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RESEARCH ARTICLE
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HYPERCORTISOLISM AND ITS CORRELATION WITH DIFFERENT ASPECTS OF METABOLIC SYNDROME

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Abstract
Serum Cortisol is a stress hormone released in acute and chronic stressful conditions. Association with non-infective and lifestyle diseases is an area of ongoing research. Metabolic syndrome (MetS) is expected to be low grade indolent chronic inflammatory state. To investigate the same, we designed a cross-sectional study of 100 subjects including 50 diagnosed cases of metabolic syndrome and 50 healthy controls in whom fasting serum cortisol values were measured and compared with different parameters of MetS. Raised serum cortisol levels were seen in 62%(n=31) cases with a mean value of 26.11 ± 11.63 mcg/dL as compared to controls with no sex predilection. Significant association of high cortisol levels were seen with raised fasting glucose and low serum HDL levels.

Keywords- Metabolic syndrome, Serum cortisol, Cushing's syndrome, Obesity.

INTRODUCTION

Metabolic syndrome (MetS) or syndrome X is a cluster of risk factors including abdominal obesity, impaired fasting glucose , hypertension and dyslipidemia that predispose to the development of diabetes, atherosclerosis, and CVD.[1] It is estimated that approximately 25% of the world's population has MetS.[2]

Both overt and subclinical Cushing's syndrome (CS) share many clinical and biochemical features with metabolic syndrome. The visceral fat deposition is somehow associated with increased release of proinflammatory cytokines like Tumor Necrosis Factor(TNF)-alpha, Interleukin(IL)-6, C-reactive protein(CRP), and altered levels of adiponectin and resistin.[3] Since MetS shares many characteristics of CS, it has been proposed that the pathogenesis both the conditions involves prolonged and excessive glucocorticoid exposure eventually leading to thus central adiposity and insulin resistance.[3,4] Visceral fat deposition has been linked with increased cortisol levels in the past,[5] thus it could be hypothesized that persons with metabolic syndrome have a higher baseline morning serum cortisol levels. These similarities between the two entities renewed interests on role of glucocorticoids and therefore inspired this research. Therefore, the purpose of this report is to investigate the association between MetS and morning serum cortisol levels in a cohort of overweight adults.

MATERIAL AND METHODS

A cross-sectional analysis was performed on serum samples from 50 patients of metabolic syndrome attending medicine outdoor clinics of a tertiary care centre in Delhi between august 2017 and December 2018 plus 50 healthy controls matched according to age and sex. All participants gave written informed consent before participation. The local ethics review committee of the hospital approved the study protocol.

Demographic and anthropometric data including height, weight in light clothing, and waist circumference were all measured in the MEC using standardized techniques and calibrated equipment. Standardized techniques were used to obtain the blood pressure measurements. Fasting morning blood samples after 8-12 hours of fasting at 8 am were drawn from the examinee's arm for cortisol, lipids and glucose assays. Any cortisol value above the laboratory normal reference range(24 mcg/dL) was considered to be raised.

Metabolic Syndrome was classified according to the International Diabetic federation Criteria.[6] Patients who were pregnant or having coronary heart disease, acute or chronic renal failure, congestive heart failure, liver failure, thyroid disorders, acute infections, cerebrovascular diseases, PCOD, any psychiatric illnesses were excluded from the study. History of smoking, substance abuse, use of glucocorticoid drugs, ketoconazole and hospital admission within the past six months for any illness qualified for exclusion from study group. Any subject doing exercise for more than 30 min three times a week was also exclude from the study. Serum cortisol concentration was measured by Electrochemiluminescence immunoassay "ECLIA" using the MODULAR ANALYTICS E170 (Elecsys module) immunoassay analyser.

STATISTICAL ANALYSIS

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used.

Statistical tests were applied as follows-

1. Quantitative variables were compared using Mann-Whitney Test (as the data sets were not normally distributed) between the two groups.
2. Spearman rank correlation coefficient was used to assess the correlation of various parameters with cortisol. In the analysis, a p value of <0.05 was considered statistically significant.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

Keeping in mind that metabolic syndrome is a less profound form of Cushing syndrome[7] and central adiposity might be linked to random fasting serum cortisol levels it was the primary target to analyse the cortisol levels in an obese group of patients and compare them with different parameters of MetS. The mean age of study group was 52.42±7.52 yr and that of controls was 51.02±8.06 yr. (p=0.186) indicating greater likelihood of MetS in elderly and there was no sex predilection. Mean BMI of study group was 33.43 ± 2.68 Kg/m2.

Serum cortisol levels were significantly high in almost 62% (n= 31) of cases with mean cortisol values of 26.11±11.63 mcg/dL. The control group however had almost normal levels of cortisol with mean values of around 16.73 ± 11.1 mcg/dL (Figure 1). Difference in mean of serum cortisol in both groups was statistically significant (p=0.0001). Females had relatively higher values of serum cortisol (28.46 ± 12.2) than males (23.75 ± 10.77) but the difference was not statistically significant. (p = 0.13) as illustrated in Table 1.

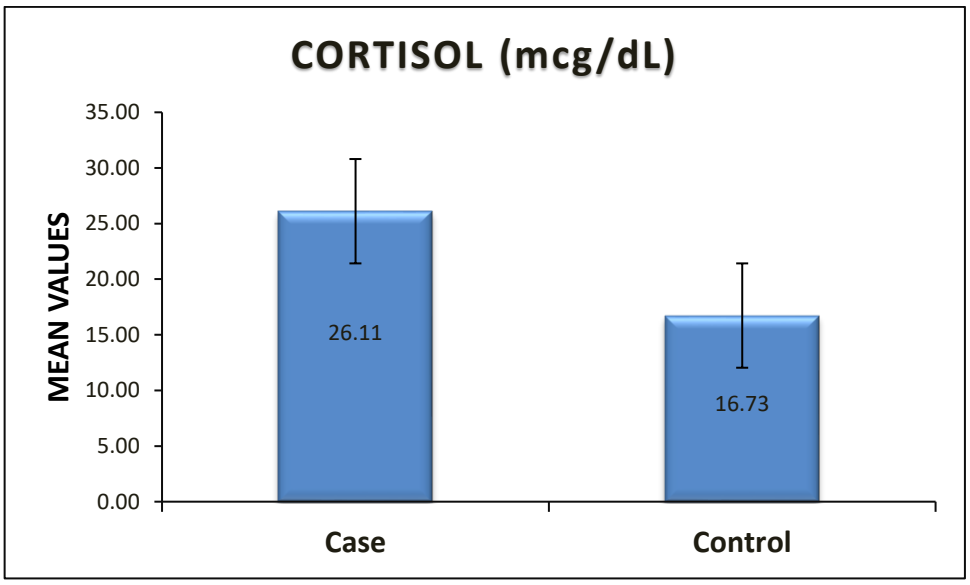

Figure 1: Mean cortisol values in both study groups

Table 1: Cortisol levels in different study groups

Group	Gender	N	Mean ± SD (mcg/dL)	p-value
Cases	Males	25	23.75 ± 10.77	0.639
	Females	25	28.46 ± 12.2	
Controls	Males	22	20.12±12.07	0.054
	Females	28	14.06±9.66	
The *p* value of <0.05 was considered statistically significant.				

About 70 % of subject had raised BMI above 30 kg/m2. The mean waist circumference of cases came out to be 102.68 ±6.92 cm. ($p<0.001$) and the difference was statistically significant but there was no association of serum cortisol and WC in our results with $p = 0.114$. Elevated levels of plasma fasting glucose(FG) levels were seen in 80% with mean levels of 120.04± 22.36 mg/dL. Rise in FG was significantly correlated with morning cortisol levels. (p value =0.0008). These patients also had mean cortisol levels much above the normal serum levels indicating the trend and positive relationship of insulin resistance with cortisol levels in these patients.

The Triglyceride (TG) levels of subjects with MetS was significaltly raised with mean values 174.56 ±37.39 mg/dL. Mean serum HDL levels were 40.26±9.26 mg/dL and a negative association was seen with rise in cortisol levels with p value <0.05.

Both systolic and diastolic blood pressure values were raised in about 38 patients and mostly had high cortisol values.. All clinical and laboratory parameters are mentioned with their mean and median values in Table 2.

Table 2. Mean values of baseline characteristics and different laboratory parameters (sample size= 50)

	Mean ± SD	Median	Min-Max
AGE (Years)	52.42 ± 7.52	52.5	34-68
WAIST CIRCUMFERENCE (cm)	102.68 ± 6.92	103.5	88.5-126
BMI (Kg/m^2)	33.43 ± 2.68	33.05	30-40
BP (SYSTOLIC) mmHg	139.34 ± 11.83	140	120-160
BP(DIASTOLIC) mmHg	84.24 ± 8.37	82	60-105
Hb (g/dL)	11.51 ± 1.29	11.35	9.3-14.5
TLC ($Count/mm^3$)	7471.32 ± 1338.54	7200	4600-9900
PLATELET COUNT (lakh/microliter)	2.59 ± 0.76	2.45	1.3-4.3
Cortisol (mcg/dL)	26.11 ± 11.63	28.52	2.84-55

Fasting glucose (mg/dL)	116.68 ± 17.99	117.5	90-146
Serum Calcium (mg/dL)	7.73 ± 0.88	7.6	6-9.6
Serum Phosphate (mg/dL)	3.72 ± 1.13	3.8	1-5.6
Blood Urea (mg/dL)	22.1 ± 7.6	21	8-35
Serum Creatinine (mg/dL)	0.93 ± 0.31	1	0.2-1.6
Serum Uric acid (mg/dL)	6.12 ± 2.16	6	3-11
Serum Potassium (mEq/L)	4.32 ± 0.48	4.35	3.5-5.3
Serum Protein (g/dL)	7.16 ± 0.83	7.4	5-8.3
HDL (mg/dL)	40.84 ± 8.97	40	28-58
Serum Triglyceride (Tg) (mg/dL)	174.56 ± 37.39	176.5	100-260

When comparing the serum cortisol levels with different parameters of MetS it was found that it was positively correlated with both Fasting blood glucose levels(p=0.0008) and negatively with serum HDL levels (p=0.0002) as depicted in Figure 2 and 3. None of the other parameters showed any significant correlation with cortisol levels individually.

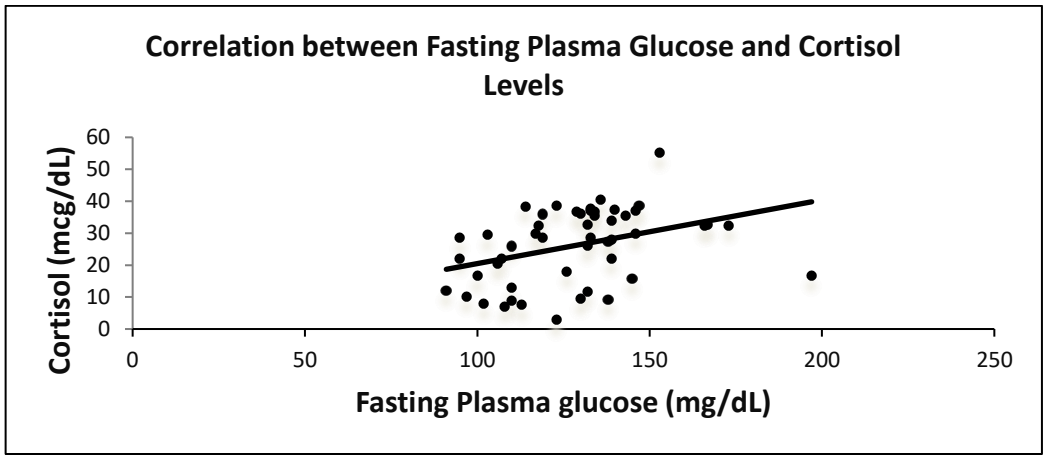

Figure 2. Correlation of serum cortisol and fasting glucose levels

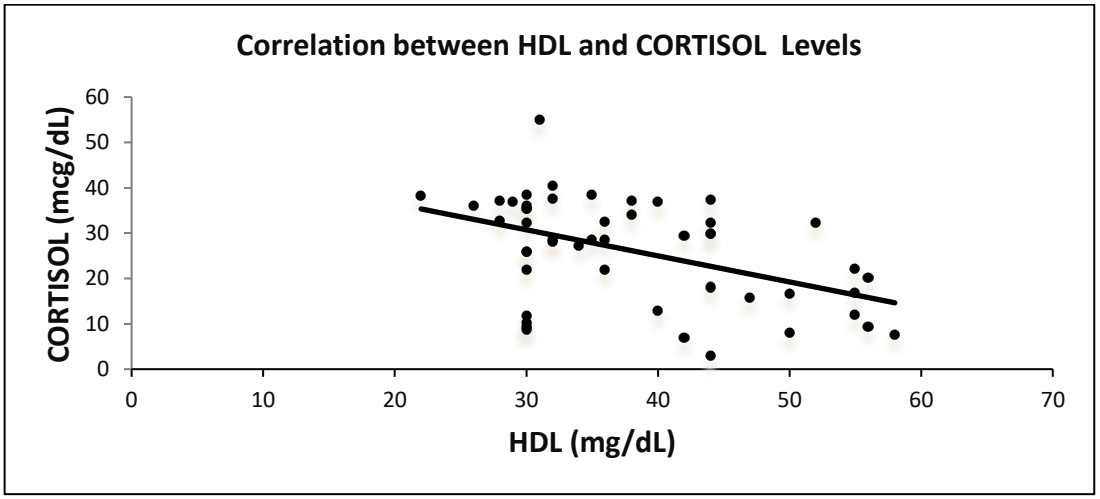

Figure 3. Correlation of serum cortisol levels with HDL levels

DISCUSSION

Metabolic syndrome (MetS) is a cluster of abnormalities that predispose to the development of diabetes, atherosclerosis, and Cardio Vascular Disease(CVD), although many patients with MetS may already have diabetes and/or vascular disease. Because MetS shares many clinical characteristics of Cushing's syndrome (CS), it was proposed that the pathogenesis of MetS and central obesity involves prolonged and excessive glucocorticoid exposure.[3,8] The pathogenetic mechanisms might include direct and indirect cortisol action on lipolysis, free fatty acid production and turnover, very-low-density lipoprotein synthesis and fatty acid accumulation in the liver.[9]

As per the third National Health and Nutrition Examination Survey (NHANES III) there is predilection of higher age group being affected by metabolic syndrome and with increasing BMI in the western population and the similar trend is depicted in the South Asian population as studied by Misra et al.[10] The likelihood of disassociation between cortisol levels and BMI is also seen in our results which is in concordance with the findings of Praveen et al [11] and many others as visceral adiposity is mainly responsible for metabolic syndrome and cortisol rise promotes overall obesity. The cause–effect relationship of obesity and cortisol is not clearly known but may be due to an altered HPA axis , resulting in a blunted diurnal variation in cortisol levels and adiponectins.[5]

Most of the patients resided in urban dwellings (72%) and majority of the female subjects were housewives (36%), and followed by businessman (30%). Thus, the urban population is more prone to all the risk factors of the metabolic syndrome due to the sedentary lifestyle, stressful occupation and poor dietary choices. Data regarding gender effect are conflicting with the majority of the studies finding the highest prevalence of MetS and an equally higher levels of cortisol in women compared to men, while the collaborative European analysis found no gender difference.[12] The conflicting results with respect to gender effect may partly be explained by the application of different definitions for the metabolic syndrome worldwide.

Our observation of higher morning plasma cortisol in obese subjects (62%) is in agreement with the reports of Weigensberg et al who observed higher morning serum cortisol in overweight Latino youths with MetS.[13] Similarly after reviewing almost all the previous literature we came to a conclusion that there is a state of hypercortisolism in these patients as supported by our results. The clinical features and biochemical analysis further revealed that MetS could be another form of subclinical Cushing's syndrome as the cortisol levels were not so high in our patients to fit into the spectrum of full blown Cushing's syndrome and they also lack the typical stigmata of cortisol hypersecretion (i.e. moon face, truncal obesity, thin extremities, proximal myopathy, easy bruising, cutaneous purple striae).

It was not surprising though to find no relationship between cortisol and waist circumference, in accordance with studies conducted by Ward et al[14], on a South Indian population which also stated that no concrete outcome has been noted till date between both parameters. There could be several explanations for this as waist circumference was relatively less for Indian cohort as compared to the western counterparts. Despite the lack of relationship with waist circumference, dyslipidemia and central adiposity may account, in part, for the relationship between cortisol and MetS.[15] Several lines of study have shown that cortisol levels have been an important factor for the development of dyslipidemia and insulin resistance in obese patients. The negative correlation we observed between HDL and cortisol levels were supported by the findings of Fraser and colleagues[16] and Wallerius[17] et al. A significant association with decreased HDL levels was also in favour of atherogenic dyslipidemia which is a major cause of morbidity and mortality among this subgroup of population. Halpern et al[18] also mentioned in their studies the association of body lipids with cortisol and MetS in the same manner which is already mentioned earlier.

Glucocorticoids can also adversely affect glucose metabolism[19], and indeed it was supported by the significant associations between increased Cortisol and Fasting glucose levels in our study. Central adiposity and insulin resistance are the key pathophysiological changes linked to the degree of hypercortisolism in obese patients due to a decrease in both hepatic and extrahepatic sensitivity to insulin.[20] However, a separate analysis in our cohort showed that patients with impaired fasting glucose (n = 49) did have a significantly higher morning cortisol levels than those with normal fasting glucose (n = 51). These patients had mean cortisol levels much above the normal serum levels indicating the trend and positive relationship of insulin resistance with cortisol levels in these patients.(p value 0.0008) These results were in concordance with the findings of Philips et al. And Wallerius et al.[17,21]

Although hypercortisolism may directly influence blood pressure through its effects on salt and water retention or vascular smooth muscle tone, it has been suggested that this relationship is more likely indicative of a general increase in the stress response, which includes both elevated HPA axis activity and heightened autonomic nervous system sympathetic tone.[22] There was no significant association noted between morning cortisol levels and other parameters of MetS apart from fasting glucose and HDL levels. Likely explanation being the pattern of cortisol metabolism and diurnal rythm which is also different in different subgroup of population, so is the index of 11beta-hydroxysteroid dehydrogenase activity which could be lower in Indian population.[23]

Thus, early morning serum cortisol levels trends to increase with rising blood glucose levels and falling HDL levels depicting a strong cause- effect relationship of hypercortisolism in the pathogenesis of the insulin resistance and dyslipidaemia in the patients of MetS. Although there was positive correlation noted with all the other parameters but not to significance when compared individually. This could be partly explained by the fact that the results of our study were in the range of 24-55 mcg/dL which lies in the spectrum of subclinical Cushing's syndrome whereby clinical manifestation are not much appreciated and seen neither do these levels pose any long-term risk of hypertension and osteoporosis. Thus we can say that there is is speculation on the possibility of subtle abnormalities of cortisol biosynthesis/metabolism in the pathogenesis of MetS and also possibility of overactivity of the HPA axis which could be proved by additional tests for serum Adrenocorticotrophic hormone (ACTH) levels.

The main limitation of the present study is that it is based on a single morning cortisol value and that too of a small subgroup of patients. Also, the cross-sectional nature of study might be the limiting factor for the non-association of rest of the features of METS. Also, we could not perform the more sensitive and specific tests of hypercortisolism such as 24 hour urinary or midnight salivary cortisol levels. Fasting insulin levels and ACTH levels might have added a wider spectrum to the study.

The novelty and strength of the study is that the each component of MetS was correlated and analysed with the levels of serum cortisol. We can say now that cortisol bears more strong relationship with the syndrome as a whole than with individual components. Additional studies are needed to tease apart these relationships and delineate the role of relative hypercortisolism and chronic stress in obesity-related metabolic disorders in adults.

CONCLUSION

Our report has documented higher plasma cortisol values in MetS patients than in healthy subjects. Serum cortisol levels were high in almost 62% of patients of metabolic syndrome. When associated with individual parameters we found positive correlation with fasting glucose levels and negative with serum HDL levels. There is speculation on the possibility of subtle abnormalities of cortisol biosynthesis/metabolism in the pathogenesis of MetS and also overactivity of the HPA axis. However, the relationship between different MetS components and serum cortisol is not consistent. Thus, raised cortisol levels are definitely linked to the altered HPA axis and insulin resistance in these subgroups of population with no definite cause-effect relationship. In short, we observed additive effects of dyslipidemia and fasting plasma glucose on morning plasma cortisol, opening the spectrum for further therapeutic aspects in these patients.

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