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Correlation between Epicardial Adipose Tissue Thickness and Insulin Resistance in Non-Diabetic Young Adults

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Abstract

Introduction: Insulin resistance is a major contributor to mortality in adult populations worldwide, with alarming projections for the future. This condition can lead to hyperglycemia, hypertension, dyslipidemia, hyperuricemia, inflammation, endothelial dysfunction, a prothrombic state, type 2 diabetes mellitus, and cardiovascular disorders. Epicardial adipose tissue (EAT) has been linked to various conditions such as obesity, diabetes, hypertension, and coronary heart disease. This study investigated the correlation between EAT thickness and insulin resistance in non-diabetic young adults in Makassar.

Methods: This observational cross-sectional study included 89 non-diabetic young adults who met the inclusion criteria. The study was conducted at Wahidin Sudirohusodo General Hospital and Hasanuddin University Teaching Hospital from September to November 2022. Epicardial fat thickness was measured using the GE Vivid E95 echocardiograph, and insulin resistance was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).

Results: This study found a positive correlation between increased EAT thickness and insulin resistance. The mean EAT thickness in the insulin-resistant group was 2.36 ± 0.78 mm, while the mean EAT thickness in the non-insulin-resistant group was 1.72 ± 0.839 mm. Spearman correlation analysis confirmed a significant positive correlation between EAT thickness and HOMA-IR (R-value 0.320, p = 0.002).

Conclusion: Our findings suggest that individuals with insulin resistance have thicker epicardial adipose tissue. The association between EAT and insulin resistance may be influenced by other factors such as obesity and dyslipidemia.

Keywords: epicardial adipose tissue, insulin resistance, healthy adults.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in individuals with metabolic syndrome and insulin resistance. Excess caloric intake leads to fat accumulation not only in subcutaneous tissue but also in other organs such as the liver, pancreas, muscles, and heart, contributing to obesity. Fat accumulates around the heart as intramyocardial triglyceride (IMC-TG), extra-pericardial adipose tissue (PAT), and epicardial adipose tissue (EAT). Due to its proximity to the heart and coronary arteries, EAT has been the primary focus of research on cardiac fat deposition in humans.[1] Studies have linked ectopic fat deposition to lipotoxicity, local and systemic metabolic dysfunction, insulin resistance, heart failure, atherosclerosis, and systemic inflammation.[1]

Epicardial adipose tissue (EAT) is visceral adipose tissue located between the myocardial and visceral pericardium in the atrioventricular and interventricular grooves of the adult human heart.[2,3] It receives blood supply from the coronary arteries and is situated both physically and functionally close to the myocardium and cardiac arteries.[4] The majority of this tissue is restricted to the base and apex of the heart.[5] EAT is derived from splanchnopleuric mesoderm and comprises immune, stromovascular, adipocyte, and ganglia cells. While EAT makes up only 1% of total body fat mass, it plays a crucial role in the pathophysiology of obesity-related cardiovascular diseases,[2] as it has been strongly associated with acute coronary syndrome, atherosclerosis, and metabolic diseases. Visceral fat deposits from EAT constitute approximately 20% of the total mass of the heart and 80% of the total surface tissue of the heart.[6]

Physiologically, EAT acts as a cardioprotective agent by regulating free fatty acid levels in coronary arteries, preventing toxic lipid accumulation in cardiomyocytes, and producing anti-inflammatory adipokines.[4,5] It also provides mechanical protection to the heart.[7,8] Additionally, it possesses a thermogenic function, protecting the heart from hypothermia. Based on embryological, histological, and functional aspects, adipose tissue is divided into two large groups: white and brown adipose. Epicardial adipose tissue is primarily white adipose tissue but exhibits characteristics of brown adipose tissue, releasing various mediators through gene expression.[5,7,9]

Epicardial adipose tissue also possesses endocrine, paracrine, vasocrine, and inflammatory properties linked to metabolic syndrome, insulin resistance, coronary artery disease, and hypertension. For this reason, it is essential to measure EAT thickness. Cardiovascular magnetic resonance imaging (MRI), cardiac computed tomography (CT), and transthoracic echocardiography (TEA) are all viable methods to measure EAT thickness.[10] TEA is the preferred method for evaluation due to its ease of use, affordability, lack of radiation exposure, speed, and reproducibility.[9]

Epicardial adipose tissue has been linked to several conditions, including obesity, diabetes, hypertension, and coronary heart disease. Patients with diabetes have a dysfunction in their beta (β) cells, making them less responsive to insulin exposure. Insulin is a peptide hormone generated by β cells in the pancreatic islets of Langerhans. It regulates protein, lipid, and carbohydrate metabolism, aids in cellular glucose uptake, and stimulates cell division and development through its

mitogenic activities to maintain normal blood glucose levels.[11] Insulin resistance is the main mechanism causing the emergence of diabetes.[11]

Insulin resistance is defined as a condition in which normal or elevated insulin levels lead to an attenuated biological response, classically referring to impaired sensitivity to insulin-mediated glucose disposal.[11] Insulin resistance is a major contributor to mortality in adult populations worldwide, with an estimated prevalence of 33% in adults in the United States by 2050.[12]

Insulin resistance is also defined as an impaired biological response to insulin stimulation in target tissues, particularly the liver, muscle, and adipose tissue. This impaired glucose disposal leads to compensatory increases in beta cell insulin production and hyperinsulinemia.[13] Insulin resistance is one of the leading causes of death in adult populations worldwide, with alarming projections for its prevalence in the future.[12] It can trigger a cascade of health issues, including hyperglycemia, hypertension, dyslipidemia, hyperuricemia, increased inflammatory markers, endothelial dysfunction, a prothrombic state, type 2 diabetes mellitus, and cardiovascular disorders, including excessive EAT accumulation.[1,13]

Insulin resistance is a major pathogenic factor in the development of metabolic syndrome and cardiovascular disease. Excessive EAT accumulation in insulin-resistant patients has been demonstrated in several publications. The insulin-dependent glucose uptake and anti-lipolytic function of insulin are reduced in epicardial adipocytes, even under physiological conditions, which is linked to the need to maintain high lipolysis activity. Several publications report a similar

decrease in insulin sensitivity of epicardial adipocytes in patients with type 2 diabetes.[14]

In a 2013 study by Narumi *et al*. involving 102 subjects with insulin resistance and 88 subjects with coronary artery disease, EAT volume was independently associated with insulin resistance and coronary artery disease even in non-obese subjects without metabolic syndrome.[15] Another 2013 study by Iacobellis and Leonetti on 30 obese subjects with a body mass index of 43.91 kg/m^2 who underwent a transthoracic echocardiogram to evaluate the thickness of EAT found that EAT is significantly related to insulin resistance in obesity.[16]

A 2014 cross-sectional study by Muñoz *et al*. involving 34 post-menopausal women found that EAT measured by echocardiography was related to adipose tissue and other obesity parameters. EAT is higher in post-menopausal women with metabolic syndrome. Therefore, echocardiographic assessment of epicardial fat may also serve as a simple and reliable marker for cardiovascular risk in post-menopausal women.[17]

Given this background, this study aims to evaluate the relationship between EAT thickness and insulin resistance in non-diabetic young adults in Makassar. By elucidating this relationship, we hope to contribute to the prevention and management of insulin resistance.

Methods

Study design and population

This cross-sectional study was conducted at the Hasanuddin University Teaching Hospital and the Integrated Heart Center of Dr. Wahidin Sudirohusodo

Makassar General Hospital from September 2022 until the required sample size is met.

The study population consisted of participants in the Hasanuddin University Internal Medicine Residency Program who met the following inclusion criteria: age between 25 and 40; non-pregnant; no history of diabetes mellitus; and willing to participate and provide informed consent. Non-diabetic is defined as an individual who does not have a history of diabetes mellitus, fasting blood glucose (FBG) level < 126 mg/dL, and HbA1c level < 6.5%. Dyslipidemia is defined as triglyceride levels ≥ 150 mg/dL in women and men, and total cholesterol ≥ 200 mg/dL, or HDL cholesterol levels < 40 mg/dL for men or < 50 mg/dL for women according to the ATP III definition and IDF criteria for metabolic syndrome. Obesity is defined as body mass index (BMI) ≥ 25 kg/m^2.

Consecutive sampling was employed, meaning that eligible subjects were enrolled in the study until the target sample size of 85 individuals was reached.

Study procedure

1. All subjects underwent a comprehensive medical history interview to ensure that they met the inclusion criteria.
2. The study procedures were explained, and informed consent was obtained from all willing participants.
3. Fasting insulin and blood glucose levels were measured using the Dimension tool and the hexokinase-glucose-6-phosphate dehydrogenase method, and the results were expressed in mg/dL.

4. Epicardial fat thickness (EAT) measurements were carried out at the Integrated Heart Center of Dr. Wahidin Sudirohusodo Makassar General Hospital using the GE Vivid E95 echocardiograph. EAT was identified as an echo-free space in the pericardial layer, and its thickness was measured perpendicularly to the right ventricular free wall from the parasternal long-axis view at end-diastole. Laboratory examinations are conducted to obtain fasting blood glucose and fasting insulin levels.
5. Insulin resistance was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), which is an insulin resistance index calculated from FBG and insulin levels. A high HOMA-IR value indicates a large degree of insulin resistance.

   The HOMA-IR formula used to assess insulin resistance is derived from the following: fasting insulin (microunits/ml) times fasting blood sugar (mg/dl), divided by 405.

   $$\text{HOMA - IR} = \frac{FBG\ (mg/dl) \times FASTING\ INSULIN\ (\mu/ml)}{405}$$

   As there is no established cut-off for insulin resistance, tertiles of HOMA-IR values were used to classify participants in this study.

Statistical analysis

Data analysis was performed using SPSS version 25. Statistical tests and descriptive methods made up the analysis approach. Descriptive statistics were used to summarize the study samples. The mean value, standard deviation (SD), and frequency distribution are calculated using statistical methods. The Chi-Square test was employed to assess relationships between variables. Statistical significance was

set at a p-value < 0.05. Results are presented in narrative form, supplemented with tables and figures.

Results

Characteristics of Research Subjects

This study, conducted from September to November 2022, included subjects in the Hasanuddin University Internal Medicine Residency Program aged 25 to 40 without diabetes mellitus. Initially, 90 subjects were recruited, but one was excluded due to diabetes mellitus, resulting in a final sample of 89 non-diabetic young adults. Anthropometric measurements, blood samples, and echocardiograms were obtained from all participants.

Data were analyzed using SPSS version 25. Statistical analyses include the calculation of descriptive statistics and frequency distribution. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. The Chi-square test, Mann-Whitney test, and Spearman's correlation test were employed to assess relationships between variables. Statistical test results are significant if the p-value is <0.05.

The characteristics of the research subjects can be seen in Table 1.

Table 1. Baseline characteristics of the research subjects

Variable	N = 89
Age	
Mean ± SD	30.99 ± 3.335
Median	**31.00**
Range (min-max)	**20.00-39.00**
BMI	
Mean ± SD	26.17 ± 4.684

Median	**25.24**
Range (min-max)	**18.70-49.23**
Fasting Blood Glucose	
Mean ± SD	88.25 ± 7.265
Median	**87.00**
Range (min-max)	**72.00-116.00**
Fasting Insulin	
Mean ± SD	9.89 ± 9.161
Median	**7.90**
Range (min-max)	**3.00-71.00**
Triglycerides	
Mean ± SD	94.94 ± 54.472
Median	**77.00**
Range (min-max)	**29.00-326.00**
Total Cholesterol	
Mean ± SD	**202.02 ± 38.013**
Median	201.00
Range (min-max)	105.00-289.00
LDL	
Mean ± SD	**134.99 ± 35.103**
Median	133.00
Range (min-max)	47.00-212.00
HDL	
Mean ± SD	**54.24 ± 12.969**
Median	52.00
Range (min-max)	30.00-94.00
HbA1c	
Mean ± SD	5.29 ± 0.338
Median	**5.30**
Range (min-max)	**4.50-6.40**
EAT	
Mean ± SD	1.92 ± 0.869

Median	**2.00**
Range (min-max)	**1.00-5.00**
HOMA-IR	
Mean ± SD	2.24 ± 2.514
Median	**1.67**
Range (min-max)	**0.61-20.32**
Sex	
Man	43 (48.3%)
Woman	46 (51.7%)
Age Group	
20-29 years old	28 (31.5%)
30-39 years old	61 (68.5%)
Obesity	
Yes	49 (55.1%)
No	40 (44.9%)
Dyslipidemia	
Yes	19 (21.3%)
No	70 (78.7%)
HOMA-IR tertile	
Tertile 1	32 (36.0%)
Tertile 2	29 (32.6%)
Tertile 3	28 (31.5%)
Insulin Resistance	
Yes	28 (31.5%)
No	61 (68.5%)

Note: Categorical data is presented in number/frequency and percentage, while numerical data is presented in mean, standard deviation, median, and range**.**

The average age of the study subjects was 30.99 ± 3.34 years, with 46 females (51.7%) and 43 males (48.3%). The mean body mass index (BMI) was 26.17 ± 4.68 kg/m^2. The average fasting blood glucose level was 88.25 ± 7.27

mg/dL, and the average fasting insulin was 9.89 ± 9.16 µU/mL. The mean triglyceride, total cholesterol, and LDL cholesterol levels were 94.94 ± 54.47 mg/dL, 202.02 ± 38.01 mg/dL, and 134.99 ± 35.10 mg/dL, respectively. The mean HbA1C, EAT thickness, HOMA-IR, and HDL cholesterol levels were 5.29 ± 0.34%, 1.92 ± 0.87 mm, 2.24 ± 2.51, and 54.24 ± 12.97 mg/dL, respectively (Table 1).

In terms of HOMA-IR, 32 subjects (36.0%) were in Tertile 1, 29 (32.6%) in Tertile 2 and 28 (31.5%) in Tertile 3. Participants were classified as insulin resistant if they fell into Tertile 3 (28 participants, 31.5%) and as non-insulin resistant if they fell into Tertile 1 or 2 (61 participants, 68.5%) (Table 1).

Spearman's correlation analysis revealed a significant positive correlation between EAT thickness and HOMA-IR in non-diabetic young adults (R = 0.320; p-value = 0.002) (Figure 1).

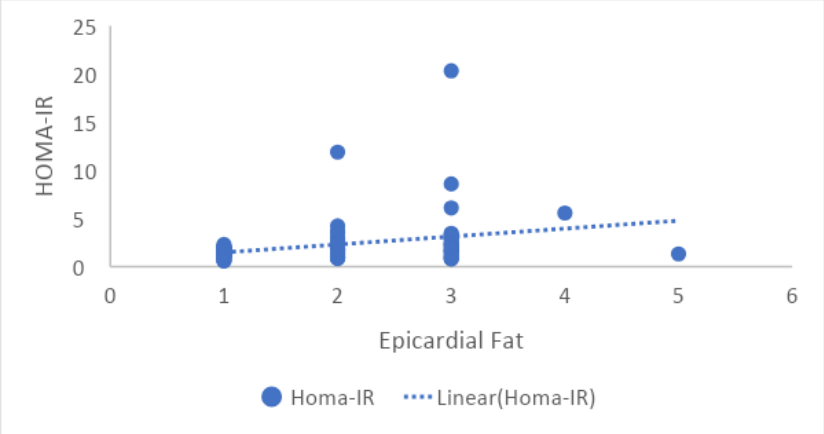

Figure 1. Correlation between Epicardial Adipose Tissue and HOMA-IR

Table 2 presents the results of the Spearman correlation analysis between EAT thickness and HOMA-IR. The Guilford criteria can be used to assess how closely the relationship is. A significant positive correlation was found (R = 0.320, p = 0.002), indicating that higher EAT thickness is associated with higher insulin resistance, as measured by HOMA-IR (low to moderate relationship). To further examine this relationship, HOMA-IR values were divided into tertiles: Tertile 1 (≤ 1.35), Tertile 2 (1.36 - 1.97), and Tertile 3 (≥ 1.98). Subjects in Tertile 3, with HOMA-IR values ≥ 1.98, were considered to have insulin resistance.

Table 2. Comparison of Epicardial Adipose Tissue based on the presence of Insulin Resistance and Correlation Analysis between EAT and Insulin Resistance (HOMA-IR)

Variable	Insulin Resistance		P value
	Yes	**No**	
	N=28	**N=61**	
EAT			**0.001***
Mean ± SD	2.36 ± 0.780	1.72 ± 0.839	
Median	**2.00**	**2.00**	
Range (min-max)	**1.00-4.00**	**1.00-5.00**	

Variable	**Correlation**	**R**	**P value**
Correlation between EAT and HOMA-IR	Spearman	**0.320**	**0.002***

The mean EAT thickness in the insulin resistance group (HOMA-IR Tertile 3) was 2.36 ± 0.78 mm, while in the non-insulin resistant group (HOMA-IR Tertiles 1 and 2) was 1.72 ± 0.84 mm. Due to the non-normal distribution of EAT thickness, the Mann-Whitney U test was used to analyze the numerical data. The statistical

tests conducted to assess the difference in EAT thickness between the insulin resistance and non-insulin resistance groups revealed a p value smaller than 0.05, indicating a statistical significance (Table 2).

The Role of Confounding Factors in Insulin Resistance

Table 3. Confounding Factors for Insulin Resistance

Variable	Insulin Resistance		P value
	Yes N = 28	No N = 61	
Sex			**0.829**
Man	14 (50.0%)	29 (47.5%)	
Woman	14 (50.0%)	32 (52.5%)	
Age Group			**0.374**
20-29 years old	7 (25.0%)	21 (34.4%)	
30-39 years old	21 (75.0%)	40 (65.6%)	
Obesity			**0.0001****
Yes	26 (92.9%)	23 (37.7%)	
No	2 (7.1%)	38 (62.3%)	
Dyslipidemia			**0.005***
Yes	11 (39.3%)	8 (13.1%)	
No	17 (60.7%)	53 (86.9%)	

Note: For categorical data, the p-value is calculated based on the Chi-Square test with the alternative Kolmogorov-Smirnov and Fisher's Exact tests if the Chi-Square conditions are not met. The results are considered significance at p-value of <0.05.

Table 3 presents the results of the Chi-square tests analyzing the association between categorical variables (sex, age, obesity, and dyslipidemia) and insulin resistance. The analysis revealed no significant association between sex ($p > 0.05$) or age ($p > 0.05$) and insulin resistance. This suggests that the proportion of individuals with insulin resistance did not differ significantly between males and

females or between different age groups.

However, the P value between the variables related to obesity and dyslipidemia is smaller than 0.05, indicating that the difference in proportion between the variables is statistically significant (Table 3).

Table 4. Comparison of Epicardial Adipose Tissue and Insulin Resistance in Obese/Non-Obese and Dyslipidemic/Non-Dyslipidemic Groups

Variable	Insulin Resistance		P value
	Yes	No	
Obesity			
EAT	**N = 26**	**N = 23**	**0.006***
Mean ± SD	2.42 ± 0.758	1.83 ± 0.984	
Median	**2.50**	**2.00**	
Range (min-max)	**1.00-4.00**	**1.00-5.00**	
Non-Obese			
EAT	**N = 2**	**N = 38**	**0.877**
Mean ± SD	1.50 ± 0.707	1.66 ± 0.745	
Median	**1.50**	**1.50**	
Range (min-max)	**1.00-2.00**	**1.00-3.00**	
Dyslipidemia			
EAT	**N = 11**	**N = 8**	**0.012***
Mean ± SD	2.45 ± 0.688	1.50 ± 0.535	
Median	**3.00**	**1.50**	
Range (min-max)	**1.00-3.00**	**1.00-2.00**	
Not Dyslipidemia			
EAT	**N = 17**	**N = 53**	**0.018***
Mean ± SD	2.29 ± 0.849	1.75 ± 0.875	
Median	**2.00**	**2.00**	
Range (min-max)	**1.00-4.00**	**1.00-5.00**	

Note: For numerical data, the p-value is tested using the unpaired T-test if the data is normally distributed with the alternative Mann-Whitney test if the data is non-normally distributed. The results are considered significance at p-value <0.05.

Table 4 presents the comparison of EAT thickness between insulin resistance groups stratified by obesity and dyslipidemia status. In the non-obese group, there was no statistically significant difference in mean EAT thickness between those with and without insulin resistance ($p > 0.05$). This suggests that in non-obese individuals, insulin resistance may not be associated with increased EAT thickness.

However, in both the dyslipidemic and non-dyslipidemic groups, there was a statistically significant difference in mean EAT thickness between those with and without insulin resistance ($p < 0.05$). This indicates that regardless of dyslipidemia status, individuals with insulin resistance tend to have thicker EAT compared to those without insulin resistance (Table 4).

Discussion

Epicardial adipose tissue (EAT) is the visceral fat located within the pericardial sac, between the visceral pericardium and the outer wall of the myocardium. Epicardial adipose tissue has the same origin as intra-abdominal visceral adipose tissue and is thus a metabolically active adipose tissue.[6] While there is no gold standard for EAT measurement,[5] transthoracic echocardiography (TTE) has emerged as a preferred method (compared to cardiac computed tomography or MRI) due to its accessibility, affordability, lack of radiation exposure, long durability, and reproducibility.[8,10]

In this study, EAT thickness was measured using a GE Vivid E95 echocardiograph. While the reliability of TTE for EAT assessment is still under investigation, it can provide new information easily every day and at an affordable cost. EAT research is still developing and echocardiography is becoming a promising tool for assessing cardiovascular and metabolic risk in clinical practice.[8] Studies suggest that TTE is a simple and practical method for measuring EAT in obese individuals and may provide valuable cardiac parameters in both obese and diabetic patients with insulin resistance.[11]

Dysglycemia is the main clinical manifestation of increased insulin resistance. The gold standard for assessing insulin resistance is the hyperinsulinemic-euglycemic glucose clamp, but it is invasive, costly, and requires specific expertise. In contrast, the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) offers a readily available and inexpensive alternative with excellent estimates.[14] This study utilized HOMA-IR to assess insulin resistance. Since HOMA-IR does not have a definite cut-off value to determine insulin resistance, this study used a cut-off value of ≥ 1.98 (third tertile) to define insulin resistance.[18]

Our results demonstrate a significant positive correlation between EAT thickness and HOMA-IR ($R = 0.320$; $p = 0.002$), indicating that thicker EAT is associated with insulin resistance in non-diabetic young adults. EAT was found to be significantly thicker in patients with insulin resistance (2.36) than in those without (1.72). This finding aligns with previous studies by Manco, *et al*. and Mancio *et al*., who found that EAT significantly predicts insulin resistance.[2,19]

However, it contrasts with the findings of Abaci *et al*., who reported no association between EAT thickness and insulin resistance, although they did note that EAT, in combination with C-reactive protein, could explain 45% of the variance in insulin resistance and identify insulin-resistant patients with good specificity and sensitivity. Circulating protein is a marker of inflammation whose levels are independent of insulin resistance in young patients.[2,20]

EAT is known to have a very high positive correlation with increased total body adiposity, especially with abdominal fat accumulation in prepubertal children who are obese.[2] Iacobellis *et al*. reported a significant association between EAT and obesity-related insulin resistance, suggesting that TTE-measured EAT may serve as a marker for increased intra-abdominal or truncal fat. They also found a significant but weak association between EAT and cardiac adipose tissue which needs to be evaluated in a larger group of patients. Additionally, EAT has been found to correlate with obesity-related characteristics such as fasting insulin, adiponectin, lipoprotein cholesterol, arterial blood pressure, and left ventricular mass.[16]

Insulin resistance rises along with increased BMI, waist circumference, and particularly the waist-to-hip ratio. Increased visceral fat leads to elevated free fatty acid (FFA) levels, promoting insulin resistance in cells and increasing VLDL synthesis in the liver. Adipose tissue also produces pro-inflammatory cytokines like TNF-α, interleukins, and PAI-1, further contributing to insulin resistance. The insulin resistance seen in obesity primarily involves the muscle and liver, with

increased FFA originating from adipocytes. FFA increases triglyceride accumulation in these tissues.[11]

In this study, obesity and dyslipidemia were significantly associated with increased EAT in the insulin resistance group ($p < 0.05$). The mean EAT thickness in obese insulin-resistant individuals was 2.42 mm. While Narumi *et al*. found an association between increased EAT volume and insulin resistance even in non-obese individuals without metabolic syndrome, our study did not observe this relationship in the non-obese group. Many reports show that excess visceral fat is more closely related to obesity-related diseases such as dyslipidemia and coronary artery disease than obesity itself. EAT is associated with insulin resistance and coronary artery disease even in non-obese subjects.[15] A study conducted by Manco *et al*. stated that EAT has a very high positive correlation with increasing total body adiposity, especially in obese prepubertal and early pubertal children.[2]

Conclusion

This study demonstrates that individuals with insulin resistance have significantly thicker epicardial adipose tissue (EAT) compared to those without insulin resistance. However, the association between EAT and insulin resistance is influenced by other factors, such as obesity and dyslipidemia. Specifically, our findings indicate a positive correlation between EAT thickness and HOMA-IR, meaning that a higher HOMA-IR value (indicating greater insulin resistance) corresponds with a thicker EAT.

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None

Conflict of Interest

There are no conflicts of interest of any of the researchers.

Ethics Committee Approval

This research was approved by the Ethics Committee of Human-Subject Biomedical Research at the Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia, based on recommendation letter number: **787/UN4.6.4.5.31/PP36/2022** with the protocol number: **UH22110666**

Author's Contribution

The principal investigators are NEP, AMA, and PT. SB, FS, and SS contributed to the research concept and design. AS contributed to the research concept, design, and statistical analysis of the data. All authors participated in drafting, revising, and evaluating the manuscript content. All authors have read and agreed to the manuscript's content and confirm the accuracy and integrity of every detail of this research.

Institutional Review Board Statement

In the implementation of this study, each action was carried out with the permission and knowledge of the research subject through an informed consent sheet and declared to meet the ethical requirements by the Human-Subject Biomedical Research Commission,

Faculty of Medicine, Hasanuddin University with ethical clearance number: 787/UN4.6.4.5.31/PP36/2022.

Data Availability Statement

Data will be made available on request

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