Original Article

Insulin Resistance and Triglyceride/HDL Cholesterol ratio: Interrelation with Atherosclerosis and Coronary Artery disease

Wafaa Hufdhy Ajam [1,6*], Mohammed Sameir Shaker [2], Marwa Fadhil Alsaffar [3], M.A. Abdelzaher [3, 4], Hawraa Saad Al-Kawaz [5], Foued Ben Hadj Slama [6]

[1] Department of Clinical Biochemistry, Hammurabi College of Medicine, University of Babylon, 51002, Hillah, Babylon, Iraq. [2] Department of Medical Microbiology, Hammurabi College of Medicine, University of Babylon, 51002, Hillah, Babylon, Iraq. [3] Medical Laboratories Techniques Department, College of Health and Medical Techniques, Al-Mustaqbal University, 51001, Babylon, Iraq. [4]Environmental Science and Industrial Development Department, Faculty of Postgraduate Studies for Advanced Sciences, Beni-Suef University, Beni-Suef 62511, Egypt. [5] Department of Pathological Analysis, College of Science, Al-Qasim Green University, Al-Qasim, 51013, Iraq. [6] Faculty of Medicine of Sousse, University of Sousse, Sousse 4002, Tunisia.

[*] Corresponding author: ham395.wafaa.hafdhe@uobabylon.edu.iq

Submission: May 3, 2024 Accepted: Jun 16, 2024 Published: Jun 30, 2024

Abstract

Background: Diabetes mellitus and its consequences have been identified as important worldwide health issues. Raised TG/HDL is considered a valid sign of insulin resistance. It increases the risk of CVD by developing insulin resistance and affecting the vessel wall. Detecting elevated TG/HDL ratios and intervening early, before individuals acquire clinical illness, can help mitigate the long-term implications of CVD. **Objectives:** detection of interrelationships with atherosclerosis and coronary artery disease by insulin resistance and triglyceride/HDL cholesterol ratio. **Material and Methods:** All subjects of this study were collected between January 2022 and September 2022. The target population of this study was one hundred (50 patients and 50 healthy people) enrolled. The age range of these subjects was 45–65 years. The patient group in the current study included people with type 2 diabetes mellitus without any systemic chronic disease. Patients with diabetic complications, renal and hepatic diseases, cardiovascular complications, T1DM, and rheumatoid arthritis were excluded. The apparently healthy individuals (the control group) have been enrolled in this study. **Results**: The mean difference in age between the control and patients is statistically insignificant ($P > 0.05$). This matching helps to eliminate differences in parameters' results, showing a statistically significant difference was observed between T2DM compared to control subjects ($p<0.05$) in the levels of BMI. While the levels of HbA1c, fasting glucose, serum insulin levels, and HOMA-IR increased significantly ($P < 0.001$) between type 2 diabetic patients compared with the normal control group, The present study showed a significant increase ($p < 0.01$) in TC/HDLc, TG/HDLc, and LDLc/HDLc ($p < 0.05$) when compared to those of the control group. **Conclusion**: Lipoprotein-based insulin resistance measures are at least as strongly related to clinical atherosclerosis progression as HOMA-IR, eliminating the requirement to measure insulin to assess the impact of insulin resistance. The easily obtained TG/HDL-C ratio may be sufficient.

Keyword: insulin resistance, atherosclerosis, type 2 diabetes mellitus, cardiovascular disease, triglyceride, high-density lipoprotein

Introduction

Coronary artery disease (CAD) occurs when lipids accumulate and atherosclerotic plaques develop underneath the tunica intima of the coronary arteries. This leads to the constriction of the arteries and, ultimately, the partial or total obstruction of blood flow. As per the Centers for Disease Control and Prevention (CDC), this is the most prevalent form of heart disease [1]. An association between type 2 diabetes mellitus (T2DM) and atherosclerosis is believed to be caused by elevated levels of blood glucose and its involvement in atherosclerotic plaques formation. Nevertheless, upon further examination, it becomes apparent that insulin resistance can lead to the development of atherosclerosis. Even after adjusting for hypertension (HTN), hyperlipidemia (HLD), and blood glucose levels, individuals with type 2 diabetes mellitus (T2DM) nevertheless have an elevated risk of cardiovascular disease, primarily attributed to insulin resistance [2]. Insulin resistance is a growing worldwide issue that is linked to both obesity and a sedentary lifestyle. A comprehensive investigation is required to gain a complete understanding of the intricate connection between insulin resistance, changes in lipid metabolism, endothelial dysfunction, and the progression of atherosclerosis [3].

Insulin resistance leads to the formation of smaller and denser LDL particles. These altered LDL particles have a higher likelihood of experiencing oxidation and can more easily penetrate the inner layer of the arteries. Oxidized LDL exerts a significant influence on the development of atherosclerosis by attracting inflammatory cells and inducing endothelial dysfunction. Insulin resistance decreases the function of lipoprotein lipase, resulting in an increase in lipoproteins containing high levels of triglycerides and the formation of more atherosclerotic plaque [4]. It is commonly recognized that insulin resistance has a key effect in the development of these illnesses by impacting the metabolism of glucose and fatty acids. There is a growing connection between insulin resistance and the ratio of triglyceride to high-density lipoprotein cholesterol (TG/HDL-C). This can be demonstrated using measurements of plasma insulin, steady-state plasma glucose during an insulin suppression test, or the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Individuals of different genders, age groups, and obesity levels have noticed connections between the TG/HDL-C ratio and indices of insulin resistance [5]. Based on the available evidence, the TG/HDL-C ratio shows potential as a reliable indicator for evaluating the risk, morbidity, and mortality associated with cardiovascular disease (CVD). It has the potential to be a useful tool for developing strategies to prevent both fundamental and secondary issues [6]. This study aims to detect of interrelationships with atherosclerosis and coronary artery disease by insulin resistance and triglyceride/HDL cholesterol ratio.

Materials and Methods

Study Design and Setting

The case-control study took place at Marjan Medical City and the Center of Diabetic Clinic and Endocrine in Babylon Governorate. For this study, we collected all subjects between January 2022 and September 2022. The study's target population was one hundred (50 patients and 50 healthy people) enrolled. The age range of these subjects was 45–65 years.

Patient Evaluation and Criteria

We designed a questionnaire to gather information from the patients and control groups. It included the name, age, gender, height, weight, medication, and disease history. To calculate their body mass index (BMI) in kg/m2, we measured their height and weight. After 12 hours of fasting, we collected five milliliters of venous blood from each patient. We collected blood specimens from both patients and healthy individuals.

Inclusion and exclusion criteria

In the current study, the patient group included people with type 2 diabetes mellitus who did not have any systemic chronic diseases. We excluded patients with diabetic complications, renal and hepatic diseases, cardiovascular complications, T1DM, and rheumatoid arthritis. This study has enrolled seemingly healthy individuals (the control group).

Statistical Analysis

Using SPSS v25, statistical analyses were performed. Mean ± SD and Pearson correlation coefficient was used to assess the correlation between continuous variables. Also, consider the significance of the difference between variables in groups. P<0.05 is considered significant.

Ethical Approval

All participants were informed before sample collection and verbal consent was obtained from each participant. The Babylon Health Directorate Ethics Committee evaluated and approved the study protocol, subject information, and permission forms (no. 118, October 27, 2022).

Results

Demographic features of study groups.

Table 1 represents the characteristics of a group. The mean difference in age between the control and patients is statistically insignificant (P > 0.05). This matching helps to eliminate differences in parameter results, showing a statistically significant difference between T2DM compared to control subjects (p<0.05) in BMI levels.

Table 1. Anthropometric data of T2DM and control groups

Variable	Study groups	Mean± SD	P value
Age (years)	T2DM	55.12 ± 6.55	0.31
	Control	55.22 ± 7.10	
BMI (kg/m^2)	T2DM	30.31 ± 3.05	0.001
	Control	26.73 ± 5.09	

* p < 0.05 is statistically significant

T2DM biochemical parameters in patients compared with control groups.

Measurement of Fasting insulin and insulin resistance (HOMA-IR)

The levels of HbA1c, fasting glucose, serum insulin levels and HOMA-IR were increased significantly (P < 0.001) difference between type 2 diabetic patients compared with normal control group.

Table 2. Comparison of the biochemical parameters among groups

Parameters	T2DM	Control	P value
Glucose (mmol/l)	7.12 ± 0.51	5.55 ± 0.26	0.001
HbA1c %	9.80 ± 2.61	5.63 ± 0.39	0.001
Insulin < 0.001 (μU/ml)	13.22 ± 1.02	7.44 ± 3.50	0.001
HOMA-IR	4.56 ± 0.32	1.42 ± 0.76	0.001

* p < 0.05 is statistically significant

Measurement of lipid profile

The study found that the T2DM group's serum levels of TC, TG, VLDLc, and LDLc all went up statistically significantly (p <0.01), while the levels of HDLc went down significantly (p<0.05), as shown in Table 3. We calculate lipoprotein ratios (TC/HDLc, TG/HDLc, and LDLc/HDLc) using the fasting serum lipid profile (TC, HDLc, TG, and LDLc). The present study showed a significant increase (p < 0.01) in TC/HDLc, TG/HDLc, and LDLc/HDLc (p <

0.05) when compared to those of the control group.

Table 3. Mean ± SD values of Total cholesterol, Triglycerides, VLDL, LDLc, HDLc and Lipoprotein ratios of T2DM and control group.

Parameters	Type of Group	Mean ± SD	P value
TC mmol/L	T2DM	5.14 ± 1.13	0.05
	Control	4.97 ± 0.72	
TG mmol/L	T2DM	2.15 ± 0.46	0.01
	Control	1.14 ± 0.48	
HDL-C mmol/L	T2DM	1.21 ± 0.52	0.05
	Control	1.37 ± 0.37	
LDL-C mmol/L	T2DM	3.12 ± 0.98	0.05
	Control	2.87 ± 0.91	
VLDL-C mmol/L	T2DM	0.91 ± 0.32	0.01
	Control	0.57 ± 0.27	
LDL/HDLc	T2DM	3.27 ± 1.83	0.01
	Control	2.56 ± 0.98	
TG/HDLc	T2DM	1.96 ± 0.56	0.01
	Control	1.52 ± 0.35	
TC/HDLc	T2DM	5.65 ± 1.28	0.01
	Control	4.31 ± 1.34	

* $p < 0.05$ is statistically significant

Correlation of lipoprotein ratios with insulin resistance (HOMA-IR) in T2DM patients

The correlation coefficient (r) evaluated the correlation between HOMA-IR and lipoprotein ratios. Table 4 shows a significant positive correlation between HOMA-IR and LDL/HDLc, TG/HDLc, TC/HDLc, and HOMA-IR.

Table 4. Correlation between lipoprotein ratios with HOMA-IR in T2DM patients

Parameters	Correlation coefficient (r)	P value
LDL/HDLc	0.380	0.02
TG/HDLc	0.442	0.001
TC/HDLc	0.417	0.01

Discussion

Our investigation found a strong correlation between insulin resistance and the triglyceride/HDL cholesterol ratio with atherosclerosis and coronary heart disease. This association remains constant irrespective of age, gender, race, BMI, or physical activity. The study shows a statistically significant difference ($p<0.05$) in the levels of BMI and age between T2DM and control patients. These factors can impact the timing and severity of interventions for risk factors in clinical decision-making and guideline-based care. These data provide more evidence for the importance of preventing or delaying the onset of Type 2 Diabetes Mellitus (T2DM) in younger patients. An earlier age at diagnosis is linked to a greater subsequent risk for all outcomes examined. Being diagnosed with T2DM at a young age was likewise linked to the highest number of years of life lost. The risks for various nonfatal cardiovascular disease outcomes are much higher in those diagnosed with type 2 diabetes mellitus at a younger age. A more recent study found that younger individuals (<55 years old) with prevalent diabetes mellitus had approximately three times higher mortality risks. However, no such concerns were observed in patients with diabetes mellitus who were beyond the age of 75 [7]. The data from the Emerging Risk Factor Collaboration also indicated that the number of years of life lost was considerably higher when diabetes mellitus was present at younger ages. However, it is important to note that this study did not specifically analyze the risks based on the age at which the diagnosis was made [8].

The values of HbA1c, fasting glucose, serum insulin, and HOMA-IR showed a substantial ($P < 0.001$) difference between individuals with type 2 diabetes and a healthy control group in our study. The fasting blood insulin concentrations and the HOMA-IR, but not the fasting glucose measurement alone, showed individual alterations in carbohydrate metabolism resulting from a lifestyle intervention program. Consequently, the HOMA-IR evaluation can assist in tailoring lifestyle therapies for obesity and accurately quantify enhancements in insulin sensitivity following therapeutic lifestyle modifications.

The lipid profile analysis revealed a statistically significant increase ($p<0.01$) in the levels of TC, TG, VLDLc, and LDLc in the sera of the T2DM group. Conversely, there was a substantial decrease ($p<0.05$) in the levels of HDLc in the sera.

The cholesterol that builds up in atherosclerotic lesions predominantly comes from plasma lipoproteins, particularly LDL. The present study also identified elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in diabetes patients, which is consistent with findings from several previous studies [9, 10]. Nevertheless, other investigations were unable to report comparable results [11]. Additionally, studies have demonstrated that glycated LDL-C may experience a reduction in its ability to attach to Apo B receptors, resulting in elevated plasma TC levels in individuals with diabetes [12]. Patients with type 2 diabetes mellitus (T2DM) exhibited a reduced level of high-density lipoprotein cholesterol (HDL-C) in their blood serum compared to the control group. Individuals diagnosed with type 2 diabetes mellitus (T2DM) seem to experience a faster rate of high-density lipoprotein (HDL) turnover, resulting in a decreased level of HDL cholesterol (HDL-C) in the blood. Additionally, patients with increased insulin levels may see a decrease in HDL-C concentrations [13]. HDL-C is frequently observed in patients with T2DM, indicating a potential association with higher rates of death and disease in coronary heart disease (CHD) [14]. Glycation of HDL reduces the transportation of cholesterol and enhances the activity of cholesteryl ester transfer [15]. Moreover, it is common for us to come across low levels of HDL-C along with elevated levels of TG, indicating a possible metabolic connection between these two conditions [16]. Managing DM results in favorable alterations in HDL-C levels [17]. The current investigation unveiled a heightened serum LDL-C level in individuals with T2DM in comparison to the control group. This aligns with the findings of other researchers [18]. Researchers have observed alterations in LDL particles, such as oxidation [21] and non-enzymatic glycation [20], in individuals with T2DM. LDL particles with such characteristics would be more prone to being taken up by macrophage scavenger receptors, resulting in the production of foam cells. Consequently, this increases the probability of developing atherosclerosis [22]. Furthermore, individuals with diabetes have LDL particles that are tiny, thick, and glycated, and these particles are closely linked to coronary heart disease (CHD) [23, 24]. Statins are clearly helpful in preventing and treating coronary heart disease (CHD) by reducing low-density lipoprotein cholesterol levels [25]. Early care of diabetes should involve initiating treatment for elevated LDL-C levels in order to achieve target values and reduce the risk of cardiovascular disease and coronary heart disease. Hypertriglyceridemia is the most commonly observed form of dyslipidemia in patients with type 2 diabetes mellitus (T2DM) and is typically linked to a higher likelihood of developing coronary heart disease (CHD) [26]. Elevated insulin levels in the blood are thought to stimulate the synthesis of more very low-density lipoprotein (VLDL), which in turn increases the levels of triglycerides (TG) in the blood. Concurrently, the extraction of more lipids and apolipoproteins from VLDL particles enhances the generation of IDL and LDL. Modifications in triglyceride (TG) levels have a positive impact [27].

Conclusions

T2DM has a profound effect on the lipid and lipoprotein profiles. Patients with T2DM have a diversity of dyslipidaemia and a higher atherogenic (LDL-C/HDL-C) ratio. As a result, these patients may be at an increased risk of accelerated and diffuse atherosclerosis, as well as a higher risk of coronary artery disease**.**

Declaration of Interest

The authors declare that they have no known competing interests that could influence the present research.

Acknowledgements

The authors would like to thank the study subjects for their participation and cooperation throughout the research.

Funding: There was no outside funding for this project.

Data Availability Statement

On request, the data used in this investigation is available.

References:

[1] Centers for Disease Control and Prevention. [(accessed on 19 January 2023)];

[2] Kosmas CE, Bousvarou MD, Kostara CE, Papakonstantinou EJ, Salamou E, Guzman E. Insulin resistance and cardiovascular disease. Journal of International Medical Research. 2023 Mar;51(3):03000605231164548.

[3] Di Pino A, DeFronzo RA. Insulin resistance and atherosclerosis: implications for insulin-sensitizing agents. Endocrine reviews. 2019 Dec;40(6):1447-67.

[4] Ashraf FU, Ghouri K, Someshwar FN, Kumar S, Kumar N, Kumari K, Bano S, Ahmad S, Khawar MH, Ramchandani L, Salame T. Insulin Resistance and Coronary Artery Disease: Untangling the Web of Endocrine-Cardiac Connections. Cureus. 2023 Dec 25;15(12).

[5] Eng D, Gregg B, Singer K, Lee JM. 997-P: TG/HDL Ratio as a Predictor of Insulin Resistance in US Adolescents: Do Age and Sex Percentiles Matter?. Diabetes. 2022 Jun 1;71(Supplement_1).

[6] Matsumoto I., Misaki A., Kurozumi M., Nanba T., Takagi Y. Impact of non fasting triglycerides/high-density lipoprotein cholesterol ratio on secondary prevention in patients treated with statins. J. Cardiol. 2018;71:10–15.

[7] Tancredi, M, Rosengren, A, Svensson, AM, Kosiborod, M, Pivodic, A, Gudbjörnsdottir, S, Wedel, H, Clements, M, Dahlqvist, S, Lind, M. Excess mortality among persons with type 2 diabetes. *N Engl J Med*. 2015;373:1720–1732. doi: 10.1056/NEJMoa1504347

[8] Rao Kondapally Seshasai, S, Kaptoge, S, Thompson, A, Di Angelantonio, E, Gao, P, Sarwar, N, Whincup, PH, Mukamal, KJ, Gillum, RF, Holme, I, Njølstad, I, Fletcher, A, Nilsson, P, Lewington, S, Collins, R, Gudnason, V, Thompson, SG, Sattar, N, Selvin, E, Hu, FB, Danesh, J; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med*. 2011;364:829–841. doi: 10.1056/NEJMoa1008862

[9] Akangi OA, Agbedana EO, Ugbode C. Plasma lipid profile in relation to diabetic

control in Nigerians, Afr J Med Sci 1989; 18: 229-234.

[10] Ristic V, Raden S, Ristic M. Manojlovic D. Nutritional status and plasma lipids in diabetic subjects. Acta Med Yugosl 1989; 43:197-203.

[11] Durlach V, Attia N, Zahouani A, Leuteneqqer M, Girard-Globa A. Postprandial cholesteryl ester transfer and high density lipoprotein composition in normtriglyceridaemic non-insulin dependent diabetic patients. Atherosclerosis 1996; 120:155-165.

[12] Witztum JL, Mahoney EM, Branks MJ, Fisher M, Elam R, Steinberg D. Non-enzymatic glycosylation of low-density lipoprotein alter its biologic activity. Diabetes 1982; 31:283-291.

[13] Chen YD, Jeng CY, Reaven GM. HDL metabolism in diabetes. Diabetes Metab Rev 1987; 3:653-668.

[14] Alaupovic P, Bard JM, Tavella M, Shafer D. Identification of Apo B containing lipoprotein families in NIDDM. Diabetes 1992; 41(Suppl 2): 18- 25.

[15] Berthezene F. Non-insulin dependent diabetes and reverse cholesterol transport. Atherosclerosis 1996; 124 (Suppl): 39-42.

[16] Okubo M, Murase T. Hypertriglyceridaemia and low HDL cholesterol in Japanese patients with NIDDM. Diabetes 1996; 45 (Suppl 3): 123-125.

[17] Erdman DM, Cook CB, Greenlund KJ, Giles WH, El-Kebbi I, Ryan GJ, et al. The impact of outpatient diabetes management on serum lipids in urban African-Americans with type 2 diabetes. Diabetes Care. 2002; 25: 9-15

[18] Erdman DM, Cook CB, Greenlund KJ, Giles WH, El-Kebbi I, Ryan GJ, et al. The impact of outpatient diabetes management on serum lipids in urban African-Americans with type 2 diabetes. Diabetes Care. 2002; 25: 9-15

[19] Lee LS, Hwang JY, Chang JJ, Hsu CH, Liao ST, Lo IL. Apolipoproteins AI and B in non-insulin dependent diabetes mellitus. Taiwan Yi Xue Hui Za Zhi 1989; 88: 1139-1142.

[20] Yegin A, Ozben T, Yegin H. Glycation of lipoprotein and accelerated atherosclerosis in non-insulin dependent diabetes mellitus. Int J clin Lab Res 1995; 25:157-161.

[21] Beaudeux JL, Guillausseau PJ, Peynet J, Flaurie F, Assayaq M, Tielmans D, et al. Enhanced susceptibility of low-density lipoprotein to invitro oxidation in type 1 and type 2 diabetic patients. Clin Chim Acta 1995; 239:131-141.

[22] Kraemer GA, Quaschning T, Greiber S, Wanner C. Potential role of lipids in the progression of diabetic nephropathy. Clin Nephrol 1996; 40:262-265.

[23] Sobenin IA, Tertov VV, Orekhov AN. Atherogenic modified LDL in diabetes. Diabetes 1996; 45 (Suppl 3): 35-39.

[24] Lamarche B, Techernof A, Mauriege P, Cantin B, Daqenais GR, Lupien PJ, et al. Fasting insulin and apolipoprotein B levels and low-density lipoprotein particle size as risk factors for ischaemic heart disease. JAMA 1998; 279:1955-1961.

[25] Tenenbaum A, Fisman EZ, Motro M, Adler Y. Atherogenic dyslipidemia in metabolic syndrome and type 2 diabetes: therapeutic options beyond statins. Cardiovasc Diabetol. 2006 26; 5: 20.

[26] Ginsbery HN. Diabetic dyslipidaemia, basic mechanisms underlying the common hypertriglyceridaemia and low HDL cholesterol levels. Diabetes 1996; 45 (Suppl 3): 27-30.

[27] DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia and atherosclerotic cardiovascular disease. Diabetes care 1991; 14:173-194.