Chapter

Endocrine Disorders Accompanying Obesity - Effect or Cause?

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Abstract

Endocrine disorders including hypothyroidism and hypercortisolism are considered as causes of secondary obesity. However, several hormonal abnormalities can also be found in individuals with primary (simple) obesity. Part of them results from the adipose tissue dysfunction that, *via* secreted adipokines, modulates the function of endocrine organs and can be reversed with weight loss. However, part of them correspond to the real endocrine disorder and require appropriate treatment. Therefore in the management of obese patients, it is essential to distinguish between obesity-related abnormal results of hormonal tests and underlying endocrine disorder. This chapter presents pathophysiological concepts of obesity-related changes in the endocrine system and briefly reviews diagnostic algorithms helpful in distinguishing them from the co-existing endocrine disorders.

Keywords: obesity, endocrine disorders, hypothyroidism, hypercortisolism, hypogonadism, hyperandrogenism

1. Introduction

According to World Health Organization reports, the incidence of obesity has tripled in the last 30 years, and it is estimated that in 2025 obese individuals will constitute about 15% of the adult population [1]. Therefore, one can expect that obese patients would appear in the doctor's office more frequently, searching for medical assistance. In addition, undiagnosed and untreated hormonal disorders, such as hypothyroidism, hypercortisolism, and hypogonadism, can contribute to the development of secondary obesity, and their exclusion is sometimes necessary for the diagnosis of so-called "simple" or primary obesity. However, simple obesity itself may affect the function of the endocrine system, and adipose tissue dysfunction seems to play a pivotal role in this phenomenon. Excessive lipid accumulation leads to several changes in the adipocyte' metabolism, causing, among others, the dysfunction of the mitochondria and the associated endoplasmic reticulum stress [2]. These entail alternations of genes' expression, and thus – changes in the profile of substances secreted by adipose tissue (adipokines). These adipokines act in an endocrine manner and affect tissues and organs throughout the body, including the endocrine glands [3].

Therefore, in everyday medical practice, it is essential to understand the obesity-related changes in the endocrine system function to distinguish between the actual

disease that requires treatment and changes secondary to obesity, where weight reduction is the best form of therapy. This chapter presents pathophysiological concepts of obesity-related changes in the functioning of the thyrotropic, adrenocorticotropic, and gonadotropic axes and briefly reviews diagnostic algorithms helpful in distinguishing them from the co-existing endocrine disorders.

2. The hypothalamic-pituitary-thyroid axis and obesity

The secretion of thyroid hormones (TH) is regulated by the hypothalamic–pituitary-thyroid (HPT) axis. The anterior pituitary lobe secretes thyroid-stimulating hormone (TSH, thyrotropin) upon the stimulation by thyrotropin-releasing hormone (TSH) produced by the hypothalamus. In turn, TH (triiodothyronine – T3 and thyroxine – T4) in a feedback inhibitory loop control both TRH and TSH release in order to ensure whole-body homeostasis. TH's pleiotropic actions include control of energy expenditure and body weight maintenance *via* regulation of a basal metabolic rate (BMR), adaptive thermogenesis, and appetite. Clinical studies suggest that thyroid status is associated with changes in body weight and adiposity. Even in euthyroid individuals, those with TSH levels in upper quintiles have higher body mass index (BMI) than those with TSH closer to the lower limit of the normal range, while variations of TH levels, even in the normal range, may promote weight gain or impair the effectiveness of weight-loss treatment [4, 5]. However, not all researcher managed to confirm this finding, that may mirror the fact that the metabolic effect of TH in target tissues is determined by variations in the activity of TH deiodinases, transporters, receptors, and availability of their corepressors and coactivators [4, 6]. Moreover, the relationship between thyroid and obesity is bidirectional since both TH and TSH affect adipose tissue metabolism, which in turn, *via* adipokines, may influence thyroid function and structure.

2.1 Influence of hypothyroidism on body mass and composition

Weight gain is a frequent complaint in hypothyroidism. Indeed, HT deficiency may increase body adiposity due to a decrease in BMR and thermogenesis. Moreover, water retention related to the accumulation of hyaluronic acid and a decreased renal flow and impaired peristalsis causing chronic constipation contributes to weight gain. However, according to observational studies, an increase in body weight related to hypothyroidism is usually of a limited extent. Moreover, supplementation with levothyroxine (LT4) leads only to a modest weight loss (usually of less than 10%) associated with excretion of excess body water, indicating that severe obesity is usually not secondary to hypothyroidism [7]. The American Thyroid Association (ATA) in the 2012 guidelines on hypothyroidism management underlines the fact that there is a lack of reliable scientific evidence in this field, and very few studies have directly assessed the association between hypothyroidism and obesity [8]. However, the European Society of Endocrinology (ESE) recommends testing routinely obese patients for hypothyroidism since HT deficiency contributes to an unfavorable lipid profile and thus potentiates their cardiovascular risk and the risk of metabolic syndrome. Of importance, untreated hypothyroidism reduces the effectiveness of weight loss therapies [5].

2.2 Obesity-related changes in thyroid function and structure

The majority of obese patients without diagnosed thyroid disease remain euthyroid [5, 9]. However, both overt hypothyroidism and subclinical hypothyroidism

(characterized by elevated TSH level with free TH concentrations within normal limits) is observed more frequently in obese subjects, compared to the patients with normal body weight and is estimated at 14.0% and 14.6%, respectively [5, 9–14]. The pathogenesis of obesity-related changes in thyroid hormone levels is complex [15]. On the one hand, an increase in TSH level in obese individuals can be explained by the central resistance to locally-produced T3 and represents an adaptive process aimed to increase basal energy expenditure. On the other, increased TSH levels in obesity correlate with an excess of leptin, an adipokine produced by adipose tissue that can directly stimulate TRH and TSH secretion [16]. Moreover, leptin was found to activate deiodinases, enzymes responsible for the increase in free T4 (fT4) to free T3 (fT3) conversion, which is believed to constitute another mechanism that aims at the increase in BMR and energy expenditure [17]. Since elevated TSH level can be a form of adaptation of the central axis to obesity-related changes in metabolism in order to boost energy expenditure to prevent further weight gain, it has been proposed that hyperthyrotropinemia is an adequate term than subclinical hypothyroidism in this case [5, 18]. In addition, in subclinical hypothyroidism, fT4 and fT3 levels are usually low normal, while in most obese individuals, thyroid hormones are in the normal or high normal range, reflecting central hypothalamus-pituitary resistance [18].

Both ATA and ESE recommend the measurement of TSH as a screening test for thyroid dysfunction in obese individuals. Normal TSH enables to rule out primary hypothyroidism as a reason for secondary obesity; however, one should remember that decreased TSH level in an obese subject may suggest pituitary–hypothalamic dysfunction (representing less than 1% of cases of hypothyroidism). Therefore, the guidelines recommend measurement of fT4 only if TSH is elevated or if disorders other than primary hypothyroidism are suspected. In turn, routine measurement of fT3 in obese individuals with elevated TSH is not recommended [5, 19].

If TSH and fT4 levels in an obese patient suggest a diagnosis of subclinical hypothyroidism, the screening test for autoimmune thyroid disorder (AITD) should be performed. In this case, the determination of thyroid antibodies is helpful not only to diagnose AITD but also to identify individuals at risk of developing overt hypothyroidism. Therefore, the guidelines recommend the determination of thyroid peroxidase (TPO) antibodies and suggest that their level > 500 IU/ml indicates a high risk of progress [20]. From the pathophysiological point of view, obesity-associated dysfunction of the immune system (related to vitamin D deficiency, abnormal adipokine, and pro-inflammatory factors expression) can promote autoimmunity in obese individuals. Indeed, a recent meta-analysis showed the correlation between the presence of TPO antibodies and obesity [13]. However, despite the high sensitivity of modern assays, a consistent number of patients with primary hypothyroidism present negative tests for TPO antibodies, and the diagnosis of AITD is established based on a hypoechoic pattern of the thyroid gland in ultrasound examination (so-called seronegative AITD) [21].

Ultrasound-based diagnosis of AITD in obese patients can be challenging since obese individuals are more likely to present hypoechoic images of thyroid parenchyma. This finding is confirmed by the epidemiological studies, where the correlation of the ultrasound image with AITD was observed in only 20.9% of obese subjects compared to 85.7% in the normal-weight controls [22]. In turn, a hypoechoic pattern of the thyroid gland in ultrasound examination with an absence of antithyroid antibodies was observed in only 1.9% non-obese individuals *vs*. 64.8% in obese patients [22]. Thus, the hypoechoic thyroid picture in obese patients results from the increased permeability of thyroid blood vessels caused by the pro-inflammatory cytokines secreted by dysfunctional adipose tissue. As a result, plasma exudation and imbibition of parenchyma occur, which was confirmed by a

fine-needle biopsy that did not show lymphocyte infiltrations ruling out Hashimoto disease as a cause of the hypoechoic pattern of the thyroid gland [22].

Given all the data presented above, a decision on the administration of TH to an obese patient with elevated TSH levels should be handled with caution. The ATA and ESE guidelines recommend treating LT4 in obese subjects with overt hypothyroidism and those with TSH ≥ 10mIU/l. The initial dose should depend on the clinical situation and be subsequently adjusted by regular assessment of TSH with the same target range as in the non-obese population [5, 19]. However, if elevated TSH (above the upper range but <10 mlU/L) is the only abnormality, without clinical symptoms, decreased fT4, thyroid antibodies, goiter, or associated thyroidal illness, it can be defined as obesity-associated hyperthyrotropinemia, and the treatment with LT4 to reduce body weight is not recommended [5, 23]. This approach seems to be justified since, until now, no randomized controlled trial nor systematic review was performed to evaluate the effectiveness of TH supplementation in obese adults with hyperthyrotropinemia.

However, some obese individuals with increased TSH level < 10 mlU/l who meet the diagnostic criteria for the mild subclinical hypothyroidism (e.g., showing clinical symptoms of hypothyroidism, TH levels in the low-normal range, present antithyroid antibodies) may benefit from LT4 supplementation. Furthermore, the same approach should be considered in women in the procreation period and pregnancy. On the contrary, age over 70 years and concurrent cardiovascular disease should direct the decision toward a follow-up strategy [5]. Especially since epidemiological studies suggest that LT4 replacement therapy for subclinical hypothyroidism does not improve health-related quality of life, survival, or decreased cardiovascular morbidity [12]. Also, administration of TH to euthyroid obese subjects to enhance weight loss is not recommended since it is associated with several adverse effects, including muscle wasting and weakness as well as cardiovascular complications [24].

Paradoxically, regardless of the method applied, the best treatment for obesity-related hyperthyreotropinemia is weight loss, leading to the reversal of the mechanisms causing central and peripheral resistance to TH. For instance, in an interventional study, after lifestyle interventions (diet combined with increased physical activity), the number of individuals with TSH level above the normal range decreased significantly after the intervention from 17.2% to 6.2%., while the mean TSH level in the whole group decreased from the mean 2.8 mU/l before the intervention to 2.2 mU/l) [25]. Similarly, regardless of the procedure, bariatric surgery results in the normalization of TSH in nearly all patients (reviewed in ref. [26]). These findings strongly suggest that obesity-associated hyperthyrotropinemia is transient and resolves after weight loss.

In summary, most obese individuals are euthyroid, even though their TSH levels usually exceed those observed in normal-weight individuals. The most common obesity-associated thyroid hormone abnormality is hyperthyrotropinemia that can be distinguished from the SH by the normal and/or high normal concentrations of thyroid hormones. In addition, obesity is associated with decreased thyroid echogenicity in ultrasound which does not mirror the presence of autoimmune thyroid disease. Independently, obesity increases the risk of thyroid autoimmunity. Patients with isolated hyperthyrotropinemia should not be treated with thyroid hormone replacement unless there are symptoms or other signs of thyroid disease. Indications for LT4 treatment in obese individuals are limited to overt hypothyroidism and some selected cases of its subclinical form. Administration of thyroid hormones to obese individuals without thyroid disease to induce weight reduction or improve metabolic profile is not justified and may lead to hyperthyroidism and its complications. Recommendations for testing for thyroid dysfunction in obese patients and their management are summarized in **Figure 1**.

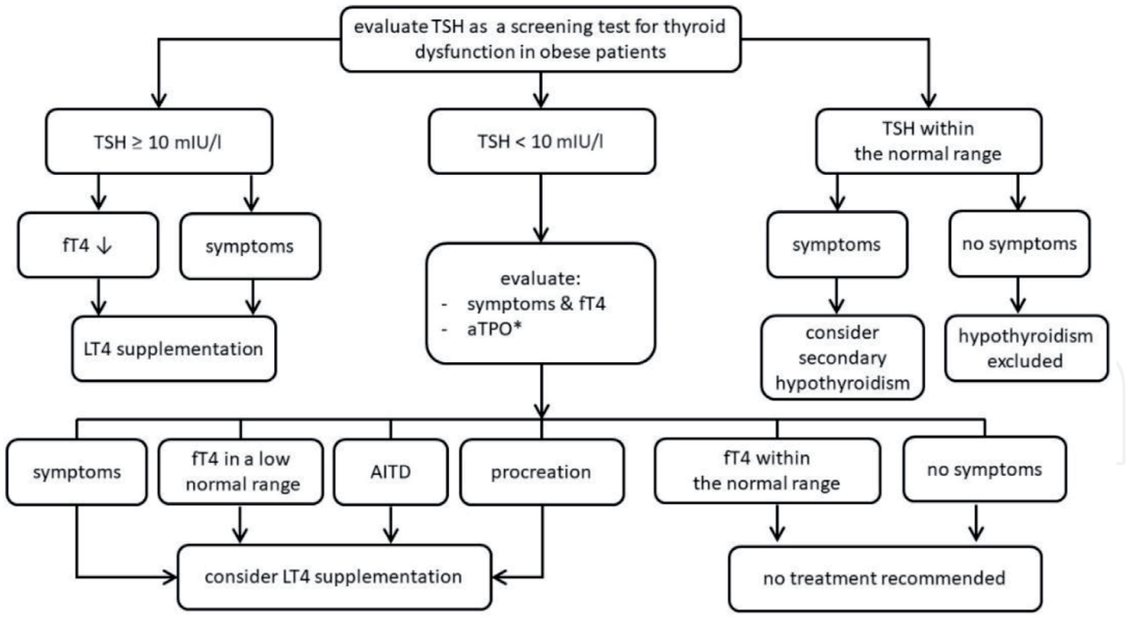

Figure 1.
*Testing for thyroid dysfunction and hypothyroidism treatment in obese patients (based on ref. [5]). AITD, autoimmune thyroid disorder; aTPO, thyroid peroxidase antibodies; fT4, free thyroxine; LT4, levothyroxine; TSH, thyroid-stimulating hormone; * If TSH and fT4 levels suggest subclinical hypothyroidism.*

Loss of weight leads to the normalization of TSH in most obese individuals; however, till now, no large-scale study showed how the echogenicity of the thyroid parenchyma changes after weight loss and whether there is a correlation with the ultrasound image and the incidence of autoimmune thyroid disease before and after weight loss.

3. The hypothalamic-pituitary-adrenal axis and obesity

Cortisol secretion is regulated by the hypothalamic–pituitary–adrenal (HPA) axis upon stimuli received from the central and peripheral nervous system and integrated into hypothalamic nuclei to counteract different types of stressors. Upon these stimuli, corticotropin-releasing hormone (CRH) and vasopressin are released by the paraventricular nucleus of the hypothalamus and stimulate the secretion of adrenocorticotropic hormone (ACTH, corticotropin). Subsequently, ACTH acts on the adrenal cortex to produce and release glucocorticoid hormones (mainly cortisol in humans). The HPA axis activity is controlled by cortisol in an inhibitory feedback loop *via* glucocorticoid receptors (GR), located mainly in the brain's hippocampus region. By interaction with GR, cortisol plays an essential role in the regulation of metabolism. In response to stress, cortisol, by mobilization of glucose, free fatty acids, and amino acids from endogenous resources, increases the availability of fuel substrates. In an emergency, these properties of cortisol assure the energy supply necessary to survive [27]. However, cortisol excess observed in patients with the Cushing's syndrome, caused either by the adrenal tumor (ACTH-independent hypercortisolism), tumors of the hypothalamic–pituitary system, or tumors outside the HPA axis that ectopically produce ACTH (ACTH-dependent hypercortisolism) or CRH, leads to the profound impairment of whole-body homeostasis [28].

3.1 Metabolic consequences of hypercortisolism

Even though proper cortisol secretion is vital for everyday existence, its excess intensifies catabolism, leading to decreased lean body mass and causing muscle

atrophy. Moreover, to increase energy uptake, glucocorticoids stimulate appetite and food consumption contributing to the development of central obesity. Furthermore, by acting on the liver, muscle, adipose tissue, and pancreas, glucocorticoids increase gluconeogenesis, impair insulin sensitivity, and increase lipolysis and lipogenesis, leading to the development of the metabolic syndrome. Moreover, there is evidence from preclinical studies that glucocorticoids may interfere with the action of adipokines: by interference with the signaling system of the leptin receptor cortisol induces leptin resistance, characteristic for individuals with primary obesity [29]. Therefore the clinical picture of patients suffering from hypercortisolism resembles in many aspects primary obesity, and obesity is commonly listed among the different entities of so-called pseudo-Cushing states [30]. However, several issues in a clinical examination should be considered during the differential diagnosis.

Firstly, adipose tissue distribution in hypercortisolism concerns mainly the abdominal area, the neck, and the face, while the extremities remain lean due to muscle atrophy. Subjects with primary obesity usually have fat accumulation all over the body, including upper and lower extremities. Next, striae in obese individuals are usually pale, narrow, and their appearance is associated with pregnancy or rapid weight gain. On the contrary, striae related to cortisol excess are reddish or live red, wider than 1 cm, and appear suddenly without any identifiable cause. Moreover, patients with cortisol excess complain of unusual brushing, skin thinning, and facial plethora that are not specific symptoms in primary obesity. Excess of cortisol or co-secretion of androgens (by the adrenal tumor or ACTH-stimulated adrenal cortex) can result in typical features of hyperandrogenism that include acne, hirsutism, and alopecia. Furthermore, cortisol-induced osteolysis leads to osteoporosis that is rarely seen in obese subjects whose bones are protected by an endocrine activity of adipose tissue. Finally, hypercortisolism is associated with an increased frequency of non-metabolic complications that include, among others, thromboembolic incidents, severe infections, depressive and psychotic episodes resulting from the action of excess cortisol on other tissues and organs [30].

Apart from the clinical picture, the final diagnosis requires endocrine testing (described in detail elsewhere), especially in the case of individuals with so-called subclinical Cushing's syndrome [28]. This endocrine disorder is observed in individuals with incidentally found adrenal adenoma and ACTH-independent cortisol secretion that is not fully restrained by pituitary feedback. Even though patients with subclinical Cushing's syndrome do not present all clinical features of the full-blown disease (e.g., only 30–50% of them are obese) and hypercortisolism is of minimal intensity, it may eventually contribute to the development of metabolic and vascular complications [31]. The reason for unmasking endogenous hypercortisolism derives from its devastating complications affecting the quality of life and life expectancy unless adequately treated [5].

Therefore the question is if the diagnostic of Cushing's syndrome should be conducted in every obese patient. The epidemiological studies estimate the prevalence of Cushing's syndrome in obese individuals to be 0.9%, and in patients with type 2 diabetes with poor metabolic control, it rises to 2–3% [14]. The incidence of subclinical Cushing's syndrome has been more common in patients with obesity than in the general population, though the precise assessment of the disease frequency is difficult since the diagnostic criteria and treatment program have not been well established yet. Therefore, assuming the epidemic proportions of obesity and the low prevalence of hypercortisolism among patients with obesity, the ESE guidelines do not recommend routine screening of Cushing's syndrome in patients with obesity. However, such testing should be performed in patients who exhibit other specific features of hypercortisolism besides obesity, such as skin atrophy, osteoporosis, spontaneous ecchymoses, proximal myopathy, or wide purple striae.

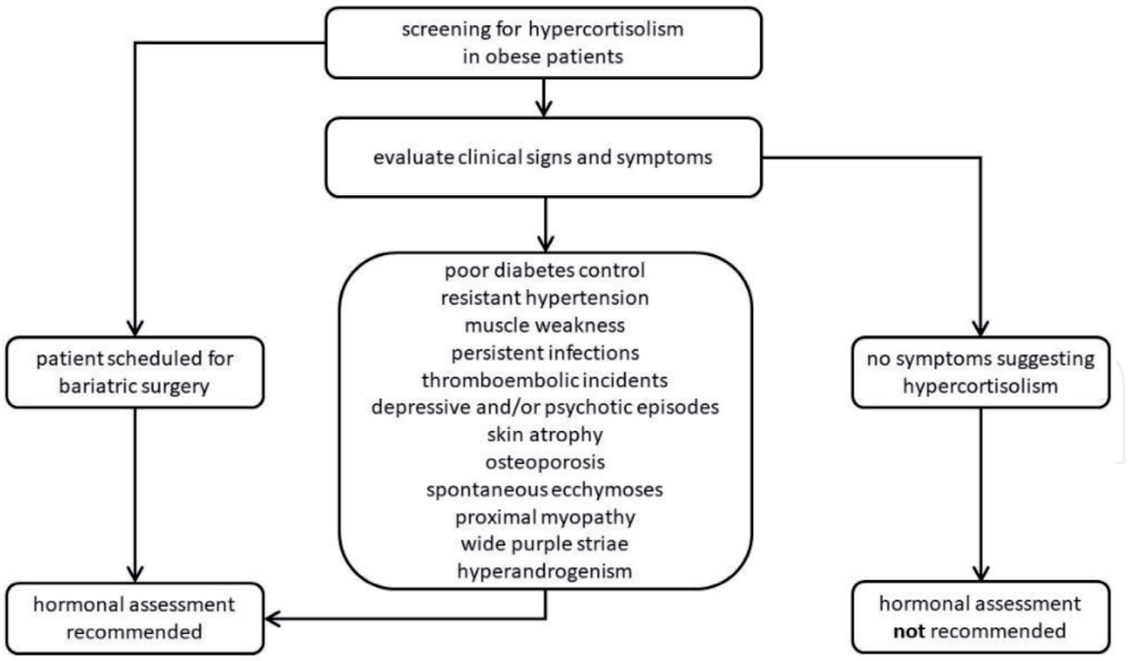

Figure 2.
Screening for hypercortisolism in obese patients (based on ref. [5]).

Moreover, given the high risk of surgical complications or adverse clinical outcomes following surgery, the screening for hypercortisolism should be considered in patients referred to bariatric surgery [5]. Recommendations for testing for hypercortisolism in obese patients are summarized in **Figure 2**.

3.2 Obesity-related HPA dysfunction

Obese patients constitute a heterogeneous population in terms of the HPA axis function [32]. Some of them have a normal circadian rhythm of cortisol secretion and its proper excretion in the urine. The remaining obese patients (especially those with abdominal obesity) present with the so-called functional hypercortisolism. This condition results both from the increased sensitivity of the HPA axis to stimuli, as well as from the increased peripheral cortisol synthesis (including the activation of 11β steroid dehydrogenase (11β-HSD) type 1, which converts cortisone into cortisol in adipose tissue) and the increased number of GR in peripheral tissues [33–36]. Clinically, in addition to some phenotypic features of Cushing's syndrome, these patients exhibit increased nocturnal ACTH and cortisol levels, increased urinary excretion of cortisol metabolites, and enlargement of adrenal glands in imaging studies [37]. The results of studies on the inhibition of cortisol secretion in the dexamethasone test (1 mg) in obese patients also indicate the existence of different phenotypes of obesity. While some patients show a normal response, in others, a low dose of dexamethasone does not inhibit the HPA axis [37, 38].

The type of HPA disturbances in obesity seems to depend not only on adipose tissue distribution (visceral *vs*. subcutaneous) but also on the individual pattern of a stress response. Individuals coping well with stress usually have normal HPA function with high morning and low evening cortisol values, a brisk response to feeding, and are sensitive to dexamethasone suppression. In contrast, patients vulnerable to stress have low variability in a circadian cortisol rhythm, a small feeding response, and do not inhibit cortisol secretion after administration of dexamethasone. This abnormal HPA axis function is associated with a worse metabolic profile, including higher waist-to-hip ratio (WHR), total and low-density lipoprotein cholesterol,

and blood pressure. Moreover, due to the interactions with other central endocrine axes, HPA axis status may determine the function of other endocrine glands. Therefore, HPA axis overactivity inhibits the secretion of sex steroids, growth hormone, and TSH [32]. However, these two reaction patterns of the HPA axis are extremes, and between them are several intermediate forms. These include, for instance, a normal, basic HPA axis activity, with high variability, stimulated by perceived stress that can explain the described above diversity of findings. Other determinants of the heterogeneous responses of the HPA axis in obese individuals include, but are not limited to: differences in GR sensitivity which can be partially genetically determined, comorbidities such as depression, or lifestyle factors such as alcohol abuse [39].

In summary, abnormalities of HPA function are a common phenomenon among obese individuals; however, due to a variety of hormonal responses, several phenotypes can be distinguished that differ in metabolic risk and health consequences. In addition, the presence of overt hypercortisolism is relatively rare. Therefore, routine testing for Cushing's syndrome in obesity is not recommended unless some typical alerting clinical features are present.

While normalization of the HPT axis after weight-loss interventions is widely described, only single studies carried out on groups of about 30 individuals show that weight loss normalizes the excretion of cortisol and cortisone metabolites in the urine, which correlates with a decrease in the expression of 11 β-HSD type 1 in subcutaneous fat [40]. However, it is unclear which of the obesity-related disturbances in the HPA axis function are reversible and which sustain despite the weight reduction.

4. The hypothalamic-pituitary-gonadal axis and obesity

The secretion of sex hormones is regulated by the hypothalamic–pituitary-gonadal (HPG) axis. Briefly, gonadotropin-releasing hormone (GnRH) is secreted by the hypothalamus and stimulates the anterior pituitary lobe to release gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH), that subsequently stimulate gonads (ovaries and testes) to secrete estrogen and testosterone, as well as to control reproduction. While testosterone in a negative feedback loop inhibits GnRH and gonadotropins secretion, the regulation is more composed in the case of female sex steroids. In females, estrogen in a positive feedback loop stimulates LH secretion to prepare the reproductive organs for ovulation and implantation. In turn, after the ovulation, progesterone released by the corpus luteum inhibits proper cells in the hypothalamus and anterior pituitary lobe and stops the estrogen-LH positive feedback loop [41]. Since sex hormone receptors are spread all over the human body, apart from their pivotal role in the regulation of reproduction, sex steroids impact the function of several organs, including the adipose tissue. However, this relation is bidirectional since adipose tissue, *via* secretion of adipokines, modulates the HPG axis [42].

4.1 Metabolic consequences of hypogonadism

Sexual dimorphism of adipose tissue distribution appears in puberty, indicating the role of sex hormones in its development [43]. Estrogens drive fat accumulation in the gluteofemoral subcutaneous depot, and during puberty in girls, increasing circulating estrogens levels correlate with an increase in fat deposition in this area. In turn, a decline in estrogen concentration during menopause is associated in women with changes in adipose tissue distribution from gluteofemoral to visceral.

On the contrary, women who are on hormone replacement therapy do not display the characteristic abdominal weight gain pattern usually associated with menopause [44]. The ability of estrogens to affect body fat distribution is not limited to women. In males, loss of estrogen signaling or its pharmacological inhibition promotes adiposity and impairs glucose metabolism [45, 46]. Preclinical studies confirmed a significant role for estrogen in regulating adipose tissue distribution, metabolism, and inflammatory activity. Activation of estrogen receptors was found to inhibit adipocyte differentiation, lipid accumulation, and the expression of adipocyte-specific genes in primary human adipocytes [47]. Since estrogen influences adipose tissue amount and its metabolism, it may modulate the risk of obesity-related complications. In clinical studies, menopause is associated with a constant decline in insulin sensitivity parallel to an increase in serum inflammatory markers and unfavorable lipid profile [48]. In turn, transdermal administration of estradiol decreases the expression of genes encoding critical lipogenic enzymes in human adipose tissue that correlates with a decrease in plasma triglyceride levels [49].

Androgens also influence adipose tissue metabolism. By binding androgen receptors (AR) present in adipose tissue, especially in the visceral depot, testosterone up-regulates adrenergic receptors β that activate lipolysis. Moreover, androgens decrease in adipose tissue activity of lipoprotein lipase (LPL) responsible for the hydrolysis of circulating triglyceride-rich lipoproteins inhibiting in this way triglyceride uptake [50]. Androgen status, responsible, among others, for the muscle mass accrual in puberty, is crucial to acquire and maintain favorable body composition in men. Accordingly, several cross-sectional and longitudinal studies have reported an inverse correlation between serum testosterone level and indices of obesity and metabolic risk (reviewed in ref. [51]). In turn, interventional studies have shown a beneficial effect of testosterone replacement therapy on BMI, adipose tissue distribution, and body composition in hypogonadal men [14]. An essential voice in the discussion on the direction and causality of the relationship between adiposity and serum testosterone levels came from the genetic studies. The genetic risk for BMI was inversely associated with serum testosterone levels, while no association was observed between the genetic risk testosterone levels and BMI, suggesting that it is mainly adiposity affecting testosterone levels rather than the other way around [52].

4.2 Obesity-related gonadal dysfunction in men

Both in men and women, hypogonadism can be the cause but also the consequence of obesity. In a recent meta-analysis, the prevalence of hypogonadism in obese men in general, when measuring total testosterone (TT), was 43,8%, while in severely obese individuals referred to bariatric surgery – 75,0% [14]. Several underlying mechanisms are responsible for the development of obesity-related hypogonadism in men. Firstly, obesity is associated with increased aromatase cytochrome P450 activity in adipose tissue, resulting in the enhanced conversion of testosterone to estradiol. Subsequently, higher estradiol levels *via* stimulation of estrogen receptor β downregulate glucose transporter (GLUT) 4 induce insulin resistance [53]. In turn, insulin resistance leads to the decreased sex-hormone-binding globulin (SHBG) synthesis in the liver, which translates to a larger amount of TT available for conversion to estradiol in adipose tissue. In turn, high estrogen levels inhibit gonadotropin secretion from the pituitary gland. Therefore, obesity impairs sperm concentration, motility, and morphology, too [54]. Furthermore, the HPG axis is modulated by adipokines. For instance, elevated leptin levels inhibit the production of testosterone by Leydig cells, while low adiponectin concentrations contribute to hepatic insulin resistance in this way, further influencing SHBG synthesis [53, 55]. In addition, described above, obesity-associated dysfunction of the HPA axis

resulting in functional hypercortisolism may contribute to the gonadotropin inhibition and, subsequently, reduced testosterone levels [56].

ESE does not recommend performing a routine hormonal screening for male hypogonadism in patients with obesity; however, testing should be considered when the clinical picture is suspicious. Then, TT plasma morning concentrations should be measured as an initial investigation, and when the result is low, the measurement should be repeated on two separate days in a fasting state. Since the equilibrium dialysis, which is the gold standard procedure to measure free testosterone, is hardly available, ESE suggests calculating bioavailable testosterone by using TT, SHBG, and albumin concentrations, when TT concentration is near the lower limit of the normal range [5, 57]. When low testosterone level is confirmed, the next step in the diagnostic algorithm includes measurement of FSH and LH to distinguish between primary and secondary hypogonadism [5]. Obesity-related hypogonadism in males is associated with low gonadotropin levels and sometimes with a predominance of FSH over LH, and its diagnosis requires exclusion of other causes of hypogonadotropic (secondary) hypogonadism [58]. When interpreting a testosterone measurement result, one should remember its level declines with age and can be affected by chronic diseases, drugs, lifestyle, and genetic predisposition [59]. Moreover, the assay technique used impacts the measurement result with the liquid chromatography–tandem mass spectrometry (LC–MS) method being a golden standard in sex steroids level determination [60]. The testosterone norms for obese individuals do not differ from the reference ranges accepted for the whole population; however, these vary between the countries [5]. In general, the diagnosis of male obesity-secondary hypogonadism should be based on a combination of low testosterone levels with clinical features of hypogonadism, including decreased sexual thoughts, erectile dysfunction, and reduced morning erections [61].

Since obesity can lead to functional male hypogonadism, which, in a vicious circle, can further promote obesity, the first-line therapy is focused on weight management. Unfortunately, non-invasive approaches focused on lifestyle modification aiming at 5% weight loss are frequently insufficient to normalize testosterone levels, and the best results can be achieved employing bariatric surgery [62]. In turn, due to the potential risks (e.g., those related to increased prothrombotic activity), testosterone replacement is not routinely recommended in obese individuals with functional male hypogonadism. However, it can be considered if testosterone levels and/or hypogonadism signs and symptoms do not improve [5].

In summary, low testosterone serum levels in obese men are frequent; however, it does not equate to androgen deficiency. Moreover, obesity-secondary hypogonadism in men is functional and can be reversed by proper weight management. The clinical assessment is of pivotal importance in assessing the causality of the relationship between body adiposity and hypogonadism. If the signs and symptoms of testosterone deficiency occurred first, before the weight gain – the diagnosis of hypogonadism as a cause of obesity can be established and testosterone replacement treatment administered. In the context of the metabolic risk, it is still unclear whether low testosterone levels in obesity are a marker or a risk factor for metabolic complications. The clinical approach to obesity-associated hypogonadism in men is summarized in **Figure 3**.

4.3 Obesity-related gonadal dysfunction in women

While obese men struggle with testosterone deficiency, the most common consequence of obesity in the context of HPG axis dysfunction in women is hyperandrogenism, frequently associated with hyperinsulinemia and infertility. The exact prevalence of biochemical hyperandrogenism in obese women is unknown

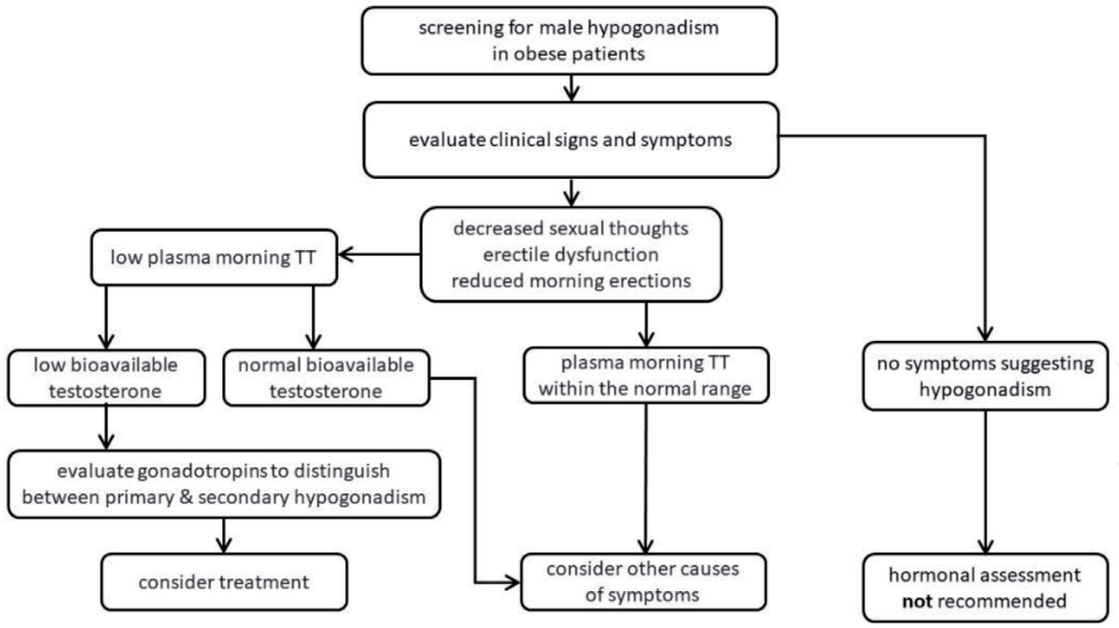

Figure 3.
The clinical approach to obesity-associated hypogonadism in men (based on ref. [5]). TT, total testosterone.

since most epidemiological studies were focused on the incidence of polycystic ovary syndrome (PCOS), which diagnosis can be established without the presence of clinical/biochemical androgen excess. However, the prevalence of PCOS in obese women is similar to the general population in reproductive age (25–29%) but increases with BMI [14].

In obese women, especially in those with visceral obesity, low SHBG levels lead to a relative increase in estrogens' concentration that stimulates the pulsatile LH secretion and subsequent steroidogenesis in the theca cell system. Similarly, high insulin and insulin-like growth factor I (IGF-I) levels stimulate 17α-hydroxylase activity in the theca cells, increasing the secretion of ovarian androgens [63]. In addition, obesity-related HPA axis dysfunction (described above) results in increased synthesis of adrenal androgens. In turn, adipose tissue of obese women is characterized by a higher activity of 5α-reductase, which transforms testosterone into a much more active androgen – dihydrotestosterone [64]. All these changes clinically manifest by hyperandrogenism (most often hirsutism) and menstrual and/or ovulation dysfunction. The cause of ovulation dysfunction in obese women may also be an increased concentration of leptin, which, by binding its receptors in the ovary, inhibits follicle maturation and steroidogenesis [65]. Furthermore, an obesity-associated increase in pro-inflammatory cytokines secretion from adipose tissue also contributes to the disturbing gonadotropin secretion in the pituitary [66]. Therefore, the percentage of ovulation cycles decreases with BMI, reaching only 12% in individuals with BMI ≥ 35 kg/m^2 and obese women, even when eumenorrheic, have reduced fecundity and worse outcomes of the *in vitro* fertilization (IVF) [67]. Apart from the HPG dysfunction, obesity negatively influences the oocyte and the embryo development that manifests by disrupted meiotic spindle formation and mitochondrial function. Moreover, obesity-associated low-grade inflammation has a toxic effect on the reproductive tissues, including the endometrium, characterized by impaired stromal decidualization that leads to impaired receptivity and placental abnormalities. In addition, chronic inflammation and the altered adipokines secretion impairs steroidogenesis and can directly affect the embryo. All these factors contribute to the higher rates of miscarriage, stillbirth, and preeclampsia in obese women [68].

Studies in women with PCOS show that weight loss achieved by a lifestyle intervention may reduce hyperinsulinemia and thus break the vicious cycle of excessive androgen synthesis [69]. Similar changes occur in obese women who experience weight loss as a result of bariatric procedures. In a recent meta-analysis, resolution of PCOS was found in 96% of affected women after bariatric surgery, which was associated with an increase in SHBG level and a decrease in serum estradiol and TT. These changes in sex hormone levels in 53% of individuals resulted in the resolution of hirsutism and 96% – in the resolution of menstrual dysfunction [70]. However, most studies on the assessment of androgen concentrations in obese women were based on measurements performed with immunoassays, which are characterized by a high percentage of false-positive results, and as it was mentioned above, currently the reference method in the measurement of androgen concentrations is LC–MS [71]. In the context of infertility, in obese women, successful weight loss improves ovulation rates and menstrual irregularity, increasing the chances of pregnancy due to natural conception and IVF. According to meta-analyses, there appears to be no significant difference between the patients after weight-loss interventions and never obese controls concerning rates of miscarriage and IVF conceptions [67]. However, there is still a lack of randomized controlled trials that would assess, for instance, the effect of weight loss on numbers of oocytes retrieved for IVF and time to conception.

ESE guidelines do not recommend routine testing for gonadal dysfunction in female obese patients unless clinical symptoms (e.g., acne, hirsutism, androgenic alopecia, acanthosis nigricans, menstrual abnormalities, oligo-anovulation, infertility) occur. When there is a clinical suspicion of PCOS, the diagnostic procedures should include hormonal testing and ovarian ultrasound. If the diagnosis of PCOS is excluded, other diseases leading to hyperandrogenism and infertility should be considered, e.g., hyperprolactinemia, thyroid dysfunction, congenital adrenal hyperplasia, and hypercortisolism. If PCOS is diagnosed, additional testing toward glucose intolerance should be performed [5].

In summary, hyperandrogenism and infertility seem to be the main manifestation of obesity-related HPG axis dysfunction in women, and in both, weight management should be considered first-line therapy. However, if the HPG axis dysfunction sustains despite the successful weight loss or if the patient presents signs and/or symptoms suggesting an underlying disease not related to obesity, the causative treatment should be undertaken.

5. Conclusions and further directions

The increasing incidence of obesity translates to the increased number of obese individuals referred to endocrinologists, either because of clinical suspicion of an underlying endocrine disease-causing weight gain or concern that obesity may have caused endocrine dysfunction. As described above, the relationship between obesity and endocrine dysfunction is bidirectional and complex and concerns all main hormonal axes. Based on the meta-analyses of observational and interventional studies, endocrine sociates proposed clinical guidelines to facilitate the management of obese individuals in everyday practice. In most cases, those guidelines advise a cautious approach and limit the diagnostics to the cases with a clear clinical picture. Apart from the TSH measurement, no other hormonal assessment is recommended to an asymptomatic obese individual unless he or she is referred to bariatric surgery when a screening toward hypercortisolism should be performed.

Since most obesity-related hormonal disturbances are reversible in the case of HPT and HPG axes, weight management should be the first-line strategy, and

treatment considered if the abnormalities sustain despite the weight loss. However, given the diversity of changes in the HPA axis that occur in obese individuals, the influence of weight management on cortisol secretion requires further investigation.

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Conflict of interest

The author declares no conflict of interest.

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