



ORIGINAL ARTICLE

Variations of Serum Leptin and Resistin levels in Healthy non-Diabetic women with different degrees of Obesity

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ABSTRACT

The role of leptin and resistin serum concentrations in pathogenesis of obesity is considered an emerging topic issue in clinical biochemistry researches. This study was carried out to evaluate the variation of leptin and resistin serum levels in women with different grades of obesity. A total of 149 non-diabetic women were included in this study: 85 women as obese group, 31 women as a overweight group and 33 women as a normal weight group. The serum of blood samples were separated by centrifuge and plasma concentration of leptin and resistin were measured by ELISA technique. The serum leptin and resistin levels were significantly higher in obese group compared to normal weight group (42.85 ± 9.46 ng/ μ l vs. 15.46 ± 5.96 ng/ μ l; $p=0.000$ and 1.97 ± 0.56 ng/ μ l vs. 1.48 ± 0.24 ng/ μ l; $p=0.000$, respectively). We failed to show a statistically significant correlation between serum leptin and resistin levels and anthropometric indices in each groups. In conclusion the results indicate that the serum leptin and resistin levels elevated in obese group, and obesity could be one of the most important factors in promotion of plasma levels of these proteins. However, further studies on large scale populations may be needed, to better understanding the pathobiology of obesity.

Key words: leptin, resistin, obesity, Body Mass Index

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INTRODUCTION

Obesity is a major risk factor for insulin resistance, type 2 diabetes, cardiovascular disease, hypertension, and many other diseases [1, 2]. However, the pathophysiology of obesity is not well understood, it has been widely accepted that obesity is a complicated, multifactorial diseases [3]. Results of studies postulate that genetic (more than one hundred gene loci), endocrine, dietary, lifestyle and psychological factors which contribute to regulation of body weight, as etiology of obesity [4].

Adipose tissue is an endocrine organ that secretes a wide variety of proteins which contribute to regulation of body weight [5-7]. These secreted proteins include hormones, cytokines, neuron related proteins and extracellular matrix proteins which have autocrine, paracrine and endocrine effects on metabolism [8]. Among of these proteins, we have focused on leptin and resistin. Human leptin is an adipose-derived protein hormone encoded by the *ob* gene that is secreted proportionally to the total amount of fat in the body [9]. Although, Leptin is synthesized predominantly by white adipose tissue, small amounts of leptin are also secreted by cells in the epithelium of intestine, placenta, muscles and brain tissues [10]. Leptin receptors are highly expressed in areas of the hypothalamus known to be important in regulating body weight, as well as in T lymphocytes and vascular endothelial cells. Leptin stimulates a subset of neurons in the hypothalamus to produce peptides that decrease feeding and promote increased energy consumption [11]. Moreover, leptin inhibits hypothalamic neurons that produce peptides promoting feeding and decreased energy consumption [12]. Therefore, Serum concentrations of Leptin determined body fat percentage and body mass index, and it rises in parallel with the increased amount of body fat storage [13-16].

Resistin is a secretory cysteine-rich protein that encoded by the *RETN* gene in human. Human resistin synthesized by adipose, heart, lung and intestine tissues contains 108 amino acids but circulating resistin in plasma as a dimeric protein consisting of two 92 amino acid polypeptides because its hydrophobic signal peptide is cleaved before it is secreted [17]. Resistin acts as a cytokine and plays many physiological roles, and seems to suppress insulin ability to stimulate glucose uptake into adipose cells [18-20]. Hence, it may be an important link between obesity and insulin resistance. However, the exact role of resistin in obesity, type 2 diabetes and insulin resistance in humans is still unclear and controversial [21].

Results of previous literatures have been indicated that expression of *ob* and *RETN* genes in adipose tissue in obese individual higher than healthy individual [22-25]. Therefore, seems there are strong positive correlation of serum leptin and resistin concentrations with obesity. On this basis, the current study was designed to evaluate of leptin and resistin serum level, and also its relationship with body mass index and other anthropometric indices in women with different grades of obesity.

MATERIALS AND METHODS

Subjects

We enrolled 149 non-diabetic women from many various regions within the Northwest of Iran that were all referred by Nutritionists which were divided into normal weight (33 women, aged 24.63±7.21 years), overweight (31 women, aged 27.32±7.86 years) and obese groups (85 women, aged 38.34±42.7 years) according to WHO classification of body mass index (BMI) (Table 1,2). Informed consent was obtained from all participants before enrolment.

Anthropometric indices assessment

Anthropometric parameters (weight, height, Body Mass Index (BMI), hip and waist circumferences and Waist-Hip Ratio (WHR)) were measured for normal weight, overweight and obese groups. To anthropometric indices measurement individuals were in the standing position and wearing light clothing without shoes. Body weight and height were measured in kilograms and in centimeters, respectively. The BMI was calculated as weight in kilograms divided by the square of height (in meters). The hip circumference was taken at the widest area of the hips at the greatest protuberance of the buttocks; the waist circumference was measured at the narrowest part of the waist, between the lowest rib and iliac crest. WHR was also calculated from the ratio of waist circumference in centimeters to hip circumference in centimeters as waist circumference divided by hip circumference.

Analysis of leptin and resistin serum concentrations

Fasting venous blood sample (5 cc from each) was taken from all subjects. The serum of blood samples were separated by centrifuging at 3000 RPM for 10 minutes and stored at -70°C until further analysis. Measurement of fasting plasma glucose concentration was carried out on all the samples by the glucose oxidase method to make sure that the participating subjects were none-diabetic. Quantitative analysis of leptin and resistin serum levels were measured by enzyme-linked immunosorbent assay (ELISA) with a commercially available kit (mediagnost, Germany) according to the manufacturer's instruction after the serum samples were thawed at room temperature. The sensitivity was 0.2 µIU/ml for leptin and 0.012 ng/ml for resistin. Intra- and inter-assay coefficients of variation were 10% in both cases for leptin and (5.9% and 7.6%) for resistin in both cases, respectively.

Statistical analysis

All statistical analysis was performed by using the SPSS software version 16 and all continuous variables were expressed as Mean ± SD. One way ANOVA test was used to compare means. Determination of the correlation between obesity parameters (BMI and WHR) with leptin and resistin levels were performed by Pearson's correlation coefficient. The data with less than 0.05 probabilities regarded as statistical significant.

RESULTS

The comparison means of anthropometric and hormonal parameters of the all studied groups are shown in Table 2. Comparison of the means for serum leptin and resistin concentrations and anthropometric indices (weight, BMI, waist-to-height rate (WHR), waist and hip circumferences) between the all study subjects showed statistically significant difference ($P < 0.05$). However, comparing total groups regarding height no difference was detected (Table 2).

Our results show that the serum leptin level were statistically significant higher in obese group compared to both groups normal weight and overweight (42.85±9.46 ng/µl vs. 15.46±5.96 ng/µl; $p = 0.000$ and 42.85±9.46 ng/µl vs. 32.78±17.7; $p = 0.000$, respectively) (Table 2, 3). Resistin level was significantly higher in obese group compared to normal weight group (1.97±0.56 ng/µl vs. 1.48±0.24 ng/µl; $p = 0.000$) (Table 2,

3). Resistin concentration was compared between normal weight and overweight groups and no meaningful differences was detected ($P < 0.05$) (Table 2, 3).

Obese group had a statistically significantly higher mean BMI value when compared normal weight and overweight groups ($37.10 \pm 4.47 \text{ kg/m}^2$ vs. $21.99 \pm 2.33 \text{ kg/m}^2$; $p = 0.000$ and $37.10 \pm 4.47 \text{ kg/m}^2$ vs. $27.62 \pm 1.37 \text{ kg/m}^2$; $p = 0.000$, respectively) and they also had a significantly higher mean WHR value when compared to normal weight (0.92 ± 0.08 vs. 0.82 ± 0.10 ; $p = 0.000$) (Table 2, 3). The mean of the WHR was higher in the overweight compared to normal weight, but did not show a statistically significant difference ($P < 0.05$) (Table 3).

A positive correlation but not statistically significant between leptin level and BMI ($R = 0.060$; $p = 0.585$) as well as with WHR ($R = 0.089$; $p = 0.420$) were detected in obese group (Table 4). We observed a positive correlation between resistin level and BMI in obese group ($R = 0.160$; $p = 0.143$) (Table 4). Negative correlations between resistin level and WHR ($R = -0.101$; $p = 0.358$) was observed in obese group (Table 4). We did not observe any statistically meaningful correlation between compared parameters in within each of groups (Table 4).

In the total study subjects, bivariate correlation analysis indicated highest positive correlation of serum leptin with weight, BMI, waist, hip, WHR and resistin (Table 5). Moreover, a positive correlation of serum resistin with weight, BMI, waist and hip were detected. On evaluating the correlation between serum resistin level and WHR in the all subjects, a positive correlation but not statistically significant was observed ($r = 0.148$, $P = 0.072$). The correlation between leptin and resistin level to height was negative in the all subjects (Table 5).

DISCUSSION

In current study, we evaluated the leptin and resistin serum levels and their relationship with obesity in non-diabetic women with different degrees of obesity. The results of our study indicate the important role of leptin and resistin in the pathogenesis of obesity.

Our results showed the mean of serum leptin level were up to approximately three times higher in obese subjects than in non-obese individuals (Table 2). Our data was concordant with some other reports in this field [26, 27]. Our results were confirmed by Considine *et al*, who reported the mean serum leptin concentrations as 31.3 ng/ml and 7.5 ng/ml for obese and normal weight individuals ($P < 0.001$) [26]. Moreover, in a study by Considine *et al*, a strong positive correlation between serum leptin concentrations and the percentage of body fat was detected ($r = 0.85$, $P < 0.001$) [26]. Matsubara *et al* evaluated serum leptin concentrations in 353 non-diabetic women and confirmed our data [27]. A study performed by Ho *et al* clarified that there is evidence to support a relationship of serum leptin concentration with obesity [28]. These result led to the view that the high serum leptin concentration in obese individuals might be associated with degrees of obesity and body fat storage. In mice, leptin decreases appetite and elevates energy expenditure, resulting in weight loss [29, 30]. If the actions of leptin in humans are similar, appetite should decrease and energy consumption elevate in obese individuals. It seems that elevating of serum leptin level in obese subjects due to decreased sensitivity or resistance to leptin. However, body weight is regulated by complicated mechanisms involving multitudinous afferent metabolic and hormonal signals informing the brain about the body's energy status [31]. Abnormal production or action of any of the afferent messengers may lead to weight gain.

Many parameters related with increasing of the serum leptin concentration in obese individuals, including body fat mass, total percentage of body fat, body mass index and body fat distribution [32]. Our results show that among of anthropometric parameters weight, Body Mass Index (BMI), hip and waist circumferences and Waist-Hip Ratio associated with serum leptin concentrations in obese subjects and the mean of these anthropometric indices increased in parallel with rising serum leptin level (Table 2, 3). However, within the group of obese women, the serum leptin levels showed a weaker positive correlation with BMI, hip circumference, waist circumference and WHR (Table 4). Most of the earlier publications have shown a strong correlation of serum leptin with BMI. Serum leptin levels correlated positively with BMI and were significantly elevated in obese individuals [26]. Ruhl and Everhart have also confirmed these data [33]. However, Rosenbaum *et al* found that leptin was not significantly correlated with BMI [34]. Peltz *et al* reported that the serum leptin concentration determined by percent body fat in Mexican-American women. Moreover, the hip circumference and waist circumference are associated with serum leptin concentration [35]. In a study by Al-Daghri *et al*, an association between serum leptin concentration and hip circumference was observed [36].

We found that serum resistin level was statistically significantly increased in obese subjects compared to normal weight and overweight groups (Table 3). Therefore; we postulate that the highest resistin concentration in obese women might be associated with degrees of obesity and it rises in parallel with the increased amount of body fat storage. There are other studies that confirm our data [37, 38]. Degawa-

Yamauchi et al reported that the mean serum resistin level as 5.3 ± 0.4 ng/ μ l and 3.6 ± 0.4 ng/ μ l for obese and normal weight subjects ($P < 0.001$) [37]. In a study by Savage et al resistin mRNA levels in whole adipose tissue were elevated in obese subjects when compared with lean controls [38]. Conversely, Silha et al were unable to observe that the mean of resistin level increased in obese subjects [39]. Lee et al reported that the circulating resistin levels are not related with obesity [40]. In sum, it appears that the role and regulation of resistin may be different in normal physiology when compared with disease states such as obesity.

Table 1. Classification of individuals according to BMI

Classification	BMI (Kg/m ²)	Number of individuals
Normal weight	18.5 - 24.9	33
Overweight	25 - 29.9	31
Obese	$30 \geq$	85

Table 2: The mean of anthropometric indices and serum leptin and resistin levels in different groups of women ^a

Parameter	Normal weight group	Over weight grou	Obese group	P value ^b
Age (year)	24.63 ± 7.21	27.32 ± 7.86	38.34 ± 42.7	0.073
Weight (kg)	57.04 ± 7.55	70.90 ± 6.39	86.65 ± 9.93	0.000
Height (cm)	160.6 ± 5.90	160.0 ± 6.24	157.7 ± 5.57	0.024
BMI (kg/m ²)	21.99 ± 2.33	27.62 ± 1.37	37.10 ± 4.47	0.000
Waist (cm)	73.63 ± 8.01	89.80 ± 8.51	108.0 ± 10.29	0.000
Hip (cm)	90.63 ± 1.06	102.9 ± 4.76	116.7 ± 8.39	0.000
WHR	0.82 ± 0.10	0.87 ± 0.08	0.92 ± 0.08	0.000
Leptin (ng/ μ l)	15.46 ± 5.96	32.78 ± 17.7	42.85 ± 9.46	0.000
Resistin (ng/ μ l)	1.48 ± 0.24	1.56 ± 0.45	1.97 ± 0.56	0.000

Abbreviations: BMI, Body Mass Index. WHR, Waist Hip Ratio.

^aData are means \pm SD

^bEvaluated by One way ANOVA test and $P \leq 0.05$ is considered significant

Table 3: Comparison of the mean anthropometric indices and serum leptin and resistin levels between groups

Parameter	Group1 ^a	Group2 ^a	P Value ^b
Age (year)	Normal weight	Over Weight	1.000
	Normal weight	Obese	0.130
	Over Weight	Obese	0.335
Weight (kg)	Normal weight	Over Weight	0.000
	Normal weight	Obese	0.000
	Over Weight	Obese	0.000
Height (cm)	Normal weight	Over Weight	1.000
	Normal weight	Obese	0.047
	Over Weight	Obese	0.177
BMI (kg/m ²)	Normal weight	Over Weight	0.000
	Normal weight	Obese	0.000
	Over Weight	Obese	0.000
Waist (cm)	Normal weight	Over Weight	0.000
	Normal weight	Obese	0.000
	Over Weight	Obese	0.000
Hip (cm)	Normal weight	Over Weight	0.000
	Normal weight	Obese	0.000
	Over Weight	Obese	0.000
WHR	Normal weight	Over Weight	0.067
	Normal weight	Obese	0.000
	Over Weight	Obese	0.014
Leptin (ng/ μ l)	Normal weight	Over Weight	0.000
	Normal weight	Obese	0.000
	Over Weight	Obese	0.000
Resistin (ng/ μ l)	Normal weight	Over Weight	1.000
	Normal weight	Obese	0.000
	Over Weight	Obese	0.000

Abbreviations: BMI, Body Mass Index. WHR, Waist Hip Ratio.

^ato show groups that compared with each other

^b $P \leq 0.05$ is considered significant

Table 4. Correlations between compared parameters in all studied groups

parameters	Normal weight group		Overweight group		Obese group	
	R	P value	R	P value	R	P value
Leptin and weight	0.270	0.128	0.147	0.431	0.155	0.157
Leptin and BMI	0.308	0.081	0.120	0.519	0.060	0.585
Leptin and waist	0.229	0.199	-0.058	0.758	0.126	0.249
Leptin and hip	0.279	0.116	0.356	0.049	0.112	0.308
Leptin and WHR	-0.081	0.656	-0.228	0.218	0.089	0.420
Leptin and resistin	-0.219	0.222	0.242	0.190	-0.025	0.823
Resistin and weight	0.023	0.897	0.225	0.224	0.265	0.014
Resistin and BMI	-0.199	0.267	0.075	0.687	0.160	0.143
Resistin and waist	-0.026	0.887	0.087	0.641	0.150	0.169
Resistin and hip	-0.189	0.291	0.147	0.431	0.217	0.046
Resistin and WHR	0.184	0.304	0.014	0.941	-0.101	0.358

Table 5: Bivariate correlation of leptin and resistin with anthropometric indices in the total study subjects

		leptin	resistin	weight	height	BMI	waist	hip	WHR
leptin	Correlation	1	0.300	0.628	-0.062	0.623	0.610	0.623	0.284
	P value	-	0.000	0.000	0.453	0.000	0.000	0.000	0.000
resistin	Correlation	0.300	1	0.453	-0.146	0.417	0.400	0.396	0.148
	P value	0.000	-	0.000	0.076	0.000	0.000	0.000	0.072

Within the group of obese women, the serum resistin level showed a weaker positive correlation with BMI, hip circumference and waist circumference (Table 4). A negative correlation was detected between resistin and WHR in obese group (Table 4). In agreement with our data, the weaker positive correlation serum resistin and BMI was previously reported by Yannakoulia et al [41]. However, Savage et al did not find any correlation of resistin level and BMI [38]. Our data were confirmed by Yannakoulia et al, who reported that the serum resistin level was negatively correlated to waist to hip ratio [41].

In conclusion, our results show that the serum leptin and resistin levels were significantly higher in obese women compared to normal weight subjects. These results suggest that leptin and resistin may be having a critical role in the pathogenesis of obesity.

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