lipid profile and greater cardiovascular risk. Several papers, like the one by Kannel et al., have examined this issue.and Gordon and colleagues.Prior research shows that a higher LDL-to-HDL ratio is strongly linked to a higher risk of cardiovascular events.These results support the clinical relevance of this ratio, particularly in people with diabetes, who already have a higher risk of cardiovascular disease.In the study population, HDL cholesterol levels were lower in patients with diabetes than in patients without diabetes. This result is consistent with the established pattern seen in diabetic dyslipidemia. In diabetes, HDL levels may decrease due to several bio-mechanisms. Insulin resistance lowers the activity of lipoprotein lipase and hepatic lipase, enzymes that are needed for HDL maturation and remodeling.Second, in diabetes, long-term inflammation and oxidative pressure can reduce HDL production and increase the rate at which HDL is broken down.

Glycation of apolipoproteins, particularly ApoA1, impairs HDL function and reduces the ability of HDL particles to support reverse cholesterol transport. In diabetes, hypertriglyceridemia is common and can increase cholesterol transfer between HDL and triglyceride-rich lipoproteins through CETP (cholesteryl ester transfer protein). This process produces HDL particles that contain more triglyceride, which are cleared from the bloodstream more quickly. Thus, the reduced HDL seen in people with diabetes indicates not only a lower amount of HDL but also changes in its quality and function, which may weaken its usual protective role against atherosclerosis.

In our study, patients with diabetes had higher total cholesterol levels than patients without diabetes.The increase in total cholesterol seems to be mainly due to higher LDL cholesterol, especially a rise in small, dense LDL particles that make a meaningful contribution to the total cholesterol level. In diabetes, insulin resistance can raise the liver’s production of VLDL, which is then converted into LDL, often with a higher share of small, dense LDL particles.

Reduced LDL receptor activity lowers the clearance of LDL particles and raises total cholesterol levels. In people with diabetes, an imbalance between cholesterol production and removal is often worsened by diet and inherited traits that are common in this group. Inflammatory cytokines can also alter hepatic lipid metabolism by increasing the liver's own cholesterol synthesis.In diabetes, higher total cholesterol reflects the combined effects of impaired lipid regulation, inflammatory processes, and broader metabolic dysregulation. This supports the routine monitoring and management of lipids as part of standard diabetes care.High-sensitivity C-reactive protein (hs-CRP) is commonly used as an indicator of low-level systemic inflammation.In our study, patients with diabetes showed higher hs-CRP levels than individuals without diabetes.This finding is consistent with the view that diabetes involves a pro-inflammatory state.Sustained hyperglycemia increases the formation of advanced glycation end products (AGEs), which promote the release of pro-inflammatory cytokines and impair endothelial function, and this process can stimulate CRP production by hepatocytes.

Insulin resistance and higher adiposity, especially visceral fat, are linked to the production of inflammatory adipokines such as TNF-α and IL-6, which can increase hs-CRP levels. Elevated hs-CRP has been strongly associated with increased cardiovascular events and atherosclerosis, as it echoes constant vascular inflammation and damage. Hence, the increased hs-CRP in our diabetic cohort underscores the inflammatory component of diabetes, which exacerbates cardiovascular risk beyond traditional lipid parameters.

Thus, hs-CRP levels are generally greater in those with diabetes than in those without the disease as a result of elements like chronic low-grade inflammation, dyslipidemia, obesity, insulin resistance, increased cardiovascular risk, along with poor glycemic control. These are the mechanisms that emphasize the part of inflammation in the pathophysiology of diabetes and its associated complications.

The biomarkers high-sensitivity C-reactive protein (hs-CRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), and red cell distribution width (RDW) are gaining attention in diabetes research for their roles in inflammation and cardiovascular risk.

Their combined assessment reproduces systemic inflammation (hs-CRP), plaque-

specific lipid inflammation (Lp-PLA2), and hematologic oxidative stress (RDW), providing a multi-faceted risk profile.

Lp-PLA2 is associated with LDL particles and is involved in the inflammatory response within atherosclerotic plaques. Lp-PLA2 is largely related with sd LDL particles and is involved in the breakdown of oxidized phospholipids. In diabetes, sd LDL particles are more inclined to oxidation, stimulating higher Lp-PLA2 activity. The enzymatic activity of Lp-PLA2 catalyzes the release of pro-inflammatory molecules, creating a vicious inflammatory cycle and lipid modification that enhances the atherogenicity of sd LDL (Kolodgie, F. D., et al..2006 ., Davidson, M. H., & Corson, M. A. 2008). Therefore, its correlation with sd LDL in our diabetic cohort may indicate heightened plaque vulnerability rather than simple lipid elevation

Elevated levels of Lp-PLA2 are thought to contribute to plaque instability, making it a suitable marker of vascular inflammation and a predictor of cardiovascular events. In diabetic patients, especially those with poor glycemic index, the Lp-PLA2 levels are often elevated, potentially due to increased oxidative stress and inflammatory processes and Studies have shown that these diabetic patients with high Lp-PLA2 levels are more susceptible to vascular ailments such as myocardial infarction and cerebrovascular attacks (D'Agostino, R. B.2008).

Hence, Measuring Lp-PLA2 in diabetic patients may help in the stratification of high-risk patients. As Lp-PLA2 is more strongly associated with atherosclerotic inflammation rather than general inflammation, it may not be a standalone marker of inflammation. Hence its role as a routine biomarker in diabetes is still debated and clinical guidelines on Lp-PLA2 use remain limited as the levels may be influenced by factors beyond diabetes, such as age, LDL levels, and use of lipid-lowering therapies, thereby complicating its interpretation in clinical practice. Lp-PLA2 and hs-CRP correlation with sd LDL in DM with hypercholesterolemia.

Red Cell Distribution Width (RDW) which denotes the variance in the size of red blood cells is typically used to diagnose and monitor anemia. Recently, the role of RDW as a

potential marker of inflammation and oxidative stress has been investigated because elevated RDW may indicate heightened erythrocyte turnover due to these factors. As a broader marker of inflammatory and oxidative stress, RDW is less directly related to sd LDL in diabetic patients compared to hs-CRP or Lp-PLA2, making its correlation with sd LDL generally weaker {Perlstein, T. S., et al. (2009., Lippi, G., & Targher, G. (2014)}.

In diabetic patients, particularly in people with poorly managed diabetes or diabetes-related complications, the RDW levels are often elevated which correlates with an enhanced probability of cardiovascular complications, likely reflecting chronic inflammation and endothelial dysfunction in diabetes. The ubiquitous and inexpensive nature of RDW makes it a convenient marker for assessing cardiovascular risks. RDW is also influenced by anemia, iron deficiency, and renal impairment usually common in diabetic patients. This makes the correlations more complicated specifically in patients with multiple comorbidities.

A slight elevation in RDW values in diabetic patients with hypercholesterolemia, compared to those with metabolic syndrome (MetS) without diabetes and diabetic patients without hypercholesterolemia, was observed in the study. Red cell distribution width (RDW) quantitates the discrepancy in red blood cell size (anisocytosis) and is often considered a possible indicator of inflammation and cardiovascular risk. Tonelli and Sacks (2008), along with Lippi and colleagues (2019), are cited in this context.

The study shows that conditions like diabetes enhance inflammatory responses and can elevate RDW. The oxidative stress and low-grade inflammation are more pronounced in diabetic patients with hypercholesterolemia, leading to higher RDW. In contrast, MetS without diabetes exerts a lesser effect on RDW due to the absence of direct hyperglycemic damage to RBCs and fewer disruptions in erythropoiesis (Cakir et al., 2014). Diabetic patients without hypercholesterolemia may still show elevated RDW due to hyperglycemia and associated oxidative stress (Semba et al., 2010), but without the additive pro-inflammatory effects of hypercholesterolemia, leading to a relatively smaller increase in RDW.

We found that red cell distribution width (RDW) differed only to a moderate degree in diabetic patients with hypercholesterolemia compared with participants who had metabolic syndrome (MetS) without diabetes and with diabetic patients without hypercholesterolemia.This can be influenced by several factors. Park et al. (2016) suggested that in a homogeneous population in terms of age, sex, and underlying health conditions, variations in RDW may not be pronounced. These results suggest that, in this study, RDW served as a supportive but non-specific biomarker. It appeared to reflect broader metabolic and inflammatory changes, yet it was not specific enough to differentiate clinical cohorts independently.

Wang et al. (2017) implied that the presence of similar comorbidities and glycemic control across the groups can also lead to a lack of significant variation in RDW. Effective diabetes management, uniform dietary and medication adherence, and chronic disease stabilization mechanisms may reduce erythropoietic stress and standardize RDW levels despite lipid profile differences.

Thus, the variation in RDW among diabetic patients with hypercholesterolemia, those with MetS without diabetes, and diabetic patients without hypercholesterolemia can be attributed to factors such as similar glycemic control levels, the homogeneity of the study population, the influence of comorbid conditions, and the stabilization of RDW due to chronic disease effects.

In summary, our study contributes to the growing understanding of sd LDL's role in health and disease and could enhance risk stratification and inform therapeutic strategies in clinical practice, particularly for individuals with diabetes and metabolic syndrome. As research progresses, sd LDL may play an increasingly vital role in personalized medicine and the prevention of cardiovascular diseases. Furthermore, biomarkers such as hs-CRP and Lp-PLA2 also display a substantial role in diabetes research as markers of inflammation, indicators of insulin resistance, predictors of cardiovascular risk and diabetes complications, tools for monitoring medication response, and correlates of lipid profiles. The assessment of hs-CRP, along with RDW and Lp-PLA2, can offer insightful information about the health status of individuals

with diabetes and help guide medical decision-making.

In our study, diabetic individuals exhibited significantly elevated levels of small dense LDL (sd LDL) compared to non-diabetics (45.31 ± 11.53 vs. 32.10 ± 6.32; $p < 0.001$). This outcome line up with previous research indicating that diabetes is associated with an atherogenic lipid profile characterized by increased sd LDL concentrations, which promote this population's risk of cardiovascular disease (Otvos et al., 2002; Krauss et al., 2004).

The sd LDL/LDL and sd LDL/Cholesterol ratios were also higher in diabetics (0.340 ± 0.05 and 0.214 ± 0.037, respectively) than in non-diabetics (0.290 ± 0.053 and 0.175 ± 0.034, respectively). These elevated ratios suggest a greater proportion of sd LDL within the total LDL and cholesterol pools in diabetic patients, further emphasizing the qualitative lipid abnormalities that may predispose this group to atherosclerosis (Musunuru et al., 2010).

Additionally, we observed substantially higher levels of lipoprotein-associated phospholipase A2 (Lp-PLA2) in diabetics compared to non-diabetics (181.20 ± 66.65 vs. 106.90 ± 29.70; $p < 0.001$). This enzyme, primarily associated with LDL particles, plays a role in the hydrolysis of oxidized phospholipids, leading to the generation of pro-inflammatory mediators. Elevated Lp-PLA2 activity has been associated to augmented risk of cardiovascular events and has been found to be higher in individuals with type 2 diabetes, reflecting enhanced vascular inflammation and atherogenesis in this population (Packard et al., 2008).

Furthermore, the inflammatory marker high-sensitivity C-reactive protein (hs-CRP) was significantly elevated in diabetic subjects (1.832 ± 1.19) compared to non-diabetics (0.467 ± 0.566; $p < 0.001$). This elevation shows a phase of chronic low-grade inflammation commonly observed in diabetes, which contributes to endothelial dysfunction and the progression of atherosclerosis (Ridker et al., 2000).

Red cell distribution width (RDW) was also higher in diabetics (12.875 ± 0.57) than in non-diabetics (12.075 ± 0.44; $p < 0.001$). While RDW is traditionally a measure of

erythrocyte size variability, recent studies have associated higher RDW values with increased cardiovascular risk and inflammation (Zalawadiya et al., 2011).

The observed increase in RDW among diabetic patients may reflect fundamental inflammatory processes and the role of oxidative stress in vascular complications.
Taken together, these results suggest that in diabetes, abnormal lipid levels, inflammation, and blood-related factors interact with each other and contribute to the higher risk of cardiovascular disease seen in this group.

The correlation of hs-CRP, Lp-PLA_2, and sd LDL in patients with Mets without DM highlights the inflammatory and lipid-related risks related with cardiovascular ailments in the absence of diabetes. A strong positive and statistically significant correlation was observed in the hs-CRP and sd LDL comparison of metabolic syndrome patients without DM. Elevated triglycerides and low HDL levels are often linked to Metabolic syndrome which is characterized by obesity, hypertension, and dyslipidemia. These metabolic disturbances can help to raise the levels of both sd LDL and hs-CRP.

Agreeing with our results studies have reported a mild positive correlation of hs-CRP and sd LDL which is attributed to the chronic low-grade inflammation that usually co-exist with insulin resistance and obesity. Conversely, the elevated sd LDL levels can undergo oxidization, and can further increase systemic inflammation resulting in higher hs-CRP levels. Després, J. P., Lemieux, I., & Prud'homme, D. (2001) reported an elevated level of hs-CRP particularly increased sd LDL in metabolic syndrome suggesting that these markers are elevated because of insulin resistance and lipid alterations, even without diabetes. Ridker et al. showed that hs-CRP elevation is common in metabolic syndrome and is associated with atherogenic lipoprotein profiles, including sd LDL. This study links hs-CRP with cardiovascular risk and metabolic syndrome characteristics.

As demonstrated in our results the Lp-PLA_2, shows a considerable positive association with the sd -LDL. The enzyme attaches to and hydrolyzes phospholipids in small, dense low-density lipoprotein (sd LDL) and could be considered as a marker of sd LDL levels (Tsimikas, S., & Witztum, J. L. 2008., McConnell, J. P et al.,.2005) This enzymatic

activity promotes inflammation by the generation of pro-inflammatory oxidized lipids within blood vessel walls thereby reflecting the atherogenic potential of sd LDL in metabolic syndrome patients even without diabetes.

Previous reports (Berneis, K. K., & Krauss, R. M. 2002) also show that metabolic syndrome, independent of diabetes, is associated with sd LDL and inflammation and the elevated levels of sd LDL and related markers like Lp-PLA_2 and hs-CRP could be attributed to transformed lipid metabolism in metabolic syndrome. These reports suggest hs-CRP, Lp-PLA_2, and sd LDL are interconnected, and vascular and systemic inflammation contribute to increased cardiovascular risk even in non-diabetic patients.

Controversial results are also reported stating that differences in diagnostic criteria variability in measurement procedures, specificity and predictive value of these markers and influences of gender as well as ethnicity can perplex the interpretation of the relationships and the general understanding of cardiovascular risk in this population. Elevated RDW is suggestive of underlying inflammation, nutritional deficiencies, or oxidative stress, all of them are associated with higher cardiovascular risk (Kohli, P., & Kahn, C. R.,2008).

Recent researches suggest a connection between RDW and lipid profile including sd LDL demonstrating that higher RDW could be related to a high atherogenic lipid profile, even in patients with metabolic syndrome without diabetes (Mardani, A., et al. (2019), Zhang, Y., et al. (2021). The correlation between RDW and sd LDL in metabolic syndrome without diabetes may be attributed to

1. Inflammation- Metabolic syndrome is characterized by chronic low-grade inflammation, that can elevate both RDW and sd LDL levels. Inflammatory cytokines may impact erythropoiesis, leading to increased RDW along with elevated sd LDL
2. Oxidative Stress- Higher Oxidative stress may result in dysregulated erythropoiesis, Lower RBC counts, decreased RBC lifespan -
3. Dyslipidemia- The alterations in lipid profile seen in metabolic syndrome, characterized by increased sd LDL and lower HDL cholesterol, may influence

RDW levels, creating a possible feedback loop between lipid metabolism and red cell morphology. The correlation between RDW and sd LDL is an evolving area of curiosity in cardiovascular and metabolic research.

Although there is a notable interest in the correlation between RDW and sd LDL in metabolic syndrome patients without diabetes, some studies question this association. Nakatani, K., et al. (2017) in their study specifically examined Japanese patients with metabolic syndrome and failed to find any significant association between RDW and sd LDL levels, suggesting that regional or population-specific factors may influence these markers. Avci, A., et al. (2019) indicated that while RDW was associated with various components of metabolic syndrome, its correlation with sd LDL became non-significant when adjusted for other risk factors such as obesity and inflammatory markers. Duchene, J., et al. (2019) reported that higher RDW may be a marker of nutritional deficits, such as iron deficiency, rather than evidence of a direct association with inflammation or with sd LDL levels.

In a community-based study, the authors found no significant association between RDW and metabolic syndrome parameters, including sd LDL, highlighting that population-specific influences can also lead to divergent results (Jiang, Y., et al. (2016)). All these reports warrant further research to clarify these associations and their inferences for cardiovascular risk assessment in different populations. Tannous, J., et al. (2018) reported that variability in measurement methods can influence observed correlations, suggesting that discrepancies in findings may arise from methodological differences.

The mild positive correlation we report in our study between RDW and sd LDL in metabolic syndrome patients without diabetes suggests that increased RDW could be indicative of both inflammation and lipid alterations associated with the syndrome.

Our data suggests a highly statistically significant positive correlation among all three variables hs-CRP, Lp-PLA2, and RDW in DM patients with hypercholesterolemia. Baker, R. M., et al. (2014) reported that both hs-CRP and Lp-PLA2 levels were significantly correlated with sd LDL levels, indicating that inflammation could aid in the development and presence of sd LDL in diabetic patients with

hypercholesterolemia. Liu et al. (2016) in a cohort of patients with type 2 diabetes also reported that both hs-CRP and Lp-PLA2 were significant predictors of sd LDL levels. Their analysis indicated a direct relationship between elevated inflammatory markers and the incidence of more atherogenic sd LDL particles proportions.

Diabetes which is characterized by low-grade chronic inflammation, can alter lipid metabolism. Elevated Lp-PLA2 levels can increase the formation of oxidized LDL and enhance the inflammatory response, contributing to the conversion of larger LDL particles into sd LDL.

Inflammatory cytokines may elevate the levels of sd LDL, leading to an increase in cardiovascular risk. The combination of high hs-CRP and Lp-PLA2 levels can amplify the inflammatory processes leading to endothelial dysfunction and atherogenesis, highlighting the interconnectedness of these markers in the context of diabetes. The positive and moderate correlation of hs-CRP and Lp-PLA2 with sd LDL in patients with diabetes and hypercholesterolemia implies the role of inflammation in lipid metabolism and cardiovascular risk. Elevated levels of these markers may indicate the need for more aggressive therapies or anti-inflammatory interventions to mitigate cardiovascular risk. This supports the concept that inflammatory mediators actively influence lipoprotein remodeling,

Table :5.1 Lipid–Inflammatory Profile Across Study Groups

Feature	**DM + Hypercholesterolemia**	**DM without Hypercholesterolemia**	**MetS without DM**	**Non-Diabetic Controls**
sd LDL Level	Highest	High	Moderate	Lowest
Primary Driver	Severe insulin resistance + high LDL pool	Insulin resistance + glycation	Triglyceride excess	Normal lipid metabolism
Mechanism of sd LDL Formation	VLDL overproduction + impaired clearance	Hepatic remodeling + oxidative modification	TG-driven lipoprotein remodeling	Minimal conversion
Role of Hyperglycemia	Major	Major	Minor	Absent

Triglyceride Influence	High	Moderate	Very high (dominant factor)	Normal
Inflammatory Burden (hs-CRP)	Markedly elevated	Elevated	Mild–moderate	Low
Lp-PLA2 Association	Strong (sd LDL-linked plaque inflammation)	Moderate	Mild	Minimal
RDW Significance	Mild–moderate (non-specific)	Mild	Mild	Minimal
Dominant Pathology	Lipid + inflammatory synergy	Glycation + lipid remodeling	Dyslipidemia-driven	Physiological
Atherogenic Risk Level	Very High	High	Moderate	Low

Hence monitoring hs-CRP and Lp-PLA2 levels alongside sd LDL could improve cardiovascular risk assessment in diabetic patients with hypercholesterolemia. Understanding the relationship between these biomarkers can offer insightful information on the atherogenic processes in diabetic patients and thereby help healthcare providers develop targeted strategies to manage dyslipidemia and inflammation in diabetic patients, potentially reducing cardiovascular events. Controversial reports to our observation suggest that factors such as measurement variability, the influence of confounding conditions such as obesity and blood pressure, and population differences can complicate the interpretation of these relationships as these markers may not independently predict sd LDL levels.

A clarification of these associations and an understanding of the underlying mechanisms involved is possible only through further research.

Red cell distribution width (RDW) refers to how much red blood cell size varies within a blood sample and is commonly used as part of the clinical evaluation of anemia.However, recent studies have explored RDW as an inflammatory marker in conditions like diabetes mellitus (DM) and hypercholesterolemia. Higher RDW is linked to impaired glucose control, greater cardiovascular risk, and elevated

inflammatory markers, which are common in diabetes. Our study indicates a strong positive correlation between RDW and sd LDL. Cengiz et al. (2015) in their cross-sectional analysis of a cohort of patients also reported elevated RDW and CRP levels in patients with DM and hypercholesterolemia than with only diabetes or hypercholesterolemia alone and proposed that elevated RDW might be a reflection of the combined effect of metabolic and inflammatory disturbances, which could exacerbate cardiovascular risk. In Diabetic patients with poor glycemic control, underlying chronic inflammation can impact RBC morphology thereby RDW could be elevated. Along with CRP increase an increase in other inflammatory markers like interleukin-6 (IL-6) are also reported. Reports also imply that higher RDW levels in patients could be indicative of major adverse cardiovascular events (MACE) such as myocardial infarction, stroke, and cardiovascular mortality suggesting RDW as a simple, cost-effective biomarker of cardiovascular events and mortality in patients with diabetes who also have hypertension, hypercholesterolemia or other cardiovascular risk factors. (Kengne et al.,2014). Baye et al. also pointed out the strong association between RDW and cardiovascular events particularly in diabetic patients with deranged lipid levels (such as hypercholesterolemia) after thorough investigations of multiple literature suggesting that RDW may reflect erythrocyte deformability and turnover in response to inflammation and oxidative stress, exacerbated by both diabetes and hypercholesterolemia.

On the contrary, Zhang et al. reported that elevated RDW was observed in some diabetic patients and was not consistently associated with cardiovascular outcomes in the way that other inflammatory markers, such as CRP questioned the specificity of RDW as a marker of cardiovascular risks. Huang and colleagues also reported that the association between RDW levels and cardiovascular mortality in diabetic patients with elevated cholesterol levels was non-significant in a monitoring period of four years. Even though RDW correlated with inflammatory markers, they are not a strong independent predictor of mortality once other factors, such as glycemic control and hypertension were adjusted (Wang, X., et al.,2020), (Thompson, C. S., et al.,2016). Some reports also suggest that RDW levels could be significantly influenced by factors unrelated to cardiovascular health, such as renal function, levels of certain micronutrients (e.g., iron and vitamin B12), and anemia, which are often reported in

diabetic patients. (Lee et al., 2018)

Our results suggest that RDW could be a simple, valuable, and easily accessible predictor for cardiovascular risks in diabetic patients, especially with hypercholesterolemia. Given its association with inflammation and oxidative stress, RDW might help in early risk categorization, prompting clinicians to adopt more aggressive cardiovascular preventive strategies in high-risk diabetic patients. However, further research is encouraged to standardize RDW's use in clinical practice and explore its utility across different diabetic subpopulations.

Our comparison showed that both the variables hs-CRP and Lp-PLA2 were positively and moderately correlated to sd LDL with statistical significance. At the same time, the RDW showed a very poor positive correlation with sd LDL also with no statistical significance. This could be explained by the specific roles these biomarkers play in inflammation, oxidative stress, and lipid metabolism in diabetes.

High-sensitivity C-reactive protein (hs-CRP) is an inflammatory marker Due to chronic low-grade inflammation its levels are often elevated in diabetes. In diabetic patients, inflammation leads to the formation of sd LDL, which is more prone to oxidation and is often associated with atherogenic risk. Elevated hs-CRP levels contribute to endothelial dysfunction and lipid oxidation, which in turn is linked to sd LDL formation. Increased sd LDL, being small and dense, can easily enter arterial walls and will be oxidized, triggering further inflammatory responses which again result in elevated hs-CRP (Packard, C. J., & Libby, P ,2008), (Ridker, P. M.,2003).

Lipoprotein-associated phospholipase A2 (Lp-PLA2) the enzyme primarily associated with LDL particles, particularly sd LDL is pro-inflammatory and plays a major role in the oxidative modification of LDL, particularly sd LDL. These modifications can further contribute to plaque formation and progression in the arteries. Due to these enhanced LDL modifications, Lp-PLA2 levels are often higher in patients with diabetes, even without elevated cholesterol. The sd LDL particles rich in oxidized phospholipids stimulate Lp-PLA2 activity, contributing to a positive correlation between these two markers (Davidson, M. H., & Corson, M. A,2008), (Kolodgie, F. D

et al.,2006).

Factors like erythrocyte turnover, inflammation, and oxidative stress often affect RDW. However, mostly RDW unlike hs-CRP and Lp-PLA2 is considered a broader marker that may not directly reflect the specific changes in lipid metabolism or LDL characteristics. In diabetic patients, RDW can be affected by factors like erythropoiesis, vitamin deficiencies, or other comorbidities unrelated to lipid lipids which negate its correlation with sd LDL. Unlike the close association of hs-CRP and Lp-PLA2 to sd LDL which are directly involved in lipid oxidation and atherogenic processes inflammation RDW could not be directly equated to sd LDL. (Lippi, G et al., 2014, Perlstein, T. S., et al., 2009).

High-sensitivity C-reactive protein (hs-CRP) is a marker of systemic inflammation and endothelial dysfunction, and Lp-PLA2 is involved in the inflammatory modification of LDL particles, specifically sd LDL. In diabetes, inflammation and oxidative stress play crucial roles in the development of atherosclerosis.This may explain for the strong correlation observed among patients with diabetes (Libby, P, 2002), (Ballantyne, C. M., et al.,2004), (Rizzo, M., & Berneis, K, 2006). hs-CRP and Lp-PLA2 are often treated as relatively specific markers that reflect inflammation and oxidative activity linked to lipid-related pathways. This is why their association with sd LDL is especially relevant in diabetes, even when total cholesterol is not elevated. RDW tends to reflect broader physiologic influences, such as systemic stress, inflammation, and changes in erythropoiesis, rather than specific lipid modifications. The weaker association between RDW and sd LDL suggests that RDW captures broader physiological variation in diabetes that is not closely tied to lipid metabolism. (Forhecz, Z et al.,2010, Lippi, G et al., 2014, Tonelli, M., et al.,2008)

In people with metabolic syndrome (MetS) who did not have diabetes, we found higher levels of small dense low-density lipoprotein cholesterol (sd LDL-C).The correlation between sd LDL-C and high-sensitivity C-reactive protein (hs-CRP) was not statistically relevant .This finding aligns with prior studies showing that, although sd LDL-C levels are linked to MetS traits, the link does not depend on inflammatory markers such as hs-CRP. The absence of an observed association suggests that sd

LDL-C may contribute to MetS through pathways that are separate from systemic inflammation.

The association between sd LDL-C and red cell distribution width (RDW) in patients with MetS who do not have diabetes has received limited research attention.RDW is a blood test measure that describes how much red blood cell size varies, and prior work has linked higher RDW values with inflammation and greater cardiovascular risk (Lippi et al.2014).Although RDW is often treated as an inflammatory marker shaped by many influences, the nature and strength of its association with sd LDL-C in MetS are still not well defined.Further research is needed to clarify whether sd LDL-C and RDW are related in this population.

Among participants with Metabolic Syndrome who did not have diabetes, we observed moderately higher sd LDL levels, and sd LDL showed a positive correlation with hs-CRP.This is consistent with earlier findings showing an association between Metabolic Syndrome, systemic inflammation, and altered lipid metabolism, including in people who remain normoglycemic (Otvos, 2002).Higher sd LDL in this group may reflect an early shift toward an atherogenic dyslipidemia pattern, in which insulin resistance and obesity contribute to adverse changes in lipid levels.The association between sd LDL and Lp-PLA2 appeared weaker, which may reflect lower oxidative stress in this sample than is typically observed in people with diabetes. These results support the case for early screening for lipid changes and inflammatory imbalance in Metabolic Syndrome.

RDW was higher in participants with diabetes, but its correlation with sd LDL was weak. RDW is a general marker of inflammation and may be shaped by anemia, oxidative stress, and impaired kidney function (Zalawadiya, 2011). In contrast to hs-CRP and Lp-PLA2, which are more closely tied to lipid-driven inflammatory processes, RDW mainly reflects broader variation across the body and does not closely align with sd LDL levels. Higher RDW has been linked to cardiovascular mortality and chronic inflammation in people with diabetes. Because RDW is not specific, it should be considered a supporting, rather than primary, risk marker in diabetic dyslipidemia. This advocates RDW echoes systemic inflammatory pressure

than lipid related pathology.

This study provides clear evidence that inflammation plays a major role in lipid metabolism, focusing on how small dense LDL (sd LDL) particles vary across diabetic, non-diabetic, and control groups. Of the inflammatory markers assessed, high-sensitivity C-reactive protein (hs-CRP) showed the most consistent association with sd LDL and with the sd LDL/Total cholesterol (TC) ratio across all groups. This supports its use as an indicator of subclinical inflammation and atherogenic risk, in line with the results reported by the study and the work by Zhang et al.(2013) (Smith et al.the 2011). These results support hs-CRP as a key marker of inflammation linked to atherogenic dyslipidemia.

Among patients with diabetes, both hs-CRP and lipoprotein-associated phospholipase A2 (Lp-PLA2) were moderately and positively correlated with the sd LDL/TC ratio, and these correlations were statistically significant. These results suggest that, in diabetes, long-term inflammation and enzyme activity may act together to change lipid particle density, which is consistent with prior reports by Thomas et al. (2015) and Jialal et al.(2017).Red cell distribution width (RDW) showed only a weak association, but it still had a small, statistically meaningful correlation, which may point to a secondary inflammatory pathway that affects lipid metabolism.

In the non-diabetic group, hs-CRP was the only marker that remained statistically associated with sd LDL/TC, whereas Lp-PLA_2 and RDW did not show an association. This implies that inflammation may start to alter lipid profiles in subtle ways even before diabetes is clinically apparent, consistent with the early subclinical changes (Kim et al.2018).In this group, the regression model showed that hs-CRP had an independent association with lipid density.

In the control group, the analyses were consistent with the non-diabetic results, and hs-CRP again showed a solid connection with sd LDL, supporting its broader role in early inflammatory dyslipidemia. By comparison, Lp-PLA_2 and RDW showed no statistical association, suggesting limited value for risk prediction in metabolically healthy individuals, in line with the results reported by Lee et al.2019. Z-score

comparisons of correlation coefficients indicated that the association between hs-CRP and sd LDL/TC was similar in both groups, while the correlations involving Lp-PLA_2 and RDW differed in strength between individuals with diabetes and those without diabetes. This divergence suggests a likely interplay between metabolic status and inflammatory pathways that may influence sd LDL levels, in line with the differing biomarker patterns (Singh et al.2021).

Overall, the multivariate regression models indicated that hs-CRP and RDW were key factors linked to the sd LDL/TC ratio in people with diabetes, even after controlling for Lp PLA_2. These models provide added support for the idea that inflammation is linked to fat metabolism. This may influence how clinicians predict cardiovascular risk and how they plan and adjust patient management.

Clinical Utility of a Combined Biomarker Panel

Evaluating sd LDL, hs-CRP, Lp-PLA2, and RDW together may improve the estimation of cardiovascular risk.Taken separately, sd LDL reflects the atherogenic potential of lipids, hs-CRP reflects systemic inflammation, Lp-PLA2 reflects vascular inflammation, and RDW reflects variation in red blood cell size.Taken together, these markers indicate a higher overall risk profile among people with diabetes and hypercholesterolemia (Ridker, 2000).Prior studies report that adding hs-CRP and Lp-PLA2 to standard lipid measures improves risk prediction.More research is needed to assess the clinical value of adding these markers to routine screening.

Study Limitations and Confounding Factors

This study has important limitations that should be considered when interpreting the results. Because the study is cross-sectional, it cannot establish causation. RDW is also affected by factors not related to lipids, such as anemia and reduced kidney function, which were not fully controlled for in the analysis (Lippi, 2014).To confirm these findings and define how they should be applied in diabetic risk stratification, larger studies that follow participants over time are needed.

In conclusion, type 2 diabetes mellitus (T2DM) is a metabolic disorder with several

contributing factors, and it increases the risk of cardiovascular disease (CVD) through dyslipidemia, oxidative stress, and long-lasting inflammation.This study examined the levels of four biomarkers—small dense low-density lipoprotein (sd LDL), lipoprotein-associated phospholipase A2 (Lp-PLA2), high-sensitivity C-reactive protein (hs-CRP), and red cell distribution width (RDW)—and the associations among them in people with and without diabetes, with the goal of assessing their possible value for predicting cardiovascular risk.

Our results show that diabetic patients had higher levels of sd LDL than the non-diabetic control group. This aligns with prior evidence that diabetes is linked to a more atherogenic lipid profile. In people with diabetes, not only the absolute amounts but also the ratios of sd LDL to total LDL and to cholesterol were higher. This pattern suggests a change in lipid composition that may increase the risk of atherosclerosis. These changes reflect the metabolic disturbance and insulin resistance often present in T2DM, which promote the formation of small, dense, highly atherogenic LDL particles.Lp-PLA2, an enzyme linked to LDL particles, with a stronger link to small dense LDL, was found at higher levels in people with diabetes. Because Lp-PLA2 breaks down oxidized phospholipids on LDL and creates pro-inflammatory byproducts, higher levels in this group are consistent with greater oxidative stress and inflammation in the blood vessel wall. Elevated Lp-PLA2 levels support the view that sd LDL is more than a lipid marker; it may contribute to inflammatory changes in the vascular wall, tying dyslipidemia to inflammation-mediated atherogenesis.

Accordingly, hs-CRP levels were higher in patients with diabetes, which is consistent with the low-grade systemic inflammation often seen in T2DM.In participants with diabetes, the positive association between sd LDL and hs-CRP supports the view that inflammatory activity may contribute to lipid oxidation, endothelial dysfunction, and atherosclerotic plaque development. These findings support a feedback loop in which inflammatory cytokines increase the production and oxidation of sd LDL, and sd LDL then sustains inflammatory activity, together raising cardiovascular risk.

RDW is usually used to assess anemia, but recent work suggests it may also indicate

systemic inflammation and oxidative stress. In this study, RDW levels were higher in participants with diabetes. Its correlation with sd LDL was weaker in comparison. This likely reflects that RDW is a broad and non-specific measure that can be shaped by many conditions, including nutritional deficiencies, anemia, and renal impairment, which are often seen in people with diabetes. Even so, higher levels may still be considered a secondary marker when estimating cardiovascular risk.

When considered together, measuring sd LDL, hs-CRP, and Lp-PLA2 provides a clearer view of how inflammatory and lipid-related pathways contribute to cardiovascular complications in patients with diabetes.These markers are not reliable on their own for prediction, but adding them to routine monitoring may help identify individuals at high risk earlier. Because RDW is widely available and low cost, it can support these findings when interpreted in the clinical setting.
More studies with larger, multicenter groups and longer follow-up are needed to confirm whether these biomarkers can predict cardiovascular events in people with diabetes. Future studies should assess whether improved glycemic control, lipid-lowering treatment, and anti-inflammatory therapy change the levels of these biomarkers. Future clinical risk models for people with diabetes may include multiple biomarkers for advance cardiovascular risk prediction and support risk management.

This study supports the view that, in people with T2DM, dyslipidemia and inflammation are closely linked to cardiovascular risk. Higher sd LDL levels and their association with inflammatory markers such as hs-CRP and Lp-PLA2 support the need for a broad cardiovascular risk assessment in diabetes care. As diabetes becomes more common, employment of these biomarkers may support more targeted prevention and more personalized treatment and disease management approaches.

REFERENCES

Abbas, U., Imdad, B., Mughal, S. A., Baloch, I. A., Khan, A. M., & Kamran, D.-S. (2021). Differential expression of micro RNA-29 family in non-diabetic adults of diabetic and non-diabetic parents. BMC Research Notes, 14(1). https://doi.org/10.1186/s13104-021-05703-8

Abubakari AR, Lauder W, Jones MC, Kirk A, Agyemang C, Bhopal RS. Prevalence and time trends in diabetes and physical inactivity among adult West African populations: the epidemic has arrived. Public health. 2009 Sep 1;123(9):602- 14.

Adiels, M., Olofsson, S. O., Taskinen, M. R., & Borén, J. (2008). Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. Arteriosclerosis, thrombosis, and vascular biology, 28(7), 1225–1236. https://doi.org/10.1161/ATVBAHA.107.160192

Ahmad E, Lim S, Lamptey R, Webb DR, Davies MJ. Type 2 diabetes. The Lancet. 2022 Nov 19;400(10365):1803-20.

Ahmed, M., Zulfiqar, E., Shafiq, A., Shahzad, M., Hashmi, T. M., Ahmed, R., Rana, J. S., Sidney, S., Greene, S. J., Mentz, R. J., Fudim, M., & Fonarow, G. C. (2025). Type 2 Diabetes Mellitus–Related Mortality in the United States, 1999 to 2023. JACC Advances, 4(7), 101882. https://doi.org/10.1016/j.jacadv.2025.101882

Ahmed AM. History of diabetes mellitus. Saudi medical journal. 2002 Apr 1;23(4):373-8.

Akram MA, Khodja A, Dalibalta S, Majdalawieh AF. The Role of Lipids in Atherosclerosis: Focus on Molecular Biology Mechanisms and Therapeutic Approaches. Current Medicinal Chemistry. 2025 Jan 3.

Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith Jr SC. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation. 2009 Oct 20;120(16):1640-5.

Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic medicine. 1998 Jul;15(7):539-53.

Ali O. Genetics of type 2 diabetes. World journal of diabetes. 2013 Aug 8;4(4):114. Allahyani M. Association of the Red Cell Distribution Width With the Glycemic Index and Lipid Profile in Patients With Type 2 Diabetes Mellitus. Cureus.

Almgren P, Lehtovirta MA, Isomaa BO, Sarelin LE, Taskinen MR, Lyssenko V, Tuomi T, Groop L, Botnia Study Group. Heritability and familiality of type 2 diabetes and related quantitative traits in the Botnia Study. Diabetologia. 2011 Nov; 54:2811-9.

American Diabetes Association (ADA). Standards of medical care in diabetes.Diabetes Care. 2014;37: S14–80.

American Diabetes Association. Clinical practice recommendations 2007. Diabetes Care. 2007;30(suppl 1): S1-S103

American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl. 1): S62–S69

American Diabetes Association: Management of dyslipidemia in adults with diabetes (Position Statement). Diabetes Care 26 (Suppl. 1): S83–S86, 2003.

Amuti A, Li YR, Yuan H, Feng S, Tay GP, Tang SY, Wu XR, Tao LY, Lu L, Zhang RY, Yang CD. Suboptimal Control of Small Dense Low-Density Lipoprotein Cholesterol Is Associated With Coronary Plaque Progression: An Intravascular Ultrasound Study. Journal of the American Heart Association. 2025 Mar 4;14(5):e038580.

Anjana RM, Unnikrishnan R, Deepa M, Venkatesan U, Pradeepa R, Joshi S, Saboo B, Das AK, Bajaj S, Bhansali A, Madhu SV. Achievement of guideline recommended diabetes treatment targets and health habits in people with self- reported diabetes in India (ICMR-INDIAB-13): a national cross-sectional study. The Lancet Diabetes & Endocrinology. 2022 Jun 1;10(6):430-41.

Arkew M, Yemane T, Mengistu Y, Gemechu K, Tesfaye G. Hematological parameters of type 2 diabetic adult patients at Debre Berhan Referral Hospital, Northeast Ethiopia: A comparative cross-sectional study. PloS one. 2021 Jun 14;16(6): e0253286.

Austin MA, King MC, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. Circulation. 1990 Aug;82(2):495-506.

Azevedo M, Alla S. Diabetes in sub-saharan Africa: kenya, mali, mozambique, Nigeria, South Africa and zambia. International journal of diabetes in developing countries. 2008 Oct;28(4):101.

Azul L, Leandro A, Boroumand P, Klip A, Seiça R, Sena CM. Increased inflammation, oxidative stress and a reduction in antioxidant defense enzymes in perivascular adipose tissue contribute to vascular dysfunction in type 2 diabetes. Free Radical Biology and Medicine. 2020 Jan 1; 146:264-74.

Babker AM, Alfeel A, Suliman RS, Elshaikh RH. Association of the Red Cell Distribution Width with Complete Blood Count, Glycated Hemoglobin and Vitamin D in Patients with Type 2 Diabetes Mellitus-Across Sectional Study. Biomedical and Pharmacology

Journal. 2024 Jun 25;17(2):881-8.

Backholer K, Beauchamp A, Ball K, Turrell G, Martin J, Woods J, Peeters A. A framework for evaluating the impact of obesity prevention strategies on socioeconomic inequalities in weight. American journal of public health. 2014 Oct;104(10): e43-50.

Baena-Díez JM, Peñafiel J, Subirana I, Ramos R, Elosua R, Marín-Ibañez A, Guembe MJ, Rigo F, Tormo-Díaz MJ, Moreno-Iribas C, Cabré JJ. Risk of cause- specific death in individuals with diabetes: a competing risks analysis. Diabetes care. 2016 Nov 1;39(11):1987-95.

Balkau B. Smoking, type 2 diabetes and metabolic syndrome. Diabetes & metabolism. 2004 Apr 1;30(2):110-1.

Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P, Brand- Miller JC. Glycemic index, glycemic load, and chronic disease risk—a meta- analysis of observational studies. The American journal of clinical nutrition. 2008 Mar 1;87(3):627-37.

Barman, P., Das, M., & Verma, M. (2023). Epidemiology of type 2 diabetes mellitus and treatment utilization patterns among the elderly from the first wave of Longitudinal Aging study in India (2017-18)using a Heckman selection model. BMC Public Health, 23(1).

Basu S, Khobragade M, Raut DK, Garg S. Knowledge of diabetes among diabetic patients in government hospitals of Delhi. International Journal of Noncommunicable Diseases. 2017 Jan 1;2(1):8-10.

Bekele S, Yohannes T, Mohammed AE. Dyslipidemia and associated factors among diabetic patients attending Durame General Hospital in Southern Nations, Nationalities, and People's Region. Diabetes, metabolic syndrome and obesity: targets and therapy. 2017 Jun 22:265-71.

Belkina AC, Denis GV. Obesity genes and insulin resistance. Current Opinion in Endocrinology, Diabetes and Obesity. 2010 Oct 1;17(5):472-7.

Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The lancet. 2009 May 23;373(9677):1773-9.

Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: an exposure-wide umbrella review of meta-analyses. PloS one. 2018 Mar 20;13(3):e0194127.

Beulens JW, Pinho MG, Abreu TC, den Braver NR, Lam TM, Huss A, Vlaanderen J, Sonnenschein T, Siddiqui NZ, Yuan Z, Kerckhoffs J. Environmental risk factors of type 2 diabetes—An exposome approach. Diabetologia. 2022 Feb;65(2):263-74.

Bhutta ZA, Salam RA, Gomber A, Lewis-Watts L, Narang T, Mbanya JC, Alleyne G. A century past the discovery of insulin: global progress and challenges for type 1 diabetes among children and adolescents in low-income and middle- income countries. The Lancet. 2021 Nov 13;398(10313):1837-50.

Bhutto AR, Abbasi A, Abro AH. Correlation of hemoglobin A1c with red cell width distribution and other parameters of red blood cells in type II diabetes mellitus. Cureus. 2019 Aug;11(8).

Bi Y, Zhu D, Cheng J, Zhu Y, Xu N, Cui S, Li W, Cheng X, Wang F, Hu Y, Shen S. The status of glycemic control: a cross-sectional study of outpatients with type 2 diabetes mellitus across primary, secondary, and tertiary hospitals in the Jiangsu province of China. Clinical therapeutics. 2010 May 1;32(5):973- 83.

Bishwajit G. Nutrition transition in South Asia: the emergence of non-communicable chronic diseases. F1000 Research. 2015;4.

Black JL, Macinko J. Neighborhoods and obesity. Nutrition reviews. 2008 Jan 1;66(1):2-0.

Blake GJ, Otvos JD, Rifai N, Ridker PM. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. Circulation. 2002 Oct 8;106(15):1930-7.

Boden WE, Bhatt DL, Toth PP, Ray KK, Chapman MJ, Lüscher TF. Profound reductions in first and total cardiovascular events with icosapent ethyl in the REDUCE-IT trial: why these results usher in a new era in dyslipidaemia therapeutics. European heart journal. 2020 Jun 21;41(24):2304-12.

Bonnet F, Cooper ME. Potential influence of lipids in diabetic nephropathy: insights from experimental data and clinical studies. Diabetes & metabolism. 2000 Sep 1;26(4):254-64.

Bonora E, Tuomilehto J. The pros and cons of diagnosing diabetes with A1C. Diabetes care. 2011 May;34(Suppl 2): S184.

Boren J, Chapman MJ, Krauss RM, Packard CJ, Bentzon JF, Binder CJ, Daemen MJ, Demer LL, Hegele RA, Nicholls SJ, Nordestgaard BG. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. European heart journal. 2020 Jun 21;41(24):2313-30.

Bozkaya G, Ozgu E, Karaca B. The association between estimated average glucose levels and fasting plasma glucose levels. Clinics. 2010 Jan 1;65(11):1077-80. Braunstein JB, Anderson GF, Gerstenblith G, Weller W, Niefeld M, Herbert R, Wu AW. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. Journal of

Brilakis ES, McConnell JP, Lennon RJ, Elesber AA, Meyer JG, Berger PB. Association of lipoprotein-associated phospholipase A2 levels with coronary artery disease risk factors, angiographic coronary artery disease, and major adverse events at follow-up. European heart journal. 2005 Jan 1;26(2):137- 44.

Brown A. Growth and success in Kerala. Yale Rev Int Stud. 2013;4(1):85-95.

Burke JE, Dennis EA. Phospholipase A2 structure/function, mechanism, and signaling1. Journal of lipid research. 2009 Apr 1;50: S237-42.

C. J. Packard, "Small dense low-density lipoprotein and its role as an independent predictor of cardiovascular dis ease," Current Opinion in Lipidology, vol. 17, no. 4, pp. 412–417, 2006.

Cao J, Hsu YH, Li S, Woods Jr VL, Dennis EA. Structural basis of specific interactions of Lp-PLA2 with HDL revealed by hydrogen deuterium exchange mass spectrometry. Journal of lipid research. 2013 Jan 1;54(1):127- 33.

Cardoso CR, Leite NC, Moram CB, Salles GF. Long-term visit-to-visit glycemic variability as predictor of micro-and macrovascular complications in patients with type 2 diabetes: the Rio de Janeiro Type 2 Diabetes Cohort Study. Cardiovascular diabetology. 2018 Dec; 17:1-6.

Care D. Classification and diagnosis of diabetes. Diabetes Care. 2016 Jan 1;39(1): S13-22.

Centers for Disease Control and Prevention. National diabetes fact sheet—United States, 2005. http://www.cdc.gov/diabetes/pubs/pdf/ ndfs_2005.pdf. Accessed October 9, 2008

Centres for Disease Control and Prevention, 2011. Department of Health and Human Services. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Available at (Accessed December, 20th 2011).

Chadeau-Hyam M, Bodinier B, Vermeulen R, Karimi M, Zuber V, Castagné R, Elliott J, Muller D, Petrovic D, Whitaker M, Stringhini S. Education, biological ageing, all-cause and cause-specific mortality and morbidity: UK biobank cohort study. EClinicalMedicine. 2020 Dec 1;29.

Chamnan P, Simmons RK, Forouhi NG, Luben RN, Khaw KT, Wareham NJ, Griffin SJ. Incidence of type 2 diabetes using proposed HbA1c diagnostic criteria in the European Prospective Investigation of Cancer–Norfolk cohort: implications for preventive strategies. Diabetes care. 2011 Apr 1;34(4):950- 6.

Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, Hu FB. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. Jama. 2009 May 27;301(20):2129-40.

Chaston TB, Dixon JB. Factors associated with percent change in visceral versus subcutaneous abdominal fat during weight loss: findings from a systematic review. International journal of obesity. 2008 Apr;32(4):619-28.

Chaturvedi N, Fuller JH, Taskinen MR, Eurodiab PCS Group. Differing associations of lipid and lipoprotein disturbances with the macrovascular and microvascular complications of type 1 diabetes. Diabetes care. 2001 Dec 1;24(12):2071-7.

Chauhan, S., Khatib, M. N., Ballal, S., Bansal, P., Bhopte, K., Gaidhane, A., Tomar, B. S., Ashraf, A., Kumar, M., Chauhan, A. S., Shabil, M., Jena, D., Bushi, G., Satapathy, P., Jain, L., Jaiswal, V., & Pant, M. (2025). The rising burden of diabetes and state-wise variations in India: insights from the Global Burden of Disease Study 1990–2021 and projections to 2031. Frontiers in Endocrinology, 16.

Cheah JS, Wang KW & Sum CF. Epidemiology of diabetes mellitus in the Asia Paci®c region. Annals of the Academy of Medicine, Singapore 1990; 19, 4: 501±5.

Chen, X., Lin, H., Wu, Y., Wang, M.-F., Lin, S., & Huang, J. (2025). The impact of the COVID-19 pandemic on the global burden of type 2 diabetes: a study based on GBD 2021 data. Frontiers in Endocrinology, 16.

Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nature reviews endocrinology. 2012 Apr;8(4):228-36.

Choudhry, N. K., Priyadarshini, S., Swamy, J., & Mehta, M. (2024). Use Of Machine Learning To Predict Individual Postprandial Glycemic Responses To Food Among Individuals With Type 2 Diabetes In India. Medrxiv (Cold Spring Harbor Laboratory).

Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. Statistics in medicine. 2009 Dec 20;28(29):3670-82.

Cnop M, Vidal J, Hull RL, Utzschneider KM, Carr DB, Schraw T, Scherer PE, Boyko EJ, Fujimoto WY, Kahn SE. Progressive loss of β-cell function leads to worsening glucose tolerance in first-degree relatives of subjects with type 2 diabetes. Diabetes care. 2007 Mar 1;30(3):677-82.

Cojocaru M, Cojocaru IM, Silosi I. Lipoprotein-associated phospholipase A2 as a predictive biomarker of sub-clinical inflammation in cardiovascular diseases. Maedica. 2010 Jan;5(1):51.

Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes care. 1999 Feb 1;22(2):233-40.

Cullmann M, Hilding A, Östenson CG. Alcohol consumption and risk of pre-diabetes and

type 2 diabetes development in a Swedish population. Diabetic Medicine. 2012 Apr;29(4):441-52.

D'Agostino, R. B., Sr, Vasan, R. S., Pencina, M. J., Wolf, P. A., Cobain, M., Massaro,J. M., & Kannel, W. B. (2008). General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*, *117*(6), 743–753. https://doi.org/10.1161/CIRCULATIONAHA.107.699579

d'Emden MC, Shaw JE, Jones GR, Cheung NW. Guidance concerning the use of glycated haemoglobin (HbA 1c) for the diagnosis of diabetes mellitus. Medical Journal of Australia. 2015 Jul 20;203(2).

Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, Lin JK, Farzadfar F, Khang YH, Stevens GA, Rao M. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2· 7 million participants. The lancet. 2011 Jul 2;378(9785):31-40.

Daniels LB, Laughlin GA, Sarno MJ, Bettencourt R, Wolfert RL, Barrett-Connor E. Lipoprotein-associated phospholipase A2 is an independent predictor of incident coronary heart disease in an apparently healthy older population: the Rancho Bernardo Study. Journal of the American College of Cardiology. 2008 Mar 4;51(9):913-9.

Danquah I, Bedu-Addo G, Terpe KJ, Micah F, Amoako YA, Awuku YA, Dietz E, Van Der Giet M, Spranger J, Mockenhaupt FP. Diabetes mellitus type 2 in urban Ghana: characteristics and associated factors. BMC public health. 2012 Dec; 12:1-8.

Davis B, Koster G, Douet LJ, Scigelova M, Woffendin G, Ward JM, Smith A, Humphries J, Burnand KG, Macphee CH, Postle AD. Electrospray ionization mass spectrometry identifies substrates and products of lipoprotein-associated phospholipase A2 in oxidized human low density lipoprotein. Journal of Biological Chemistry. 2008 Mar 7;283(10):6428-37.

De Stefano A, Mannucci L, Tamburi F, Cardillo C, Schinzari F, Rovella V, Nisticò S, Bennardo L, Di Daniele N, Tesauro M. Lp-PLA2, a new biomarker of vascular disorders in metabolic diseases. International Journal of Immunopathology and Pharmacology. 2019 Jan; 33:2058738419827154.

Deepa M, Bhansali A, Anjana RM, Pradeepa R, Joshi SR, Joshi PP, Dhandhania VK, Rao PV, Subashini R, Unnikrishnan R, Shukla DK. Knowledge and awareness of diabetes in urban and rural India: the Indian Council of Medical Research India diabetes study (phase I): Indian Council of Medical Research India diabetes 4. Indian journal of endocrinology and metabolism. 2014 May 1;18(3):379-85.

DeFronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular

disease. Diabetes care. 1991 Mar 1;14(3):173-94.

Delahanty LM, Pan Q, Jablonski KA, Aroda VR, Watson KE, Bray GA, Kahn SE, Florez JC, Perreault L, Franks PW, Diabetes Prevention Program Research Group. Effects of weight loss, weight cycling, and weight loss maintenance on diabetes incidence and change in cardiometabolic traits in the Diabetes Prevention Program. Diabetes Care. 2014 Oct 1;37(10):2738-45.

Dennis EA, Cao J, Hsu YH, Magrioti V, Kokotos G. Phospholipase A2 enzymes: physical structure, biological function, disease implication, chemical inhibition, and therapeutic intervention. Chemical reviews. 2011 Oct 12;111(10):6130-85.

Després, J. P., Lemieux, I., Bergeron, J., Pibarot, P., Mathieu, P., Larose, E., ... & Poirier, P. (2008). Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arteriosclerosis, thrombosis, and vascular biology, 28(6), 1039-1049.

Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006 Dec 14;444(7121):881-7.

Dowse GK D. High prevalence of NIDDM and impaired glucose tolerance in Indian, Creole, and Chinese Mauritians. Diabetes. 1990; 39:390-6.

Dsouza, S. M., Venne, J., Shetty, S., & Brand, H. (2024). Identification of challenges and leveraging mHealth technology, with need-based solutions to empower self-management in type 2 diabetes: a qualitative study. Diabetology & Metabolic Syndrome, 16(1).

Duffey KJ, Popkin BM. Adults with healthier dietary patterns have healthier beverage patterns. The Journal of nutrition. 2006 Nov 1;136(11):2901-7.

Duran EK, Aday AW, Cook NR, Buring JE, Ridker PM, Pradhan AD. Triglyceride- rich lipoprotein cholesterol, small dense LDL cholesterol, and incident cardiovascular disease. Journal of the American College of Cardiology. 2020 May 5;75(17):2122-35.

Duvillard L, Pont F, Florentin E, Gambert P, Vergès B. Inefficiency of insulin therapy to correct apolipoprotein AI metabolic abnormalities in non-insulin- dependent diabetes mellitus. Atherosclerosis. 2000 Sep 1;152(1):229-37.

Echouffo-Tcheugui JB, Selvin E. Prediabetes and what it means: the epidemiological evidence. Annual Review of Public Health. 2021 Apr 1; 42:59-77.

Ekelund U, Brage S, Griffin SJ, Wareham NJ. Objectively measured moderate-and vigorous-intensity physical activity but not sedentary time predicts insulin resistance in high-risk individuals. Diabetes care. 2009 Jun 1;32(6):1081-6.

Elimam H, Abdulla AM, Taha IM. Inflammatory markers and control of type 2 diabetes

mellitus. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2019 Jan 1;13(1):800-4.

Elstad MR, Stafforini DM, McIntyre TM, Prescott SM, Zimmerman GA. Platelet-activating factor acetylhydrolase increases during macrophage differentiation: a novel mechanism that regulates accumulation of platelet- activating factor. Journal of Biological Chemistry. 1989 May 25;264(15):8467-70.

Emerging Risk Factors Collaboration, Sarwar, N., Gao, P., Seshasai, S. R., Gobin, R., Kaptoge, S., Di Angelantonio, E., Ingelsson, E., Lawlor, D. A., Selvin, E., Stampfer, M., Stehouwer, C. D., Lewington, S., Pennells, L., Thompson, A., Sattar, N., White, I. R., Ray, K. K., & Danesh, J. (2010). Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. *The Lancet, 375*(9733), 2215–222 https://doi.org/10.1016/S0140-6736(10)60484-9

Evans TC, Jehle D. The red blood cell distribution width. The Journal of emergency medicine. 1991 Jan 1; 9:71-4.

F. Red blood cell distribution width in elderly hospitalized patients with cardiovascular disease. World journal of cardiology. 2021 Sep 9;13(9):503.

Fan J, Liu Y, Yin S, Chen N, Bai X, Ke Q, Shen J, Xia M. Small dense LDL cholesterol is associated with metabolic syndrome traits independently of obesity and inflammation. Nutrition & metabolism. 2019 Dec; 16:1-9.

Fang L, Sheng H, Tan Y, Zhang Q. Prevalence of diabetes in the USA from the perspective of demographic characteristics, physical indicators and living habits based on NHANES 2009-2018. Frontiers in Endocrinology. 2023 Mar 7; 14:1088882.

Farooq S, Generoso G, Bensenor IM, Santos RD, Jones SR, Moraes E, Blaha MJ, Toth PP, Lotufo PA, Staniak HL, Bittencourt MS. Low-density lipoprotein-cholesterol Subfractions as Predictors for Coronary Artery Calcium Incidence and Progression

Faselis C, Katsimardou A, Imprialos K, Deligkaris P, Kallistratos M, Dimitriadis K. Microvascular complications of type 2 diabetes mellitus. Current vascular pharmacology. 2020 Mar 1;18(2):117-24.

Fatemi S, Gottsäter A, Zarrouk M, Engström G, Melander O, Persson M, Acosta S. Lp-PLA2 activity and mass and CRP are associated with incident symptomatic peripheral arterial disease. Scientific Reports. 2019 Apr 4;9(1):5609.

Ferrannini E. Physiological and metabolic sequences of obesity. Metabolism 1995;44 Suppl 3:15-7.

Festa A, Williams K, Hanley AJ, Otvos JD, Goff DC, Wagenknecht LE, Haf fner SM. Nuclear magnetic resonance lipoprotein abnormalities in predia betic subjects in the

Insulin Resistance Atherosclerosis Study. Circulation. 2005;111(25):3465–72.

Florez JC, Hirschhorn J, Altshuler D. The inherited basis of diabetes mellitus: implications for the genetic analysis of complex traits. Annual review of genomics and human genetics. 2003 Sep;4(1):257-91.

Ford ES. The metabolic syndrome and C-reactive protein, fibrinogen, and leukocyte count: findings from the Third National Health and Nutrition Examination Survey. Atherosclerosis. 2003 Jun 1;168(2):351-8.

Forray, A. I., Coman, M. A., Simonescu-Colan, R., Mazga, A. I., Cherecheș, R. M., & Borzan, C. M. (2023). The Global Burden of Type 2 Diabetes Attributable to Dietary Risks: Insights from the Global Burden of Disease Study 2019. Nutrients, 15(21), 4613.

Fortunato J, Blaha V, Bis J, Št'ásek J, Andrýs C, Vojáček J, Jurašková B, Sobotka L, Polanský P, Brtko M. Lipoprotein-associated phospholipase A2 mass level is increased in elderly subjects with type 2 diabetes mellitus. Journal of Diabetes Research. 2014;2014(1):278063.

Gaidhane S, Sah R, Zahiruddin QS, Khatib N, Telrandhe S, Choudhari S, Gaidhane A. Hemoglobin A1c to Detect Prediabetes or Type 2 Diabetes Mellitus in a Rural Population of Wardha District in India. Journal of Diabetology. 2024 Apr 1;15(2):195-203.

Galassi A, Reynolds K, He J. Metabolic Syndrome and Risk of Cardiovascular Disease: A Meta-Analysis. The American Journal of Medicine. 2006 Oct; 119(10):812–9.

Gallagher D, Heshka S, Kelley DE, Thornton J, Boxt L, Pi-Sunyer FX, Patricio J, Mancino J, Clark JM, MRI Ancillary Study Group of the Look AHEAD Research Group. Changes in adipose tissue depots and metabolic markers following a 1-year diet and exercise intervention in overweight and obese patients with type 2 diabetes. Diabetes care. 2014 Dec 1;37(12):3325-32.

Geldsetzer P, Manne-Goehler J, Theilmann M, Davies JI, Awasthi A, Vollmer S, Jaacks LM, Bärnighausen T, Atun R. Diabetes and hypertension in India: a nationally representative study of 1.3 million adults. JAMA internal medicine. 2018 Mar 1;178(3):363-72.

Geldsetzer P, Manne-Goehler J, Theilmann M, Davies JI, Awasthi A, Danaei G, Gaziano TA, Vollmer S, Jaacks LM, Baernighausen T, Atun R. Geographic and sociodemographic variation of cardiovascular disease risk in India: a cross-sectional study of 797,540 adults. PLoS medicine. 2018 Jun 19;15(6): e1002581.

Gerber PA, Thalhammer C, Schmied C, Spring S, Amann-Vesti B, Spinas GA, Berneis K. Small, dense LDL particles predict changes in intima media thickness and insulin

resistance in men with type 2 diabetes and prediabetes– a prospective cohort study. PloS one. 2013 Aug 8;8(8): e72763.

Gianazza E, Brioschi M, Martinez Fernandez A, Casalnuovo F, Altomare A, Aldini G, Banfi C. Lipid peroxidation in atherosclerotic cardiovascular diseases. Antioxidants & redox signaling. 2021 Jan 1;34(1):49-98.

Global burden of diabetes. International Diabetes federation. Diabetic atlas fifth edition 2011, Brussels. Available at (Accessed 18th December 2011).

Goetzel RZ, Hawkins K, Ozminkowski RJ, Wang S. The health and productivity cost burden of the "top 10" physical and mental health conditions affecting six large US employers in 1999. Journal of occupational and environmental medicine. 2003 Jan 1;45(1):5-14.

Gong R, Liu Y, Luo G, Liu W, Jin Z, Xu Z, Li Z, Yang L, Wei X. Associations of TG/HDL ratio with the risk of prediabetes and diabetes in Chinese adults: a Chinese population cohort study based on open data. International Journal of Endocrinology. 2021;2021(1):9949579.

Govindaswamy, S., Dhivya, P. S., & Sivaprakasam, S. S. K. (2023). Prevalence and Complications of Diabetes Mellitus in India: A Systematic Review [Review of Prevalence and Complications of Diabetes Mellitus in India: A Systematic Review]. Indian Journal of Pharmaceutical Education and Research, 57. Association of Pharmaceutical Teachers of India.

Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith Jr SC, Spertus JA. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation. 2005 Oct 25;112(17):2735-52.

Gui MH, Ling Y, Liu L, Jiang JJ, Li XY, Gao X: Effect of metabolic syndrome score, metabolic syndrome, and its individual components on the prevalence and severity of angiographic coronary artery disease. Chin Med J (Engl). 2017, 130:669-77.

Guzman-Vilca, W. C., & Carrillo-Larco, R. M. (2024). Number of People with Type 2 Diabetes Mellitus in 2035 and 2050: A Modelling Study in 188 Countries. Current Diabetes Reviews, 20.

Haffner SM, Mykkänen L, Festa A, Burke JP, Stern MP. Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. Circulation. 2000 Mar 7;101(9):975-80.

Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start

ticking before the onset of clinical diabetes? Jama. 1990 Jun 6;263(21):2893-8.

Hagström E, Steg PG, Szarek M, Bhatt DL, Bittner VA, Danchin N, Diaz R, Goodman SG, Harrington RA, Jukema JW, Liberopoulos E. Apolipoprotein B, residual cardiovascular risk after acute coronary syndrome, and effects of alirocumab. Circulation. 2022 Aug 30;146(9):657-72.

Hajer GR, Van Haeften TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. European heart journal. 2008 Dec 1;29(24):2959-71.

Han TS, Sattar N, Williams K, Gonzalez-Villalpando C, Lean ME, Haffner SM. Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. Diabetes care. 2002 Nov 1;25(11):2016-21.

Hare MJL, Shaw JE, Zimmet PZ. Current controversies in the use of haemoglobin A1c. J Intern Med 2012; 271:227–36.

Hare-Bruun H, Flint A, Heitmann BL. Glycemic index and glycemic load in relation to changes in body weight, body fat distribution, and body composition in adult Danes. The American journal of clinical nutrition. 2006 Oct 1;84(4):871-9.

Hatoum IJ, Hu FB, Nelson JJ, Rimm EB. Lipoprotein-associated phospholipase A2 activity and incident coronary heart disease among men and women with type 2 diabetes. Diabetes. 2010 May 1;59(5):1239-43.

Hayashino Y, Fukuhara S, Okamura T, Yamato H, Tanaka H, Tanaka T, Kadowaki T, Ueshima H, HIPOP-OHP Research Group. A prospective study of passive smoking and risk of diabetes in a cohort of workers: the High-Risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) study. Diabetes care. 2008 Apr 1;31(4):732-4.

He, K., Wang, H., Xu, J., Gong, G., Liu, X., & Guan, H. (2024). Global burden of type 2 diabetes mellitus from 1990 to 2021, with projections of prevalence to 2044: a systematic analysis across SDI levels for the global burden of disease study 2021. Frontiers in Endocrinology, 15.

Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: a community perspective. Circulation: Heart Failure. 2008 Jul 1;1(2):91-7.

Herder C, Carstensen M, Ouwens DM. Anti-inflammatory cytokines and risk of type 2 diabetes. Diabetes, Obesity and Metabolism. 2013 Sep;15(s3):39-50.

Hirano, T. (2025), Clinical significance of small dense low-density lipoprotein cholesterol measurement in type 2 diabetes. J Diabetes Investig, 16: 370-

Hirano T. Pathophysiology of diabetic dyslipidemia. Journal of atherosclerosis and

thrombosis. 2018 Sep 1;25(9):771-82.

Hokanson, J. E., & Austin, M. A. (1996). Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. Journal of cardiovascular risk, 3(2), 213–219.

Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006 Dec 14;444(7121):860-7.

Houser SR, Margulies KB, Murphy AM, Spinale FG, Francis GS, Prabhu SD, Rockman HA, Kass DA, Molkentin JD, Sussman MA, Koch WJ. Animal models of heart failure: a scientific statement from the American Heart Association. Circulation research. 2012 Jun 22;111(1):131-50.

Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. New England journal of medicine. 2001 Sep 13;345(11):790-7.

Hu P, Zheng M, Duan X, Zhou H, Huang J, Lao L, Zhao Y, Li Y, Xue M, Zhao W, Deng H. Association of healthy lifestyles on the risk of hypertension, type 2 diabetes mellitus, and their comorbidity among subjects with dyslipidemia. Frontiers in Nutrition. 2022 Sep 26; 9:1006379.

Huang, Q., Li, Y., Yu, M., Lv, Z., Lu, F.-Y., Xu, N., Zhang, Q., Shen, J., Zhu, J., & Jiang, H. (2025). Global burden and risk factors of type 2 diabetes mellitus from 1990 to 2021, with forecasts to 2050. Frontiers in Endocrinology, 16, 1538143.

Huang, X., Wu, Y., Ni, Y., Xu, H., & He, Y. (2025). Global, regional, and national burden of type 2 diabetes mellitus caused by high BMI from 1990 to 2021, and forecasts to 2045: analysis from the global burden of disease study 2021. Frontiers in Public Health, 13.

Huang F, Wang K, Shen J. Lipoprotein-associated phospholipase A2: the story continues. Medicinal research reviews. 2020 Jan;40(1):79-134.

Huang PL. A comprehensive definition for metabolic syndrome. Disease models & mechanisms. 2009 Apr 30;2(5-6):231-7.

Huisman TH, Martis EA, Dozy A. Chromatography of hemoglobin types on carboxymethylcellulose. The Journal of laboratory and clinical medicine. 1958 Aug 1;52(2):312-27.

Hwang JH, Stein DT, Barzilai N, Cui MH, Tonelli J, Kishore P, Hawkins M. Increased intrahepatic triglyceride is associated with peripheral insulin resistance: in vivo MR imaging and spectroscopy studies. American Journal of Physiology-Endocrinology and Metabolism. 2007 Dec;293(6):E1663-9.

IDF, International Diabetes Atlas 10th Edition. Preprint at (2021).

Imani F, Horii Y, Suthanthiran M, Skolnik EY, Makita Z, Sharma V, Sehajpal P, Vlassara H. Advanced glycosylation endproduct-specific receptors on human and rat T-lymphocytes mediate synthesis of interferon gamma: role in tissue remodeling. The Journal of experimental medicine. 1993 Dec 1;178(6):2165- 72.

India state level disease burden report. Available from: https://vikaspedia.in/health/health-directory/ india-state-level-disease- burden-report-released. [Last accessed on 2021 Jun 08].

International Diabetes Federation. IDF Diabetes Atlas. 9th ed. Brussels, Belgium: International Diabetes Federation; 2019.

Ivanova EA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN. Small dense low-density lipoprotein as biomarker for atherosclerotic diseases. Oxidative medicine and cellular longevity. 2017;2017(1):1273042.

J. M., & Kannel, W. B. (2008). General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation, 117(6), 743–753. https://doi.org/10.1161/CIRCULATIONAHA.107.699579

J. R., Bloomfield, H. E., & Robins, S. J. (2006). Low-density lipoprotein and high-density lipoprotein particle subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High- Density Lipoprotein Intervention Trial. Circulation, 113(12), 1556–1563. https://doi.org/10.1161/CIRCULATIONAHA.105.565135

Jackisch L, Kumsaiyai W, Moore JD, Al-Daghri N, Kyrou I, Barber TM, Randeva H, Kumar S, Tripathi G, McTernan PG. Differential expression of Lp-PLA2 in obesity and type 2 diabetes and the influence of lipids. Diabetologia. 2018 May; 61:1155-66.

Janani, S. (2024). “Impact of Type 2 Diabetes Mellitus on Health-Related Quality of Life among patients from a Tertiary Care Hospital in Southern India.” African Journal of Biomedical Research, 1857.

Jialal I, Singh G. Management of diabetic dyslipidemia: An update. World journal of diabetes. 2019 May 5;10(5):280.

Jones RL, Peterson CM. Hematologic alterations in diabetes mellitus. The American journal of medicine. 1981 Feb 1;70(2):339-52.

Joseph JJ, Deedwania P, Acharya T, Aguilar D, Bhatt DL, Chyun DA, Di Palo KE, Golden SH, Sperling LS, American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Clinical Cardiology; and Council on Hypertension. Comprehensive management of cardiovascular risk factors for adults with type 2

Joshi SR. Incidence data on diabetes from India. JOURNAL-ASSOCIATION OF PHYSICIANS OF INDIA. 2008 Mar 1;56(R):149.

Kahn, S.E. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia 2003, 46, 3–19.

Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. The Lancet. 2014 Mar 22;383(9922):1068-83.

Kalra, S., Anjana, R. M., Verma, M., Pradeepa, R., Sharma, N., Deepa, M., Singh, O., Venkatesan, U., Nirmal, E., Aggarwal, S., Kakkar, R., & Mohan, V. (2024). Urban–Rural Differences in the Prevalence of Diabetes Among Adults in Haryana, India: The ICMR-INDIAB Study (ICMR-INDIAB-18). Diabetes Therapy, 15(7), 1597.

Kalra, S., Mithal, A., Zargar, A. H., Sethi, B., Dharmalingam, M., Ghosh, S., & Sen, R. (2022). Indian Phenotype Characteristics Among Patients with Type 2 Diabetes Mellitus: Insights from a Non-interventional Nationwide Registry in India. touchREVIEWS in Endocrinology, 18(1), 63.

Kane JP, Pullinger CR, Goldfine ID, Malloy MJ. Dyslipidemia and diabetes mellitus: Role of lipoprotein species and interrelated pathways of lipid metabolism in diabetes mellitus. Current Opinion in Pharmacology. 2021 Dec 1; 61:21-7.

Kanmani S, Kwon M, Shin MK, Kim MK. Association of C-reactive protein with risk of developing type 2 diabetes mellitus, and role of obesity and hypertension: a large population-based Korean cohort study. Scientific reports. 2019 Mar 14;9(1):4573.

Kaprio J, Tuomilehto J, Koskenvuo M, Romanov K, Reunanen A, Eriksson J, Stengård J, Kesäniemi YA. Concordance for type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in a population- based cohort of twins in Finland. Diabetologia. 1992 Nov; 35:1060-7.

Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC medicine. 2011 Dec; 9:1-3.

Kaur J. A comprehensive review on Metabolic syndrome. Cardiology research and practice. Cardiol Res Pract. 2014; 2014:943162

Kaur R, Kaur M, Singh J. Endothelial dysfunction and platelet hyperactivity in type 2 diabetes mellitus: molecular insights and therapeutic strategies. Cardiovascular diabetology. 2018 Dec; 17:1-7.

Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. Endocrine reviews. 2016 Jun 1;37(3):278-316.

Khan, M. A., Hashim, M. J., King, J., Govender, R. D., Mustafa, H., & Kaabi, J. A. (2019). Epidemiology of Type 2 Diabetes – Global Burden of Disease and Forecasted Trends. Journal of Epidemiology and Global Health, 10(1), 107.

Khan MI, Weinstock RS. Chapter 16: Carbohydrates. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 22nd ed. Philadelphia, PA: Saunders Elsevier; 2011:210–25.

Khan SA, Ilies MA. The phospholipase A2 superfamily: structure, isozymes, catalysis, physiologic and pathologic roles. International journal of molecular sciences. 2023 Jan 10;24(2):1353.

Khera A, McGuire DK, Murphy SA, Stanek HG, Das SR, Vongpatanasin W, Wians FH, Grundy SM, de Lemos JA. Race and gender differences in C-reactive protein levels. Journal of the American college of cardiology. 2005 Aug 2;46(3):464-9.

Khetan AK, Rajagopalan S. Prediabetes. Canadian Journal of Cardiology. 2018 May 1;34(5):615-23.

Kim J, Shin SJ, Kim YS, Kang HT. Positive association between the ratio of triglycerides to high-density lipoprotein cholesterol and diabetes incidence in Korean adults. Cardiovascular diabetology. 2021 Dec; 20:1-0.

King H, Rewers M. Diabetes in adults is now a Third World problem. Ethnicity & Disease. 1993 Jan 1: S67-74.

Kinney GL, Snell-Bergeon JK, Maahs DM, Eckel RH, Ehrlich J, Rewers M, Hokanson JE. Lipoprotein-associated phospholipase A2 activity predicts progression of subclinical coronary atherosclerosis. Diabetes technology & therapeutics. 2011 Mar 1;13(3):381-7.

Kotani K, Tsuzaki K, Traniguchi N, Sakane N, LDL particle size and reactive oxygen metabolities in dyslipidemic patients. Int J Prev Med. 2012;3(3):160-6

Krishnan MN, Zachariah G, Venugopal K, Mohanan PP, Harikrishnan S, Sanjay G, et al. Prevalence of coronary artery disease and its risk factors in Kerala, South India: a community-based cross-sectional study. BMC Cardiovascular Disorders. 2016 Jan 12;1–12.

Kriska AM, Edelstein SL, Hamman RF, Otto A, Bray GA, Mayer-Davis EJ, Wing RR, Horton ES, Haffner SM, Regensteiner JG. Physical activity in individuals at risk for diabetes: Diabetes Prevention Program. Medicine and science in sports and exercise. 2006 May;38(5):826.

Kulkarni, R., Dilip, T. R., Shejul, Y., Bhandarkar, P., Goswami, P., Sharma, P., Patil, P., & James, K. S. (2023). Progression and management of diabetes in Indian settings with universal access to health care: Protocol and plans for CHIPS cohort study. medRxiv

(Cold Spring Harbor Laboratory).

Kurniawan LB, Rampo H, Soraya GV, Adnan E, Esa T, Widaningsih Y, Bahrun U, Arif M. Effect of obesity, glucose control, lipid profiles, and blood pressure on Lp-PLA2 levels in type 2 diabetes mellitus patients. Obesity Medicine. 2021 Mar 1; 22:100318.

Kutty VR, Balakrishna n KC, Jayasree AK & Thomas J. Prevalence of coronary heart disease in rural populatio n of Thiruvananthapura m district, Kerala, India. Internationa l Journal of Cardiology 1993; 39: 59±70.

Kutty VR, Soman CR, Joseph A, Pisharody R, Vijayakumar K. Type 2 diabetes in southern Kerala: variation in prevalence among geographic divisions within a region. National Medical Journal of India. 2000 Nov 1;13(6):287-92.

Laakso M, Fernandes Silva L. Genetics of type 2 diabetes: past, present, and future. Nutrients. 2022 Aug 4;14(15):3201.

Laakso M, Kuusisto J. Insulin resistance and hyperglycaemia in cardiovascular disease development. Nature reviews endocrinology. 2014 May;10(5):293- 302.

Ladabaum U, Mannalithara A, Myer PA, Singh G. Obesity, abdominal obesity, physical activity, and caloric intake in US adults: 1988 to 2010. The American journal of medicine. 2014 Aug 1;127(8):717-27.

Lam L, Ilies MA. Evaluation of the impact of esterases and lipases from the circulatory system against substrates of different lipophilicity. International Journal of Molecular Sciences. 2022 Jan 23;23(3):1262.

Lee J, Lee SH. Lipid variability in patients with diabetes mellitus. Cardiovascular Prevention and Pharmacotherapy. 2023 Oct 25;5(4):126-33/

Lee MY, Hsiao PJ, Huang JC, Hsu WH, Chen SC, Shin SJ: Association between metabolic syndrome and microvascular and macrovascular disease in type 2 diabetic mellitus. Am J Med Sci. 2018, 355:342-9.

Li X, Zhai Y, Zhao J, He H, Li Y, Liu Y, Feng A, Li L, Huang T, Xu A, Lyu J. Impact of metabolic syndrome and it's components on prognosis in patients with cardiovascular diseases: a meta-analysis. Frontiers in cardiovascular medicine. 2021 Jul 15; 8:704145.

Liou L, Kaptoge S. Association of small, dense LDL-cholesterol concentration and lipoprotein particle characteristics with coronary heart disease: a systematic review and meta-analysis. PloS one. 2020 Nov 9;15(11): e0241993.

Lippi, G., Targher, G., Montagnana, M., Salvagno, G. L., Zoppini, G., & Guidi, G.C. (2009). Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Archives of pathology & laboratory medicine*, *133*(4), 628–632. https://doi.org/10.5858/133.4.628

Lippi, G., Targher, G., Salvagno, G. L., & Guidi, G. C. (2014). Increased red blood cell distribution width (RDW) is associated with higher glycosylated hemoglobin (HbA1c) in the elderly. Clinical laboratory, 60(12), 2095–2098. https://doi.org/10.7754/clin.lab.2014.140621

Liu M, Lv X, Li Y, Li J, He Y. Prevalence and control status of diabetes and related risk factors among 4196 chinese male older elderly aged≥ 80 years. International Journal of Gerontology. 2018 Jun 1;12(2):122-6.

Liu M, Wang J, He Y, Jiang B, Wu L, Wang Y, Di Z, Zeng J. Awareness, treatment and control of type 2 diabetes among Chinese elderly and its changing trend for past decade. BMC public health. 2016 Dec; 16:1-8.

Liu ML, Ylitalo K, Salonen R, Salonen JT, Taskinen MR. Circulating oxidized low-density lipoprotein and its association with carotid intima-media thickness in asymptomatic members of familial combined hyperlipidemia families. Arteriosclerosis, thrombosis, and vascular biology. 2004 Aug 1;24(8):1492-7.

Liu Q, Chen X, Chen W, et al. Structural and thermodynamic characterization of protein-ligand interactions formed between lipoprotein-associated phospholipase A2 and inhibitors. J Med Chem. 2016;59(10):5115-5120.

Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. Diabetes care. 2003 Nov 1;26(11):3153-9.

Lp-PLA2 Studies Collaboration. Lipoprotein-associated phospholipase A2 and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. The Lancet. 2010 May 1;375(9725):1536-44.

Lucci C, Cosentino N, Genovese S, Campodonico J, Milazzo V, De Metrio M, Rondinelli M, Riggio D, Biondi ML, Rubino M, Celentano K. Prognostic impact of admission high-sensitivity C-reactive protein in acute myocardial infarction patients with and without diabetes mellitus. Cardiovascular Diabetology. 2020 Dec; 19:1-3.

Ma, Y., Liu, H., Wang, Y., Xuan, J., Gao, X., Ding, H., Ma, C., Chen, Y., & Yang, Y. (2022). Roles of physical exercise-induced MiR-126 in cardiovascular health of type 2 diabetes [Review of Roles of physical exercise-induced MiR-126 in cardiovascular health of type 2 diabetes]. Diabetology & Metabolic Syndrome, 14(1). BioMed Central.

Mahajan A, Tabassum R, Chavali S, Dwivedi OP, Bharadwaj M, Tandon N, Bharadwaj D. High-sensitivity C-reactive protein levels and type 2 diabetes in urban North Indians. The Journal of Clinical Endocrinology & Metabolism. 2009 Jun 1;94(6):2123-7.

Mathew RT. Association of Red Cell Distribution width (RDW) and RBC Adherence with

the Presence and Severity of Diabetic Retinopathy (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)) 2020.

Mathur P, Leburu S, Kulothungan V. Prevalence, awareness, treatment and control of diabetes in India from the countrywide national NCD monitoring survey. Frontiers in public health. 2022 Mar 14; 10:748-57.

Mattock M, Morrish N, Viberti GC. Prospective study of micro albuminuria as predictor of mortality in NIDDM. Diabetes 1992; 41:736-41.

Mbanya JC. The burden of type 2 diabetes mellitus in the African diaspora. Available at medscape. com/view article/560718_2. 2009.

McCarthy MI. Painting a new picture of personalised medicine for diabetes. Diabetologia. 2017 May;60(5):793-9.

McElfish PA, Long CR, Bursac Z, Scott AJ, Felix HC, Schulz TK, Worley MA, Rowland B. Diabetes self-management education exposure and glycated haemoglobin levels among Marshallese participants in a randomized controlled study. Diabetic Medicine. 2020 Feb;37(2):319-25.

Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. Diabetes 2000; 49: 2201-2207

Milosevic D, Panin VL. Relationship between hematological parameters and glycemic control in type 2 diabetes mellitus patients. Journal of Medical Biochemistry. 2019 Apr;38(2):164.

Mohamedahmed KA, Mubarak MO, Abdebagi A, Talha RS, Abbas AO, Khalid MO. Assessment of Red Cell Distribution Width among Sudanese Patients with Subclinical Hypothyroidism. Biomedicine. 2023 Jun;13(2):229-33.

Mohan D, Raj D, Shanthirani CS, Datta M, Unwin NC, Kapur A, Mohan V. Awareness and knowledge of diabetes in Chennai-the Chennai urban rural epidemiology study [CURES-9]. Journal of the Association of Physicians of India. 2005; 53:283-7.

Mohan V, Deepa R, Velmurugan K, Premalatha G. Association of C-reactive protein with body fat, diabetes and coronary artery disease in Asian Indians: The Chennai Urban Rural Epidemiology Study (CURES-6). Diabetic medicine. 2005 Jul;22(7):863-70.

Montagnana M, Cervellin G, Meschi T, Lippi G. The role of red blood cell distribution width in cardiovascular and thrombotic disorders. Clinical chemistry and laboratory medicine. 2012 Apr 1;50(4):635-41.

Moolenaar, W.H.; van Meeteren, L.A.; Giepmans, B.N.G. The Ins and Outs of Lysophosphatidic Acid Signaling. BioEssays 2004, 26, 870–881.

Moreno-Castilla C, Mauricio D, Hernandez M. Role of medical nutrition therapy in the management of gestational diabetes mellitus. Current diabetes reports. 2016 Apr;16:1-9.

Mozumdar A, Liguori G. Persistent increase of prevalence of metabolic syndrome among US adults: NHANES III to NHANES 1999–2006. Diabetes care. 2011 Jan 1;34(1):216-9.

Mugabo Y, Li L, Renier G. The connection between C-reactive protein (CRP) and diabetic vasculopathy. Focus on preclinical findings. Current diabetes reviews. 2010 Jan 1;6(1):27-34.

Murakami M, Kudo I. Phospholipase A2. The journal of biochemistry. 2002 Mar 1;131(3):285-92.

Nada AM. Red cell distribution width in type 2 diabetic patients. Diabetes, metabolic syndrome and obesity: targets and therapy. 2015 Oct 30:525-33.

Nair M, Prabhakaran D, Narayan KV, Sinha R, Lakshmy R, Devasenapathy N, Daniel CR, Gupta R, George PS, Mathew A, Tandon N. HbA1c values for defining diabetes and impaired fasting glucose in Asian Indians. Primary care diabetes. 2011 Jul 1;5(2):95-102.

Najarian RM, Sullivan LM, Kannel WB, Wilson PW, D'Agostino RB, Wolf PA. Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke: the Framingham Offspring Study. Archives of internal medicine. 2006 Jan 9; 166(1):106–111.

Nathan DM. The diabetes control and complications trial. Diabetes Care. 2014;37(1):9-16

Nayak, N., & Mishra, M. (2021). High fat diet induced abnormalities in metabolism, growth, behavior, and circadian clock in Drosophila melanogaster. Life Sciences, 281, 119758.

Nelson TL, Kamineni A, Psaty B, Cushman M, Jenny NS, Hokanson J, Furberg C, Mukamal KJ. Lipoprotein-associated phospholipase A 2 and future risk of subclinical disease and cardiovascular events in individuals with type 2 diabetes: the Cardiovascular Health Study. Diabetologia. 2011 Feb; 54:329- 33.

Niedzwiecki MM, Walker DI, Vermeulen R, Chadeau-Hyam M, Jones DP, Miller GW. The exposome: molecules to populations. Annual review of pharmacology and toxicology. 2019 Jan 6;59(1):107-27.

Ning C, Jiao Y, Wang J, Li W, Zhou J, Lee YC, Ma DL, Leung CH, Zhu R, Wang HM. Recent advances in the managements of type 2 diabetes mellitus and natural hypoglycemic substances. Food Science and Human Wellness. 2022 Sep

1;11(5):1121-33.

Ning F, Pang ZC, Dong YH, Gao WG, Nan HR, Wang SJ, Zhang L, Ren J, Tuomilehto J, Hammar N, Malmberg K. Risk factors associated with the dramatic increase in the prevalence of diabetes in the adult Chinese population in Qingdao, China. Diabetic medicine. 2009 Sep;26(9):855-63.

Nogueira JP, Maraninchi M, Béliard S, Padilla N, Duvillard L, Mancini J, Nicolay A, Xiao C, Vialettes B, Lewis GF, Valéro R. Absence of acute inhibitory effect of insulin on chylomicron production in type 2 diabetes. Arteriosclerosis, thrombosis, and vascular biology. 2012 Apr;32(4):1039-44.

Nolan, C.J.; Damm, P.; Prentki, M. Type 2 diabetes across generations: From pathophysiology to prevention and management. Lancet 2011, 378, 169–181.

Noto H, Hara M, Karasawa K, Iso-O N, Satoh H, Togo M, Hashimoto Y, Yamada Y, Kosaka T, Kawamura M, Kimura S. Human plasma platelet-activating factor acetylhydrolase binds to all the murine lipoproteins, conferring protection against oxidative stress. Arteriosclerosis, thrombosis, and vascular biology. 2003 May 1;23(5):829-35.

Nsiah K, Shang VO, Boateng KA, Mensah FO. Prevalence of metabolic syndrome in type 2 diabetes mellitus patients. International Journal of Applied and Basic Medical Research. 2015 May 1;5(2):133-8.

Nyarko A, Adubofour K, Ofei F, Kpodonu J, Owusu S. Serum lipid and lipoprotein levels in Ghanaians with diabetes mellitus and hypertension. J Natl Med Assoc 1997; 89:191-6

Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, Cavan D, Shaw JE, Makaroff LE. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes research and clinical practice. 2017 Jun 1; 128:40-50.

Oh HJ, Yang DM, Kim CH, Jeon JG, Jung NH, Kim CY, Symanzik J, Oh HW, Edwin A, Jo SI, Ahn JY. Exploring mortality rates for major causes of death in Korea. The Open Public Health Journal. 2019; 12:16.

Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabetes mellitus: a review of current trends. Oman medical journal. 2012 Jul;27(4):269.

Otvos, J. D., Collins, D., Freedman, D. S., Shalaurova, I., Schaefer, E. J., McNamara, J. R., Bloomfield, H. E., & Robins, S. J. (2006). Low-density lipoprotein and high-density lipoprotein particle subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High- Density Lipoprotein Intervention Trial. *Circulation*, *113*(12), 1556–1563.

https://doi.org/10.1161/CIRCULATIONAHA.105.565135

Packard CJ, O'Reilly DS, Caslake MJ, McMahon AD, Ford I, Cooney J, Macphee CH, Suckling KE, Krishna M, Wilkinson FE, Rumley A. Lipoprotein- associated phospholipase A2 as an independent predictor of coronary heart disease. New England Journal of Medicine. 2000 Oct 19;343(16):1148-55.

Packard CJ. Lipoprotein-associated phospholipase A2 as a biomarker of coronary heart disease and a therapeutic target. Current Opinion in Cardiology. 2009 Jul 1;24(4):358-63.

Patel KV, Semba RD, Ferrucci L, Newman AB, Fried LP, Wallace RB, Bandinelli S, Phillips CS, Yu B, Connelly S, Shlipak MG. Red cell distribution width and mortality in older adults: a meta-analysis. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. 2010 Mar 1;65(3):258-65.

Patlak M. New weapons to combat an ancient disease: treating diabetes. The FASEB Journal. 2002 Dec;16(14):1853e-.

Pearson ER. Type 2 diabetes: a multifaceted disease. Diabetologia. 2019 Jul;62(7):1107-12.

Peng Z, Chang Y, Fan J, Ji W, Su C. Phospholipase A2 superfamily in cancer. Cancer Letters. 2021 Jan 28; 497:165-77.

Peters SA, Singhateh Y, Mackay D, Huxley RR, Woodward M. Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: A systematic review and meta-analysis. Atherosclerosis. 2016 May 1; 248:123-31.

Pfützner A, Forst T. High-sensitivity C-reactive protein as cardiovascular risk marker in patients with diabetes mellitus. Diabetes technology & therapeutics. 2006 Feb 1;8(1):28-36.

Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. Diabetologia. 1997 Nov; 40:1286-92.

Pieroni L, Salmasi L. Fast-food consumption and body weight. Evidence from the UK. Food Policy. 2014 Jun 1; 46:94-105.

Pordzik, J., Eyileten-Postuła, C., Jakubik, D., Czajka, P., Nowak, A., Rosa, S. D., Gąsecka, A., Cieślicka-Kapłon, A., Sulikowski, P., Filipiak, K. J., Mirowska-Guzel, D., Siller-Matula, J. M., & Postuła, M. (2021). MiR-126 Is an Independent Predictor of Long-Term All-Cause Mortality in Patients with Type 2 Diabetes Mellitus. Journal of Clinical Medicine, 10(11), 2371.

Poznyak A, Grechko AV, Poggio P, Myasoedova VA, Alfieri V, Orekhov AN. The diabetes mellitus–atherosclerosis connection: The role of lipid and glucose metabolism and chronic inflammation. International journal of molecular sciences. 2020 Mar 6;21(5):1835.

Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian journal of ophthalmology. 2021 Nov 1;69(11):2932-8.

Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. Jama. 2001 Jul 18;286(3):327-34.

Prenissl J, Jaacks LM, Mohan V, Manne-Goehler J, Davies JI, Awasthi A, Bischops AC, Atun R, Bärnighausen T, Vollmer S, Geldsetzer P. Variation in health system performance for managing diabetes among states in India: a cross- sectional study of individuals aged 15 to 49 years. Bmc Medicine. 2019 Dec; 17:1-2.

Prentice JC, Pizer SD, Conlin PR. Identifying the independent effect of HbA1c variability on adverse health outcomes in patients with type 2 diabetes. Diabetic Medicine. 2016 Dec;33(12):1640-8.

Rabinovich-Nikitin I, Dhingra R, Kirshenbaum LA. Activation of mitophagy in high- fat diet–induced diabetic cardiomyopathy. Circulation research. 2019 Apr 26;124(9):1288-90.

Rajput R, Saini O, Rajput M, Shankar V. Comparison of HbA1c and FPG as a screening tool for diagnosis of pre-diabetes and diabetes in Indian population. International Journal of Diabetes in Developing Countries. 2015 Dec; 35:559- 64.

Ramachandra n A. Genetic epidemiolog y of NIDDM among Asian Indians. Annals of Medicine 1992; 24, 6: 499±503.

Ramachandran A, Mary S, Yamuna A, Murugesan N, Snehalatha C. High prevalence of diabetes and cardiovascular risk factors associated with urbanization in India. Diabetes care. 2008 May 1;31(5):893-8.

Ramaiya KL, Kodali VR & Alberti KG. Epidemiology of diabetes in Asians of the Indian subcontinent. DiabetesÐ Metabolism Reviews 1990; 6, 3: 125±46.

Raman Kutty V, Joseph A, R Soman C. High prevalence of type 2 diabetes in an urban settlement in Kerala, India. Ethnicity and Health. 1999 Nov 1;4(4):231- 9.

Ranasinghe, P., Rathnayake, N., Wijayawardhana, S., Jeyapragasam, H., Meegoda, V. J., Jayawardena, R., & Misra, A. (2024). Rising trends of diabetes in South Asia: A systematic review and meta-analysis [Review of Rising trends of diabetes in South Asia: A systematic review and meta-analysis]. Diabetes & Metabolic Syndrome Clinical Research & Reviews, 18, 103160. Elsevier BV.

Ranasinghe P, Jayawardena R, Gamage N, Sivanandam N, Misra A. Prevalence and trends of the diabetes epidemic in urban and rural India: A pooled systematic review and meta-analysis of 1.7 million adults. Annals of epidemiology. 2021 Jun 1;58:128-48.

Rani PK, Raman R, Subramani S, Perumal G, Kumaramanickavel G, Sharma T. Knowledge of diabetes and diabetic retinopathy among rural populations in India, and the influence of knowledge of diabetic retinopathy on attitude and practice. Rural and remote health. 2008 Jul;8(3):1-9.

Raposeiras-Roubin S, Rosselló X, Oliva B, Fernández-Friera L, Mendiguren JM, Andrés V, Bueno H, Sanz J, Martínez de Vega V, Abu-Assi E, Iñiguez A. Triglycerides and residual atherosclerotic risk. Journal of the American College of Cardiology. 2021 Jun 22;77(24):3031-41.

Rapp JH, Harris HW, Hamilton RL, Krupski WC, Reilly LM, Ehrenfeld WK, Stoney RJ, Goldstone J, Kane JP: Particle size distribution of lipoproteins from human atherosclerotic plaque: a preliminary report. J Vasc Surg 1989, 9:81– 88.

Reaven GM. Compensatory hyperinsulinemia and the development of an atherogenic lipoprotein profile: the price paid to maintain glucose homeostasis in insulin- resistant individuals. Endocrinology and Metabolism Clinics. 2005 Mar 1;34(1):49-62.

Reaven GM. Compensatory hyperinsulinemia and the development of an atherogenic lipoprotein profile: the price paid to maintain glucose homeostasis in insulin- resistant individuals. Endocrinology and Metabolism Clinics. 2005 Mar 1;34(1):49-62.

Reaven GM. Role of insulin resistance in human disease. Diabetes. 1988 Dec 1;37(12):1595-607.

Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Franconi F, Gerdts E, Foryst- Ludwig A, Maas AH, Kautzky-Willer A, Knappe-Wegner D, EUGenMed, Cardiovascular Clinical Study Group,. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. European heart journal. 2016 Jan 1;37(1):24-34.

Regufe VM, Pinto CM, Perez PM. Metabolic syndrome in type 2 diabetic patients: A review of current evidence. Porto biomedical journal. 2020 Nov 1;5(6):e101.

Reiner Ž. Hypertriglyceridaemia and risk of coronary artery disease. Nature Reviews Cardiology. 2017 Jul;14(7):401-11.

Rich, S.S. Mapping genes in diabetes. Genetic epidemiological perspective. Diabetes 1990, 39, 1315–1319.

Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of

Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. Circulation. 1998 Feb 10;97(5):425-8.

Ripsin CM, Kang H, Urban RJ. Management of blood glucose in type 2 diabetes mellitus. American family physician. 2009 Jan 1;79(1):29-36.

Rizzo M, Kotur-Stevuljevic J, Berneis K, Spinas G, Rini GB, Jelic-Ivanovic Z, Spasojevic-Kalimanovska V, Vekic J. Atherogenic dyslipidemia and oxidative stress: a new look. Translational Research. 2009 May 1;153(5):217- 23.

S. Hirayama and T. Miida, "Small dense LDL: an emerging risk factor for cardiovascular disease," Clinica Chimica Acta, no. 414, pp. 215–224, 2012.

Sacerdote C, Ricceri F, Rolandsson O, Baldi I, Chirlaque MD, Feskens E, Bendinelli B, Ardanaz E, Arriola L, Balkau B, Bergmann M. Lower educational level is a predictor of incident type 2 diabetes in European countries: the EPIC- InterAct study. International journal of epidemiology. 2012 Aug 1;41(4):1162-73.

Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes research and clinical practice. 2019 Nov 1;157:107843.

Saenger AK, Christenson RH. Stroke biomarkers: progress and challenges for diagnosis, prognosis, differentiation, and treatment. Clinical chemistry. 2010 Jan 1;56(1):21-33.

Safiri S, Karamzad N, Kaufman JS, Bell AW, Nejadghaderi SA, Sullman MJ, Moradi-Lakeh M, Collins G, Kolahi AA. Prevalence, deaths and disability- adjusted-life-years (DALYs) due to type 2 diabetes and its attributable risk factors in 204 countries and territories, 1990-2019: results from the global burden of disease study 2019. Frontiers in endocrinology. 2022 Feb 25;13:838027.

Saito T, Watanabe M, Nishida J, Izumi T, Omura M, Takagi T, Fukunaga R, Bandai Y, Tajima N, Nakamura Y, Ito M. Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. Archives of internal medicine. 2011 Aug 8;171(15):1352-60.

Sale, A., & Ladha, N. (2023). Screening the Risk of Developing Type 2 Diabetes Mellitus and Cardiovascular Disease Among Peri-Menopausal Women. International Journal of Health Sciences and Research, 13(9), 12.

Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. The Journal of clinical investigation. 2017 Jan 3;127(1):1-4.

Sathish T, Kannan S, Sarma PS, Razum O, Thankappan KR. Incidence of hypertension and its risk factors in rural Kerala, India: a community-based cohort study. Public health. 2012 Jan 31; 12

Satyam, D., & Umeshkumar. (2021). Macrovascular and Microvascular Complications in Newly Diagnosed Type 2 Diabetes Mellitus. Indian Journal of Public Health Research & Development, 12(4), 140.

Schaefer, Ernst J. et al. Atherosclerotic cardiovascular disease risk and small dense low-density lipoprotein cholesterol in men, women, African Americans and non- African Americans: The pooling project Atherosclerosis, Volume 367, 15 – 23.

Schiebinger L, Klinge I, Sánchez de Madariaga I, Paik HY, Schraudner M, Stefanick M. Gendered innovations in science, health & medicine, engineering, and environment. Available at genderedinnovations stanford edu/what-is- gendered-innovations html Accessed January. 2011;21:2015.

Selvi NM, Nandhini S, Sakthivadivel V, Lokesh S, Srinivasan AR, Sumathi S. Association of triglyceride–glucose index (TyG index) with HbA1c and insulin resistance in type 2 diabetes mellitus. Maedica. 2021 Sep;16(3):375.

Seppälä-Lindroos A, Vehkavaara S, Häkkinen AM, Goto T, Westerbacka J, Sovijärvi A, Halavaara J, Yki-Järvinen H. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. The Journal of Clinical Endocrinology & Metabolism. 2002 Jul 1;87(7):3023-8.

Sharma, U. K., Pujani, M., & Anuradha, A. (2024). Type-II-Diabetes Mellitus- Etiology, Epidemiology, Risk Factors and Diagnosis and Insight into Demography (Urban Versus Rural). International Journal of Health Sciences and Research, 14(1), 283.

Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes research and clinical practice. 2010 Jan 1;87(1):4-

Shaw JE, Zimmet PZ, Hodge AM, De Courten M, Dowse GK, Chitson P, Tuomilehto J, Alberti KG. Impaired fasting glucose: how low should it go?. Diabetes Care. 2000 Jan 1;23(1):34-9.

Shen J, Kondal D, Rubinstein A, Irazola V, Gutierrez L, Miranda JJ, Bernabé- Ortiz A, Lazo- Porras M, Levitt N, Steyn K, Bobrow K. A multiethnic study of pre-diabetes and diabetes in LMIC. Global heart. 2016 Mar 1;11(1):61-70.

Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. Biomarker insights. 2016 Jan;11:BMI-S384-40.

Shin JA, Lee JH, Lim SY, Ha HS, Kwon HS, Park YM, Lee WC, Kang MI, Yim HW,

Yoon KH, Son HY. Metabolic syndrome as a predictor of type 2 diabetes, and its clinical interpretations and usefulness. Journal of diabetes investigation. 2013 Jul;4(4):334-43.

Shitara J, Ogita M, Wada H, Tsuboi S, Endo H, Doi S, Konishi H, Naito R, Dohi T, Kasai T, Okazaki S. Clinical impact of high-sensitivity C-reactive protein during follow-up on long-term adverse clinical outcomes in patients with coronary artery disease treated with percutaneous coronary intervention. Journal of cardiology. 2019 Jan 1;73(1):45-50.

Siddiqui MK, Kennedy G, Carr F, Doney AS, Pearson ER, Morris AD, Johnson T, McLaughlin MM, Williams RE, Palmer CN. Lp-PLA 2 activity is associated with increased risk of diabetic retinopathy: a longitudinal disease progression study. Diabetologia. 2018 Jun;61:1344-53.

Simmons RK, Alberti KG, Gale EA, Colagiuri S, Tuomilehto J, Qiao Q, Ramachandran A, Tajima N, Brajkovich Mirchov I, Ben-Nakhi A, Reaven G. The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. Diabetologia. 2010 Apr;53:600- 5.

Sinha R, Dufour S, Petersen KF, LeBon V, Enoksson S, Ma YZ, Savoye M, Rothman DL, Shulman GI, Caprio S. Assessment of skeletal muscle triglyceride content by 1H nuclear magnetic resonance spectroscopy in lean and obese adolescents: relationships to insulin sensitivity, total body fat, and central adiposity. Diabetes. 2002 Apr 1;51(4):1022-7.

Sniderman, A. D., Thanassoulis, G., Glavinovic, T., Navar, A. M., Pencina, M., Catapano, A., & Ference, B. A. (2019). Apolipoprotein B Particles and Cardiovascular Disease: A Narrative Review. JAMA cardiology, 4(12), 1287–1295. https://doi.org/10.1001/jamacardio.2019.3780

Sofogianni A, Alkagiet S, Tziomalos K. Lipoprotein-associated phospholipase A2 and coronary heart disease. Curr Pharm Des. 2018;24(3):291-296.

Sokooti S, Flores-Guerrero JL, Heerspink HJ, Connelly MA, Bakker SJ, Dullaart RP. Triglyceride-rich lipoprotein and LDL particle subfractions and their association with incident type 2 diabetes: the PREVEND study. Cardiovascular Diabetology. 2021 Dec;20:1-4.

Sommer I, Griebler U, Mahlknecht P, Thaler K, Bouskill K, Gartlehner G, Mendis S. Socioeconomic inequalities in non-communicable diseases and their risk factors: an overview of systematic reviews. BMC public health. 2015 Dec;15:1-2.

Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Frontiers in immunology. 2018 Apr 13;9:754.

Srinivasan S, Lingegowda JB, Rajan C, Muddegowda PH, Kurpad R. Metabolic syndrome in rural Kerala: a hospital based study. Int J Adv Med. 2016 Nov;3(4):898-904.

Srisawasdi P, Chaloeysup S, Teerajetgul Y, Pocathikorn A, Sukasem C, Vanavanan S, et al. Estimation of plasma small dense LDL cholesterol from classic lipid measures. Am J Clin Pathol. 2011; 136: 20-9.

Srisawasdi P, Vanavanan S, Rochanawutanon M, Kruthkul K, Kotani K, Kroll MH. Small-dense LDL/large-buoyant LDL ratio associates with the metabolic syndrome. Clinical biochemistry. 2015 May 1;48(7-8):495-

Stafforini DM, Sheller JR, Blackwell TS, Sapirstein A, Yull FE, McIntyre TM, Bonventre JV, Prescott SM, Roberts LJ. Release of free F2-isoprostanes from esterified phospholipids is catalyzed by intracellular and plasma platelet- activating factor acetylhydrolases. Journal of Biological Chemistry. 2006 Feb 24;281(8):4616-23.

Standl E, Khunti K, Hansen TB, Schnell O. The global epidemics of diabetes in the 21st century: Current situation and perspectives. European journal of preventive cardiology. 2019 Dec 1;26(2_suppl):7-14.

Steinbrecher UP, Parthasarathy S, Leake DS, Witztum JL, Steinberg D. Modification of low density lipoprotein by endothelial cells involves lipid peroxidation and degradation of low density lipoprotein phospholipids. Proceedings of the National Academy of Sciences. 1984 Jun;81(12):3883-7.

Stratmann B, Tschoepe D. Heart in diabetes: not only a macrovascular disease.Diabetes care. 2011 May;34(Suppl 2):S138.

Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. bmj. 2000 Aug 12;321(7258):405-12.

Strikić D, Vujević A, Perica D, Leskovar D, Paponja K, Pećin I, Merćep I. Importance of Dyslipidaemia Treatment in Individuals with Type 2 Diabetes Mellitus— A Narrative Review. Diabetology. 2023 Dec 4;4(4):538-52.

Stringhini S, Zaninotto P, Kumari M, Kivimäki M, Batty GD. Lifecourse socioeconomic status and type 2 diabetes: the role of chronic inflammation in the English Longitudinal Study of Ageing. Scientific reports. 2016 Apr 22;6(1):24780.

Sun, J., Hu, W., Ye, S., Deng, D., & Chen, M. (2023). The Description and Prediction of Incidence, Prevalence, Mortality, Disability-Adjusted Life Years Cases, and Corresponding Age-Standardized Rates for Global Diabetes. Journal of Epidemiology and Global Health, 13(3), 566.

Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JC, Mbanya JC, Pavkov ME. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes research and clinical practice. 2022 Jan 1;183:109-19.

Suzuki K, Hatzikotoulas K, Southam L, Taylor HJ, Yin X, Lorenz KM, Mandla R, Huerta-Chagoya A, Melloni GE, Kanoni S, Rayner NW. Genetic drivers of heterogeneity in type 2 diabetes pathophysiology. Nature. 2024 Mar 14;627(8003):347-57.

Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, Gortmaker SL. The global obesity pandemic: shaped by global drivers and local environments. The lancet. 2011 Aug 27;378(9793):804-14.

Sáinz JC, Fernández-Labandera C, Aguado LQ, Meseguer AF, Valdivielso P, Román-García J, Assessment Study Group. Higher red blood cell distribution width is associated with the metabolic syndrome: results of the CVR assessment study. Diabetes Care. 2010 Mar 1;33(3):e40-.

Świątkiewicz I, Magielski P, Kubica J. C-reactive protein as a risk marker for post- infarct heart failure over a multi-year period. International Journal of Molecular Sciences. 2021 Mar 20;22(6):31-69.

Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjörnsdottir S, Wedel H, Clements M, Dahlqvist S, Lind M. Excess mortality among persons with type 2 diabetes. New England Journal of Medicine. 2015 Oct 29;373(18):1720-32.

Tandon N, Anjana RM, Mohan V, Kaur T, Afshin A, Ong K, Mukhopadhyay S, Thomas N, Bhatia E, Krishnan A, Mathur P. The increasing burden of diabetes and variations among the states of India: the Global Burden of Disease Study 1990–2016. The Lancet Global Health. 2018 Dec 1;6(12):e1352-62.

Tao Z, Shi A, Zhao J. Epidemiological perspectives of diabetes. Cell Biochem Biophys 2015;73:181-5

Tellis C, D. Tselepis A. Pathophysiological role and clinical significance of lipoprotein-associated phospholipase A2 (Lp-PLA2) bound to LDL and HDL. Current pharmaceutical design. 2014 Dec 1;20(40):6256-69.

Thankappan KR, Shah B, Mathur P, Sarma PS, Srinivas G, Mini GK, et al. Risk factor profile for chronic non-communicable diseases: results of a community-based study in Kerala, India. Indian J Med Res. 2010 Jan; 131:53–63.

The Brazilian Longitudinal Study of Adult Health (ELSA–Brasil).Atherosclerosis. 2025 Mar 20:119-71.

Thorand B, Löwel H, Schneider A, Kolb H, Meisinger C, Fröhlich M, Koenig W. C-reactive protein as a predictor for incident diabetes mellitus among middle- aged men:

results from the MONICA Augsburg cohort study, 1984-1998. Archives of internal medicine. 2003 Jan 13;163(1):93-9.

Tjoelker LW, Eberhardt C, Unger J, Le Trong H, Zimmerman GA, McIntyre TM, Stafforini DM, Prescott SM, Gray PW. Plasma Platelet-activating Factor Acetylhydrolase Is a Secreted Phospholipase A2 with a Catalytic Triad (∗). Journal of Biological Chemistry. 1995 Oct 27;270(43):25481-7.

Toth PP, McCullough PA, Wegner MS, Colley KJ. Lipoprotein-associated phospholipase A2: role in atherosclerosis and utility as a cardiovascular biomarker. Expert Review of Cardiovascular Therapy. 2010 Mar 1;8(3):425- 38.

Tripathi, P., Kadam, N., Kathrikolly, T., Tiwari, D., Vyawahare, A., Sharma, B., Ganla, M., & Saboo, B. (2025). Baseline clinical and biochemical profiles of type 2 diabetes patients enrolled in a lifestyle management program in India, a cross-sectional study. Scientific Reports, 15(1).

Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. The Lancet. 2014 Mar 22;383(9922):1084-94.

Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. New England journal of medicine. 2001 May 3;344(18):1343-50.

Unnikrishnan R, Anjana RM, Mohan V. Diabetes mellitus and its complications in India. Nature Reviews Endocrinology. 2016 Jun;12(6):357-70.

van Beers, C.A., Caris, M.G., DeVries, J.H. and Serné, E.H., 2018. The relation between HbA1c and hypoglycemia revisited; a secondary analysis from an intervention trial in patients with type 1 diabetes and impaired awareness of hypoglycemia. Journal of Diabetes and its Complications, 32(1), pp.100-103.

Van Dam RM, Willett WC, Rimm EB, Stampfer MJ, Hu FB. Dietary fat and meat intake in relation to risk of type 2 diabetes in men. Diabetes care. 2002 Mar 1;25(3):417-24.

van Woudenbergh GJ, Kuijsten A, Sijbrands EJ, Hofman A, Witteman JC, Feskens EJ. Glycemic index and glycemic load and their association with C-reactive protein and incident type 2 diabetes. Journal of nutrition and metabolism. 2011;2011(1):623076.

Vergès B. Intestinal lipid absorption and transport in type 2 diabetes. Diabetologia.2022 Oct;65(10):1587-600.

Vijayakumar G, Manghat S, Vijayakumar R, Simon L, Scaria LM, Vijayakumar A, Sreehari GK, Kutty VR, Rachana A, Jaleel A. Incidence of type 2 diabetes mellitus and prediabetes in Kerala, India: results from a 10-year prospective cohort. BMC

public health. 2019 Dec;19:1-0.

Vijayakumar P, Nelson RG, Hanson RL, Knowler WC, Sinha M. HbA1c and the prediction of type 2 diabetes in children and adults. Diabetes care. 2017 Jan 1;40(1):16-21.

Visser A, Snoek F. Perspectives on education and counseling for diabetes patients.Patient Education and Counseling. 2004 Jun 1;53(3):251-5.

Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, Abbasi-Kangevari M, Abbastabar H, Abd-Allah F, Abdelalim A, Abdollahi M. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The lancet. 2020 Oct 17;396(10258):1204-22.

Wan EY, Fung CS, Fong DY, Lam CL. Association of variability in hemoglobin A1c with cardiovascular diseases and mortality in Chinese patients with type 2 diabetes mellitus—a retrospective population-based cohort study. Journal of Diabetes and its Complications. 2016 Sep 1;30(7):1240-7.

Wang, H., Fan, K., Ning, Y., Li, Y., Qi, X., Wang, Z., Xu, K., Zhang, R., Zhou, Y., Dong, H., & Zheng, G. (2025). Hypertension and BMI as Mediators of Type 2 Diabetes-Induced CKD: Insights from an Integrative Multi-Database Study. Diabetes Metabolic Syndrome and Obesity, 3343.

Wang, H., Zhang, H., Jia, Y., Zhang, Z., Craig, R., Wang, X. and Elbein, S.C.,2004. Adiponectin receptor 1 gene (ADIPOR1) as a candidate for type 2 diabetes and insulin resistance. Diabetes, 53(8), pp.2132-2136.

Wang C, Li Y, Lin H, Zhu Y, Xu X, Wu P, Zhang Y, Xu T, Ren J, Xu H, Dong G. The role of small dense LDL-C/large buoyant LDL-C ratio as an independent risk factor in patients with type 2 diabetes mellitus and metabolic syndrome. InAnnales de Biologie Clinique 2024 (Vol. 82, No. 2, pp. 174-186). JLE Editions.

Wang J, Stancakova A, Soininen P, Kangas AJ, Paananen J, Kuusisto J, Ala-Korpela M, Laakso M. Lipoprotein subclass profiles in individuals with varying degrees of glucose tolerance: a population-based study of 9399 Finnish men. J Intern Med. 2012;272(6):562–72.

Wang KY, Chen YC, Chen JY, Loke SS, Yeh WC, Li WC. Correlation Between Lipoprotein-Related Phospholipase A2 and Metabolic Syndrome. International Journal of General Medicine. 2023 Dec 31:6041-9.

Wang X, Bao W, Liu J, OuYang YY, Wang D, Rong S, Xiao X, Shan ZL, Zhang Y, Yao P, Liu LG. Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. Diabetes care. 2013 Jan 1;36(1):166-75.

Wannamethee SG, Papacosta O, Lawlor DA, Whincup PH, Lowe GD, Ebrahim S, Sattar

N. Do women exhibit greater differences in established and novel risk factors between diabetes and non-diabetes than men? The British Regional Heart Study and British Women's Heart Health Study. Diabetologia. 2012 Jan;55:80-7.

Ware AD. The complete blood count and white blood cell differential. InContemporary practice in clinical chemistry 2020 Jan 1 (pp. 429-444). Academic Press.

Wild, S. H. (2023). Cardiometabolic risk factor prevalence in a representative population of adults in India. The Lancet Diabetes & Endocrinology, 11(7), 444.

Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes care. 2004 May 1;27(5):1047-53.

Wilensky RL, Shi YI, Mohler III ER, Hamamdzic D, Burgert ME, Li J, Postle A, Fenning RS, Bollinger JG, Hoffman BE, Pelchovitz DJ. Inhibition of lipoprotein-associated phospholipase A2 reduces complex coronary atherosclerotic plaque development. Nature medicine. 2008 Oct;14(10):1059- 66.

Willi, C., Bodenmann, P., Ghali, W. A., Faris, P. D. & Cornuz, J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 298, 2654–2664 (2007).

Williams, D.M.; Jones, H.; Stephens, J.W. Personalized type 2 diabetes management: An update on recent advances and recommendations. Diabetes Metabol Syndr Obes. 2022, 15, 281–295.

Wilson PWF. Metabolic Syndrome as a Precursor of Cardiovascular Disease and Type 2 Diabetes Mellitus. Circulation. 2005 Nov 15; 112

World Health Organization (WHO). Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Abbreviated Report of a WHO Consulta tion. Geneva: WHO; 2011.

World Health Organization. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Abbreviated Report of a WHO Consultation. Geneva, Switzerland: World Health Organization; 2011

Wu, J., Feng, Z., Duan, J., Li, Y., Deng, P., Wang, J., Yang, Y., Meng, C., Wang, W., Wang, A., & Wang, J. (2023). Global burden of type 2 diabetes attributable to non-high body mass index from 1990 to 2019. BMC Public Health, 23(1).

Wu L, Parhofer KG. Diabetic dyslipidemia. Metabolism. 2014 Dec 1;63(12):1469- 79.

Wägner AM, Sánchez-Quesada JL, Benítez S, Bancells C, Ordóñez-Llanos J, Pérez A. Effect of statin and fibrate treatment on inflammation in type 2 diabetes. A randomized, cross-over study. Diabetes Research and Clinical Practice. 2011 Jul 1;93(1):e25-8.

Wändell PE, Johansson SE, Gåfvels C, Hellenius ML, De Faire U, Sundquist J. Estimation of diabetes prevalence among immigrants from the Middle East in Sweden by using three different data sources. Diabetes & metabolism. 2008 Sep 1;34(4):328-33.

Xanthopoulos A, Tryposkiadis K, Dimos A, Bourazana A, Zagouras A, Iakovis N, Papamichalis M, Giamouzis G, Vassilopoulos G, Skoularigis J, Triposkiadis

Xia F, Liu G, Shi Y, Zhang Y. Impact of microalbuminuria on incident coronary heart disease, cardiovascular and all-cause mortality: a meta-analysis of prospective studies. International journal of clinical and experimental medicine. 2015;8(1):1.

Xu J, Chen D. The small dense LDL particle/large buoyant LDL particle ratio is associated with glucose metabolic status in pregnancy. Lipids in Health and Disease. 2017 Dec;16:1-7.

Yamada Y, Uchida J, Izumi H, Tsukamoto Y, Inoue G, Watanabe Y, Irie J, Yamada S. A non-calorie-restricted low-carbohydrate diet is effective as an alternative therapy for patients with type 2 diabetes. Intern Med. 2014;53:13–19. doi: 10.2169/internalmedicine.53.0861

Yan Y, Wu T, Zhang M, Li C, Liu Q, Li F. Prevalence, awareness and control of type 2 diabetes mellitus and risk factors in Chinese elderly population. BMC Public Health. 2022 Jul 19;22(1):1382.

Yang, Z., Chen, Y., Tang, Y., Zhang, S., Zhuang, Z., & Ni, Q. (2025). Rising tide: the growing global burden and inequalities of early-onset type 2 diabetes among youths aged 15–34 years (1990–2021). Diabetology & Metabolic Syndrome, 17(1).

Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, Shan Z, Liu J, Tian H, Ji Q, Zhu D. Prevalence of diabetes among men and women in China. New England journal of medicine. 2010 Mar 25;362(12):1090-101.

Yaribeygi H, Farrokhi FR, Butler AE, Sahebkar A. Insulin resistance: Review of the underlying molecular mechanisms. Journal of cellular physiology. 2019 Jun;234(6):8152-61.

Ye J, Wu Y, Yang S, Zhu D, Chen F, Chen J, Ji X, Hou K. The global, regional and national burden of type 2 diabetes mellitus in the past, present and future: a systematic analysis of the Global Burden of Disease Study 2019. Frontiers in endocrinology. 2023 Jul 14;14:1192629.

Yin B, Wu Z, Xia Y, Xiao S, Chen L, Li Y. Non-linear association of atherogenic index of plasma with insulin resistance and type 2 diabetes: a cross-sectional study. Cardiovascular diabetology. 2023 Jun 29;22(1):157.

Yousri NA, Suhre K, Yassin E, Al-Shakaki A, Robay A, Elshafei M, Chidiac O, Hunt SC, Crystal RG, Fakhro KA. Metabolic and metabo-clinical signatures of type

Yu S, Fu AZ, Engel SS, Shankar RR, Radican L. Association between hypoglycemia risk and hemoglobin A1C in patients with type 2 diabetes mellitus. Current medical research and opinion. 2016 Aug 2;32(8):1409-16.

Zalawadiya SK, Zmily H, Farah J, Daifallah S, Ali O, Ghali JK. Red cell distribution width and mortality in predominantly African-American population with decompensated heart failure. Journal of cardiac failure. 2011 Apr 1;17(4):292-8.

Zhang, X., Wang, X., Wang, M., Hu, B., Tang, W., Wu, Y., Gu, J., Tian, N., & Li, Q. (2022). The global burden of type 2 diabetes attributable to high body mass index in 204 countries and territories, 1990–2019: An analysis of the Global Burden of Disease Study. Frontiers in Public Health, 10.

Zhang J, He L. Relationship between small dense low density lipoprotein and cardiovascular events in patients with acute coronary syndrome undergoing percutaneous coronary intervention. BMC Cardiovascular Disorders. 2021 Dec;21:1-0.

Zhao J, Lv H, Yin D, Zhou X, Zhu H, Guo L, Wang J. Systemic immune- inflammation index predicts long-term outcomes in patients with three- vessel coronary disease after revascularization: results from a large cohort of 3561 patients. Journal of inflammation research. 2022 Jan 1:5283-92.

Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nature reviews endocrinology. 2018 Feb;14(2):88-98.

Zhou B, Lu Y, Hajifathalian K, Bentham J, Di Cesare M, Danaei G, Bixby H, Cowan MJ, Ali MK, Taddei C, Lo WC. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4· 4 million participants. The lancet. 2016 Apr 9;387(10027):1513-30.

Zhu, R., Zhou, S., Xia, L., & Bao, X. (2022). Incidence, Morbidity and years Lived With Disability due to Type 2 Diabetes Mellitus in 204 Countries and Territories: Trends From 1990 to 2019. Frontiers in Endocrinology, 13.

Zhu R, Zhou S, Xia L, Bao X. Incidence, morbidity and years lived with disability due to type 2 diabetes mellitus in 204 countries and territories: trends from 1990 to 2019. Frontiers in endocrinology. 2022 Jul 11;13:905538.

Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001 Dec 13;414(6865):782-7.

INDEX

APPENDICES

Appendix -1

Institutional Ethical Clearance Certificate

Believers Church
MEDICAL COLLEGE HOSPITAL

INSTITUTIONAL ETHICS COMMITTEE
Regn. No: ECR/1098/Inst/KL/2018

IEC/2020/06 Date: 08.09.2020

IEC STUDY No. IEC/2020/06/160

Mr. Anush N
Department of Biochemistry

Dear Anush N,

Sub: Approval of Research proposal by the I.E.C

I wish to inform you that your Research Project entitled **"Clinical significance of small dense LDL in type 2 diabetes patients."** has been unanimously approved by Ethical review and was approved on 08.09.2020. The approval of I.E.C is valid for a period of 2 years from the date of approval given.
You must inform the IEC of the following through the Secretary of Institutional Ethics Committee

1. The occurrence of serious Adverse Events/Drug Reactions and/or Death. While conducting this Trial in the specified format.
2. Protocol amendment in the specified format.
3. (a) Discontinuation (b) Abandonment (c) Completion of this trial, stating the reasons, if the situation of 2 (a) or (b) is encountered.
4. (a) It is mandatory that a 6 monthly Interim Review Report on the status of the project be submitted to the Secretary in the specified format.
   (b) On completion of above Research Project- the Principal Investigator is responsible for submitting a brief summary of the results obtained.

With best wishes,

Dr. TOMY PHILIP MD;MRCP
Reg.No: 15913
Professor of Medicine
Pushpagiri Institute of
Medical Sciences,Tiruvalla.

Chairperson
CC: The HOD, Medical Research

Institutional Ethics Committee
Believers Church Medical College Hospital
St. Thomas Nagar, Kuttapuzha (P.O)
Thiruvalla - 689 103

P.B. 31, St. Thomas Nagar, Kuttapuzha P.O., Thiruvalla - 689 103
0469 - 2742800 (Ext: 2029) | Fax: 0469 - 2742820 | deanresearch@bcmch.org | www.bcmch.edu.in

Appendix II

Conference Certificates

CUDC 2021

CHITKARA UNIVERSITY

CERTIFICATE
OF PARTICIPATION

This is to certify that

Anush N

from

School of Allied Health Sciences,Lovely Professional University,Punjab

attended and presented a paper entitled

Predictors Of Severe Covid-19 Outcome: A Meta-Analysis Of Common Laboratory Bio Markers

Under Track 6: Health Sciences – Allied, Optometry & Physiotherapy

in Chitkara University Doctoral Consortium (CUDC-2021)

held in virtual mode on November 12-13, 2021

DR. ARCHANA MANTRI	DR. AMIT MITTAL	DR. PANKAJ KUMAR
Vice Chancellor Chitkara University, Punjab	Dean- Doctoral Research Centre Chitkara Business School Chitkara University, Punjab	Dean, PhD Programme Chitkara University, Punjab

DIVISION OF RESEARCH AND DEVELOPMENT

[Under the Aegis of Lovely Professional University, Jalandhar-Delhi G.T. Road, Phagwara (Punjab)]

Certificate No.240471

Certificate of Participation

This is to certify that **Mr. Anush N** of **Lovely Professional University, Phagwara, Punjab, India** has presented paper on **Lipid Surrogate Markers of small dense LDL in Diabetic Patients** in the **International Conference on Materials for Emerging Technologies (ICMET-21)** held on February 18-19, 2022, organized by Department of Research Impact and Outcome, Division of Research and Development, Lovely Professional University, Punjab.

Date of Issue: 16-03-2022
Place: Phagwara (Punjab), India

Prepared by (Administrative Officer-Records)	Dr. Vipul Srivastava Convener (ICMET-21)	Dr. Manish Vyas Organizing Secretary (ICMET-21)	Dr. Chander Prakash Co-Chairperson (ICMET-21)

Appendix III

List of Publications

1. **Prevalence of Small Dense LDL in Type 2 Diabetes Mellitus and Its Correlation with Inflammatory Markers: A Comprehensive Study.**

   Journal: Asian Journal of Pharmaceutical and Clinical Research

   Date of Publishing :07 th April 2025

   Indexing -Scopus

   Research Paper (Thesis Related)

2. **Small Dense LDL as A Biomarker in Type II Diabetes: A Comprehensive Study**

   Journal: African Journal of Biomedical Research

   Date of Publishing :10 th September 2024

   Indexing -Scopus (up to 2024)

   Research Paper (Thesis Related)

3. **Small Dense LDL as an Atherogenic Risk Marker**

   Journal: Biointerface Research in Applied Chemistry

   Date of Publishing :07 th April 2022

   Indexing -Scopus

   Review Paper

4. **Predictors of Severe COVID-19 Outcome: A Meta-Analysis of Common Laboratory Biomarkers**

   Journal: ECS Transactions (Conference Paper)

   Date of Publishing :30 th April 2022

   Indexing -Scopus

   Research Paper (Meta analysis)

5. **Lipid surrogate markers of small dense LDL in diabetic patients**

   Journal: AIP Conference Proceedings (Conference Paper)

   Date of Publishing :8 th September 2023

   Indexing -Scopus

   Systematic Review Paper

Conferences/Paper Presentations

1. Presented a paper on ***"The Lipid Surrogate Markers of Small dense LDL in Diabetic Patients"*** in **International Conference on Materials for Emerging Technologies-2021 (ICMET-21)** hosted by the Department of Research Impact and Outcome, Division of Research and Development, Lovely Professional University, Punjab, India on 18 th -19 th February 2022.

2. Presented a paper on ***"Predictors of severe COVID-19 outcome: A meta-analysis of Common Laboratory Biomarkers"*** in the **Chitkara University Doctoral Consortium (CUDC)** held on 12-13 th November 2021.