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RESEARCH ARTICLE

Hypothalamic Pituitary Adrenal Axis Activity in Relation to Obesity in Metabolic Syndrome Patients

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Abstract

Background and Aim: The prevalence of the metabolic syndrome is considerable among obese adolescents. There are striking similarities between Cushing's syndrome and the metabolic syndrome. Our aim was to evaluate the activity of HPA axis and serum cortisol in metabolic syndrome patients. **Methods:** Our study was conducted on 120 subjects divided into 2 groups : 60 of them were diagnosed with metabolic syndrome (group A) and 60 healthy non metabolic syndrome patients (group B), each group was further classified into 2 groups (I,II),(III,IV) according to obese (BMI>30) and non obese subjects(BMI<25). Full history taking , clinical evaluation, fasting blood sugar, serum insulin, HOMA-IR, lipid profile, serum cortisol before and after overnight 1 mg dexamethasone suppression test were measured in all subjects. **Results:** On comparing the four studied groups there was a significant statistical difference as regards serum cortisol (pretest) and serum cortisol after overnight dexamethasone suppression test, fasting blood sugar and HOMA-IR.(P=0.000,0.000, 0.000,.0026 respectively). On comparing group I and IV; group II and III: There was a non statistical significant difference as regards pretest and post suppression serum cortisol (P value > 0.05). There was none significant correlation between pretest serum cortisol and fasting blood glucose, insulin and HOMA-IR, total cholesterol and serum triglycerides (P value > 0.05). **Conclusion:** There was none statistical significant difference in serum cortisol before and after 1 mg over night dexamethasone suppression test in obese and non - obese patients with metabolic syndrome which implicates minor role for cortisol in obesity of metabolic syndrome.

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INTRODUCTION

The metabolic syndrome is a clustering of metabolic abnormalities that have been associated with an increased risk of coronary heart disease, stroke and cardiovascular mortality compared to the presence of an individual component (Mazza, 2008)**.**

The prevalence of metabolic syndrome manifestations is rapidly increasing worldwide, and is becoming an important health problem. Actually, metabolic syndrome includes a combination of clinical complications such as obesity (central adiposity), insulin resistance, glucose intolerance, dyslipidemia, non-alcoholic fatty liver disease and hypertension. All these alterations predispose individuals to type 2 diabetes and cardiovascular disease inducing earlier mortality rates among people (Martínez et al., 2011).

Obesity typically results in insulin and leptin resistance and a shift from expansion of subcutaneous fat to deposition of abdominal and ectopic fat. These conditions cause metabolic dysregulation (Gade et al., 2010). Increased body weight plays the most important role in metabolic syndrome, it was shown recently that each 11 cm increase in waist circumference is associated with an adjusted 80% increased risk for developing the syndrome within 5 years (Palaniappan et al., 2004).

There are striking similarities between Cushing's syndrome and the metabolic syndrome as both are characterized by central obesity, hypertension, insulin resistance and glucose intolerance, several lines of evidence from different studies consistently support the view that subclinical Cushing's syndrome (autonomous cortisol secretion) may be associated with the clinical phenotype of the insulin resistance syndrome that fosters several unwanted metabolic and vascular manifestations **(**Alberti et al., 2009).

High glucocorticoid levels lead to muscle, liver and adipocyte insulin resistance. Almost all patients with Cushing's syndrome are obese or overweight and have abdominal visceral adiposity (Newell-Price et al., 2002)**.** Metabolic syndrome therefore may be a clue to the presence of Cushing syndrome, however relatively high prevalence of occult CS was found in some studies up to 26 % (Bo, 2007)..
Our aim was to evaluate the role of HPA (hypothalamic pituitary adrenal axis) activity in relation to obesity in metabolic syndrome patients by using the overnight 1 mg dexamethasone suppression test.

Materials and methods:

This is a case control study was conducted on 120 subjects selected from the outpatient clinic of Endocrinology of Ain Shams University Hospitals. The study was conducted during the period from December 2012 to February 2014. Selected subjects were divided into 2 groups: Group A: 60 patients diagnosed as metabolic syndrome with at least 3 of 5 criteria of metabolic syndrome according to the most updated definition (Alberti et al., 2009) (serum Triglycerides >150mg/dl, HDL- cholesterol<40mg/dl in men and <50mg/dl in women, Elevated blood pressure ; systolic BP>130mmHg or diastolic BP>85mmHg, fasting blood picture >100mg/dl and increased waist circumference in Egypt >115cm in men and >105cm in women (Fareed et al., 2011)**.,** and were further classified into group I (obese BMI ≥ 30) and II (non obese BMI < 25). Group B: 60 healthy non metabolic syndrome patients as a control group. They were further classified into group III (non obese BMI < 25).and IV (obese BMI ≥ 30).

All included subjects submitted to full history taking, full clinical evaluation (including waist circumference, waist/hip ratio and BMI), fasting blood sugar , 2hours post prandial blood sugar, serum insulin measured by using: Accu Bind ELISA microwells kits, HOMA-IR (insulin resistance):(serum insulin (µU/ml) × fasting blood sugar (mmol/ l) /22.5 (Matthews et al., 1985), full lipid profile(triglycerides, cholesterol, HDL- cholesterol and LDL- cholesterol), renal functions, liver functions and serum cortisol measured before and after the dexamethasone 1mg overnight suppression test using commercial kits (Dia Metra- CORTISOL ELISA).

Overnight 1 mg dexamethasone suppression test: morning serum cortisol level is measured between 8:00 AM and 9:00AM then patients were instructed to take 1 mg dexamethasone at 11: 00 PM.; between 8:00 AM and 9:00AM, the following morning, blood was drawn from participant and serum cortisol level measured. Suppression of serum cortisol to < 3µg/dl after dexamethasone administration was chosen as the cut-off point for normal suppression, over 5µg/dl for diagnosis of Cushing's syndrome.

Exclusion criteria included subjects with significant renal, hepatic and cardiac diseases, severe associated acute illness, and factors known to affect the dexamethasone suppression test (alcoholism, depression, pregnancy or morbid obesity BMI > 40).

Patients with obvious clinical Cushing syndrome or complaining of recent unexpected weight gain and excessive fatigue, as well as clinical assessment for thin skin easy bruising, abnormal supraclavicular and dorsocervical pads of fat and facial plethora were excluded
This study was approved by the internal review board of Ain Shams University. All subjects provided written informed consent before the study.

Results:

The studied groups were age and sex matched ($p > 0.05$). There was a statistically significant difference ($p < 0.05$) between studied four groups regarding BMI, fasting Blood glucose, pre and post dexamethasone suppression serum cortisol levels and HOMA-IR (Table 1, Figure 1). On comparing obese (group I) and non obese (group II) subjects with metabolic syndrome, we found that there was a highly statistical significant difference as regard BMI ($P<0.001$) but there was none statistical significant difference as regards TG, cholesterol, systolic blood pressure, diastolic blood pressure, serum insulin, fasting blood sugar, HOMA-IR, serum cortisol (pretest) and serum cortisol after overnight dexamethasone suppression test (P value = 0.408, 0.237, 0.912, 0.504, 0.490, 0.489, 0.448, 0.0130, 0.767 respectively) . On comparing obese subjects with metabolic syndrome (group I) and obese subjects without metabolic syndrome as control group (group IV), there was a statistical significant difference as regards fasting blood sugar, HOMA-IR,TG, cholesterol, systolic blood pressure and diastolic blood pressure (P value= 0.000, 0.005, 0.043, 0.033, 0.032, 0.041 respectively) but there was none statistical significant difference as regard serum insulin, BMI, serum cortisol (pretest) and serum cortisol after overnight dexamethasone suppression test. (P value = 0.367, 0.076, 0.221, 0.052 respectively). On comparing non obese subjects with metabolic syndrome (group II) and non obese healthy subjects (group III), there was a statistical significant difference as regard fasting blood sugar, HOMA-IR ,TG, Cholesterol, systolic blood pressure and diastolic blood pressure.(P value = 0.000, 0.006, 0.003, 0.002, 0.042, 0.031 respectively) but there was none statistical significant difference as regards serum insulin, BMI, serum cortisol (pretest) and serum cortisol after overnight dexamethasone suppression test (P value = 0.740, 0.086, 0.503, 0 respectively).

There was none significant correlation between pre test serum cortisol and different studied parameters as BMI, systolic and diastolic blood pressure, fasting serum insulin, blood glucose and HOMA-IR (Table 2).

Table (1): Comparison between the different studied groups

		Group I			Group II			Group III			Group IV			ANOVA	
														F	P-value
BMI Kg /m²	**Range**	31.100	-	60.000	23.200	-	25.200	21.200	-	24.800	27.500	-	34.000	65.482	0.000*
	Mean±SD	38.751	±	7.346	24.664	±	0.410	23.279	±	1.303	23.279	±	1.802		
s.Cortisol Pre µcg/dl	**Range**	25.000	-	360.000	10.000	-	370.000	5.000	-	200.000	25.000	-	320.000	3.78225	0.000*
	Mean±SD	133.833	±	77.767	168.700	±	97.121	69.124	±	64.133	110.333	±	109.111		
s.Cortisol Post µcg/dl	**Range**	5.000	-	300.000	5.000	-	360.000	5.000	-	150.000	5.000	-	200.000	3.78225	0.000*
	Mean±SD	41.667	±	66.816	47.433	±	82.337	61.333	±	46.270	76.333	±	60.222		
S.Insuln µIU/ml	**Range**	5.000	-	58.000	4.000	-	58.000	5.000	-	36.000	5.000	-	28.000	0.313	0.816
	Mean±SD	13.667	±	11.845	16.167	±	15.746	16.933	±	10.215	14.733	±	7.206		
FBS mg/dl	**Range**	129.00	-	352.000	154.000	-	521.00	71.000	-	120.000	75.000	-	112.000	42.768	0.000*
	Mean±SD	231.40	±	55.682	243.767	±	79.815	93.800	±	15.321	93.333	±	10.828		
HOMA.IR	**Range**	34.220	-	680.000	32.440	-	943.000	26.600	-	129.600	16.660	-	139.300	3.252	0.026*
	Mean±SD	148.614	±	147.267	185.371	±	218.760	64.626	±	31.681	63.397	±	35.704		

Table (2): Correlation between S. cortisol (pre) and other studied parameters by Correlation Pearson test

	S.Cortisol (pre) µcg/dl	
	R	**P-value**
S.Insulin (µIU/ml)	-0.088	0.502
FBS (mg/dl)	-0.048	0.713
HOMA.IR %	-0.049	0.712
BMI (Kg/m²)	-0.208	0.110
TGS (mg/dl)	0.001	0.994
Cholesterol (mg/dl)	-0.047	0.723
SBP (mmHg)	-0.118	0.370
DBP (mmHg)	0.126	0.336

Figures

Figure 1: Comparison between groups I, II, III, IV as regards pre s. Cortisol and post.s. Cortisol (ng/ml)

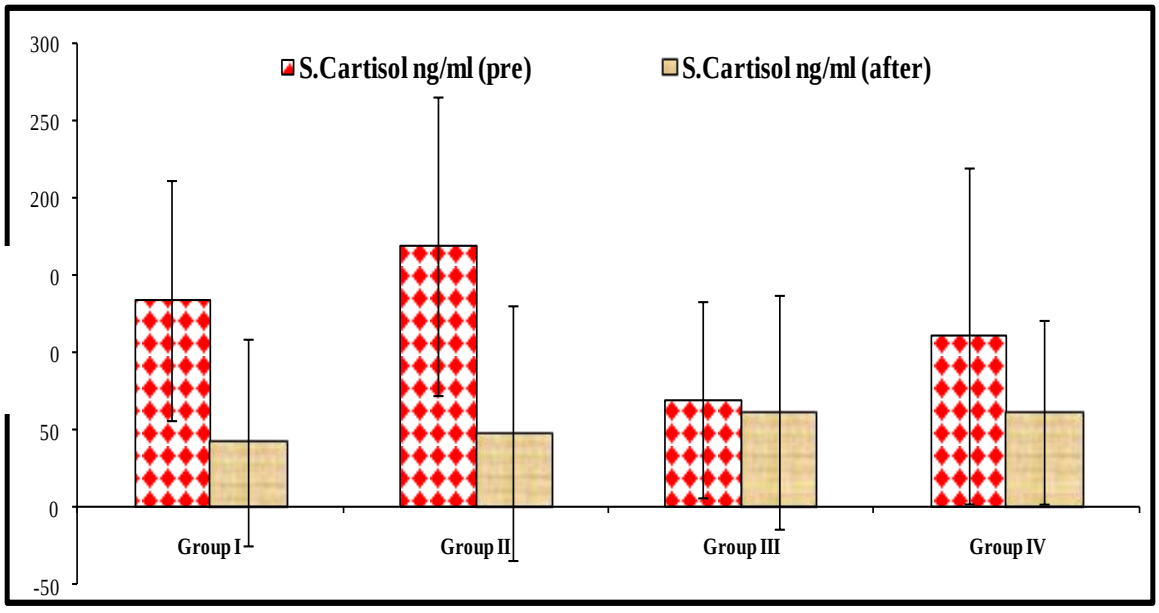

Figure (1)

Discussion:

In our study the metabolic syndrome patients group A (both obese group I and non-obese group II) showed high levels of serum cortisol compared to group B (healthy control) with significant response to suppression to overnight dexamethasone suppression test. However, there was none statistical significant difference between subgroups of group A (group I and group II) in response to suppression with P- value 0.767, which therefore, indicates that in our study, serum cortisol is irrelevant as a cause of obesity in Obese metabolic syndrome patients rather than non-obese metabolic syndrome patients.

On comparison between metabolic obese patients and healthy obese control: Serum cortisol was found elevated in obese healthy control with positive significant response to dexamethasone suppression test which may indicate a state of pseudo Cushing's syndrome.

In agreement to our study a cross-sectional study, 30 females with metabolic syndrome chosen from Endocrinology Clinic, Cairo University, without any phenotypical features of Cushing's syndrome, three patients (10%) didn't show positive dexamethasone suppression test (occult Cushing's syndrome) and the rest of the patients (27) showed positive test (Mansour et al., 2013). Another study done in the same issue showed that serum cortisol is not increased in obesity, however, it is possible that there is an increase in the local production of cortisol in the fat tissue and this in turn could lead to increased local action of cortisol with the subsequent metabolic consequences known to occur in obesity, This hypothesis is purely speculative (Pascuali, 2008). A cross sectional study of 369 Overweight and obese subjects had at least two other features of Cushing's syndrome. Assessment of serum cortisol was done by different methods (24 h urine cortisol excretion (UFC), bedtime salivary cortisol, 1 mg dexamethasone suppression test) and metabolic parameters (BMI, blood pressure (BP); fasting serum triglycerides, HDL, insulin, and glucose) was done and emerged data didn't support a strong relationship between systemic cortisol or stress and obesity or Metabolic- Syndrome (Esteghamati et al., 2011).

On contrary to our study, A pathological study showed that patients with Metabolic-Syndrome show hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to a state of "functional hypercortisolism." The cause for this activation of the HPA axis remains uncertain but may be partly associated with chronic stress and/or low birth weight, which are both associated with increased circulating cortisol levels and greater responsiveness of the HPA axis. Increased exposure to cortisol contributes to increased fat accumulation in visceral depots. However, cortisol metabolism is not only centrally regulated. The action of 11β-hydroxysteroid dehydrogenase-1 at the tissue level also modulates cortisol metabolism. Increased 11β-hydroxysteroid dehydrogenase-1 activity in adipose tissue and liver might contribute to the development of several features of the Metabolic- Syndrome, and so cortisol might play a role in the development of Metabolic- Syndrome at both a central and a peripheral level (Anagnostis et al., 2009).

Another study done over 205 overweight, Latino youth (age 8–13 yr, body mass index percentile > 85, with family history positive for type 2 diabetes showed that metabolic syndrome is associated with higher morning serum cortisol levels, independent of body fat and insulin sensitivity (Weigensberg et al., 2008).

In a cohort study done over 370 men aged (59-70 years old) studied in Hertfordshire, England, a positive correlation between fasting serum cortisol and features of metabolic syndrome (obesity, hypertension, hyperlipidemia, glucose intolerance) was found that indicates activated HPA axis and a role for hypercortisolism in such patients (Walker, 2006) **.** This theory is going along with, a study showing that cortisol secretion in obese subjects is elevated but that circulatory concentrations are normal or low, suggesting that peripheral disappearance rate is elevated (Bjorntorp, 2000) .

In a 3-month randomized, double-blind, placebo-controlled trial over thirty women, 49-65 yr old, with visceral obesity, insulin resistance and Type 2 diabetes were treated with ketoconazole 400 mg daily, in order to down-regulate cortisol activity, in. demonstrated that a down-regulation of cortisol secretion can favorably affect most of the multiple risk factors associated with the metabolic syndrome. This includes improvement in insulin resistance, glucose homeostasis, total cholesterol, blood pressure and hepatic steatosis (Martin et al., 2010).

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