

HORMONAL PROFILE IN SUBJECTS WITH METABOLIC SYNDROME

RUCSANDRA DĂNCIULESCU MIULESCU¹, MĂDĂLINA MUȘAT¹,
CĂTĂLINA POIANĂ¹, SUZANA DĂNOIU²

¹*“Carol Davila” University of Medicine and Pharmacy, Bucharest*

²*University of Medicine and Pharmacy Craiova*

**corresponding author: rucsandra_m@yahoo.com*

Abstract

The term “Metabolic Syndrome” is generally used to indicate a clinical situation in which different degrees of hypertension, impaired glucose tolerance, atherogenic dyslipidemia, central fat accumulation, insulin resistance, as well as prothrombotic and proinflammatory states cluster together in the same individual. The etiology of the metabolic syndrome has not been established definitively. One hypothesis presumes that the primary cause is insulin resistance. Another hypothesis incriminates hormonal changes for the development of abdominal obesity. The aim of the present study is to evaluate the interaction of hormones with features of metabolic syndrome.

18 patients with metabolic syndrome were recruited for this study. Subjects were fasting for 12 h before blood sampling, which was done between 8.00 and 9.00 a.m. Serum growth hormone (GH), insulin like growth factor 1 (IGF-1), cortisol, insulin, glucose, triglycerides, and HDL were measured. Estimates of insulin resistance were derived from the HOMA (Homeostasis Model Assessment) index (basal glucose mmol/l x basal insulin μ IU/ml/22.5); insulin-resistant were defined by HOMA >3. Results were compared with measurements in 12 healthy subjects.

There were statistically significant differences in the recorded parameters in patients with metabolic syndrome versus control group.

Fasting blood glucose, basal insulin, HOMA, serum triglycerides were higher in patients with the metabolic syndrome supporting the concept that these patients have a higher cardiovascular risk. Most subjects had hormone levels within the normal range, but there were significant difference between mean levels of metabolic syndrome group when they were compared to control group. Cortisol levels in patients with metabolic syndrome are within the normal range, but significantly higher compared to control group. The results sustain the hypothesis that cortisol is critical for the development and maintenance of abdominal visceral obesity. The levels of the growth hormone and insulin like growth factor-I are within the normal range, but the metabolic syndrome group had an increased IGF-1 associated with the decrease of GH concentrations.

Hormonal profile of patients with metabolic syndrome in this study suggests an excess of morning plasma cortisol and lower GH levels in association with central adiposity, as compared to control group. However a bigger cohort is necessary to confirm these preliminary data.

Rezumat

Sindromul metabolic poate fi definit ca un dezechilibru metabolic, caracterizat printr-o simptomatologie complexă, ce include hipertensiunea arterială, intoleranța la glucoză, rezistență la insulină, dislipidemie aterogenă, stări protrombotice și proinflamatorii.

Studiul clinic prezentat a inclus două grupuri de pacienți: un grup format din 18 pacienți diagnosticați cu sindrom metabolic și un grup-control, cu 12 subiecți sănătoși. Pentru subiecții luați în studiu au fost înregistrați parametrii antropometrici, tensiunea arterială, unii parametrii ai profilelor glucidic și lipidic, precum și unii parametrii hormonal specifici: concentrația plasmatică a cortizolului, a hormonului de creștere și a factorului de creștere asemănător insulinei (*insulin-like growth factor, IGF*).

Key words: metabolic syndrome, insulin resistance, GH, cortisol, IGF-1

Introduction

The term “Metabolic Syndrome” is generally used to indicate a clinical situation in which different degrees of hypertension, impaired glucose tolerance, atherogenic dyslipidemia, central fat accumulation, insulin resistance, as well as prothrombotic and proinflammatory states cluster together in the same individual. A definition of the Metabolic Syndrome was given by the World Health Organization (WHO) Working Group on Diabetes in 1998, modified in 1999, with a list of criteria for the clinical diagnosis. In particular the WHO definition stated that diabetes type 2 or impaired glucose tolerance (IGT), together with at least 2 of 4 other factors: hypertension (blood pressure $>140/90$ mmHg), hyperlipidemia (serum triglycerides >150 mg/dl or HDL-cholesterol <35 mg/dl in men and <39 mg/dl in women), microalbuminuria (urinary albumin excretion rate >20 μ g/min), obesity (BMI >30 kg/m² and/or waist-to-hip ratio >0.90 in men or >0.85 in women). In case of normal glucose tolerance the evidence of insulin resistance is needed [1]. According to the International Diabetes Federation definition, the criteria for metabolic syndrome includes central obesity (waist circumference ≥ 94 cm for European Men and 80 cm for European women with ethnicity specific values for other groups) and at least two of the following criteria: serum triglycerides ≥ 150 mg/dl or known treatment, HDL ≤ 40 mg/dl in men or known treatment, blood pressure $\geq 130/85$ mmHg or known treatment, fasting plasma glucose ≥ 100 mg/dl or previously diagnosed diabetes [2].

The etiology of the metabolic syndrome has not been established definitively. One hypothesis presumes that the primary cause is insulin resistance. The second hypothesis blames hormonal changes for the development of abdominal obesity. Insulin resistance is the cardinal feature of the metabolic syndrome. Several insulin antagonist hormones have mechanisms of action that reduce the biological actions of insulin and, therefore, induce insulin resistance. Since insulin antagonist hormones induce insulin resistance, these hormones may contribute to the pathogenesis of the metabolic syndrome.

The metabolic syndrome and glucocorticoid hormone action.

Glucocorticoids are important regulators of the protein, glucose and lipid metabolism. There are a lot of common features in metabolic syndrome and Cushing syndrome that suggest a common key factor could be the excess of cortisol that could have an important role in triggering diabetes mellitus in predisposed individuals [6]. Despite the similarities between the two syndromes mentioned, serum or urine cortisol have not been found increased in obese patients with type 2 diabetes mellitus or insulin resistance [3, 4, 5, 14]. Cortisol major source is the adrenal cortex, but the hormone is also produced in the omental fat [8, 9]. In obese people the levels of cortisol in adipose tissue are increased by reducing cortisone (inactive biomolecule) into cortisol (active hormone) by the 11- β -hydroxysteroid dehydrogenase type 1 (11- β -HSD1) which is present in humans in adipose tissue [10] and in the liver [11]. 11- β -HSD1 is sometimes over-expressed in visceral adipose tissue as compared to subcutaneous fat and it could act as a paracrine factor, increasing cortisol in abdominal fat, but not in the systemic circulation [4]. The studies of transgenic mice overexpressing the gene coding for 11- β -HSD1 in adipocytes showed increased glucocorticoids levels in the adipose tissue and portal vein and induced visceral obesity, insulin resistance, hypertension and dyslipidemia. However, data from mouse studies cannot be extended in humans [3].

The metabolic syndrome, the GH-IGF (growth factor – insulin-like growth factor) axis and insulin sensitivity. The metabolic syndrome is associated with changes throughout the GH-IGF axis, which may reduce IGF-1 activity. In obesity, GH secretion is diminished and clearance is enhanced, resulting in reduced free IGF-1 levels [12].

Several studies have shown that there is a high prevalence of low testosterone levels in men with the metabolic syndrome. Studies have revealed that a low testosterone level is an independent risk factor for the later onset of the metabolic syndrome. In men, hypoandrogenism is associated with features of the metabolic syndrome, but the role of sex hormones in the pathogenesis of the metabolic syndrome and diabetes is not well understood. In clinical studies, low levels of total and free testosterone in men have been associated with visceral obesity, insulin resistance or hyperinsulinemia, dyslipidemia. The association of testosterone with an altered lipid profile is partly secondary to abdominal fat accumulation, but there also appears to be an independent relationship between low levels of testosterone and hyperinsulinemia and dyslipidemia. Low levels of testosterone have also predicted worsening abdominal obesity. Recent studies reports up that one

third of individuals have levels of free and bioavailable testosterone in the range compatible with testosterone deficiency [13].

The main of the study is to evaluate the interaction of several hormones with features of metabolic syndrome.

Materials and methods

18 patients (10 women and 8 men) with metabolic syndrome were recruited for this study. Anthropometric, biochemical and hormonal parameters were determined. Blood pressure was recorded. The anthropometric measurement included waist circumference (WC) and body mass index (BMI). BMI was computed as a ratio of weight to the square of height (kg/m^2). Waist circumference was taken at the midpoint between the lowest rib and the iliac crest. Blood pressure was measured with a mercury sphygmomanometer. The measurement protocol included three measurements; the mean of all 3 measurements was used as systolic and diastolic blood pressure. Subjects were asked to fast for 12 h before blood sampling, which was done between 8.00 and 9.00 a.m. Serum growth hormone (GH), insulin-like growth hormone-1 (IGF-1), cortisol, insulin, glucose, triglycerides, and HDL were measured. Plasma glucose, serum triglycerides, serum HDL were measured enzymatically. GH, cortisol, insulin were measured using commercial kits RIA/IRMA with high sensitivity. Estimates of insulin resistance were derived from the HOMA (Homeostasis Model Assessment) index ($\text{basal glucose mmol/l} \times \text{basal insulin } \mu\text{IU/ml}/22.5$); insulino-resistant were defined by $\text{HOMA} > 3$. The metabolic syndrome as defined by the International Diabetes Federation was central obesity and at least two of the following criteria: serum triglycerides $\geq 150 \text{ mg/dl}$ or known treatment, $\text{HDL} \leq 40 \text{ mg/dl}$ in men or known treatment, blood pressure $\geq 130/85 \text{ mmHg}$ or known treatment, fasting plasma glucose $\geq 100 \text{ mg/dl}$ or previously diagnosed diabetes. Results were compared with measurements in 12 subjects (7 women and 5 men) without metabolic syndrome.

Results and discussion

There were significant differences for the recorded parameters between patients with metabolic syndrome and control group. Age, diastolic blood pressure and serum HDL were similar in both groups, but BMI, waist circumference, systolic blood pressure, fasting blood glucose, basal insulin, HOMA, serum triglycerides were higher in patients with the metabolic syndrome. The prevalence of insulin resistance ($\text{HOMA} > 3$) was 61.11% (11 patients) in subjects with metabolic syndrome and 16.66% (2 patients)

in control group. Most subjects had hormone levels within the normal range, but there were significant difference between mean levels of metabolic syndrome group versus control group (table I, II and III).

Table I

Anthropometric parameters and blood pressure for the two studied groups of patients (the metabolic syndrome group of patients and the control group)

Parameter	Subjects with metabolic syndrome	Control group	P
Age (years)	47.38 ± 7.57	44.75 ± 7.05	> 0.05
BMI (kg/m ²)	29.36 ± 1.78	25.70 ± 0.95	< 0.001
Waist circumference (cm)	96.44 ± 6.45	82.83 ± 5.35	< 0.001
Systolic blood pressure (mmHg)	138.88 ± 10.78	130 ± 7.38	< 0.02
Diastolic blood pressure (mmHg)	76.66 ± 6.85	75.00 ± 5.22	> 0.05

Table II

Glucidic and lipidic profiles of the two studied groups of patients (the metabolic syndrome group of patients and the control group)

Parameter	Subjects with metabolic syndrome	Control group	P
Fasting blood glucose (mg/dl)	125.55 ± 29.87	95.91 ± 6.63	< 0.01
HOMA	4.13 ± 1.92	2.13 ± 0.59	< 0.001
Serum triglycerides (mg/dl)	202.22 ± 56.85	144.83 ± 31.69	< 0.01
Serum HDL cholesterol (mg/dl)	41.77 ± 6.95	45.16 ± 7.20	> 0.05

Table III

Hormonal profile of the two studied groups of patients (the metabolic syndrome group of patients and the control group)

Parameter	Subjects with metabolic syndrome	Control group	P
Insulin (μU/ml)	13.54 ± 4.78	9.03 ± 2.43	< 0.01
GH (ng/ml)	1.93 ± 0.33	3.17 ± 0.21	< 0.001
IGF-I (ng/ml)	246.11 ± 28.84	162.00 ± 8.09	< 0.001
Cortisol (μg/dl)	12.62 ± 0.80	9.28 ± 0.27	< 0.001

There were statistically significant differences in the recorded parameters in patients with metabolic syndrome and controls. Age, diastolic blood pressure and serum HDL cholesterol was similar in both groups, but BMI, waist circumference, systolic blood pressure, fasting blood glucose, basal insulin, HOMA, serum triglycerides were higher in patients with the metabolic syndrome, supporting the concept that these patients have a higher cardiovascular risk. In metabolic syndrome group 10 patients (55.55%) were overweight (BMI: 25-29.9 kg/m²) and 8 patients (44.44%) were obese (BMI over 30 kg/m²). In control group 8 subjects were overweight (66.66%) and 3 subjects had central obesity. In metabolic syndrome group 4 patients (22.22%) had previously diagnosed diabetes and

6 patients (33.33%) had impaired fasting glucose. The prevalence of insulin resistance (HOMA >3) was 61.11% (11 patients) in subjects with metabolic syndrome and 16.66% (2 patients) in control group.

Most subjects had hormone levels within the normal range, but there were significant difference between mean levels of metabolic syndrome group when they were compared to the control group.

Cortisol is an important regulator of the protein, glucose and lipid metabolism. It has various metabolic effects in the liver, adipose tissue, and muscle. In the liver, cortisol serves as the key promoters of gluconeogenesis by activation of pyruvate carboxylase and phosphoenolpyruvate carboxykinase and stimulates hepatic uptake of amino acids and glycerol. At the level of adipose tissue and muscle, cortisol antagonizes insulin-mediated uptake and use of glucose. Glucocorticoids also exert a permissive effect on lipolysis by promoting the activation of cAMP-dependent hormone-sensitive lipase, a key enzyme inhibited by insulin. The net clinical effect of glucocorticoid excess in humans is a relocation of fat deposits, which results in the typical central obesity of Cushing syndrome. Despite the similarities between the two syndromes mentioned, serum or urine cortisol have not been found increased in obese patients with type 2 diabetes mellitus or insulin resistance. Cortisol level in patients with metabolic syndrome is within the normal range, but significantly higher compared to control group. The results sustain the hypothesis that cortisol is critical for the development and maintenance of abdominal visceral obesity.

The levels of the growth hormone and IGF-1 are within the normal range, but there were significant differences between mean levels of metabolic syndrome group as compared to control group. The metabolic syndrome group had an increased level of IGF-1 associated with a decreased GH plasma concentration.

The results suggest that production of hormones of hypothalamic-pituitary-adrenal axis and GH/IGF-I axis is different in metabolic syndrome compared with control group.

Conclusion

In this study we found significant differences for the recorded parameters between patients with metabolic syndrome and subjects without metabolic syndrome.

The systolic blood pressure, fasting blood glucose, basal insulin, HOMA, serum triglycerides were higher in patients with the metabolic syndrome, supporting the concept that these patients have a higher cardiovascular risk.

Hormonal profile of patients with metabolic syndrome in this study suggests an excess of morning plasma cortisol and lower growth hormone (GH) levels in association with central adiposity, as compared to control group. However a bigger cohort is necessary to confirm these preliminary data.

References

1. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Geneva, 1999.
2. Alberti KG, Zimmet P, Shaw J. IDF Epidemiology Task Force Consensus Group. The metabolic Syndrome-a new worldwide definition et al. *Lancet* 2005, 366:1059-62
3. Mohora M., Greabu M., Totan A., Mitrea N., Battino M., Redox-sensitive signaling factors and antioxidants, *Farmacia* 2009, 57(4), 399- 411
4. Aldhahi,W, Mun,E, Goldfine, AB: Portal and peripheral cortisol levels in obese humans. *Diabetologia* 2004, 47:833-836
5. Homma,M, Tanaka,A, Hino,K, Takamura,H, Hirano,T, Oka,K, Kanazawa,M, Miwa,T, Notoya,Y, Niitsuma,T, Hayashi,T: Assessing systemic 11beta-hydroxysteroid dehydrogenase with serum cortisone/cortisol ratios in healthy subjects and patients with diabetes mellitus and chronic renal failure. *Metabolism* 2001, 50:801-804
6. Dănciulescu Miulescu R, Mușat M., Neamțu C., The impact of short and medium-term glucocorticoid treatment on glucose homeostasis, *Farmacia* 2009, 57(1), 17- 23
7. Marin,P, Darin,N, Amemiya,T, Andersson,B, Jern,S, Bjorntorp,P: Cortisol secretion in relation to body fat distribution in obese premenopausal women. *Metabolism* 1992, 41:882-886
8. Bujalska,IJ, Kumar,S, Stewart,PM: Does central obesity reflect "Cushing's disease of the omentum"? *Lancet* 1997, 349:1210-1213
9. Walker,BR: Is "Cushing's disease of the omentum" an affliction of mouse and men? *Diabetologia* 2004, 47:767-769
10. Katz,JR, Mohamed-Ali,V, Wood,PJ, Yudkin,JS, Coppack,SW: An *in vivo* study of the cortisol-cortisone shuttle in subcutaneous abdominal adipose tissue. *Clin.Endocrinol. (Oxf)* 1999, 50:63-68
11. Walker,BR, Campbell,JC, Fraser,R, Stewart,PM, Edwards,CR: Mineralocorticoid excess and inhibition of 11 beta-hydroxysteroid dehydrogenase in patients with ectopic ACTH syndrome. *Clin.Endocrinol.(Oxf)* 1992, 37:483-492
12. Saitoh H, Kamoda T, Nakahara S, Hirano T, Nakamura N. Serum concentrations of insulin, insulin-like growth factor (IGF)-I, IGF binding protein (IGFBP)-1 and -3 and growth hormone binding protein in obese children: fasting IGFBP-1 is suppressed in normoinsulinaemic obese children. *Clin Endocrinol*, 1998, 48: 487-92
13. Jones TH, The role of testosterone in the metabolic syndrome the 1st congress on Controversies in Obesity, Diabetes and Hypertension, 2006, Berlin
14. Grădinaru D., Mitrea N., Margină D., Arsene A., Gruia V., Drăgoi C., Nicolae A., Borșa C., Gherasim P., Evaluation of serum osteocalcin in elderly patients with type-2 diabetes mellitus, *Farmacia* 2009, 57(3), 331- 338

Manuscript received: 20.05.2009