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Cortisol Metabolism in Obese Women with Normal and Impaired Glucose Tolerance

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ABSTRACT

Objectives: Increases in fasting plasma cortisol level in the morning has been associated with glucose intolerance and insulin resistance in patients with metabolic syndrome. This study investigated the relationship between fasting morning cortisol and insulin resistance defined by homeostasis model assessment for insulin resistance (HOMA-IR) in obese women with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT).

Methods: The study was carried out in the Obesity outpatient clinic between June and September 2005. Total body fat mass, lean body mass, total body fluid, and basal metabolic rate were calculated via bioelectrical impedance analysis. Body mass index (BMI), fasting plasma glucose, insulin, HOMA-IR, basal cortisol, 24-h urinary free cortisol, overnight dexamethasone suppression test, lipids, oral glucose tolerance test results, and thyroid function tests were obtained from patient files in the obesity clinic.

Results: This study included 38 obese women, 21 (55.3%) of which had NGT. There was no significant difference between NGT and IGT cases in terms of age, BMI, waist circumference, insulin, HOMA-IR, basal cortisol, and 24-h urinary free cortisol ($p=0.484$, $p=0.399$, $p=0.517$, $p=0.639$, $p=0.973$, $p=0.758$, $p=0.161$, respectively). There was no correlation between basal cortisol levels in patients with NGT, however, there was a moderate correlation between basal cortisol and HOMA-IR in patients with IGT ($p=0.464$, $r=0.629$ and $p=0.007$).

Conclusion: Although the basal cortisol levels of NGT and IGT patients were similar, a moderate correlation exists between basal cortisol and HOMA-IR in patients with IGT.

Keywords: Cushing's syndrome, obesity, insulin resistance, impaired glucose tolerance



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INTRODUCTION

Hypercortisolism has two forms, the first is systemic and the second is observed at the tissue or cellular level.^[1] Measuring plasma cortisol levels may be accepted to demonstrate a good reflection of systemic cortisol metabolism. However, no method exists to measure hypercortisolemia in tissues or cells.

Cortisol production rate (CPR) is an important parameter used to evaluate hypercortisolemia determined via excretion measurement of 17-hydroxycorticoids in 24-h urine.^[2] CPR values should be corrected according to the active metabolic body mass in obesity. Various studies have used body surface area, lean body mass, and urinary creatinine excretion for this correction, and they have almost uniformly reported that corrected CPR values were similar in obese and non-obese individuals.^[3] Several authors have suggested that obesity is associated with an increased rate of cortisol metabolic removal.^[4] Interestingly, both human and

mouse obesity studies have revealed the elevated activity of 11 β -hydroxysteroid dehydrogenase-1 (11 β -HSD type 1), which is the enzyme that converts cortisone to cortisol, thereby causing intracellular cortisol excess.^[4,5] Whether the change in the activity of this enzyme is a cause or a result of obesity remains unknown.^[1] Additionally, it should be noted that studies evaluating the hypothalamus–pituitary–adrenal (HPA) axis have shown that the HPA axis responds normally to dexamethasone suppression.^[6] Evaluating hypercortisolemia in obesity is difficult because obesity has many similarities with Cushing’s syndrome. In fact, it is one of the conditions defined as a pseudo-Cushing syndrome.^[7]

Increased fasting morning plasma cortisol level is associated with glucose intolerance and insulin resistance in patients with metabolic syndrome.^[8] Furthermore, the presence of differences in glucose tolerance tests depend on the time of day during which the tests were performed, making this an interesting point to note. For instance, patients that have impaired glucose tolerance (IGT) in the morning may demonstrate perfectly normal results in the evening, suggesting a possible role for diurnal patterns.^[9]

No comparisons were noted concerning central or peripheral obesity in studies that showed increased cortisol production in obese persons.^[10] However, these studies did not take insulin and glucose metabolism into account. This study aimed to investigate the relationships between basal serum cortisol level and insulin resistance defined by homeostasis model assessment for insulin resistance (HOMA-IR) in obese women with normal glucose tolerance (NGT) and those with IGT.

METHOD

The study was carried out between June and September 2005 in the Obesity outpatient clinic, Selçuk University Meram Medical Faculty, Konya, Turkey. The patient records of all patients were evaluated retrospectively. Patients who did not have diabetes but had fasting plasma glucose (FPG) levels between 100 and 125 mg/dL were defined as IGT. Those with fasting blood glucose levels <100 mg/dL were defined as NGT. Clinical, demographic and anthropometric features were recorded from endocrinology patient file. Patients were weighed using the TANITA device (type BC-418MA, Tokyo, Japan) which utilizes the bioelectrical impedance method to report body fat mass, body fat percentage, fat-free body mass, total body water, and basal metabolic rate (BMR) data. Body mass index (BMI) was calculated by dividing the body weight (in kilograms) by the square of the body height (in meters). In addition, FPG, serum insulin, serum basal cortisol, and 24-h urinary free cortisol levels were recorded and thyroid function tests,

overnight dexamethasone suppression test, and 75-g oral glucose tolerance tests were conducted. Moreover, HOMA-IR was calculated using the formula as [fasting plasma insulin (mU/L)×FPG (mmol/L)]/22.5.^[11] Plasma cortisol and urinary free cortisol measurements were performed with the DXI 800 autoanalyzer (Beckman Coulter, USA) using the chemiluminescence method.

Patients who had other known causes of pseudo-Cushing syndrome (history of diabetes, neuropsychiatric disorders, alcoholism, polycystic ovary syndrome, and eating disorders) were excluded from the study. Patients with chronic diseases other than obesity and those that had been using regular medications were also excluded from the study. Besides, patients with cortisol levels higher than 1.8 μ g/dL as a result of overnight dexamethasone suppression tests were also excluded.

The Statistical Package for the Social Sciences for Windows 10.0 program was used for the statistical analysis of the findings obtained in the study. Categorical variables were expressed as frequency and percentage. The continuous variables were presented as mean and standard deviation. Student’s t-test was used to compare the quantitative data and the groups with normal distribution. The Pearson correlation test was used to compare continuous variables. The results were evaluated in the 95% confidence interval and the significance level was $p < 0.05$.

RESULTS

This study retrospectively evaluated 38 obese women, 21 (55.3%) with NGT and 17 (44.7%) with IGT. The mean age of the patients was 40.6 ± 9.7 years. Age, body composition measurements and BMR in patients with NGT and IGT are summarized in Table 1.

A moderate positive correlation was noted between HOMA-IR and basal serum cortisol level in patients with IGT, whereas no such correlation was found in patients with NGT ($r=0.629$ and $p=0.007$; $p=0.464$, respectively). Laboratory parameters of the patients with NGT and IGT are summarized in Table 2.

DISCUSSION

This study examined the possible relationships between obesity, IGT, insulin resistance, and cortisol level. Insulin and HOMA-IR levels were found to be similar in obese patients with NGT and IGT. A moderate positive correlation exists between HOMA-IR and basal serum cortisol levels in patients with IGT.

IGT can be directly inferred to be associated with increased insulin level (to compensate for the resistance). Sainaghi et

Table 1. Age, body composition measurements and basal metabolic rate in patients with normal and impaired glucose tolerance

	NGT Group (n=21)	IGT Group (n=17)	p
Age (years)	39.6±9.5	41.9±10.1	0.484
BMI (kg/m ²)	39.0±5.1	41.3±9.9	0.399
Waist circumference (cm)	107.3±10.5	109.9±14.5	0.517
WHR	0.8±0.1	0.9±0.1	0.815
Body fat (%)	42.7±4.9	44.1±5.0	0.409
Total fat mass (kg)	42.7±11.0	46.2±15.5	0.419
Lean body mass (kg)	55.8±5.3	56.4±6.4	0.732
Total body water (L)	40.8±3.8	41.3±4.7	0.699
BMR (J/(h.kg))	1708.1±161.4	1737.4±220.0	0.640

BMI: Body mass index; BMR: Basal metabolic rate; IGT: Impaired glucose tolerance; NGT: Normal glucose tolerance; WHR: Waist-to-hip ratio.

Data is given as mean±standard deviation.

Student t test.

Table 2. Laboratory parameters of the patients with normal and impaired glucose tolerance

	NGT Group (n=21)	IGT Group (n=17)	p
Insulin (μU/mL)	12.6±7.6	11.6±4.7	0.639
HOMA-IR (mg/dL)	3.0±1.8	3.0±1.3	0.973
Total cholesterol (mg/dL)	192.3±32.0	205.3±33.6	0.231
HDL cholesterol (mg/dL)	39.9±7.3	44.0±8.0	0.107
LDL cholesterol (mg/dL)	124.8±28.5	132.2±28.9	0.437
Triglyceride (mg/dL)	141.7±57.8	145.3±55.1	0.847
Basal serum cortisol (mg/dl)	12.2±4.2	11.8±4.8	0.758
UFC (μg/24-h)	137.9±68.4	168.4±60.6	0.161

HDL: High-density lipoprotein; HOMA-IR: Homeostasis model assessment for insulin resistance; IGT: Impaired glucose tolerance; LDL: Low-density lipoprotein; NGT: Normal glucose tolerance; UFC: Urinary free cortisol.

Data are given as mean±standard deviation.

Student t test.

al. showed that the HOMA-IR value was significantly higher in obese cases with IGT compared with obese cases with NGT. However, they found that insulin levels were similar between groups.^[12] No significant difference was noted between the NGT and IGT groups in terms of neither insulin nor HOMA-IR values in the current study. The lack of differences was attributed to the inclusion of obese patients in both groups. In agreement with this hypothesis, a previous study demonstrated that obesity increased insulin resistance and insulin levels independent of IGT.^[12] Moreover, patients with diabetes were excluded in the current study, indicating a possible cause for the similarities in insulin levels and insulin resistance among groups.

Cortisol counteracts insulin by keeping glucose in the blood where it is easily accessible for use. Thus, if increased corti-

sol levels are at an important level, it may be expected to affect insulin and glucose levels.^[13] Reynolds et al. showed that plasma cortisol levels in men with IGT were significantly higher compared to cases with NGT.^[14] Bjorntorp et al. also found that increased fasting morning plasma cortisol level was associated with glucose intolerance and insulin resistance in patients with metabolic syndrome.^[8] Moreover, Gerards et al. showed that the frequency of having type 2 diabetes mellitus or IGT was significantly higher in patients with high cortisol levels. The authors emphasized that increased cortisol may be an important cause of insulin resistance.^[15] Praveen et al. showed that the morning cortisol levels of IGT cases were higher than the NGT cases.^[16] Furthermore, Ward et al. reported that fasting cortisol levels showed significant associations with many variables, including FPG, blood pressure, and insulin resistance.^[17] A

moderate positive correlation also exists between HOMA-IR and serum cortisol levels in obese patients with IGT in the current study, following the literature.

Basal cortisol levels were similar among the groups in the current study. Contrary to the results of this study, Praveen et al. reported that obese patients with NGT had lower cortisol levels in the morning compared with patients with IGT.^[16] The relationship between increased cortisol and IGT in obese patients has not been clearly explained in previous studies. However, many different studies have shown an increase in cortisol levels in obese cases.^[18] Two different explanations exist for this situation in the literature. First, this situation is explained by the HPA axis—which is impaired in obesity—and the loss of diurnal rhythm.^[19] Second, it is explained by an increase in cortisol secretion due to increased cortisol clearance in obese patients.^[20] Obesity is characterized by an increased CPR, but the fractional turnover rate of cortisol is also increased.^[8] Therefore, it has been previously hypothesized that circulating plasma cortisol level is normal or low-normal compared with the normal-weight subjects despite the increased production of cortisol in obese cases.

The endocrine axis is dynamic, and hormones are well-known to adhere to rhythmic patterns.^[21] Dark and light cycles of the day and seasons are among the major environmental stimulants of the metabolic clock. Circadian rhythms are controlled by these circadian timing mechanisms. Many hormones are secreted in a circadian rhythm.^[22-24] Moreover, impaired circadian rhythm is an important finding of endocrinological diseases. Adrenal cortisol release reaches its highest level with ACTH peak early in the morning. Loss of circadian ACTH or cortisol secretion is a feature of Cushing's disease. Likewise, disruption in circadian rhythm has been associated with insulin resistance and obesity in human and mouse studies.

It has been reported that IGT can be detected in the morning but not in the evening in some cases.^[9] This difference in glucose tolerance in IGT patients could be due to the overactivation of the HPA axis and increased secretion of counter-regulatory hormones, especially cortisol, in the morning. The HPA axis may be more active in patients with IGT compared with those with NGT. However, this difference may not be evident in blood measurements due to the possibility of higher cortisol turnover.

The low number of patients and retrospective study design were among the limitations of the current study. The increased sensitivity of the HPA axis and the impaired response of the counter-regulatory system may be only a

hypothesis due to very limited evidence. However, inhibition of endogenous glucocorticoid metabolism has been targeted in diabetes mellitus (with success) and inhibitors for the 11 β -HSD type 1 enzyme have been developed for use in diabetes.^[17]

CONCLUSION

This study found a significant correlation between fasting plasma cortisol levels and HOMA-IR only in patients with IGT. This correlation could not be demonstrated in obese women with NGT. Thus, the relationship between basal cortisol and insulin resistance may be related to increased sensitivity of the HPA axis or disruption of the circadian rhythm.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Funding: None.

Ethics Committee Approval: This study was produced from the thesis, which was performed as retrospectively a file examination in Obesity Outpatient Clinic, Selçuk University Meram Medical Faculty between 2005-2006. All patients provided written informed consent for study participation, and all steps of the study conformed to the Declaration of Helsinki and its most recent amendments.

Authorship Contributions: Concept – M.S.G.; Design – K.G.; Supervision – M.S.G.; Materials – K.G.; Data collection &/or processing – K.G.; Analysis and/or interpretation – K.G.; Literature search – N.D.G.; Writing – N.D.G.; Critical review – M.S.G.

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