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Functional Hypercorticism Relations to the Metabolic Syndrome

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Abstract

Functional hypercorticism (FH) is characterized with visceral body fat distribution (VFD), hypersensitive hypothalamic-pituitary-adrenal (HPA) axis with increased sensitivity to stimuli and decreased sensitivity to inhibition, reduced cortisol suppression during OGTT, hyperplasia of the adrenal glands and indicates positive dependence on the age.

The aim of this study was to determine the relationship of the FH, expressed as a percentage of reduction of basal cortisol levels (CS%) during OGTT, with the parameters of the metabolic syndrome (MS): homeostatic assessment model (HOMA) as an index of insulin resistance (IR), basal insulin levels, lipid profile, blood pressure, BFD as well as adrenal glands magnitude. The examinees were 127 healthy women, divided in 3 groups according to CS%: 1st gr. with CS%>60% (good suppression), 2nd gr. with CS% 40-60 % (moderate suppression) and 3rd gr. with FH and CS%<40% (very bad suppression). Anthropometric measurements included body mass index (BMI, kg/m^2), as well as waist/hip ratio (WHR) and waist/thigh ratio (WTR) as indexes of VFD. IR was assessed by HOMA. Lipid profile was determined also. Adrenal glands surfaces and volumes were determined by echotomography.

HOMA values were 3.94±2.56 in the 1st gr., (5.77±2.96) in the 2nd gr. and (8.55±7.22) in the 3rd gr. HOMA values were significantly (p<0.0001) highest in the 3rd group. Insulin levels in the 1st gr were 17±11μU/ml, in the 2nd gr were 23.6±11μU/ml and in the 3rdgr were 30.96±33μU/ml. The 3rd group with functional hypercorticism was hyperinsulinemic and insulin resistant with significantly highest HOMA and insulin values (p<0,0001). WHR was 0.89±0.009 in the 1st gr, (0.98±0.009) in the 2nd gr., and (1.03±0.1) in the 3rd group. WTR in the 1st group was 1.49±0.14, in the 2nd gr was 1.66±0.14 and in the 3rd gr was 1.79±0.19. The 3rd group with functional hypercorticism was characterized with increased values of anthropometric indexes of VFD. WHR and WTR were significantly highest in the 3rd group (p<0.0001). BMI was 30±8kg/m^2, 39±9kg/m^2, and 40±9kg/m^2 in the correspondent groups. Sistolic blood pressure was 120±16 mmHg, in the 1st gr, (135±19 mmHg) in the 2ndgr, and (139±19 mmHg) in the 3rd gr. It was significantly highest in the 3rd group (p<0.001). Right adrenal gland volume was 3±2 cm^3 in the 1stgr., (5.1±3 cm^3) in the 2ndgr. and (6.64±3.74 cm^3) in the 3rdgr. Left adrenal volume was 3±2.9cm^3 in the 1st gr., (5.1±2 cm^3) in the 2nd gr. and significantly highest in the 3rd group (6,43±3.74cm^3). TG levels were significantly different between the groups (1.25±0,56; 1.57±0.68 and 1.78±0.82 mmol/l) (p<0,008), as well as HDL ch (1.13±0.46; 1.08±0.26; and 0.9±0.2 mmol/l) (p<0,05). The 3rd group with functional hypercorticism was characterized with dyslipidemic profile.

Conclusion: functional hypercorticism is characterized with hyperinsulinemia and insulin resistance (increased HOMA values), obesity, visceral body fat distribution, increased adrenal glands magnitude, increased blood pressure and dyslipidemic profile. This indicates that the functional hypercorticism which is characterized with the disturbance of the adrenal glands function, namely reduced CS% during OGTT and increased adrenal glands magnitude is positively related to the parameters of the metabolic syndrome and it could be considered as an important etiologic factor of the metabolic syndrome.

Introduction

Obesity, particularly central obesity, insulin resistance, hyperinsulinemia, glucose intolerance, hypertension and dyslipidemia, has been categorized as a single syndrome termed "metabolic syndrome". Each component of the MS is an established cardiovascular risk factor in individuals with and without diabetes. When combined in MS, these risk factors become much more powerful. Many studies have documented the superior role of abdominal adiposity as a risk factor for cardiovascular morbidity/mortality compared with overall obesity estimated by BMI. Even lean individuals with central weight gain can have the MS.

Cushing's syndrome and the MS share clinical similarities. These similarities led to the hypothesis that a dysregulation of the HPA axis in the form of "functional hypercortisolism" (FH) could be a cause for abdominal obesity and its different metabolic consequences (1). The previous study discovered that reduced CS% during OGTT was associated with exaggerated visceral obesity and increased AGM, it enabled estimate of the adrenal glands function, and could be used as a clinical diagnostic criterion for discovery of the HPA axis disturbance in FH. In this study, the relationship between CS% as a diagnostic parameter of FH and features of the MS was investigated, and it was correlated with the overall phenotype of the MS in a cohort of healthy women, in order to discover it as an etiologic factor of the MS.

Materials and methods

The examinees were 127 healthy women. Endocrine, cardiovascular, hepatal, renal and other diseases were excluded and use of any medication. BMI was determined as weight to height ratio (kg/m^2). Central obesity was quantified clinically with a measuring tape: waist circumference was measured in standing subjects midway between the lowest rib and the iliac crest. Hip cicrcumference was measured over the trochanter major and WHR was calculated as a measure of central obesity, as well as WTR, which was calculated as a ratio of waist to thigh circumference measured at its highest level. Each

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individual underwent 75-g oral glucose tolerance test (OGTT). Cortisol levels (C), glucose and insulin levels were determined in 127 healthy women in 0, 30, 60, 90, 120 and 180 min of the test. CS% as a determinant of adrenal gland function was calculated as a percentage of reduction of the basal to the lowest C during the test, which was corrected in cases with C increase in the 30th and 60th min. The examinees were divided in 3 groups according to CS%: 1st gr. with CS%>60% (good suppression), 2nd gr. with CS% 40-60 % (moderate suppression) and 3rd gr. with FH and CS%<40% (very bad suppression). Adrenal glands surfaces and volumes were determined by echotomography in 56 women. HOMA [fasting insulin (mU/ml) x fasting plasma glucose (mmol/l)/22,5] was applied to obtain an estimate of IR. Following lipid parameters were determined: triglyceride levels (TG), total cholesterol (TH), HDL chol., LDL chol, TH/HDL, LDL/HDL. Statistical analysis was performed by SPSS 8,0.

Results

CS% correlated significantly negatively with WHR, WTR,BMI, AGV (p<0,0001), also with AGSright (p<0,011) and AGSleft (p<0,006). Their increase was associated with reduction of CS%. The 3rd gr. with FH and reduced CS% was characterized with increased age and extreme visceral obesity, as well as increased adrenal glands magnitude, insulin and HOMA levels, blood pressure, lipid fractions and reduced HDL.

Graph 1. Anthropometric, hormonal, metabolic and ultrasound results in dependence on CS%

	gr1	gr2	gr3	P
age (years)	31,41±11,99	35,59±10,39	42,86±12,62	0,0001
body weight (kg)	78,42±24,48	100,31±22,82	101,23±23,38	0,0001
BMI (kg/m2)	30,14±8,94	39,27±9,22	40,18±9,17	0,0001
WHR	0,89±0,009	0,98±0,009	1,03±0,1	0,0001
WTR	1,49±0,14	1,66±0,14	1,79±0,19	0,0001
CS%	63,35±7,99	44,52±3,32	35,08±8,59	0,0001
HOMA	3,94±2,56	5,77±2,96	8,55±7,22	0,0001
Insulin (μU/ml)	17±11	23,6±11	30,96±33	0,0001
Sistolic blood pressure	120±16	135±19	139±19	0,001
Diastolic blood pressure	77±10	86±13	88±11	0,001
TG (mmol/l)	1,25±0,56	1,57±0,68	1,78±0,82	0,008
HDL (mmol/l)	1,13±0,46	1,08±0,26	0,9±0,2	0,05
LDL/HDL	3,22±1,25	3,53±1,26	4,09±1,54	0,05
TH/HDL	4,83±1,53	5,99±1,94	6,5±1,35	0,027
AGS left	2,57±1,12	3,84±1,99	4,41±2,5	0,027
AGS right	2,67±2,09	3,77±2,25	4,06±2,02	0,05
AGV left (cm^3)	3±2,9	5,1±2	6,43±3,78	0,001
AGV right (cm^3)	3±2	5,1±3	6,64±3,74	0,003

Discusion

The combination of obesity, especially abdominal obesity, IR, dyslipidemia, hypertension, has been described as a "metabolic syndrome" that is a strong determinant of type 2 diabetes and cardiovascular disease. Obesity is a multi-factorial, multihormonl chronic disease characterized with an accumulation of excess fat sufficient to harm health. Central obesity is a powerful predictor for disease (1). For a given BMI, mortality is higher in patients with central compared to generalized obesity. Clinicians who treat patients with type 2 diabetes and MS often make the observation that many of these patients appear Cushingoid. The highly prevalent MS resembles Cushing's syndrome. They show similar symptoms, but there is one major difference: plasma C is not elevated in the MS (2). Cushing's syndrome have highlighted the link between C and central obesity. Excessive glucocorticoid exposure alters body fat distribution, causes central obesity (truncal adiposity), hypertension, dyslipidaemia and insulin resistance, as seen with elevated plasma C in Cushing's syndrome (3). The conspicuous similarities between Cushing's syndrome and the MS open up the possibility that disturbed adrenal function is involved also in the latter. A mild dysregulation of the HPA axis, occurring with elevated WHR independent of the BMI was suggested (4). The MS has in all likelihood a central neuroendocrine origin in the form of enhanced engagement of the HPA axis, and the peripheral endocrine perturbations act as triggers for both central obesity and the metabolic abnormalities (5). Recent work performed that stress may be a significant factor in the pathogenesis of insulin resistance and the MS (6). Upon perceived stress HPA axis is altered and followed by the MS with "burned-out" C secretion, and lower C levels in visceral obese. It is accompanied with decreased sex steroid and growth hormone secretions (4). The ACTH response to oCRH was significantly higher in obese. ACTH incremental area under the curve (iAUC) correlated with age, HOMA, and sagittal diameter. Abdominal obesity appears to be associated with slight hypocortisolemia and increased

sensitivity to exogenous adrenocorticotropin stimulation, which may contribute to the hyperinsulinemia and related metabolic changes. These data support the concept that C production is enhanced in the MS. Adverse cardiovascular risk was greatest in those with the combination of obesity and failure to downregulate plasma C levels, that was discovered in this study in obese women with FH and reduced CS% during OGTT. These data suggest that progressive malfunction of the HPA axis, and reduction in levels of sex steroids and growth hormone, which in normal concentrations antagonize the C effects, is associated with visceral accumulation of fat, probably by direct storage of fat and enlargement of these visceral depots (7). Furthermore, these hormonal abnormalities most likely at least contribute to the creation of IR with additional effects of elevated fatty acids (FFA) from central fat depots, which are sensitive to lipid mobilization agents. This chain of events indicates the central role of the hypersensitive HPA axis which is associated with FH and contributes to the state of IR. The endocrine abnormalities are probably responsible for the anthropometric and metabolic abnormalities. Increased abdominal adipose tissue mass is a hallmark for the MS.

Visceral fat is more resistant to the suppressive effects of insulin on lipolysis, and is more sensitive to FFA mobilizing stimuli of catecholamines and C than subcutaneous fat, increasing the flux of FFA to the liver, which is involved in the induction of visceral obesity-related IR via activation of the HPA axis and sympathetic system. An increased mobilization of FFA, as occurs in the MS with abdominal obesity, cause hypertriglyceridemia which is accompanied by low levels of HDL, and they are included in the diagnostic criteria of the dyslipidemia in MS. Beside the increase of the triglyceride rich lipoproteins, in particular of large VLDL1, increase of the sdLDL (subtype B) which are particularly atherogenic could be found. IR and compensatory hyperinsulinemia are associated with a dyslipidemia characterized by a high plasma TG, low HDL-C concentration, higher level of oxidized LDL cholesterol, decreased LDL particle diameter and postprandial accumulation of remnant lipoproteins, and blood pressure raising effects by various mechanisms. IR has been suggested to be an important risk factor in the development of the MS, and it is a condition in which increased amounts of insulin are required to produce a normal metabolic response. Hyperinsulinemia is an expression of the reduced peripheral insulin action. Fasting insulin alone was as accurate in predicting IR in normoglycemic population as well as HOMA. C excess impairs glucose tolerance by decreasing both insulin action and glucose effectiveness and counteracts the insulin activation of glycogen synthase in muscle, decrease glucose utilization in muscle, reduce the binding affinity of insulin receptors, reduce sinthesis and function of GLUT4, antagonize the insulin inhibition of hepatic glucose production (gluconeogenesis) and the insulin inhibition of lipolysis in adipose tissue, leading to the well-established systemic IR, ultimately promoting visceral adiposity and the MS.

Hypertension occurs in up to one third of those with the MS, and it is strongly associated with insulin levels and with IR, in visceral obese as well as in Sy Cushing, and is associated with disturbed HPA axis. Increased insulin levels may increase sympathetic nervous system activity and sodium retention. Increased blood pressure might be a consequence of central stimulation of the sympathetic nervous system, with added effects of insulin. The autonomic nervous system and HPA axis are reported as activated in excess in hypertensive morbidly obese.

In this study, we addressed the potential impact of HPA axis activity on established anthropometric, metabolic and haemodynamic risk factors in the MS. HOMA and CS% correlated significantly negatively with BMI, and highly significantly negatively with WHR, WTR, cofirming that C suppression disturbance in FH is associated with obesity, especially with visceral obesity. HOMA and CS% correlated significantly positively with the surfaces especially with the volumes of the adrenal glands. Reduced CS% during OGTT was associated with hyperinsulinemia and increased HOMA, confirming that insulin and glucose inhibitory effects on C during OGTT are reduced in extreme visceral obese. CS% correlated significantly with TG, LDL/HDL, TG/HDL, cholesterol/HDL and HDL ch., confirming that C disturbance is associated with dyslipidemic profile especially with increased atherogenic indexes. HOMA and CS% correlated significantly with the blood pressure. The 3rd group with FH was characterized with reduced CS% during OGTT and was associated with abdominal obesity with increased BMI and anthropometric indexes of visceral obesity, as well as increased surfices and volumes of the adrenal glands, significantly increased blood pressure, HOMA and insulin levels and dyslipidemic profile. It is confirmed that the alteration of the HPA axis in FH determined by reduced CS% during OGTT is associated with visceral obesity in healthy obese women, increased adrenal glands magnitude, hyperinsulinemia and IR, dyslipidemic profile, hypertension, which are characteristics of the MS. FH could be considered as an etiologic factor of MS.

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