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

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Abstract

Background: Subjects with normal weight obesity (NOW) are supposed to cardiometabolic disorders. The aim of this study was to investigate the circulating levels of vaspin and leptin and their association with glycemic and lipid profiles in women with NWO compared to controls

Material & Methods: Forty women with BMI:18.5-24.9 kg/m^2 and FM ≥ 30% as a NOW group and 30 age matched women with same BMI range and FM<30% as control group were enrolled. Anthropometric measurement, fasting serum levels of fasting blood sugar (FBS), insulin, HbA1c, lipid profiles and also, leptin and vaspin were measured.

Results: The mean ± SD of age were 28.76±4.76 years in NWO group and 29.23 ± 4.50 years in controls. Subjects in NWO group had higher serum level 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 HOMA-IR (33.77 ± 20.71 vs. 23.48 ± 10.03, p=0.009) compared to the NWNO group. Serum level of vaspin was higher in NWO (34.82 pg/ml) than control group (27.72 pg/ml),(p=0.12). In NWO subjects, serum level of leptin showed positive association 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: We observed that women with NWO had statistically significant increased concentration of insulin and HOMA-IR index compared to the controls. Higher levels of leptin and vaspin in NWO were associated with glycemic profiles in NWO.

Introduction

Obesity as a major public health problem is progressively increasing to the pandemic level in worldwide[1]. It’s well-known that obesity defined as excess body fat accumulation, is the main risk factor of many chronic disease 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/ m^2 in practical and research medicine. Other anthropometric indexes such as waist circumference (WC), waist to hip ratio (WHR) used in addition to the BMI 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 et al (2006) in the literature to define 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, which usedto identify a large number of cytokines and bioactive mediators are produced and released from fat tissues. Adipose tissue

secrets various hormones including adiponectin, leptin, resistin, visfatin, omentine, and cytokines such as tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6). Recently, the review study reported that upregulation of adipocytokines like resistin, vaspin, apelin and TNF-α are 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,which are 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 and 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 tocontrol group who were women with normal weight and normal body fat. Secondary aims were to investigate the association between these adipocytokines with glycemic indices and lipid profile in studied groups of women.

Materials And Methods

Subjects

In this case-control study, 40 women with BMI = 18.5–24.9 kg/m^2 and FM ≥ 30% as a NOW group and 30 age matched women with BMI = 18.5–24.9 kg/m^2 and FM < 30% as control group (NWNO: normal weight no obese) were selected from sport clubs in Tehran, Iran. Inclusion criteria were;1) subjects with a normal BMI (18.5–24.9 kg/m^2); 2) between the ages of 19 and 39 years old. Women with pregnancy or lactation in the time of study or had any history of diabetes, endocrine or metabolic disorders, liver and kidney dysfunction, hypertension, gastrointestinal,cardiovascular, thyroid and autoimmune diseases or diagnose infectionwere excluded from the study. The ethics committee of Shahid Beheshti University of Medical Sciences approved the study. Informed consent was obtained from all theparticipants before the beginning of the study.

Anthropometric measurements

Weight (Wt) and height (Ht) 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) calculated as Wt (kilograms) divided by the square of the Ht (meters).

Waist (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 defined by dividing of WC (cm) to HC (cm).

Percentageof body fat (BF) was assessed by bioelectrical impedance using a Tanita body composition analyzer (Model TBF-300; Tanita, Tokyo, Japan). Subjectswererequired 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

Fasting venous blood samples (5 ml) were collected fromeach participant. The samples were centrifuged (3000 gfor 10 min at 4 °C) within 1 hour, stored at 20 °C and analyzed within a week. Fasting serum concentration of glucose, totalcholesterol (TC), triglyceride (TG), and high density lipoprotein (HDL-C), and complement C3 were measured by a Hitachi 912autoanalyser(Hitachi, Mannheim, Germany) using commercial kits [Pars-Asmun kits, Iran].The low-density lipoprotein cholesterol (LDL-C) level was calculated using the Friedewald formula in subjects with serum triglyceride concentrations < 400 mg/ mL using the following formula:

(LDL cholesterol = total cholesterol - HDL cholesterol − 1/5 triglycerides)

Glycated hemoglobin (HbA1c) was measured using the ion exchange chromatography method (Biosystems S.A. Barcelona, Spain). Glycated hemoglobin (HbA1c) level was measuredby ion exchange chromatography with a DS5 set [DREW, United Kingdom].The serum insulin level was assessedusingby an immune enzymometric assay [Monobind Inc., USA]. The intra- and interassay coefficients of variation (CVs) for insulin were 5.9% and 9.2%, respectively. Homeostasis model assessment of insulin resistance (HOMA-IR) as an index of insulin resistance (IR) calculated based on following equation: HOMA-IR: [Insulin] (in mU/l) × [glucose] (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 □ times with a diluting buffer.

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

Statistical analysis

Statisticalanalysesperformedusing SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA).The normal distribution of continuousvariables was assessed using Kolmogrov-smirnov test.Continuousvariables with and without normal distribution are expressed as mean ± standard deviation (SD) and as median (interquartile range) respectively. Categoricalvariables are expressed as number (%). Continuous variables between NWO and NWNO were compared using t-test. Pearson and Spearman correlation test used for

evaluate the association of vaspin and leptin with glycemic indices and lipid profile.A valueof $p < 0.05$ considered as a statistically significant.

Results

The mean ± SD of age were 28.76 ± 4.76 years in patients with NWO and 29.23 ± 4.50 years in NWNO which was not statistically significant (P = 0.69). Anthropometric measures according to type of study groups summarized in Table 1. As we expected, the mean ± SD of fat mass was statistically higher in NWO group compared to the controls; while all participants had BMI in normal range (19.00–24.80 kg/m^2) with no statistical differences between two groups. Patients with NWO had higher WC and HC compared to the healthy controls (P < 0.001 for both). However, WHR was not statistically different between groups.

Table 1
Anthropometric measures according to study group

Variables	NWO (n = 40)	Control (n = 30)	P-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 two groups of NWO patients and healthy control subjects were summarized in Table 2. In comparison between two investigated groups, FBSshowed no significant difference between two groups; while the fasting serum level of insulin was higher in NWO group compared to the healthy controls (P = 0.009). Accordingly, HOMA-IR was significantly higher in NWO compared to the control group, (P = 0.02). Regarding to the lipid profile, no significant differences were observed in NWO group compared to 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). Level of vapin was not statistically different between groups.

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[a] (pg/ml)	17.31 ± 8.10	9.94 ± 4.30	< 0.001
Vaspin[b] (pg/ml)	34.82	27.72	0.12

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

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

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

P < 0.05 is statistically significant

Table 3 shows the correlation coefficient between the serum levels of leptin and vaspin with glycemia and lipid profiles in NWO and control groups. These results reported positive and statistically significant 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 NOW subjects. Serum level of vaspin showed significant correlation with fasting level of insulin in NWO group (P = 0.02).

The relationship of vaspin and leptin with lipid profile in both NWO and control groups were non-significant.No significant correlations were observed between serum level of vaspin and leptin with glycemia and lipid profile in control women.

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

Variables	Vaspin*		leptin**	
	NOW (n = 40)	Control (n = 30)	NOW (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(µIU/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				

Based on the results of this study, the serum concentration of leptin showed significant correlation with HC (R = 0.39, P = 0.01) and body fat (R = 0.36, P = 0.02) in NWO women; while the serum level of vaspin had significant inverse correlation with HC (R= -0.58, P = 0.002) and body fat (R= -0.39, P = 0.05) in control group. We verified a positive relationship between blood concentrations of leptin (r = 0.42, p = 0.001) and vaspin (r = 0.13, p = 0.28) with complement C3, which was only statistically significant for leptin

Discussion

In our study, we observed that women with NWO had statistically significant increased concentration of insulin and insulin resistance that evaluated by HOMA-IR index compared to the control women who had normal BMI and BF.

In previous studies, the prevalence of cardiometabolic abnormalities in patients with NWO have reported compared to normal and or obese counterparts. The results of Huang, et al., study among youngJapanese female cohort reported that NWO women had higher concentration of fasting insulin levels than lean and or normal weight normal obesity (NWNO) (non-significant) but lower level 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 NWNOwhile, it was lower compared to the obese women[10].

The result of this study was important for us, because this study performed among Asian women. Body fat mass deposition and distribution is influenced by race. The prevalence of fat mass accumulation in the upper body region is higher in Asian 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 among Japans women, BF ≥ 30% of body weight considered as excess body fat.

Madeira et al., conducted a study among 1222 men and women in Brazil and found normal weight obesity was associated with NWO was also associated with HOMA2-IR, low insulin sensitivity, and high insulin secretion[12].

The positive association between increased body fat tissue and cardiomatabolic disorders, despite having normal body weight, have reported among adolescences. Heijden and colleagues have shown that in Hispanic adolescent girls with normal BMI (< 85th percentile) and high body fat (≥ 27%), abdominal and hepatic fat content, insulin resistance, plasma leptin and Hs-CRP concentrations increased significantly in comparison to the girls 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 parallel to increase the percentage of body fat tissues in adults and adolescents [14–16].

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

One of the theories to describe the association between the excessive body fat tissues with component of metabolic syndrome is related to adipokine secretion. The results of the present study reported the higher serum level of leptin and vaspin in NWO women than controls.The results of our study in increasing the concentration of leptin were confirmed in previous studies. Romero-Corral et al., reported the increased the concentration of leptin among American individuals with NWO which was consistence with the results of our study[14]. Another study amongSwiss population showed higher leptin concentration in women with NWO than women in normal range of BMI and BF%[20].

It was confirmed the obese patients have higher level of leptin in comparison to the individuals with normal weight, which is attributed to the leptin resistance in obesity[21].

Leptin is one of the primary hormones that diagnosis as an adipocytokine which is secreted from adipose tissues. Therefore, according to the previous studies, there is positive relationship between blood level of leptin and percentage of body fat[22]. We observed similar results in our study among women with NWO ($r = 0.36$, $P = 0.02$). Our data have shown 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 be increase atherogenesis and insulin resistance or may have antiatherogensis and increase insulin sensitivity. Koh et al reported that these opposite effects of leptin is in balanced conditions in healthy individuals and is disrupted in obesity[23]. It seemed that the action of leptin in increase insulin resistance in subjects with NWO is similar to the patients with obesity.

Otherwise, leptin has positive association with the markers of pro-inflammatory and inflammatory status, which can be describe the role of higher level of leptin in increase the risk factors of cardiometabolic disorders[24, 25].

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

Vaspin, a serine protease inhibitor, is another adipokine secreted from adipose tissue. Experimental study showed that injection of vaspin to obese mice improves glucose tolerance by increase insulin sensitivity[26].

Compared to the leptin and adiponectine, limited studies have performed about vaspine in humans and most of the 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 including “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 [27].

Based on the results of Genske, et al., study among 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 (VAT), subcutaneous adipose tissue (SAT), or liver fat content (LFC)[28].

In 3T3-L1 cells, it was shown that endogenous vaspin positively associated with insulin signaling which is describes by the role of vaspin in increasing insulin-stimulated phosphorylation of the key mediator protein kinase B (AKT)[29].

On the other hand, the results of experimental study in mice, reported that injection of insulin in fasting status increased positively the hepatic expression of vaspin[30].

Previous studies have identified that the serum concentration of vaspin was increased with worsening insulin resistance in children and with impaired glucose tolerance and obesity in adults[31–33].

This study obtained similar findings to previous studies and we observed statistically significant positive association between serum levels of vaspin and insulin in women with NWO. Therefore, it can be proposed that serum level of vaspin is increased as a compensatory response to elevated concentration

of insulin and insulin resistance. According to our knowledge, this is the first study regarding the changes in serum level of vaspin in individuals with NWO. More investigation are needed regarding the changes in the serum concentration of adipkines and their interaction between each other and with component of metabolic syndrome components.

Limitation

Comparing the results of studies regarding to the NWO patricians is difficult because of the difference in the ethnics of study subjects, tools using to assess body composition (bioelectrical impedance *vs*. DXA) and diverse cutoff points to diagnosis of NWO by considering ethnics and gender.

Declarations

Acknowledgment

This article is approved by Student Research Committee, Shahid Beheshti University of Medical Sciences (Code No. 16705).

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.

Conflict of interest

The authors declare they have no conflict of interest.

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