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Original Investigation

The Relationship between Insulin Resistance and Cortisole Levels

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Abstract

Objective: It is known that cortisol, which is controlled by hypothalamic–pituitary–adrenal axis and produced by the adrenal gland results in glucose intolerance, obesity, and hypertension (such as in Cushing's syndrome). Insulin resistance is understood as the down regulation of insulin-mediated glucose release from the liver or impaired insulin-mediated peripheral glucose utilization. Glucocorticoids (cortisol), as counter-insulin hormones, suppress insulin secretion from pancreatic beta cells. On the other hand, they increase vagal stimuli to release insulin as the central effect. The balance between these effects may cause compensatory hyperinsulinemia and hyperglycemia. In this study, we investigate the relationship between cortisol levels, insulin, and glucose metabolism of 154 patients with obesity who were admitted to the endocrinology outpatient clinic.

Methods: One hundred and fifty-four patients who were admitted to the endocrinology outpatient clinic (42 males and 112 females) were investigated with cross-sectional and retrospective statistical methods.

Results: The main features of patients (average±standard deviation) were as follows: age: 49.8±14.8 years; weight: 84.5±18.7 kg; BMI: 32.24±7.51 kg/m^2; waist circumference: 98.97±16.34 cm; waist-to-hip ratio: 0.87±0.07; systolic blood pressure: 128±19.26 mmHg; diastolic blood pressure: 78.3±9.6 mmHg; fasting blood glucose: 110.3±48.62 mg/dL; HbAlc: 5.74%±1.35%; insulin: 12.21±1.41 µU/mL; C-peptide: 3.04±l.71 ng/mL; cortisol: 14.30±7.75 µg/dL; LDL-cholesterol: 145.20±64.03 mg/dL; HDL-cholesterol: 43.31±12.25 mg/dL. It was observed that cortisol levels increased with age, therefore, increasing fasting plasma glucose, HbAlc, and C-peptide levels, and low HDL levels. In addition, the upper limit levels of cortisol were found to be together with minimal elevated levels of prolactin and, particularly waist-to-hip ratio (WHR), which is an indicator of abdominal obesity.

Conclusion: Increased cortisol release can disrupt glucose tolerance and insulin secretion, particularly for individuals with abdominal obesity.

Keywords: Cortisol, insulin resistance, obesity

Introduction

Insulin resistance is characterized by the lack of biological responsiveness to endogenous or exogenous insulin. It is generally accompanied by hyperinsulinemia, but not always with hyperglycemia. Hyperglycemia is the advanced stage of insulin resistance (1). Insulin resistance is understood as the downregulation of insulin-mediated glucose secretion from the liver and/or, again, the impairment of insulin-mediated peripheral glucose use (2).

Cortisol is produced in the adrenal gland. Cortisol, which causes gluconeogenesis, fat and protein breakdown, and mobilization of extrahepatic amino acids and ketone bodies, shows its effect as an insulin antagonist. It suppresses insulin secretion from pancreatic beta cells. On the other hand, glucocorticoids increase the vagal stimulus regarding insulin secretion with their central effect. The balance between these effects can cause insulin resistance together with compensatory hyperinsulinemia and hyperglycemia in the blood (2). As a result, the blood glucose level elevates, and glycogen formation increases in the liver (3).

The frequency of diabetes mellitus increases by age. Glucose-mediated insulin secretion decreases, and impairment in glucose tolerance occurs, particularly in the 3rd decade with mechanisms such as impairment in insulin-mediated glucose intake, impaired renal function and increased sympathetic nervous system activity, and post-receptor impairment in the fat tissue (4). However, it was shown in various studies that cortisol secretion does not change by age, and a decrease was observed in its catabolism (5).

As a result of the increase in the free fatty acid secretion with factors secreted from the enlarged fat cells of obese patients, fatty acid entry into the liver and peripheral tissues increases, insulin breakdown by the liver decreases, and insulin level in circulation increases. This plays a role in the development of insulin resistance (6). Cortisol hypersecretion is present particularly in central obesity. This contributes to the decreased insulin sensitivity in the muscles and liver (Figure 1) (7).

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The hypothalamic-pituitary-adrenal axis abnormalities such as increased cortisol are common in diabetic patients. In diabetic patients with a counter-regulatory hormone such as increased plasma cortisol, insulin resistance increases such as a high insulin level are observed (2).

It is known that cortisol, which is one of the main glucocorticoid hormones supervised by the hypothalamic-pituitary-adrenal axes and produced in the adrenal cortex, contributes to glucose intolerance, obesity, and hypertension (as in Cushing's disease). Insulin resistance is understood as the downregulation of insulin-mediated glucose secretion from the liver and/or, again, the impairment of insulin-mediated peripheral glucose use. As counter-insulin hormones, glucocorticoids (cortisol) suppress insulin secretion from pancreatic beta cells (Figure 2). On the other hand, glucocorticoids increase the vagal stimulus regarding insulin secretion with their central effect. This, in turn, can cause insulin resistance together with compensatory hyperinsulinemia and hyperglycemia in the blood (2). In this study, we investigated the relationship between the blood cortisol levels and insulin and glucose metabolism in 154 obese patients applying to the Outpatient Clinic of Endocrinology.

Methods

In total, 154 endocrine polyclinic patients (42 male and 112 female) were examined sectionally and retrospectively using statistical methods.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 22 (IBM Cooperation, New York, USA) program was used for statistical analysis in the Istanbul Training and Research Hospital. The results of all parameters belonging to the case groups were presented as the average±standard deviation. In addition to using descriptive statistical methods (average, standard deviation) in the evaluation of the data, Student's t-test was used in the comparison of pairs. The significance level of acquired results was interpreted using the p-value. $P<0.05$ was interpreted as statistically significant.

Results

The main features of patients were as follows (average±standard deviation): age: 49.8±14.8 years, weight: 84.5±18.7 kg, body mass index (BMI): 32.24±7.51 kg/m^2, waist circumference: 98.97±16.34 cm, waist-to-hip ratio (WHR): 0.87±0.07, systolic blood pressure (BP): 128.28±19.26 mmHg, diastolic BP: 78.3±9.6 mmHg, FBS: 110.30±48.62 mg/dL, HbAlc: 5.74±1.35%, insulin: 12.21±11.41 µU/mL, C-peptide: 3.04±l.71 ng/mL, cortisol: 14.30±7.75|µg/dL, LDL-cholesterol: 145.20±64.03 mg/dL, and HDL-cholesterol: 43.31±12.25 mg/dL (Table 1).

It was observed that the cortisol levels that increase by age (p=0.03) increases FBS (p=0.02), HbAlc (p=0.03) and C-peptide (p=0.04) levels and decreases HDL-cholesterol (p=0.04). Furthermore, cortisol elevation was found to accompany minimal prolactin elevation (p=0.01) and particularly elevated WHR (p=0.03) (Table 2).

Discussion

In this study, we aimed to investigate the relationship between insulin resistance and cortisol levels. We sectionally and retrospectively

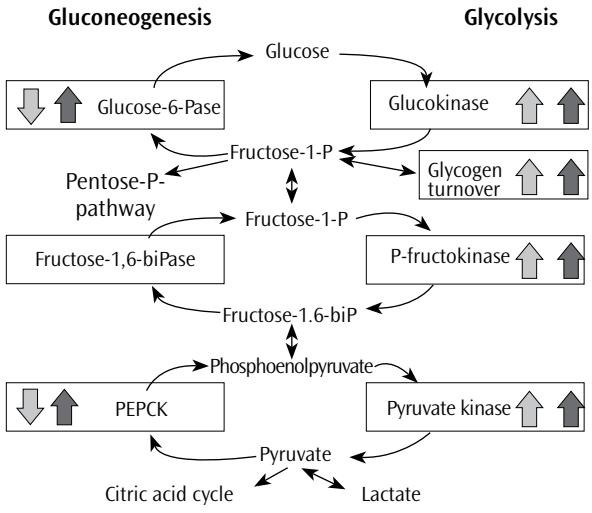

Figure 1. The effects of glucocorticoids on the metabolism of hepatic glucose (7)

The main metabolism of glucose in the liver is shown. The duties of glucocorticoids (gray arrows) and insulin (dashed arrows) are demonstrated as positive (up arrow) or negative (down arrow) effects. In some areas, particularly in gluconeogenesis (PEPCK) and glucose release from glucose-6 phosphate, insulin and glucocorticoids counteract the effects of each other.

On the other hand, in other areas, particularly in triggering oxidative glycolysis and increasing the conversion between glucose-6 phosphate and glycogen, insulin, and glucocorticoids do not counteract the effects of each other.

P: phosphate; PEPCK: phosphoenolpyruvate carboxykinase

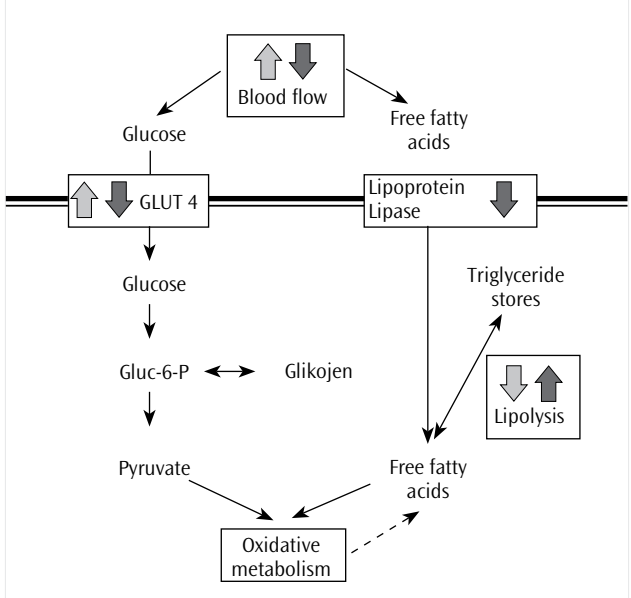

Figure 2. The effects of glucocorticoids on peripheral glucose uptake (7)

The pattern schema of insulin-sensitive cells is shown above. Although glycogen synthesis or oxidative pathways (pyruvate or free fatty acids) are dominant in the skeletal muscle, lipogenic pathways are dominant in adipocytes. GLUT 4 is mainly released from the skeletal muscle, lipoprotein lipase, and fat tissue. The duties of glucocorticoids (gray arrows) and insulin (dashed arrows) are shown as positive (up arrow) or negative (down arrow) effects. The major effects of glucocorticoids are to decrease insulin-mediated vasodilatation, to reduce the translocation of GLUT 4 on the surface of the cell, and to increase lipolysis. Perhaps, it induces local adrenalin synthesis, and thus, increases the competition between free fatty acids and pyruvate for mitochondrial oxidative metabolism.

P: phosphate

Table 1. General features of patients

	Mean±SD
Age (years)	49.75±14.87
Height (cm)	162.35±7.83
Weight (kg)	84.58±18.76
BMI (kg/m^2)	32.24±7.51
Waist circumference (cm)	98.87±16.34
Hip circumference (cm)	113.71±16.77
WHR (waist/hip)	0.87±0.75
FBG (mg/dL)	110.30±48.62
Systolic arterial pressure (mmHg)	128.28±19.26
Diastolic arterial pressure (mmHg)	78.34±9.63
LDL (mg/dL)	145.20±64.03
HDL (mg/dL)	43.31±12.25
Triglyceride (mg/dL)	153.56±92.24
T-Chol (mg/dL)	219.21±72.35
HbA1c (%)	5.74±1.35
Insulin (µU/mL)	12.21±11.41
C-peptide (ng/mL)	3.04±1.71
Cortisol (µg/dL)	14.30±7.75
Prolactin (ng/mL)	11.29±8.36

BMI: body mass index; WHR: waist-to-hip ratio; FBG: fasting blood glucose; LDL: low-density lipoprotein; HDL: high-density lipoprotein; T-chol: total cholesterol; HbA1c: hemoglobin A1c

scanned 154 endocrine polyclinic patients. As with the physiological changes that occur because of aging and as shown in various other studies, an increase in the average plasma concentration of the cortisol was detected in our study as well with the decrease in cortisol catabolism (5). In several public studies, it was shown that fasting blood sugar levels increase by 1–2 mg/dL and postprandial values increase by 4–5 mg/dL in every decade and that glucose intolerance develops as a result of the increase in the insulin resistance ratio and the decrease in insulin response to glucose (8). In our study, as well, a significant relationship between increased cortisol levels due to aging and increased fasting blood sugar (p=0.02), HbAlc (p=0.03), and C-peptide levels (p=0.04) was detected.

Compared with normal individuals, a disrupted circadian rhythm of cortisol in patients with abdominal obesity increases the activity of the hypothalamic-pituitary-adrenal axis and causes higher cortisol levels (9). Even if the cortisol elevation is subclinical, it is characterized by a weak glycemic control (10). In a study conducted by Rasmond et al. (11), a positive relationship was detected between plasma cortisol levels and BMI, WHR, and total cholesterol levels. In another study conducted in Scotland, cortisol's relationship with HDL was detected, but its effect on total cholesterol could not be demonstrated. HDL and cortisol have an inverse relationship, and it is detected at quite a significant level in both male and female patients (12). The accompaniment of cortisol level elevation with HDL (p=0.04) and, in particular, with a high BMI (p=0.03) was demonstrated in our study as well.

Additionally, the relationship of increased cortisol levels with minimal prolactin elevation (p=0.01) was detected in our study.

Table 2. Comparisons according to basal cortisol levels

	Cortisol ≤10 µg/dL	Cortisol >10 µg/dL	p<
Age (years)	47.47±12.10	53.56±15.55	0.03
Height (cm)	162.08±6.20	163.75±8.46	0.01
Weight (kg)	80.56±14.58	82.03±20.01	0.01
BMI (kg/m^2)	30.77±5.82	30.71±7.84	0.01
Waist circumference (cm)	94.78±13.89	96.10±16.86	NS
Hip circumference (cm)	112.92±15.05	108.88±16.48	NS
WHR (waist/hip)	0.83±0.05	0.88±0.07	0.003
FBG (mg/dL)	94.31±11.71	115.61±56.04	0.02
Systolic arterial pressure (mmHg)	125.83±17.17	125.85±18.22	NS
Diastolic arterial pressure (mmHg)	76.53±8.84	77.93±10.24	NS
LDL (mg/dL)	154.19±57.92	144.61±68.26	NS
HDL (mg/dL)	46.03±10.05	41.05±13.43	NS
Triglyceride (mg/dL)	131.53±61.13	146.39±78.59	NS
T-Chol (mg/dL)	227.83±63.62	214.66±78.99	NS
HbA1c (%)	5.18±0.95	5.74±1.43	0.03
Insulin (µU/mL)	10.19±8.89	11.95±13.53	NS
C-peptide (ng/mL)	2.46±0.99	3.23±2.09	0.04
Cortisol (µg/dL)	7.54±1.87	17.26±7.50	NS
Prolactin (ng/mL)	7.74±3.25	12.13±9.84	0.01

BMI: body mass index; WHR: waist-to-hip ratio; FBG: fasting blood glucose; LDL: low-density lipoprotein; HDL: high-density lipoprotein; T-chol: total cholesterol; HbA1c: hemoglobin A1c

NS: not significant

The limiting aspects of our study were the exclusion of patients whose complete data could not be obtained in file scans and who continue their follow-up treatments in other hospitals. Furthermore, subgroup categorizations based on their diseases and a more comprehensive endocrinological data were not available.

Conclusion

Increased cortisol secretion can disrupt glucose tolerance and insulin secretion, particularly in patients with abdominal obesity.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was not obtained from patients due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed

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Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Metabolik sendrom kılavuzu, Türkiye Endokrinoloji ve Metabolizma Derneği, Ankara: Tuna Matbaacılık San Tic. A.Ş., 2009.
2. Newell-Price J, Trainer P, Perry L, Wass J, Grossman A, Besser M. A single sleeping midnight cortisol has 100% sensitivity for the diagnosis of Cushing's syndrome. Clin Endocrinol 1995; 43: 545-50. [CrossRef]
3. Jeremy M Berg, John L Tymoczko, and Lubert Stryer. Biochemistry 5th ed. New York: W H Freeman; 2002. p.688-96.
4. Tails CR, Fillit MH. Geriatric Medicine and Gerontology. 6th ed. London: Churchill Livingstone; 2003:1081-86.
5. Ohashi M, Fujio N, Kato K, Nawata H, Ibayashi H. Aging is without effect on the pituitary adrenal axis in men. Gerontology 1986; 32: 335-9. [CrossRef]
6. Goossens GH, Blaak EE, Amer P, Saris WH, van Baak MA. Angiotensin II: a hormone that affects lipid metabolism in adipose tissue. International Journal of Obesity 2007; 31: 382-4. [CrossRef]
7. Andrews RC, Walker BR. Glucocorticoids and insulin resistance: old hormones, new targets. Clinical Science 1999; 96: 513-23. [CrossRef]
8. Perry HM. The endocrinology of aging. Clinical Chemistry 1999; 45: 1369-76.
9. Björntorp P, Holm G, Rosmond R. Hypothalamic arousal, insulin resistance and Type 2 diabetes mellitus. Diabet Med 1999; 16: 373-83. [CrossRef]
10. Rossi R, Tauchmanova L, Luciano A, Di Martino M, Battista C, Del Viscovo L, et al. Subclinical Cushing's syndrome in patients with adrenal incidentaloma: clinical and biochemical features. J Clin Endocrinol Metab 2000; 85: 1440-8.
11. Rosmond R, Dallman MF, Björntorp P. Stress-related cortisol secretion in men: relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities. J Clin Endocrinol Metab 1998; 83:1853-9. [CrossRef]
12. Fraser R, Ingram MC, Anderson NH, Morrison C, Davies E, Connell JM. Cortisol effects on body mass, blood pressure, and cholesterol in the general population. Hypertension 1999; 33: 1364-8. [CrossRef]