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Research Article

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ARE PITUITARY FUNCTIONS DIFFERENT IN OBESE PATIENTS ACCORDING TO BODY MASS INDEX CLASSES?

Neslihan Çuhacı Seyrek[1]

[1]Department of Endocrinology and Metabolism, Ankara Yildirim Beyazit University, Faculty of Medicine, Ankara

Correspondence:
Neslihan Çuhacı Seyrek (e-mail: neslihan_cuhaci@yahoo.com)

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Ankara Yıldırım Beyazıt University Faculty of Medicine
Department of Family Medicine

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Abstract

Objectives: In this study, we aimed to evaluate whether there is a difference in the pituitary functions in obese patients according to the different body mass index (BMI) classes

Materials and Methods: We retrospectively evaluated 192 patients with obesity. According to the obesity degree, patients were divided into class I (BMI;30.0-34.9 kg/m^2), class II (BMI; 35.0-39.9 kg/m^2) or class III (BMI; ≥40 kg/m^2) obesity. The demographic data of the patients (sex, age), thyroid function tests, estrogen (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH), insulin-like growth factor-I (IGF-I), total and free testosterone, cortisol, adrenocorticotrophic hormone (ACTH) levels were measured. Also, 24-hour urine-free cortisol levels and a 1 mg dexamethasone suppression test were performed.

Results: Total of the 192 patients, 44 (22.92%) were male, 148 (77.08%) were female. According to BMI classes, 12 (6.25%) patients were in class I, 38 (19.79%) patients were in class II and 142 (73.96%) patients were in class III obesity. No significant difference was found between the groups in hormonal parameters except the IGF-I level. 1 mg dexamethasone suppression test was suppressed in all patients.

Conclusion: In our study, we found that there was no difference in pituitary functions according to obesity classes, except for the IGF-I level. Further studies are needed to investigate these functions in different classes of obesity.

Keywords: Obesity, body mass index, pituitary functions, insulin-like growth factor-I.

Introduction

The prevalence of obesity, especially severe obesity, is increasing in a threatening state worldwide.[1] Obesity is associated with some disorders such as type 2 diabetes mellitus (DM), dyslipidemia, hypertension (HT), cardiovascular and respiratory system diseases, and some cancer types. Also, it can lead to some endocrine dysfunctions, and all endocrine organs/systems can be affected directly/indirectly due to excessive fat content.[2] Increase in adipocyte size leads to inflammation, cytokine production, and release of adipokines. These changes play an important role in the pathophysiology of endocrine dysregulation, which is seen in obesity.[3] Therefore, obesity is associated with adaptive and sensitive changes that lead to various biochemical and clinical changes and are tightly regulated by the feedback loops of these systems.[4] In addition, obesity is thought to be both cause and a consequence of endocrine dysfunction.[5,6] This bidirectional relationship is complex and not fully understood.[6,7]

In our study, we aimed to evaluate whether there is a difference in the pituitary functions in obese patients according to the different body mass index (BMI) classes.

Materials and Methods

We retrospectively evaluated the patients with a body mass index ≥30 kg/m^2 and who have admitted to our endocrinology clinic between May 2019 and March 2020 for a workup of obesity. Demographic data (sex, age), medical history, drugs they used and the laboratory data of the patients were evaluated from medical records.

Patients who have <18 years old have previously known or unknown thyroid dysfunction, taking thyroid-related medication, use drugs that affect thyroid functions and pituitary functions, have a previous history of head and neck radiation, history of pituitary dysfunction, bariatric surgery, pregnancy and chronic disease (DM, renal insufficiency, adrenal insufficiency, or any other systemic disease), were excluded from the study. Cushing's syndrome is also excluded.

Body measurements were performed on fasting patients wearing light underwear. Weight and height were measured to the nearest 0.10 kg and 0.10 cm, respectively, and BMI was expressed as body mass (kg)/height (m^2). Body mass index ≥ 30 kg/m^2 is used as obesity criteria which are defined by World Health Organization (WHO). Obesity is classified as class I (BMI;30.0-34.9 kg/m^2), class II (BMI; 35.0-39.9 kg/m^2) and class III obesity (BMI ≥40 kg/m^2).

All participants had taken fasting blood samples in the early morning in order to evaluate the thyroid function and pituitary function tests. Serum thyrotrophin (TSH), free triiodothyronine (fT3), and free thyroxine (fT4)

levels were measured by chemiluminescence methods. The normal ranges for TSH, fT3, and fT4 were 0.55–4.78 mU/L, 2.30–4.20 ng/L, and 0.89–1.76 ng/dl, respectively. Serum estrogen (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH), insulin-like growth factor-I (IGF-I), total testosterone, cortisol, adrenocorticotrophic hormone (ACTH), were measured by chemiluminescent immunoassays (CLIA), free testosterone were measured by radioimmunoassay (RIA). Also, 24-hour urine-free cortisol levels and a 1 mg dexamethasone suppression test were performed.

Statistical analysis

All statistical analyses were performed with the SPSS 15.0 software package (SPSS Inc., Chicago, IL, USA). Descriptive analyses were presented using mean ± standard deviation (SD) for normally distributed variables, median and range (min-max) for non-normally distributed variables and as number of cases and (%) for nominal variables. The Chi-square test was used to investigate the difference between the groups regarding the categorical variables. The comparisons between groups were performed by the ANOVA for parametric variables and the Kruskal Wallis test for non-parametric variables to determine the best predictor(s). A p-value less than 0.05 was accepted as statistically significant.

Results

We retrospectively evaluated 192 patients with obesity. The mean age of the patients was 36.94±11.18 years. Total of the 192 patients, 44 (22.92%) were male, and 148 (77.08%) were female. The mean weight, height and BMI of the patients were 120.79±20.39 kg, 165.20±9.61 cm and 44.13±6.54, respectively. According to BMI classes, 12 (6.25%) patients were in class I, 38 (19.79%) patients were in class II and 142 (73.96%) patients were in class III obesity. According to the obesity classes, the number and percentage of female/male patients are shown in Table 1. There was no significant difference between the groups in terms of gender. The mean age of the patients was similar between the groups. No significant difference was found between the groups in hormonal parameters except IGF-I level (table 1). Also, in female patients, E2 levels were not different between the groups. Additionally, 1 mg dexamethasone suppression test was suppressed in all patients.

Table 1. Demographic data and the results of the patients according to the BMI classes

	Class I obesity (BMI; 30.0-34.9 kg/m²)	**Class II obesity (BMI; 35.0-39.9 kg/m²)**	**Class III obesity (BMI ≥40 kg/m²)**	**p-value**
Number of patients (n)/(%)	12 (6.25)	38 (19.79)	142 (73.96)	
Female/Male (number/percentage)	11 (91.67%) / 1 (8.33%)	25 (65.79%)/ 13 (34.21%)	112 (78.87%)/ 30 (%21.13)	0.108
Age (years)	36±13.20	38.34±11.75	36.64±10.90	0.680
Height (cm)	167.91±6.41	166.83±10.34	164.53±9.60	0.261
Weight (kg)	93.42±7.72	105.97±13.55	127.06±18.64	<0.001
BMI (kg/m²)	33.09±1.20	37.89±1.32	46.74±5.45	<0.001
fT3	3.21±0.46	3.32±0.57	3.28±0.49	0.593
fT4	1.06±0.11	1.18±0.11	1.18±0.29	0.050
TSH	2.45±1.26	2.02±0.84	2.26±0.87	0.363
LH (median; min-max)	4.35 (1.80-7.00)	4 (1.39-53.20)	5.40 (0.40-42.10)	0.081
FSH (median; min-max)	4.65 (2.60-9.60)	5.80 (1.90-122.20)	6.25 (1.20-82.20)	0.296
Total testosterone median (min-max)	24.00 (12-288)	22 (0.15-402.00)	33.00 (0.10-436)	0.318
Free testosterone median (min-max)	1.57 (0.94-16.21)	2.68 (0.76-15.05)	2.96 (0.43-15.83)	0.201
GH (median; min-max)	0.45 (0.05-1.20)	0.10 (0.05-5.20)	0.10 (4.50-114)	0.382
IGF-1 (median; min-max)	156 (126-184)	130 (53-981)	112 (15-981)	**0.034**
Cortisol	10.66±3.39	13.93±5.24	13.06±4.58	0.201
ACTH (median; min-max)	16.60 (6.30-39.60)	20.70 (6.70-84.40)	20.70 (4.50-114)	0.658
24-hour urine-free cortisol (median; min-max)	12.02 (8.94-21.22)	15.21 (4.47-159.14)	16.26 (3.08-95.30)	0.404

(BMI; body mass index, fT3; free triiodothyronine, fT4; free thyroxine, TSH; thyrotrophin, LH; luteinizing hormone, FSH; follicle stimulating hormone, GH; growth hormone, IGF-I; insulin-like growth factor-I, ACTH; adrenocorticotrophic hormone)

Discussion

GH and IGF-I have a crucial role in the regulation of metabolism and maintenance of body composition.[2] GH has both anabolic and catabolic effects on different tissues. It stimulates lipolysis in adipose tissue and protein

synthesis in muscle tissue. Therefore, reduced GH levels prone to weight gain, abdominal fat deposition and decreased muscle mass.[2] An inverse relationship was found between GH and BMI/visceral obesity regardless of age and gender.[4] In adult patients with obesity, GH secretion is blunted compared to lean individuals. It is found that both basal and stimulated GH levels have been reduced in patients with morbid obesity.[8] Studies related to IGF-I in obesity reported discordance results, but most of these studies showed decreased IGF-I levels.[9-12] These differences may be due to; methodological differences in measuring the IGF-I levels, diurnal variations of IGF-I and IGFBP-1, fasting or other hour-to-hour factors affecting the free IGF-I levels.[2] Another possible explanation may be the type of fat distribution since it has been demonstrated that visceral fat mass, rather than adiposity, is inversely correlated with IGF-I levels. In our study, we found that IGF-I levels decreased as the BMI classes increased.

There is a bilateral relationship between obesity and thyroid functions. While the thyroid gland is involved in the control of thermogenesis and appetite, its dysfunction is associated with secondary changes in body weight and composition.[13] Obesity is associated with modifications in the hypothalamus-pituitary-thyroid (HPT) axis, which leads to changes in thyroid functions.[2] The underlying mechanisms of these changes are not fully understood, and several hypotheses are suggested.[2] One of the most accepted explanations is that hyperthyrotropinaemia may be an adaptive response to increase thermogenesis and energy expenditure and minimize weight gain.[13] But, it has been suggested that if the increase in TSH levels was the main issue of this response, an increase in serum thyroid hormones would also be expected.[14] Furthermore, peripheral mechanisms can play a role in the changes in the HPT axis in obesity. In relation to that, Nannipieri et al. demonstrated that weight loss is associated with increased thyroid hormone receptors in subcutan fat tissue.[15] There is discordance between studies on thyroid hormone levels in patients with obesity. In the Danish DanThyr 1997–1998 population cohort, it is demonstrated that BMI is negatively correlated with fT4, but no correlation is found with total T3 and fT3 levels.[16] While later studies showed similar results,[17,18] other studies found opposite results or no relation.[19,20] Mele et al.,[14] showed that as the BMI class increased, there was an increase in TSH levels in women and a decrease in fT4 levels in men. In our study, we did not find any difference between fT3,fT4 and TSH levels and obesity classes. But fT4 levels were higher in class II and III obesity than class I obesity group (p=0.050).

There is a complex relationship between obesity and the hypothalamus-pituitary-adrenal axis (HPA). Steroid dysregulation in obesity may be due to a physiological increase in the HPA axis, changes in cortisol binding globulin (CBG), and increased activation of cortisol through the 11-hydroxy steroid dehydrogenase type 1.[4] Activation of the HPA axis in obesity leads to an increase in corticotropin-releasing hormone (CRH) and cortisol.[4] Most of the serum cortisol is bounded to CBG; only approximately 10% of cortisol is free and biologically active.[4] Hyperinsulinemia and obesity inhibit CBG and result in increased free cortisol levels.[4] But serum total cortisol levels are usually in normal ranges. This is probably due to the suppression of elevated

cortisol levels by negative feedback and, finally, inhibition of ACTH and CRH release. However, urine-free cortisol levels are often mildly elevated in these conditions.[4] When evaluating the obese patient, it is important not to miss Cushing syndrome (CS). Some conditions such as obesity, pregnancy, chronic alcoholism and severe depression are a spectrum of physiological to pathological states of hypercortisolemia and makes both the clinical and biochemical diagnosis more challenging.[4] In these conditions, investigations sometimes give false positive results, such as mildly elevated free urine cortisol levels and rarely a lack of cortisol suppression to dexamethasone. [21] In our study, there was no significant difference between BMI classes and cortisol and ACTH levels, as well as 24-hour urine-free cortisol. Also, the 1 mg dexamethasone suppression test was suppressed in all patients.

The effect of obesity on the gonadal axis shows a sexual dimorphism, usually accepted as hypogonadism in men, but hyperandrogenism in women affects fertility in both sexes.[2] Testosterone and estrogen have a crucial role in the maintenance of skeletal integrity, muscle mass, decreasing fat, as well as maintenance of sexual functions and several risk factors related to metabolic and cardiovascular diseases.[4] Obesity is a risk factor for hypogonadism by affecting the release of gonadotropin-releasing hormone (GnRH) and changing the luteinizing hormone pulse amplitude.[4,22] Adipose tissue worsens testosterone deficiency by increasing the aromatase enzyme, which converts the free testosterone to estrogen.[4,22] Also, as a result of negative feedback of a change in testosterone-estrogen ratio, decrease in the GnRH secretion from the hypothalamus, which later changes the LH amplitude and finally results in low testosterone levels.[22] It is often difficult to interpret the serum testosterone levels in patients with obesity. This is because of the multiple mechanisms, including; low total testosterone with normal free testosterone levels, low sex hormone binding globulin, and low free testosterone secondary to low GnRH levels.[4] In general, there is a negative correlation between BMI and free testosterone levels, and patients with obesity appear to have lower total testosterone levels compared with normal-weight men of similar age.[23] These biochemical parameters often improve with weight loss.[23] In women with obesity hyperandrogenism is common and is often associated with hyperinsulinemia and infertility similar to features seen in polycystic ovarian syndrome (PCOS). The aromatase enzyme found in adipose tissue increase the conversion of androgens to estrogen especially to estrone and result with endometrial hyperplasia and difficulty in fertility.[4] There was no significant difference was found between obesity classes and FSH, LH, total and free testosterone and E2 levels in our study.

Obesity can lead to endocrine dysfunction involving the thyrotropic, gonadotropic, somatotropic, and corticotropic axis. In this study, we found that there was no difference in these functions according to obesity classes, except for the IGF-I level. Further studies are needed to investigate these functions in different classes of obesity.

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Ethical Considerations: The present study was approved by the local ethics committee (Date: 22.02.2023, Number: 3328).

Conflict of Interest: The authors declare no conflict of interest.

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