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Serum Vascular Endothelial Growth Factor in Egyptian Obese Women with Insulin Resistance

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Abstract

BACKGROUND: Obesity is a major factor in the development of several sub-clinical anomalies. Insulin resistance (IR) is associated with obesity. Vascular endothelial growth factor (VEGF) plays a significant role in inflammation and vascular neogenesis. However the precise relationships of its levels with clinical, lipid, and metabolic profiles are unknown.

AIM: This study aimed to examine the association between serum VEGF concentrations with IR risk and metabolic and lipid parameters in obese women.

METHODS: Serum VEGF, metabolic biomarkers and anthropometry were measured in 83 obese women with IR and 50 healthy women. Fat distributions in the abdominal, subcutaneous and visceral area were assessed. Homeostasis model assessment for insulin resistance index (HOMA-IR) was calculated. For analytical purposes, VEGF levels were categorised into three tertiles groups.

RESULTS: Obese women with IR showed significantly higher levels of serum VEGF as compared with the control group. Moreover, obese women in the highest VEGF tertile had significantly higher values of obesity indices, visceral fat index, abnormal lipid levels and HOMA-IR compared to with those in the lower tertile.

CONCLUSION: Elevated VEGF levels are associated with IR and high visceral fat index in obese women which in turn increased the risk for metabolic complications.

Introduction

Obesity is a major health issue and considered as an epidemic disease that is still rising all over the world. It leads to and can be accompanied by other diseases; predominantly type 2 diabetes mellitus (T2DM) and cardiovascular complications [1]. However, it is not completely clear how obesity leads to atherosclerosis and cardiovascular diseases. Obesity involves an increase in adipose tissue mass. Therefore, the angiogenesis is required to supply the adipose tissue with sufficient oxygen and nutrients [2]. However, several studies suggested that the expansion of the vascular network does not provide sufficient oxygen to all adipocytes causing local hypoxia [3], [4]. The insufficient blood flow in the adipose tissue has been supposed to provoke insulin resistance through effects on inflammation, adipokine expression, and/or adipocyte differentiation [5]. In obese patients, it is hard to predict the development of diabetes as some of the obese individuals could be metabolically healthy, and several studies have found negative IR status and no complications in severely obese patients [6]. Therefore, the relationship between T2DM and obesity could not be determined by the absolute amount of the stored fat [7].

Vascular endothelial growth factor (VEGF) is responsible for most of the angiogenic actions in adipose tissue [8], in addition to its pathological role in the vascular disease processes [2]. However, its expression was found to be not specific to endothelial cells [9]. Insulin has a vascular-specific action in the endothelium as it is regulating the expression of VEGF, at physiological concentrations insulin can increase the expression of VEGF [10]. Few studies

have explored the relationship between adipose tissue angiogenic capacity, obesity and IR [11]. It is known that the development of adipose tissue necessitates adipogenesis and angiogenesis. The major angiogenic pathway is through the action of the VEGF factor on the VEGF receptor-2 [12]. It has been previously demonstrated that VEGF is responsible for lots of the angiogenic activity of adipose tissue [13].

Higher circulating levels of VEGF have been found in overweight and obese cases [14]. A positive correlation has been observed between concentrations of VEGF and body mass index (BMI) regardless of the insulin sensitivity [15]. However, according to a population-based cross-sectional study, it has been observed that the VEGF has a small effect on the development of atherosclerosis [16].

Therefore, in the present study, the relationship between VEGF and IR in obese women was examined to assess its pathological significance in the acceleration of metabolic complications. This could be of great importance in the management of metabolic diseases and understanding of the pathophysiological alterations in obese women.

Subjects and Methods

Subjects

Eighty-three obese women with IR aged between 18 and 35 years were included in the present study in addition to 50 age-matched healthy non-obese controls. Cases and controls were chosen between October 2016 and January 2018 from obesity Clinic at National Research Centre, Egypt.

Clinical and biochemical assessment

Full medical history and clinical examination for all patients and controls have been done. Anthropometric measurements including body mass index (BMI), waist circumference (WC) and hip circumference (HC) have been measured as previously described [17]. Consequently, the Waist-to-Hip-Ratio (WHR) was calculated as WC divided by HC. The sum of skinfolds (sum SF) was calculated for each subject and control from the skin-fold thickness measured at the biceps, triceps, subscapular, supra-iliac, and abdominal areas using Holtain calliper.

Blood pressure was measured using calibrated sphygmomanometer and brachial inflation cuff (HEM-7200 M3, Omron Healthcare, Kyoto, Japan). Systolic and diastolic blood pressures (SBP and DBP) were measured twice, and then the average is used for analysis. Visceral adiposity index (VAI) was calculated as follows [18]:

$$\text{VAI} = \left(\frac{\text{WC}}{36.58+(1.89\times\text{BMI})}\right) \times \left(\frac{\text{TG}}{0.81}\right) \times \left(\frac{1.52}{\text{HDL}}\right)$$

Laboratory measurements

Blood samples were collected after fasting for a minimum of 12 h. Fasting plasma glucose and serum lipids comprising total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) have been measured. Low-density lipoprotein cholesterol (LDL-C) was calculated according to the equation LDL-C = Total cholesterol - Triglycerides/5+ HDL-C) [19]. Serum insulin concentration was analyzed by chemiluminescent immunoassay (Immulite2000, Siemens, Germany. Insulin resistance has been estimated by the Homeostasis Model Insulin Resistance (HOMA-IR) as previously described [20]. The Human Vascular Endothelial Growth Factor (VEGF) levels were measured using a solid-phase enzyme-linked immune sorbent assay sandwich ELISA kit developed by NOVA NO. 18, Keyuan Road, DaXing Industry Zone, Beijing, China.

Statistical analysis

All the statistical analyses have been performed using SPSS version 16.0 software. We explored the distribution of the variables using the Kolmogorov-Smirnov test of normality. While means ± SDs were used to describe the normally distributed data, logarithmic transformation was performed to all skewed variables. Triglycerides and serum VEGF levels have shown skewness necessitating using median and tertile ranges. For analytical purposes, VEGF levels were categorised into three groups according to tertiles. A one-way analysis of variance was performed for the comparison of more than two groups. The unpaired t-test or the Mann-Whitney U test was used, as appropriate, to evaluate differences between the two groups of continuous variables. Regression analysis was used to investigate the association between VEGF levels and obesity indices. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the clinical and biochemical characteristics of both obese and healthy women. Significantly higher concentrations of serum VEGF have been observed in obese cases with IR compared to controls. Obese-IR patients also showed significantly higher levels of BMI, WC, WHR, and total cholesterol, TG, LDL-C and HOMA-IR relative to controls ($p < 0.05$).

Table 1: Clinical and biochemical characteristics of obese women with IR and healthy controls

	Controls N = 50 Mean ± SD	Patients N = 83 Mean ± SD
Age (years)	27.0 1± 3.09	28.14± 4.37
BMI (kg/m^2)	22.47 ± 2.36	33.41± 6.06**
WC (cm)	82.9 ± 7.4	90.4 ± 9.9**
WHR	0.78 ± 0.08	0.83 ± .06*
Sum SF	100.5 ± 22. 9	150.1 ± 21.1**
VAI	3.57 ± 2.52	9.57 ± 2.52**
SBP (mmHg)	98.75 ± 15.86	103.33 ± 17.575
DBP (mmHg)	64. 8 ± 5.4	67.46 ± 8.79
HOMA-IR	2.86 ± 1.2	5.86 ± 2.70**
Total cholesterol (mg/dl)	163.06 ± 46.5	201.17 ± 54.8**
TG (mg/dl)	79.61 ± 33.53	104.45 ± 40.5**
HDL-C (mg/dl)	44.39 ± 10.777	45.77 ± 10.69
LDL-C (mg/dl)	106.47 ± 44.561	153.78 ± 50.8*
VEGF (pg/ml)	80.68 ± 17.64	156.64 ± 14.35*

BMI: body mass index; WC: waist circumference; Sum SF: sum of skin folds; SBP: systolic blood pressure; DBP: diastolic blood pressure; VAI: visceral adiposity index; TG: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment-insulin resistance; VEGF: vascular endothelial growth factor; *p < 0.05; ** p < 0.001.

The clinical and biochemical parameters of obese-IR women were further analysed by tertiles of serum VEGF levels (Table 2). The concentration of VEGF in the Lower tertile was ≤ 79.04, while the intermediate tertile ranged from 79.05-143.26 and the higher tertile was ≥ 143.27. Obese subjects in the higher tertiles showed significantly higher values of WHR, the sum of skinfolds, visceral adiposity index (VAI), total cholesterol, TG and LDL-C, and HOMA-IR compared to those in the lower tertile.

Table 2: Clinical and anthropometric parameters of obese women with IR, divided according to tertiles of circulating VEGF concentrations

Characteristic	Lower tertile VEGF ≤ 79.04 pg/ml	Intermediate tertile VEGF between 79.05 and 143.26 pg/ml	Higher tertile VEGF ≥ 143.27 pg/ml
WHR	0.8 ± 0.06	0.8 ± 0.07	0.9 ± 0.05*
Sum SF	131.4 ± 10.9	133.7 ± 11.6	149.2 ± 12.0*
VAI	5.57 ± 2.52	6.71 ± 4.89	10.28 ± .5.01**
SBP (mmHg)	110.3 ± 11.4	118.4 ± 9.3	125.4 ± 9.3
DBP (mmHg)	74.3 ± 7.4	75.3 ± 6.8	89.9 ± 8.2
HOMA-IR	3.5 ± 1.2	4.4 ± .9	5.2 ± .7*
Total cholesterol (mg/dl)	142 ± 25.5	155.9 ± 22.1	199.9 ± 20.9*
TG (mg/dl)	142. 5± 26.7	153.6 ± 25.9	196.6 ± 26.7*
HDL-C (mg/dl)	46.5 ± 26.2	44.8 ± 23.8	44. 6 ± 24.4
LDL-C (mg/dl)	128.6 ± 21.8	1 40± 20.7	157. 4± 21.9*

WHR: waist-hip ratio; Sum SF: sum of skin folds; VAI: visceral adiposity index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HOMA-IR: homeostasis model assessment-insulin resistance; TG: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; *p < 0.05; ** p < 0.001 indicates a significant increase.

Regression analysis showed a positive association between VEGF serum concentration and VAI (Figure 1).

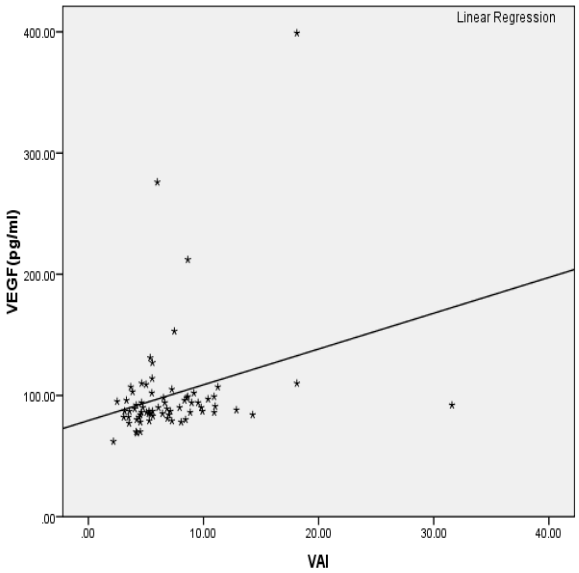

Figure 1: Relation between visceral adiposity index and serum vascular endothelial growth factor in obese women with IR

Discussion

Vascular endothelial growth factor (VEGF) is engaged in vessel formation in both the normal and pathological conditions. It is a key factor involved in adipose tissue angiogenesis. The fats that accumulate intra-abdominally might be a source of many risk factor syndromes via insulin resistance.

Lots of studies suggested that the vascular network expansion during obesity does not give enough oxygen supply to all adipocytes. Consequently, local hypoxia occurs [21], [22], [23]. In the present study, significantly increased levels of serum VEGF have been observed in obese IR women relative to the control group ($p < 0.05$). Furthermore, obese IR patients that have the highest VEGF levels showed also higher values of the waist to hip ratio, visceral fat index, lipid and HOMA-IR levels compared to other obese IR with lower VEGF values. A significant correlation between the VEGF concentrations and visceral fat and WHR have also been found. Our findings are in agreement with another study [24] that reported the presence of correlation between VEGF levels and visceral fat accumulation. The authors also performed stepwise regression analysis and demonstrated that although the visceral fat is an independent factor, it is the most important factor in the determination of serum VEGF levels. Furthermore, the reduction in the body weight and the subsequent decline in the visceral fat area caused a decrement in the VEGF concentrations. Subsequently, it was suggested that serum VEGF concentration is regulated by the adipose tissue secretions particularly, the area of the visceral fat [24].

The vascular endothelium plays a substantial role in the regulation of vasomotor functions, maintenance of vessel walls, and anti-platelet aggregation in addition to the endocrine functions in the human body. Several stimuli such as injury and cardiovascular risk factors could cause the impaired function of the vascular endothelium [25]. Various studies indicated that endothelial cell dysfunction is an early pathophysiological indicator of cardiovascular diseases (CVD). VEGF, among other substances, is secreted by the vascular endothelium and could be a substantial indicator of endothelial cell function [26].

Different signalling pathways are activated by the binding of VEGF to their corresponding receptors [27]. Various stimuli such as growth factors, inflammatory cytokines, and hypoxia could induce the VEGF secretion. Previous studies reported significantly higher VEGF levels in overweight and obese patients compared with slim subjects [14]. It has been proposed that high adiposity in obese patients induce secretion of various inflammatory cytokines, such as interleukin-6 (IL-6) that in turn causing increased VEGF secretion [25], [27].

However, other study suggested that the overexpression of VEGF-A in adipose tissue enhancing thermogenesis and energy expenditure resulting in decreasing obesity [28]. And in addition to the role of VEGF in vasculogenesis and angiogenesis, it also exerts metabolic effects and controls energy metabolism [29], [30]. In the present study, a significantly higher concentration of VEGF has been found in obese IR patients.

Previously, body mass index and blood pressure were found to be the independent determinants of VEGF [31]. It was also suggested that hyperglycemia without associated dyslipidemia is responsible for vascular endothelial lesions [32]. Additionally, higher levels of VEGF have been observed in patients with type -1 diabetes relative to healthy controls [33]. Significantly increased levels of VEGF have been found in metabolic syndrome cases compared to healthy control [34].

In conclusion, our results suggest an association between elevated serum levels of VEGF and IR in obese women. So elevation of VEGF might be responsible for the occurrence of metabolic abnormalities, highlighting the important role of obesity and visceral adiposity on insulin sensitivity.

Declarations

Ethics approval and consent to participate

After a complete description of the study, written informed consent has been obtained from all participants. The Ethical Committee of National Research Centre, Egypt (number = 16361) has authorised the research in conformity with the World Medical Association's Declaration of Helsinki (2013).

Availability of data and material

The data used and analysed during the current study are available from the corresponding author on reasonable request.

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