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Original Article

Association of Non High Density Lipoprotein-Cholesterol and HbA1c in Type 2 Diabetes Mellitus

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Abstract

Background

Dyslipidemia is a common issue among diabetic patients and is associated with an increased risk of cardiovascular disease. Non-High Density Lipoprotein-cholesterol has emerged as a valuable marker for assessing combined cardiovascular risk in diabetes. Measures to improve the Non-High Density Lipoprotein-cholesterol within optimal level might improve the glycemic status and decrease the cardiovascular risk. This study aims to examine the relationship between Non-High Density Lipoprotein-cholesterol and glycated hemoglobin levels in type 2 diabetic patients.

Materials and Methods

A hospital-based comparative cross-sectional study was conducted on 544 individuals diagnosed with type 2 diabetes. The classification of lipid profile and glycemic control was carried out as per the National Cholesterol Education Program Adult Treatment Plan III and American Diabetes Association guidelines.

Results

Our study found that Non-High Density Lipoprotein-cholesterol levels was higher in uncontrolled diabetes (157.9±46.8) compared to controlled diabetes (132.6±40.6), with a statistically significant difference (P<0.001). There was a weak positive correlation between Non-High Density Lipoprotein-cholesterol and glycated hemoglobin levels (r=0.37). Among the total participants, 226 (41.5%) had optimal Non-High Density Lipoprotein-cholesterol level whereas 318 (58.5%) had high Non-High Density Lipoprotein-cholesterol.

Conclusion

This study confirms a positive correlation between Non-High Density Lipoprotein-cholesterol and HbA1c levels in type 2 diabetic patients. Dyslipidemia prevalence was substantial, emphasizing the importance of achieving target Non-High Density Lipoprotein-cholesterol levels for improved glycemic control and cardiovascular risk reduction.

Keywords: *Dyslipidemia, Glycated hemoglobin, Type 2 diabetes*

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Introduction

Dyslipidemia is a common issue among diabetic patients and is associated with an increased risk of cardiovascular disease [1]. Cardiovascular disease (CVD) is the primary cause of morbidity and mortality in patients with diabetes [2]. Efforts to decrease cardiovascular risks have led to the improvement in HbA1c levels even without specific intervention targeted at improving glycemic control [3]. In type 2 diabetes, there is a typical dyslipidemia that includes high levels of triglycerides, low levels of High Density Lipoprotein cholesterol (HDL-C), and Low Density Lipoprotein (LDL) particles that are altered in composition [4, 5]. Some researchers have suggested that measuring non-HDL cholesterol, which is total cholesterol minus HDL cholesterol and includes all apolipoprotein B-containing atherogenic lipoproteins, might be a useful marker of this combined risk [6, 7]. Non-HDL-C has been found to be more effective than other routine lipid parameters in predicting both subclinical atherosclerosis and negative clinical outcomes. The National Cholesterol Education Program Adult Treatment Panel (NCEP ATP-III) has also recommended using Non-HDL cholesterol in assessing CVD risk in patients with diabetes [8]. It can be calculated directly from routine lipid panels and does not require additional expense or special preparation by the patient [9]. Non-HDL-C level measurement in type 2 diabetic patients is simple, cost-effective, and offers an opportunity to clinicians to use it as a routine measurement criterion in clinical settings [10].

Investigating the correlation between non-HDL-C levels and glycemic status in patients with type 2 diabetes could provide valuable insights into potential measures to enhance glycemic control and reduce cardiovascular risk. By focusing on improving non-HDL-C levels and maintaining them within the optimal range, it is possible that the overall glycemic status of patients could be positively influenced. This, in turn, may contribute to a decrease in cardiovascular risk factors for individuals with diabetes.

To the author's knowledge, the direct relationship between non-HDL-C and glycemic status in type 2 diabetic patients have not been explored in our settings. Hence, the relationship between non-HDL-C levels and glycosylated hemoglobin (HbA1c) in patients diagnosed with type 2 diabetes visiting tertiary hospital of Nepal was examined in this study.

Materials and Methods

This hospital based comparative cross-sectional study was conducted at the department of clinical biochemistry of Dhulikhel hospital from January 2022 to October 2022. The study recruited 544 individuals who were 18 years or older, had been diagnosed with type 2 diabetes (based on elevated blood glucose/HbA1C level or under oral hypoglycemic/insulin therapy) and provided written consent. Pregnant women and those with known acute or chronic illness were excluded from the study. Sample size was calculated based on the correlation coefficient (r= 0.18) between glycated hemoglobin and total cholesterol in a recent study conducted in Nepal [11]. We computed the standard normal deviate for α as $Z\alpha = 1.96$, and the standard normal deviate for β as $Z\beta = 1.28$.From the above mentioned data, sample size was calculated as: $N= [(Z\alpha+Z\beta)/C]2 +3=320$, where $C=0.5*[(1+r)/(1-r)]=0.182$. However, we took all the available sample during the study period so the final sample size came out to be 544. Ethical approval to carry out the study was granted by Institutional Review Committee of Kathmandu University School of Medical Sciences. For the biochemical measurements purposes, the venous blood samples were collected from all patients following their written consents. The serum obtained from the blood samples was used for the measurement of lipid profile parameters, including HDL Cholesterol, serum Total Cholesterol (TC), Triacylglycerol, LDL-Cholesterol. The conventional lipid profile test was carried out on BA-400 (Biosystem, Spain). Non-HDL-C was calculated through subtracting HDL-C from the TC. For the estimation of HbA1c sample was collected in separate EDTA vial and the estimation was done by HPLC method using Adams A1c lite (ARKRAY, Japan).

The lipid profile and glycemic control were categorized according to the guidelines outlined in the "Expert plan on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," specifically the Adult Treatment Panel III and American Diabetes Association (ADA) [8,12]. According to this classification, LDL-C levels were considered optimal if they were below 100 mg/dL. Total cholesterol levels were considered desirable if they were below 200 mg/dL, borderline if they fell within the range of 200-239 mg/dL, and high if they were equal to or greater than 240 mg/dL. HDL-C levels were categorized as low if they were below 40 mg/dL, optimal if they were

between 40 and less than 60 mg/dL, and high if they were equal to or greater than 60 mg/dL. Triglyceride levels were expected to be below 150 mg/dL, and HbA1c levels were considered optimal if they were 7.0% or below.

The data collected was entered into MS Excel 2013, and analyzed with Statistical Package for Social Sciences (SPSS Inc., Chicago, USA) version 21.0.The prevalence was presented through frequency and percentage, while continuous biochemical indicators were expressed as mean ± standard deviation or medians with interquartile ranges. The correlation between Non HDL-C and LDL cholesterol with HbA1c was examined using Pearson's correlation. A P-value less than 0.05 was considered as statistically significant difference.

Results

The study included a total of 544 participants, of which 230 (42.3%) were female and 314 (57.7%) were male. The mean age of the participants was 55.6±10.58 years (Range 35 to 79 years). The mean concentration of various biochemical parameters were as follows: HbA1c (7.2±1.83%), Triglyceride (149.5 (111, 224) mg/dl), total cholesterol (189.7±47.5), HDL-C (39.4±10.8), LDL (101.9±36.6) and Non HDL-C (143.3±45.1). The baseline biochemical characteristics of the participants is shown in table 1.

Table1: Baseline biochemical characteristics of the participants (n=544)

Parameters	Female (n=314)	Male (n=230)	P value
HbA1c (%)	7.2±1.9	7.2±1.7	0.90[a]
Triglyceride (mg/dL)	138 (105,191)	160 (116, 233)	0.02[b]
Total Cholesterol (mg/dL)	182.4±46.2	182.9±48.5	0.90[a]
HDL-C (mg/dL)	41.9±11.6	37.6±9.8	0.001[a]
LDL-C (mg/dL)	102.9±38.5	101.1±35.1	0.55[a]
Non HDL-C (mg/dL)	140.5±43.3	145.3±46.2	0.21[a]

[a]Independent sample t-test; [b]Mann-Whitney U test

Among the total participants, 226 (41.5%) had optimal Non HDL-C level (<130 mg/dl) whereas 318 (58.5%) had high Non HDL-C (>130 mg/dl). The frequency of participants among different lipid parameters group is shown in table 2. Similarly, the frequency of participants with controlled diabetes (HbA1c ≤ 7.0%) was 315 (57.9%) and those with uncontrolled diabetes (HbA1c >7.0%) was 229 (42.1%). The frequency of dyslipidemia according to the glycemic control is also shown in table 2.

Table 2: Prevalence of dyslipidemia according to the glycemic control in type 2 diabetic patients

Lipid profile parameter	Classification of lipid profile parameter	Frequency (%) among total participants	Frequency (%) among controlled diabetes	Frequency (%) among uncontrolled diabetes
Total Cholesterol	Desirable (<200)	372 (68.4%)	239 (75.87%)	133 (58.07%)
	Borderline high (200-239)	117 (21.5%)	55 (17.46%)	62 (27.07%)
	High (≥240)	55 (10.1%)	21 (6.66%)	34 (14.84%)
LDL-C (mg/dL)	Optimal (<100)	277 (50.9%)	179 (56.82%)	98 (42.79%)
	Above Optimal (100-129)	157 (28.8%)	85 (26.98%)	72 (31.44%)
	Borderline high (130-159)	72 (13.2%)	36 (11.42%)	36 (15.72%)
	High (≥160)	38 (7%)	15 (4.76%)	23 (10.04%)
HDL-C (mg/dL)	Low (<40)	302 (55.5%)	175 (55.55%)	127 (55.45%)
	Normal (40-59)	222 (40.8%)	122 (38.73%)	100 (43.66%)
	High (≥60)	20 (3.7%)	18 (5.71%)	2 (0.87%)
Non HDL-C (mg/dL)	Optimal (<130);	226 (41.5%)	160 (50.79%)	66 (28.82%)
	High (≥130)	318 (58.5%)	155 (49.2%)	163 (71.17%)
Triglyceride (mg/dL)	Normal (<150)	272 (50%)	193 (61.26%)	79 (34.49%)
	Borderline high (150-199)	107 (19.7%)	63 (20%)	44 (19.21%)
	High (≥200)	165 (30.4%)	59 (18.73%)	106 (46.28%)

There was a statistically significant difference of the lipid profile parameters including non-HDL-C among patents with controlled and uncontrolled diabetes. The details about the lipid profile parameters among the two groups is shown in table 3.

Table 3: Biochemical Characteristics among controlled and uncontrolled diabetes

Parameters	Controlled diabetes (n=315)	Uncontrolled diabetes (n=229)	p Value
HbA1c	6.1±0.4	8.7±1.9	0.001[a]
Total Cholesterol	172.9±43.8	196.2±49.2	0.001[a]
LDL-C	97.1±35.2	108.4±37.4	0.001[a]
HDL-C	40.2±11.5	38.3±9.5	0.03[a]
Non HDL-C	132.6±40.6	157.9±46.8	0.001[a]
Triglyceride	132 (100,180)	186 (136, 294)	0.001[b]

[a]Independent sample t-test; [b]Mann-Whitney U test

The correlation of non HDL C with HbA1c was examined and showed a weak positive correlation (r = 0.37) as shown in Figure 1. Though HbA1c correlated with both parameters, a slightly advantageous correlation was seen with Non-HDL-C.

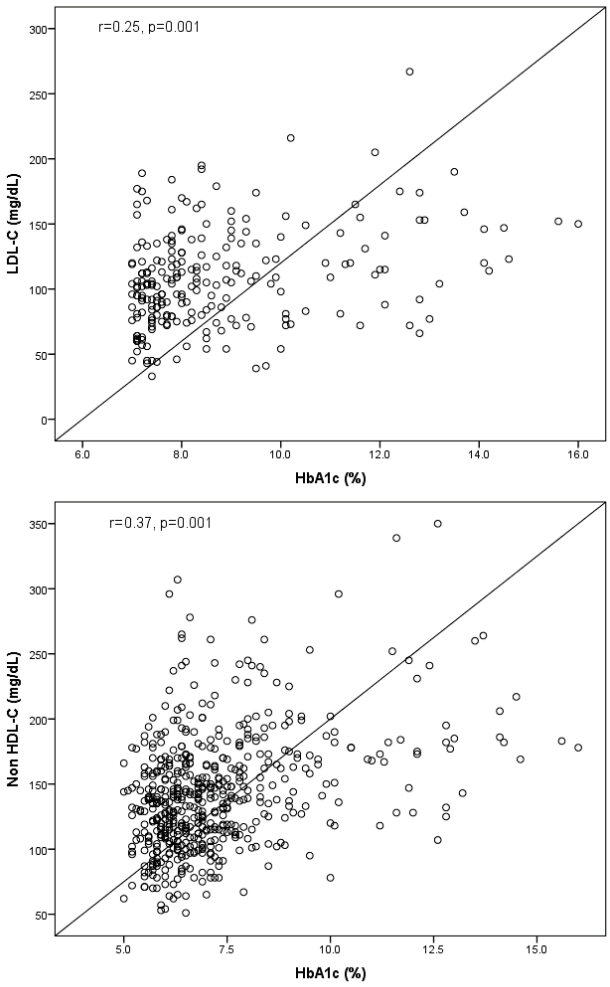

Figure 1: Correlation of LDL-C and Non-HDL-C with HbA1c

Discussion

Non-HDL cholesterol, which is calculated as the difference between total cholesterol and HDL cholesterol, has gained recognition as a valuable marker for assessing combined cardiovascular risk. It has shown superior predictive ability for subclinical atherosclerosis and adverse clinical outcomes compared to other lipid parameters commonly used in clinical practice. Numerous studies have provided evidence of the significant predictive value of Non-HDL-C in assessing cardiovascular risk across different populations, including individuals of various ages, genders, and those with or without diabetes [13]. Recognizing its importance, the American Diabetes Association has set a target goal for diabetic patients to reduce Non-HDL-C levels to below 130 mg/dL, in addition to lowering LDL-C [14]. Non-HDL-C is a cost-effective and easily calculated parameter that offers a more accurate reflection of triglyceride-rich lipoprotein levels, making it a superior tool for evaluating dyslipidemia in diabetes and predicting adverse cardiovascular events [15].

The primary objective of our study was to examine the correlation between Non-HDL-C and HbA1c levels in individuals with type 2 diabetes. Our findings provide compelling evidence of a positive correlation between Non-HDL-C and HbA1c levels in this patient population. Our study's findings align with previous research conducted in various regions worldwide. In a cross-sectional study conducted at the Duhok Diabetes Center of Azadi Teaching Hospital, the researcher observed a significant positive correlation between Non-HDL-C and HbA1c ($r = 0.30$, $P < 0.001$). Non-HDL-C was the only independent risk factor associated with higher HbA1c levels in type 2 diabetic patients ($P = 0.002$) in that study [16]. Furthermore, Sherhan et al [17] also revealed a significant relationship between Non-HDL-C and the degree of glycemic control ($P<0.01$) via a study conducted at the Endocrine and Diabetic Center in Al-Mawani General Hospital. These studies highlight the importance of improving non-HDL-C levels which could potentially lead to better glycemic control in patients with type 2 diabetes. This, in turn, may help reduce the risk of cardiovascular complications associated with diabetes.

The prevalence of dyslipidemia among our study participants was found to be substantial, with a majority of patients exhibiting elevated levels of non-HDL cholesterol. Numerous studies conucted worldwide have consistently reported significant dyslipidemia among individuals with diabetes mellitus [11, 18-20]. Specifically, 43.18% of the total participants exhibited high LDL-C levels, 55.5% had low HDL-C levels, and 49.2% had elevated non-HDL-C levels. Notably, these percentages increased significantly when focusing on participants with uncontrolled diabetes mellitus. Among those with uncontrolled diabetes, 57.21% had high LDL-C levels, and a staggering 71.17% had elevated non-HDL-C levels. Furthermore, our study depicted that individuals with uncontrolled diabetes had significantly higher levels of Non-HDL-C (157.9±46.8) compared to those with controlled diabetes (132.6±40.6), with the difference being statistically significant ($P=0.001$). Our finding is in line with the study conducted by Pandey et al. [18] where significant differences were observed in lipid profile parameters between diabetic (156±46.2 mg/dL) and non-diabetic individuals (124.1±39.0 mg/dL). These findings underscore the importance of achieving the target Non-HDL-C levels for improved glycemic control. It is possible that the inadequate control of blood glucose level might have contributed to the poor attainment of the Non-

HDL-C goal. Interestingly, our study found that only 57.9% of patients had controlled diabetes (HbA1c ≤ 7.0%), while 42.1% had uncontrolled diabetes (HbA1c >7.0%). Non-HDL-C has been identified as an independent risk factor for HbA1c, further emphasizing its relevance in assessing glycemic control and cardiovascular risk.

The findings depicted in our study is concerning, as dyslipidemia is a well-established major risk factor for cardiovascular disease, which remains a leading cause of morbidity and mortality in individuals with type 2 diabetes. Moreover, our study revealed that a substantial proportion of patients did not achieve the target goal for Non-HDL cholesterol, emphasizing the need for intensified efforts to manage dyslipidemia effectively in this patient population. Furthermore, increased level of Non-HDL-C among the patients have contributed to the high level of HbA1c in our study population. Incorporating Non-HDL cholesterol measurement into routine lipid panel assessments in clinical settings can offer clinicians a simple and cost-effective tool to identify patients at higher cardiovascular risk and tailor appropriate interventions.

Several limitations should be considered when interpreting the results of our study. Firstly, the cross-sectional design of our study limits our ability to establish cause and effect relationships between Non-HDL cholesterol and HbA1c levels. Another important limitation is that our study's observational nature prevents us from determining the effects of lipid-lowering medications on Non-HDL cholesterol and LDL cholesterol goals. These limitations highlight the need for further research, including longitudinal studies and randomized controlled trials, to provide more robust evidence on the relationship between Non-HDL cholesterol and cardiovascular outcomes in individuals with type 2 diabetes.

Conclusion

Our study supports the positive correlation between Non-HDL cholesterol and HbA1c levels in individuals with type 2 diabetes, indicating the potential of Non-HDL cholesterol as a valuable biomarker for assessing dyslipidemia and cardiovascular risk. Incorporating Non-HDL cholesterol measurement into routine lipid panel assessments can serve as a simple and cost-effective tool for identifying patients at higher cardiovascular risk. Optimal management strategies that target dyslipidemia, in addition to glycemic control, are essential for reducing the burden of cardiovascular disease in individuals with type 2 diabetes. Future research should focus on interventions aimed at improving Non-HDL cholesterol levels and investigating their impact on glycemic status and cardiovascular outcomes in this patient population.

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Conflict of interest: None

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