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Research Article
Integration of FAM19A5 Expression, Plasma Atherogenic Index and Coronary Artery Histopathology in Diet-Induced Obese Rats

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Abstract

Background and Objective: Subclinical atherosclerosis in obesity is often not detected early. The FAM19A5 is a novel adipokin that is atheroprotective, known to play a role in inhibiting the proliferation and migration of Vascular Smooth Muscle Cells (VSMC), but its expression in adipose tissue and its association with vascular lesions remain unclear. The Plasma Atherogenic Index (PAI) is also a predictive indicator of cardiovascular risk, but its association with coronary histopathological changes has not been widely evaluated experimentally. The study assesses the relationship between FAM19A5 levels and expression, as well as PAI values, with the histopathological picture of coronary arteries in the obesity model Rattus induced by a high-fat and high-fructose diet. **Materials and Methods:** Fourteen male Sprague Dawley rats were divided into a control group (standard feed) and an obesity group (a high-fat and high-fructose diet for 12 weeks). An examination of FAM19A5 levels (ELISA), expression of mRNA FAM19A5 in adipose tissue (qRT-PCR), plasma lipid levels, PAI calculations and histopathological examination of coronary arteries. All analyses were conducted using SPSS version 25 and a p-value<0.05 was considered statistically significant. **Results:** Circulating FAM19A5 levels were slightly higher in the obese group than in the control group, but not statistically significant. The expression of mRNA FAM19A5 is not detected in adipose tissue. The PAI value was higher in the obesity group. There was a significant difference in FAM19A5 levels in circulation between groups of coronary artery histopathological scores (p<0.05). The diet model successfully induces multistratified atherosclerotic lesions without additional proinflammatory substances. **Conclusion:** The integration of FAM19A5 levels, PAI values and the histopathological picture of coronary arteries provides a preliminary understanding of the progression of subclinical atherosclerosis in obesity. The findings of undetected FAM19A5 mRNA expression support the hypothesis that FAM19A5 is not the primary adipokine and that its role in atherosclerosis is likely systemic or compensatory in nature.

Key words: Coronary arteries, FAM19A5, obesity, plasma atherogenic index, histopathological

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Atherosclerosis is a chronic inflammatory disease of the arteries characterized by the accumulation of lipids, inflammatory cells and the formation of fibrotic plaques. This condition is the main cause of Coronary Heart Disease (CHD), one of the leading causes of death globally[1]. Obesity is a major contributor to the development of atherosclerosis and cardiovascular disease, largely through the promotion of chronic low-grade inflammation, lipid dysregulation and endothelial dysfunction. While overt atherosclerotic disease is often preceded by a long subclinical phase, early detection remains a clinical challenge, especially in metabolically obese individuals[2,3].

Obesity as a major risk factor increases systemic inflammation, insulin resistance and dyslipidemia, which is characterized by an increase in Low-Density Lipoprotein (LDL), a decrease in High-Density Lipoprotein (HDL) and hypertriglyceridemia[2]. Atherosclerosis research in obese populations has so far largely focused on conventional lipid biomarkers such as total cholesterol, LDL, HDL and triglycerides, as well as some adipokines such as adiponectin[4-8].

This combination of lipid profiles can be calculated through the Plasma Atherogenic Index (PAI), the logarithmic ratio of triglycerides to HDL, which is strongly correlated with the risk of atherosclerosis and CHD[9,10]. Recent studies have shown a positive association between PAI and increased thickness of carotid intima-media, as a marker of subclinical atherosclerosis[11,12].

Emerging biomarkers such as FAM19A5, a novel adipokine with suggested atheroprotective properties, have been proposed as early indicators of vascular injury. The FAM19A5 has been shown to inhibit Vascular Smooth Muscle Cell (VSMC) proliferation and migration, processes that are critical in the pathogenesis of atherosclerotic plaque formation[13,14]. Clinical studies have reported reduced levels of circulating FAM19A5 in patients with established atherosclerotic cardiovascular disease[15-17]. However, its expression in adipose tissue remains underexplored, particularly in the context of obesity-related vascular remodeling.

Histopathological examination is important to directly assess the structure of atherosclerotic lesions, such as intima thickness, lipid necrosis and inflammatory infiltration, which are not visible through circulatory biomarkers alone. Nonetheless, few experimental studies have evaluated the relationship between PAI and histopathological changes in the coronary arteries.

Despite increasing interest in these biomarkers, integrated studies that simultaneously evaluate circulating FAM19A5 levels, adipose tissue expression, PAI and vascular pathology are lacking, particularly in diet-induced obese animal models that mimic gradual metabolic changes without pharmacological or inflammatory triggers.

Therefore, this study aimed to investigate the association between FAM19A5 levels and gene expression, plasma atherogenic index and histopathological features of coronary arteries in a rat model of obesity induced by a high-fat and high-fructose diet.

MATERIALS AND METHODS

Study area and duration: The study was conducted from May to August, 2025 at the Biomedical and Anatomical Pathology Laboratories, Faculty of Medicine andalas and at the Biomedical Laboratory and Animal House, Faculty of Medicine, Baiturrahmah University, Indonesia.

Research design and experimental animals: This study is an *in vivo* experimental study with a post-test only control group design. A total of 14 male rats of *the Rattus norvegicus* species of the Sprague-Dawley strain were used and randomly divided into two groups (n = 7) and the control group (AIN-93 diet) and the obesity model group received a high-fat and high-fructose diet (HFHF) for 12 weeks. The HFHF diet is a modification of the Western diet with the addition of solid fructose (100 g/kg) and trans oils (200 g/kg). The Western diet plays a role in accelerating the process of atherosclerosis in rats. The Western diet is made to resemble the diet of most of the population in Western countries, which consists of 21% fat and 0.15% cholesterol[18,19]. High Fatty Diets (HFDs) such as the western diet have been shown to cause obesity in *Sprague Dawley* strain rats in many studies[20,21]. The control group of rats in this study was given an AIN-93 diet[22]. The high-fat and fructose diet (HFHF) in this study has been proximately tested and the result of crude fat content is 10.42% while the AIN-93 diet is 2.13%.

Rats in both groups were acclimatized for one week before the study. The control group received a standard AIN-93 diet for 12 weeks. Body weight was recorded weekly throughout the study period. At the end of the 12th week, the rats were humanely euthanized. Rats in the obesity model group were induced to develop obesity by being fed a high-fat and high-fructose (HFHF) diet for 12 weeks, with body weight monitored weekly throughout the intervention period. The composition of the diets provided to the control and obesity model groups is presented in the following Table 1.

Table 1: Composition of experimental animal diet ingredients

	AIN 93	HFHF
Ingredients	1 kg	1 kg
Cornstarch	619.4	419.4
Casein	140	140
Sucrose	100	-
Corn oil	40	40
Alpha selulosa	50	50
Mineral mix	35	35
Vitamin mix	10	10
DL-methionine	3	3
Choline chlorida	2.5	2.5
Fructose	-	100
Trans oil	-	200

Rats are said to be obese when the Lee index value exceeds 300. The rats were measured in weight using a scale and their length was measured using a ruler. The results of measuring the weight and body length of the rats were then calculated to determine the body mass index using the following formula[23]:

$$\text{Lee index} = \frac{\sqrt[3]{\text{Weight}}}{\text{NAL}} \times 1000$$

$$\text{Lee index} = \frac{\text{Body weigth (g)}^{1/3}}{\text{Naso} - \text{anal length (cm)}} \times 10^3$$

At the end of the 12-week treatment period, the rats were humanely euthanized in accordance with institutional ethical guidelines. Blood samples were collected from the retro-orbital plexus under light anesthesia using capillary tubes, following institutional animal care guidelines. Visceral adipose tissue was harvested from the abdominal cavity. The left coronary arteries were carefully isolated and collected for histopathological analysis.

Plasma is obtained from venous blood collected in an EDTA tube and centrifuged at 4000 g for 20 min. Triglyceride (TG) and HDL levels were checked in a duplex using an automated chemistry analyzer. The plasma atherogenic index (PAI) is calculated using the log formula (TG/HDL) in mmol/L. The FAM19A5 rate was measured using an ELISA kit (MyBioSource MBS9391391). The ELISA plates are coated with anti-FAM19A5 antibodies, blocked with BSA and incubated with detection antibodies as well as HRP conjugates according to the manufacturer's protocol. Readings were taken at a wavelength of 450 nm. Standard curves are arranged, ranging from 100 to 51,200 pg/mL.

Abdominal adipose tissue is homogenized and total RNA is extracted using Genezol reagents. The RNA purity was assessed with a spectrophotometer (Nanodrop) and reverse transcription was performed with the RevertAid and SensiFAST kits. The qRT-PCR reaction was performed using the SYBR Green Master Mix on the QuantStudio 3 device, with two housekeeping genes (β-actin and GAPDH) as internal controls. The primer FAM19A5, designed based on RefSeq *Rattus norvegicus* (NM_001191991.1), yields an amplicon of ±151 bp. Validation of the amplification results was carried out through a melt-curve analysis and 2% gel electrophoresis. As a positive control, the hypothalamus and epididymal adipose tissues were used. The expression is positive when an exponential amplification curve, a single melt-curve peak and the product size are appropriate.

Histopathological Microscopic Assessment was carried out using an Olympus BX51 microscope equipped with a DP2-BSW camera. Coronary artery tissue preparations were stained using Hematoxylin-Eosin (H&E) staining, then observed at five fields of view per test animal with an original magnification of 400× (20 µm scale bar). Intima tunica thickness measurements were taken from the lumen surface to the boundary of the internal elastic lamina in the five fields of view of each animal's coronary arteries, using ImageJ software. The measurement results are displayed in micrometers (µm) and then the average value is calculated for further analysis. A morphological assessment of coronary artery tissue was also performed at five fields of view per sample, using a native magnification of 400×.

The determination of the degree of atherosclerosis was carried out based on the following classification of histopathological picture scores of atherosclerosis plaques: Score 0 = No signs of atherosclerosis; score 1 = Initiation stage: foam cells found, endothelial discontinuity; score 2 = Proliferation stage: Increased number of foam cells, presence of disorientation and proliferation of VSMC, or collagen fibrosis; score 3 = Complication stage: Plaque has ruptured, ulcerated plaque, thrombus, or calcification process.

Ethical statement: All experimental procedures involving animals were reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Andalas, Indonesia (Approval No: 435/UN.16.2/KEP-FK/2024), dated August 14, 2024. The procedures were conducted per institutional guidelines and international standards for the care and use of laboratory animals.

Statistical analysis: The data was tested for normality with the Shapiro Wilk test. Comparisons between groups were analyzed using unpaired t-tests or Mann Whitney. Comparative analysis of PAI values, FAM19A5 mRNA expression and FAM19A5 levels across categories of coronary artery histopathological scores was performed using the Kruskal Wallis test. All analyses were conducted using SPSS version 25 with a significance level of $p<0.05$.

RESULTS AND DISCUSSION

Seven rats in the HFHF group showed significant weight gain compared to the control group after 12 weeks of treatment. The Lee index value of all rats in the obesity group was above 300, indicating a morphometric obesity status. No deaths or complications were found during the period of dietary induction. Comparative analysis was performed using the Mann-Whitney U test with exact significance values, due to the small sample size and non-normal distribution of data, are shown in the following Table 2.

To compare the control and obesity groups, a non-parametric statistical test Mann Whitney U test was applied, given the small sample size and non-normal distribution of the data. This test compares the ranks of two independent groups and provides a U statistic and exact p-value, with $p<0.05$ considered statistically significant.

Both initial and final body weights were significantly higher in the obesity group, indicating effective weight gain following HFHF diet administration. Lee's index was also significantly elevated ($U = 0.0$; $p = 0.002$), confirming the success of obesity induction. Interestingly, triglyceride levels were significantly lower in the obesity group compared to the control, while HDL levels were significantly reduced ($U = 6.0$; $p = 0.018$), aligning with typical dyslipidemia patterns in obesity. Although Plasma Atherogenic Index and FAM19A5 levels showed higher trends in the obesity group, the differences were not statistically significant.

The mean tunica intima thickness was also greater in the obesity group compared to the control group, but the difference did not reach significance. In contrast, coronary artery histopathological scores showed a significant difference between groups. All rats in the control group exhibited a histopathological score of 0 (no lesions), whereas rats in the obesity group demonstrated lesion scores ranging from 1 to 2, indicating the progression of atherosclerotic changes after 12 weeks of obesogenic diet exposure.

The qRT-PCR analysis revealed that FAM19A5 mRNA expression was undetectable in the abdominal adipose tissue of all samples. Amplification and melt-curve analyses confirmed the absence of specific expression, despite valid amplification observed in the positive controls.

Table 3 presents the results of the Kruskal Wallis test assessing plasma atherogenic index (IAP) values across coronary artery histopathological score categories. Although groups with scores of 1 and 2 showed slightly higher mean ranks compared with score 0, these differences were not statistically significant ($H = 2.00$, $df = 2$, $p = 0.368$). This indicates no meaningful variation in IAP values among the groups.

Table 4 displays the differences in circulating FAM19A5 levels across histopathological score categories. The Kruskal-Wallis test revealed a statistically significant variation among groups ($H = 7.01$, $df = 2$, $p = 0.030$). Notably, the highest mean rank was observed in the score 2 group, suggesting that elevated FAM19A5 levels may be associated with more advanced vascular injury.

This study employed male Sprague–Dawley rats, divided into two groups: A control group and an obesity model group. Obesity was induced in the model group by providing a high-fat and high-fructose (HFHF) diet ad libitum for 12 weeks. The Sprague-Dawley strain was chosen due to its well-established capacity to mimic human metabolic responses to high-fat diets and its consistent performance in diet-induced obesity models, despite some degree of individual variability in dietary response.

Induction of obesity using a high-fat and high-fructose (HFHF) diet for 12 weeks was effective in increasing body weight by approximately 12%. This was evidenced by the rise in mean body weight from 261.71±12.98 to 299.14±17.66 g, accompanied by an increase in Lee's index to 339.22±6.27. This value significantly exceeds the commonly used cut-off point of >300 for classifying obesity in rats[24].

A significant increase in average weight and Lee's index demonstrated the success of the obesity model in this study. The value of the Lee index in this study is higher than a Lee index value of 309 after 8 weeks of HFD, as well as showing the Lee index of the obesity group of 309.76±9.36. The research used a similar duration and type of diet obtained a Lee index of around 287.65 and did not reach the category of obesity, although abdominal circumference increased significantly and weight gain by 11.94%[25-27].

This study showed that a model of obese rats fed a diet high in fat and fructose for 12 weeks was able to induce progressive coronary atherosclerotic lesions, even without the addition of proinflammatory substances such as vitamin D3 or exogenous cholesterol. The differences in coronary artery histopathological features across the lesion scores are illustrated in the three images below. Representative coronary artery sections of the control group (score 0) showed intact endothelial cells and the absence of foam cells (Fig. 1). In coronary arteries with a histopathological score of 1, discontinuity of the endothelial layer and the presence of foam cells were observed (Fig. 2). Lesions with a histopathological score of 2 demonstrated a higher number of foam cells, endothelial discontinuity and initial disorientation of smooth muscle cells, indicating early atherosclerotic changes (Fig. 3).

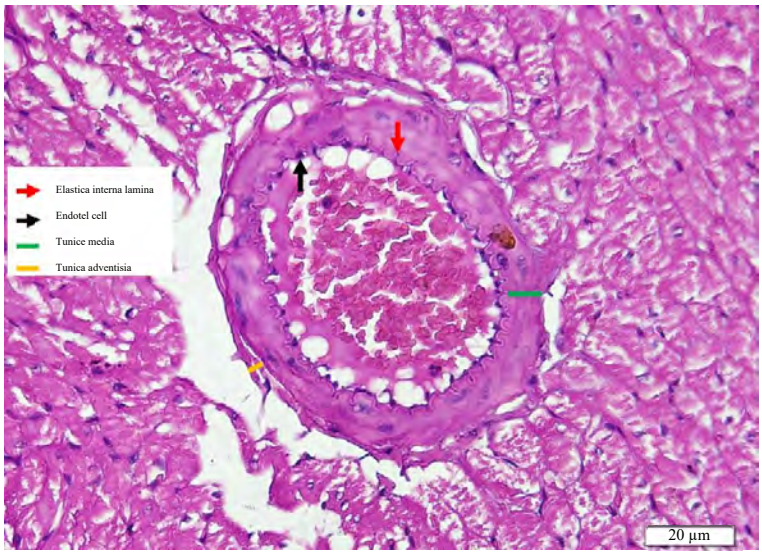

Fig. 1: Coronary artery of rats with a score of 0

Histological structure of the coronary artery of rats with a histopathological score of 0, observed under light microscopy at 400× magnification (H&E staining). Red arrows indicate the intact endothelial lining, black arrows show normal endothelial cells and green arrows represent the tunica adventitia. The internal elastic lamina and tunica media are preserved without evidence of foam cells. Description: Endothelial cells intact, foam cells absent

Table 2: Sample characteristics of control and model obese rat groups

Parameter	Control	Obese	Mann-Whitney U	Exact p-value	Significance (p<0.05)
Initial body weight (g)	221.57±23.11	261.71±12.98	3.5	0.007	Significant
Final body weight (g)	249.29±12.46	299.14±17.66	0.0	0.002	Significant
Lee index	295.67±4.61	339.22±6.27	0.0	0.002	Significant
Triglyceride (mg/dL)	119.18±11.03	99.11±5.98	0.5	0.002	Significant
HDL (mg/dL)	82.3±4.34	56.51±12.6	6.0	0.018	Significant
Plasma atherogenic index	0.19±0.08	0.29±0.03	8.0	0.035	Significant
FAM19A5 (ng/mL)	1.01±0.10	1.06±0.24	20.5	0.609	Not significant
Mean tunica intima thickness (mm)	8.23±1.73	11.77±3.41	13.0	0.142	Not significant
Coronary artery histopathology		Score 0: 7 rats (100%)	10.5	0.025	Significant
		Score 0 = 3 rats (42.8%)			
		Score 1 = 2 rats (28.6%)			
		Score 2 = 2 rats (28.6%)			

Table 3: Differences in plasma atherogenic index values between categories of coronary artery histopathological scores

Histopathological score	N	Mean rank	Kruskal-Wallis	p-value
0	10	6.5		
1	2	10	H = 2.00; df = 2	0.368
2	2	10		

Table 3 presents the Kruskal-Wallis test revealed no significant differences in IAP values across the categories of coronary artery histopathological scores. Although the mean ranks tended to be higher in groups with scores of 1 and 2 compared to scores 0, these differences were not statistically significant (p>0.05)

Table 4: Differences in FAM19A5 levels between categories of coronary artery histopathological scores

Histopathological score	N	Mean rank	Kruskal-Wallis	p-value
0	10	7.3		
1	2	2.5	H = 7.01; df = 2	0.030
2	2	13.5		

This confirms that an obesogenic diet alone is sufficient to trigger early vascular remodeling, according to the results of research that used a high-fat diet model to stimulate the formation of atherosclerotic plaques[28,29].

Biochemically, FAM19A5 levels in the obesity group in this study appeared to be slightly increased compared to controls, although statistically insignificant. These findings differ from most human studies, which showed a decrease in FAM19A5 levels in patients with metabolic syndrome or atherosclerosis[15,16]. These differences can be due to variation between species, different disease stages (subclinical vs. clinical), or FAM19A5 compensation regulatory mechanisms in response to metabolic stress and mild inflammation. The Kruskal-Wallis test (Table 4) revealed a significant difference

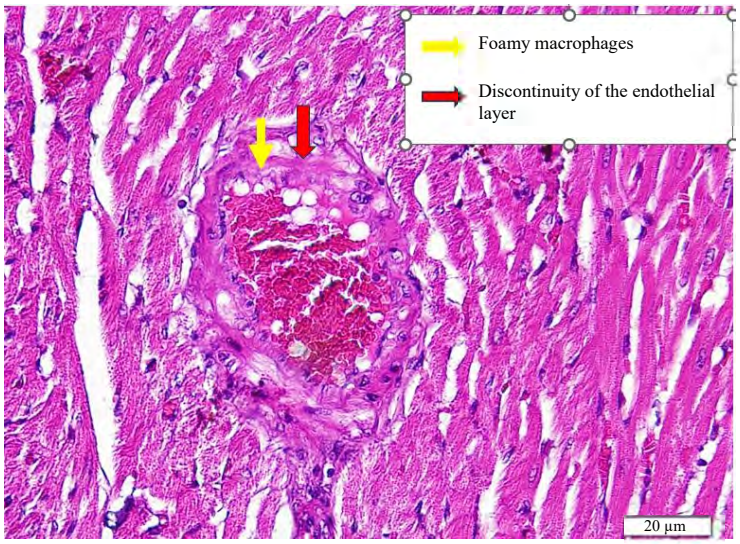

Fig. 2: Coronary artery of rats with a score of 1

Histological structure of the coronary artery of rats with a histopathological score of 1, observed under light microscopy at 400× magnification (H&E staining). Red arrows indicate endothelial discontinuity and yellow arrows show the presence of initial foam cells within the intimal layer. Early structural changes are present but without significant smooth muscle cell disorientation. Description: Endothelial discontinuity, foam cells present

Fig. 3: Coronary artery of rats with a score of 2

Histological structure of the coronary artery of rats with a histopathological score of 2, observed under light microscopy at 400× magnification (H&E staining). Red arrows indicate accumulation of foam cells, white arrows show smooth muscle cell disorientation in the tunica media and yellow arrows demonstrate extracellular lipid deposition. These features indicate progressive atherosclerotic lesion formation. Description: Multiple foam cells (++), smooth muscle cell disorientation, extracellular lipid deposition

in FAM19A5 levels among the categories of coronary artery histopathological scores. The highest mean rank was observed in the score 2 group (13.5), whereas the score 1 group showed the lowest mean rank (2.5). These findings suggest that FAM19A5 levels tend to increase with more severe lesions, although the distribution pattern was not entirely linear.

The absence of FAM19A5 mRNA expression in adipose tissue represents a significant observation, suggesting that this gene may not be actively transcribed in adipose tissue under obesogenic conditions. This supports the study, which showed that FAM19A5 is predominantly expressed in the central nervous system, rather than in fat tissue, so it cannot

be classified as a major adipokine. This fact makes it clear that circulating levels of FAM19A5 are most likely sourced from other tissues (e.g., hypothalamus or vascular) and play a role in the systemic regulation of inflammation and remodeling of blood vessels[30].

The increased FAM19A5 levels found in a portion of obese mice with higher lesion scores in this study reflect the compensatory mechanisms or systemic role of FAM19A5 in responding to endothelial dysfunction and vascular inflammation. These results are in line with the study, which found an increase in FAM19A5 in DM patients compared to controls[31]. This is consistent with the hypothesis that FAM19A5, although not adipokines produced by peripheral tissues, may increase in circulation in response to metabolic stress, mild systemic inflammation, or early vascular damage commonly found in obesity models due to high-fat diets[30,32].

From a metabolic aspect, an increased PAI value in the obese group indicates the presence of atherogenic dyslipidemia, although triglyceride levels are relatively low. This phenomenon can be explained through the mechanism of enterocyte dysfunction that leads to intracellular lipid accumulation and disruption of chylomicron release. This suggests that PAI remains relevant as a risk marker, even though the TG component appears to be low in absolute terms[33,34].

Overall, the integration between FAM19A5, PAI and histopathological picture suggests a consistent relationship direction to the progression of subclinical atherosclerosis. These results open up the opportunity to evaluate FAM19A5 as a non-invasive systemic biomarker that has the potential to be used in the early stages of atherosclerosis, especially in obese populations. The results suggest the need for further research with larger sample counts, as well as additional molecular approaches such as immunohistochemistry (IHC) to assess FAM19A5 expression in tissue directly.

CONCLUSION

This study evaluates the integration of plasma atherogenic index, FAM19A5 levels and coronary artery histopathological findings in a diet-induced obesity model. The findings demonstrated that although statistical correlations were not significant, the direction of associations supports the potential role of FAM19A5 as a systemic biomarker related to early vascular changes. These results fulfill the study's objective and highlight the importance of further investigation in this area.

SIGNIFICANCE STATEMENT

This study discovered the potential role of circulating FAM19A5 levels as a systemic biomarker associated with early vascular alterations in diet-induced obesity, which can be beneficial for predicting subclinical atherosclerosis before overt clinical manifestations occur. In addition, the study highlights the utility of the plasma atherogenic index (PAI) as a complementary indicator of cardiovascular risk, offering valuable insight into vascular pathology in obesity models. The absence of detectable FAM19A5 mRNA expression in adipose tissue further supports its systemic rather than local adipokine function, which broadens the understanding of its biological significance. This study will help the researchers to uncover the critical areas of obesity-related vascular injury that many researchers were not able to explore. Thus a new theory on adipokine-mediated vascular protection may be arrived at.

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