ORIGINAL RESEARCH

Alireza Esteghamati MD
Afsaneh Morteza MD, MPH
Omid Khalilzadeh, MD, MPH
Sina Noshad MD, MPH
Leila Novin MD
Manouchehr Nakhjavani MD

Endocrinology and Metabolism Research Center (EMRC), Vali-Asr Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Association of serum cortisol levels with parameters of metabolic syndrome in men and women

Abstract

Purpose: Central fat distribution is significantly associated with an increased cortisol levels. We hypothesized that men with metabolic syndrome have a higher serum cortisol levels compared to women. The purpose of this study was to compare serum cortisol levels, and its correlation with serum leptin levels, between men and women with and without metabolic syndrome.

Methods: A cross sectional study was performed with 120 untreated patients with metabolic syndrome and 165 healthy volunteers as controls. Serum lipid profile, fasting blood sugar, insulin, cortisol and leptin levels were measured for both groups.

Results: Men with metabolic syndrome had a higher serum cortisol levels, while serum leptin levels were significantly higher in women. The higher serum cortisol level in men with metabolic syndrome was significant after multiple adjustments for age, BMI and waist circumference (17.74 ± 5.1 vs 14.07 ± 4.3 ; $p < 0.05$) using general linear model; however, these difference were no longer significant when the waist-to-hip ratio was added as one of the adjustment factors (16.7 ± 1.2 vs. 14.9 ± 0.5 ; $p < 0.2$). Serum cortisol levels was significantly correlated with serum leptin ($r = 0.33$, $p < 0.05$), cholesterol ($r = 0.35$, $p < 0.05$), triglyceride ($r = 0.25$, $p < 0.05$), waist circumference ($r = 0.41$, $p < 0.01$) and waist-to-hip ratio ($r = 0.32$, $p < 0.01$) in women with metabolic syndrome, after controlling for age and BMI.

Conclusion: Serum cortisol levels are significantly higher in men with metabolic syndrome. This effect is independent of waist circumference.

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Correspondence to:

Alireza Esteghamati MD,
Professor of Endocrinology and Metabolism,
Endocrinology and Metabolism Research Center (EMRC),
Vali-Asr Hospital,
Tehran, Iran
E-mail: esteghamati@tums.ac.ir

Metabolic syndrome is a cluster of metabolic risk factors associated with cardiovascular disease and type 2 diabetes [1]. The major components of metabolic syndrome include excess abdominal fat, dyslipidemia, hypertension, hyperglycemia and increased inflammatory state [1]. For any given body mass index (BMI), mortality is higher if fat is distributed centrally, which is the major component of metabolic syndrome [2].

Cross-sectional studies showed that morning cortisol levels are significantly correlated with the symptoms of metabolic syndrome, such as visceral obesity, high blood pressure and a poor lipid profile [3-5]. Further studies suggest that metabolic syndrome is a less profound form of Cushing's syndrome, which is characterized by a rise in serum cortisol levels [4,6-9]. This hypothesis is based on the simple observation that patients with Cushing's syndrome develop central obesity, which improves with the resolution of hypercortisolism [10,11].

It is known that men with metabolic syndrome are more frequently affected with android obesity. Central fat distribution is significantly associated with increased cortisol levels [12,13], so it could be hypothesized that men with metabolic syndrome have a higher serum cortisol levels, due to increased abdominal obesity compared with women. On the other hand, adipose tissue is known as an endocrine organ, producing a number of cytokines including leptin [14,15]. There may be a gender difference in the correlation of serum cortisol and leptin levels in men and women with metabolic syndrome. In this study, we aimed to compare serum cortisol levels, and its correlation with serum leptin levels, between men and women with and without metabolic syndrome.

Methods

A cross sectional analysis was performed with serum samples from 120 patients with metabolic syndrome from diabetes clinic of Vali-Asr hospital affiliated with Tehran University of Medical Science, plus 165 healthy controls. Metabolic syndrome was defined according to the criteria of National Cholesterol Education Program, Adult Treatment Panel III [16]. Under the ATP III criteria, metabolic syndrome was defined as the presence of three or more of the following risk factors: abdominal obesity (waist circumference ≥ 102 cm [men] or ≥ 88 cm [women]), triglyceride ≥ 150 mg/dL, HDL-cholesterol < 40 mg/dL (men) or < 50 mg/dL (women), blood pressure $\geq 130/85$ mmHg and fasting plasma glucose ≥ 100 mg/dL (or diabetes). Exclusion criteria were pregnancy, acute or chronic renal failure, congestive heart failure, thyroid disorders, acute infections, stroke, use of glucocorticoid drugs and hospital admission within the past six months. Demographic and anthropometric data, including age, sex, height, weight in light clothing and blood pressure in sitting position, were recorded. Blood pressure was measured twice within 5 minutes and the values were averaged. BMI (kg/m^2) was calculated according to the Quetelet formula. The biochemical tests, fasting blood sugar (FBS), lipid profile, urine creatinine, serum insulin, cortisol and leptin levels were measured in all participants. All participants gave written informed consent before participation. The research was carried out according to the Principles of the Declaration of Helsinki. The local ethics review committee of Tehran University of Medical Science approved the study protocol.

Blood samples

Blood samples were collected after 12 hours of fasting at 8 am, and serum creatinine, FBS, total cholesterol, triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), cortisol and insulin levels were measured. Glucose measurements (intra-assay coefficient of variants [CV] 2.1%, inter-assay CV 2.6%) were carried out using the glucose oxidase method. Cholesterol, HDL-C, LDL-C and TG were determined using direct enzymatic methods (Parsazmun, Karaj, Iran). Insulin was measured by radioimmunoassay, using an antibody with no cross reaction against pro-insulin and C-peptide (Immunotech, Prague, Czech Republic). The intra- and inter-assay coefficients of variation were lower than 4.3 and 3.4, respectively. Serum leptin concentration was determined by an enzyme-linked immunosorbent assay (DRG Instruments GmbH, Marburg, Germany) with an intra-assay coefficient of variation of 5.9–6.9% and an inter-assay coefficient of variation of 8.6–11.5%. Serum cortisol concentration was measured by radioimmunoassay, using an antibody (Immunotech, Prague, Czech Republic) with an intra-assay coefficient of variation of 3.5–5.1% and an inter-assay coefficient of variation of 5.4–9.2%. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (mU/l) $\times$ fasting plasma glucose (mg/dl)/405, as described by Matthews *et al.* [17].

Blood samples

Statistical analysis

The statistical package SPSS 16 for Windows (Chicago, Illinois, USA) was used for analysis. Quantitative variables are presented as mean $\pm$ standard deviation (SD). For comparison of serum cortisol levels, lipid profile and other variables among the patients with and without metabolic syndrome, and also men and women in each group, independent sample t-test and Mann-Whitney U test were employed as appropriate. General

TABLE 1. Characteristics of the participants with and without metabolic syndrome

	Without Metabolic Syndrome (n=165)	With Metabolic Syndrome (n=120)	P value
Age (years)	33.84±10.22	36.78±11.56	<0.05
Body Mass Index (kg/m ²)	28.36±5.94	39.10±24.76	<0.001
Waist Circumference (cm)	92.30±12.82	109.79±12.18	<0.001
Hip Circumference (cm)	104.78±11.25	120.11±12.95	<0.001
Waist-to-hip ratio	0.87±0.05	0.92±0.07	<0.001
Systolic Blood Pressure (mmHg)	110.90±12.51	118.45±16.29	<0.001
Diastolic Blood Pressure (mmHg)	73.16±7.97	78.83±9.78	<0.001
Fasting Blood Glucose (mg/dl)	87.27±8.64	107.50±23.26	<0.001
Insulin (mg/dl)	8.50±4.18	14.47±7.61	<0.001
Triglyceride (mg/dl)	119.38±37.22	197.09±89.24	<0.001
LDL-C (mg/dl)	112.11±28.65	136.66±36.32	<0.001
HDL-C (mg/dl)	46.84±9.26	37.91±8.55	<0.001
Cholesterol (mg/dl)	185.46±31.05	216.22±42.65	<0.001
Cortisol (µg/dl)	14.56±4.66	15.16±5.04	NS
HOMA-IR	1.87±1.04	3.86±2.17	<0.001
Leptin (ng/ml)	13.08±14.36	27.48±17.83	<0.001

Variables are presented as Mean±Standard Deviation (SD).

LDL-C: Low Density Lipoprotein Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; NS: Non-significant; HOMA-IR: homeostasis model assessment of insulin resistance

linear models were employed to compare serum cortisol levels between men and women with metabolic syndrome after multiple adjustments for age, waist circumference and BMI. The later analysis was repeated after multiple adjustments for waist-to-hip ratio. Significance was set at $P < 0.05$.

Results

Characteristics of the participants are summarized in Table 1. Serum cortisol levels did not differ between patients with and without metabolic syndrome. There was a significant difference between patients with and without metabolic syndrome in other studied variables.

To study the role of gender on serum cortisol and leptin levels, the participants in each group were stratified into male and female for further analysis (Table 2). Serum cortisol levels were significantly higher in men with metabolic syndrome, whereas serum leptin levels were significantly higher in women with metabolic syndrome (Table 2). A higher serum cortisol level in men with metabolic syndrome was significant after multiple adjustments for age, BMI and waist circumference (17.74 ± 5.1 vs 14.07 ± 4.3 ; $p < 0.05$) using general linear model; however, differences were no long significant when waist-to-hip ratio was included as one of the adjustment factors (16.7 ± 1.2 vs 14.9 ± 0.5 ; $p < 0.2$).

Men and women without metabolic syndrome did not differ significantly in serum cortisol levels when there was a significant difference in waist circumference, hip circumference, waist-to-hip ratio, lipid profile, systolic and diastolic blood pressure, serum insulin and leptin levels. Table 3 presents the correlation of serum cortisol levels with other studied variables. Serum cortisol levels was significantly correlated with serum leptin ($r = 0.33$, $p < 0.05$), cholesterol ($r = 0.35$, $p < 0.05$), TG ($r = 0.25$, $p < 0.05$), waist circumference ($r = 0.41$, $p < 0.01$) and waist-to-hip ratio ($r = 0.32$, $p < 0.01$) in women with metabolic syndrome, after controlling for age and BMI. There was no significant correlation between serum cortisol level and any of the studied variables in men with metabolic syndrome (Table 3).

Discussion

Our findings clearly demonstrate that men with metabolic syndrome have a higher serum cortisol levels compared with women, although there was no such sexual dimorphism in those without metabolic syndrome. The higher serum cortisol levels in men with metabolic syndrome were significant after multiple adjustments for age, BMI and waist circumference; however, differences were no long significant when waist-to-hip ratio was included as one of the adjusting variables. Furthermore, serum cortisol levels were shown to be significantly

TABLE 2. Characteristics of the male and female participants with and without metabolic syndrome

	Without metabolic syndrome		With metabolic syndrome	
	Female (n=66)	Male (n=99)	Female (n=95)	Male (n=25)
Age (years)	31.97±10.96	35.12±9.53	38.15±11.13	29.47±11.33*
Body Mass Index (kg/m ²)	32.1±6.4	25.8±3.9**	40.5±26.7	33.9±5.89**
Waist (cm)	98.09±14.12	88.32±10.14**	110.07±11.87	108.26±13.99**
Hip (cm)	112.21±11.47	99.67±7.73**	121.40±13.12	113.26±9.65**
Waist-to-hip ratio	0.87±0.071	0.88±0.04	0.90±0.07	0.95±0.07*
Systolic Blood Pressure (mmHg)	105.07±13.90	114.90±9.65**	119.05±16.38	115.26±15.85
Diastolic Blood Pressure (mmHg)	70.68±9.35	74.87±6.36**	79.25±9.80	76.57±9.58
Cholesterol (mg/dl)	189.36±37.01	182.82±26.15	216.02±43.29	217.26±40.19
FBS (mg/dl)	92.28±7.43	83.75±7.66	108.90±24.51	100.10±13.0
HDL-C (mg/dl)	42.68±9.498	49.65±7.99**	38.38±8.20	35.42±10.07
LDL-C (mg/dl)	123.10±32.30	104.60±23.19**	138.09±37.83	128.35±25.07
Triglyceride (mg/dl)	104.18±32.84	130.11±36.546**	192.16±87.50	224.50±96.31
Insulin (mg/dl)	9.59±4.95	7.76±3.38**	14.06±7.11	16.61±9.81
Leptin (ng/ml)	24.22±17.2	5.66±2.8**	30.11±16.57	13.6±18.24**
Cortisol (µg/dl)	14.12±5.97	14.84±3.56	14.66±5.04	17.79±4.29*

Variables distributed are expressed as Mean±Standard Deviation (SD). *: P<0.05, **: P<0.01, when comparing females with males in participants with or without metabolic syndrome

correlated with waist circumference, waist-to-hip ratio, TG, total cholesterol and leptin levels in women with metabolic syndrome, after multiple adjustments for age and BMI.

The finding of a higher serum cortisol levels in men with metabolic syndrome is in general agreement with previous studies [18,19]. Lamb *et al.* first reported a higher urine free cortisol excretion rate in 15 men compared with 18 women, using radioimmunoassay [19]. They studied healthy individuals and showed that this effect was not correlated with the measurement techniques [19]. Fraser *et al.* suggested that serum cortisol levels are significantly higher in men with cardiovascular risk factors [20]. Using steady-state infusion of a tracer amount of stable isotope over 24 hour in 24 men and 30 women, Purnell *et al.* showed that an increased cortisol production rate is selectively correlated with visceral fat, not abdominal fat [21]. Furthermore, they showed that men have a significantly higher cortisol production rate, higher 24 h plasma free cortisol levels and a lower 24-h cortisol binding globulin (CBG) than women [21].

Consistent with the data obtained from the national surveillance of waist circumference [22], all studied women had a higher waist circumference compared with that seen in men with metabolic syndrome. On the other hand, men with metabolic syndrome had a higher waist-to-hip ratio, although this was not the case in patients without metabolic syndrome. Interestingly, the observed increase in serum cortisol levels seen

in men with metabolic syndrome was no longer significant when waist-to-hip ratio was included in the analysis. Serum cortisol levels were also shown to be significantly correlated with serum leptin, cholesterol, TG, waist circumference and waist-to-hip ratio in women with metabolic syndrome after multiple adjustments for age and BMI, whereas there was no significant correlation between serum cortisol levels and any of the studied variables in men with metabolic syndrome. Waist-to-hip ratio is used as a measurement of obesity, which in turn is a possible indicator of other more serious health conditions. Waist-to-hip ratio has been found to be a more efficient predictor of mortality in older people than waist circumference or (BMI) [23]. A possible explanation for this observation would be that an increased serum cortisol level in men with metabolic syndrome may be associated with waist-to-hip ratio, however the direct correlation may be vanished due to the confounding effect of unknown variables.

But why are serum cortisol levels correlated with risk factors of metabolic syndrome only in women with metabolic syndrome, despite relatively "normal" values and a lower serum cortisol levels than men? Previous studies suggested that increased serum cortisol level in men is mainly mediated through 11b-hydroxysteroid dehydrogenase type 1 (11b-HSD1) activity [24,25]. 11b-HSD1 is a bidirectional enzyme, located in the abdominal fat mass and omental subcutaneous tissue, and mediates the conversion of cortisone to cortisol [26,27]. Fur-

TABLE 3. Partial correlation coefficient (r) between serum cortisol level and the studied variables, after controlling for age and BMI in males and females stratified according to metabolic syndrome.

	Female without Metabolic Syndrome	Male without Metabolic Syndrome	Female with Metabolic Syndrome	Male with Metabolic Syndrome
Waist (cm)	-0.27*	0.16	0.41**	0.38
Hip (cm)	0.09	0.12	0.14	0.256
Waist-to-hip ratio	-0.30*	0.091	0.32**	0.17
Systolic Blood Pressure (mmHg)	-0.18	0.14	0.16	0.17
Diastolic Blood Pressure (mmHg)	-0.13	0.23*	-0.06	0.09
Insulin (mg/dl)	0.13	0.09	0.13	-0.12
FBS (mg/dl)	0.244	0.117	0.145	-0.02
Triglyceride (mg/dl)	0.16	0.04	0.25*	0.224
LDL-C (mg/dl)	0.06	-0.10	0.15	0.281
HDL-C (mg/dl)	0.20	0.13	-0.11	-0.36
Cholesterol (mg/dl)	0.14	-0.05	0.35*	0.05
Leptin (ng/ml)	0.007	0.078	0.33*	0.15
HOMA-IR	0.17	0.08	0.15	-0.10

Variables are presented as Mean $\pm$ Standard Deviation (SD).

LDL-C: Low Density Lipoprotein Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; NS: Non-significant; HOMA-IR: homeostasis model assessment of insulin resistance

*: $P < 0.05$, **: $P < 0.01$

thermore there are gender differences in 11 β -HSD1 activity, which is greater in men [20], and 5 α -reductase activity, which is greater in women [28]. This difference in enzyme activity may result in an increase in serum cortisol levels in men and would alter its degree of correlation with parameters associated with metabolic syndrome. As this would not happen in women with metabolic syndrome, the correlation is observed only in women.

Studies have demonstrated a direct relationship between stress-related psychopathologic symptoms and serum leptin levels [29]. Recently, it has been suggested that leptin can attenuate several parameters of cortisol secretion in female rhesus monkeys and thus play a role in the response of adrenal gland to socio-environmental stimuli [30]. Serum leptin and cortisol levels predicts acute inflammatory reactions [31]. Furthermore, inhibiting serum cortisol would inhibit the rise in serum leptin levels [32]. Leptin is known to increase after glucocorticoid administration and in Cushing's syndrome [33,34]. Leptin is a cytokine and is found at significantly higher levels in women with metabolic syndrome [35], so it could be hypothesized that it has more influence on HPA axis in women. Consistent with this hypothesis, this study found a significant positive correlation between serum cortisol and leptin levels in women with metabolic syndrome. It has been repeatedly shown that women with metabolic syndrome have a higher risk of progression to cardiovascular disorders than men [36-37]. This may be

another explanation for the observed association between serum leptin and cortisol levels in women.

In conclusion, increased serum cortisol levels were seen in men with metabolic syndrome. The principal limitation of the present study is its cross-sectional nature, which precludes the determination of the direction of causality. Furthermore, CBG and ACTH were not measured, so simultaneously enhanced pituitary signaling could not be verified. On the other hand, we took advantage of a relatively large sample size and a close similarity between the groups for most of the potentially confounding clinical and laboratory variables.

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