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ORIGINAL ARTICLE

Body mass index and its effect on serum cortisol level

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Abstract

Introduction: Cortisol measurement is indicated in suspected over or underproduction of cortisol by the adrenal cortex. The finding of low cortisol can create concern and initiate further investigations for the exclusion of adrenal insufficiency. Cushing's syndrome is frequently included in the differential diagnosis of obesity. Some literature describes reduced serum cortisol levels in obesity, however, this is not a well-recognized phenomenon.

Aim: The aim of this study was to determine the relationship between body mass index (BMI) and serum cortisol levels.

Subjects, Materials and Methods: Seventy healthy participants agreed to take part in the study. The anthropometric measurements (weight, height, and waist and hip circumferences) were done. Exclusion criteria include those with a history of adrenal/pituitary disease or medications altering cortisol level. The basal cortisol (BC) sample was taken at 8 a.m. immediately before administration of an intravenous bolus injection of 250 μg adrenocorticotropic hormone (ACTH). BMI categories were defined as normal and high if BMI was 18.5-24.99 kg/m^2 and ≥ 25 kg/m^2, respectively.

Results: Forty (57.1%) participants had normal BMI while 30 (42.9%) participants had BMI ≥ 25 kg/m^2 (P = 0.053). The mean BC level was lower in participants with BMI ≥ 25 kg/m^2 but not significant. There was a negative correlation between BMI and BC level (r = −0.205, P = 0.88) while a positive correlation existed between stimulated cortisol level and BMI (r = 0.009, P = 0.944).

Conclusion: Persons with BMI above 25 kg/m^2 had lower BC level though not statistically significant, the trend was noticed. Subjecting people whose BMI is above 25 kg/m^2 to further stimulation with ACTH because of low BC is not advised because their response to ACTH stimulation was similar to those who have normal BMI.

Key words: Adrenal gland, adrenocorticotropic hormone, body mass index, cortisol, obesity

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Introduction

The adrenal cortex synthesizes cortisol which is the most important glucocorticoid. In the serum, over 90% of cortisol is bound to a carrier protein (Cortisol binding globulin, or transcortin).[1] Cortisol measurement is indicated in suspected over or underproduction of cortisol by the adrenal cortex.[1] The finding of low cortisol can create concern and initiate further investigations for the exclusion of adrenal insufficiency. The gold standard investigation of adrenal insufficiency is the Synacthen stimulation test, however, this test confers small but definite risks for the patient.[1] Cushing's syndrome is frequently included in the differential diagnosis of obesity and patients with abdominal obesity have many features in common with patients with authentic Cushing's. However, Cushing's syndrome due to excessive endogenous corticosteroids is rare. In Cushing's syndrome, serum cortisol level is elevated, and obesity is one of its presentations.[1,2] Some literature describes reduced serum cortisol levels in obesity, however, this is not a well-recognized phenomenon.[3,4] Understanding factors which may result in a lowered serum cortisol is, therefore, important in interpreting results correctly and may help avoid unnecessary further testing. The aim of this study was to determine the relationship between body mass index (BMI) and serum cortisol levels.

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Subjects, Materials and Methods

Seventy healthy participants agreed to take part in the study. Informed consent was obtained from all subjects, and the study was approved by the Ethics and Research Committee. A data collection sheet, filled by the investigator, was used to obtain information from the subjects. Information obtained from each participant included the biodata, presence of weakness, fatigue, weight loss, a history of glucocorticoid use. The anthropometric measurements (weight, height, and waist and hip circumferences) were done. BMI was calculated using weight (kg) divided by square of the height (m). BMI categories were defined as normal and high if BMI was 18.5-24.9 kg/m^2 and ≥25 kg/m^2 respectively.[5]

Exclusion criteria include those with a history of adrenal/pituitary disease or medications altering cortisol level. These medications included Oestrogens (Oral contraceptive pill, Oestrogen implant); inhaled steroids (Becotide, Flixotide, Serotide); injected steroids (for arthritis and fasciitis); oral steroids (Prednisolone, Cortisone, Dexamethasone and Methylprednisolone); topical steroids (for skin conditions) and herbal medications. Persons who have had recent treatment with ketoconazole were also excluded from the study. Pregnant women, children, and shift workers were also excluded.

The participants were divided into batches of 5 subjects per day. The subjects were admitted overnight to eliminate the effect of stress on cortisol level. A 21-G canulla was inserted into a cubital vein and kept patent with heparinized saline. The basal cortisol (BC) sample was taken at 8 a.m. the following morning. Synacthen® test was performed as follows: A baseline blood sample for cortisol, fasting plasma glucose, full blood counts, and electrolytes were collected immediately before administration of adrenocorticotropic hormone (ACTH). ACTH testing was conducted between 08.00 and 9.00 h. After the samples had been taken, the subject received an intravenous bolus injection of 250 μg ACTH (Alliance Pharmaceuticals Ltd., Chippenham, Wiltshire SN15 2BB, England). After the bolus was administered, the blood sample was drawn for cortisol level at 30 min. The samples were separated and transported on an ice slab to the laboratory where the plasma were stored at −20°°C until assayed. Normal BMI was defined as BMI of 18.5-24.9 kg/m^2 and high BMI is defined as BMI ≥ 25 kg/m^2.[5] Normal waist circumference (WC) for female was defined as WC < 88 cm; while for male it was defined as WC < 102 cm.[5]

Assay

Serum cortisol levels were determined by an ELISA technique using the Diagnostic Automation Inc., cortisol assay method. It is a competitive immunoenzymatic colorimetric method for quantitative determination of cortisol concentration in serum. The respective intraassay and interassay coefficients of variation percentage of 4.5 and 3.1% for serum cortisol were within the acceptable range of variation.

Statistical analysis

Calculations and analysis were done using the SPSS 19.0 software (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp). Continuous variables were expressed as means ± standard deviation. Student's *t*-test was used for the comparison of means between two groups. Chi-square was used for comparison of proportions between two groups. Pearson's correlation coefficient analysis was used to determine associations between BMI and cortisol level. The level of statistical significance was taken as $P < 0.05$.

Results

A summary of the demographic parameters is as shown in Table 1. The BMI is significantly lower in males compared with the female participants. The BC and the stimulated cortisol (SC) levels, though higher in the males, were comparable in both genders. Forty (57.1%) participants (24 males and 16 females), had normal BMI (18.5-24.9 kg/m^2) while 30 (42.9%) participants (11 males and 19 females) had BMI ≥25 kg/m^2 ($\chi^2 = 3.733$, $P = 0.053$). The mean BC level was lower in participants with BMI greater or equal to 25 kg/m^2 but not significant [Table 2]. There was a negative correlation between BMI and BC level ($r = -0.205$, $P = 0.88$) while a positive correlation existed between SC level and BMI ($r = 0.009$, $P = 0.944$). The mean BC level was lower in female participants with high WC (>88 cm) [Table 3] while all the male participants had normal

Table 1: Demographic data of the study participants

Parameter	Participants (*n*=70)	Male (*n*=35)	Female (*n*=35)	*P*
Age (years)	38.09±12.52	37.34±12.35	38.83±12.84	0.623
BMI (kg/m^2)	24.45±3.30	23.63±2.95*	25.26±3.46	0.037
WC (cm)	82.19±9.31	81.43±7.63	82.94±10.79	0.500
SBP (mmHg)	119.39±12.21	118.74±12.50	120.03±12.07	0.663
DBP (mmHg)	76.24±9.63	76.11±10.23	76.37±9.14	0.912
FPG (mmol/L)	4.85±0.64	4.84±0.72	4.87±0.56	0.830
BC (nmol/L)	262.48±105.57	281.82±97.53	243.14±111.07	0.126
SC (nmol/L)	917.17±268.97	925.13±276.19	909.20±265.35	0.806

BMI=Body mass index, WC=Waist circumference, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, FPG=Fasting plasma glucose, BC=Basal cortisol, SC=Stimulated cortisol. *P<0.05

Table 2: Serum cortisol levels and BMI category

Cortisol level	BMI category		*P*
	Normal	High	
Basal (nmol/L)	279.35±119.04	239.99±80.91	0.123
Stimulated (nmol/L)	900.06±299.09	939.98±225.58	0.543

Normal BMI=18.5-24.9 kg/m^2, High BMI=≥25 kg/m^2. BMI=Body mass index

Table 3: Serum cortisol levels and a WC category in female participants

Cortisol level	WC category		*P*
	Normal	High	
Basal (nmol/L)	244.21±130.64	241.54±77.50	0.946
Stimulated (nmol/L)	918.00±283.48	896.01±245.35	0.814

Normal WC in females=<88 cm, High WC=≥88 cm.
WC=Waist circumference

Table 4: Correlations matrix for male participants

Anthropometric measurement	WC	BC	SC
WC			
Pearson correlation	1	−0.095	0.109
Significant (two-tailed)		0.589	0.534
N	35	35	35
BC			
Pearson correlation	−0.095	1	0.275
Significant (two-tailed)	0.589		0.110
N	35	35	35
SC			
Pearson correlation	0.109	0.275	1
Significant (two-tailed)	0.534	0.110	
N	35	35	35

WC=Waist circumference, BC=Basal cortisol, SC=Stimulated cortisol

Table 5: Correlations matrix for female participants

Anthropometric measurement	WC	BC	SC
WC			
Pearson correlation	1	−0.215	0.019
Significant (two-tailed)		0.216	0.914
N	35	35	35
BC			
Pearson correlation	−0.215	1	0.276
Significant (two-tailed)	0.216		0.109
N	35	35	35
SC			
Pearson correlation	0.019	0.276	1
Significant (two-tailed)	0.914	0.109	
N	35	35	35

WC=Waist circumference, BC=Basal cortisol, SC=Stimulated cortisol

WC with mean basal and SC levels of 281.82 ± 97.53 and 925.13 ± 276.19 mmol/L respectively. There was an overall negative correlation between WC and BC level ($r = -0.179$, $P = 0.137$) while a positive correlation also existed between WC and the SC level ($r = 0.053$, $P = 0.661$). This correlation was maintained in both male and female participants as shown in the correlation matrices in Tables 4 and 5, respectively.

Discussion

Serum cortisol is a commonly requested test. It may be requested in the setting of investigation of possible adrenal insufficiency as a first-line test, or requested less appropriately as first-line investigation of possible Cushing syndrome.[6] In either setting, the finding of low or borderline low cortisol may generate concern and further investigations. Understanding factors which influence serum cortisol and which may result in a reduction in cortisol are, therefore, important. The serum concentration of cortisol is generally normal in obesity, however, some literature suggests that obese subjects may have lower than expected cortisol levels,[3,4,7] while some several studies over the last several years have tried to demonstrate the opposite.[8-10] The measurement of early morning cortisol is currently used as a first-line test for the assessment of adrenal insufficiency.[1,6] Assessing 08:00-09:00 h cortisol levels is less expensive, more practical and presents minimal risk when compared to diagnostic tests such as the Synacthen stimulation test. We observed from this study that the female had a higher BMI. Apart from this, the participants were similar in all parameters. Findings from this study suggest that assessing 08:00-09:00 h cortisol levels as a method of screening may not be accurate for an obese population. BC was lower in people with high BMI than in people with normal BMI. Even though this was not at a significant level as shown in other studies,[4] this trend was however noticed in this study. The sample size in this study may explain why this was so. Our observation of lower plasma cortisol in subjects with BMI ≥ 25 kg/m^2 is in agreement with that of Travison *et al.* who observed lower plasma cortisol in subjects with BMI ≥ 25 kg/m^2 than in subjects with normal BMI.[4] Most of the studies reported higher BC level in overweight and obese subjects.[4,11,12] This study raises important questions about the assessment of morning cortisol in obese subjects. More obese patients could be subjected to follow-up testing in order to exclude adrenal insufficiency.

The same trend was noticed when the WC was compared with the various timed cortisol levels. Female participants with WC > 88 cm had lower BC level compared with those who had WC < 88 cm. All the males in this study had normal WC. There was a negative correlation between WC circumference and BC though, not at significant level in both male and female participants. This is also similar to what was reported in some studies.[7,13,14] Women with increased WC have been found to have lower 24-h mean plasma cortisol concentrations due to increased hormone clearance not adequately compensated by an increased cortisol production rate.[11]

We went a step further by stimulating the adrenal of subjects with normal and increase BMI with ACTH. Subjects with BMI ≥ 25 kg/m^2 had higher cortisol level after stimulation compared with those with normal BMI. The cortisol level post ACTH stimulation in those with increased WC was comparable to those with normal WC. A cause–effect relationship of obesity and cortisol is not clearly known. This may be due to an altered hypothalamic-pituitary-adrenal axis in obesity, resulting in a blunted diurnal variation

in cortisol levels, with lower morning cortisol and higher evening cortisol.[15] Another explanation of lower morning cortisol could be the enhanced metabolic clearance of cortisol in obesity, which is compensated for only partly by enhanced cortisol secretion.[16]

Increased subject numbers across a wider BMI range may help to confirm the findings of this study. Further data would also be helpful to determine an obesity specific cortisol reference range.

Conclusion

We have shown that persons with BMI above 25 kg/m^2 had lower BC level. Even though it is not significant statistically, the trend was noticed. Subjecting people whose BMI is above 25 kg/m^2 to further stimulation with ACTH because of low BC is not advised because their response to ACTH stimulation is similar to those who has normal BMI.

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