

Association of Adipocytokines with Lipid and Glycemic Profiles in Women with Normal Weight Obesity

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Abstract

Background: Individuals with normal weight obesity (NWO) are prone to cardiometabolic disorders. The aim of this study is to investigate the circulating levels of vaspin and leptin and their association with glycemic and lipid profiles in women with NWO.

Methods: Forty women with body mass index (BMI)=18.5-24.9 kg/m² and fat mass (FM) \geq 30% were assigned in the NWO group and thirty age-matched women with identical BMI range and FM<30% (normal weight non-obese; NWNNO) as control group were invited. Anthropometric measurement, fasting blood sugar (FBS), insulin, glycated hemoglobin (HbA1c), lipid profiles and also, leptin and vaspin were measured.

Results: The mean \pm standard deviation (SD) age was 28.76 ± 4.76 years in the NWO group and 29.23 ± 4.50 years in the control condition. The NWO group had higher mean serum levels of insulin (9.02 ± 4.75 vs. 6.24 ± 2.51 , $P = 0.009$), leptin (17.31 ± 8.10 vs. 9.94 ± 4.30 , $P < 0.001$) and homeostatic model assessment of insulin resistance (HOMA-IR) (33.77 ± 20.71 vs. 23.48 ± 10.03 , $P = 0.009$) compared to the NWNNO group. Serum level of vaspin was higher in the NWO group compared to the control group (34.82 pg/ml vs. 27.72 pg/ml, respectively, $P = 0.12$). In NWO group, serum levels of leptin correlated positively with FBS ($r = 0.45$, $P = 0.02$), insulin ($r = 0.51$, $P = 0.008$), and HOMA-IR ($r = 0.46$, $P = 0.02$) and vaspin concentration was positively associated with insulin ($r = 0.36$, $P = 0.02$) and HOMA-IR ($r = 0.30$, $P = 0.06$).

Conclusion: It is concluded that concentration of insulin and HOMA-IR index were significantly higher in women with NWO compared to NWNNO. Higher levels of leptin and vaspin in the NWO group were associated with glycemic profiles.

Background

Obesity as a major public health problem is progressively increasing to the pandemic level worldwide[1]. It is well-known that obesity defined as excess body fat accumulation, is the major risk factor of many chronic diseases such as metabolic syndrome, dyslipidemia, hypertension, infertility, diabetes mellitus and even cancer and cardiometabolic diseases[2].

Obesity is assessed by body mass index (BMI) ≥ 30 kg/ m² in practical and research medicine. In addition to the BMI, other anthropometric indexes such as waist circumference (WC), waist to hip ratio (WHR) were used to determine the abdominal obesity. However, despite the wide use of BMI, it has some limitations in classification of obesity. Normal Weight Obesity (NWO) syndrome was used by De Lorenzo (2006) in the literature to define the subjects with normal BMI but high percentage of body fat, concurrently[3]. According to the BMI classification, these subjects were considered as normal ones, but previous studies have reported that subjects with NWO are exposed to the metabolic disorders including cardiometabolic disorders, metabolic syndrome, hyperlipidemia and cardiovascular risk factors[4].

Adipose tissue not only serves as a storage site for fat, but also is an active organ with endocrine and paracrine secreting function. Adipocytokines or adipokines are terms, used to identify a large number of cytokines and bioactive mediators are produced and released from fat tissues. Adipose tissue secretes various hormones including adiponectin, leptin, resistin, visfatin, omentine, and cytokines such as tumor necrosis factor-alpha (TNF- α), and interleukin-6 (IL-6). In one recent review study, researchers found that up-regulation of adipocytokines such as resistin, vaspin, apelin and TNF- α is associated with obesity and type 2 diabetes by inducing insulin resistance[5, 6].

On the other hand, skeletal muscle cells secrete signaling molecules with auto-, para- and/or endocrine functions, known as myokines[7]. Previous studies have demonstrated that both adipokines and myokines are involved in the regulation of energy metabolism, glucose and lipid metabolism, reproduction, cardiovascular function and immunity[8, 9].

Based on the definition of BMI and NWO, patients with normal weight but metabolic obesity have excess fat mass and less lean body mass in the frame of normal BMI. Therefore, patients with NWO may have imbalance level of adipokines and myokines compared to the subjects with both normal BMI and normal body composition.

The primary aim of this study was to investigate the circulating levels of some adipocytokines such as vaspin and leptin in women with NWO compared to those with normal weight and normal body fat (control group). The secondary aim of this study was to investigate the association between these adipocytokines and glycemic indices and lipid profile in the study groups.

Methods

Subjects

In this case-control study, 40 women with BMI=18.5-24.9 kg/m² and fat mass (FM) \geq 30% as a NWO group and 30 age matched women with BMI=18.5-24.9 kg/m² and FM<30% as control group (NWN: normal weight no obese) were selected from sport clubs in Tehran, Iran. The inclusion criteria were as follows: 1) subjects with a normal BMI (18.5-24.9 kg/m²) and 2) age range of 19-39 years. Women with pregnancy or lactation in the time of study or those who had a history of diabetes, endocrine or metabolic disorders, liver and kidney dysfunction, hypertension, gastrointestinal, cardiovascular, thyroid and autoimmune diseases or diagnose infection were excluded from the study. The ethics committee of Shahid Beheshti University of Medical Sciences approved the study protocol. Written informed consent was obtained from all the participants before the beginning of the study.

Anthropometric measurements

Weight (Wt) and height (Ht) was measured in standing position according to the standard protocol while they wear light clothes without stocks and shoes using (Seca725 GmbH & Co. Hamburg, Germany) to the

nears 0.1 kg and 0.5 cm, respectively. BMI (kg/m^2) was calculated as Wt (kilograms) divided by the square of the Ht (meters).

Waist circumferences (WC) and hip circumferences (HC) measured by one-trained personnel, according to the standard protocol described by the International Society for the Advancement of Kianthropometry (ISKA). Waist to hip ratio (WHR), as an indicator of abdominal obesity was determined by dividing of WC (cm) to HC (cm).

Percentage of body fat (BF) was assessed by bioelectrical impedance using a Tanita body composition analyzer (Model TBF-300; Tanita, Tokyo, Japan). Subjects were asked to follow these criteria: 1) remove all metal objects, such as earrings, etc., 2) wear light clothing before each measurement, 3) avoid eating heavy meal or drinking coffee/alcohol during 3 hours before measurement, 4) avoid smoking and exercise before measurement, 5) without any clinical sings of dehydration.

Laboratory measurements

Five milliliters fasting venous blood samples were taken from the participants. The samples were centrifuged (3000 g, 10 min, at 4 °C) for one hour, stored at 20 °C and analyzed for one week. Fasting serum glucose concentration, total cholesterol (TC), triglyceride (TG), and high density lipoprotein (HDL-C) levels were measured by a Hitachi 912 Auto-analyzer (Hitachi, Mannheim, Germany) using commercial kits [Pars-Azmoon kits, Iran]. The low-density lipoprotein cholesterol (LDL-C) level was measured in subjects with serum triglyceride concentrations <400 mg/ml using the Friedewald formula:

$$(\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - 1/5 \text{ triglycerides})$$

Glycated hemoglobin (HbA1c) was measured using the ion exchange chromatography method (Biosystems S.A. Barcelona, Spain). Glycated hemoglobin (HbA1c) level was measured by ion exchange chromatography with a DS5 set [DREW, United Kingdom]. The serum insulin level was assessed by using an immune enzymometric assay [Monobind Inc., USA]. The intra- and inter-assay coefficients of variation (CVs) were 5.9% and 9.2%, respectively. Homeostasis model assessment of insulin resistance (HOMA-IR) as an index of insulin resistance (IR) was calculated based on following equation: HOMA-IR: $[\text{Insulin}] \text{ (in mU/l)} \times [\text{glucose}] \text{ (in mg/dl)} / 405$.

Serum leptin concentration was measured by enzyme-linked immune absorbent assay (ELISA) with a commercially available human leptin ELISA kit (Bio Vendor Laboratory Medicine, Inc., GmbH) using specific human leptin antibody. The intra- and inter-assay coefficients of variation were less than 5% for leptin. Before the assay, quality controls and all sera were diluted 5 times with a diluting buffer.

Vaspin ELISA. Serum vaspin level was measured using a commercially available human vaspin ELISA kit (CUSABIO BIOTECH, Wuhan, China), following the manufactures instructions.

Statistical analysis

Statistical analyses performed using SPSS[1]version 19.0 (SPSS Inc., Chicago, IL, USA).The normal distribution of continuous variables was assessed using Kolmogorov-smirnov test. Continuous variables with and without normal distribution were expressed as mean \pm standard deviation (SD) and as median (interquartile range) respectively. Categorical variables were expressed as numbers (%). Continuous variables between NWO and NWO were compared using t-test. Pearson and Spearman correlation tests were used to evaluate the association of vaspin and leptin with glycemic indices and lipid profile. A value of $p < 0.05$ was considered as statistically significant.

[1] Statistical package for the social science

Results

The mean \pm SD of age was 28.76 ± 4.76 years in patients with NWO and 29.23 ± 4.50 years in NWO which was not statistically significant ($P = 0.69$). Anthropometric measures based on type of study groups are summarized in Table 1. As we expected, the mean \pm SD of fat mass in NWO group was significantly higher than that in controls; while all participants had BMI in normal range (19.00 - 24.80 kg/m^2) with no statistically significant differences between two groups. Patients with NWO had higher waist circumference and hip circumference compared to the healthy controls ($P < 0.001$ for both). However, no statistically significant difference was observed between the two groups with respect to waist to hip ratio.

Table 1. Anthropometric measures according to study group

Variables	NWO (N=40)	Control (N=30)	<i>P</i> value
Height (cm)	165.89 ± 4.43	165.33 ± 4.81	0.62
Weight (kg)	62.77 ± 4.77	56.98 ± 4.40	<0.001
BMI (kg/m^2)	22.66 ± 1.23	20.88 ± 1.28	<0.001
WC (cm)	74.77 ± 4.74	70.84 ± 3.03	<0.001
HC (cm)	98.90 ± 4.29	93.44 ± 2.99	<0.001
WHR	0.75 ± 0.04	0.75 ± 0.03	0.66
FM (kg)	20.47 ± 2.71	13.56 ± 1.45	<0.001
FFM (kg)	42.06 ± 2.87	43.21 ± 3.24	0.14

BMI: body mass index, WC: Waist circumference, HC: Hip circumference, FM: fat mass, WHR: Waist to hip ratio, FM: fat mass, FFM: fat free mass
T-test used to compare two groups
 $P < 0.05$ is statistically significant

The biochemical characteristics of participants in both groups were summarized in Table 2. No statistically significant difference was found between two groups in terms of FBS, while the fasting serum level of insulin in NWO group was higher than that in the healthy controls ($P = 0.009$). Accordingly, HOMA-IR was significantly higher in NWO group compared to the controls, ($P = 0.02$). No significant difference observed in NWO group with respect to lipid profile as compared with the healthy control group for fasting serum levels of TC, TG, LDL-c and HDL-c. Patients in NWO group had significantly higher blood concentration of leptin compared to the control group ($P < 0.001$). There was no statistically significant difference between the two groups in terms of vaspin level.

Table 2. Biochemical characteristics of participants according to study group

Variables	NWO (N=40)	Control (N=30)	P value
FBS ^a (mg/dl)	82.71 ± 8.16	84.44 ± 7.33	0.45
Insulin ^a (μIU/ml)	9.02 ± 4.75	6.24 ± 2.51	0.009
HOMA-IR ^a	33.77 ± 20.71	23.48 ± 10.03	0.02
TC ^a (mg/dl)	174.00 ± 29.35	173.84 ± 21.56	0.94
TG ^a (mg/dl)	87.07 ± 28.28	82.64 ± 27.18	0.53
HDL ^a (mg/dl)	59.02 ± 13.70	61.04 ± 9.10	0.52
LDL ^a (mg/dl)	90.89 ± 18.08	89/04 ± 17.23	0.68
Leptin ^b (pg/ml)	16.45 (11.70-20.00)	9.60 (6.50-13.40)	<0.001
Vaspin ^b (pg/ml)	0.16 (0.04-0.20)	0.05 (0.01-0.90)	0.57

NWO: normal weight obesity, FBS: fasting blood sugar, HOMA-IR: homeostasis model assessment of insulin resistance, TC: total cholesterol, TG: triglyceride, HDL: high density lipoprotein, LDL: low density lipoprotein, IQR: Inter quartile range

a: Data expressed as mean ± SD and compared between two groups using t-test

b: Data expressed as median (IQR) and compared between two groups using Mann-Whitney

$P < 0.05$ is statistically significant

Table 3 shows the correlation coefficients between the serum levels of leptin and vaspin and glycemia and lipid profiles in NWO and control groups. As shown in Table 3, there was a significant positive correlation between serum levels of leptin and FBS ($P = 0.02$), fasting level of insulin ($P = 0.008$) and HOMA-IR ($P = 0.02$) in NWO group. Serum level of vaspin was significantly associated with fasting level of insulin in NWO group ($P = 0.02$).

The association of vaspin and leptin levels with lipid profile in both NWO and control groups was not statistically significant. No significant associations were observed between serum levels of vaspin and

leptin with glycemia and lipid profiles in controls.

Table 3. Correlation coefficients between serum level of leptin and vaspin with glycemic indices and lipid profiles NWO and control groups

Variables	Vaspin*		leptin**	
	NWO (N=40)	Control (N=30)	NWO (N=40)	Control (N=30)
FBS (mg/dl)	-0.01 (0.93)	-0.02 (0.89)	0.45 (0.02)	0.24 (0.13)
Insulin(μ IU/ml)	0.36 (0.02)	0.009 (0.96)	0.51 (0.008)	0.23 (0.15)
HOMA-IR	0.30 (0.06)	0.02 (0.89)	0.46 (0.02)	0.30 (0.06)
TC (mg/dl)	0.11 (0.51)	0.32 (0.11)	-0.01 (0.92)	-0.04 (0.81)
LDL-c (mg/dl)	-0.01 (0.91)	0.16 (0.42)	0.01 (0.91)	0.07 (0.73)
HDL-c (mg/dl)	0.27 (0.09)	0.12 (0.54)	-0.12 (0.44)	-0.37 (0.06)
TG (mg/dl)	0.02 (0.89)	0.21 (0.31)	0.19 (0.23)	0.25 (0.22)
TC/ HDL	0.24 (0.13)	0.32 (0.04)	0.02 (0.89)	0.24 (0.24)

Data expressed as r (*P* value)

* Values expressed as Spearman coefficient

**Values expressed as Pearson coefficient

P < 0.05 is statistically significant

The results of this study demonstrated that the serum concentration of leptin was significantly associated with hip circumference($r = 0.39$, $P = 0.01$) and body fat ($r = 0.36$, $P = 0.02$) in NWO group, while the serum level of vaspin had significant inverse correlation with hip circumference ($r = -0.58$, $P = 0.002$) and body fat ($r = -0.39$, $P = 0.05$) in control group.

Discussion

In this study, we observed that concentration of insulin and insulin resistance that evaluated by HOMA-IR index were significantly increased in women with NWO compared to the control women who had normal BMI and FM. Our primary outcomes were significant higher blood concentration of leptin in women with NWO compared to women in control group. Despite the higher level of vapin in NWO group, it was statistically significant in NWO group compared to controls.

In previous studies, the prevalence of cardiometabolic abnormalities in patients with NWO have reported compared to normal and obese counterparts. The results of Huang et al. study conducted on young Japanese female demonstrated that NWO women had higher fasting insulin levels than lean women or those with normal weight normal obesity (NWN0) (non-significant) but had lower level of fasting insulin levels compared to obese women ($P = 0.003$). The same results were reported about the HOMA-IR, but the

HOMA- β cell in NWO women was higher than lean and or NWO women ,while it was lower in these women compared to the obese women[10].

The result of this study was important for us because this study performed on Asian women. Body fat mass deposition and distribution are influenced by race. The prevalence of fat mass accumulation in the upper body region is higher in Asian women compared to Caucasian whites in the same BMI[11]. For this reason, Asian women with normal BMI are more susceptible to NWO. In our study, similar to the Huang study conducted on Japans women, body fat mass ≥ 30 % of body weight was considered as excess body fat.

Madeira et al. conducted a study on 1222 men and women in Brazil and found that normal weight obesity was associated with HOMA-IR, low insulin sensitivity, and high insulin secretion[12].

The positive association between increased body fat tissue and cardiometabolic disorders, despite having normal body weight, has reported among adolescences. Heijden et al. have shown that in Hispanic adolescent girls with normal BMI (<85th percentile) and high body fat ($\geq 27\%$), abdominal and hepatic fat content, insulin resistance, plasma leptin and Hs-CRP concentrations significantly increased compared to those with normal BMI and BF[13].

Previous studies have shown that individuals with NWO are susceptible to metabolic syndrome and cardiovascular disease due to the increased prevalence of hyperglycemia, insulin resistance, low grade of pro-inflammation status, increased oxidative stress, hyperlipidemic disorders in NWO, which increased by increasing the percentage of body fat tissues in adults and adolescents [14-16].

The relationship between the abdominal fat depositions and other components of metabolic syndrome was confirmed in numerous previous studies in various populations such as subjects with overweight/obesity or type 2 diabetes or syndrome metabolic and or postmenopausal women[17-19].

Wei et al. study reported the distributed adipokines profile in obese patients with newly diagnosed type 2 diabetes (T2DM) compared to diabetic patients with normal BMI. It was shown that obese T2DM patients had increased level of leptin and reduced concentration of adiponectin compared to non-obese T2DM patients[20]. The results obtained from this study and previous studies may explain the relationship between fat mass, adipokines as a paracrine and endocrine secretion of fat tissues and cardiometabolic abnormalities as a three components of the triangle with multiple interactions and feedbacks. However, more studies are needed to demonstrate the cellular and molecular mechanism of interaction between adipokines at cellular level and endocrine disorder in clinical level.

One of the theories to describe the association between the excessive body fat tissues and components of metabolic syndrome is related to adipokine secretion. The results of the present study showed that serum levels of leptin and vaspin in NWO women were higher than those in controls. Our results indicating an increase in the concentration of leptin were consistent with previous studies. Romero-Corral et al. reported increased concentration of leptin among American individuals with NWO which was

consistent with our results [14]. Another study conducted on Swiss population showed that leptin concentration in women with NWO was higher than that in women with normal BMI and FM%[21].

It was confirmed that the obese patients had higher level of leptin compared to the individuals with normal weight, which might be due to the leptin resistance in obesity[22].

Leptin is one of the primary hormones used to diagnose adipocytokine secreted from adipose tissues. Therefore, according to the previous studies, there is positive relationship between blood level of leptin and percentage of body fat[23]. We observed similar results in our study among women with NWO ($r = 0.36$, $P = 0.02$). Our secondary outcomes were a positive association between concentration of leptin with fasting levels of FBS and insulin and HOMA-IR.

According to the past investigations, leptin shows paradox actions which can increase atherogenesis and insulin resistance or may have antiatherogenesis and increase insulin sensitivity. Koh et al. reported that the opposite effects of leptin are in balanced conditions in healthy individuals and disrupted in obesity[24]. It seemed that the action of leptin increasing insulin resistance in subjects with NWO is similar to the patients with obesity.

Otherwise, leptin level has a positive correlation with the markers of pro-inflammatory and inflammatory status, which can describe the role of higher level of leptin in increasing the risk factors of cardiometabolic disorders[25, 26].

Similar to the leptin, our results showed there was a statistically significant association between vaspin concentration and fasting insulin level and HOMA-IR in women with NWO.

Vaspin, as a serine protease inhibitor, is another adipokine secreted from adipose tissue. A experimental study showed that injection of vaspin to obese mice can improve glucose tolerance by increasing insulin sensitivity[27].

Compared to the leptin and adiponectine, limited studies have performed about vaspin in humans and most studies have focused on animal models of obesity and type 2 diabetes.

Based on the physiological functions of adipokines, they are classified into two categories: "healthy" adipokines such as adiponectine and omentin and "unhealthy" adipokines. In addition to the TNF- α , IL-6, plasminogen activator inhibitor-1, adipocyte fatty acid-binding protein, lipocalin-2, chemerin, visfatin and resistin, vaspin and leptin are considered as unhealthy adipokines[28].

Based on the results of Genske, et al. study conducted on 1825 participants of the study of Health in Pomerania, they found no clear conclusion with respect to the association between blood concentration of vaspin and distribution fat tissues including visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), or liver fat content (LFC)[29].

In 3T3-L1 cells, it was shown that endogenous vaspin positively associated with insulin signaling which could be described by the role of vaspin in increasing insulin-stimulated phosphorylation of the key mediator protein kinase B[30].

On the other hand, the results of experimental study in mice, reported that injection of insulin in fasting status positively increased the hepatic expression of vaspin[31].

Previous studies have indicated that the serum concentration of vaspin was increased with worsening insulin resistance in children and impaired glucose tolerance and obesity in adults[32-34].

Our results are consistent with those of previous studies and we found a positive significant association between serum levels of vaspin and insulin in women with NWO. Therefore, it suggested that serum levels of vaspin are increased as a compensatory response to elevated concentration of insulin and insulin resistance. Vaspin mRNA expression is higher in patients with type 2 diabetes and in addition in obese patients due to the higher percentage of FM. Patients with NWO phenotypically have both impaired glucose intolerance and higher FM%. Regarding to the compensatory effect of vaspin, Heiker et al. proposed that increasing insulin sensitivity through the reduction of kallikrein 7 (hk7) induced insulin degradation. They demonstrated hk7 as the target protease of vaspin in human tissues[35]. On the other hand, obesity due to the higher body fat mass induced the chronic low-grade inflammation. Previous studies have shown that vaspin may inhibit inflammatory processes under the control of peroxisome proliferator-activated receptor (PPAR)[36]. More studies are needed to find the mechanism of adipokines effects on the glycemic responses in NWO patients.

To our knowledge, this is the first study on the changes in serum level of vaspin in individuals with NWO. More studies are needed to investigate the changes in the serum concentration of adipokines and their interaction between each other and component of metabolic syndrome.

Limitations

Comparing the results of studies regarding normal weight obesity is difficult because of the ethnic differences in the study subjects, tools used to assess body composition (bioelectrical impedance vs. DXA) and diverse cutoff points for diagnosis of NWO by considering ethnics and gender.

Abbreviations

NOW: normal weight obesity; BMI: body mass index; FM: fat mass; HbA1c: Glycated hemoglobin; HOMA-IR: homeostatic model assessment for insulin resistance; NWN: normal weight non-obese ; WC: waist circumference; WHR: waist to hip ratio; TNF- α :tumor necrosis factor-alpha; IL-6:interleukin-6; HC: hip circumferences; BF: body fat; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; LFC: liver fat content; hk7:kallikrein 7; PPAR :peroxisome proliferator-activated receptor

Declarations

Acknowledgments

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Authors' contributions

ET: Contributed to the study conception, design and data collection and drafting the manuscript. MQ: Contributed to the interpretation of data, data analysis, revising the paper critically and giving final approval. SH: Contributed to the interpretation of data, revising the paper critically and giving final approval. PM: revising the paper critically and giving final approval

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study protocol was approved by the Ethics Research Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran. All participants provided written informed consent prior to study participation.

Consent for publication

Not applicable

Competing interest

The authors declare they have no conflict of interest.

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