

Adrenal Glands Magnitude and Function in Visceral Obese Women

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Abstract

Visceral obesity is associated with alteration of the hypothalamic-pituitary-adrenal (HPA) axis, characterized mainly by an increased sensitivity to stimuli and decreased sensitivity to inhibition, and disturbed adrenal glands function. The relationship between adrenal glands magnitude (AGM) and visceral body fat distribution (BFD) has not yet been discovered precisely by anyone. Adrenal glands magnitude has to be dependent on adrenal glands function.

The aim of this study was to discover the association of visceral BFD with the disturbance of the adrenal glands function and AGM.

Adrenal glands function was determined by the percentage of cortisol suppression (CS%) during OGTT in 135 healthy women, and the percentage of ACTH suppression (ACTH%) was also determined in 55 women. Adrenal glands surfaces (AGS) and volumes (AGV) were determined in 56 women by adrenal glands echotomography. Anthropometric measurements included body mass index (BMI, kg/m²), as well as waist/hip ratio (WHR) and waist/thigh ratio (WTR) as an indexes of BFD. The examinees were divided in 3 groups according to their BFD: 1st group with normal BFD with waist/hip ratio (WHR)<0,85 and waist/thigh ratio (WTR)<1,45; 2nd group with moderate visceral obesity with WHR (0,85-1,0) and WTR (1,45-1,7) and the 3rd group with extreme visceral obesity with WHR> 1,0 and WTR>1,7.

WHR and WTR correlated significantly positively with adrenal glands surfaces and volumes (p<0,0001). WHR correlated significantly negatively with CS% (p<0,0001) and ACTH% (p<0,008). WTR correlated significantly negatively with CS% (p<0,0001) and ACTH% (p<0,004). BMI in the 1st gr. was 27±8 kg/m², in the 2nd gr. was 36±8 kg/m², and in the 3rd gr. was 40±7,9 kg/m², that confirms the 3rd group as extreme obese. CS% was 61,81±10% in the 1st gr., (52,43±40%) in the 2nd gr. and (40,64±9,92%) in the 3rd gr. CS% was significantly different between the groups, and significantly reduced in the 3rd extreme visceral obese group, compared to the 1st and 2nd group. ACTH% was 48,65±34.4 % in the 1st gr., (34,9±40%) in the 2nd, and (6,22±67%) in the 3rd gr. ACTH% was lowest in the 3rd group, and significantly different between the groups. Adrenal glands surfaces were significantly higher in the 3rd gr. compared to the 1st and 2nd gr. Left and right AGV were 1,99±1,37cm³ and (1,74±0,69cm³) in the 1st gr., (3,92±3,31cm³ and 4±3,9cm³) in the 2nd gr. and (6±3,78cm³ and 6,25±3,89cm³) in the 3rd gr. Adrenal glands volumes were the highest significantly in the 3rd extreme visceral obese group compared to the other two groups (p<0,0001). CS% correlated significantly negatively to adrenal glands volumes (p<0,0001) and adrenal glands surfaces (p<0,001).

Conclusion: AGM was in a positive relation to the disturbance of the adrenal glands function characterized with reduced cortisol and ACTH suppression during OGTT, as well as to the visceral body fat distribution. Adrenal hyperplasia in visceral obesity could be discovered with great certainty and diagnostic security by echotomographic assessment of the adrenal glands. Extreme visceral obesity is characterized with significantly increased adrenal glands surfaces and volumes and reduced cortisol and ACTH suppression as indicators of disturbed adrenal glands function and decreased sensitivity to inhibition of the HPA axis discovering the central origin of the adrenal glands dysfunction in obese healthy women.

Introduction

Glucocorticoids may alter body fat distribution, increasing truncal adiposity (1). In Cushing's syndrome, cortisol (C) causes fat accumulation in specific sites, notably in omental adipose. Patients with Cushing's syndrome display a number of clinical features that resemble those seen in patients with the metabolic syndrome, which is characterized with abdominal obesity and metabolic disturbances, but not elevated plasma C levels. These similarities led to the hypothesis that a dysregulation of the HPA axis in the form of "functional hypercorticism" could potentially be a cause for abdominal obesity and its different metabolic consequences. Functional hypercorticism in visceral obesity is accompanied by alterations in the HPA axis characterized mainly with an increased sensitivity to stimuli and decreased sensitivity to inhibition. Compelling evidence suggests that progressive dysfunction of the HPA axis is implicated in the development of visceral obesity. The HPA axis

perturbations associated with visceral obesity can be accounted for, in part, by increased environmental stress that destabilizes the hypothalamic-pituitary system in individuals with genetic susceptibility (2).

The purpose of this study was to discover CS% and ACTH% during OGTT as a diagnostic parameters of the adrenal glands function disturbance and HPA axis alteration in functional hypercorticism in obese healthy women. The relationship of BFD to C and ACTH responses during OGTT, as well as to AGM was examined in this study.

Materials and methods

The examinees were 135 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/m²). Central, abdominal obesity was quantified clinically with a measuring tape:

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waist circumference was measured in standing subjects midway between the lowest rib and the iliac crest. Hip circumference was measured over the trochanter major and waist/hip ratio (WHR) was calculated as a measure of central obesity, as well as waist/thigh ratio (WTR), which was calculated as a ratio of waist to thigh circumference measured at its highest level. The examinees were divided in 3 groups according to their BFD determined by their anthropometric indexes: 1st group with normal BFD and WHR<0,85 and WTR<1,45; 2nd group with moderate visceral obesity with WHR (0,85-1,0) and WTR (1,45-1,7) and the 3rd group with extreme visceral obesity with WHR> 1,0 and WTR>1,7. AGV was determined by echotomography in 56 subjects. Each individual underwent 75-g oral glucose tolerance test (OGTT). C levels were determined in 135 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 determination of the ACTH% was the same as CS%. 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% and ACTH%. The 3rd gr. with extreme visceral obesity was characterized with significantly higher age, BMI and anthropometric indexes of visceral BFD, AGM and reduced CS% and ACTH%. Hormonal, anthropometric and ultrasound results are presented on graph 1.

Graph 1. Age, anthropometric indexes, CS%, ACTH%, AGS and AGV in dependence on body fat distribution

	gr1	gr2	gr3	P
age (years)	28±11	35±10	44±12	0,0001
body weight (kg)	71,44±22	93±23	99,64±21	0,0001
BMI (kg/m2)	27±8	36±8	40±7,9	0,0001
WHR	0,8±0,05	0,96±0,04	1,06±0,04	0,0001
WTR	1,39±0,05	1,58±0,07	1,87±0,12	0,0001
CS%	61,81±10	52,43±40	40,64±9,92	0,0001
C ₀ (nmol/l)	494,39±196	438,63±188	485,49±211	NS
C _{min} (nmol/l)	200±114	220±106	274±126	0,002
ACTH%	48,65±34,4	34,9±40	6,22±67	0,011
ACTH ₀	31,75±28	30,63±39	14,87±14	0,03
ACTH _{min}	14,79±16,26	10,86±5,63	9,61±7	NS
AGS left	1,98±0,99	3,04±1,69	3,65±1,63	0,001
AGS right	1,78±0,75	2,89±1,99	3,83±2,03	0,001
AGV left	1,99±1,37	3,92±3,31	6±3,78	0,0001
AGV right	1,74±0,69	4±3,9	6,25±3,89	0,0001

C₀-basal C; C_{min}-minimal C level

ACTH₀-basal ACTH; ACTH_{min}-minimal ACTH level

Discussion

Abdominal obesity has a key role in the pathogenesis of prevalent and serious diseases and has been shown to be associated with an altered HPA axis function, which seems to be hypersensitive in abdominal obesity. The HPA axis is stimulated by central factors, which are often called stress (3). The HPA axis disturbances are similar to those seen after prolonged exposure to environmental stress. Psychosocial and socioeconomic factors, alcohol, smoking, depressive traits and anxiety are linked to HPA axis abnormalities, and are probably central inducers of hyperactivity of the HPA axis in subjects with abdominal preponderance of fat stores (4). Constant uncontrollable stress can lead to a prolonged period of HPA axis stimulation, which is followed by a continuous degradation of the regulatory mechanisms. This is followed by discrete, periodical elevations of C secretion during every day conditions. An end stage is a 'burned-out' condition with a

rigid C secretion, with a flat, rigid day curve and low or normal plasma C morning values and diminished function of the feed-back control that was discovered in this study (5,6,7). The feedback control of C secretion by central glucocorticoid receptors (GR) is blunted, and the function of the GR is suggested to be abnormal. This psychoneuroendocrinological process is named hypothalamic arousal syndrome, and is characterized with parallel activation of the HPA axis and the central sympathetic nervous system, accompanied with diminished secretion of growth and sex steroid hormones (7). It is suggested that this syndrome is probably based on environmental pressures in genetically susceptible individuals. The net effects of this cascade of neuroendocrine-endocrine perturbations is visceral accumulation of body fat that contributes to increase of circulating levels of free fatty acids, which have stimulative

HPA axis effect, and all these factors are implicated in the development of insulin resistance (4).

Assessment of the HPA axis relies on the interpretation of serum C in response to dynamic tests of the HPA axis. Salivary C secretion frequently is elevated in stress-related condition. Midnight serum cortisol appears as a sensitive marker of the metabolic effects of subclinical Cushing's syndrome. ACTH secretion in obesity may be altered with increased pulsatile frequency but decreased pulse amplitudes. Obesity is associated with increased activity of the HPA axis as supported by augmented ACTH and beta-lipotrophin secretion in response to insulin-induced hypoglycaemia, significantly higher ACTH response to oCRH in obese, and the positive association between the C and ACTH response and the body weight and visceral BFD in obese women. Also, C and ACTH responded more to CRH/AVP stimulation test in the abdominal-BFD than in peripheral-BFD and control groups, as well as C responded to ACTH stimulative test. Dexamethasone suppression of C secretion is reduced in visceral obese, but it is used only in the differential diagnosis of Cushing's syndrome. Obese subjects have shown resistance to steroid-induced inhibition of the ACTH response to hypoglycemia, compared with controls confirming relative insensitivity to glucocorticoid feedback, which is most marked during the night. In contrast to normal subjects, patients with adrenal incidentalomas had significantly higher mean C values after oral glucose intake (8). Reduction of plasma C during OGTT was discovered in all subjects in this study, but the percentage of C reduction was lowest in the visceral obese group, and highest in control group with normal BFD.

Ultrasound (US) is an established imaging modality for the assessment of the kidneys and adrenal glands. The advantages include its lack of ionizing radiation, speed, multiplanar real time evaluation, and cost compared with more expensive modalities (9). Adrenal US is highly dependent on the operator's skill and experience and require meticulous scanning techniques. Fetal adrenal gland volume on US is highly correlated with fetal weight and gestational age. Adrenal gland bodies are reduced in M. Addisoni, indicative of significant adrenal atrophy. ACTH-dependent Cushing's syndromes usually present diffusely hyperplastic adrenal glands. Reduced CS% and increased values of the anthropometric indexes of visceral obesity were associated with increased AGM in this study. These

data confirm that AGM is dependent on adrenal gland function, and is associated with visceral BFD.

There are still no tests and diagnostic criteria in clinical practice for determining the HPA axis disturbance in functional hypercorticism, and its association with visceral BFD and AGM. This study discovered that reduced CS% was associated with exaggerated visceral obesity and increased adrenal glands magnitude. It can be concluded that visceral obesity is associated with increased AGV, normal basal C levels and reduced CS% during OGTT, which could be used as a clinical diagnostic criterion for discovering of the HPA axis disturbance in functional hypercorticism in healthy obese women, and reduced ACTH% discovered central origin of the adrenal glands dysfunction.

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