Hypogonadotropic Hypogonadism Associated With Obesity: A Case Report

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ABSTRACT

One of the critical factors with a broad impact on health is obesity. Besides its cardiovascular comorbidities, obesity’s probable association with hypogonadotropic hypogonadism in men will be discussed in this article by reporting a severely obese boy, presenting with the absence of secondary sexual characteristics and hypertension. The hypothalamus-pituitary-gonadal axis can be influenced by several mechanisms at different levels of the axis. Some of these pathophysiological mechanisms, related to our case are explained to explore the association of obesity with reproductive disorders. Adipose tissue plays a prominent role in the metabolism of hormones that are secreted by other glands. Obesity as a preventable risk factor is valuable to be researched, to decrease the burden of its morbidity and mortality. Thus more studies should be done in the future to determine the complex network of factors contributing to hormonal imbalances seen in obese people.

Introduction

Unlike in past decades, obesity and its complications have nowadays become one of the most common health concerns. The increasing prevalence of obesity, both in developed and developing countries shows its important impact on the health of societies [1, 2].

Body Mass Index (BMI), as an indicator of diagnosing and treating obesity, is calculated by the body weight in kilograms divided by the height in meters squared. Based on WHO guidelines, people with a BMI of higher than 30 are considered obese. Obese people are categorized into 3 grades of obesity: Grade 1 (BMI of 30 to 35), grade 2 (BMI of 35 to 40), and grade 3 (BMI greater than 40) [3-5].

The causal association between obesity and some chronic diseases such as diabetes, dyslipidemia, hypertension, cardiovascular disease, sleep apnea, respiratory disorders, Non-alcoholic Fatty Liver Diseases (NAFLD), and cancer has been discussed and confirmed frequent-
It is documented by past investigations that fat accumulation in the visceral and abdominal reservoir has a greater risk of cardiovascular events [10, 11]. Because of the role of adipose tissue in the metabolism of hormones secreted by other glands, including sex steroid hormones, the percentage of human body fat component influences the reproductive system function [12]. The role of obesity in reproductive disorder and infertility has recently received more attention.

The different amount and distribution of fat content in each gender explain the different outcomes of obesity seen in men and women [12]. Disorders of androgen excess like Polycystic Ovarian Syndrome (PCOS) and idiopathic hyperandrogenism present more in obese women, while androgen deficiency is reported in men with obesity [13-15], especially in this article we discuss hypogonadotropic hypogonadism in men associated with obesity.

The main functions of the testes are sperm and testosterone production. Male hypogonadism refers to impaired one or both of the above tasks. Both testes’ abnormality (primary hypogonadism) and dysfunction of the hypothalamic-pituitary-gonadal (HPG) axis (secondary hypogonadism) can lead to hypogonadism. Based on the existence of hypogonadism signs and symptoms accompanied by low total testosterone level at 8-10 AM (measured on two occasions) diagnosis of hypogonadism will be established [16]. Low energy and low libido are the symptoms of hypogonadism and on the physical exam we may obtain the following findings: small testes, small phallus, decreased body, and facial hair, decreased muscle mass, and gynecomastia [17-19].

The lab tests in primary hypogonadism show an increased level of Luteinizing Hormone (LH) and or follicle-stimulating hormone (FSH), while in secondary hypogonadism normal or low LH and or FSH concentrations are seen with low testosterone level at the same time [20].

Despite the numerous studies about obesity-associated hypogonadotropic hypogonadism, more research should be done to understand better the pathophysiology of this link [3, 21, 22]. Hypogonadotropic hypogonadism as an important outcome of obesity will be discussed in this article in detail. A case of hypogonadotropic hypogonadism associated with obesity will be introduced and discussion about it will come along.

**Case Presentation**

A 17-year-old boy presented to our clinic with the absence of secondary sexual characteristics and bilateral gynecomastia in the setting of morbid obesity. He also complained of general fatigue. Past medical and birth history revealed the following information. He was born of a non-consanguineous marriage, as a result of normal pregnancy ended with normal vaginal delivery. His birth weight was 3800 g. Except for obesity since childhood, he had a normal physical and neuropsychiatric development with updated immunizations. Rapid weight gain happened at age two, simultaneously with the change of dietary habits. Others describe him as a very picky eater.

A family history of hypertension was found in his father and both of his brothers and paternal uncles. He had no history of previous surgery or using medications. Habitual history was negative. He was a high school student who had never smoked or drunk alcohol. On physical examination, his blood pressure was 170/80 mm Hg (above 99th percentile). The pulse rate was 82. Bodyweight was 112 kg. Height was 165 cm. Body mass index (BMI) was calculated as 41.1 kg/m², suggestive of class 3 of obesity.

On head and neck examination, he did not have a goiter, and acanthosis nigricans was not seen. Cardiopulmonary examination showed clear lungs and normal heart with normal jugular vein distention. The abdomen was broad, flabby with silver striae and pigmented spots. The striae were less than 1 cm. Its color and diameter were in favor of obesity-related skin changes. Upper and lower extremity pulses were equally bilaterally. The notable findings on genital examinations were as follows.

Atrophied palpable testes bilaterally. Small-sized scrotums with normal consistency (tanner stage 3) [23]. Penis was circumcised with a stretched length of 4 cm (micropenis). Pubic and axillary hairs were absent and bilateral gynecomastia was another remarkable finding discovered on physical examination.

Routine lab tests, including complete blood count, hemoglobin, sedimentation rate, biochemistries, blood urea nitrogen, creatinine, urine analysis, thyroid function test, and liver function tests were within normal ranges. Chest x-ray, ECG, echocardiography, ultrasonography of abdomen, and color Doppler ultrasonography of renal vessels showed normal.

Some of the above tests like renal color Doppler ultrasonography were done to exclude secondary causes of renal failure.
of hypertension which should be workup, especially in early age presentation of hypertension. Some other tests to exclude differential diagnoses were serum ACTH, cortisol and aldosterone level, and plasma renin activity. All of them were within normal limits. However, subsequent tests revealed low testosterone (210 ng/dL; reference range: 260 - 1080 ng/dL) and low LH, FSH, compatible with hypogonadotrophic hypogonadism.

Discussion

Some pathophysiological hypotheses are trying to explain the hypogonadotropic hypogonadism (HH) in obese people:

First, about the role of estradiol in the adipose tissue, enzyme aromatase acts like a converter of testosterone and androstenedione to the estradiol and estrone [24]. This excessive amount of estrogen secretion may lead to suppressing gonadotropin-releasing hormone (GnRH). So the final result will be hypogonadotropic hypogonadism [25-27]. In the elderly population, both low estradiol and low testosterone level are observed which shows low testosterone concentration in these people is not related to the GnRH suppression caused by estradiol level seen in obese patients [28].

The second hypothesis describes the possible action of insulin on the preservation of the HPG axis, which has been revealed in some interventional studies done on mice previously [25, 29].

Also, some other studies discussed the role of inflammatory mediators increased in obesity like CRP and their inverse relationship with free testosterone levels. These mediators were thought to be suppressers of the HPG axis contributing to HH in obese people [25]. Also, obstructive sleep apnea may cause malfunction of the HPG axis contributing to the reduction of LH secretion overnight and a final result of reduced testosterone level [30].

Because of the inhibitory effect of androgens on adipogenesis, low testosterone levels contribute to more fat accumulation leading to a vicious cycle. So bidirectional relationship is seen between obesity and hypogonadism [22, 31]. In summary, the HPG axis can be influenced by multi mechanisms at different levels of the axis leading to HH in obese people.

Despite all the above explanations, one confounding factor of the diagnosis of HH is the technique of measurement, since the decreased sex hormone-binding globulin and variation of binding proteins associated with obesity, may cause decreased total testosterone level. This issue impairs the concomitant diagnosis of hypogonadism in obese people [32].

Our patient with truncal obesity and BMI of 41.1 kg/m² was in grade 3 of obesity (refer to the introduction part to see the different grades of obesity). He had small testes, micropenis, low-grade virilization, and bilateral gynecomastia as the findings in hypogonadal people. He also had a decreased level of testosterone 210 (reference range: 260-1080 ng/d) accompanied by low LH and FSH level in favor of hypogonadotropic hypogonadism associated with obesity as the final diagnosis.

When hypertension is seen along with such obesity of our case, first of all, secondary causes of hypertension like Cushing syndrome, congenital adrenal hyperplasia, and hyperaldosteronism should be rolled out, as we did.

Unlike his Cushingoid appearance, his serum cortisol and ACTH level, serum aldosterone, and plasma renin activity were within the normal range. After rolling out secondary causes of hypertension, the diagnosis of essential hypertension in the patient justifies his strong family history of hypertension and his severe obesity.

Based on the studies, weight gain may contribute to 78% of the essential hypertension risk. A nearly linear association between BMI and blood pressure was seen in previous investigations. On the other hand, weight loss was a preventive and reducing factor of high blood pressure in such studies [33, 34].

We proposed to our case non-pharmacologic treatments based on lifestyle modification like healthy dietary regimens and physical activity leading to weight loss. Besides pharmacological treatment, he was advised for follow-up.

Conclusions

Studies concerning obesity and its burden of diseases receive more value these days, because of obesity’s comprehensive impact on the health of populations. Among numerous comorbidities associated with obesity, hormonal disturbances may find in obese people, including estrogen excess and HPG axis dysfunction that should be more investigated by more studies to identify real pathophysiological factors involved in this possible association.

In addition to collecting more data about this issue, weight loss programs should be considered in all social, financial, educational, and cultural executive programs.
in societies to achieve the goal of decreasing morbidities and mortalities caused by obesity. Unless difficult to attain, obesity can be prevented or controlled with provisional planning taken at the level of society or the person in society.

**Ethical Considerations**

**Compliance with ethical guidelines**

All ethical principles were considered in this article.

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**Conflict of interest**

The authors declared no conflict of interest.

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