Association of LDL Cholesterol and hs-CRP with Subtypes of Heart Failure in Type 2 Diabetes Mellitus Patients: A Cross-sectional Study

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ABSTRACT

Introduction: Heart Failure (HF) in patients with Type 2 Diabetes Mellitus (T2DM) is classified based on Ejection Fraction (EF) into HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF). Low-Density Lipoprotein Cholesterol (LDL-C), a marker of dyslipidaemia, and high-sensitivity C-Reactive Protein (hs-CRP), an inflammatory biomarker, are recognised for their roles in contributing to cardiovascular diseases and HF progression in T2DM patients.

Aim: To explore the clinical and aetiological characteristics of HF in T2DM patients and to analyse the association between LDL-C and hs-CRP levels with different HF subtypes.

Materials and Methods: The present cross-sectional study was conducted from October 2023 to March 2025 at a tertiary care hospital in Western Maharashtra, India. The study included 100 patients over 18 years of age with Type 2 Diabetes and HF, in whom LDL-C and hs-CRP levels were elevated. LDL-C was calculated using the Friedewald formula, and hs-CRP was measured using the nephelometry method. The Statistical Package for Social Sciences (SPSS) statistics package version 20 was used for statistical analysis. The χ^2 test, t-test, and non-parametric tests were employed, with statistical significance acknowledged at the p-value <0.05 level.

Results: The study included 100 T2DM patients with HF. hs-CRP levels were elevated in both the HFrEF and HFpEF groups; however, no significant difference was found between them (p-value=0.698). LDL-C showed no statistically significant association with HF type (p-value=0.931). HbA1c was higher in the HFrEF group (9.84±1.6) compared to the HFpEF group (8.73±1.4), with statistical significance (p-value=0.001).

Conclusion: LDL-C and hs-CRP levels showed no significant association with HF subtypes, although trends suggested an inverse correlation with EF that was not statistically significant. A significant inverse relationship between HbA1c and EF highlighted the impact of poor glycaemic control on cardiac function. These findings support the need for comprehensive metabolic and inflammatory profiling in diabetic HF patients.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM), which accounts for approximately 90-95% of all diabetes cases, represents a significant global health issue associated with increased morbidity and mortality [1,2]. In 2021, over 10.5% of adults aged 20 to 79 years-approximately 536.6 million individuals-were diagnosed with diabetes. This figure is projected to rise to 643 million by 2045 [3]. T2DM increases the risk of several health complications, particularly atherosclerosis, cardiovascular disease, and HF [4]. HF is a significant and growing concern, affecting around 1 to 2% of the global population [5]. Common risk factors for HF include Coronary Artery Disease (CAD), hypertension, diabetes, and tobacco use [6].

Recent studies have shown that systemic inflammation plays a significant role in the development of HF [7-10]. Inflammation is now recognised as a key contributor to both atherosclerosis and HF. High-sensitivity C-Reactive Protein (hs-CRP), a widely used biomarker of inflammation, has been shown to predict cardiovascular events and the development of HF independently of other risk factors [11-14]. Several studies, including extensive clinical trials such as JUPITER [14] and PROVE-IT TIMI-22 [15], have demonstrated that reducing hs-CRP levels alongside lowering LDL-C can improve cardiovascular outcomes. These findings suggest that inflammation and dyslipidaemia together contribute to increased cardiovascular risk.

Individuals with T2DM commonly exhibit dyslipidaemia, characterised by elevated LDL-C, reduced High-Density Lipoprotein Cholesterol (HDL-C), and increased triglycerides all of which raise the risk of vascular injury [16,17]. Elevated LDL-C is linked to arterial plaque buildup, while low HDL-C impairs the body's ability to remove cholesterol and modulate inflammation [17]. Furthermore, chronic inflammation in diabetes can worsen insulin resistance and damage blood vessels, thereby increasing the risk of cardiovascular complications [18].

Although many studies have examined the individual roles of LDL-C and hs-CRP in heart disease [15-18], few have explored their combined association with different types of HF-specifically, HF with preserved EF (HFpEF) and HF with reduced EF (HFrEF)-in patients with T2DM [19-21]. Investigating these associations may improve our understanding of how metabolic and inflammatory changes contribute to HF in diabetic individuals.

The present cross-sectional study aimed to evaluate the relationship between LDL-C and hs-CRP levels and different types of HF in individuals with T2DM. The findings may aid in early detection, guide treatment strategies, and strengthen preventive efforts in this high-risk population.

MATERIALS AND METHODS

The present cross-sectional study was conducted over 18 months, from October 2023 to March 2025, at Dr. D. Y. Patil Medical College,

Hospital and Research Centre, Dr. D. Y. Patil Vidyapeeth, Pimpri, Pune, in Western Maharashtra, India. The study was approved by the Institutional Ethics Sub-Committee of Dr. D. Y. Patil Medical College, Pune, India (approval number IESC/PGS/2023/12). Participants were thoroughly informed about the nature and purpose of the study, and written informed consent was obtained from each participant. Measures were taken to ensure the confidentiality and privacy of patient information, and data were anonymised to maintain participant confidentiality.

Inclusion criteria: The study included all patients with Type 2 Diabetes (fasting plasma glucose levels >126 mg/dL, HbA1c >6.5%, and post prandial glucose levels >200 mg/dL) over the age of 18, with clinical symptoms and signs suggestive of HF.

Exclusion criteria: Patients with Type 1 Diabetes Mellitus, known cases of congenital heart disease, known cases of valvular heart disease, severe anaemia (Haemoglobin <5 g%), pregnant women, and patients with thyroid disorders or infections (procalcitonin levels >0.05) were excluded.

Sample size calculation: Considering that 40% of DM had acute HF in the study by Rosano GM et al., with a 95% confidence interval, an acceptable difference of 10%, using prevalence study sample size formula n=4 pq/l2, where P=40%, q=100-p; l=allowable error; 10% of p, the calculated sample size was 93 but for study purpose 100 cases were taken. The software used for this calculation was WinPepi [22].

Study Procedure

A detailed history, NYHA classification of HF [23], anthropometry, and clinical examinations were carried out after obtaining informed consent from the patients [23]. All patients in the study underwent investigations including complete blood counts, blood sugar levels, hs-CRP, NT-Pro BNP, electrocardiograms, chest X-rays, lipid profiles, and Two-Dimensional (2D) echocardiography. Details of the reports were entered into the clinical proforma used for the study. The EF in 2D echo was calculated using the Simpson's method in which LVEF%=LVEDV-LVESV/LVEDV multiplied by 100 [24]. The 2D echocardiography findings were classified based on diastolic dysfunction as Grades 1, 2, and 3, HFrEF, and HFpEF, as well as mild, moderate, and severe Left Ventricular Hypertrophy (LVH) [23]. Blood glucose (fasting and postprandial) was tested using the hexokinase method. LDL-C was calculated using the Friedewald formula, and hs-CRP was measured using the nephelometry method.

STATISTICAL ANALYSIS

The percentages and frequencies for the categorical variables were displayed. The mean and Standard Deviation (SD) were shown for the quantitative variables. The χ^2 test was utilised to evaluate differences between groups for qualitative variables, while the t-test was employed for quantitative variables with a normal distribution, and non-parametric tests were used for those without a normal distribution. Statistical significance was acknowledged for every analysis at the p-value <0.05 level. The SPSS statistics package version 20 was used to conduct the statistical analysis.

RESULTS

There were a total of 100 study participants, included in the present study out of which the highest number were in the age group of 51-60 years (31), followed by 41-50 years (23) and 61-70 years (20). The mean age was 61.31±12.10 years, with an age range of 30-84 years. Among the 100 study participants, 60 were male and 40 were female, resulting in a male-to-female ratio of 1.5:1. Seventeen participants had a BMI >30 kg/m², 42 had a BMI between 25 and 29.9 kg/m², and 41 had a normal BMI. The most common complaint was breathlessness, reported by 38 participants, followed by cough, reported by 25 participants. Out of 100 participants, 41 had a family history of diabetes, 28 had isolated hypertension as a co-morbidity alongside diabetes, 43 were addicted to smoking, 30 were alcoholics, and 19 were tobacco chewers [Table/Fig-1].

Parameters	Total number n (%)
Age in years (Mean±SD)	61.3±12.1
Gender	
Male	60 (60%)
Female	40 (40%)
Complaints	
Breathlessness	38 (38%)
Cough	25 (25%)
Chest pain	21 (21%)
Pedal oedema	18 (18%)
Fever	2 (2%)
Abdominal pain	2 (2%)
Co-morbidities	
Hypertention	28 (28%)
Family history (hypertension+diabetes mellitus)	41 (41%)
Addiction	
Smoking	43 (43%)
Alchohol	30 (30%)
Tobacco	19 (19%)

[Table/Fig-1]: Demographic and clinical profile of participants (N=100).

[Table/Fig-2] shows the distribution of patients by New York Heart Association (NYHA) classification, with the majority in Class II (40%) and Class III (35%).

NYHA classification	Frequency	Percent
Class I	15	15
Class II	40	40
Class III	35	35
Class IV	10	10

[Table/Fig-2]: Distribution of patients by NYHA classification.

On 2D echocardiographic analysis, it was found that 51 cases exhibited Regional Wall Motion Abnormality (RWMA). The analysis also revealed that 49 cases had no diastolic dysfunction, 30 had Grade 1 diastolic dysfunction, 18 had Grade 2 diastolic dysfunction, and 3 had Grade 3 diastolic dysfunction. Furthermore, the 2D echo analysis indicated that 10 had mild concentric Left Ventricular Hypertrophy (LVH), 6 had moderate concentric LVH, 4 had severe concentric LVH, and 16 showed chamber dilatation. Among the dilated chambers, the most common finding was left atrial dilatation, and all four chambers were dilated in two cases [Table/Fig-3].

2D echo findings (N=100)	Total number n (%)
Regional wall motion abnormality	51 (51%)
Diastolic dysfunction (n=51)	
Grade 1	30 (58.8%)
Grade 2	18 (35.2%)
Grade 3	3 (5.8%)
Left ventricular hypertrophy (n=20)	
Mild	10 (50%)
Moderate	6 (30%)
Severe	4 (20%)
Chamber dilated (n=16)	
All chambers	2 (12.5%)
Left atrium	11 (68.7%)
Left ventricle	7 (43.7%)
Right atrium	3 (18.7%)
Right ventricle	3 (18.7%)

No. of chambers (n=16)	
4	2 (12.5%)
2	10 (62.5%)
1	4 (25%)

[Table/Fig-3]: 2D echo findings.

[Table/Fig-4] shows that the 100 participants were divided into HFpEF (n=31) and HFrEF (n=69) groups based on echocardiographic diagnosis. The mean values of different continuous variables were compared between these two groups, and the statistical significance of the mean values was calculated using the t-test. After comparative analysis, it was found that the mean values of lipid profile parameters, hs-CRP, NT-proBNP, and blood sugar levels (fasting and postprandial) did not show any statistical significance between the two groups (p-value >0.05), but the mean HbA1c showed a statistically significant difference between the two groups (p-value <0.05).

Variables	HFpEF (n=31)	HFrEF (n=69)	p-value
Total cholesterol (milligrams/deciliter) (mg/dL)	149.52±37.9	172.78±59.4	0.048
HDL (mg/dL)	36.35±18.4	36.12±22.27	0.958
VLDL (mg/dL)	38.87±26.9	43.25±38.22	0.566
TG (mg/dL)	115.48±46.51	129.77±81.51	0.365
LDL (mg/dL)	89.9±37.04	96.23±57.28	0.574
hs-CRP (mg/dL)	46.33±69.4	49.09±77.3	0.865
NTPROBNP Picograms/mL (pg/mL)	8843.03±9144.76	11534.13±12216.12	0.276
Fasting blood sugar (mg/dL)	164.16±16.18	160.41±14.36	0.248
Postprandial blood sugar (mg/dL)	254.29±22.21	255.07+23.34	0.875
HbA1c (gram %)	8.73±1.4	9.84±1.6	0.001

[Table/Fig-4]: Comparison of the mean value of lipid parameters by types of Heart Failure (HF).

[Table/Fig-5] shows the relationship between HbA1c, LDL, NT-proBNP range, hs-CRP, and type of HF. There was no significant association of HbA1c with the two HF groups (p>0.05). Among the HFrEF group, 40 (57.9%) had LDL values within the normal limit, and 29 (42.1%) had raised LDL levels. In the HFpEF group, 17 had LDL values within the normal limit, and 14 had raised LDL levels. There was no significant association of LDL with the two HF groups (p-value >0.05). Similarly, there was no significant association of NT-proBNP and hs-CRP with the two HF groups (p-value >0.05).

Biomarkers	HFrEF (n=69) n (%)	HFpEF (n=31) n (%)	Total (N=100) n (%)	p-value
HbA1c (%)				
6.5-8	16 (23.2%)	08 (25.8%)	24 (24%)	0.365
8.1-10	28 (40.6%)	13 (41.9%)	41 (41%)	
>10	25 (26.2%)	10 (32.3%)	35 (35%)	
LDL levels (mg/dL)				
Normal	40 (57.9%)	17 (54.8%)	57 (57%)	0.931
Raised	29 (42.1%)	14 (46.2%)	43 (43%)	
NTpro BNP range (pg/mL)				
Upto 1000	12 (17.5%)	4 (12.9%)	16 (16%)	0.619
1001-2000	6 (8.6%)	2 (6.5%)	8 (8%)	
>2000	51 (73.9%)	25 (80.6%)	76 (76%)	
Hs-CRP (mg/dL)				
1 to 10	26 (37.7%)	9 (29.1%)	35 (35%)	0.698
>10	43 (62.3%)	22 (70.9%)	65 (65%)	

[Table/Fig-5]: Comparison of laboratory parameters between HFpEF and HFrEF patients (N=100).

[Table/Fig-6] shows the correlation of study variables with EF. Analysis using the Pearson correlation test revealed no statistically significant correlation among most of the variables with EF (p-value >0.05). However, there was an inverse significant correlation between HbA1c and EF (p-value <0.05).

Variables	r value	p-value
Age	-0.022	0.829
BMI (kg/m²)	-0.136	0.177
Fasting blood sugar (mg/dL)	-0.002	0.983
Postprandial blood sugar (mg/dL)	0.017	0.869
HbA1c (mg/dL)	-0.227	**0.023**
Nitro BNP (pg/mL)	-0.145	0.15
LDL (mg/dL)	-0.025	0.805
hs-CRP (mg/dL)	-0.124	0.221

[Table/Fig-6]: Correlation of study variables with Ejection Fraction (EF).

DISCUSSION

The present study investigated the association between LDL-C, hs-CRP, and HF subtypes (HFpEF and HFrEF) in patients with T2DM. The results revealed no statistically significant association between LDL-C or hs-CRP levels and HF subtypes, although trends suggested an inverse correlation with EF. Notably, HbA1c exhibited a significant inverse relationship with EF, reinforcing the detrimental impact of poor glycaemic control on cardiac function. These findings contributed to the growing understanding of the complex interplay between metabolic dysregulation, inflammation, and HF in diabetic patients.

The lack of a significant association between LDL-C and HF subtypes aligns with some prior studies but contrasts with others. Dunlay SM et al., (2017) emphasised metabolic risk factors in HFpEF, but noted that dyslipidaemia alone might not be a primary driver of HF subtypes [25]. Similarly, Kenny HC and Abel ED (2019) highlighted that while dyslipidaemia exacerbated cardiovascular risk in T2DM, its direct association with HF subtypes remained inconsistent [26]. This discrepancy might be due to the multifactorial nature of HF in diabetes, where insulin resistance, hyperglycaemia, and microvascular dysfunction play more dominant roles than lipid abnormalities alone [27]. However, other studies suggested that dyslipidaemia contributed to myocardial remodelling and diastolic dysfunction, particularly in HFpEF [28]. The absence of a strong LDL-HF subtype link in the current study might reflect the relatively small sample size or the influence of concurrent lipid-lowering therapies, as Canakinumab has been shown to modify cardiovascular risk irrespective of HF subtype [29].

The lack of a significant association between hs-CRP and HF subtypes was unexpected, given the well-established role of inflammation in HF progression [5]. However, McDonagh TA et al., (2023) found that while inflammatory markers like hs-CRP were elevated in HF patients, their discriminatory power for HF subtypes might be limited [30]. This aligned with the current findings, suggesting that systemic inflammation was a common feature of both HFpEF and HFrEF rather than a distinguishing factor.

The JUPITER trial demonstrated that reducing hs-CRP alongside LDL-C improves cardiovascular outcomes [14], but the current study indicated that hs-CRP alone might not differentiate HF subtypes in T2DM. This could imply that inflammation in diabetic HF was more closely linked to metabolic dysfunction than to structural heart disease phenotypes. Recent research supported this notion, showing that anti-inflammatory therapies (e.g., Canakinumab) reduced cardiovascular events but did not specifically target HF subtypes [29].

The significant inverse correlation between HbA1c and EF supported previous findings that poor glycaemic control exacerbates myocardial dysfunction, particularly in HF with reduced EF (HFrEF) [31]. Packer M (2018) identified hyperglycaemia as a key contributor to diabetic

cardiomyopathy, leading to fibrosis, oxidative stress, and impaired ventricular function [27]. The results of the current study further reinforced the clinical importance of glycaemic control, as higher HbA1c levels were associated with worse systolic function, consistent with studies showing that intensive glucose management reduces hospitalisations due to HF [32].

Additionally, Dauriz M et al., (2017) demonstrated that diabetes worsens long-term HF outcomes, with glycaemic control being a modifiable risk factor [33]. The fact that HbA1c levels were significantly higher in HFrEF patients suggests that hyperglycaemia might preferentially impair systolic function, possibly through mechanisms such as Advanced Glycation End-product (AGE) accumulation and mitochondrial dysfunction [26].

This study underscores the importance of comprehensive metabolic profiling in T2DM patients with HF. While LDL-C and hs-CRP did not differentiate HF subtypes, their elevated levels in both groups highlighted the need for holistic management of dyslipidaemia and inflammation [34]. Given the strong association between HbA1c and EF, aggressive glycaemic control should be prioritised in diabetic HF patients to mitigate cardiac dysfunction.

Recent advancements in HF treatment, such as SGLT2 inhibitors, aligned with the findings of the current study. McMurray JJ et al., (2019) demonstrated that dapagliflozin reduces hospitalisations due to HF in both HFrEF and HFpEF, independent of glucose control [35]. Similarly, Solomon SD et al., (2019) showed that sacubitril/valsartan improved outcomes in HFpEF, suggesting that neurohormonal modulation was beneficial regardless of EF [31]. These therapies, combined with optimal glycaemic control, represent a paradigm shift in the management of diabetic HF.

Furthermore, phenotype-specific approaches might be necessary, as HFpEF and HFrEF have distinct pathophysiological mechanisms [36]. For example, spironolactone had shown benefits in HFpEF with renal dysfunction [37], while GLP-1 receptor agonists might improve diastolic function in obese diabetic patients [38].

Limitation(s)

The major limitation of this study was that it was conducted at a single tertiary care hospital, which limits the generalisability of the findings to other populations or healthcare settings. Validating these results and improving HF risk classification models in diabetic populations would require extensive prospective research. The cross-sectional nature of this study design restricts the ability to infer a causal relationship between the biomarkers and HF types. Larger sample sizes and longer study durations are needed to conduct prospective studies.

CONCLUSION(S)

LDL-C and hs-CRP levels showed no significant association with HF subtypes, although trends suggested an inverse correlation with EF. NT-proBNP effectively indicated HF severity, while a significant inverse relationship between HbA1c and EF highlighted the impact of poor glycaemic control on cardiac function. These findings support the need for comprehensive metabolic and inflammatory profiling in patients with diabetic HF.

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