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Original Article

# Correlation between Non-high-density Lipoprotein-Cholesterol and the Degree of Glycemic Control in Type 2 Diabetes Mellitus

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## Abstract

**Backgrounds:** Diabetic dyslipidemia is regarded as a modifiable risk factor for cardiovascular diseases (CVDs). Non-high-density lipoprotein-cholesterol (non-HDL-C) is a better measure of CVDs' prediction in contrast with glycosylated hemoglobin (HbA1c) in type 2 diabetic patients. **Objectives:** In the present study, the prevalence of dyslipidemia and correlation of non-HDL-C with HbA1c were examined and evaluated in patients with type 2 diabetes mellitus. **Patients and Methods:** In this cross-sectional study, 210 patients aged 18 years and older of both gender previously diagnosed regardless of their sociodemographic characteristics were invited for the assessment of dyslipidemia indicators and HbA1c in Duhok Diabetes Center, Duhok, Iraq, in 2017. **Results:** The mean age of the study patients was 55.56 (10.48) years and had diabetes for about 7.99 (4.50) years. The study showed a high level of dyslipidemia, including triglyceride, low-density lipoprotein-cholesterol, and non-HDL-C, and low level of HDL-C with a high level of uncontrollable HbA1c. The study revealed a significant positive correlation between HbA1c and non-HDL-C ($r = 0.30$, $P < 0.001$). Non-HDL-C was found to be only independent risk factor for higher HbA1c in type 2 diabetic patients ($P = 0.002$). **Conclusions:** The present study showed that non-HDL-C can be used as a predictor of HbA1c in type-2 diabetic patients, and its level directly correlated with glycemic control as measured by HbA1c. It is recommended that non-HDL-C to be used by clinicians for routine clinical purposes.

**Keywords:** Glycosylated hemoglobin, nonhigh-density lipoprotein, type 2 diabetes mellitus

## Introduction

Diabetes mellitus (DM) has been documented to be the common metabolic disorder affecting the people throughout the world, including developed and developing countries. Type 2 DM, dyslipidemia, and obesity are independent risk factors for cerebrovascular and coronary heart diseases.[1-3] Dyslipidemia is a common phenomenon in diabetic patients and may correspond with increasing risk of cardiovascular disease (CVD) in type 2 diabetic patients.[4-6]

In type 2 diabetic patients, dyslipidemia is depicted by raised triglyceride and triglyceride-rich lipoproteins, including very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL), decreased high-density lipoprotein cholesterol (HDL-C), and small dense LDL particles.[7] Usually, patients with type 2 diabetes have atherogenic lipid profile increasing the risk of coronary vascular disease compared to it among people without DM. It has been confirmed that an early intervention to normalize circulating lipids enables to decrease the cardiovascular-related complications and mortality.[8]

Non-HDL-C calculating through total cholesterol (TC) minus HDL-C is an appropriate indicator for the cholesterol content of all atherogenic lipoproteins. Hence, elevated levels of atherogenic triglyceride-rich remnants add a potential risk related with LDL-cholesterol (LDL-C).[9]

It has been shown that non-HDL-C is a strong predictor for future cardiovascular risk in patients with or without exhibit symptoms of vascular diseases. Furthermore, it has been suggested as a secondary therapeutic target following LDL-C among patients with raised Triglyceride (TG) by the National

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Cholesterol Education Program Adult Treatment Panel III[10] owing to its proatherogenic, apo-B-containing lipoprotein fraction of circulating lipid.[11] Type 2 diabetic patients have significantly elevated levels of non-HDL-C compared to controls; therefore, it can be used as a dyslipidemia marker and a predictor for CVD[6,12,13] and vascular inflammation[14] in type 2 diabetic patients.

Non-HDL-C level measurement in type 2 diabetic patients is simple, cost-effectiveness, and appropriate as it does not need 12-h fasting giving an opportunity to clinicians to use it a routine measurement criterion in clinical settings.[15] To the author's knowledge, a few studies have attempted to examine the correlation of non-HDL-C with glycosylated hemoglobin (HbA1c) in type 2 diabetic patients.[16,17] Therefore, the level of non-HDL in dyslipidemic type 2 diabetic patients in correlation with glycemic control was examined in the present study.

## Patients and Methods

### Study design and sampling

In the current, prospective, cross-sectional investigation, a total of 218 patients aged 29–85 year and previously diagnosed with type 2 diabetes recorded in their medical records and confirmed by the study author, internist, in Duhok Diabetes Center of Azadi Teaching Hospital, a tertiary hospital in Duhok city, were invited for the study purposes between December 2017 and April 2018.

The patients met eligibility criteria if they were male or female, aged 18 years and older, on insulin, oral hyperglycemic agents, or its combination regardless of their sociodemographic aspects and taking lipid-lowering therapy. Of the total 218 patients met eligibility criteria for the present study, eight of them did not show their interest to partake in the study, and finally, laboratory investigations of 210 patients were used for the study analysis.

The patients with pregnancy, Type 1, or gestational diabetes and those with acute conditions such as acute myocardial infarction, acute diabetic ketoacidosis, acute pulmonary embolism, acute pulmonary edema, and acute chest infection were not included in the study.

### Diagnosis and measurement criteria

The diagnosis of type 2 diabetes was established in the time, and HbA1c was ≥6.5% according to the American Diabetes Association.[18]

#### *Biochemical measurements*

For the biochemical measurements purposes, the venous blood samples were collected from all patients after at least 8 h fasting in Medical Laboratory of Azadi Teaching Hospital by an experienced technician in Duhok following taking their written consents. The serum obtained from the blood samples were used to calculate the lipid profile parameters, including HDL-C, serum TC, TG, LDL-C, and HbA1c by Roche autoanalyzer 6000 Cobas (Roche Diagnostics, Mannheim, Germany). Non-HDL-C was calculated through subtracting HDL-C from the TC.

The classification of lipid plan and glycemic measurement was established according to the "Expert Plan on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults" Adult Treatment Panel III.[10] According to its classification, the LDL was scaled as optimal when LDL <100 mg/dL; TC as desirable <200 mg/dL; borderline 200–239 mg/dL, and high ≥240 mg/dL; HDL scaled as low <40 mg/dL, optimal ≥40–<60 mg/dL, and high ≥60 mg/dL; TG <130 mg/dL; and HbA1c scales optimal ≤7%.

#### *Anthropometric measurements*

The anthropometric markers measured for the study purposes were height (cm), weight (kg), and body mass index (BMI) and obtained in barefoot and light clothing. The BMI was calculated through dividing the weight (kg) by the squared height in meter.

### Statistical methods

The prevalence of dyslipidemia and hyperglycemia was presented through frequency and percentage and continuous biochemical indicators were expressed as mean ± standard deviation or medians with interquartile ranges. The correlation of non-HDL with HbA1c was examined through the Pearson's correlation through SPSS statistics program version 23, (IBM, Armonk, NY, United states of America). The $P < 0.05$ was considered statistically significant difference. A total sample of 197 patients were estimated according to the prevalence of 75.0% for uncontrolled HbA1c (≥7.0%) determined in the pilot study and to reach 63.0% with actual power 0.95 through the G*Power 3.1.9 statistical software (Heinrich, Heine University Dusseldorf; Germany).

### Ethical considerations

Ethical clearance of the present study was obtained from the local scientific committee of the College of Medicine, University of Duhok, Iraq, in accordance with the Declaration of Helsinki.[19] The consent form was taken from all patients before study recruitment in the study, and the participation was completely optional.

## Results

Of the total 210 type 2 diabetic patients recruited in the present study, majority of them (60.5%) were females and nonsmokers (74.5%) and had diabetes for about 7.9 years ago. The mean age of the patients was 55.56 (10.48) years and mean BMI was 29.49 (4.49) as shown in Table 1.

The means of lipid profile parameters were 191.50 (40.07), 108.96 (32.10), 41.17 (14.62), and 150.33 (40.36) mg/dL for TC, LDL-C, HDL-C, and non-HDL-C, respectively, and median (interquartile range) for TG was 206.00 (133.5) mg/dL. The mean of HbA1c was 8.66 (2.08%). More than half of the patients had hypertension (51.2%), and majority of them were on oral hyperglycemic agents (81.9%) as shown in Table 2.

The prevalence rates of dyslipidemia parameters are presented in Table 3. The study revealed that more than half of the patients had desirable TC (57.1%); however, majority of them had high level of LDL (61.4%), TG (51.2%), and non-HDL-C (68.1%)

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and low level of HDL (52.2%), and majority had uncontrollable HbA1c (76.7%).

The correlation of non-HDL-C with HbA1c was examined and showed a positive correlation with the significant difference ($r = 0.30$, $P = 0.001$) as shown in Figure 1.

In the univariate logistic analysis, HbA1c was considered as dependent variables and its interaction was found with lipid profile parameters as shown in Table 4. The study showed that non-HDL is only independent risk factor of HbA1c in type 2 diabetic patients ($F = 9.968$, $P = 0.002$).

## Discussion

The current study showed the elevated levels of lipid profile parameters and a significant positive correlation of HbA1c level with non-HDL-C in type 2 diabetic patients. In addition, the non-HDL-C was found to be the only independent risk factors for elevated HbA1c when considering with other lipid profile parameters.

A few studies have attempted to examine and evaluate the correlation of HbA1c levels with non-HDL-C in type 2 diabetic patients. For example, a recent study conducted by Senghor and William[20] revealed that the comparison of lipid profiles parameters was performed between 60 patients with controlled DM (HbA1c <6.5%) and 60 patients with uncontrolled DM (HbA1c ≥6.5%) with disease duration between 1 and 5 years. In agreement with the current study, they found

**Table 1: Baseline characteristics of dyslipidemia type 2 diabetic patients recruited in the study (*n*=210)**

| Patients' characteristic | Frequency distribution | |
|---|---|---|
| | Mean | SD |
| Age (year) | 55.56 | 10.48 |
| BMI (weight/height$^2$) | 29.49 | 4.49 |
| Disease duration (year) | 7.99 | 4.50 |
| **Patients' characteristic** | **Frequency (%)** | |
| Gender | | |
| Male | 83 (39.5) | |
| Female | 127 (**60.5**) | |
| Smoking | | |
| Smoker | 44 (21.2) | |
| Nonsmoker | 155 (**74.5**) | |
| Ex-smoker | 9 (4.3) | |

SD: Standard deviation, BMI: Body mass index, and the bold numbers show the highest percentages

**Table 2: Baseline clinical and biochemical characteristics of the patients (*n*=210)**

| Patients' characteristic | Frequency distribution | |
|---|---|---|
| | Mean | SD |
| HbA1c (%) | 8.66 | 2.08 |
| Lipid profile | | |
| Total cholesterol (mg/dL) | 191.50 | 40.07 |
| LDL (mg/dL) | 108.96 | 32.10 |
| HDL (mg/dL) | 41.17 | 14.62 |
| NHDL-C (mg/dL) | 150.33 | 40.36 |
| TG (mg/dL) | 206.00 (median) | 133.5 (interquartile range) |
| **Patients' characteristic** | **Frequency (%)** | |
| Hypertension (yes) | 107 (51.2) | |
| Treatment type | | |
| OHA | 172 (81.9) | |
| Insulin | 9 (4.3) | |
| Combined | 29 (13.8) | |

OHA: Oral hypoglycemic agent, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density Lipoprotein-cholesterol, TG: Triglyceride, NHDL-C: Non-HDL-C, HbA1c: Glycosylated hemoglobin

**Table 3: Prevalence of dyslipidemia and poor glycemic control in type 2 diabetic patients of the study (*n*=210)**

| Patients' characteristic | Frequency distribution, frequency (%) |
|---|---|
| TC (mg/dL) | |
| Desirable (<200) | 120 (57.1) |
| Borderline (200-239) | 63 (30.1) |
| High (≥240) | 26 (12.4) |
| LDL-C (mg/dL) | |
| Optimal (<100) | 81 (38.6) |
| High (≥100) | 129 (61.4) |
| HDL-C (mg/dL) | |
| Optimal (≥40-<60) | 90 (43.1) |
| Low (<40) | 109 (52.2) |
| High (≥60) | 10 (4.8) |
| TG (mg/dL) | |
| Optimal (<150) | 56 (26.8) |
| Borderline (50-199) | 46 (22.0) |
| High (≥200) | 107 (51.2) |
| NHDL-C (mg/dL) | |
| Optimal (<130) | 67 (31.9) |
| High (≥130) | 143 (68.1) |
| HbA1c | |
| Optimal (≤7%) | 49 (23.3) |
| Uncontrollable (>7%) | 161 (76.7) |

HbA1c: Glycosylated hemoglobin, TC: Total cholesterol, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, TG: Triglyceride, NHDL-C: Non-HDL-C

**Table 4: Univariate logistic analysis of glycosylated hemoglobin as dependent variable with lipid profile parameters (*n*=210)**

| Independent biochemical characteristics | df | *F* | *P* (two-tailed) |
|---|---|---|---|
| TC | 2 | 1.107 | 0.332 |
| LDL-C | 1 | 0.127 | 0.722 |
| HDL-C | 2 | 2.663 | 0.072 |
| TG | 2 | 0.286 | 0.752 |
| NHDL-C | 1 | 9.968 | 0.002 |

$R^2$=0.956 (adjusted $R^2$=0.954); dependent variable: HbA1c.
HbA1c: Glycosylated hemoglobin, TC: Total cholesterol, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, TG: Triglyceride, NHDL-C: Non-HDL-C

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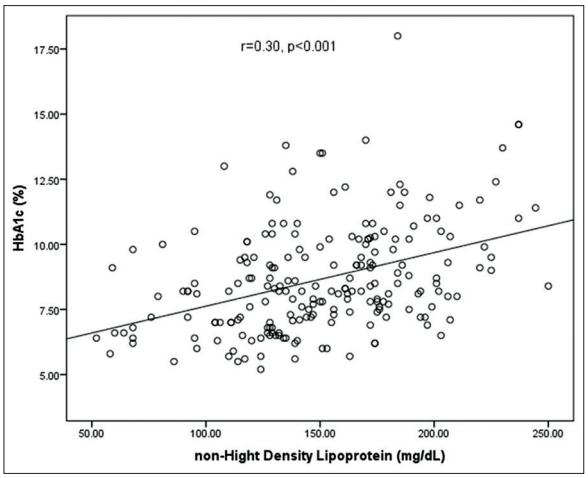


**Figure 1:** Correlation of nonhigh-density lipoprotein-cholesterol with glycosylated hemoglobin in type 2 diabetic patients

a high level of LDL-C, triglycerides, and non-HDL-C among the patients with uncontrolled HbA1c. In addition, a positive correlation was found between non-HDL-C and HbA1c ($r = 0.49$, $P < 0.05$). The positive correlation was found by Hammed *et al*.[21] between HbA1c and non-HDL ($P < 0.001$) among 450 patients with type 2 diabetes with a mean age of 55.5 (9.35) years in accordance with the study by Thambiah *et al*.[17]

The present study showed that the level of dyslipidemia parameters are very high in type 2 diabetic patients, 61.4% with a high level of LDL, 52.2% with a low level of HDL, 51.2% with a high level of TG, and 68.1% with a high level of non-HDL. The findings are in agreement with the previous studies; for instance, a large cross-sectional study conducted among 1352 type 2 diabetic patients in Pakistan, showed that the patients with LDL <100 and non-HDL <130 mg/dL represented 48% of the patients.[15] This result was in accordance with several authors worldwide.[22,23]

LDL-C is being used as the primary therapeutic target to lower lipids for primary and secondary prevention of CVDs.[24,25] However, still, the patients have a risk of recurrent coronary artery disease despite achievement in LDL goal.[26] The possible analysis for this residual risk could be a high level of non-HDL-C in these kinds of patients. Therefore, the particular importance must be given to measuring non-HDL-C in type 2 diabetes patients in routine clinical practices as it has been shown to be a superior predictor for risk of CVD.[12,27-30] In addition, it has all cholesterol contents for atherogenic particles, including LDL, VLDL, lipoprotein A, VLDL remnant, and IDL.[31-33]

The present study showed that 68.1% of the patients have not achieved the target goal for non-DHL-C in accordance with other studies.[15] The reason for poor its goal achievement may back to that non-HDL-C is not reported in routine lipid profile parameters, and clinicians and healthcare providers have less awareness on its importance. It is recommended to involve the non-HDL-C lipid plan parameters in routine clinical practice as it has been shown to improve the goal achievement.[15,34] Importantly, although HbA1c has been considered to be a reliable measure for chronic hyperglycemia and is associated with risk of long-term diabetes complications, HbA1c single test has not been mentioned to be used a reliable biomarker for diabetes diagnosis and prognosis and some testing strategies and cutoffs are still being discussed and debated.[35]

The studies conducted on different groups showed inconsistent results with criteria of HbA1c use. For example, Khan *et al*.[36] showed that 484 of 12,785 male diabetic patients were false negative (3.78%), suggesting that the patients with HbA1c between 6.0% and 6.5% could be considered as probable diabetic. Therefore, they suggest to be confirmed through combination of fasting plasma glucose and HbA1c criteria. In addition, Khan *et al*.[37] showed that HbA1c is not only a beneficial biomarker for long-term glycemic control but also a good predictor for lipid profile.

The findings reported in the current study must be analyzed in the illumination of the study design as a cross-sectional study precludes the cause-effect establishment. Making a between-study comparison has some difficulties owing to heterogeneity used in various study designs as all study patients in the present study were Kurdish and from one region facing an issue to generalize to other ethnicity groups across the country. The different cutoff values for HbA1c have been used in the literature. In addition, the author is unable to report any findings on effect of statin and other lipid-lowering medicines on non-HDL-C and LDL-C goals owing to the observational enhancement of the study.

## Conclusions

The current study showed that non-HDL-C is above the optimal line and has positive correlation with HbA1c in type 2 diabetic patients. It is recommended to use non-HDL-C level for routine clinical purposes to type 2 diabetic patients as it is a simple, cost-effective tool and has better representation for diabetic dyslipidemia.

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### Conflicts of interest

There are no conflicts of interest.

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