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Elevated Blood Levels of VEGF Exhibiting Positive Correlation with HIF-1α in Obesity: A Single Center Study

Nazmiye ULUERGÜVEN[1], Durkadın DEMİR EKŞİ[2], Erkan MAYTALMAN[3] ✉, Ramazan GÜNEŞAÇAR[4]

[1]Alanya Alaaddin Keykubat University Faculty of Medicine, Department of Molecular Medicine, Antalya, Türkiye
[2]Alanya Alaaddin Keykubat University Faculty of Medicine, Department of Medical Biology, Antalya, Türkiye
[3]Alanya Alaaddin Keykubat University Faculty of Medicine, Department of Pharmacology, Antalya, Türkiye
[4]Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Medical Biology, Hatay, Türkiye

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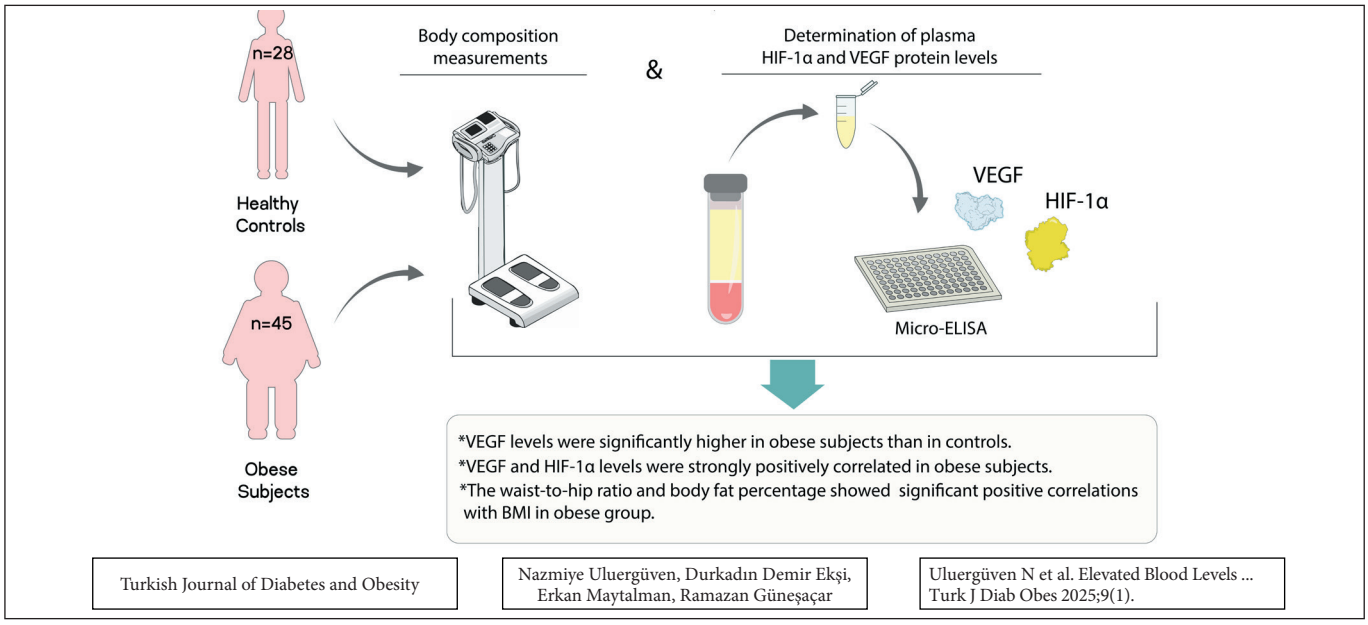
GRAPHICAL ABSTRACT



ABSTRACT

Aim: The objective of this study was to investigate the relevance of plasma hypoxia-inducible factor-1 alpha (HIF-1α) and vascular endothelial growth factor (VEGF) levels in obesity and their associations with body mass index (BMI), body fat percentage, and waist-to-hip ratio.

Material and Methods: The study included 45 obese subjects and 28 healthy controls recruited from a private clinic in Manavgat, Antalya. The measurement of BMI, percentage of body fat, and waist-to-hip ratio was conducted in all subjects using a bioelectrical impedance analysis device. The plasma levels of HIF-1α and VEGF were measured using the micro-ELISA method.

Results: In the Mann-Whitney U test, HIF-1α levels were similar in obese subjects (median=1.439 ng/L [Interquartile range (IQR)=11.62, min-max=0.904-12.53] and control group (median=1.377 ng/L [1.323, 0.852-2.175], p=0.0821). VEGF levels were found to be significantly higher in obese subjects compared to the controls (medians; 729.8 ng/L [5515, 485.3-6000] vs. 589.5 ng/L, [416.8,

ORCID: Nazmiye Uluergüven / 0000-0003-2976-3311, Durkadın Demir Ekşi / 0000-0002-5887-3141, Erkan Maytalman / 0000-0001-5284-7439, Ramazan Güneşaçar / 0000-0002-2547-5585

Correspondence Address / Yazışma Adresi:
Erkan MAYTALMAN
Alanya Alaaddin Keykubat University Faculty of Medicine, Department of Pharmacology, Antalya, Türkiye,
Phone: +90 (242) 510 60 60 • E-mail: erkan.maytalman@alanya.edu.tr

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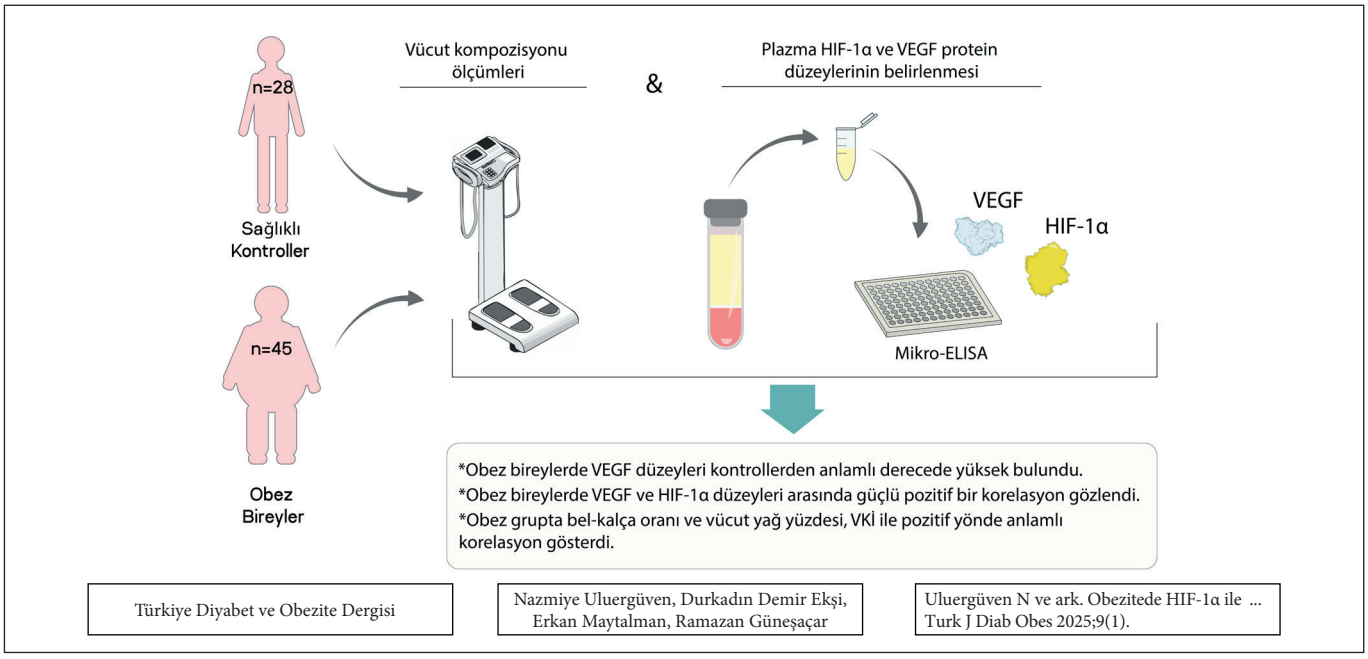
396.4-813.2], respectively, p<0.0001). In Spearman correlation analysis, VEGF and HIF-1α levels were shown to be strongly positively correlated in obese subjects (rho=0.598, p<0.00001). Both the waist-to-hip ratio and body fat percentage also showed significant positive correlations with BMI in the obese group (rho=0.663, p<0.0001 for waist-to-hip ratio, and rho=0.313, p=0.036 for body fat percentage). In addition, circulating VEGF exhibited strong potential as a biomarker for obesity (AUC=0.813, p=0.001).

Conclusion: Elevated plasma levels of VEGF and the strong positive correlation between HIF-1α and VEGF indicate the potential involvement of hypoxia in the progression of obesity. These findings underscore the potential significance of HIF-1α and VEGF in the pathogenesis of obesity. In this study, VEGF was found to be a potential biomarker for obesity.

Keywords: *Obesity, Vascular endothelial growth factor, Hypoxia-inducible factor 1 alpha, Body mass index*

Obezitede HIF-1α ile Pozitif Korelasyon Gösteren Yüksek VEGF Kan Seviyeleri: Tek Merkez Çalışması

GRAFİKSEL ÖZET



ÖZ

Amaç: Hipoksi indükleyici faktör 1 alfa (HIF-1α) ve vasküler endotelyal büyüme faktörü (VEGF) plazma düzeylerinin obezite ile ilişkisinin ve bu düzeylerin vücut kütle indeksi (VKİ), vücut yağ yüzdesi ve bel/kalça oranı ile ilişkilerinin incelenmesini amaçladık.

Gereç ve Yöntemler: Çalışmaya, Antalya'nın Manavgat ilçesindeki özel bir klinikten sağlanan 45 obez olgu ve 28 sağlıklı kontrol dahil edildi. Tüm bireylerde VKİ, vücut yağ yüzdesi ve bel/kalça oranı bir biyoelektrik empedans analiz cihazı kullanılarak ölçüldü. Plazma HIF-1α ve VEGF düzeyleri mikro-ELISA yöntemiyle ölçüldü.

Bulgular: Mann-Whitney U testinde, HIF-1α düzeyleri obez bireylerde (medyan=1,439 ng/L [Interquartile range (IQR)=11,62 (min-max=0,904-12,53)] ve kontrol grubunda (medyan=1,377 ng/L [1,323 (0,852-2,175)], p=0,0821) benzer bulundu. VEGF düzeyleri ise obez bireylerde kontrol grubuna kıyasla anlamlı derecede yüksekti (medyan değerleri sırasıyla; 729,8 ng/L [5515 (485,3-6000)]'e karşın 589,5 ng/L, [416,8 (396,4-813,2)], p<0,0001). Spearman korelasyon analizinde, obez olgularda VEGF ve HIF-1α düzeyleri arasında güçlü bir pozitif korelasyon gözlendi (rho=0,598, p<0,00001). Obez grupta bel/kalça oranı ve vücut yağ yüzdesi de VKİ ile anlamlı pozitif korelasyonlar gösterdi (bel kalça oranı için rho=0,663, p<0,0001; vücut yağ oranı için rho=0,313, p=0,036). Ayrıca dolaşımdaki VEGF, obezitede güçlü potansiyel bir biyobelirteç olarak belirlendi (AUC=0,813, p=0,001).

Sonuç: Yüksek plazma VEGF seviyeleri ve HIF-1α ile VEGF arasındaki güçlü pozitif korelasyon, obezitenin ilerlemesinde hipoksinin potansiyel rolüne işaret etmektedir. Bu bulgular, obezite patogenezinde HIF-1α ve VEGF'nin potansiyel önemini vurgulamaktadır. Çalışmamızda VEGF'in obezite için potansiyel bir biyobelirteci olduğu gösterilmiştir.

Anahtar Sözcükler: *Obezite, Vasküler endotelyal büyüme faktörü, Hipoksi indükleyici faktör 1 alfa, Vücut kütle indeksi*

INTRODUCTION

Obesity is an important public health issue caused by genetic, environmental, and social factors, that affects individuals of all ages, in both genders, and from different socioeconomic backgrounds. Obesity is characterized by a body mass index (BMI) equal to or exceeding 30, and is known to be linked with a wide range of health complications such as diabetes mellitus, cardiovascular and cerebrovascular diseases, and particular forms of cancer (1-3).

Hypoxia-inducible factor 1 alpha (HIF-1α) is a protein, that plays a crucial role in response to hypoxia. It is suggested that HIF-1α contributes to obesity by promoting angiogenesis in the adipose tissue, allowing fat tissue to be expanded. HIF-1α can increase the expression of genes involved in glucose uptake and energy metabolism, which may contribute to the development of insulin resistance, a key feature of obesity (4, 5).

The vascular endothelial growth factor (VEGF) is a significant protein involved in the angiogenic processes that drive the growth and development of blood vessels. Studies have shown that VEGF expression is increased in adipose tissue, particularly in obese individuals, indicating that it may play a role in the development of obesity (6, 7).

Accordingly, this study aims to investigate the relationship between obesity and circulating levels of HIF-1α and VEGF in individuals clinically diagnosed with obesity.

MATERIAL and METHODS

Subjects

This study was carried out at the Faculty of Medicine, Alanya Alaaddin Keykubat University, between June 2021 and January 2022. The study included 45 subjects with a diagnosis of obesity (23 females and 22 males) and 28 healthy controls (15 females and 13 males), who had no known medical conditions and no familial relationship with the obese subjects. The subjects were recruited from a private clinic in Manavgat, Antalya, Türkiye. G*Power software (G*Power 3.1.9.7 for Windows - https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower) was used for power analysis. The power analysis indicated that a sample size of 37 subjects was necessary for each of the control and patient groups with 80% power, a 5% margin of error, and an effect size of 0.50.

Ethics Approval

The research protocol was approved by the Ethics Committee on Clinical Research at Alanya Keykubat University Faculty of Medicine with approval granted on September 18, 2020 (approval number: 23-22). Before participation, all eligible individuals provided informed consent by completing a Minimum Informed Consent Form, prepared in compliance with the regulations outlined by the Ethics Committee on Clinical Research of Alanya Alaaddin Keykubat University, School of Medicine.

Blood Samples and The Measurement of Body Composition

Following a 12-hour fasting period, 5 mL venous blood samples were collected from all individuals in the morning. The blood samples were transferred into EDTA (anticoagulant) tubes and then subjected to a gentle whirling process at room temperature for a period of between five and ten minutes. Subsequently, the tubes were centrifuged at 2000 rpm for 10 minutes using a refrigerated centrifuge. The plasma samples obtained were divided into aliquots and stored at -20°C until analysis. The samples were thawed at ambient temperature, vortexed, and homogenized on the day of analysis. Measurements of body composition, including fat mass, muscle mass, body fluid levels, soft tissue measurements, BMI calculations, and waist-to-hip ratio were performed using a bioelectrical impedance analyzer (Inbody 270, South Korea).

ELISA Assay

Utilizing micro-ELISA test kits (BT LAB, China, Catalog No: E0422HU and BT LAB, China, Catalog No: E0422HU, respectively) following the manufacturer's protocol, plasma HIF-1α and VEGF levels were examined in obese participants and healthy controls. Using an online calculator (https://www.arigobio.com/elisa-calculator), the levels of HIF-1α and VEGF were determined for both the obese and control groups.

Statistical Analysis

GraphPad Prism (v7.0) software was used to perform the statistical analysis. Kolmogorov-Smirnov test was applied to examine the conformity of the data to normal distribution. Parametric data were evaluated using Student's T-tests, while non-parametric data were analyzed utilizing the Mann-Whitney U test. Spearman's correlation analysis was performed to test the correlation between groups. The diagnostic effectiveness of plasma biomarker expression was evaluated across the research groups using receiver operating characteristic (ROC) curve analysis. A p value of <0.05 was considered statistically significant.

RESULTS

The study's cohort consisted of obese cases with a mean age of 39.04±1.592 years, while healthy controls exhibited a mean age of 38.32±2.46 years. It was found that age and sex

distributions were comparable between obese subjects and healthy controls. In comparison to the control group, individuals in the obese cohort exhibited significantly elevated levels of BMI, body fat percentage, and waist-to-hip ratios (p<0.0001 for all parameters). Moreover, obese subjects exhibited notably elevated plasma levels of VEGF (p=0.0141) in comparison to the controls (Table 1).

As shown in Table 2, HIF-1α, VEGF, BMI, body fat percentage, and waist-hip ratio were compared between obese subjects without any known diseases (n=26) and those with at least one concomitant metabolic disorder (n=19). The most common obesity comorbidities in 19 obese individuals were: hypothyroidism (6 patients), hypertension (4 patients), diabetes mellitus (3 patients), hypertension plus diabetes (2 patients), hypertension plus asthma (1 patient), coronary artery disease (1 patient), asthma (1 patient) and arrhythmia (1 patient). When obese subjects were divided into two groups: those without any known diseases and those with at least one comorbid metabolic disease, the age (years) (p=0.0006) and body fat percentage (p=0.0083) of subjects with comorbid metabolic diseases were significantly higher than those of subjects without such diseases. However, no significant difference was found in remaining parameters (p>0.05) (Table 2).

A robust positive connection (rho=0.598, p<0.00001) was seen in the correlation study between the levels of VEGF and HIF-1α in subjects who were obese (Table 3). Significant positive correlations were also seen in obese subjects between BMI and waist/hip ratio (rho=0.663, p<0.0001) and between body fat percentage and BMI (rho=0.313, p=0.036) (Figure 1). However, no significant relationship was found between BMI and HIF-1α or VEGF (HIF-1α: rho=-0.266, p=0.077; VEGF: rho=-0.118, p=0.439) in the obese group.

ROC curve analysis indicated that HIF1-α did not demonstrate significant potential as a biomarker for obesity (AUC=0.621, p=0.081). However, VEGF exhibited strong potential as a biomarker for obesity (AUC=0.918, p<0.0001) (Figure 2).

DISCUSSION

Obesity, a complex metabolic condition, is often associated with several co-morbidities, including, but not limited to, type 2 diabetes mellitus, cardiovascular, cerebrovascular diseases, hyperlipidemia, hepatic steatosis, gallstones,

Table 1. Mean values for age, sex, HIF-1α, BMI, body fat percentage, and waist/hip ratio of control and obese groups

Characteristics*	Control (n=28)	Obese (n=45)	p
Age (years)	35.5 [42 (19-61)]	37 [37 (24-61)]	0.6743
Gender (Female/Male)	15/13	23/22	0.1000
HIF-1α (ng/L)	1.377 [1.323 (0.852-2.175)]	1.439 [11.62 (0.904-12.53)]	0.0821
VEGF (ng/L)	589.5 [416.8 (396.4-813.2)]	729.8 [5515 (485.3-6000)]	<0.0001
BMI (kg/m^2)	24.20 [7.20 (17.7-24.9)]	33.20 [12.50 (30-42.5)]	<0.0001
Body Fat Percentage (%)	25.25 [27.9 (11.5-39.4)]	40.1 [24.8 (28.4-53.2)]	<0.0001
Waist/Hip ratio	0.875 [0.25 (0.77-1.02)]	1 [0.33 (0.92-1.25)]	<0.0001

*(**Median [IQR (min-max)]**). **Min:** minimum, **max:** maximum, **HIF-1α:** Hypoxia-inducible factor 1 alpha, **VEGF:** Vascular endothelial growth factor, **BMI:** Body mass index

Table 2. Mean values for age, gender, HIF-1α, VEGF, BMI, body fat percentage, and waist-hip ratio of obese subjects with and without at least one accompanying metabolic disease

Parameters*	Obese with at least one accompanying disease (n=19)	Obese without any accompanying disease (n=26)	p
Age (years)	43 [32 (29-61)]	33 [31 (24-55)]	0.0006
Sex (Female/Male)	14/5	9/17	
HIF-1α (ng/L)	1.377 [11.47 (1.059-12.53)]	1.517 [11.29 (0.9-12.19)]	0.1057
VEGF (ng/L)	688.6 [5740 (529.9-6000)]	797.2 [5515 (485.3-6000)]	0.2754
BMI (kg/m^2)	33.9 [12.5 (30-42.5)]	32.25 [11.8 (30-41.8)]	0.3015
Body Fat Percentage (%)	42.1 [20.6 (32.6-53.2)]	36.85 [21.9 (28.4-50.3)]	0.0083
Waist/Hip ratio	0.99 [0.33 (0.92-1.25)]	1.025 [0.21 (0.94-1.15)]	0.3633

*(**Median [IQR (min-max)]**). **X:** Mean, **SEM:** Standard Error Mean, **HIF-1α:** Hypoxia-inducible factor alpha, **VEGF:** Vascular Endothelial Growth Factor, **BMI:** Body Mass Index

Table 3. Correlation analysis of HIF-1α, VEGF, body fat percentage, and waist/hip ratio in the obese group.

Correlation analysis	HIF-1α	VEGF	BMI	Body Fat Percentage (%)	Waist/Hip Ratio
HIF-1α		**rho=0.598 p=0.00001**	rho=-0.266 p=0.077	rho=-0.117 p=0.445	rho=-0.057 p=0.710
VEGF	**rho=0.598 p=0.00001**		rho=-0.118 p=0.439	rho=-0.207 p=0.172	rho=0.020 p=0.898
BMI	rho=-0.266 p=0.077	rho=-0.118 p=0.439		**rho=0.313 p=0.036**	**rho=0.663 p=0.0001**
Body Fat Percentage (%)	rho=-0.117 p=0.445	rho=-0.207 p=0.172	**rho=0.313 p=0.036**		rho=0.086 p=0.573
Waist/Hip Ratio	rho=-0.057 p=0.710	rho=0.020 p=0.898	**rho=0.663 p=0.0001**	rho=0.086 p=0.573	

HIF-1α: Hypoxia-inducible factor alpha, **VEGF:** Vascular Endothelial Growth Factor, **BMI:** Body Mass Index

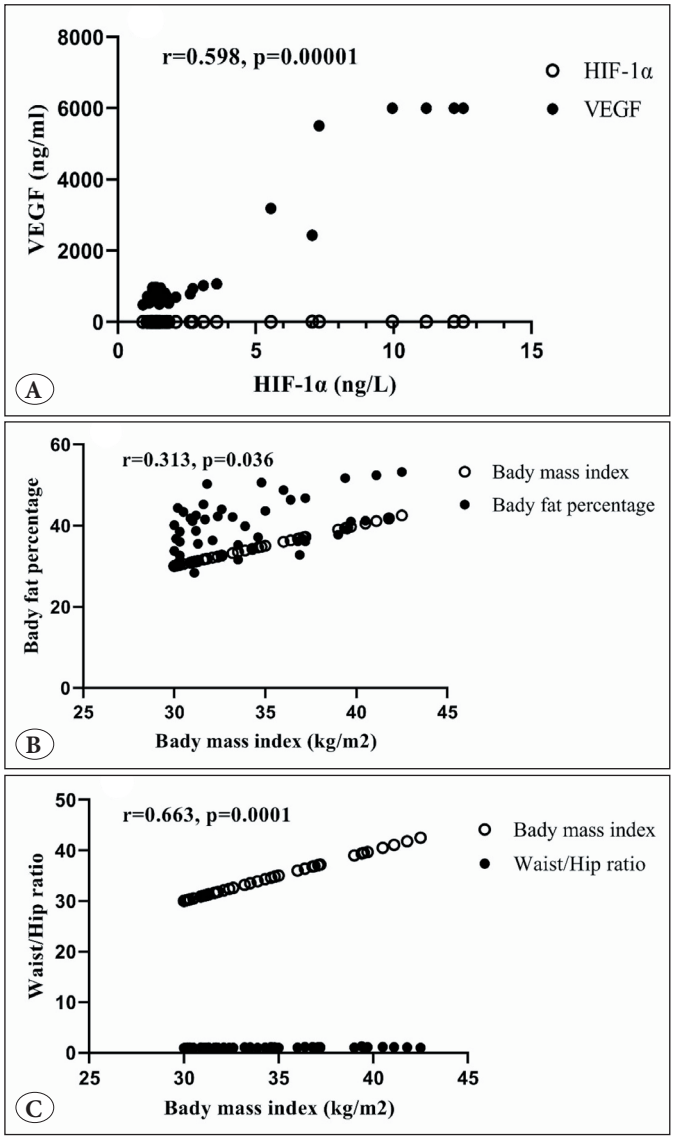


Figure 1: Correlation graphics: The graphs indicate positive correlations between HIF-1α and VEGF **(A)**, body fat percentage and body mass index **(B)**, and waist/hip ratio and body mass index **(C)** in obese individuals.

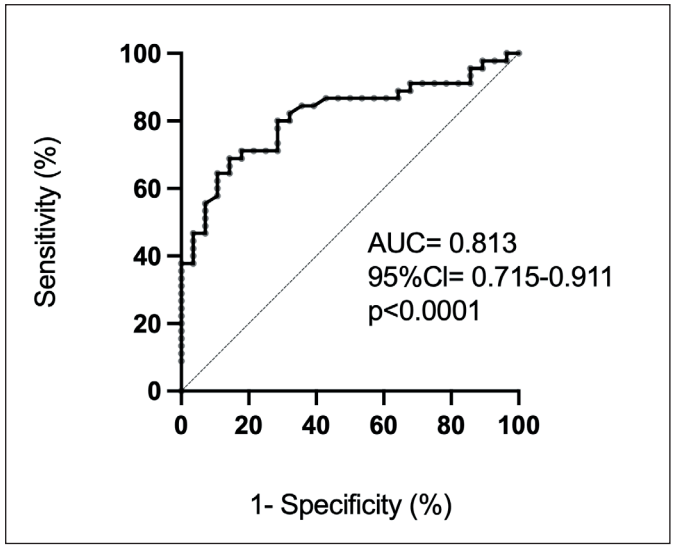


Figure 2: The area under the receiver operating characteristic curve (AUC) for VEGF in obese subjects and controls. VEGF exhibited strong potential as a biomarker for obesity.

osteoarthritis, sleep apnea, asthma, and various malignancies. Many of these conditions are closely associated with impaired vascular function (8-11). VEGF is an important cytokine known to increase vascular permeability and vasodilation, which is produced at substantial amounts by adipose tissue (12, 13). VEGF promotes angiogenesis, which is a necessary process for adipocyte differentiation and adipose tissue growth (14-17). Adipocytes express high levels of VEGF to stimulate angiogenesis and increase adipose tissue capacity (18-20). However, the molecular mechanism underlying VEGF expression in adipocytes hasn't been fully understood.

Studies have shown that circulating VEGF levels are elevated in overweight and obese individuals (21-24). Additionally, it has been shown that blood and adipose tissue VEGF

levels, which are initially high, are decreased in parallel to weight loss in obese individuals who experienced dramatic weight loss after treatment (21, 23, 25). Consistent with these studies, we found high plasma VEGF levels in obese subjects compared to the non-obese group (p = 0.0141). The finding of high plasma VEGF levels in obese subjects in our study suggests a potential significance of VEGF in the etiology of obesity. However, prior research has reported that there is no relationship between obesity and circulating VEGF levels (26). Discrepancies among studies may arise from limitations such as inadequate sample sizes and/or variances in ethnic backgrounds.

Currently, there exists no consensus regarding the association between VEGF levels and BMI among individuals with obesity. Loebig and colleagues have shown that VEGF levels were notably elevated in obese individuals compared to healthy controls with a positive correlation between VEGF levels and BMI. The authors reported that high serum VEGF levels might have a beneficial role for obese individuals compared to lean individuals (27). In addition, many studies have reported positive correlations between serum VEGF levels, BMI, and increased visceral index (23, 24, 28, 29). In our study, no correlation was observed between plasma VEGF levels and BMI (rho=-0.118, p=0.439). There is a need for further studies with larger populations to determine the relationships between VEGF and BMI.

HIF-1α is a transcription factor induced by hypoxia, that is used as an indicator for hypoxia in adipose tissue (30-33). Several studies have shown that adipose tissue hypoxia and HIF-1α up-regulation were positively correlated in obesity (34, 35). Jiang et al. also reported that adipocyte-specific inhibition of HIF-1α in high-fed diet mice provided protection against obesity and insulin resistance (36). HIF-1α is a regulatory protein that stimulates the transcription of over 60 specific genes, including VEGF and erythropoietin. The target genes controlled by HIF-1α comprise angiogenic elements, factors that promote cell proliferation and survival, glucose transporters, and enzymes involved in glycolysis. These molecules play a crucial role in enhancing erythropoiesis and angiogenesis by facilitating glucose transport and metabolism, ultimately leading to increased oxygen availability (4, 37, 38). Hypoxic conditions trigger angiogenesis, either pathologically or physiologically, as a results of the upregulation of pro-angiogenic genes (4, 39, 40). Hypoxia has also been shown to stimulate the expression of VEGF protein and VEGF mRNA, suggesting that hypoxia is a stimulant for up-regulation of angiogenesis (41-45). Increased transcriptional activation of HIF-1 has been reported to result in increased VEGF mRNA levels (46). In our study, a strong correlation was observed between plasma levels of HIF-1α and VEGF in obese subjects (rho=0.598, p=0.00001), suggesting a close relationship between HIF-1α and VEGF.

To our current knowledge, there is just a single study that measured serum HIF-1α levels in obese subjects. Fifteen subjects with morbid obesity were included in the study (11 female, 4 male) who had a gastric sleeve resection. Their mean BMI was 42.6±6.5. Figueroa-Vega et al. (47) reported that BMI values were decreased to 34.4±5.0 and 32.2±4.2, while HIF-1α levels were decreased from 2.6±2.6 at baseline to 2.1±2.5 and 1.4±2.1 ng/L at postoperative months 3 and 6, respectively. The authors suggested that the reduction in HIF-1α expression among morbidly obese individuals resulted from decreased metabolic activity subsequent to weight loss. They also reported that the correlation between HIF-1α levels and the insulin resistance index (HOMA-IR) suggested that HIF-1α may have an impact on insulin resistance. In our study, the median BMI was found to be 33.20 kg/m^2 in 45 obese subjects and although there was no statistical difference, the plasma HIF-1α levels were slightly higher in obese subjects when compared to the control group (medians; 1.439 [IQR= 11.62 (0.904-12.53)] vs. 1.377 [IQR= 1.323 (0.852-2.175)], respectively). In the study by Figueroa-Vega and our study, circulating HIF-1α may indicate the importance of hypoxia in obesity.

In our study, a positive correlation was determined between HIF-1α and VEGF in obese subjects but not in non-obese subjects. This supports the idea that the upregulation of VEGF mediated by HIF-1α expression is a result of increased adipose tissue mass in obesity. Moreover, we identified that circulating VEGF could be a potential biomarker for obesity. Recent studies suggest that VEGF is a novel regulator in energy homeostasis, food intake processes, and obesity. In 2022, Parvaneh and colleagues found that circulating VEGF could serve as a prognostic marker for obesity-related metabolic disorders (48).

Our study has the following limitations: The study's sample size may not have been sufficiently large to capture all potential relationships between HIF-1α, VEGF, and obesity. Larger studies with diverse populations are needed to validate these findings. There may be several factors that could influence plasma HIF-1α and VEGF levels in both the obese and control groups. These factors include lifestyle variables such as dietary patterns, physical activity levels, smoking habits, and concurrent health conditions. However, these factors were not assessed within the scope of our study. While the study found a correlation between HIF-1α and VEGF levels in obese subjects, the exact mechanisms underlying this relationship were not elucidated.

HIF-1α is a marker for adipose tissue hypoxia and has been found to be up-regulated in obesity. Our study showed that the robust correlation between plasma levels of HIF-1α and VEGF in obese subjects may suggest their interplay in processes related to obesity. Our findings support the notion that the upregulation of VEGF mediated by HIF-1α expression is a consequence of increased adipose tissue mass in obesity. Furthermore, we propose that circulating VEGF could serve as a potential biomarker for obesity. Nevertheless, additional research is required to comprehensively understand the association between HIF-1α and VEGF in the context of obesity and its potential role in the pathogenesis of metabolic disorders.

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The Authors Contributions
Study Design: **Nazmiye Uluergüven, Ramazan Güneşaçar,** Methodology and Technical Support: **Nazmiye Uluergüven, Durkadın Demir Ekşi, Erkan Maytalman, Ramazan Güneşaçar,** Data Collection: **Nazmiye Uluergüven, Ramazan Güneşaçar,** Laboratory Studies and Data Analysis, Manuscript Draft, Critical Review of Content: **Nazmiye Uluergüven, Durkadın Demir Ekşi, Erkan Maytalman, Ramazan Güneşaçar,** Supervision: **Ramazan Güneşaçar.**

Conflict of Interest
The authors state that they have no conflicts of interest to disclose.

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Ethics Committee Approval
The research protocol received approval from the Ethics Committee on Clinical Research at Alanya Keykubat University Faculty of Medicine with approval granted on September 18, 2020 (approval number: 23-22).

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Extremely and externally peer-reviewed and accepted.

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