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RESEARCH ARTICLE

Morning Hypercortisolism: A Marker Of Obesity Rather Than Metabolic Syndrome

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Abstract

Background: The metabolic syndrome (MS) has emerged as a clinical and public health crisis. The incidence of the MS has reached epidemic proportions, with more than 1 in 4 adults affected by this disorder worldwide. Cardiovascular mortality in the MS is increased 2-fold compared to those without MS. **Aim:** The aim of this work was to study the role of cortisol and its circadian rhythm in the MS, the correlation of cortisol to insulin resistance using HOMA model and the correlation of cortisol to various components of the MS. **Patients and methods:** 50 Subjects were included in this study, they were divided into 3 groups: Group I: Included 10 apparently healthy subjects as a control group. Group II: Included 20 obese non diabetic normotensive subjects. Group III: included 20 MS patients (obese, hypertensive and type 2 diabetic). All subjects of the study were subjected to through history and physical examination including anthropometric measures, routine investigations and measurement of plasma fasting and evening cortisol, fasting insulin, estimation of insulin resistance by HOMA index, estimation of B cell function and C-reactive protein. **Results:** There was a significant increase in the fasting glucose, fasting insulin, and HOMA index in MS group compared to control group and obese group: HOMA-IR was 1.36±0.175 in control group, 3.3±0.6 in obese group and 11.4±4.5 in MS group. Obese group also showed significant increase in the fasting insulin, HOMA index compared to control group. The results also showed significant increase in total cholesterol, LDL cholesterol, triglycerides and CRP and significant decrease in HDL cholesterol in both obese group and MS group compared to control group. The results showed significant increase in fasting cortisol in both obese group and MS group compared to control group: fasting cortisol in ng/ml was 128±46.2 in control group, 210±79.1 in obese group and 235.1±76.8 in MS group, while no significant difference was found in the evening cortisol in the different groups: evening cortisol in ng/ml was 54.2±22.4 in control group, 59.2±30.6 in obese group and 83.6±35.7 in MS group. Fasting cortisol level was positively correlated with waist circumference, diastolic blood pressure, fasting glucose, total cholesterol, LDL cholesterol, triglycerides and negatively correlated with HDL cholesterol in MS group. While, in obese group fasting cortisol level was found to be positively correlated with waist circumference, total cholesterol, LDL cholesterol, triglycerides and negatively correlated with HDL cholesterol. **Conclusion:** Fasting cortisol is increased in central obesity and in MS. Evening cortisol in not increased in central obesity or MS. Fasting cortisol level can be used as a marker for central obesity which is

considered the main factor in the MS, but can't be used as a marker for MS itself. Fasting cortisol is correlated with many features of the MS denoting its role in the pathophysiology of the MS. Further work is still needed to justify the role of cortisol in MS regarding its role in diagnosis, prognosis and therapy.

Introduction

Metabolic syndrome (MS) is a cluster of interrelated common clinical disorders, including obesity, insulin resistance, glucose intolerance, hypertension and dyslipidemia[(1).] MS has emerged as a clinical and public health crisis. The incidence of the MS has reached epidemic proportions, with more than 1 in 4 adults affected by this disorder in the United States and worldwide[(2).] In the adult USA population, 20% are estimated to have MS, with prevalence approaching 50% in elderly individuals. Prevalence of the MS among overweight USA adolescents exceeds 30 %[(3).]

The major pathogenic factor in MS is central obesity **(4).** Cortisol secretion was found to be higher in patients who have the MS than in the general population and allelic variants of glucocorticoid receptor are associated with the progression of the MS**(4).**

The aim of this work was to study the role of cortisol and its circadian rhythm in the MS, the correlation of cortisol to insulin resistance using HOMA model and the correlation of cortisol to various aspects of MS.

SUBJECTS AND METHODS

Subjects: Our study was observational, cross sectional, analytic cohort study. This study had been carried out in the Internal Medicine Department "Endocrine & Metabolism Unit" and its Outpatient Clinics Faculty of Medicine, Zagazig University, during 2013. It included 50 subjects (10 apparently healthy subjects as controls, 20 obese subjects and 20 patients fulfilling criteria of the MS). Group I (control group): This group included 10 apparently healthy subjects, with no past history of diabetes mellitus or hypertension, with their age and sex matched with other groups of the study and their body mass index (BMI) and waist circumferences (WC) matched normal healthy individuals. They were 5 males and 5 females, their ages ranged from 40 to 60 years, their mean ages±SD was 52.1±4.8, the WC of the males ranged from 72 to 82 cm with mean WC±SD was 77.6±3.8 cm and the WC of the females ranged from 69 to 75 cm with mean WC±SD was 72±2.8 cm. Group II (Obese group): This group included 20 obese non diabetic normotensive subjects, their BMI>30. They were 10 males and 10 females, their ages ranged from 36-60 years, their mean age±SD was 48.6±7.7. The WC of the males ranged from 102-109 cm with mean WC±SD was 102.8±4.13 cm and the WC of the females ranged from 93-135 cm with mean WC±SD was 106.6±12.1 cm. Group III (MS group): This group included 20 obese hypertensive type 2 diabetic patients. This group includes 11 males and 9 females, their ages ranged from 40-60 years, their mean age±SD was 50±6.0, the WC of the males ranged from 102-125 cm with mean WC±SD was 105.6±12.7 cm and the WC of the females ranged from 91 to 132 cm with mean WC±SD was 108.4±15.97 cm. MS was diagnosed according to guidelines from the National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA), metabolic syndrome is diagnosed when a patient has at least 3 of the following 5 conditions: Fasting glucose ≥100 mg/dL (or receiving drug therapy for hyperglycemia), Blood pressure ≥130/85 mm Hg (or receiving drug therapy for hypertension), Triglycerides ≥150 mg/dL (or receiving drug therapy for hypertriglyceridemia), HDL-C < 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C) and Waist circumference ≥102 cm (40 in) in men or ≥88 cm (35 in) in women**(1)**

Exclusion criteria: Patients on insulin therapy, Patients on corticosteroid therapy, history of cerebrovascular stroke or ischemic Heart disease, patients receiving drugs that affect insulin sensitivity (metformin, thiazoliendiaone, B-blockers and thiazides) and patients with liver or renal impairment.

Ethical Clearance: Informed written consent from the patient relatives to participate in the study was done.

Methods: All eligible subjects of the study were subjected to full history taking and thorough physical examination including anthropometric measures (BMI=body weight in Kg/height^2 in cm^2 and WC, WHO, 1997). Blood collection and storage, 7 ml of fasting venous blood at 9 A.M and 2 ml at 6 P.M were withdrawn. The morning sample was divided into 2 ml was put in EDTA tube for complete blood picture (CBC), 5 ml was centrifuged at 4000 rpm and was stored in deep freezer at –20c for calculation of fasting glucose, fasting insulin, lipid profile and liver and kidney function tests and fasting plasma cortisol. Routine investigations: CBC (by automated blood

counter), liver and kidney function tests measured by colorimetric method, fasting plasma glucose by enzymatic method, lipid profile (total cholesterol, HDL cholesterol and triglyceride were measured by ADVIA 1650, Payer, Germany and LDL cholesterol was calculated using Friedewald formula, Kaplan et al., 1988. Special investigations including measurement of plasma fasting and evening cortisol by Cortisol(1-25) RIA kits produced by Sorin Biomedica, diagnostic division, Italy [5,6], fasting Insulin by Kits manufactured by BioSource Europe S.A, estimation of HOMA index (HOMA-IR) = (fasting insulin μIU/ml) × (fasting blood glucose mmol/L)/22.5[7], also estimation of β-cell function by equation = (fasting insulin μIU/ml) × 20 / (fasting blood glucose mmol/L) - 3.5, and C-reactive protein quantitatively by turbitimeter which is manufactured by Behring Diagnostics, Germany[8], expected reference values ranges between 0.7 and 0.96 mg/l. All data were coded, checked, entered and analyzed using SPSS software version 17; (Levesque, 2010).

RESULTS

Table (1): showed the clinical characteristics of the different groups of the study: A statistically significant difference in BMI, WC, diastolic blood pressure and systolic blood pressure was found in the studied groups ($p<0.001$ for each). The least significant difference (LSD) was done as regard WC, systolic blood pressure and diastolic blood pressure: significant increase was found between obese group and metabolic syndrome group compared with control group ($p<0.001$) for each but no significant difference was found between control and obese group.

Table (2): The biochemical characteristics of the different groups of the study: A statistically significant difference in total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol and CRP was found in the studied groups ($p<0.001$ for each). LSD was done as regard total cholesterol, triglycerides, HDL-C, LDL-C and CRP: Significant increase was found between metabolic syndrome group and obese group compared with control group ($p<0.001$) for each but no significant difference was found between metabolic syndrome group and obese group.

Table (3): showed the glycemic characteristics of the different groups of the study: A statistically significant difference in the fasting glucose, fasting insulin, HOMA index and B cell function was found in the studied groups ($p<0.001$ for each). LSD was done as regard fasting glucose: Significant increase was found between MS compared with control and obese groups ($p<0.001$), no significant difference was found between control group and obese group. LSD was done as regard fasting insulin: Significant increase was found between MS compared with control group ($p<0.001$), also significant increase was found between MS compared with obese group ($p<0.01$). Significant increase was found between obese group compared with control group ($p<0.001$). LSD was done as regard HOMA index: Significant increase was found between MS compared with control group ($p<0.001$), also significant increase was found between MS compared with obese group ($p<0.01$). Significant increase was found between obese group compared with control group ($p<0.001$). LSD was done as regard B-cell function: Significant decrease was found between MS compared with control group ($p<0.001$), also significant decrease was found between MS compared with obese group ($p<0.01$). Significant increase was found between obese group compared with control group ($p<0.001$).

Table (4): showed comparison between mean±SD of fasting and evening cortisol in the different groups of the study: A statistically significant increase was found as regard the mean±SD of fasting cortisol ($P<0.001$), no significant difference was found as regard to the mean±SD of evening cortisol. LSD was done as regard fasting cortisol: showed high significant difference in MS group in comparison to control group ($p<0.001$), also there is high significant difference in obese group in comparison to control group ($p<0.001$) however, no significant difference was found between group II and group III.

Table (5): showed correlation between fasting cortisol and other parameters of the study in obese group: showed statistically positive correlation of fasting cortisol with WC ($P<0.05$) and triglycerides ($P<0.05$), total cholesterol ($p<0.05$), HDL cholesterol ($p<0.001$), LDL cholesterol ($p<0.001$) while no significant correlation with systolic or diastolic blood pressure or CRP or fasting glucose or fasting insulin or B cell function. Correlation between fasting cortisol and other parameters of the study in the MS group: showed statistically positive correlation of fasting cortisol with WC ($P<0.05$) and diastolic blood pressure ($P<0.05$) and triglycerides ($P<0.05$), total cholesterol ($P<0.05$), HDL cholesterol ($P<0.01$), and LDL cholesterol ($P<0.01$), fasting glucose ($P<0.001$), while no significant correlation with systolic blood pressure or CRP or fasting insulin or B cell function.

Table(1):The clinical characteristics of the different groups of the study

	Controls N=10	GroupII (Obese) N=20	GroupIII (MS group) N=20	Test of significance	P	LSD
Sex Male Female	 5 5	 10 10	 11 9	X^2= 0.12	0.9	NA
Age(years) mean±SD (Range)	 52.1±4.8 (46-60)	 48.6 ±7.7 (36-60)	 50 ± 6.0 (40- 60)	F= 0.931	0.59	NA
BMI mean±SD (Range)	 23.6± 0.8 (22–4.7)	 34.6 ± 2.3 (30.1–41)	 34.97 ± 3.2 (30.1–42.4)	F= 76.9	<0.001	*<0.001 **<0.001 *** NS
WC(cm) mean±SD (Range)	 74.8± 4.3 (69–82)	 104.7± 9.0 (9–135)	 104± 13.9 (90–132)	F=0.62	<0.001	*<0.001 **<0.001 *** NS
SBP mean±SD (Range)	 122± 9.2 (110–140)	 120.5± 10.5 (100 – 130)	 149.2 13.1 (135-180)	F= 36.8	<0.001	*<NS **<0.001 ***<0.001
DBP mean±SD (Range)	 75.2±4.96 70 -80	 85± 6.3 60 - 85	 96.5 ± 9.5 85 – 115	F= 50.7	<0.001	*<NS **<0.001 ***<0.001

Comparison* I vs. II **I vs. III ***II vs. III, NA: not applicable

Table(2):Comparison between mean value ± SD of lipid profile (mg/dl) & CRP (mg/l) of the different groups of the study using ANOVA test & LSD.

	Controls	Group II (Obese group)	Group III (MS)	F	P	LSD
TC(mg/dl) mean±SD (Range)	 170.8 ± 23.4 128 – 200	 248.8 ± 38.2 198- 305	 240.1 ± 35 200 - 300	18.5	<0.001	*<0.001 **<0.001 *** NS
TG(mg/dl) mean±SD (Range)	 125± 18.8 95– 150	 143.9± 49.1 185 – 340	 232.2± 57.5 185 – 360	21.7	<0.001	*<0.001 **<0.001 *** NS
HDL (mg/dl) mean±SD (Range)	 54.4± 6.1 44– 63	 40± 6.7 31 – 58	 36.6 ± 3.8 31 – 42	35.1	<0.001	*<0.001 **<0.001 *** NS
LDL(mg/dl) mean±SD (Range)	 ± 18.6 72 – 144	 158.9 ± 29.8 106 – 205	 158 ± 30.4 120 – 200	14.8	<0.001	*<0.001 **<0.001 *** NS
CRP(mg/l) mean±SD (Range)	 0.84 ± 0.08 0.7 – 0.96	 2.6 ± 0.9 0.99 – 4.5	 3.5 ± 1.1 1.2 – 5.8	25.8	< 0.001	*<0.001 **<0.001 *** NS

Comparison* I vs. II **I vs. III ***II vs. III

Table(3):Comparison between mean± SD of fasting plasma glucose (FG) (mmol/l), fasting insulin (µIU/ml), HOMA index, and B cell function of the different groups of the study ANOVA & LSD.

	Group I (Controls)	group II (Obese)	GroupIII (MS group)	F	P	LSD
FPG				86.3	<0.001	*<NS
mean±SD	5.18± 0.39	5.3 ± 0.6	12.6 ± 3.5			**<0.001
(Range)	4.8 –6	4.2 – 6	7.2 – 18			***<0.001
F.insulin				25.9	<0.001	*<0.001
mean±SD	6.01 ± 1.1	14.4 ± 3.3	19.7 ± 6.9			**<0.001
(Range)	4.3 – 7.2	9.5 – 16	11 – 30			***<0.01
HOMA				56.8	<0.001	*<0.001
mean±SD	1.36 ± 0.175	3.3 ± 0.6	11.4 ± 4.5			**<0.001
(Range)	1.07 – 1.53	2.3 – 4.3	4.6 – 19.4			***<0.01
B-cell				19.8	<0.001	*<0.001
function	76.7 ± 25.5	157.7 ± 84.9	47.3 ± 20.1			**<0.001
mean±SD	36 110	86.4 – 428.5	18 – 95.2			***<0.01
(Range)						

Comparison* I vs. II **I vs. III ***II vs. III

Table(4):Comparison between mean±SD of fasting and evening cortisol (ng/ml) of the different groups of the study using ANOVA test & LSD.

	GroupI(Controls)	GroupII(Obese)	GroupIII(MS)	F	P	LSD
Fasting cortisol	128 ± 46.2	210 ± 79.1	235.1 ± 76.8			*<0.001
	69 – 205	40 – 310	97 – 354.0	7.29	<0.001	**<0.001
						*** NS
Evening cortisol	54.2 ± 22.4	59.2 ± 30.6	83.6 ± 35.7			*<0.001
	29 – 102	10 – 145	35 – 174	4.17	0.02	**<0.001
						*** NS

Comparison* I vs. II **I vs. III ***II vs. III

Table(5):Correlation between cortisol and other parameters of the study in the different studied groups

	Control		Obese group		MS group	
	R	P	R	P	R	P
Age	0.05	> 0.05	-0.44	< 0.05	0.3	> 0.05
BMI	-0.49	> 0.05	0.05	> 0.05	0.3	> 0.05
WC	0.001	> 0.05	0.46	<0.05	0.45	< 0.05
SBP	0.22	> 0.05	0.04	> 0.05	0.11	> 0.05
DBP	0.34	> 0.05	0.04	>0.05	0.48	< 0.05
Cholesterol	0.69	> 0.05	0.03	> 0.05	0.26	> 0.05
TG	0.48	> 0.05	0.51	0.05	0.48	<0.05
HDL	-0.12	> 0.05	-0.5	<0.001	-0.49	<0.01
LDL	0.72	> 0.05	0.5	<0.01	0.53	<0.01
CRP	0.56	> 0.05	0.1	< 0.05	0.28	> 0.05
FG	-0.14	> 0.05	-0.25	> 0.05	0.58	<0.001
Fasting insulin	0.29	> 0.05	0.21	> 0.05	0.02	> 0.05
HOMA	0.29	> 0.05	0.12	> 0.05	0.15	> 0.05
β-cell function	0.24	> 0.05	0.46	< 0.05	0.33	> 0.05

DISCUSSION

This work showed a high significant increase in the WC in the obese group and the MS group when compared to control subjects. The major pathogenic factor in the MS is central obesity; the excess accumulation of visceral adipose tissue (VAT) appears to play a high significant pathogenic role [5].

Our study found that there is high significant increase in the systolic and diastolic blood pressure. It also showed a positive correlation between fasting cortisol and diastolic blood pressure in the MS group, GCs are agonists of mineralocorticoid receptor (MR), which upon activation leads to renal salt retention and elevated blood pressure [6]. Cortisol excess as a result of increased 11β-HSD1 activity leads to MR activation and hypertension. Cortisol also increases aortic vasoconstriction through unknown mechanisms [7].

The work also showed a significant higher level of triglycerides, LDL cholesterol, and low levels of HDL cholesterol in the MS group. This was in agreement with Chen, 1998, who stated that hyperinsulinemia could be the cause of dyslipidaemia which is a feature of the MS [8].

The work showed positive correlation between fasting cortisol and triglyceride and LDL cholesterol and negative correlation with HDL cholesterol. In liver, cortisol increase the activities of enzymes involved in fatty acid synthesis and promote the secretion of lipoproteins the hepatic lipogenic effect of cortisol is consistent with clinical findings that cortisol therapy causes triglyceride accumulation within the liver [9]. Since liver fat appears to be involved in the negative regulation of hepatic insulin sensitivity and is associated with certain features of the MS independent of visceral fat mass. Hepatic fat accumulation promoted by cortisol is likely to contribute to the pathophysiology of the MS [10].

The work also showed a significant higher level in CRP level in the two studied groups, this was in agreement with McLaughlin et al, 2002, who stated that CRP concentrations are elevated predominantly in obese individuals who are also insulin resistant [11]. This was also in agreement with Greenfield et al., 2002, who suggested that, CRP was strongly related to total and central abdominal obesity, blood pressure, and lipid levels [12].

This work showed a high significant increase in the fasting insulin in the obese and the MS groups when compared to control subjects. Fasting insulin was higher in obese diabetic hypertensive patients than in obese non diabetic normotensive subjects. The recorded hyperinsulinemia in obese patients could be explained by insulin resistance. Obesity linked type 2 diabetes is a disease of insulin resistance combined with beta cell dysfunction. It is proposed that in early obesity an increase in beta cell mass and function might compensate for peripheral insulin resistance. However, as time and severity of obesity continue, there is decay in such adaptation and the beta cell mass becomes inadequate [13]. It is possible that prevailing hyperinsulinemia, which is commonly observed in abdominal obesity and other insulin resistance syndromes, may be partly responsible for increased HPA axis activity. In fact, insulin crosses the blood-brain barrier. It has been demonstrated that the hippocampus represents a key area in the regulation of HPA axis activity and has a high insulin receptor concentration [14].

In this work there is increase is increase in HOMA index and lower beta cell function in MS group than obese and control groups, also there is increase in HOMA index and lower beta cell function in obese group than control group. This was explained by Reaven et al., 2000 [15], their work also showed a significant higher level in fasting cortisol level in the two studied groups, this was in agreement with Wallerius et al., 2003 [16], who stated that the rise of morning cortisol values was positively associated with body mass index, waist/hip ratio, abdominal sagittal diameter, insulin, and triglycerides. Fasting cortisol was positively correlated with fasting glucose in the metabolic syndrome group, but not correlated with fasting insulin, or insulin resistance measured by HOMA index or beta cell function. Also Khani and Tayek, 2001 [17], stated that android obesity is associated with increased cortisol secretion and smaller increases in serum cortisol may contribute to the abnormal glucose metabolism known to occur in the metabolic syndrome. This was in contrast to Bahr et al, 2002 [18], who stated that plasma cortisol is not elevated in the MS. Evidence is presented, that by the action of 11 beta-hydroxysteroid dehydrogenase 1 (11 beta HSD1) higher intracellular cortisol concentration may be created that may be relevant to induce insulin resistance and metabolic disturbances.

Evening cortisol showed no difference between control group and subjects groups and this was in agreement with Brunner et al., 2002 [19], who stated that Urinary cortisol metabolite excretion was increased in metabolic syndrome cases, whereas salivary cortisol measurements in the afternoon and evening revealed no difference between cases and controls.The work also showed no significant difference between fasting cortisol in obese group and MS group. Rask et al., 2002 [20], observed that both impaired hepatic regeneration of cortisol by 11β-HSD1 and elevated adipose 11β-HSD1 activity in obese humans are present, the association of adipose 11β-HSD1 activity with obesity, insulin resistance and other features of the metabolic syndrome has been consistently observed in different groups of obese subjects, including obese men and women . However, no difference in 11β-HSD1 activity was detected between obese type 2 diabetics and their obese controls, suggesting the dysregulation of 11β-HSD1 is better associated with obesity than the diabetic phenotype [21].

Our work was supported by **Weigensberg et al 2008** [22], they found that, in overweight, Latino youth, MS is associated with higher morning serum cortisol levels, independent of body fat and insulin sensitivity and **Stalder et al 2013** [23], supported our results, they found that normal physiological differences in long-term cortisol secretion, as assessed in hair, showed relevant relationships with MS and individual cardiometabolic parameters.

Also in our line **Esteghamati et al 2011** [24], who concluded that, serum cortisol levels are significantly higher in men with MS, this effect is independent of waist circumference. Furthermore **Treviño-Villarreal et al 2012** [25], found that, there was a relationship between the SC and the number of MS components as well as with excessive intake of foods of animal origin, sugars, and fats in obese children. Moreover, in study of **Kazakou et al 2012** [26], for evaluation of HPA in MS**,** they found that patients with MS had serum cortisol levels after an overnight dexamethasone suppression test significantly higher than controls, plasma ACTH levels were higher in patients with MS compared to controls, whereas SC levels were comparable to control, plasma ACTH was also correlated with most of the components of MS and concluded that the HPA axis in patients with MS seems to be more active as evidenced by the higher SC after the overnight dexamethasone suppression test and by the higher ACTH levels during OGTT so, this functional hypercortisolism might be involved in the pathogenesis of the metabolic syndrome.

But against our results **Abraham et al 2013** [27], did not find, in their meta-analysis, significant relationship between systemic cortisol or stress and obesity or metabolic syndrome, this is against our results. Also, **Reinehr et al 2014** [28], found that, there was only slightly increased urinary free cortisol (UFC) concentrations in 30.7% of the obese children and obese children with MS had significantly higher UFC levels compared to obese children without MS. In this study girls demonstrated significantly higher UFC concentrations compared to boys independent of pubertal stage. Also UFC and serum cortisol (SC) levels were significantly related to features of the MetS, but the associations were stronger for UFC. Furthermore in this recent study, none of the features of MS but HOMA index was correlated with UFC, while SC demonstrated no significant association to any parameter of MS or HOMA, so their findings supported the hypothesis that changes in the hypothalamic pituitary axis (HPA) are related to the MS in obesity and UFC seems to be a suitable marker for this relationship and in study of **Guzzetti et al 2014** [29], they found that in obese children and adolescents, SC was only weakly associated with components of the MS and concluded that their findings did not support a major role for SC in the development of MS. So we can conclude that, fasting cortisol is increased in central obesity and in metabolic syndrome. Evening cortisol in not increased in central obesity or MS.

Fasting cortisol level could be used as a marker for central obesity which is considered the main factor in the MS, but can't be used as a marker for MS itself. Fasting cortisol is correlated with many features of the MS denoting its role in the pathophysiology of the MS. Further work up still recommended to justify the role of cortisol in MS regarding its role in diagnosis, prognosis and therapy.

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