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Relationship Between IGF-1 and Cortisol/ DHEA-S Ratio in Adult Men With Diabetic Metabolic Syndrome Versus Non-Diabetic Metabolic Syndrome

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Abstract

Background: Metabolic syndrome (MS) is a strong risk factor for cardiovascular disease and type 2 diabetes mellitus. Previous studies have suggested that low insulin like growth factor-1 (IGF-1), low dehydroepiandrosterone sulfate (DHEA-S) and high cortisol are significant correlates of MS. The aim of the present study was to examine the relationships between serum IGF-1, cortisol, DHEA-S and cortisol/ DHEA-S ratio in adult men with MS either diabetic or non-diabetic.

Methods: One hundred adult men were enrolled in this study, divided into three groups: group 1 included 30 patients with diabetic MS, group 2 included 30 patients with non-diabetic MS and group 3 included 40 age and sex-matched controls. Anthropometric measurements, Homeostasis model assessment of insulin resistance (HOMA), lipid profile, IGF-1, cortisol, DHEA-S and cortisol/ DHEA-S ratio were assessed.

Results: IGF-1 and DHEA-S levels were significantly lower while serum cortisol and cortisol/ DHEA-S ratio were higher in both diabetic MS and non-diabetic MS adult men than healthy controls; they were also significantly different in the diabetic than in non-diabetic adult men with MS. IGF-1 was significantly and independently correlated with waist circumference, blood pressure, fasting blood glucose, HOMA, cortisol, DHEA-S and cortisol/ DHEA-S ratio. Cortisol/ DHEA-S ratio was significantly and independently correlated with blood pressure, fasting blood glucose, insulin, HOMA, triglyceride, high density lipoprotein cholesterol, cortisol and DHEA-S.

Conclusions: IGF-1 concentration is reduced and cortisol/ DHEA-S ratio is increased along with insulin resistance in adult men with diabetic MS. IR may be responsible for multiple multihormonal dysregulation in MS.

Keywords: Metabolic syndrome; IGF-1; Cortisol/ DHEA-S ratio

Introduction

Metabolic syndrome (MS) is the complex clustering of several interrelated physiological and metabolic alterations, including insulin resistance, dyslipidemia, abdominal fat, and a proinflammatory prothrombotic state. MS is a strong risk factor for cardiovascular disease and type 2 diabetes mellitus [1, 2]. Recent reports estimate that about one fourth of the world's adult population has MS [3], with a prevalence that increases with age and higher in men than women [2, 4].

Insulin like growth factor-1 (IGF-I) is the most powerful naturally-occurring peptide with glucose lowering effects after insulin [5]. IGF-1 increases insulin sensitivity and peripheral glucose uptake, decreases hepatic glucose production, and improves the lipid profile [6, 7]. Insulin appears to be necessary for normal liver growth hormone (GH) responsiveness, probably by maintaining liver GH receptor levels [8].

Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) ester are the most abundant circulating adrenal steroids in humans [9]. DHEA-S which is converted to the active form DHEA represents the circulating hormonal pool of DHEA. DHEA is known to be a weak androgen contributing to androgenecity mainly after peripheral conversion to more potent androgens, testosterone and dihydrotestosterone. Administration of DHEA has been reported to have striking beneficial effects on obesity [10], hyperlipidemia, diabetes [11], and atherosclerosis [12] in obese rodents. Furthermore, previous studies have suggested that low

Table 1. Anthropometric and Biochemical Characteristics of Study Subjects

Characteristics	Group1 (n = 30)	Group2 (n = 30)	Group3 (n = 40)
Age (years)	42.37 ± 5.05	42.87 ± 5.6	40.4 ± 5.9
BMI (kg/m²)	37 ± 5.3*	36.6 ± 3.9¤	22.2 ± 1.5
WC (cm)	120.3 ± 10.6*	114.4 ± 10.4¤¶	74.5 ± 4.9
SBP (mm Hg)	156.6 ± 14.2*	151.6 ± 12.8¤	111 ± 13.3
DBP (mm Hg)	93.6 ± 8.99*	92.3 ± 6.78¤	70.75 ± 8.6
FBG (mg /dl)	163.4 ± 58.6*	102.3 ± 10.98¤¶	81.05 ± 14.6
Insulin (µU/ml)	25.3 ± 4.08*	19.8 ± 2.6¤¶	7.4 ± 4.6
HOMA	10.8 ± 3.5*	4.9 ± 0.62¤¶	1.4 ± 0.84
TC (mg %)	209.7 ± 36.8 *	182.7 ± 32.3¤¶	157 .5± 27.4
TG (mg %)	155.7 ±55.02*	123.3 ± 29.54¤¶	100.6 ±19.5
LDL-c (mg %)	135.8 ± 37.4*	118.6 ± 28.6¤¶	95.6 ± 20.9
HDL-c (mg %)	36.5± 5.1*	42.7± 6.4¤¶	52.8 ± 2.1
IGF-1(ng/ ml)	141.8 ± 22.6*	161.7 ± 43.6 ¤¶	211± 28.5
Cortisol (nmol/L)	241.7 ± 145.08*	159.1±39.3¤¶	110.5 ± 40.18
DHEA-S (µmol/L)	0.67 ± 0.28*	0.82 ± 0.28¤¶	3.2 ± 3.4
Cortisol/DHEA-S ratio	360.7 ± 117.6*	193.8 ± 31.6¤¶	34.5 ± 11.8

Data are expressed as mean ± standard deviation. * $p \leq 0.05$, group 1 vs. group 3; ¤ $p \leq 0.05$, group 2 vs. group 3; ¶ $p \leq 0.05$, group 1 vs. group 2; Group 1: diabetic metabolic syndrome subjects; Group 2: non-diabetic metabolic syndrome subjects; Group 3: normal controls; BMI: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: fasting blood glucose, HOMA: Homeostasis model assessment of insulin resistance; TC: Total cholesterol; TG: Triglyceride; LDL-c: Low density lipoprotein cholesterol; HDL-c: High density lipoprotein cholesterol; DHEA-S: dehydroepiandrosterone sulfate; IGF-1:insulin like growth factor-1.

IGF-1 and high cortisol are significant correlates of MS [13-15].

The aim of the present study was to examine the relationships between serum IGF-1, cortisol, DHEA-S and cortisol/ DHEA-S ratio in adult men with MS either diabetic or non-diabetic.

Subjects and Methods

One hundred adult men were enrolled in the study, divided into three groups (Table 1). Group 1 included 30 patients with diabetic MS. Group 2 included 30 patients with non-diabetic MS. Group 3 included 40 age and sex-matched healthy subjects (control group). The mean ages were 42.37 ± 5.05, 42.87 ± 5.6 and 40.4 ± 5.9, respectively. All patients signed an informed consent to be included in our study. This study was approved by the local ethical committee of Mansoura University Hospital, Internal Medicine Department.

All participants were subjected to thorough medical history and clinical examination. Anthropometric measurements including weight, height, body mass index (BMI) calculated as weight/ height² (kg/m²) and waist circumference (WC) were obtained using standardized techniques. Blood pressure was taken in the sitting position after 10-min rest using a random-zero sphygmomanometer. Exclusion criteria included the presence of renal, hepatic disease, and diabetic patients under insulin therapy.

MS was defined using the International Diabetes Federation (IDF) consensus group guidelines as abdominal obesity (WC ≥ 90 cm for men) plus two or more of the following risk factors: blood pressure ≥ 130/85 mm Hg or taking anti-hypertensive medication, fasting plasma glucose ≥ 100 mg/ dl or pre-existing diabetes, serum triglycerides ≥ 1.7 mmol/l (≥ 150 mg/l) and HDL levels < 1.03 mmol /l (< 40 mg/dl) for men (16).

Assay

Fasting plasma glucose (FBG) was estimated using commer-

Table 2. Correlation Between IGF-1 and Cortisol/ DHEA-S Ratio and Clinical and Metabolic Parameters in Diabetic Metabolic Syndrome Subjects

Characteristics	IGF-1		Cortisol/DHEA-S	
	r	P-value	r	P-value
BMI (kg/m²)	- 0.417	0.03*	0.36	0.04*
WC (cm)	- 0.358	0.05*	0.52	0.03*
SBP (mm Hg)	- 0.477	0.04*	0.48	0.03*
DBP (mm Hg)	- 0.615	< 0.001***	0.67	0.006**
FBG (mg /dl)	- 0.39	0.04*	0.44	0.03*
Insulin (µU/ml)	- 0.52	0.02*	0.55	0.02*
HOMA	- 0.78	< 0.001***	0.63	0.002**
TC (mg %)	- 0.44	0.03*	0.46	0.03*
TG (mg %)	- 0.52	0.02*	0.48	0.04*
LDL-c (mg %)	- 0.59	0.006**	0.52	0.03*
HDL-c (mg %)	0.62	0.009**	- 0.53	0.002*
Cortisol (nmol/L)	- 0.72	< 0.001***	0.69	< 0.001***
DHEA-S (µmol/L)	0.47	0.04*	- 0.55	0.003**
Cortisol/DHEA-S ratio	- 0.85	< 0.001***	-	-

* p ≤ 0.05; ** p < 0.01; *** p < 0.001; BMI: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: fasting blood glucose, HOMA: Homeostasis model assessment of insulin resistance; TC: Total cholesterol; TG: Triglyceride; LDL-c: Low density lipoprotein cholesterol; HDL-c: High density lipoprotein cholesterol; DHEA-S: dehydroepiandrosterone sulfate; IGF-1:insulin like growth factor-1.

cially available kit supplied by Human (Germany). Fasting serum insulin was assayed by a solid-phase and enzyme-labeled chemiluminescent immunometric assay using immulite analyzer supplied by Siemens (USA). Basal insulin resistance index (HOMA) was calculated according to the formula [17]: Insulin resistance = fasting insulin (µU/ml) x fasting glucose (mmol/l) / 22.5. Serum total cholesterol (TC), triglyceride (TG), and high density lipoprotein cholesterol (HDL-c) were assayed by commercially available kits. Low density lipoprotein cholesterol (LDL-c) was calculated according to Friedewald *et al*. (18). Serum IGF-1 was estimated by immunoenzymometric assay supplied by Roy Bio (USA). Serum fasting cortisol and DHEA-S were determined by a solid-phase competitive chemiluminescent enzyme immunoassay using immulite analyzer supplied by Siemens (USA).

Statistical analysis

SPSS packages version 10 (spss, inc., Chicago, IL, USA) was used for the statistical analysis of data. The data were expressed as mean (±) SD for continuous data and frequency and proportion for categorical data. For continuous data, Student's t-test was used to compare two groups. A Chi-square test was used to compare categorical data. Correlation coefficients were calculated to evaluate associations between variables. Multiple regression analysis was also performed with IGF-1 and Cortisol/ DHEA-S ratio as the dependent variables and all other variables as independent variables. P value of < 0.05 indicates significant results.

Results

Baseline characteristics of the three groups are given in Table 1. Diabetic metabolic syndrome subjects (group 1) and non-diabetic metabolic syndrome subjects (group 2) had significantly higher BMI, WC, systolic and diastolic blood pressure (SBP and DBP), FBG, insulin, HOMA, TC, TG and LDL than normal controls (group 3). WC, FBG, insulin, HOMA, TC, TG and LDL were also significantly higher in group 2 than group 3. HDL-c was significantly lower in group 1 than groups 2 and 3 as well between group 2 and group 3.

Table 3. Multiple Regression Analysis With IGF-1 and Cortisol/ DHEA-S as the Dependent Variables and Other Parameters as the Independent Variables in Diabetic Metabolic Syndrome Subjects

Characteristics	IGF-1		Cortisol/DHEA-S	
	β	P-value	β	P-value
BMI (kg/m²)	- 0.21	0.25	0.01	0.9
WC (cm)	- 0.31	0.03*	0.06	0.7
SBP (mm Hg)	- 0.31	0.04*	0.36	0.02*
DBP (mm Hg)	- 0.37	0.01*	0.35	0.01*
FBG (mg /dl)	- 0.58	0.009**	0.69	< 0.001***
Insulin (μU/ml)	- 0.16	0.4	0.36	0.01*
HOMA	- 0.61	0.005**	0.55	0.002**
TC (mg %)	- 0.14	0.4	0.05	0.7
TG (mg %)	- 0.12	0.4	0.32	0.03**
LDL-c (mg %)	- 0.01	0.9	0.92	0.1
HDL-c (mg %)	0.23	0.2	- 0.39	0.01*
Cortisol (nmol/L)	- 0.29	0.03*	0.26	0.04*
DHEA-S (μmol/L)	0.49	0.01*	- 0.29	0.04*
Cortisol/DHEA-S ratio	- 0.35	0.02*	-	-

* p ≤ 0.05; ** p < 0.01; *** p < 0.001; β is standardized β co-efficiency; BMI: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: fasting blood glucose, HOMA: Homeostasis model assessment of insulin resistance; TC: Total cholesterol; TG: Triglyceride; LDL-c: Low density lipoprotein cholesterol; HDL-c: High density lipoprotein cholesterol; DHEA-S: dehydroepiandrosterone sulfate; IGF-1:insulin like growth factor-1.

IGF-1 levels were significantly lower in group 1 (141.8 ± 22.6) than groups 2 (161.7 ± 43.6) and 3 (211± 28.5) with p < 0.001and p < 0.001 respectively; they were also significantly lower in group 2 than group 3 (p = 0.03). DHEA-S levels were significantly lower in group 1 (0.67 ± 0.28) than groups 2 (0.82 ± 0.28) and 3 (33.2 ± 3.4) with p = 0.04 and p < 0.001 respectively; they were also lower in group 2 than group 3 (p = 0.04). Serum cortisol and cortisol/ DHEA-S ratio were significantly higher in groups 1 and 2 than group 3; they were also higher in group 1 than group 2. Table 2 showed urivariate correlation of IGF-1 and Cortisol/ DHEA-S ratio with clinical and metabolic parameters in the adult men with diabetic MS. IGF-1 levels were negatively correlated with BMI, WC, SBP, DBP, FBG, insulin, HOMA, TC, TG, LDL-c, cortisol and cortisol/ DHEA-S and positively correlated with HDL-c and DHEA-S while cortisol/ DHEA-S were positively correlated with BMI, WC, SBP, DBP, FBG, insulin, HOMA, TC, TG, LDL-c and cortisol, and negatively correlated with HDL-c, IGF-1 and DHEA-S.

A multiple regression analysis to assess the independent

effect of studied variables on IGF-1 and cortisol/ DHEA-S in group 1 was also performed. WC, SBP, DBP, FBG, HOMA, cortisol, DHEA-S and cortisol/ DHEA-S ratio remained significantly and independently correlated with IGF-1. SBP, DBP, FBG, insulin, HOMA, TG, HDL, cortisol and DHEA-S remained significantly and independently correlated with cortisol/ DHEA-S ratio in Table 3.

Discussion

The main finding of the current study was the association of both IGF-1 and Cortisol/ DHEA- ratio with MS and most of its individual components but in opposite directions. We reported an inverse relationship between IGF-1 and Cortisol/ DHEA-S ratio.

In the present study, IGF-1 was significantly lower in adult men with diabetic MS than non-diabetic MS and healthy controls. We also found significant correlations between IGF-1 and WC, BP, FBG, HOMA, cortisol and

DHEA-S in adult men with diabetic MS.

Several epidemiological studies have linked low circulating total IGF-1 to an increased risk of the metabolic syndrome and its individual components [19-21]. In addition, patients with type 2 diabetes often exhibit reduced circulating total IGF-1 levels [14]. Lower concentrations have been also associated with obesity [22], disturbed glucose metabolism [14, 23], fasting insulin and HOMA-IR [24], high blood pressure [25], and adverse lipid profiles [22] independently of body mass.

The majority of circulating IGF-1 is bound to six IGF binding proteins (IGFBPs) that are important in determining IGF-1 availability and activity [26]. The increase in IGF-1 bioactivity in subjects with one to three components of the metabolic syndrome may be due to an insulin-mediated suppression of IGFBP-1 levels (potentially inhibitory) [27]. This is probably a compensatory mechanism to maintain normal glucose tolerance, since raised IGF-1 bioactivity improves insulin sensitivity [28]. High IGF-1 bioactivity may suppresses GH secretion as part of a negative feedback system, thereby inducing lower total IGF-1 levels [22]. This may explain why low total IGF-1 levels have been previously reported to be associated with the metabolic syndrome [21]. Moreover, chronic hyperinsulinemia induces GH receptor resistance; it reduces both GH receptor expression and signaling in the liver [29]. On the other hand, GH deficiency in humans is associated with the accumulation of visceral adipose tissue and decreases in lean body mass [30].

Glucocorticoids directly inhibit pituitary gonadotropin and growth hormone and make the target tissue of sex steroids and growth factors resistant to these substances [31]. 11β-hydroxysteroid dehydrogenase type 1 (11 β-HSD1) which catalyzes the conversion of inert cortisone to active cortisol [32] is inhibited by GH and /or IGF1 [33]. Paulsen et al. [34] found that the mRNA expression of 11 β-HSD1 is negatively correlated with IGF-1, suggesting that in human adipose tissue, 11 β-HSD1 is down regulated by IGF-1. Furthermore, GH treatment in GH deficiency patients markedly decreases the gene expression of 11 β-HSD1 in sc abdominal tissue. So, the relative insufficiency of GH seen in truncal obesity [35] may play a role in the development of the MS.

We observed that the serum cortisol levels were significantly higher in adult men with diabetic MS than non-diabetic MS and normal controls. This result was in parallel with previous preliminary data which suggested that circulating cortisol concentrations were higher in patients with MS compared with healthy subjects, both in basal conditions and during dynamic stimulation [36, 37]. In studies that included subjects with type 2 diabetes alone, elevated basal plasma cortisol levels [38] have been also reported. In contrast, some studies have reported no association between cortisol and MS [39, 40].

Stress and hyperactivation of the hypothalamic-pituitary-adrenal axis have been observed in patients with MS [13]. Recent studies have suggested that a subtle increase in plasma cortisol might underlie the cluster of cardiovascular risk factors comprising the MS. Higher cortisol concentrations are related to reduced insulin secretion, a finding consistent with in vivo and in vitro data showing that glucocorticoids regulate insulin secretion [41]. Interestingly, cortisol clearance seems to be inversely correlated with insulin sensitivity, and this correlation is independent of body fat [42]. On the other hand, glucocorticoids regulate adipose tissue differentiation, function and distribution, and when in excess, cause central obesity, which is one of the main features of MS [43].

Our results also showed significant reduction of DHEA-S levels in adult men with diabetic MS than non-diabetic and normal controls. It has been postulated that low levels of DHEA-S are associated with unfavorable levels of several strong cardiovascular risk factors, such as lipids [44], blood pressure [45] and IR [46] which are components of the metabolic syndrome [47, 48]. Furthermore, Muller et al. [49] suggested that lower DHEA-S concentrations characterize individual with MS. However, this is not a universal observation [39, 40].

Both cortisol and DHEA/DHEA-S secretion are under the regulatory influence of pituitary ACTH, and excessive cortisol production will lead to a down-regulation of ACTH, resulting in reduced DHEA secretion, as frequently observed in patients with an adrenal cortisol-producing adenoma. The protective effect indicated by higher DHEA-S is particularly interesting, and the anti-glucocorticoid actions of its precursor, DHEA, are well documented [50, 51]. Higher levels of DHEA or DHEA-S might lead to lower effective cortisol action, particularly at a tissue-specific level, e.g. adipose tissue and immune cells [52]. Indeed, Butcher et al. [53] showed that DHEA-S can overcome the suppressive effects of cortisol upon immune cell function, specifically the generation of superoxide by neutrophils, supporting the proposal that it is the ratio of these two hormones that will determine biological outcome in vivo [54]. Furthermore, DHEA-S supplementation improves endothelial function and insulin sensitivity in men [55]. DHEA-S also plays a role in prevention of platelet aggregation [56], reduction of cholesterol uptake [12] and decrease of vascular smooth muscle cells proliferation [57].

We confirmed significant elevation of Cortisol/ DHEA-S ratio in adult men with diabetic MS than non-diabetic MS and normal controls. In addition, we found significant independent correlations between Cortisol/ DHEA-S and BP, FBG, HOMA, TG and HDL in diabetic MS. These results are consistent with those from a study by Phillips et al. [58], who demonstrated that the Cortisol/ DHEA-S ratio was positively associated with MS and the ratio was significantly related to most of its individual components.

Multiple regression analysis revealed that IGF-1 and

Cortisol/ DHEA-S were independently correlated with each other and with IR in adult men with MS. Thus Cortisol/ DHEA-S excess, IGF-1 deficiency and IR associated with MS seem evidently coherent.

The favorable effect of insulin sensitizers and lifestyle modifications need to be the focuses of advice in those patients.

Conclusion

IGF-1 concentration is reduced and cortisol/ DHEA-S ratio is increased along with insulin resistance in adult men with diabetic MS. IR may be responsible for multiple multihormonal dysregulation in MS.

Competing Interests

The authors declare that they have no competing interests.

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