Original Article

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Correlation of Various Levels of Body Mass Index to Vascular Endothelial Growth Factor-A

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Abstract

Background: Obesity, reflected by high body mass index (BMI) value, has become a global health concern. Both obesity and vascular endothelial growth factor-A (VEGF-A) are major risk factors for cardiometabolic diseases. Although many studies have shown that obesity induces angiogenesis through increased VEGF-A, there remains a gap regarding the correlation between BMI categories and VEGF-A levels. This study aimed to analyze the correlation between various level of BMI and VEGF-A concentrations.

Methods: This cross-sectional in vivo study analyzed blood samples from 90 adults enrolled in the Universitas Padjadjaran Wellness Program (December 2022–June 2023) selected using simple random sampling. VEGF-A concentrations were measured using multiplex ELISA assays. Data normality was assessed using the Kolmogorov-Smirnov test. Differences between BMI groups were analyze with ANOVA, and correlations were evaluated using Pearson's test.

Results: Of the 90 samples, 62 were included and grouped as normal weight (29%), overweight (32.2%), obesity class I (30.6%), obesity class II (6.4%), and obesity class III (1.6%). Mean VEGF-A concentrations showed an increasing trend with higher BMI, though differences between groups were not statistically significant (p=0.482). A weak positive correlation was observed between BMI and VEGF-A levels (r=0.267; p=0.036).

Conclusion: Higher BMI is associated with higher VEGF-A, indicating obesity-induced inflammation and angiogenic activity. These findings highlight the importance of weight control through balanced diet and physical activity to mitigate long-term risks of cardiometabolic and chronic diseases.

Keywords: Angiogenesis, body mass index, inflammation, obesity, vascular endothelial growth factor-A

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Introduction

Overweight and obesity are major global health concerns. In 2016, the World Health Organization (WHO) reported that 1.9 billion adults worldwide were overweight, and 650 million were obese.[1] In Indonesia, obesity prevalence has also risen, from 14.8% in 2013 to 21.8% in 2018.[2] Furthermore, 20.7% of Indonesians are obese with a body mass index (BMI) exceeding 27 kg/m^2, and 33.5% have a BMI over 25 kg/m^2.[3]

Obesity is primarily caused by chronic disruptions in energy homeostasis and is linked to abnormal adipose tissue accumulation. It is widely recognized as a leading preventable cause of death.[4] Over the last half century, obesity has become an epidemic driven by complex interactions between genetic susceptibility and environmental factors, contributing to the development of multiplechronic diseases.[5] It is also a hallmark of metabolic syndrome, characterized by elevated inflammatory cytokines such as

vascular endothelial growth factor A (VEGF-A), leading to dysregulated angiogenesis and subsequent endothelial dysfunction, which drive cardiometabolic diseases.[6,7] Furthermore, higher BMI has been associated with activation of the innate immune system, increased release of inflammatory mediators and reduced adiponectin levels, all contributing to chronic low-grade inflammation.[8–11]

Given its associations with both BMI and inflammatory markers, VEGF-A is a candidate biomarker for obesity-induced angiogenesis.[12] However, the mechanisms linking BMI, inflammation, and angiogenesis remain incompletely understood. Moreover, research on VEGF-A in relation to BMI categories is limited, particularly in Indonesia. This study aimed to analyze the correlation between BMI categories and VEGF-A concentrations, providing novel insights into obesity-induced inflammation and pathological angiogenesis.

Methods

This study used a cross-sectional quantitative design, analyzing in vivo blood samples obtained from archived biological material from the Universitas Padjadjaran Wellness Program 2022. Ethical approval was granted by the Research Ethics Committee of Universitas Padjadjaran (No. 515/UN6.KEP/EC/2023).

The inclusion criteria were individuals who had fully participated in the Wellness Program for three months, were free from physical injury, had no history of chronic diseases, were not currently using medication, and were not enrolled in other wellness or dietary programs. Exclusion criteria were participants who withdrew before completion. All eligible participants underwent anthropometric measurements including body weight, body height, and BMI calculation. Participants were then grouped according to the WHO BMI categories: normal weight (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), obese class I (30 to 34.9 kg/m^2), obese class II (35 to 39.9 kg/m^2), obese class III (40 kg/m^2 or higher).

Archived serum samples were randomly selected using lottery method. VEGF-A concentrations were measured using amultiplex ELISA kit (Merck Millipore, USA) at the Biological Activity Laboratory, Central Laboratory, Universitas Padjadjaran. Standard laboratory protocols were followed.

In brief, a 96-well plate was washed with 200 µL of wash buffer and wells were designated for background, seven standard concentrations, two controls, and test samples. Each well received 25 µL of assay buffer, serum matrix, controls, or samples, followed by 25 µL of beads. The plate was sealed, incubated at 600 rpm for 2 hours, and washed three times with a handheld magnet. Next, 25 µL of detection antibody was added and incubated for 1 hour, followed by washing. Subsequently, 25 µL of streptavidin-phycoerythrin was added and incubated for 30 minutes, then washed three times. Finally, 150 µL of sheath fluid was added, and beads were resuspended by shaking for 5 minutes before reading on a Luminex instrument. Results were expressed as median fluorescent intensity (MFI) and analyte concentrations were calculated using a

Table 1 Demographic Characteristics of Participants (n=62)

Variable	Frequency (n)	Percentage (%)
Gender		
Male	36	58.0
Female	26	41.9
Age (years)		
37–46	16	25.8
47–56	24	38.7
57–66	17	27.4
>67	5	8.0
Body mass index*		
Normal weight	18	29.0
Overweight	20	32.2
Obesity class I	19	30.6
Obesity class II	4	6.4
Obesity class III	1	1.6

Note: *BMI classification: Normal weight: 18.5 to 24.9 kg/m^2; Overweight: 25 to 29.9 kg/m^2 ; Obese Class I: 30 to 34.9 kg/m^2; Obese Class II: 35 to 39.9 kg/m^2; Obese Class III: ≥40 kg/m^2.

Table 2 Mean VEGF-A by BMI Category

BMI Category	Mean	SD	SEM	p-value**
Normal	288.72	183.49	43.25	0.482
Overweight	366.95	241.84	54.07	
Obesity class I	383.39	220.75	50.64	
Obesity class II	607.97	108.49	54.24	
Obesity class III	715.91	-	-	

Note: BMI=body mass index, ** ANOVA p-value= 0.482 (not significant). SD= standard deviation; SEM= standard error of the mean, p-values based on ANOVA analysis

five-parameter logistic (5-PL) or spline curve-fitting method.

Data collected were then analyzed using Microsoft® Excel 2016 and/or IBM® SPSS® version 29 and displayed in tabular form and graph. Normality was tested using the Kolmogorov-Smirnov test. Group differences in VEGF-A across BMI categories were analyzed using one-wayANOVA. Pearson correlation was performed to assess the correlation between BMI and VEGF-A, and between age and BMI. A p-value <0.05 was considered statistically significant.

Results

A total of 62 subjects were included and classified based on their BMI. The majority were male (58.06%), and the most common age group was 47 to 56 years (38.70%). The largest proportion of participants was classified as overweight (32.2%), followed by obesity class I (30.6%) (Table 1).

Mean VEGF-A concentrations across BMI categories showed a trend of higher VEGF-A levels with increasing BMI (Figure 1). However, the differences between groups were not statistically significant (ANOVA, p=0.482) (Table 2).

Correlation analysis demonstrated a weak but statistically significant positive correlation between BMI and serum VEGF-A concentration (r=0.267, p=0.036) (Figure 2). This indicates that higher BMI was associated with higher VEGF-A levels.

Discussion

This study demonstrated a weak but significant positive correlation between BMI and VEGF-A concentrations. Although group comparisons using ANOVA were not statistically significant, the trend toward higher VEGF concentrations with increasing BMI was evident, supporting the role of obesity in upregulating agiogenic activity. These findings are in line with a study conducted in Germany, which reported a positive correlation between BMI and VEGF under controlled conditions.[13]

The relationship between obesity and VEGF-A may be explained by the proangiogenic activity of adipose tissue. Adipocytes are closely associated with endothelial cells through paracrine and autocrine signaling,

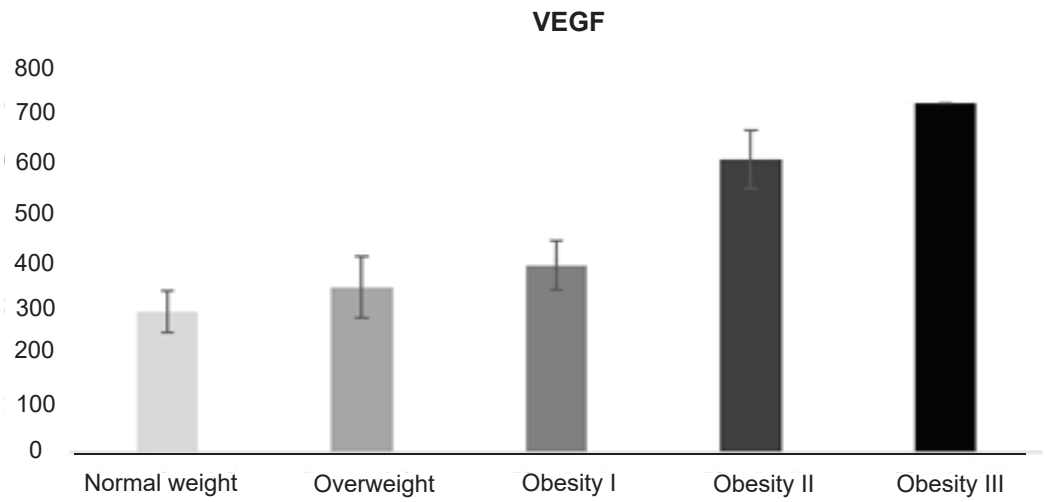

Figure 1 Mean and Standard Error for VEGF-A based on BMI Categories.

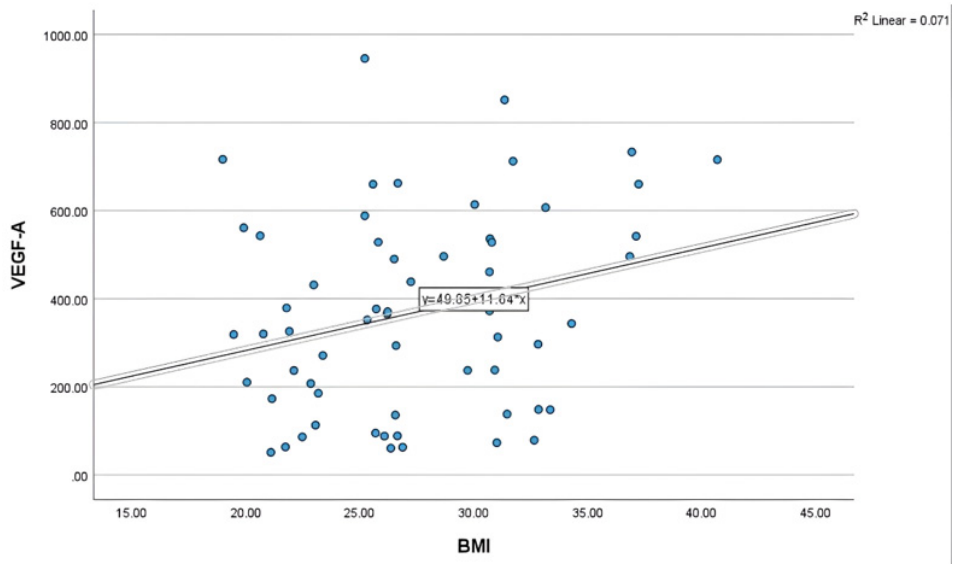

Figure 2 Correlation between BMI and VEGF-A Concentration
Note: r = 0.267, p = 0.036, indicating a weak positive correlation.

regulating angiogenic factors, hormones, and cytokines.[14] Disruption of endothelial function in obesity contributes to low-grade chronic inflammation.[15] Angiogenesis in obesity is a compensatory mechanism triggered by adipose tissue expansion, hypoxia, and inflammation.[16] Pro-inflammatory cytokines such as TNF-alpha and IL-1 increase VEGF-A concentrations, while the crosstalk between VEGF-A and TNF-alpha via NF-κB further amplifies inflammatory responses.[17–19] Moreover, VEGF induces pro-inflammatory genes such as IL-8, preserve chronic inflammation.[20]

VEGF-A mainly signals through VEGF-Receptor 2 (VEGFR-2), which activates pathways like Delta-like 4 (Dll4) and PI3K/Akt, promoting angiogenesis, endothelial permeability, and reduced apoptosis.[14,17,21] While physiological angiogenesis supports oxygen and nutrient delivery, in obesity it sustains inflammation and recruits macrophages and neutrophils, creating a vicious cycle.[17] A study from Poland confirmed that VEGF-A levels were higher in obese patients compared to those with peripheral artery disease but normal BMI, showing VEGF-A dysregulation in obesity.[22,23]

Furthermore, elevated VEGF-A has also been linked to abnormal cell proliferation, tumor development, and triglyceride accumulation, all of which increase the risk of cardiometabolic disease and cancer.[24–26] Thus, Anti-angiogenic therapies such as VEGF-neutralizing antibodies, such as bevacizumab, and small-molecule kinase inhibitors have shown promise in reducing VEGF-A–driven pathological processes.[27]

However, despite these association, our findings revealed only a weak correlation. Several factors may account for this. First, age may influence VEGF-A levels, as aging reduces endothelial cell proliferation and upregulates cyclin-dependent kinase inhibitors like p19ARF, suppressing VEGF-A production. In this study, however, age was not significantly correlated with VEGF-A levels. Second, body composition was not assessed. Since BMI does not distinguish fat from lean mass, variations in muscle mass may confound VEGF-A levels, as VEGF also participates in muscle fiber hypertrophy.[28] Third, cytokine profiles were not evaluated. While cytokines such as TNF-α stimulate angiogenesis, others like IL-12 and IL-23 inhibit it through natural killer cell activity, leading to variability in VEGF-A expression.[29]

This study has several limitations, including a small sample size, uneven age and BMI group distribution, and restricted laboratory resources that limited assessment of body composition and cytokine levels. Future studies with larger, more diverse populations and additional biomarkers are needed to clarify the mechanistic relationship between BMI and VEGF-A.

In conclusion, this study reveals a weak but significant positive correlation between BMI and VEGF-A concentrations, suggesting that higher BMI is associated with obesity-

induced inflammation and increased risk of cardiometabolic diseases, tumors, and cancer. Maintaining a healthy body weight through lifestyle modifications, such as balanced diet and regular physical activity, may help regulate VEGF-A levels, reduce long-term risks of chronic diseases, and promote healthy aging.

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