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Obesity-related endocrine disorders

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ABSTRACT

Introduction and Purpose: Several endocrine disorders, including diabetes, insulinoma, Cushing syndrome, hypothyroidism, polycystic ovarian syndrome, and growth hormone deficiency, are associated with obesity. The mechanisms underlying the development of obesity vary according to the abnormalities of endocrine function. This review examines the hormonal disturbances linked to obesity, extending beyond just diabetes. It explores the prevalence, clinical features, screening, diagnosis, and management of these related conditions.

Materials and Methods: A comprehensive survey of articles published in scientific journals was conducted via PubMed and Google Scholar online research platforms. Articles were searched by entering keywords in the appropriate configuration: "obesity," "hypothyroidism", "hypercortisolism", "hypogonadism" and "PCOS**".**

Description of current knowledge: Prediabetes and diabetes are the most frequently encountered endocrine conditions by physicians and endocrinologists. Other common endocrine disorders seen in specialty clinics include hypothyroidism, Cushing's syndrome, androgen excess in women, and hypogonadism in men.

Summary: With our expanding knowledge of obesity, it is vital to acknowledge the influential role of fat cells in hormone synthesis. Physicians caring for obese patients should adopt a meticulous approach, screening for hormonal imbalances beyond just diabetes, to ensure comprehensive patient management.

Keywords: "obesity," "hypothyroidism", "hypercortisolism", "hypogonadism", "PCOS**"**

Introduction

Obesity, a global epidemic affecting millions worldwide, is not merely a cosmetic concern but a complex medical condition with far-reaching implications for an individual's health and well-being. The accumulation of excess body fat, a hallmark of obesity, is associated with a myriad of endocrine disorders that can profoundly impact an individual's physiological and metabolic functions [1] [2] [3]. The relationship between the endocrine system and obesity is twofold: some diseases of the endocrine glands may contribute to the development of obesity, but obesity also causes endocrine disorders, which can make diagnosis difficult.

Most often, endocrine disorders in obese patients are secondary and reflect adaptive changes that occur with weight gain. Obesity can lead to insulin resistance, impaired glucose tolerance, and even type 2 diabetes, as the body struggles to maintain normal glycemic levels. Moreover several endocrine disorders, including Cushing syndrome, hypothyroidism, polycystic ovarian syndrome, and growth hormone deficiency, are associated with obesity. In obese patients, peripheral thyroxine consumption is increased, which may be the cause of moderately increased serum thyrotropin (thyrotropic hormone - TSH) levels. In addition, increased insulin and leptin levels may also be responsible for the increased TSH levels. In addition to hypothyroidism, endocrine disorders that occur in obese patients include hypogonadism in men, hyperandrogenemia in women.

Hypothyroidism

Hypothyroidism and obesity are closely related conditions because hypothyroidism can contribute to weight gain by reducing thermogenesis and decreasing resting energy expenditure [4]. Hypothyroidism can also lead to elevated cholesterol levels and reduced insulin effectiveness. Untreated clinically apparent hypothyroidism markedly diminishes patients' well-being, heightens the risk of cardiovascular complications, and hinders the effective management of obesity. Additionally, obesity is associated with a higher frequency of thyroid cancer. While hypothyroidism may contribute to weight gain, the increase is typically modest and primarily due to changes in body composition. Additionally, treating hypothyroidism results in only a modest weight loss, indicating that severe obesity is usually not a direct consequence of this endocrine disorder [5].

Even in people with normal thyroid function, obesity is associated with changes in thyroid-related measures. Obese individuals tend to have higher thyroid-stimulating hormone levels compared to age-, gender-, and weight-matched individuals with normal weight [5]. Even without thyroid dysfunction or autoimmunity, the chronic inflammation associated with obesity can influence the structure of the thyroid gland. Individuals with severe obesity exhibit notable changes on thyroid ultrasound, including an enlarged thyroid volume and a hypoechogenic (low-echogenicity) pattern. These alterations are reversible following weight loss through bariatric surgery [6]. Chronic autoimmune thyroiditis, frequently associated with thyroid antibodies such as anti-thyroid peroxidase, is a common cause of hypothyroidism. Elevated levels of anti-TPO are predictive of the transition from subclinical to overt hypothyroidism [7]. However, there is limited evidence supporting the testing for thyroglobulin antibodies in obese individuals [8]. The prevalence of subclinical and overt clinical hypothyroidism in obese individuals is estimated at 14.6% and 14%, respectively [9]. Several studies have observed an increase in thyroid-stimulating hormone levels in obese individuals, despite normal or low-normal free thyroxine (T4) and triiodothyronine (T3) concentrations [10]. The underlying mechanisms driving this relationship are not yet fully understood, but several explanations have been proposed. Obesity is a chronic state of low-grade inflammation, and the cytokines and other inflammatory mediators produced by the excess adipose tissue, such as interleukin-1, IL-6, and tumor necrosis factor alpha, are increased in obese individuals [11]. The elevated inflammatory cytokines associated with obesity may disrupt the expression of genes responsible for sodium-iodide symporter activity, potentially impacting iodine uptake in human thyroid cells [12]. For individuals diagnosed with obesity, it is recommended to measure serum TSH levels. If the TSH levels are elevated, the free thyroxine and anti-thyroxine oxidase antibodies should also be assessed.

Hypogonadism in men

Obesity also affects the reproductive system and is associated with polycystic ovarian syndrome (PCOS) in women and testosterone deficiency, causing hypogonadism in men [13]. The most common cause of male hypogonadism in adults is obesity The prevalence of hypogonadism in adolescent and young adult males with obesity varies anywhere from 30–60% based on different criteria used for the diagnosis and severity of obesity [14] [15]. Clinical signs of hypogonadism include: erectile dysfunction, decreased libido, depressed mood, and metabolic

complications. This signs are also a significant and increasingly frequent cause of fertility disorders in men [16].

The pathophysiology of obesity-related hypogonadism involves a complex interplay between excess adiposity, dysregulated sex steroid metabolism, and diminished pituitary-testicular axis function. In people with obesity, elevated aromatase enzymes from adipose tissue decrease testosterone levels and raise estrogen levels. This testosterone deficiency promotes further adipocyte differentiation, adipocyte inflammation, and insulin resistance. The subsequent increase in estrogen, leptin, insulin, and inflammatory cytokines leads to impairment of the hypothalamic-pituitary-testicular axis [17]. Additionally, obesity has been associated with dysregulation of the hypothalamic-pituitary-adrenal axis, leading to functional hypercortisolism, which can result in inhibition of gonadotropin and testosterone secretion [18].

For men with obesity and suspected hypogonadism, type 2 diabetes, or metabolic syndrome, measuring serum total testosterone is the recommended initial test. If the results are abnormal, further hormonal evaluations should be conducted (sex hormone binding globulin [SHBG], free testosterone, luteinizing hormone [LH], folliculotropic hormone [FSH], prolactin) [9]. If testosterone level is low, measuring pituitary gonadotropin levels is recommended to differentiate central from primary hypogonadism. Obese individuals with functional secondary hypogonadism typically have reduced LH and FSH levels, in contrast to the high levels seen in primary hypogonadism. Before diagnosing functional secondary hypogonadism of obesity, other conditions associated with hypogonadotropic hypogonadism, such as hyperprolactinemia, leptin signaling abnormalities, and syndromic obesity, should be ruled out. Additionally, a hypothalamic pituitary MRI may be required, and if negative, further assessment of leptin and genetic factors may be considered [19]. Lifestyle changes are the primary approach for managing male obesity-related secondary hypogonadism, as this enhances the patient's overall well-being and can potentially alleviate symptoms of androgen deficiency, regardless of the impact on testosterone levels. Furthermore, excess insulin levels can act on the kisspeptin neurons, leading to reduced kisspeptin signaling. This, in turn, can impair the function of the GnRH neurons, resulting in decreased GnRH release and consequently lower LH secretion [20]. The literature consistently demonstrates that weight loss, particularly via bariatric surgery, can significantly improve testosterone levels in men with obesity-related hypogonadism [21]. Studies indicate that obese men with hypogonadism can see an increase in their testosterone levels if they achieve a weight loss of at least 5-10% of their body weight [22].

Hypercortisolism

Cortisol is the primary active glucocorticoid hormone in humans and plays a crucial role in regulating various physiological processes, especially during periods of stress or illness [23]. The secretion of glucocorticoids by the adrenal cortex is typically regulated by the hypothalamic-pituitary-adrenal axis. However, chronic overproduction of cortisol, known as hypercortisolism or Cushing's syndrome, can have detrimental effects on an individual's physical and mental health. The prevalence of hypercortisolemia in obese patients is about 0.9%, so diagnosis for Cushing's syndrome is not recommended for all patients. In fact, a higher prevalence of hypercortisolism has been observed in obese patients with type 2 diabetes who exhibit poor metabolic regulation [24].For individuals undergoing bariatric surgery, it is essential to carefully evaluate the potential presence of Cushing's syndrome in patients presenting with concerning clinical symptoms. Clinically obese individuals exhibiting signs suggestive of Cushing's syndrome should undergo hormone evaluation (including subcutaneous hemorrhages, red skin striae, proximal muscle myopathy, hirsutism and acne in women, and abdominal obesity with coexisting type 2 diabetes, NT and/or osteoporosis). A cortisol suppression test with 1 mg of dexamethasone is the recommended screening test for hypercortisolemia. The 1 mg dexamethasone suppression test is a sensitive screening tool for identifying hypercortisolism, with post-dexamethasone cortisol levels ≤ 1.8 μg/dL considered the threshold to exclude the condition. There is currently no evidence supporting the need for different testing methodologies or cutoff values specifically for obese individuals. False-positive results can arise in severe obesity and other conditions such as depression, alcoholism, chronic stress, and obstructive sleep apnea. When interpreting test results, it is crucial to account for these factors [25]. When it comes to ACTH measurements, they are not significantly affected by obesity. However, it is crucial to conduct these assessments to distinguish between ACTH-dependent and non-ACTH-dependent forms of Cushing's syndrome. This differentiation informs the selection of imaging modalities and suitable treatment interventions [26]. For obese patients, the essential treatment is addressing the underlying obesity, as sustained weight loss is crucial for restoring hormonal balance, since mild endocrine disorders do not manifest the typical symptoms.While hypercortisolism is a contributing factor to weight gain, weight normalization is often not achieved even after specific treatment of Cushing's syndrome. This suggests that endogenous hypercortisolism is one of the contributing factors, but not the sole underlying cause of weight gain.

Polycystic ovary syndrome

Polycystic ovary syndrome encompasses a multifaceted set of disorders characterized by clinical and/or laboratory signs of hyperandrogenism, irregular ovulation, and metabolic abnormalities, including insulin resistance. These individuals often struggle with being overweight or having excessive abdominal fat, as well as type 2 diabetes, abnormal cholesterol levels, and an increased risk of cardiovascular disease [27]. The pathophysiology of PCOS-related obesity likely involves excess androgens as a key driver. Obesity can both cause and result from PCOS. This disorder is characterized by a self-reinforcing cycle of hyperandrogenism, insulin resistance, and increased visceral fat, which together promote the development of PCOS [28]. Obesity can contribute to fertility challenges and a higher risk of pregnancy loss, even in individuals without polycystic ovary syndrome [29]. Clinically obese or overweight women exhibiting signs such as acne, hirsutism, or angrogenic allopecia, as well as those experiencing menstrual irregularities or fertility issues, should undergo endocrine assessment. This assessment seeks to confirm or rule out the presence of hyperandrogenemia, anovulation, polycystic ovary syndrome, and insulin resistance. PCOS is diagnosed according to the Rotterdam criteria, which require the presence of at least two of the following: hyperandrogenism, chronic anovulation, and polycystic ovarian morphology on ultrasound. In PCOS, levels of total testosterone, free T3, free T4, and androstenedione are typically elevated, while sex hormone-binding globulin is reduced. Furthermore, a high ratio of luteinizing hormone to follicle-stimulating hormone may be observed, although this is not universally present. Along with ovarian ultrasonography, clinicians may also recommend HbA1c testing and oral glucose tolerance assessments [30]. Late-onset congenital adrenal hyperplasia, although less prevalent than PCOS, can present a similar clinical picture. Therefore, clinicians should measure plasma 17-hydroxyprogesterone to rule out the possibility of 21-hydroxylase deficiency [31]. Evaluating the levels of gonadotropins, estradiol, progesterone, and prolactin can help assess gonadal dysfunction and distinguish between secondary and primary hypogonadism in women with ovulatory disorders. Primary hypogonadism is characterized by elevated circulating gonadotropin levels, in contrast to the low levels seen in central (secondary) hypogonadism. Special attention should be given to the FSH level, as it is characteristically elevated in primary ovarian failure, but low in typical polycystic ovary syndrome and central hypogonadism [32]. Metformin, an insulin-sensitizing medication, can enhance insulin sensitivity in the liver, muscles, and adipose tissue. This can lead to improvements in the cardiometabolic risk profile, menstrual irregularities, and fertility in women with PCOS. Given

the potential role of insulin resistance in driving hyperandrogenism and anovulation, metformin can be a suitable therapeutic approach for PCOS patients with prediabetes or type 2 diabetes, in combination with lifestyle interventions focused on weight management. However, in the absence of diabetes or prediabetes, metformin should not be the primary treatment prescribed solely for weight loss. Instead, other anti-obesity medications such as GLP-1 receptor agonists (e.g., liraglutide or semaglutide) or orlistat may be more suitable, used in combination with lifestyle interventions, when the primary goal is weight reduction [33]. Initial treatment for women with PCOS typically involves using combined oral contraceptives in addition to weight loss. Contraceptive formulations with low doses of estrogens and progestins that lack androgenic or antiandrogenic properties are recommended. Low-estrogen contraceptive options are preferred due to the associated lower risk of venous thromboembolism [34].

TABLE 1.

Other obesity-related diseases
Type 2 diabetes
High blood pressure
Stroke
Osteoarthritis
Fatty liver diseases
Gallbladder stones

Obstructive sleep apnoea
Kidney disease

Summary

Obesity is a chronic disease with no tendency to resolve on its own, recurring and potentially leading to the development of more than 200 chronic diseases: metabolic, cardiovascular and non-metabolic complications of obesity. Obesity is closely intertwined with hormonal imbalances, extending beyond the well-documented insulin resistance. Other endocrine conditions are strongly associated with obesity and elevated body mass index, including hypothyroidism, Cushing's syndrome, male hypogonadism, and excess androgens in females. As our understanding of obesity deepens, it is crucial to recognize the role of fat cells in hormone production. Physicians managing obese patients should maintain a vigilant approach, screening for hormonal disorders beyond just diabetes, to provide comprehensive care.

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Aleksandra Kiełczewska: Conceptualization, Writing-rough preparation

Anna Kiełczewska: Methodology, Investigation Resources

Grzegorz Szcześniak: Formal analysis, Visualisation, Writing-review and editing

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