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Non-High Density Lipoprotein -Cholesterol as Predictor Marker for Cardiovascular Risk in Hypothyroidism Patients with and without Diabetic

Maryam Qusay Isaa, MSc* Dhamyaa Obaid Shalgam, MSc** Israa Qusay Falih, PhD*** Noor Thair Tahir, PhD**

ABSTRACT

Non–high-density lipoprotein cholesterol (non–HDL-C) encompasses all atherogenic lipoprotein fractions and is considered a strong indicator of cardiovascular risk. This study aimed to assess the predictive value of non–HDL-C for atherosclerotic cardiovascular disease (ASCVD) risk among hypothyroidism patients with and without diabetes mellitus.A total of 120 participants were enrolled and divided into three groups: Group 1 (G1) — 40 hypothyroid patients with diabetes, Group 2 (G2) — 40 hypothyroid patients without diabetes, and Group 3 (G3) — 40 healthy controls. Fasting serum glucose (FSG), glycosylated hemoglobin (HbA1C), lipid profile [total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and non–HDL-C calculated as (TC – HDL-C)] and thyroid function tests were determined. Non–HDL-C showed a significant positive correlation with body weight, total cholesterol, and thyroxine ($P < 0.05$) in both hypothyroid groups. Strong positive correlations were also observed between non–HDL-C and FSG, HbA1C, TG, and LDL-C ($P < 0.01$), while an inverse correlation was found with HDL-C.The findings suggest that non–HDL-C serves as a superior and reliable biomarker for evaluating cardiovascular risk in hypothyroid patients, regardless of diabetic status. Its inclusion in clinical evaluation may enhance early detection and prevention of cardiovascular complications.

Keywords: Non-HDL-C, Hypothyroidism, atherosclerotic cardiovascular disease, Diabetes Mellitus.

INTRODUCTION

Hypothyroidism is a clinical condition characterized by a deficiency in thyroid hormone levels, resulting from various etiologies and presenting with diverse clinical manifestations. It is generally categorized into primary hypothyroidism and secondary (central) hypothyroidism. In primary hypothyroidism, the thyroid gland fails to synthesize adequate amounts of thyroid hormones, whereas in secondary or central hypothyroidism, the thyroid gland remains structurally normal, but its function is impaired due to abnormal activity of the pituitary gland or hypothalamus[1]. The most common causes of hypothyroidism include autoimmune thyroiditis and iodine deficiency, while central hypothyroidism remains relatively rare. The thyroid gland, an essential component of the endocrine system, plays a pivotal role in regulating the body's metabolic processes through the secretion of thyroid hormones[2]. Insufficient production of these hormones leads to disorder in metabolic state that affects multiple physiological systems. Thyroid hormones and insulin, which are closely associated with diabetes mellitus act synergistically to regulate energy metabolism[3]. Thyroid dysfunction has been reported to be significantly more prevalent among individuals with type 2 diabetes mellitus[4]. Dyslipidemia, a key metabolic abnormality observed in hypothyroidism and diabetes, contributes to an increased risk of atherosclerotic cardiovascular disease (ASCVD) by disrupting the balance of serum lipid components. Traditionally, low-density lipoprotein cholesterol (LDL-C) has been the primary target in the management of dyslipidemia. However, non–high-density lipoprotein cholesterol (non–HDL-C) has gained recognition as a more comprehensive and reliable marker of atherogenic lipoproteins. Non–HDL-C encompasses all cholesterol-containing particles other than HDL, including lipoprotein (a) [Lp(a)], triglyceride-rich lipoproteins (TRL), TRL remnants, and LDL. Several components of non–HDL-C have demonstrated atherogenic potential, thereby contributing to the pathogenesis of arterial disease[5-7]. A subgroup of individuals with elevated LDL particle number levels was identified by combining an increase in non-HDL-C levels with normal LDL-C values. Apo B levels were higher, and LDL had a dense, tiny shape[8,9]. The cost of measuring apo B and LDL particle concentration is increased, it is generally not standardized, and major national cholesterol therapy guidelines in the US do not now support its use. Conversely, non-HDL-C incurs no additional costs, is supported in that computation by current standards, and may be calculated using a conventional lipid panel (fasting or non-fasting). It may be possible to avoid costly tests that assess LDL particle number, total apo B concentration, or LDL phenotype (type A or B) by focusing on non-HDL-C[10,11]. This research's objective is to elucidation the effect of Non-High Density Lipoprotein Cholesterol among study group (Hypothyroidism with diabetes patients, Hypothyroidism without diabetes patients and control) and consider a risk marker for heart disease in thyroid disorder patients.

MATERIALS AND METHODS

Materials: A total of 120 patients participated in this study. All participants were recruited from the National Diabetes Center (NDC), Al-Mustansiriyah University, during the period from January 2024 to June 2024. The participants, aged 40–60 years, included both males and females. They were categorized into three groups:

* Middle Technical University
Institute of Medical Technology ALMansoure
Baghdad, Iraq.
Email: maryam.issa@mtu.edu.iq
** National Diabetes Center, Mustansiriyah University
Baghdad, Iraq.
*** Department of Chemistry, College of Science
University of Misan, Maysan, Iraq.

- Group 1 (G1): Forty hypothyroid patients with diabetes mellitus.
- Group 2 (G2): Forty hypothyroid patients without diabetes mellitus.
- Group 3 (G3): Forty healthy individuals serving as controls.

Demographic and anthropometric data, including age, sex, weight, height, and body mass index (BMI), were recorded. Laboratory investigations included the measurement of glycosylated hemoglobin (HbA1C), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) using colorimetric methods in accordance with the manufacturer's protocol provided with the Cobas c111 analyzer (Roche Diagnostics, Germany). Non–HDL-C was calculated as (TC – HDL-C).Thyroid function parameters — total triiodothyronine (TT3), total thyroxine (TT4), and thyroid-stimulating hormone (TSH) — were determined using the Mini Vidas analyzer (bioMérieux, France). Statistical analyses were performed using Microsoft Excel 2010. Data were expressed as mean ± standard deviation (SD). A p-value of less than 0.05 was considered statistically significant, whereas a p-value of less than 0.01 was considered highly significant[12].

Ethical Approval: This study was approved by the Ethics Committee of the National Diabetes Center. Prior to enrollment, all participants received oral instructions outlining the purpose and potential benefits of the study. Informed consent was obtained from each participant in accordance with the ethical standards and clinical research protocol on May 1, 2024.

Inclusion criteria: Family history of hypothyroidism and newly diagnosis of diabetes.

Exclusion criteria: Cardiovascular disease, Kidney failure patients, Liver disease, and Dyslipidemia patients.

RESULTS AND DISCUSSION

This study included a total of 120 participants, comprising 60 males and 60 females, who were categorized into three groups: Group 1 (G1) hypothyroidism with diabetes, Group 2 (G2) hypothyroidism without diabetes, and Group 3 (G3) healthy controls. No significant difference was observed among the groups with respect to age (Table 1).

Regarding diabetic indices, parameters such as body weight, body mass index (BMI), fasting serum glucose (FSG), and glycosylated hemoglobin (HbA1C) showed a statistically significant increase ($P \leq 0.05$ and $P \leq 0.01$) across the three groups (G1, G2, and G3), respectively. Similarly, lipid profile parameters—including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and non–high-density lipoprotein cholesterol (non–HDL-C)—demonstrated a highly significant elevation ($P \leq 0.01$) when compared among the study groups. These findings are consistent with previously reported studies[13-15].

n=number; Data are given as mean± SD; Significantly, P<0.05, high significant, P<0.01, and P<0.001 are the P-values.

A highly significant increase ($P \leq 0.01$) was observed in TSH and TT4 levels when comparing G1 vs. G2 and G3, and vice versa, whereas TT3 showed a statistically significant difference at ($P \leq 0.05$) (Table 2). Alterations in the lipid profile represent one of the major metabolic disturbances associated with thyroid dysfunction and are among the most consistent biochemical findings in hypothyroidism. Consequently, hypercholesterolemia and hypertriglyceridemia were evident features among hypothyroid patients.The influence of thyroid hormones on serum non–HDL-C concentrations remain a subject of debate, as studies have reported conflicting results regarding their interaction. Nonetheless, accumulating evidence indicates that elevated non–HDL-C levels play a substantial role in the pathogenesis of coronary heart disease (CHD)[16,17].

n=number; Data are given as mean± SD; Significantly, P<0.05, high significant, P<0.01, and P<0.001 are the P-values.

The findings presented in Table 2 demonstrate significant alterations in thyroid hormone levels among the study groups. Patients with hypothyroidism, particularly those with concomitant diabetes (G1), exhibited markedly elevated TSH and reduced TT3 and TT4 concentrations compared with non-diabetic hypothyroid and control groups. These hormonal disturbances reflect impaired thyroid function and reduced metabolic rate, both of which are known to adversely influence lipid metabolism.

Thyroid hormones play a pivotal role in regulating hepatic lipid synthesis and clearance. Elevated TSH levels have been associated with increased hepatic cholesterol synthesis and decreased LDL receptor activity, leading to higher circulating levels of LDL-C and non–HDL-C, both of which are established atherogenic lipoproteins. Consequently, these biochemical abnormalities contribute to endothelial dysfunction, arterial stiffness, and ultimately to an increased risk of atherosclerotic cardiovascular disease (ASCVD).

Table 1. Comparison of Biochemical parameters among study group (Hypothyroidism with diabetes patients, Hypothyroidism without diabetes patients and control).

Parameters	Hypothyroidism with diabetes patients	Hypothyroidism without diabetes patients	Control	(P value)	(P value)	(P value)
	G1	G2	G3	(G1 vs G2)	(G1 vs G3)	(G2 vs G3)
	N=(20M\20F) Mean±SD	N=(20M\20F) Mean±SD	N=(20M\20F) Mean±SD			
Age (years)	47.32±4.42	46.17±8.46	43.1±5.83	0.147	0.11	0.125
High (cm)	168.8±5.73	161.17±6.42	165.0±0.8	0.06	0.42	0.131
Weight kg))	83.75±7.20	79.32±4.12	73.82±5.81	0.05	0.05	0.05
BMI(Kg/m^2)	27.54±2.14	24.47±2.30	21.23±1.85	0.01	0.01	0.01
FSG (mg/dl)	145.47±25.38	89.32±14.00	77.20±4.71	0.01	0.01	0.01
HbA1C %	7.96±1.67	5.81±0.90	5.23±0.35	0.01	0.01	0.211
TC (mg/dl)	220.11±40.21	196.32±33.20	180.07±8.74	0.01	0.01	0.01
TG (mg/dl)	159.92±42.1	142.14±33.2	113.05±16.7	0.01	0.01	0.01
HDL-C (mg/dl)	47.9±6.62	50.21±2.14	54.25±3.92	0.12	0.241	0.106
LDL-C(mg/dl)	120.10±14.12	102.17±24.12	93.84±8.10	0.01	0.01	0.01
Non –HDL-C (mg/dl)	153.82±6.63	141.27±3.71	126.45±8.32	0.01	0.01	0.01

Table 2. Thyroid Function Test: among study groups (Hypothyroidism with diabetes patients, Hypothyroidism without diabetes patients and control).

Parameters	Hypothyroidism with diabetes patients	Hypothyroidism without diabetes patients	Control	(P value)	(P value)	(P value)
	G1	G2	G3	(G1 vs G2)	(G1 vs G3)	(G2 vs G3)
	N=(20M\20F) Mean±SD	N=(20M\20F) Mean±SD	N=(20M\20F) Mean±SD			
TT3 (nmole/L)	0.63±0.19	0.80±0.19	1.22±0.24	0.05	0.05	0.05
TT4(nmole/L)	45.32±6.81	55.51±9.52	78.55±7.24	0.01	0.01	0.01
TSH (IU/L)	18.97±6.03	14.71±6.45	3.69±1.36	0.01	0.01	0.01

Table 3. Atherogenic lipid ratios among study groups (Hypothyroidism with diabetes patients, Hypothyroidism without diabetes patients and control).

Hypothyroidism with diabetes patients	Hypothyroidism without diabetes patients	Control	(P value)	(P value)	(P value)
G1	G2	G3	(G1 vs G2)	(G1 vs G3)	(G2 vs G3)
N=(20M\20F) Mean±SD	N=(20M\20F) Mean±SD	N=(20M\20F) Mean±SD			
4.24± 0.91	3.58± 0.87	2.34 ± 0.24	0.05	0.05	0.05
3.40±1.05	2.09 ±0.68	1.92±1.05	0.05	0.05	0.05
4.21±0.92	2.97±0.85	1.92±0.22	0.05	0.05	0.05
3.24±0.91	2.58±0.78	.34±0.24	0.05	0.05	0.05

In this study, the concurrent rise in TSH and dyslipidemic indices particularly non–HDL-C supports the hypothesis that thyroid dysfunction potentiates atherosclerosis through metabolic and hormonal pathways. Thus, monitoring thyroid status in diabetic and non-diabetic patients provides an important predictive tool for cardiovascular risk stratification[18].

n=number; Data are given as mean± SD; Significantly, P<0.05, high significant, P<0.01, and P<0.001 are the P-values.

Table 3 demonstrates that atherogenic lipid ratios including TC/HDL-C, LDL/HDL-C, TG/HDL-C, and Non-HDL/HDL-C were significantly elevated (P ≤ 0.05) in hypothyroid patients with and without diabetes when compared with control subjects. These lipid ratios are widely recognized as sensitive predictors of cardiovascular risk, as they reflect the balance between atherogenic and anti-atherogenic lipoproteins[19].

An increased TC/HDL-C and LDL/HDL-C ratio indicates a predominance of cholesterol-rich lipoproteins (LDL and VLDL) over protective HDL particles, which enhances cholesterol deposition within arterial walls, promoting atherosclerosis. Similarly, a higher TG/HDL-C ratio is strongly associated with insulin resistance and endothelial dysfunction, both of which accelerate coronary artery disease (CAD) progression.

Most notably, elevated Non-HDL/HDL-C ratio observed in both hypothyroid groups (G1 and G2) reflects the overall atherogenic burden of all ApoB-containing lipoproteins (VLDL, IDL, LDL, and remnants). This parameter is now considered a superior marker of atherogenic dyslipidemia compared to LDL-C alone and correlates more closely with cardiovascular morbidity and mortality. Therefore, the significant rise in these ratios among hypothyroid subjects—especially those with concomitant diabetes—suggests an enhanced risk of atherosclerotic cardiovascular disease (ASCVD) through mechanisms involving lipid metabolism disruption, oxidative stress, and endothelial damage induced by thyroid hormone deficiency.

The statistical correlation data presented in Table 4 indicated that Non-HDL-C showed a significant positive correlation with weight, total cholesterol (TC), and TT4 (P < 0.05) in hypothyroid patients, both with and without diabetes. Moreover, a strong positive correlation (P < 0.01) was observed between Non-HDL-C and fasting serum glucose (FSG), HbA1C, triglycerides (TG), and LDL-C in the same groups. Conversely, Non-HDL-C demonstrated a negative correlation with HDL-C in hypothyroid patients, regardless of diabetic status.

Global guidelines recommend screening for non-HDL-C as a primary marker for cardiovascular risk assessment and dyslipidemia management, while some reports suggest its use as a secondary measure in patients with atherosclerosis[20]. Non-HDL-C closely correlates with ApoB100 and, together with LDL-C, captures most of its variability, making additional ApoB100 testing unnecessary for ASCVD risk prediction[21-23]. Thyroid hormone (TH) deficiency and elevated TSH levels significantly impact cardiovascular and metabolic health. TH deficiency disrupts lipid metabolism, leading to elevated LDL-C and triglycerides, a low LDL-C/HDL-C ratio, and increased LDL oxidation, thereby promoting atherosclerosis[24-27]. Both the vascular endothelium and myocardium express TH receptors, and reduced TH levels lower nitric oxide (NO) production, causing endothelial dysfunction. This impairs vascular tone regulation and anti-

Table 4. Correlation between Non HDL-C with variance parameters.

Parameters	Non HDL-C level Hypothyroidism with diabetes patients	Non HDL-C level Hypothyroidism without diabetes patients
	r	r
Age(years)	0.122	0.133
Weight (kg)	0.312*	0.336*
High (cm)	0.158	139
FSG (mg/dl)	0.585**	0.503**
HbA1C	0.558**	0.529**
TC (mg/dl)	0.313*	0.305*
TG (mg/dl)	0.514**	0.536**
HDL-C (mg/dl)	-0.149	-0.142
LDL-C (mg/dl)	0.620**	0.336*
TT3 (ng/ml)	0.125	0.145
TT4(ng/ml)	0.320*	0.328*
TSH (μIU/l)	0.756**	0.361*

* Significant correlation exists at the 0.05 level; **significant correlation exists at the 0.01 level

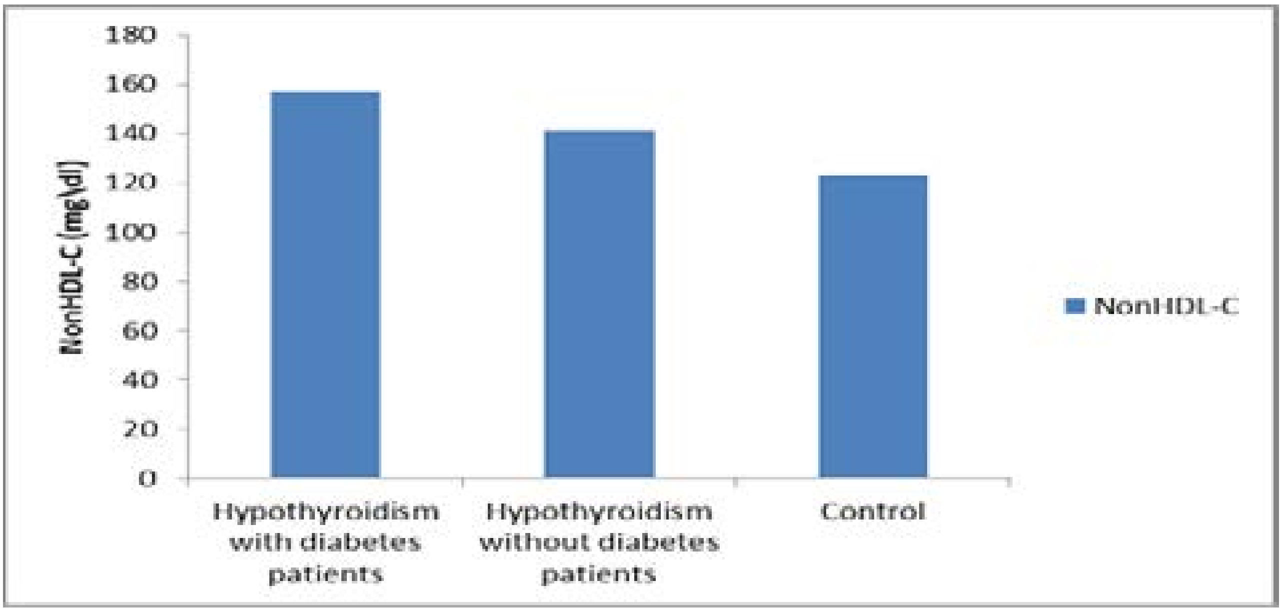

Figure 1. Non-HDL-C levels in patients and control.

atherosclerotic functions, triggering a cascade that includes diminished flow-mediated dilation, increased platelet and monocyte adhesion, LDL oxidation, thrombogenic factor expression, and smooth muscle cell proliferation[24,11]. Elevated TSH contributes to hyperglycemia and insulin resistance via increased circulating free fatty acids, impaired GLUT4 translocation, suppression of hypothalamic leptin signaling, and enhanced hepatic glucose production through glucose-6-phosphatase and PEPCK stimulation[17]. Collectively, these mechanisms highlight the central role of thyroid dysfunction in the development of atherosclerosis, dyslipidemia, and insulin resistance (Figure 1).

CONCLUSIONS

Thyroid dysfunction contributes to dyslipidemia, insulin resistance, and cardiovascular disease by impairing lipid metabolism, promoting LDL oxidation, and causing endothelial and myocardial dysfunction. Elevated TSH further exacerbates hyperglycemia and insulin resistance. Non-HDL-C is a reliable marker for assessing cardiovascular risk and can guide management in patients with thyroid abnormalities.

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Competing Interest: None

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