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Correlation of Lipid Profile and Apolipoprotein B/A-I Ratio with Insulin Resistance in Non-Diabetes Mellitus Subjects

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ABSTRACT

Obesity is an increase in body mass due to excess fat, as measured by body mass index. Obesity affects metabolism, such as insulin resistance, which promotes the development of chronic diseases. An alternative method used in evaluating insulin resistance is the HOMA-IR. The lipid profile ratio and Apo B/Apo A-I ratio can be considered as additional assessments, especially in patients at high risk of cardiovascular disease such as diabetes. This study aims to evaluate the correlation between lipid profile ratio and Apo B/Apo A-I ratio with insulin resistance in non-diabetes mellitus adult subjects. The method used in this study was a cross-sectional study involving a total of 80 non-diabetes mellitus adult subjects, 42 obese and 38 non-obese, consisting of 38 males and 42 females. The results of the comparative study showed significant differences between non-obese vs. obese non-diabetes mellitus adult subjects on the CHOL/HDL (4.64±2.18 vs. 5.23±1.87; p=0.045) ratio, TG/HDL (2.38±1.20 vs. 3.18±1.77; p=0.013), and Apo B/Apo A-I (0.58±0.17 vs. 0.66±0.17, p=0.035) but no significant difference of LDL/HDL (p=0.117). A moderate correlation was obtained between TG/HDL, CHOL/HDL, and Apo B/Apo A-I with HOMA-IR (p<0.001, r=0.402; p=0.005, r=0.308; p=0.019, r=0.261) and a weak correlation between LDL/HDL with HOMA-IR (p=0.037, r=0.233) in non-diabetes mellitus adult subjects. It was concluded that there was a significant correlation between lipid profile ratio and Apo B/Apo A-I ratio with insulin resistance in non-diabetes mellitus adult subjects.

Keywords: Obesity, insulin resistance, lipid profile ratio, Apo B/Apo A-I ratio

INTRODUCTION

The most prevalent chronic illness in the world is obesity. More than one billion people will reportedly be obese by the year 2030, with greater rates of fatalities from obesity-related causes and its comorbidities, which include diabetes, chronic kidney disease, several cancers, and cardiovascular illness. One hundred and sixty million disability-related deaths and five million fatalities every year on average.[1] Obesity is defined as an increase in total body mass due to excess fat, as measured by body mass index. Obesity is a complex disease resulting from the interaction between genetic background, behavior, and environment. Once the individual is affected, metabolic changes, such as insulin resistance can exacerbate the condition and trigger a vicious cycle that leads to further health problems and contributes to various chronic diseases, including cancer, diabetes, metabolic syndrome, and cardiovascular disease.[2,3]

There are several causes of obesity, the main cause is excess energy stored far more than the energy used by the body. Excess energy is stored in fat cells, thereby developing the pathology of obesity. The pathogenesis of obesity involves the regulation of caloric utilization, appetite, and physical activity, but has complex interactions with the availability of the health care system, the role of socioeconomic status, and the underlying heredity and environment.[4] Excess energy absorption induces adipocyte hypertrophy, hyperplasia, and the formation of visceral fat in other non-adipose tissues increasing cardiovascular and liver disease. Adipose tissue can also secrete adipokines and inflammatory cytokines to affect the local microenvironment, induce insulin resistance, and hyperglycemia, and activate associated inflammatory signaling pathways.[5]

Type 2 diabetes and obesity are both linked to insulin sensitivity, but most obese people do not have insulin resistance with hyperglycemia. Under

typical conditions, the beta cells of the pancreas increase the amount of insulin released to keep blood sugar levels normal. During normal life, insulin sensitivity varies, and insulin resistance is observed in adolescence, pregnancy, and old age. NEFAs (non-esterified fatty acids) can cause insulin resistance and affect pancreatic beta cell function. Lifestyle changes, such as regular exercise and eating habits, can improve insulin sensitivity.[6]

Insulin resistance is an abnormality in the muscle, adipose, and liver are among the target tissues that have a physiologic response to insulin stimulation. Insulin sensitivity impacts glucose elimination, increasing the synthesis of beta-cell insulin as a coping mechanism and hyperinsulinemia, higher than normal insulin levels are necessary to maintain normal insulin function.[7,8]

The quantitative method using a hyperinsulinemic normal glucometer is the ideal method for identifying insulin resistance. However, the process is very complicated, cumbersome, expensive, and time-consuming to implement. The establishment of the so-called "Homeostasis Model Assessment of IR" (HOMA-IR) is usually used as a substitute and is a more convenient, faster, and cheaper way to test for insulin resistance.[9]

High levels of free fatty acids in obese individuals have several negative effects in addition to reduced glucose utilization and increased hepatic glucose production. Free fatty acids also affect lipid metabolism. As a result, the liver produces less HDL and more LDL, which are two different types of lipoproteins. The smaller particles (such as LDL) are more atherogenic than larger particles and are able to breach the arterial wall more effectively. They are also more prone to oxidation and glycation. Although atherogenic agents are at greater risk due to smaller LDL particles, LDL cholesterol levels do not change significantly.[10]

An apolipoprotein known as apo B-100 (apo B) is found in LDL, which makes up 60-70% of total cholesterol in the blood. The most important atherogenic lipoprotein and the one that must be addressed in the treatment of dyslipidemia is LDL cholesterol. 20-30% of total blood cholesterol is HDL cholesterol, ApoAI and A-II.[10] Several clinical and epidemiological studies have shown that the ratio of Apo B to Apo AI is a better marker of cardiovascular diseases compared to lipids and lipoproteins.[11] The ratio of particles that cause and prevent heart disease is represented by the higher the ApoB/ApoA-I ratio, the greater the risk for cardiovascular disease. Insulin resistance has a high correlation with the apoB/apoA1 ratio.[12] In their research, Gao *et al*. suggested that the ApoB/ApoA-I ratio is good information for predicting insulin resistance. Powered by research from Lind *et al.* regarding ApoB and ApoA-I also showed that the ApoB/ApoA-I ratio is an ideal marker for lipid disorders and is associated with Insulin Resistance (IR) and metabolic syndrome.[13]

This study compares the results of the ratio of lipid profiles and the ratio of apolipoprotein B to apolipoprotein AI with insulin resistance in non-diabetic adult subjects.

METHODS

A cross-sectional study with obese or nonobese in nondiabetic adult subjects. This study was carried out at the UPK Laboratory at the South Sulawesi Provincial Health Office, the Clinical Pathology Laboratory at Hasanuddin University Hospital (RSUH), and the Clinical Pathology Laboratory at Labuan Baji Hospital. The Health Research Ethics Commission's (KEPK) ethics permission was required for this study by the Faculty of Medicine, Hasanuddin University, Hasanuddin University Hospital (RSUH), and Wahidin Sudirohusodo Hospital (RSWS), with ethical number 201/UN4.6.4.5.31/PP36/2023.

Samples collected from venous blood (5 ml), were allowed to clot for 30 minutes, then were centrifuged for 10 minutes at 3000 rpm to obtain serum. The samples were then analyzed by examining total cholesterol, HDL, LDL, triglycerides, Apolipoprotein B, Apolipoprotein AI, fasting blood sugar, and insulin, and then calculating the ratio of CHOL/HDL, LDL/HDL, TG/HDL, ApoB/ApoA-I, and HOMA-IR. The Cobas C111 using the enzymatic method was used to calculate the amount of cholesterol, HDL, LDL, and triglycerides; the Cobas C311 equipped with an immunoturbidimetric technique was used to calculate apolipoprotein B and apolipoprotein I levels; the ABX Pentra used the enzymatic method to measure the levels of glucose; and the Cobas E601 used the sandwich method to measure the levels of insulin.

The data was processed using the Windows application SPSS Version 22. The data was analyzed by including all factors, including age, gender, and laboratory testing. The data was examined determining whether or not the distribution was normal using the Kolmogorov-Smirnov test. Data was analyzed bivariate using Mann-Whitney and independent T-tests for comparison, followed by correlation testing using Spearman's test. If $p < 0.05$, the test results were significant.

RESULTS AND DISCUSSIONS

This study involved non-diabetes mellitus subjects divided into obese and non-obese groups, with as many as 80 subjects in total, consisting of 38 (47.5%) male and 42 (52.5%) female subjects. The subjects of the study consisted of 38 (47.5%) non-obese groups and 42 (52.5%) obese (Table 1).

Comparison of CHOL/HDL, LDL/HDL, TG/HDL, ApoB/ApoA-I ratio, and HOMA-IR in non-obese and obese adults of non-diabetes mellitus subjects are shown in Table 2. Statistical tests found that the mean ratio of CHOL/HDL, LDL/HDL, TG/HDL, ApoB/ApoA-I, and HOMA-IR in obese non-diabetic mellitus adult subjects were higher than in non-obese non-diabetic mellitus adult subjects (4.64±2.18 vs. 5.23±1.87; 2.50±0.90 vs. 2.82±0.87, 2.38±1.20 vs. 3.18±1.77; 0.58±0.17 vs. 0.66±0.17 and 1.47±0.80 vs. 3.34±4.37). There were significant differences between the ratios of CHOL/HDL, TG/HDL, Apo B/Apo A-I, and HOMA-IR in non-obese and obese non-DM adult subjects (p=0.045, p=0.013, p=0.035 and p=0.000), and there was no discernible variation between LDL/HDL (p= 0.117).

Correlation of CHOL/HDL ratio with HOMA-IR, LDL/HDL ratio with HOMA-IR, TG/HDL ratio with HOMA-IR, ApoB/ApoA-I ratio with HOMA-IR in non-diabetic mellitus adult subjects are shown in Table 3. the Spearman correlation test, between ratio of CHOL/HDL and HOMA-IR showed a strong association (p=0.05, r=0.308), LDL/HDL with HOMA-IR (p=0.037, r=0.233), TG/HDL with HOMA-IR (p=0.000, r=0.402) and Apo B/Apo-I with HOMA-IR (p=0.19, r=0.261).

Table 1. Characteristics of research subjects

Variable	N = 80 (%)	Mean±SD	Median	Min-Max
Age (years old)	-	31.40±4.096	31	22-40
18 – 23 years old	2 (2.5)	-	-	-
24 – 29 years old	27 (33.8)	-	-	-
30 – 35 years old	35 (43.8)	-	-	-
36 – 40 years old	16 (20.0)	-	-	-
Gender				
Male	38 (47.5)	-	-	-
Female	42 (52.5)	-	-	-
Group				
Non-obese	38 (47.5)	-	-	-
Obese	42 (52.5)	-	-	-
Anthropometry				
BW (kg)	-	69.18±14.74	70,>80	42.4–125.0
Height(cm)	-	162.13±8.89	162.00	144-186
BMI (kg/m^2)	-	26.21±4.77	25.51	16.98–39.50
Laboratory results				
CHOL (mg/dL)	-	210.00±61.90	202,33	109.81-596.41
Chol-HDL (mg/dL)	-	44.79±10.00	44,22	21.83–75.62
Chol-LDL (mg/dL)	-	113.87±27.29	113.87	46.30–178.33
TG (mg/dL)	-	116.26±49.53	105,53	50.89–342.16
CHOL/HDL ratio	-	4.95±2.03	4.69	1.82–15.63
LDL/HDL ratio	-	2.67±0.89	2.61	0.62–5.48
TG/HDL ratio	-	2.80±1.57	2.43	0.73 – 11.33
ApoB (mg/dL)	-	100.20±23.25	102.90	51.10–147.10
ApoA-I (mg/dL)	-	164.25±23.59	162.30	118.10–223.60
ApoB/ApoA-I ratio	-	0.62 ± 0.17	0.62	0.30–0.99
Fasting glucose(mg/dL)	-	68.73±13.91	65,15	48.6–106.8
Insulin (uIU/mL)	-	13.91±15.82	9,91	2.6–128.20
HOMA-IR	-	2.45±3.33	1.66	0.34–28.55

Source: Primary data

Information: BW = Body Weight, BMI = Body Mass Index, ApoB = Apolipoprotein B, ApoA-I=Apolipoprotein A-I, CHOL=Total Cholesterol, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, TG=Triglyceride, Median=Middle Value, Mean=Average, Min=Minimum, Max=Maximum, SD=Standard Deviation

Table 2. Comparison of CHOL/HDL, LDL/HDL, TG/HDL, ApoB/ApoA-I ratio and HOMA-IR in non-diabetes mellitus non-obese and obese adults

Variable	N		Non-Obese		Obese		p
	Non-Obese	Obese	Mean±SD	Median	Mean±SD	Median	
CHOL/HDL	38	42	4.64±2.18	4.18	5.23±1.87	4.88	0.045*
LDL/HDL	38	42	2.50±0.90	2.37	2.82±0.87	2.75	0.117**
TG/HDL	38	42	2.38±1.20	2.09	3.18±1.77	3.07	0.013*
ApoB/ApoA-I	38	42	0.58±0.17	0.55	0.66±0.17	0.67	0.035**
HOMA-IR	38	42	1.47±0.80	1.39	3.34±4.37	2.37	0.000*

Source: Primary data
Description: p = *Mann-Whitney test, ** Independent T-test

Table 3. Correlation of CHOL/HDL, LDL/HDL, TG/HDL, ApoB/ApoA-I ratio with HOMA-IR in non-diabetes mellitus adult subjects

Variable	HOMA-IR		
	r	P	n
CHOL/HDL	0.308	0.005	80
LDL/HDL	0.233	0.037	80
TG/HDL	0.402	0.000	80
ApoB/ApoA-I	0.261	0.019	80

Source: Primary data
Description: r = correlation coefficient, p = Spearman correlation test

This study determined the correlation between the ratio of lipid profiles and apolipoprotein B to apolipoprotein A-I ratio in non-diabetic adult subjects, conducted from April to May 2023. This study involved 80 non-diabetic adult subjects in total, consisting of 38 male and 42 female subjects.

Excess and buildup of body fat contribute to obesity. The pathogenic response that extra fat might cause in a person's adipocytes and adipose tissue is a factor in metabolic diseases. In accordance with research interview data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES), clinical examinations, laboratory examinations, and the SHIELD study aim to enhance the early detection and management of risk factors for diabetes, which used a screening questionnaire in 2004, weight gain is linked to a higher incidence of hypertension, type 2 diabetes, and dyslipidemia.[14]

Abnormalities in lipid metabolism are frequently seen in the obese. Dyslipidemia affects 60–70% of the obese. Lipid abnormalities in obese adults include high levels of apolipoprotein B, non-HDL-C, VLDL, and blood triglycerides. Reduced clearance of triglyceride-rich lipoproteins and increased synthesis of VLDL particles in the liver are the two factors contributing to the rise in blood triglycerides. Serum triglycerides are increased, and HDL values are typically low. LDL levels are frequently within the normal range, while sdLDL levels have increased.[15]

For several reasons, it is suspected that these small-diameter LDL particles are more proatherogenic than big LDL particles. Due to their reduced affinity for the LDL receptor, sdLDL particles circulate for a longer period. Furthermore, compared to large particles, these small ones penetrate the arterial wall readily and bind more tightly trapping the intra-arterial proteoglycans.[15] The affinity of sdLDL particles to the LDL receptors is reduced, causing a longer circulation duration. The intra-artery proteoglycans are trapped in the arterial walls by these little particles and bind more strongly than big particles, also penetrating the artery walls more easily and attaching securely to them. Obesity might affect how the body uses lipids, depending on where the adipose tissues are located. Higher triglyceride and lower HDL levels are linked to increases in visceral and subcutaneous adipose tissue, while higher levels of subcutaneous adipose tissue are linked to reduced triglycerides. There are correlations between increases in visceral adipose tissue, subcutaneous adipose tissue in the upper body, and insulin resistance that might affect lipid changes.[15]

Diabetes or metabolic syndrome patients may have normal LDL cholesterol levels but an atherogenic lipid profile, as evidenced by a high ratio of ApoB/ApoA-I. Heart disease is strongly predicted by the ApoB/ApoA-I ratio. Furthermore, the findings of Lind et al. study on ApoB and ApoA-I revealed that the ApoB/ApoA-I ratio is an ideal marker for lipid diseases and is related to Insulin Resistance (IR) and metabolic syndrome.[16] A high ApoB/ApoA-I ratio value surpassing the limit, indicates that the plasma contains a high level of cholesterol. This cholesterol adheres to the arterial walls, causing cardiovascular disease risk factors and atherogenesis. While lowApoB/ApoA-I ratio, indicates a decreased transport of cholesterol to the peripheral blood, therefore the transport of cholesterol to the liver is larger, which is beneficial to the body since the risk of

cardiovascular disease is reduced. According to Apolipoprotein-related Mortality Risk (AMORIS) research, a high ApoB/ApoA-I ratio predicts a higher risk of fatal myocardial infarction and is a better predictor than LDL, total cholesterol, and triglycerides.[17]

The outcomes of the Spearman correlation analysis revealed a correlation between the ratio of lipid profiles (CHOL/HDL, LDL/HDL, TG/HDL) and the ratio of ApoB/ApoA-I with HOMA-IR in non-diabetic adult subjects. Kansal *et al*. discovered a significant rise in the ratios of TC, LDL, TG, and VLDL, as well as the ratios of TG/HDL and LDL/HDL, were higher when comparing prediabetic people to healthy, normal controls ($p<0.05$), while HDL values were lower in prediabetic individuals. Pre-diabetics had considerably lower levels than controls ($p< 0.05$). In a similar study, the TG/HDL ratio and Metabolic Syndrome (MS) have a positive relationship, according to Spanish researchers from the Metabolic Syndrome in Active Subjects (MESYAS) group. They discovered that the male subjects were more likely to have MS (18.8%) than females (6.1%), and each component of MS was associated with a higher mean TG/HDL ratio of 2.50 to 2.2. The TG/HDL ratio was two times higher in MS subjects compared to controls ($p<0.001$). A TG/HDL ratio of >2.75 in males and >1.65 in females was found to be substantially predictive of MS, with a sensitivity of 80% and a specificity of 78%. As a result, TG/HDL is regarded as one of the most useful markers for identifying insulin-resistant conditions.[18] In another study conducted by Behiry *et al*., the triglyceride/HDL ratio obtained a $p=0.01$, which means that there is a significant correlation between triglyceride and HDL and HOMA-IR.[19]

Research by Qu *et al.* states that the ratio of triglycerides/HDL can be used to detect complications of hypertension, diabetes, and obesity. Research by Aryal *et al.* states that an increase in the ratio of triglycerides/HDL and LDL /HDL indicates future cardiovascular disease. People with type 2 diabetes mellitus have an increased risk of illness. An increase in the ratio of triglycerides/HDL can predict insulin resistance, LDL particle size, the presence of small, dense LDL, and the risk of heart disease.[20]

Kimm *et al*. discovered that in individuals without MS, the lipid ratios of TG/HDL, Insulin resistance, and MS were consistently correlated with LDL-C/HDL, TG/HDL, and TG and HDL. Kohli et al. conducted a study in India 121 healthy, young, and middle-aged Indian males between the ages of 25 and 44 were studied for their TG/HDL ratio patterns, as well as their relationships with lipids, other non-lipid factors, and markers of adiposity including body mass index, body fat, and others.[21] The apoB/apoA-I ratio is calculated by comparing the levels of apolipoprotein B (a protein found in LDL) with apolipoprotein A-I (found in HDL). The ApoB/ApoA-I ratio describes the balance between LDL cholesterol (atherogenic) and HDL cholesterol (antiatherogenic), both of which are substantial predictors of heart disease.[17] Afandi *et al.* study on 100 patients with type 2 diabetes mellitus, found a significant association between the HOMA-IR value and the ratio of apoB/apoA-I ($r=0.610$, $p<0.05$) The balance between HDL (antiatherogenic) and LDL (atherogenic) cholesterol is shown by the ApoB/ApoA-I ratio, which are strong markers in predicting heart disease.[17]

The findings of this study can be explained in a variety of ways. A key hormone called insulin controls cell metabolism in a variety of bodily tissues. Insulin sensitivity is characterized by deficiencies in glucose absorption and oxidation, decreased glycogen production, and the capacity to control lipids.[22]

An increased risk of micro- and macrovascular diseases is associated with insulin resistance, a crucial metabolic component of the metabolic syndrome and obesity macrovascular problems. Insulin resistance affects triglyceride, HDL, LDL, and VLDL metabolism via many mechanisms. In insulin resistance, lipolysis increases, increasing free fatty acids in plasma, which increases free fatty acid absorption into the liver. hyperinsulinemia increases brand new transcription factor Sterol Regulatory Element Binding Protein (SREBP1c) that turns on genes involved in lipogenesis in the liver, increasing TG production in the liver. Cholesterol ester protein transferase and hepatic lipase are also elevated, resulting in elevated VLDL, which eventually transforms into tiny, dense LDL. This rise in VLDL levels promotes an increase in HDL catabolism, resulting in low HDL levels. Apart from transporting fat to the liver, HDL has been demonstrated to block LDL oxidation and adhesion molecules, hence preventing foam cell production and, as a result, the development of atherosclerosis. The protective impact is considerably reduced when HDL levels are low.[22,23]

Based on results and theories related to how insulin resistance is caused, examination of markers for the ratio of lipid profile ratios and Apolipoprotein B/Apolipoprotein A-I ratio can be an early diagnostic test to detect the presence of insulin resistance if there is no diagnostic support in the form of a hyperinsulinemic-euglycemic clamp is considered the industry standard for detecting insulin resistance as well as HOMA-IR, a homeostatic model evaluation for insulin resistance as an alternative investigation.

CONCLUSIONS AND SUGGESTIONS

The study's findings suggest that the CHOL/HDL, LDL/HDL, TG/HDL, and ApoB/ApoA-I ratios were higher in non-diabetic adults with obesity than non-diabetic adults without obesity. There is a significant correlation between the ratio of the lipid profile (CHOL/HDL, LDL/HDL, and TG/HDL) and the ratio of ApoB/ApoA-I in non-diabetic adult subjects. It is suggested to future researchers to analyze the relationship between small-density LDL and insulin resistance in non-diabetic mellitus adult subjects.

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