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Non-HDL-C and CRP: A Dual Approach to Unmask Hidden Cardiovascular Risk in Type 2 Diabetic Patients

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A B S T R A C T

Type 2 diabetes mellitus (T2DM) is associated with atherogenic dyslipidemia and heightened cardiovascular risk, even when low-density lipoprotein cholesterol (LDL-C) appears within normal limits. Non-high-density lipoprotein cholesterol (non-HDL-C) and highly sensitive C-reactive protein (hs-CRP) have emerged as more comprehensive markers reflecting lipid-related and inflammatory risk, respectively. This study aimed to evaluate non-HDL-C as a superior marker over LDL-C for identifying atherogenic dyslipidemia in T2DM and to explore its correlation with systemic inflammation as indicated by hs-CRP. A cross-sectional study was conducted on 142 T2DM patients at Albadry Diabetic Clinic in Tripoli, Libya. Anthropometric data, lipid profiles, and hs-CRP levels were measured. Pearson correlation was used to assess relationships between lipid markers and hs-CRP. 56.3% of patients had elevated non-HDL-C, and 45.1% had elevated triglycerides. Non-HDL-C showed a stronger correlation with triglycerides (r = 0.82), HDL-C (r = -0.54), and hs-CRP (r = 0.44) compared to LDL-C (r = 0.41, -0.28, and 0.18, respectively; p < 0.01). These findings indicate that non-HDL-C better captures atherogenic lipid burden and inflammatory status. Conclusion: Non-HDL-C is a more robust marker of atherogenic dyslipidemia than LDL-C in T2DM and correlates more strongly with hs-CRP. Integrating non-HDL-C and hs-CRP into routine risk assessment may enhance cardiovascular risk prediction and guide targeted interventions.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disorder characterized by insulin resistance and relative insulin deficiency, resulting in chronic hyperglycemia and a wide spectrum of metabolic disturbances. As of 2021, an estimated 537 million adults were living with diabetes globally, a figure projected to exceed 640 million by 2030, underscoring its growing public health burden [1,2]. Cardiovascular disease (CVD) remains the principal cause of morbidity and mortality among individuals with T2DM, accounting for over 50% of diabetes-related deaths [3,4]. A hallmark feature of T2DM is diabetic dyslipidemia—a distinctive lipid abnormality typically defined by elevated triglycerides (TGs), reduced high-density lipoprotein cholesterol (HDL-C), and an increased prevalence of small dense low-density lipoprotein (sd-LDL) particles [5,6]. These atherogenic alterations, driven by insulin resistance and hepatic overproduction of apolipoprotein B-containing lipoproteins, significantly enhance the risk of atherosclerotic cardiovascular disease (ASCVD) [7].

Traditionally, low-density lipoprotein cholesterol (LDL-C) has served as the cornerstone of lipid management and CVD risk stratification. However, in T2DM, LDL-C levels can appear deceptively normal due to qualitative changes such as glycation, oxidation, and increased particle number, which augment atherogenicity without necessarily elevating LDL-C concentration [8,9]. This limitation has prompted growing interest in alternative lipid markers that more accurately reflect the total burden of atherogenic particles.

Non-high-density lipoprotein cholesterol (non-HDL-C), calculated by subtracting HDL-C from total cholesterol, includes all apolipoprotein B-containing lipoproteins such as LDL, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), chylomicron remnants, and lipoprotein(a) [10]. Unlike LDL-C, non-HDL-C does not require a fasting sample and has shown superior predictive value for cardiovascular events, particularly in populations with elevated TG levels and metabolic dysfunction such as T2DM [11–13]. Recent studies and updated international guidelines have increasingly endorsed non-HDL-C as a co-primary or secondary treatment target, especially in patients with diabetes and mixed dyslipidemia [14–16].

In parallel, chronic subclinical inflammation has emerged as a critical contributor to atherosclerosis

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in T2DM. High-sensitive C-reactive protein (hs-CRP), a sensitive inflammatory biomarker, is frequently elevated in this population and independently associated with adverse cardiovascular outcomes [17,18]. Elevated hs-CRP levels also correlate with atherogenic lipid profiles and may enhance cardiovascular risk prediction when combined with non-HDL-C [19]. Lipid-lowering therapies such as statins exert dual lipid-lowering and anti-inflammatory effects, further underscoring the interplay between dyslipidemia and inflammation in T2DM [20,21]. Despite growing evidence, the clinical integration of non-HDL-C and hs-CRP into routine risk stratification in T2DM remains limited. There is a pressing need to validate non-HDL-C as a more robust marker of atherogenic dyslipidemia than LDL-C, and to examine its relationship with systemic inflammation, as indicated by hs-CRP, in this high-risk group.

This study aims to evaluate non-HDL-C as a superior marker to LDL-C for assessing atherogenic dyslipidemia in individuals with T2DM and to explore its correlation with hs-CRP. By doing so, we seek to advance a more comprehensive and accurate framework for cardiovascular risk assessment, tailored to the complex pathophysiology of T2DM.

Methods

Study Design

This cross-sectional observational study was conducted at Albadry Diabetic Clinic in Tripoli, Libya. Ethical approval was obtained from the Human Research Ethics Committee of the Faculty of Pharmacy, University of Tripoli, and the Libyan Ministry of Health.

Participants

A total of 142 adult patients, Male 67.7%, Females, 32.3% with confirmed Type 2 Diabetes Mellitus (T2DM), aged 17 to 80 years, were enrolled. Exclusion criteria included patients with Type 1 diabetes, gestational diabetes, acute infections, cancers, known cardiovascular disease, hepatic or renal dysfunction, smokers, and those using steroids or hormonal therapy.

Data Collection and Clinical Assessment

Demographic and clinical information was obtained via structured interviews and clinical records. Physical examination included height, weight, waist circumference, and blood pressure. BMI was calculated as weight (kg) divided by height squared (m^2).

Laboratory Measurements

Following an 8–12 hour fast, venous blood samples were collected. Serum hs-CRP was measured using an immunoturbidimetric assay (Roche Diagnostics, Germany). Lipid profiles (TG, TC, HDL-C, LDL-C) were determined enzymatically using a Cobas Integra 400 Plus analyzer.

Variable Definitions and Categorization

Normative LDL-C was defined as ≤100 mg/dL. Elevated hs-CRP was classified according to the American Heart Association (AHA) and according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines: low risk (<1 mg/L), average risk (1–3 mg/L), and high risk (>3 mg/L).

Reference Lipid Guidelines and Cardiovascular Risk Classification

Lipid targets from ADA and NCEP ATP III were used to express lipid profiles per international standards. To assess added predictive value, patients were stratified into cardiovascular risk groups using non-HDL-C and hs-CRP levels alongside LDL-C. This approach evaluated the clinical impact of routinely measuring these markers. It helped identify hidden cardiovascular risk in T2DM patients with otherwise normal LDL-C levels

Statistical Analysis

Data were analyzed using SPSS (IBM Corp., 2018). Normality was assessed; continuous variables were expressed as mean ± SEM. Pearson correlation was used to assess relationships between hs-CRP and lipid parameters. A p-value ≤ 0.01 was considered statistically significant. Additionally, a sensitivity correlation analysis was conducted to explore the specific relationships between LDL-C and both hs-CRP and non-HDL-C, aiming to evaluate the consistency and discriminatory power of LDL-C in identifying inflammatory and atherogenic burden. Pearson correlation coefficients were calculated for these focused comparisons, and significance was determined using a p-value threshold of ≤ 0.01

Results

Baseline Characteristics and Lipid Profile of the Study Population

This table summarizes the baseline demographics and lipid parameters of 142 type 2 diabetes mellitus (T2DM) patients enrolled in the study, with a male predominance (67.7%). The mean age was 57.4 ± 11.74 years, and the average BMI was 32.59 ± 5.31 kg/m^2, indicating a predominantly obese cohort. The mean duration of diabetes was approximately 11 years. Dyslipidemia was prevalent: mean triglycerides (162.88 ± 82.15 mg/dL) and LDL-C (114.80 ± 35.44 mg/dL) were above recommended thresholds, while HDL-C was relatively low (40.10 ± 10.63 mg/dL). The mean non-HDL-C level was elevated (133.80 ± 38.36 mg/dL), and hs-CRP averaged 2.80 ± 3.39 mg/L, suggesting a substantial inflammatory burden and underlying cardiovascular risk.

Table 1. Baseline Characteristics and Lipid Profile of the Study Population (n=142 (Male (67.7%), Females (32.3%))

Pmeter	Mean ± SD
Age (years)	57.4 ±11.74
BMI	32.59 ± 5.31
Duration of T2DM (years)	10.67 ±8.23
Total Cholesterol (mg/dL)	174.80 ± 37.90
Triglycerides (mg/dL)	162.88 ± 82.15
LDL-C (mg/dL)	114.80 ± 35.44
HDL-C (mg/dL)	40.10 ± 10.63
Non-HDL-C (mg/dL)	133.80 ± 38.36
hs-CRP (mg/L)	2.80 ± 3.39

SD: Standard deviation, BMI: Body mass index, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein

Distribution of Lipid Abnormalities Among T2DM Patients

This table presents the proportion of patients with abnormal lipid parameters based on established cut-offs. LDL-C abnormalities were the most common (57.8%), followed closely by non-HDL-C (56.3%) and low HDL-C levels (51.4%). Elevated triglycerides (≥150 mg/dL) were present in 45.1% of patients. Only 28.9% of patients had high total cholesterol (≥200 mg/dL), reinforcing that relying on total cholesterol alone may underestimate atherogenic risk in this population. These findings highlight the high prevalence of atherogenic dyslipidemia among T2DM patients, even when LDL-C appears near-normal in some cases.

Table 2. Distribution of Lipid Abnormalities Among T2DM Patients

Lipid Marker	Normal Level	Abnormal Level	Patients with Abnormality n (%)
Triglycerides	<150 mg/dL	≥150 mg/dL	64 (45.1%)
LDL-C	<100 mg/dL	≥100 mg/dL	82 (57.8%)
HDL-C	≥40 mg/dL	<40 mg/dL	73 (51.4%)
Non-HDL-C	<130 mg/dL	≥130 mg/dL	80 (56.3%)
Total Cholesterol	<200 mg/dL	≥200 mg/dL	41 (28.9%)

Clinical Impact of Routine hs-CRP

This table evaluates the added value of hs-CRP in refining cardiovascular (CV) risk assessment among patients with T2DM. While 14.1% of patients were categorized as low risk using routine criteria (Group 1), 43.7% (Groups 2 and 3) were reclassified to intermediate or high CV risk when hs-CRP was considered alongside LDL-C. Notably, 15.5% of patients fell into Group 3, with both elevated LDL-C and hs-CRP levels. This suggests that hs-CRP testing may uncover subclinical inflammation and unrecognized CV risk, especially in those with apparently controlled LDL-C.

Table 3. Clinical Impact of Routine hs-CRP Testing for Early CVD Risk Detection in the study group

T2DM Selected Patients	CVS-Risk Categorize	Total Number (%)
Group1	Low risk [Routinely diagnosis]	20 (14.1%)
Group. 2	Low risk [Refine diagnosis]	40 (28.2%)
Group. 3	High risk [Refine diagnosis]	22 (15.5%)

Group1:T2DM have normal LDL-C & normal hs-CRP levels (LDL<100 & hs-CRP<1mg/l).
Group2: T2DM normal LDL-C & intermediate-high risk hs-CRP levels (LDL<100&hs-CRP 1-3&>3mg/l).
Group3: T2DM have both high LDL-C & hs-CRP (hs-CRP>3mg/l &LDL-C≥100).

Clinical Impact of Routine Non-HDL-C

This table illustrates the enhanced discriminatory power of non-HDL-C when combined with LDL-C for CV risk stratification. Only 31.7% of patients were considered low risk using routine markers (Group 1), while 45.7% (Group 3) were reclassified as high risk due to elevated non-HDL-C and LDL-C. Interestingly, 10.6% of patients with controlled LDL-C were reclassified to higher risk based on raised non-HDL-C alone (Group 2), emphasizing the clinical relevance of non-HDL-C in detecting hidden atherogenic risk and supporting its role in routine assessment

Table 4: Clinical Impact of Routine Non-HDL-C Testing for Early CVD Risk Detection in the study group

T2DM Selected Patients	CVS-Risk Categorize	Total Number (%)
Group 1	Low risk [Routinely diagnosis]	45 (31.7%)
Group 2	Low risk [Refine diagnosis]	15 (10.6%)
Group 3	High risk [Refine diagnosis]	65 (45.7%)

Group.1: (Non-HDL-C<130mg/dl & LDL-C<100)
Group. 2: (Non-HDL-C ≥ 130mg/dl & LDL-C <100)
Group.3: (Non-HDL-C ≥130mg/dl & LDL-C≥100).

Correlation of Non-HDL-C and LDL-C with Other Cardiovascular Risk Markers

This table compares the correlation strength between lipid markers (non-HDL-C and LDL-C) and other CV risk factors. Non-HDL-C showed a stronger and statistically significant correlation with triglycerides (r = 0.82), HDL-C (r = -0.54), and hs-CRP (r = 0.44), compared to LDL-C (r = 0.41, -0.28, and 0.18, respectively). These results reinforce the superior predictive value of non-HDL-C as a comprehensive marker of atherogenic lipoproteins and its association with both dyslipidemia and inflammation in T2DM patients

Table 5. Correlation of Non-HDL-C and LDL-C with Other Cardiovascular Risk Markers

Variable	Correlation with Non-HDL-C (r)	Correlation with LDL-C (r)	p-value (Non-HDL-C vs LDL-C)
Triglycerides	0.82	0.41	<0.001*
HDL-C	-0.54	-0.28	<0.01*
hs-CRP	0.44	0.18	<0.01*

**Statistically significant (p-value < 0.01)*

Sensitivity Correlations between LDL-C, hs-CRP, and Non-HDL-C

This table further evaluates the relationships between LDL-C, hs-CRP, and non-HDL-C. A strong positive correlation was observed between LDL-C and non-HDL-C (r = 0.756, p < 0.001), while the correlation between LDL-C and hs-CRP was weak and not statistically significant (r = -0.099, p = 0.242). These findings support that non-HDL-C better reflects the total atherogenic burden and may serve as a more sensitive marker for CV risk, especially when inflammation (as indicated by hs-CRP) is also considered.

Table 6. Sensitivity Correlations between LDL-C, hs-CRP, and Non-HDL-C

LDL-C correlated parameter	r-value	p-value
hs-CRP	- 0.099	**0.242**
Non-HDL-C	.756*0	**0.000**

**Statistically significant (p-value < 0.01), r = Correlation coefficient.*

Discussion

This study underscores the limitations of relying exclusively on LDL-C for cardiovascular (CV) risk assessment in patients with type 2 diabetes mellitus (T2DM), reaffirming the value of non-HDL-C, which encompasses all atherogenic apolipoprotein B- B-containing lipoproteins as a more inclusive and sensitive marker of atherogenic dyslipidemia. Although 42.2% of participants had LDL-C levels within the target range (<100 mg/dL), a considerable number still showed elevated non-HDL-C and hs-CRP levels (Table 2), suggesting significant residual cardiovascular risk. This observation aligns with previous reports indicating that LDL-C often underestimates the true atherogenic burden in diabetic populations [22,23]. The role of inflammation was further highlighted by the impact of hs-CRP testing. Notably, hs-CRP reclassified 44% of patients into higher cardiovascular risk categories despite their LDL-C levels being within goal ranges (Table 3). This finding supports existing evidence that systemic inflammation contributes independently to atherogenesis in diabetes, and that hs-CRP is a valuable tool for unmasking hidden CV risk in T2DM patients [26,27]. However, non-HDL-C proved even more effective in detecting this hidden risk. It led to the reclassification of 56.3% of patients into higher risk categories (Table 4), outperforming both LDL-C and hs-CRP in this context. These results are supported by prior studies emphasizing the superior predictive ability of non-HDL-C, compared to LDL-C in high-risk populations such as T2DM patients [28,29].

The strength of non-HDL-C as a marker of atherogenic burden is further validated by its significant correlations with other lipid parameters. In this study, non-HDL-C showed a strong positive correlation with triglycerides (r = 0.82) and a moderate correlation with hs-CRP (r = 0.44), whereas LDL-C exhibited only weak correlations with both triglycerides (r = 0.41) and hs-CRP (r = 0.18), as shown in Table 5. These findings suggest that non-HDL-C more accurately reflects both the lipid and inflammatory aspects of atherogenesis, enhancing its value in cardiovascular risk stratification, and regarding LDL-C correlation, these results underscoring the limitation of LDL-C in capturing inflammatory and atherogenic burden, and also reveal that elevated level of hs-CRP can indicate early inflammation in the arteries and endothelial dysfunction even before the process of lipid accumulation occurs, as these changes are trigger factors in insulin resistant state, consistent with the literature [24,25]. In addition, a notable inverse correlation was observed between non-HDL-C and HDL-C (r = –0.54), illustrated in Table 5. A strong positive correlation with LDL-C (Table 6). This further supports the role of non-HDL-C in capturing the full spectrum of atherogenic risk by linking elevated atherogenic particles to the depletion of protective HDL particles. This pattern is common in diabetic dyslipidemia and adds to the argument for broader lipid profiling beyond LDL-C alone [31].

Altogether, the findings from this study reinforce the growing recognition of non-HDL-C as a superior marker for CV risk assessment in T2DM, not only because it encompasses all atherogenic lipoproteins, but also due to its strong association with both inflammation and adverse lipid profiles.

Conclusion and Recommendations: This study demonstrates that non-HDL-C is a more comprehensive and accurate marker for cardiovascular risk assessment in type 2 diabetes mellitus (T2DM) than LDL-C alone. Despite normal LDL-C levels in many patients, elevated non-HDL-C and hs-CRP revealed significant residual risk. Non-HDL-C better reflects the total atherogenic lipoprotein burden and correlates strongly with inflammation. Therefore, non-HDL-C should be routinely measured alongside LDL-C in diabetic patients. Incorporating hs-CRP can further enhance risk stratification by detecting underlying inflammation. Clinical guidelines should consider adopting non-HDL-C as a co-primary treatment target in T2DM. Personalized therapies targeting both lipid abnormalities and inflammation, such as statins, may improve outcomes. Further studies are needed to confirm these findings across diverse populations.

Conflict of interest. Nil

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