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The Association between Midnight Salivary Cortisol and Metabolic Syndrome in Korean Adults

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Background: The common characteristics of metabolic syndrome (MetS) and Cushing's syndrome suggest that excess cortisol may be involved in the pathogenesis of MetS. Salivary cortisol measurements are simple and can be surrogates for plasma free cortisol, which is the most biologically active form. We evaluated the association between levels of midnight salivary cortisol and MetS in Korean adults.
Methods: A total of 46 subjects, aged 20 to 70 years, who visited the Health Care Center at Konkuk University Hospital from August 2008 to August 2009 were enrolled. We compared the levels of midnight salivary cortisol in subjects with MetS with those in subjects without MetS. We analyzed the associations between midnight salivary cortisol levels and components of MetS.
Results: Midnight salivary cortisol levels were higher in the MetS group (70±42.4 ng/dL, $n=12$) than that in the group without MetS (48.1±36.8 ng/dL, $n=34$) ($P=0.001$). Positive correlations were observed between midnight salivary cortisol levels and waist circumference, fasting blood glucose, and homeostasis model assessment of insulin resistance. The risk for MetS was significantly higher in subjects with midnight salivary cortisol levels ≥100 ng/dL than in those with levels <50 ng/dL (odds ratio, 5.9; 95% confidence interval, 2.35 to 36.4).
Conclusion: The results showed a positive correlation between midnight salivary cortisol levels and MetS, suggesting that hypercortisolism may be related to MetS.

Keywords: Corticosteroid; Insulin resistance; Metabolic syndrome

INTRODUCTION

Metabolic syndrome (MetS) is characterized by abdominal obesity, dyslipidemia, hyperglycemia, and hypertension, and was firmly established as a clinically important syndrome by Reaven in 1998 [1,2]. MetS is associated with the future development of type 2 diabetes and coronary heart disease [3].

The prevalence of MetS has increased rapidly worldwide, and has become an important public health challenge [4]. The prevalence of MetS is 30% to 33.7% in Korean adults by the International Diabetes Federation (IDF) criteria and it has increased as central obesity has increased [5,6]. However, the pathogenesis of MetS remains controversial.

MetS and Cushing's syndrome are both characterized by a cluster of common abnormalities such as abdominal obesity, hyperglycemia, hypertension, reduced high-density lipoprotein cholesterol (HDL-C), and elevated triglycerides. The common characteristics of MetS and Cushing's syndrome suggest that the production of excess cortisol may be involved in the pathogenesis of MetS. Evidence supporting this hypothesis include the association of increased stress-related cortisol secretion with features of MetS, and higher circulating cortisol concentrations and increased urinary cortisol metabolite secretion in men with MetS [7,8].

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It has been convincingly demonstrated in adults and children that an elevated midnight salivary cortisol level is an excellent surrogate for increased midnight serum cortisol, which means disruption of diurnal variation in the diagnosis of Cushing's syndrome [9-13]. In addition, measuring salivary cortisol has several advantages. It reflects the unbound fraction of circulating cortisol, and, thus, is not affected by any alterations in cortisol-binding globulin and is not influenced by salivary flow rate [14]. Furthermore, salivary cortisol levels provide a more sensitive approach to assess the subtle activation of the hypothalamus-pituitary-adrenal (HPA) axis than urine-free corticosteroids [14,15].

This study was designed to evaluate the potential contribution of hypercortisolism to the development of MetS in Korean adults using midnight salivary cortisol as a marker for endogenous cortisol status.

METHODS

Subjects

A total of 46 subjects aged 20 to 70 years, who visited the Health Care Center at Konkuk University Hospital for a regular health check-up from August 2008 to August 2009 were enrolled. Informed consent was obtained from all subjects, and the protocols were approved by the Konkuk University Hospital Institutional Review Board.

Exclusion criteria were as follows: 1) type 1 diabetes; 2) type 2 diabetes with a glycated hemoglobin >10%; 3) Cushing's syndrome (Cushingoid appearance or midnight salivary cortisol >145 ng/dL) or pseudo-Cushing's syndrome (alcoholic or depressive disorder); 4) adrenal insufficiency; 5) serum creatinine level >2 mg/dL; 6) aspartate aminotransferasse and alanine aminotransferase levels more than three times the upper normal limit; 7) receiving steroid medications (including topical agents); 8) malignant tumor; and 9) poor oral hygiene.

Measurements

Systolic and diastolic blood pressures were measured on the left upper arm after 5 minutes of rest in the sitting position using an automatic blood pressure monitor (HEM-907-E; OMROM, Tokyo, Japan). Abdominal circumference was measured in the standing position at the midway between the lower costal margin and the iliac crest. Blood glucose, total cholesterol, triglycerides, HDL-C, low density lipoprotein cholesterol, insulin, and other biochemical tests were performed after a 12-hour fast. Saliva samples were obtained between 23:00 and 24:00; a cotton stick was placed in the mouth for 2 to 3 minutes and then replaced into the saliva-collecting device (Salicap; IBL, Hamburg, Germany). Because food ingestion and physical stress can increase circulating cortisol levels, subjects were requested to abstain from physical activity and food from 21:00 until they were sampled. Samples were stored at -20°C until assay and then centrifuged at 500 rpm for 5 minutes. Salivary cortisol concentrations were determined using a competitive enzyme immunoassay kit (Salimetrics Inc., State College, PA, USA). The detection limit range of the kit was 3 to 3,000 ng/dL. The average intra-assay coefficient of variation was 8.2% and the inter-assay coefficient of variation was 12.8%.

Insulin resistance was calculated from fasting insulin and glucose values using the homeostasis model assessment-insulin resistance (HOMA-IR). The formula was as follows:

HOMA-IR = fasting insulin (U/mL) × fasting blood glucose (mmol/L)/22.5

Definition of MetS

MetS was diagnosed based on the criteria of the IDF. Subjects were identified as having MetS if they had abdominal obesity (waist circumference ≥90 cm in men, ≥80 cm in women) plus two or more of the following criteria:

1) Triglycerides: ≥150 mg/dL
2) HDL-C: <40 mg/dL in men, <50 mg/dL in women
3) Blood pressure: systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or treatment for previously diagnosed hypertension
4) Fasting blood glucose: ≥100 mg/dL or previously diagnosed type 2 diabetes

Statistical analysis

The statistical analysis was performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA), and data are presented as medians (interquartile range). The Mann-Whitney *U* test and chi-squared test were used to assess differences in clinical characteristics between those with and without MetS. Partial correlation was used to assess the association between midnight salivary cortisol and abdominal circumference, blood pressure, triglycerides, HDL-C, fasting blood glucose, HOMA-IR, and high sensitivity C-reactive protein. A logistic regression analysis was carried out to test the association between midnight salivary cortisol and MetS. Statistical significance was defined at $P<0.05$.

RESULTS

General subject characteristics

Table 1 shows a comparison of the characteristics of those with and without MetS. The participants consisted of 27 men and 19 women, and 12 subjects (26%) were diagnosed with MetS.

Abdominal circumference ($P<0.001$), body mass index ($P=0.023$), the concentration of fasting blood glucose ($P<0.001$), triglycerides ($P<0.001$), and midnight salivary cortisol were significantly higher ($P=0.001$), and the concentration of HDL-C was lower in subjects with MetS ($P=0.001$) than those without MetS. Serum insulin concentrations were higher in subjects with MetS ($P=0.046$), and subjects with MetS were more insulin resistant than subjects without MetS based on the HOMA-IR.

Partial correlation analysis between midnight salivary cortisol, HOMA-IR, and individual MetS components

Midnight salivary cortisol concentrations were significantly and positively correlated with abdominal circumference ($r=0.21$, $P=0.001$), fasting blood glucose ($r=0.21$, $P=0.001$), and HOMA-IR ($r=0.17$, $P=0.013$), but not with blood pressure, triglycerides, or HDL-C (Table 2). The correlation between midnight salivary cortisol and fasting blood glucose was positive after excepting two patients with diabetes ($r=0.21$, $P=0.012$).

Table 2. Correlations between midnight salivary cortisol and components of metabolic syndrome, HOMA-IR, or hs-CRP

Variable	Midnight salivary cortisol	
	r[a]	P value
Age, yr ($n=46$)	0.14	0.121
AC, cm ($n=46$)	0.21	0.001
SBP, mm Hg ($n=46$)	0.11	0.692
DBP, mm Hg ($n=46$)	-0.02	0.891
TG, mg/dL ($n=46$)	0.12	0.081
HDL-C, mg/dL ($n=46$)	-0.04	0.092
FBG, mg/dL ($n=46$)	0.21	0.001
HOMA-IR ($n=39$)	0.17	0.013
hs-CRP, mg/dL ($n=38$)	0.09	0.092

HOMA-IR, homeostasis model assessment-insulin resistance; hs-CRP, high sensitivity C-reactive protein; AC, abdominal circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose.
[a]Partial correlation coefficient adjusted for age and gender.

Table 1. General characteristics of the study subjects

Variable	Total ($n=46$)	MetS (+) ($n=12$)	MetS (-) ($n=34$)	P value vs. MetS (-)
Age, yr	40.0 (34.0-82.0)	47.5 (39.3-54.8)	38 (34.0-52.0)	0.122
Sex, M/F	27/19	7/5	20/14	0.271
Diabetes	2 (4.3)	1 (8.3)	1 (2.9)	0.458
AC, cm	87.3 (79.6-92.4)	92.2 (91.3-93.4)	84.2 (76.2-89.5)	0.001
BMI, kg/m^2	24.3 (22.4-26.6)	26.2 (24.1-27.6)	23.5 (21.7-26.1)	0.023
SBP, mm Hg	121 (114.0-133.0)	132 (124.3-137.8)	118 (111-128)	0.375
DBP, mm Hg	80.0 (73.0-89.0)	87.5 (85.3-92.5)	78.0 (71-86)	0.321
TG, mg/dL	110.0 (84.0-154)	219.0 (184.8-290.5)	98.0 (75.0-118.0)	<0.001
HDL-C, mg/dL	54.0 (45.0-66.0)	45.5 (39.0-49.5)	58.0 (49.0-70.0)	0.001
FBG, mg/dL	86.0 (80.0-97.0)	99.5 (92.5-115.8)	83.0 (78.0-90.0)	<0.001
Insulin, mg/mL	4.7 (2.1-7.5)	7.5 (5.0-8.0)	4.3 (2.0-5.8)	0.046
HOMA-IR	1.40 (1.1-1.72)	2.73 (2.21-3.10)	0.95 (0.82- 1.10)	0.048
hs-CRP, mg/dL	0.11 (0.08-0.12)	0.15 (0.10-0.19)	0.09 (0.07-0.11)	0.232
Midnight salivary cortisol, ng/dL	34.0 (17.0-52.0)	82 .0 (57.8-123.8)	28.0 (14.0-41.7)	0.001

Values are presented as median (interquartile range) or number (%).
Continuous variables were compared using the Mann-Whitney U test, and categorical variables were compared with the chi-square test.
MetS, metabolic syndrome; AC, abdominal circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment-insulin resistance; hs-CRP, high-sensitivity C-reactive protein.

Table 3. Logistic regression to predict metabolic syndrome

Variable	OR	95% CI	*P* value
Unadjusted model			
Midnight salivary cortisol, ng/dL			
<50 (*n*=30)	1		
50≤, <100 (*n*=9)	1.5	0.3-7.4	0.27
≥100 (*n*=7)	6.0	1.8-44.3	0.001
Adjusted model			
Midnight salivary cortisol, ng/dL			
<50 (*n*=30)	1		0.045
50≤, <100 (*n*=9)	1.7	0.6-33.2	0.451
≥100 (*n*=7)	5.9	2.35-36.4	0.013
Abdominal obesity	1.34	0.7-11.5	0.812
IFG (glucose ≥100)	6.6	1.1-26.5	0.047

OR, odds ratio; CI, confidence interval; IFG, impaired fasting glucose.

Logistic regression analysis between midnight salivary cortisol levels and MetS

A univariate regression analysis revealed that high midnight salivary cortisol concentrations (100 to 150 ng/dL) were related to increased odds for MetS (odds ratio [OR], 6.0; 95% confidence interval [CI], 1.8 to 44.3; *P*=0.001) compared to low midnight salivary cortisol concentrations (<50 ng/dL) (Table 3). This finding remained significant in the multivariate analysis after adjusting for abdominal obesity and impaired fasting glucose (OR, 5.9; 95% CI, 2.35 to 36.4).

DISCUSSION

We have shown that individuals with MetS had two-fold higher midnight salivary cortisol concentrations than those without MetS. Midnight salivary cortisol concentrations were positively correlated with abdominal circumference, fasting blood glucose, and HOMA-IR. Furthermore, increased midnight salivary cortisol levels were associated with an increased OR for MetS. The increased risk was independent of abdominal obesity.

These observations are consistent with the hypothesis that excess production of cortisol might be involved in MetS pathogenesis. These results agree with those of previous studies that found that circulating cortisol concentrations were higher in subjects with MetS compared to healthy subjects [16-18].

Several bodies of evidence suggest that hypercortisolism is associated with individual components of MetS. Ward et al. [19] found that a higher fasting plasma cortisol level was associated with abdominal circumference, triglycerides, and insulin resistance. Philips et al. [20] reported an association between fasting plasma cortisol level and blood pressure, fasting glucose level, and insulin resistance. Plasma cortisol is less sensitive to the HPA axis than salivary cortisol. Nevertheless, most previous studies have used plasma cortisol levels to evaluate the relationship between hypercortisolism and MetS [21]. The results of this study are meaningful in that we used salivary cortisol level, which is a more sensitive index of endogenous cortisol status and biological activity, to demonstrate the relationship between MetS and hypercortisolism.

We did not find a significant association between midnight salivary cortisol level and blood pressure, which was previously observed by Kidambi et al. [22]. The reason for this discrepancy is unclear, but there are a few possible explanations. First, the number of participants enrolled in our study was small. Second, because several participants (*n*=7, 15.2%) were taking antihypertensive drugs, there may not have been a statistical difference in blood pressure between subjects with and without MetS.

Hypercortisolism may contribute to MetS pathophysiology through various mechanisms. First, cortisol promotes differentiation and proliferation of human adipocytes, and cortisol receptors are more abundant in viscera adipose tissue than that in subcutaneous adipose tissue [23]. Cortisol also redistributes adiposity from peripheral to central depots, and increases the size and number of adipocytes [24]. Consequently, excess cortisol causes abdominal obesity, which is an essential component of MetS.

Second, higher cortisol levels increase blood glucose levels. In patients with MetS, serum cortisol levels are significantly associated with fasting blood glucose levels [16-18,25]. The effects of cortisol oppose those of insulin. As a result, cortisol induces a state of insulin resistance, leading to diminished suppression of glucose production and reduced peripheral glucose uptake [26]. Additionally, cortisol may reduce glucose delivery to some tissues by impairing local blood flow [27]. Cortisol also suppresses insulin secretion and basal pulsatility [28,29]. As a result, cortisol increases blood glucose and the development of glucose intolerance and diabetes mellitus.

Higher cortisol levels are also associated with hypertension. A possible mechanism by which cortisol elevates blood pressure seems to be an increased responsiveness to vasoconstric-

tors along with decreased vasodilator production, as some studies have shown that reduced nitric oxide production or bioavailability contributes to cortisol-induced hypertension [30]. In addition, the endothelin system is activated in patients with Cushing's syndrome, leading to elevated plasma endothelin-1 levels, which probably play a role in the pathogenesis of hypertension and early atherosclerosis [30].

Recently, DeSantis et al. [31] published a study on the association between salivary cortisol levels and MetS and its components. The study used data from the Multi-Ethnic Study of Atherosclerosis (MESA). It showed that the presence of MetS was not associated with cortisol parameters among healthy adults. There are some differences between the MESA study and ours and there are a few possible explanations for this discrepancy with our study. First, the MESA study participants were selected for the absence of clinical cardiovascular disease and diabetic patients. Therefore, the proportion of participants with adverse metabolic conditions was smaller than in our study. Second, the specific cortisol parameter we used differed from that of the MESA study. We examined salivary cortisol only at midnight, and the MESA study measured cortisol patterns throughout the day.

Our study has several limitations. First, the number of participants enrolled in our study was small. Second, as our study was cross-sectional, the results could have limitations with regard to identifying causal relationships.

However, our results are meaningful in that this was the first study in Korean adults to evaluate the association of midnight salivary cortisol with MetS, and we showed that midnight salivary cortisol was higher in subjects with MetS than those without MetS. We also showed a positive correlation between midnight salivary cortisol level and several MetS components. These results support the hypothesis that MetS is associated with hypercortisolism.

Further research is needed to confirm a causal relationship between higher midnight salivary cortisol levels and MetS. Manipulations that reduce cortisol action may have a role in the treatment of MetS.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article are reported.

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