

Correlation of HbA1c with Ratio of Total Cholesterol/HDL, LDL/HDL, TG/HDL and Apolipoprotein B / Apolipoprotein A-1 Ratio in Patients with Type 2 Diabetes Mellitus

Correlación de HbA1c con el cociente Colesterol Total/HDL, LDL/HDL, TG/HDL y el cociente Apolipoproteína B/Apolipoproteína A en pacientes con Diabetes Mellitus tipo 2

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SUMMARY

Background: *The lipid and Apo B/Apo A-1 ratios may be considered additional risk factor assessments, especially in patients with a high risk of cardiovascular diseases, such as diabetes. Blood glucose level can be assessed by measuring glycated hemoglobin (HbA1c), which is used as a long-term control and monitoring.*

Objective: *This study aimed to determine the relationship between HbA1c with lipid ratio and Apolipoprotein B/Apolipoprotein A-1 ratio in patients with type 2 diabetes mellitus.*

Methods: *A cross-sectional study was employed, and there were 60 subjects with type 2 diabetes involved, comprising 26 males and 34 females.*

Results: *The statistical analysis results revealed significant differences in CHOL/HDL, LDL/HDL, and Apo B/Apo A-1 between controlled and uncontrolled type 2 DM subjects ($p=0.037$; $p=0.006$; $p=0.004$), but no significant difference was found in TG/HDL ($p=0.244$). Meanwhile, the Spearman correlation test displayed a significant correlation between HbA1c levels and CHOL/HDL ($p=0.021$; $r=0.298$), LDL/HDL ($p=0.002$; $r=0.393$), and Apo B / Apo A-1 ($p=0.017$; $r=0.308$) in patients with type 2 diabetes mellitus. However, no significant correlation was observed between HbA1c levels and TG/HDL ($p=0.165$; $r=0.181$).*

Conclusions: *There is a significant correlation between HbA1c levels, CHOL/HDL, LDL/HDL, and Apo B/Apo A-1, while HbA1c levels with TG/HDL have no significant correlation.*

Keywords: *Type 2 Diabetes Mellitus, HbA1c, lipid ratio, Apo B/Apo A-1 ratio.*

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RESUMEN

Antecedentes: *Los índices de lípidos y Apo B/Apo A-1 pueden considerarse evaluaciones de factor de riesgo adicionales, especialmente en pacientes con alto riesgo de enfermedades cardiovasculares, como la diabetes. El nivel de glucosa en sangre se puede*

evaluar midiendo la hemoglobina glicosilada (HbA1c), que se utiliza como control y seguimiento a largo plazo.

Objetivo: *Este estudio tiene como objetivo determinar la relación entre la HbA1c y el cociente lipídico y el cociente Apolipoproteína B/Apolipoproteína A-1 en pacientes con diabetes mellitus tipo 2.*

Métodos: *Se empleó un estudio transversal, y hubo 60 sujetos con diabetes tipo 2 involucrados, que consisten en 26 hombres y 34 mujeres.*

Resultados: *Los resultados del análisis estadístico revelaron diferencias significativas en CHOL/HDL, LDL/HDL y Apo B/Apo A-1 entre sujetos con DM tipo 2 controlados y no controlados ($p=0,037$; $p=0,006$; $p=0,004$), pero no se encontró diferencia significativa en TG/HDL ($p=0,244$). Por su parte, la prueba de correlación de Spearman mostró una correlación significativa entre los niveles de HbA1c y CHOL/HDL ($p=0,021$; $r=0,298$), LDL/HDL ($p=0,002$; $r=0,393$) y Apo B/Apo A-1 ($p=0,017$; $r=0,308$) en pacientes con diabetes mellitus tipo 2. Sin embargo, no se observó una correlación significativa entre los niveles de HbA1c y TG/HDL ($p=0,165$; $r=0,181$).*

Conclusiones: *Existe una correlación significativa entre los niveles de HbA1c, CHOL/HDL, LDL/HDL y Apo B/Apo A-1, mientras que los niveles de HbA1c con TG/HDL no tienen correlación significativa.*

Palabras clave: *Diabetes Mellitus tipo 2, HbA1c, relación lípidos, relación Apo B/Apo A-1.*

INTRODUCTION

Diabetes is considered the most common metabolic disorder. This disease has clinically become a global pandemic in recent decades and a major healthcare burden worldwide. The occurrence of diabetes continues to rise. The World Health Organization (WHO) defines diabetes as a “metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbance of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The most common form of diabetes is type 2 diabetes (DM). WHO estimates that >590 million patients will be diagnosed with diabetes by 2035 (2).

Rather than caused by the insufficient secretion of the insulin hormone, type 2 diabetes mellitus occurs due to the failure of the body’s cells to respond to the hormone. This condition is commonly called “insulin resistance” (3). Insulin resistance is mainly caused by obesity, aging, and lack of physical activity. Insulin resistance plays a significant role in the development of atherogenic dyslipidemia, which involves increased

levels of total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and decreased levels of high-density lipoprotein (HDL) cholesterol (4).

Individuals with diabetes mellitus may experience lipid abnormalities or conditions commonly called dyslipidemia. Serum lipid abnormalities (dyslipidemia) are frequently observed in the diabetic population regardless of whether they have insulin deficiency or insulin resistance. Type 2 diabetes mellitus patients are susceptible to developing diabetic dyslipidemia, which increases the likelihood of complications related to cardiovascular disease (5). Lipid toxicity can trigger the process of atherogenesis to become more progressive. Lipoproteins will change due to metabolic changes in DM, such as glycation and oxidation processes (6). This may lead to a higher risk of insulin resistance, resulting in type 2 DM (7).

Lipid metabolism dysfunction in DM is directly associated with a risk for atherosclerotic cardiovascular events. There is evidence showing that death in DM patients is mostly caused by atherosclerosis, accounting for approximately 80 % of cases. As many as 75 % are caused by coronary heart disease (CHD), and the remaining 25 % are caused by stroke (8). Cardiovascular diseases like coronary heart disease largely cause mortality and morbidity in diabetic patients. One of the risk factors for coronary heart disease in patients with type 2 diabetes mellitus is the lipid profile characterized by an increase in total cholesterol, LDL, or triglycerides and a decrease in HDL (4).

Apolipoproteins, also called apoproteins, are important components of lipoprotein clusters found in the lipoproteins (9). Apolipoprotein B is a protein component that is the most important atherogenic element in VLDL, IDL, and LDL (10). In a previous study about Apolipoprotein related mortality risk (AMORIS), the Apo B/Apo A-1 ratio was also investigated; the result indicated that apolipoprotein B (Apo B) and apolipoprotein A-1 (Apo A-1) concentrations, as well as the Apo B/Apo A-1 ratio, were able to enhance the prediction of cardiovascular disease risk (11).

The measurement of glycated hemoglobin (HbA1c) can be utilized to determine the blood glucose levels for long-term control and monitoring; HbA1c reflects average plasma glucose over the previous eight to 12 weeks and can serve as a basis for assessing and considering the risk of complications in diabetic patients (12). It can be performed at any time of the

day and does not require any special preparation such as fasting. These properties have made it the preferred test for assessing glycaemic control in people with diabetes. More recently, there has been substantial interest in using it as a diagnostic test for diabetes and as a screening test for persons at high risk of diabetes. HbA1c is formed when a ketoamine reaction occurs between glucose and the N-terminal amino acid valine of the β chain of hemoglobin. Initially, an unstable bond is formed between glucose and the hemoglobin molecule. With time, this bond rearranges to form a more stable compound in which glucose is covalently bound to the hemoglobin molecule. The amount of the unstable form may rise rapidly in the presence of a high blood glucose level, whereas the stable form changes slowly and provides a time-average integral of the blood glucose concentration through the 120-day lifespan of the red blood cell. Thus, glycohemoglobin levels provide an objective measurement of averaged diabetic control over time (13). According to the American Diabetes Association (ADA) (2022), the recommended target for appropriate diabetes mellitus (DM) control is maintaining an HbA1c value $< 7\%$, and the higher the HbA1c value, the higher the risk of DM complications (14).

Theoretically, there is a connection between HbA1c and lipid profile where reduced insulin function leads to increased lipase-sensitive hormones (15). This, in turn, triggers lipolysis, releasing fatty acids and glycerol into the bloodstream, ultimately leading to an increase in free fatty acids (16). Consequently, if an excessive amount of these fatty acids reaches the liver, they will undergo fat metabolism and be converted into phospholipids, cholesterol, and triglycerides. This process causes the level of cholesterol and triglyceride to increase, which then are transported into circulation via lipoproteins, namely LDL and HDL (17).

The measurement of HbA1c levels that can determine glucose control in patients with type 2 diabetes mellitus and estimate the risk of complications leads to develop an interest in investigating the correlation between HbA1c and lipid ratios, as well as Apolipoprotein B/ Apolipoprotein A-1 ratios, in patients with type 2 DM.

METHODS

Study Design and Population

A cross-sectional study was employed as the study design. The current study population was type 2

DM patients who visited the Hasanuddin University Hospital (RSPTN-UH) for treatment. A total of 60 samples were involved, comprising 26 males and 34 females. This study was conducted at the Clinical Pathology Laboratory of Hasanuddin University Hospital (RSUH), the Clinical Pathology Laboratory of Labuang Baji Hospital, and the Health Service Unit (UPK) Laboratory of Makassar City Health Service Center. The study received ethical approval from the Health Research Ethics Committee (KEPK) of the Faculty of Medicine, Hasanuddin University, RSPTN-UH, with ethical number 164/UN4.6.4.5.31/PP36/2023.

Measurement of HbA1c, Total Cholesterol, LDL, TG, HDL, Apo B, and Apo A-1 Levels

The participant's identities were recorded. Before blood sampling, the patients underwent a fasting period. Whole blood samples were collected for the HbA1c examination using the EDTA tubes. In contrast, the serum sample for the total cholesterol, LDL, TG, HDL, Apo B, and Apo A-1 was collected using tubes without an anti-coagulant. Then, the blood sample in the tube without an anti-coagulant was centrifuged at 3000 rpm for 10 - 15 minutes to separate the serum from the blood cell component. The serum obtained was then stored at -20°C . The HbA1c assessment was done using the Alere Afinion AS100 instrument with the Boronette Affinity Assay method. Total cholesterol, LDL, TG, and HDL were analyzed using the Enzymatic Colorimetric method on the Cobas C111 instrument. On the other hand, Apo B and Apo A-1 were measured using the immunoturbidimetric method on the Cobas C311 device.

Data Analysis

The data obtained were then analyzed using SPSS software version 22. Data were analyzed by entering all variables, including age, gender, and laboratory examination results. The Kolmogorov-Smirnov test was conducted to determine the normality of the data distribution using a significant value ($\alpha = 0.05$). A non-parametric Spearman correlation test was employed if the data is not normally distributed.

RESULTS

A total of 60 participants with type 2 diabetes mellitus were involved in this study, comprising 26

males and 34 females. The subjects were divided into age groups, including 6 participants aged 36-45 years, 14 participants aged 46-55 years, 32 participants aged 56-65, and 8 participants over 65 years (Table 1).

Table 1. Research Subjects' Characteristics

Characteristics	Category	Type 2 DM n	%	Mean
Gender	Male	26	43.3	-
	Female	34	56.7	-
Age	36-45 years	6	10.0	-
	46-55 years	14	23.3	-
	56-65 years	32	53.3	-
	>65 years	8	13.3	-
			60	100
HbA1c		60	100	118.07
Apo B		60	100	128.70
Apo A-1		60	100	1.09
Apo B/Apo A-1		60	100	215.5
CHOL		60	100	118.61
LDL		60	100	31.63
HDL		60	100	168.15
TG		60	100	7.70
CHOL/HDL		60	100	4.28
LDL/HDL		60	100	6.14
TG/HDL		60	100	

Normality Test

As shown in Table 2, the Kolmogorov-Smirnov test results revealed that the p-value for HbA1c in individuals with type 2 DM was 0.055 ($p>0.05$), indicating that the data is normally distributed. On the other hand, the p-value of Apo B/Apo A-1 in

type 2 DM subjects was 0.0001 ($p<0.05$), suggesting that the data does not exhibit a normal distribution. Similarly, the p-values for CHOL/HDL, LDL/HDL, and TG/HDL in type 2 diabetes mellitus subjects were all determined to be 0.0001 ($p<0.05$), indicating that the data for these variables were not normally distributed.

Table 2. Kolmogorov-Smirnov Normality Test

Statistics	Type 2 DM		P
	N		
HbA1c	60	0.113	0.055
Apo B/Apo A-1	60	0.258	0.0001
CHOL/HDL	60	0.179	0.0001
LDL/HDL	60	0.194	0.0001
TG/HDL	60	0.171	0.0001

Comparison Test***Comparison of CHOL/HDL in Controlled and Uncontrolled Type 2 DM***

According to a normality test conducted on the CHOL/HDL data in both controlled and uncontrolled type 2 DM groups, it was determined that there were non-normally distributed data. Consequently, the Mann-Whitney test was employed to assess the difference in CHOL/HDL levels between controlled

and uncontrolled type 2 DM (Table 3). By conducting the Mann-Whitney statistical test, a p-value = 0.037 was obtained. Since the p-value < α (alpha=0.05), it can be concluded that there is a significant difference in CHOL/HDL levels between controlled and uncontrolled type 2 DM subjects.

Comparison of LDL/HDL Levels in Controlled and Uncontrolled Type 2 DM

Based on the normality test performed on the LDL/HDL data in controlled and uncontrolled type 2 DM, it was concluded that non-normally distributed data were obtained. Thus, the Mann-Whitney test was carried out to determine the difference between LDL/HDL levels in controlled and uncontrolled type 2 DM (Table 3). The statistical test results revealed a p-value = 0.006. Since p-value < α (alpha=0.05), it can be concluded that there is a significant difference in LDL/HDL levels between the controlled and uncontrolled type 2 DM subjects.

Comparison of TG/HDL Levels in Controlled and Uncontrolled Type 2 DM

After a normality test was conducted on the LDL/HDL data in both controlled and uncontrolled type 2 DM groups, it was determined that the data was not normally distributed. Consequently, the Mann-Whitney test was carried out to assess the disparity in TG/HDL levels between both groups (Table 3). The results of the Mann-Whitney statistical test revealed a p-value = 0.244. Since p-value > α (alpha=0.05), it can be concluded that no significant difference was found in TG/HDL levels between controlled and uncontrolled type 2 DM subjects.

Comparison of Apo B/Apo A-1 Levels in Controlled and Uncontrolled Type 2 DM

Based on the normality test of Apo B/Apo A-1 data in controlled and uncontrolled type 2 DM, it can be concluded that the data obtained were not normally distributed. Therefore, the Mann-Whitney test was carried out to determine the difference between Apo B/Apo A-1 levels in controlled and uncontrolled type 2 DM (Table 3). The result of the Mann-Whitney statistical test obtained a p-value = 0.004. Since the p-value < α (alpha=0.05) indicates a significant difference between Apo B/Apo A-1 in controlled and uncontrolled type 2 DM subjects.

Table 3. Comparison Test of CHOL/HDL, LDL/HDL, TG/HDL, Apo B/Apo A-1 Levels in Controlled and Uncontrolled Type 2 Diabetes Mellitus

Group	n	Type 2 Diabetes Mellitus			p
		Range	Median	Mean±SD	
Controlled (HbA1c <7 %)	12	3.11-8.93	5.31	5.49±1.66	0.037
Uncontrolled (HbA1c ≥7 %)	48	3.38-28.26	6.87	8.25±4.60	
		LDL/HDL			
Controlled (HbA1c <7 %)	12	0.97-6.12	2.43	2.73±1.40	0.006
Uncontrolled (HbA1c ≥7 %)	48	1.12-27.50	3.80	4.67±3.91	
		TG/HDL			
Controlled (HbA1c <7 %)	12	2.47-8.93	4.14	4.62±1.80	0.244
Uncontrolled (HbA1c ≥7 %)	48	1.60-26.62	5.13	6.52±4.76	
		Apo B/Apo A-1			
Controlled (HbA1c <7 %)	12	0.24-1.00	0.67	0.65±0.17	0.004
Uncontrolled (HbA1c ≥7 %)	48	0.30-4.42	0.99	1.19±0.85	

Correlation Test

Correlation Test between HbA1c and CHOL/HDL in Type 2 DM

The results of the Spearman correlation test between HbA1c and CHOL/HDL levels in type 2 DM subjects showed a p-value = 0.021. Since p-value

$< \alpha$ (alpha=0.05), it can be concluded that there is a significant correlation between HbA1c and CHOL/HDL levels in type 2 DM patients (Table 4).

As shown in Figure 1, the data distribution on the scatterplot forms a linear relationship pattern between the HbA1c variable and the CHOL/HDL variable. This indicates that there is a positive correlation between the HbA1c variable and the CHOL/HDL variable.

Table 4. Correlation Test between HbA1c and CHOL/HDL, LDL/HDL, TG/HDL, Apo B/Apo A-1 in Type 2 DM

Variable	CHOL/HDL		LDL/HDL		TG/HDL		Apo B/Apo A-1	
HbA1c	r =	0.298	r =	0.393	r =	0.181	r =	0.308
	p =	0.021	p =	0.002	p =	0.165	p =	0.017
	n =	60	n =	60	n =	60	n =	60

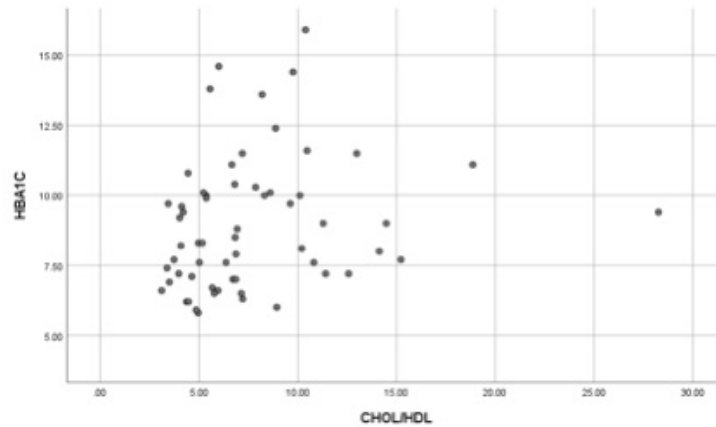


Figure 1. Scatterplot of HbA1c and CHOL/HDL

Correlation Test between HbA1c and LDL/HDL in Type 2 DM

The Spearman correlation test between HbA1c and LDL/HDL levels in type 2 DM subjects obtained a p-value = 0.002. Since p-value $< \alpha$ (alpha=0.05), it can be concluded that there is a significant correlation between HbA1c and LDL/HDL levels in type 2 DM patients (Table 4).

Figure 2 exhibits a linear relationship pattern between the HbA1c and LDL/HDL variables, as

observed from the data distribution. This indicates that there is a positive correlation between the HbA1c variable and the LDL/HDL variable.

Correlation Test between HbA1c and TG/HDL Levels in Type 2 DM

The Spearman correlation test between HbA1c and TG/HDL levels in type 2 DM subjects obtained a p-value = 0.165. Because p value $> \alpha$ (alpha=0.05), it

CORRELATION OF HbA1c WITH RATIO OF TOTAL CHOLESTEROL/HDL, LDL/HDL, TG/HDL

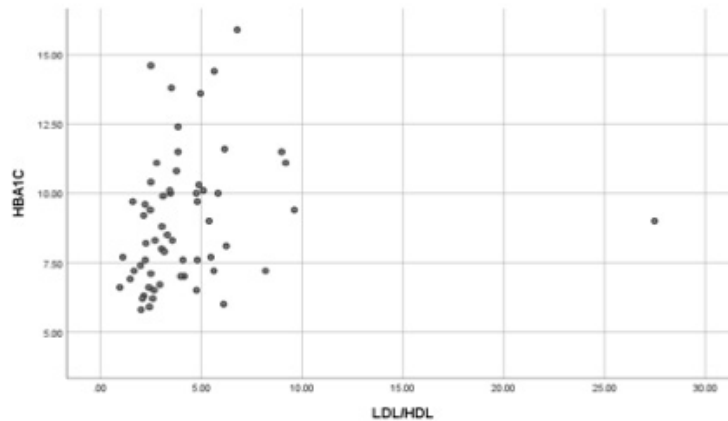


Figure 2. Scatterplot of HbA1c and LDL/HDL

can be concluded that there is no significant correlation between HbA1c and TG/HDL levels in patients with type 2 DM (Table 4).

The scatterplot in Figure 3 demonstrates a random relationship pattern between the data of the HbA1c variable and the TG/HDL variable, as evident from the data distribution. This indicates a positive but not non-significant correlation between the HbA1c and TG/HDL variables.

Correlation Test between HbA1c and Apo B/Apo A-1 in Type 2 DM

The results of the Spearman correlation test between HbA1c and Apo B/Apo A-1 levels in type 2 DM subjects showed a p-value = 0.017. Since p-value < α (alpha=0.05), it can be concluded that there is a significant correlation between HbA1c and Apo B/Apo A-1 levels in type 2 DM patients (Table 4).

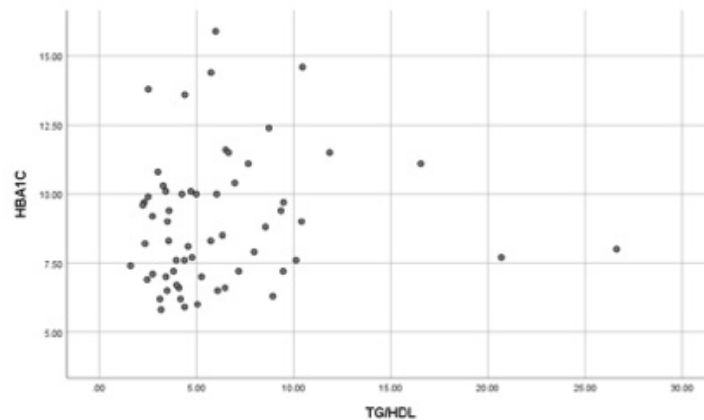


Figure 3. Scatterplot of HbA1c and TG/HDL

The scatterplot in Figure 4 above exhibits a linear relationship pattern between the HbA1c and Apo B/Apo A-1 variables, as evident from the data

distribution. This indicates a positive correlation between the HbA1c and Apo B/Apo A-1 variables.

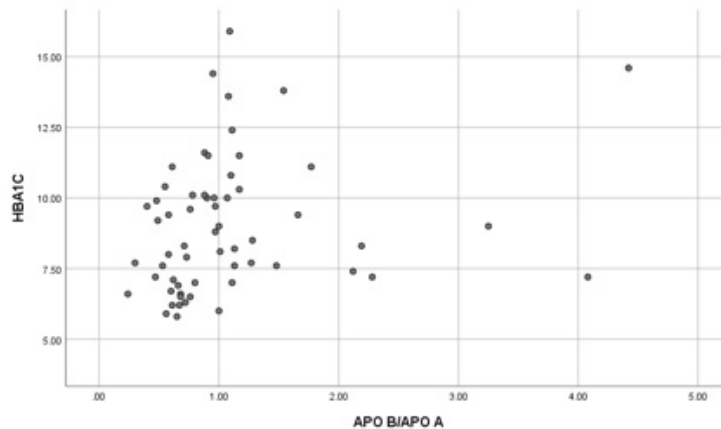


Figure 4. Scatterplot of HbA1c and Apo B/Apo A-1.

DISCUSSION

The current study determined the correlation of HbA1c with the ratio of total cholesterol/HDL, LDL, HDL, TG/HDL, and Apolipoprotein B/Apolipoprotein A-1 in type 2 DM subjects that was conducted from April to May 2023. The findings of this study revealed that the mean values of total cholesterol/HDL, LDL/HDL, TG/HDL, and Apo B/Apo A-1 ratios were higher in the uncontrolled type 2 DM group with $HbA1c \geq 7$. This is in line with the study of Pushparaj and Kirubakaran (2014), who indicated that the prevalence of inadequate glycemic control ($HbA1C \geq 7$) in the study population was 66 %. The mean values of all the lipid parameters and atherogenic risk ratios were found to be higher in the $HbA1C \geq 7$ groups and were statistically highly significant. Therefore, they concluded that HbA1C is not only a marker of chronic exposure to hyperglycemia but can also predict dyslipidemia (18). In addition, Zheng et al. investigated the associations between the ApoB/ApoA-I ratio and the risk of type 2 DM and pre-diabetes in a Chinese population and

found that the increase in the Apo B/Apo A-1 ratio was associated with increased HbA1c levels. In addition, ApoB/ApoA-I ratios were significantly increased across the spectrum of normal glucose tolerance, pre-diabetes, and T2DM (19).

HbA1c provides a value that can be used for monitoring hyperglycemia and correlates well with the risk of long-term complications associated with diabetes. Diabetes mellitus often causes macrovascular and microvascular complications (20). Insulin resistance primarily contributes to macrovascular complications, whereas chronic hyperglycemia is responsible for the onset of microvascular complications. This vascular damage begins with endothelial dysfunction due to glycosylation and oxidative stress on endothelial cells. Endothelial dysfunction is key to maintaining vascular homeostasis (21).

The Spearman correlation test results showed no significant correlation between HbA1c and TG/HDL levels. This is in correspondence with the results reported by Yan et al., who showed that when HbA1c increased, the TC/HDL and LDL/HDL ratios

also increased. Moreover, a significant correlation was observed between the HbA1c ratio and TC/HDL ($P=0.039$) and between the LDL/HDL and HbA1c ($P=0.003$). However, there was no significant correlation between HbA1c levels and TG/HDL ratio ($P=0.301$) (22). The study conducted in Indonesia to assess the correlation between the ratio of TG/HDL and HbA1c levels yielded a p -value = 0.250 ($p > 0.05$), suggesting that there is no significant relationship between HbA1c levels with TG/HDL levels (23).

The absence of a significant correlation between the TG/HDL ratio and HbA1c levels could be attributed to various influencing factors, including the use of commonly prescribed metformin medication in treating diabetic patients. Considering the pathogenesis of type 2 DM, it is likely that it plays the dominant factor in increasing the TG/HDL ratio. As the HbA1c value increases, the TG/HDL ratio rises. This can be attributed to the excess glucose in the blood, which will be stored as fat, particularly triglycerides. Consequently, if glycemic control is poor (indicated by a high HbA1c value), there will be an increase in the levels of blood glucose. Furthermore, glucose will be converted into triglycerides, increasing triglyceride levels. A decrease will follow an increase in triglyceride levels in HDL levels in the blood.

Theory suggests that individuals with diabetes will experience significant increases in various lipid components, including total cholesterol, LDL, and triglycerides. As stated before, HbA1c serves as a valuable long-term indicator of blood sugar control and a reliable predictor of lipid profile. The utilization of HbA1c for monitoring glycemic control may offer an additional advantage by enabling the identification of diabetic patients who are at a greater risk of developing cardiovascular complications (23).

The relationship between HbA1c and Apo B/Apo A-1 levels in individuals with type 2 DM indicates a significant correlation between HbA1c and Apo B/Apo A-1 levels in patients with type 2 DM. In the same way, Zheng et al. revealed a positive association between the Apo B/Apo A-1 ratio and the risk of diabetes in patients (19). Furthermore, the study on Apolipoprotein-related mortality risk (AMORIS) which examined the Apo B/Apo A-1 ratio suggested that the concentration of apolipoprotein B (Apo B) and apolipoprotein A-1 (Apo A-1), as well as the Apo B/Apo A-1 ratio, can enhance the prediction of cardiovascular disease risk (11).

CONCLUSION

According to the results, it can be concluded that uncontrolled type 2 DM subjects exhibit higher ratios of CHOL/HDL, LDL/HDL, TG/HDL, and Apo B/Apo A-1 compared to controlled type 2 DM subjects. Significant correlations were observed between HbA1c levels and CHOL/HDL, LDL/HDL, and Apo B/Apo A-1 ratios in type 2 DM subjects. However, no significant correlation was found between HbA1c levels and TG/HDL ratio.

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Declaration of competing interest

All authors declare there is no conflict of interest in this study.

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