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SERUM CORTISOL LEVELS IN METABOLIC SYNDROME AND ITS CORRELATION WITH DIFFERENT PARAMETERS OF METABOLIC SYNDROME

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ABSTRACT A cross sectional study of 100 subjects including 50 diagnosed cases of metabolic syndrome in which fasting cortisol values were measured and compared with those of healthy controls and also with different parameters of Metabolic syndrome. Raised cortisol levels were seen in 80% cases mean values of 459.49 ng/ml as compared to controls with no sex predilection. The association of cortisol was seen with fasting glucose and serum HDL levels.

KEYWORDS : Metabolic syndrome, Serum cortisol, Cushing syndrome, Obesity.

INTRODUCTION

Metabolic syndrome(MetS) or syndrome X is a cluster of risk factors including abdominal obesity, impaired glucose control, hypertension and dyslipidemia that predispose to the development of diabetes, atherosclerosis, and CVD. It is estimated that approximately 25% of the world's population has MetS.[1] The visceral fat deposition with increased release of proinflammatory cytokines like TNF-alpha, IL-6, CRP, and altered levels of adiponectin and resistin are the main pathophysiologic featuress.[2]

Overt and subclinical Cushing's syndrome share many features with metabolic syndrome including insulin resistance, abnormal fasting glucose levels, hypertension, obesity and dyslipidemia. Because MetS shares many characteristics of CS, it was proposed that the pathogenesis of MetS and central obesity involves prolonged and excessive glucocorticoid exposure thus central obesity and insulin resistance are acknowledged as important causative factors.[3,4] Central fat distribution is significantly associated with increased cortisol levels [5,6] so it could be hypothesized that persons with metabolic syndrome have a higher serum cortisol levels.[7]

The pathogenetic mechanisms include direct and indirect cortisol action on lipolysis, free fatty acid production and turnover, very-low-density lipoprotein synthesis and fatty accumulation in the liver.[8] The similarities between patients of cushing syndrome and MetS have focussed renewed interests on role of glucocorticoids and therefore inspired this review article.Therefore, the purpose of this report is to investigate the associations between MetS and levels of morning serum cortisol in a cohort of overweight adolescents.

MATERIALAND METHODS

A cross sectional analysis was performed with serum samples from 50 patients with metabolic syndrome attending medicine ward and clinic of Safdarjung Hospital between august 2013 to December 2014 plus 50 healthy controls matched according to age and sex. All participants gave written informed consent before participation. The local ethics review committee of VMMC and Safdarjung hospital approved the study protocol.

Demographic and anthropometric data, including age, sex, height, weight in light clothing and blood pressure in sitting position, were recorded. The mean age group was 52.42±7.52 yr (range 34-68yr) and mean BMI was 33.43 ±6.92 kg/m^2 (range 21-40 kg/m2).

Height, weight, 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 12 hours of fasting at 8 am were drawn from the examinee's arm for cortisol, lipid and glucose assays.

Metabolic Syndrome was classified according to the International Diabetic federation Criteria for Metabolic Syndrome. Exclusion criteria were pregnancy, coronary heart disease, acute or chronic renal failure, congestive heart failure, liver failure, thyroid disorders, acute infections, cerebrovascular diseases, PCOD, any psychiatric illnesses, smoking, substance abuse, use of glucocorticoid drugs and hospital admission within the past six months. Patients taking medications known to influence Serum Cortisol levels, eg (Ketoconazole) were also excluded. 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 analyzers.

STATISTICALANALYSIS

The statistical analysis was performed using statistical package for social sciences (SPSS) version 1 . The mean+ standard deviation , median and ranges was calculated for continuous variables whereas proportion and frequency tables were used to summarize categorical variables. Chi square test and fisher exact test was used to compare categorical variables. A p value (significance) of <.05 is deemed statistically significant. A significance of .0001 should be read as p<.0001 (very highly significant) as the software can detect significance up to 3 decimal points only.

RESULTS

Keeping in mind that metabolic syndrome is a less profound form of cushing syndrome [9] and central adiposity is well linked to the serum cortisol levels it was the primary target to analyse the cortisol levels in an obese group and compare the different parameters of MetS in them. 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 old age and there was no sex predilection.

Serum cortisol levels were high in almost 80% (n= 40) of cases with mean cortisol values of 459.49 ng/ml. The control group however had almost normal levels of cortisol with mean values of around 167.34±110.99 ng/ml .Difference in mean of serum cortisol in both groups was statistically significant (p<0.001 CI=95%). Females had relatively higher values of serum cortisol (483.64 ng/ml) than males (435.34 ng/ml) but the difference was not statistically significant. (p -0.639).

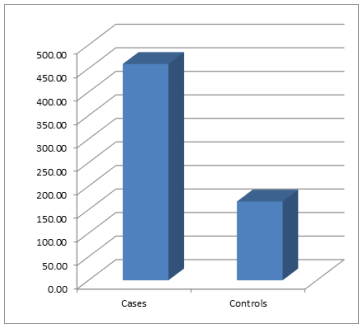

Figure 1: Mean cortisol values in both study groups

Table 1: Cortisol levels in different study groups

Group	Gender	N	Mean	±SD	p-value
Cases	Males	25	435.34	286.08	0.639
	Females	25	483.64	423.21	
Controls	Males	22	201.26	120.79	0.054
	Females	28	140.68	96.62	

There was a highly significant increase($p<0.001$) in waist circumference , fasting plasma glucose levels, BMI, Serum TG levels and blood pressure of cases and respectively decreased levels of HDL cholesterol. 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 $p = 0.114$. About 70 % of cases had raised BMI above 30 kg/m^2.

Elevated levels of plasma fasting glucose levels were seen in 80% of the cases and were significantly correlated with morning cortisol levels with $p<0.05$ and the mean levels of fasting glucose was 120.04± 22.36 mg/dl. These patients had mean cortisol levels of 393.15 ng/ml much above the normal serum levels indicating the trend and positive relationship of insulin resistance with cortisol levels in these patients. These results were in concordance with the findings of Philips et al. And Wallerius et al.[10,11]

The Triglyceride(TG) levels of cases were significaltly raised with mean values 174.56 ±37.39mg/dl. Mean serum HDL levels were 40.26±9.26 mg/dl and were associated with rise in cortisol levels with p value <0.05. Halpern et al also mentioned in their studies the association of body lipids with cortisol and MetS in the same manner which is already mentioned earlier.[12]

Both systolic and diastolic blood pressure was raised in about 38 patients and mostly had high cortisol with the mean cortisol levels of 454.04 ng/ml. In terms history of comorbid conditions in family 54%(n=27) had history of diabetes , 34 %(n=17) of hypertension and 48%(n=24) had history of metabolic syndrome in their families.

Table 2. Mean values of different parameters measured

	Cases		Controls	
	Mean	±SD	Mean	±SD
Age	52.42	7.52	51.02	8.06
BMI	33.43	2.68	24.33	1.83
Waist Circumference	102.68	6.92	87.60	7.53
Fasting Glucose	120.04	22.36	90.88	10.22
S. Cortisol	459.49	358.34	167.34	110.99
BP (Systolic)	139.34	11.83	124.20	10.20
BP (Diastolic)	84.24	8.37	79.08	5.65
S. Triglyceride	174.56	37.39	134.22	15.06
HDL	40.84	8.97	50.48	5.08

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 and serum HDL levels. Thus serum cortisol levels trends to increase with rise in fasting glucose levels and fall of serum HDL levels.

The pearson correlation factor for Cortisol and fasting glucose was 0.344 with p value =0.014 (Fig. 2) and the same for HDL was -0.290 with p value of 0.041 .(Fig.3)

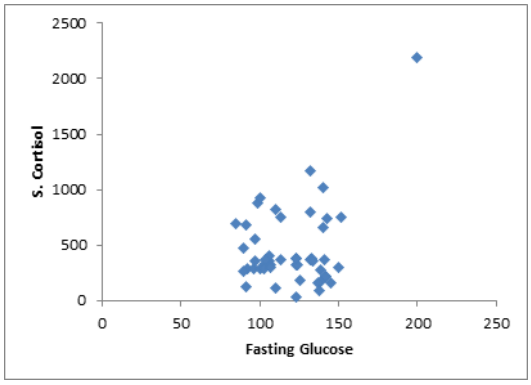

Fig.2. Correlation of serum cortisol and fasting glucose levels

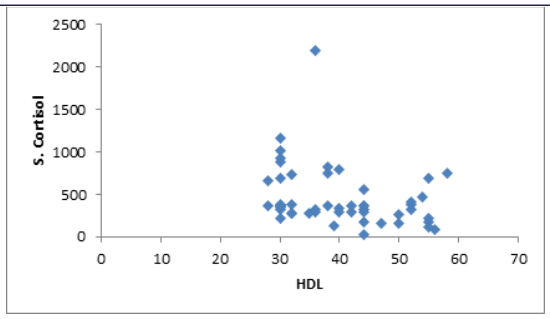

Fig3. Correlation of serum cortisol levels with HDl levels

None of the other parameters showed any positive correlation to the morning serum cortisol levels individually thus depicting a strong cause- effect relationship of serum cortisol in the pathogenesis of the insulin resistance and dyslipidemia in the patients of MetS.

Table 3: Serum cortisol levels correlated with different features of metabolic syndrome

S. Cortisol Vs	Pearson's Correlation	p-value
BMI	0.031	0.829
Waist Circumference	0.226	0.114
Fasting Glucose	0.344	0.014
HDL	-0.290	0.041
S.Triglyceride	-0.055	0.707
BP (Sys)	0.005	0.971
BP (Dia)	0.084	0.562

DISCUSSION

Metabolic syndrome(MetS) is a cluster of abnormalities that predispose to the development of diabetes, atherosclerosis, and CVD, although many patients with MetS may already have diabetes and/or vascular disease. Therefore, it is important to always specify whether MetS is or is not accompanied by diabetes. Because MetS shares many characteristics of Cushing's syndrome (CS), it was proposed that the pathogenesis of MetS and central obesity involves prolonged and excessive glucocorticoid exposure thus Central obesity and insulin resistance are acknowledged as important causative factors. [4,9]

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 [13]. We also found positive correlation between BMI and serum cortisol levels thus suspecting a direct cause-effect relationship and the prevalence of metabolic syndrome was also higher in elderly age group.

Most of the patients resided in urban dwellings (72%) and majority of the female subjects were housewives(36%), and followed by businessman(30%).Thus it can be deducted from this finding that the urban population is more prone to all the risk factors of the metabolic syndrome due to the sedentary lifestyle in urban areas.

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 . The conflicting results with respect to gender effect may partly be explained by the application of different definitions for the metabolic syndrome.

Our observation of higher morning plasma cortisol in obese subjects (80%) with mean values of 459.49 ng/ml is in agreement with the reports of Weigensberg et al who observed higher morning serum cortisol in overweight Latino youths with MS. Similarly after reviewing almost all the previous literature we came to a conclusion that there is a state of hypercortisolism in these patiens as supported in 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 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 outmcome 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. These data suggest that despite the lack of relationship with waist circumference, association with dyslipidemia and central adiposity may account, in part, for the relationship between cortisol and MetS. The metabolic clearance of cortisol is increased in obese individuals which could obscure the underlying positive association between plasma cortisol and the features of MS.

The likelihood of disassociation between cortisol and BMI is also seen in our results which is in concordance with the findings of Praveen et al[16] and many others as visceral adiposity is mainly responsible for metabolic syndrome and cortisol rise promotes central adiposity. The cause–effect relationship of obesity and cortisol is not clearly known but may be due to an altered HPA axis in obesity, resulting in a blunted diurnal variation in cortisol levels.

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(1999) and Wallerius et al(2003). [11,17]. A significant association of syndrome with increased TG and decreased HDL levels was also in favour of atherogenic dyslipidemia which is a major cause of morbidity and mortality among this subgroup of population.

As noted previously that many of the western and Asian studies collaborate to the fact that central adiposity and insulin resistance are the key pathophysiological changes linked to the degree of hypercortisolism in obese patients the results indicated that the cortisol-induced insulin resistance in man is due to a decrease in both hepatic and extrahepatic sensitivity to insulin.

There was no significant association noted between morning cortisol levels and other parameters of MetS apart from fasting glucose and HDL levels which corroborated with the works of Fraser et al. Although there was positive correlation noted with all the other parameters but not to significance when compared with cortisol individually.

This could be partly explained by the fact that the results of our study were in the range of 240-500 ng/ml 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 increased TG levels. Also the cross sectional nature of study might be the limiting factor for the non-association of rest of the features of MS.

Our results were more in accordance with the pioneer studies conducted by Fraser and colleagues who also found no correlation between cortisol and blood pressure but with HDL levels. Likely explanation being the the pattern of cortisol metabolism 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.

Although cortisol may directly influence blood pressure through its effects on salt and water retention or vascular smooth muscle tone, it has been suggested that the relationship between cortisol and blood pressure in MS 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.

All our subjects had normal liver biochemistry; however, we did not obtain information with respect to hepatic triglyceride content despite raised serum triglyceride content. Recent data have suggested that increased hepatic triglyceride content is associated with decreased 11β - HSD1 activity [15].

The novelty and strength of the study is that the effect of additive number of features of MetS with the levels of cortisol was analysed and correlated. Thus serum cortisol levels are significantly raised in patients of metabolic syndrome and also correlation factor increases with increasing the number of features of MetS in any patient. We can say now that cortisol bears more strong relationship with the syndrome as a whole than with individual components. Chronic exposure to slight cortisol excess may have clinical implications associated with a state of insulin resistance and dyslipidemia. These findings suggest that cortisol may be relevant to certain of the individual features of MS, but not to others, and that this relationship is mostly due to insulin resistance.

The main limitation of the present study is that it is a single morning cortisol measurement and that too of a small subgroup of patients. 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

Central adiposity, hepatic steatosis, dyslipidemia, muscle wasting, pancreatic beta-cell dysfunction, and glucose intolerance are features of chronic glucocorticoid excess. Many of these features are also observed in patients with prediabetes and metabolic syndrome (MS). There is speculation on the possibility of subtle abnormalities of cortisol biosynthesis/metabolism in the pathogenesis of MS. Our report has documented higher plasma cortisol in MS patients than in healthy subjects. However, the relationship between different MS components and serum cortisol is not consistent.

To summarize our findings we observed a significant raised levels of serum cortisol in out obese subjects of metabolic syndrome and when associated with individual parameter we found positive correlation with fasting glucose levels and negative with serum HDL levels. Thus rasied cortisol levels are definitely linked to the altered HPA axis and insulin resistance in these subgroup of population with no definite cause-effect relationship. In short, we observed additive effects of dyslipidemia and fasting plasma glucose on morning plasma cortisol and opening the spectrum for further therapeutic aspects in these patients.

REFERENCES

1. Azadbakht L., Mirmiran P., Esmaillzageh A., Azizi F. Dairy consumptionis inversely associated with the prevalence the metabolic syndrome in Tehranian adults. Am J clin Nutr 2005; 82: 523-530
2. Furukawa, Shigetada, et al. “Increased oxidative stress in obesity and its impact on metabolic syndrome.” Journal of Clinical Investigation 2004;114: 1752-1761.
3. Levitt NS, Lambert EV, Woods D, Hales CN, Andrew R, Seckl JR Impaired glucose tolerance and elevated blood pressure in low birth weight, nonobese, young south asian adults: early programming of cortisol axis. J Clin Endocrinol Metab 2000;85:4611-8
4. Anderson PJ, Critchley JAJH, Chan JCN et al. Factor analysis of the metabolic syndrome: obesity vs insulin resistance as the central abnormality. International Journal of Obesity 2001;25:1782
5. Filipovsky J, Ducimetiere P, Eschwege E, Richard JL, Rosselin G, Claude JR The relationship of blood pressure with glucose, insulin, heart rate, free fatty acids and plasma cortisol levels ac- cording to degree of obesity in middle-aged men. J Hypertens 1996;14:229-35.
6. Levitt NS, Lambert EV, Woods D, Hales CN, Andrew R, Seckl JR Impaired glucose tolerance and elevated blood pressure in low birth weight, nonobese, young south asian adults: early programming of cortisol axis. J Clin Endocrinol Metab 2000;85:4611-8
7. Li, Chaoyang, et al. “Association of testosterone and sex hormone–binding globulin with metabolic syndrome and insulin resistance in men.” Diabetes Care 2010;33.7: 1618-1624.
8. Arnaldi, Giorgio, et al. “Pathophysiology of dyslipidemia in Cushing’s syndrome.” Neuroendocrinology 2009;92: 86-90.
9. Anagnostis P, Athyros VG, Tziomalos K, Karagiannis A, Mikhailidis DP. Clinical review: The pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. J Clin Endocrinol Metab. 2009;94(8): 2692–2701.
10. Phillips DI, Barker DJ, Fall CH, et al. Elevated plasma cortisol concentrations: a link between low birth weight and the insulin resistance syndrome? J Clin Endocrinol Metab. 1998;83(3):757–760.
11. Wallerius S, Rosmond R, Ljung T, et al. Rise in morning saliva cortisol is associated with abdominal obesity in men: a preliminary report. J Endocrinol Invest, 2003;26:616–19.
12. Halpern, Alfredo, et al. “Metabolic syndrome, dyslipidemia, hypertension and type 2 diabetes in youth: from diagnosis to treatment.” Diabetology & metabolic syndrome 2010;2:55.
13. Misra, Anoop, and Lokesh Khurana. “The metabolic syndrome in South Asians: epidemiology, determinants, and prevention.” Metabolic syndrome and related disorders 2009;7: 497-514.
14. Ward AM, Fall CH, Stein CE, et al. Cortisol and the metabolic syndrome in South Asians. Clin Endocrinol (Oxf). 2003;58(4):500–505.
15. Valsamakis, Georgios, et al. “11β-hydroxysteroid dehydrogenase type 1 activity in lean and obese males with type 2 diabetes mellitus.” The Journal of Clinical Endocrinology & Metabolism 2004;89: 4755-4761.
16. Praveen, Edavan P., et al. “Morning cortisol is lower in obese individuals with normal glucose tolerance.” Diabetes, metabolic syndrome and obesity: targets and therapy 2011;4: 347.
17. Fraser, Robert, et al. “Cortisol effects on body mass, blood pressure, and cholesterol in the general population.” Hypertension 1999;33: 1364-1368.