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Adipose tissue as a cause of endocrine dysfunction

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Abstract

Adipose tissue is a large hormonally active organ that secretes several substances (adipokines), and an important site for the synthesis and metabolism of steroid hormones. With energy balance, the secretory and metabolic activity of adipose tissue determines the normal function of many organs, including the endocrine glands. However, in the course of overweight and obesity, adverse changes occur in the structure and function of adipocytes. Obesity-related adipose tissue dysfunction translates into a change in the profile of secreted adipokines, and it impairs steroidogenesis. These phenomena contribute to the development of obesity-related complications, which also affect the major tropic axes regulating the endocrine glands. However, there is increasing evidence that weight reduction is an effective treatment for obesity-related adipose tissue dysfunction, thereby restoring endocrine function. This narrative review presents the impact of adipose tissue on endocrine gland activity both in the physiological state and in obesity-related dysfunction. It also discusses how functional (related to excess adiposity) changes in the endocrine system can be restored with effective treatment of obesity. **(Endokrynol Pol 2023; 74 (5): 468–479)**

Key words: *adipose tissue; adipokines; hormonal homeostasis; obesity; adipose tissue dysfunction; lifestyle interventions; glucagon-like peptide 1 receptor agonists (GLP-1RAs); bariatric surgery*

Introduction

The concept and definition of the endocrine system have evolved over the past several years. Nowadays, we do not consider it only as classical endocrine glands under the control of the hypothalamic-pituitary axis, but we also incorporate the presence of other sources of hormones such as adipose tissue. There are complex interactions between "classical" and "non-classical" endocrine glands that, in a state of health, ensure the body's homeostasis. On the one hand, under- and over-activity of the "classical" endocrine glands affects the metabolism and function of adipose tissue, the effects of which are part of the clinical picture observed in, for example, patients with hypercortisolaemia, hypothyroidism, or hypogonadism. On the other hand, abnormalities in adipocyte metabolism and secretory activity, such as those seen in patients with obesity, can translate into changes in pituitary, thyroid, or gonadal function. The ability to identify the primary cause of the observed hormonal abnormalities is crucial for choosing an appropriate therapeutic strategy.

The purpose of this narrative review is to present the impact of adipose tissue on endocrine gland activity, both in the physiological state and in obesity-related dysfunction. It will also discuss how the function of the endocrine system can be restored by effective treatment of overweight and obesity.

The role of adipose tissue in hormonal homeostasis

Research over the past 20 years has changed our understanding of the role of adipose tissue in maintaining the body's homeostasis. It is no longer perceived solely as an energy store, but also as a secretory organ that produces substances (adipokines) that affect the functioning of other organs and tissues [1]. At the same time, adipose tissue is the site of synthesis and metabolism of several steroid hormones, which are released into the bloodstream and contribute to the pool of endogenous steroids [2]. The proper functioning of the endocrine system is determined by signals received from adipose tissue and by normal steroid hormone metabolism in adipocytes.

The effect of secretory activity of adipose tissue on endocrine gland function

The hypothalamic–pituitary–insulin–like growth factor 1 axis

The adipokine best studied for its modulatory effect on the hypothalamic-pituitary-insulin-like growth factor 1

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(IGF-1) axis is leptin, a pleiotropic hormone that affects multiple areas of the brain and thus regulates food intake, motivation, learning, memory, cognitive function, neuroprotection, energy expenditure, and more [3]. From the point of view of endocrine functions, the effect of leptin on growth and gonadal function is particularly important.

In animal models, intrathalamic administration of leptin increases the secretion of growth hormone-releasing hormone (GHRH) through direct effects on relevant neurons, as well as through inhibition of somatostatin secretion [4]. Moreover, leptin can stimulate growth hormone secretion via its impact on somatotropin-releasing cells in the pituitary [5]. Subsequently, individuals with congenital leptin deficiency may have growth hormone (GH) concentrations at the lower limit and decreased GH response to insulin-induced hypoglycaemia [6].

The relationship between other adipokines and GH secretion is not so direct. By influencing body composition, including adipose tissue content, GH-IGF-1 can modulate the secretion of, for example, adiponectin, resistin, or visfatin. Consequently, children with growth hormone deficiency have higher adiponectin and lower resistin concentrations than healthy peers [7].

The hypothalamic–pituitary–gonadal axis

In the brain, leptin acts also on ventral premammillary neurons, which secrete kisspeptin (Kiss1) to stimulate proper gonadotropin-releasing hormone (GnRH) pulsatility, necessary for gonadotropin release [8]. In addition to its stimulating effect at the level of the hypothalamus, leptin also exerts a direct effect on its receptors located in the anterior lobe of the pituitary. Thus, leptin can stimulate the release of luteinizing hormone (LH) and, to a lesser extent, folliculotropic hormone (FSH) [9]. In addition to affecting the secretion of GnRH and gonadotropins, leptin has a direct effect on the gonads. The presence of leptin receptors has been demonstrated on the surface of ovarian follicular cells, including granulosa cells, theca cells, and interstitial cells as well as Leydig cells [10, 11]. However, the effect of leptin on ovarian target cells is biphasic: while its physiological levels are crucial for ovulation and steroid hormone synthesis, high concentrations of leptin have an inhibitory effect on ovulation and steroidogenesis in the ovaries. In men, the prepubertal increase in leptin promotes testicular development. However, the decrease in leptin levels in prepubertal boys reflects the inhibition of leptin secretion by rising androgens. In adult men, leptin levels are between 10% and 50% of those in women, and high leptin concentrations inhibit testicular function (reviewed in [8]). Consistently, leptin deficiency (in the course of, for example, eating disorders) results in hypothalamic-pituitary-gonadal (HPG) axis dysfunction, while administration of leptins can stimulate central networks regulating gonadotropin secretion [12], whereas obesity-related hyperleptinaemia can exert an inhibitory effect on the gonads and result in impaired fertility and symptoms of hypogonadism, as discussed in the following sections.

Ovarian cells also express receptors for other adipokines. For example, resistin, through activation of its receptors present in human granulosa cells, inhibits progesterone and estradiol secretion in response to IGF-1 stimulation in vitro [13]. In addition, this pro-inflammatory adipokine, by enhancing the activity of 17α-hydroxylase, promotes the ovarian synthesis of testosterone and in a dose-dependent manner regulates LH release from the pituitary gland [14, 15]. However, the in vivo effect of resistin on the HPG axis may depend on nutritional status and co-morbidities: in women with anorexia nervosa serum resistin levels correlated positively with LH and estradiol levels, while in patients with polycystic ovarian syndrome (PCOS) it correlated negatively [16, 17]. In turn, adiponectin, by binding its receptors (AdipoR1 and AdipoR2), was found to decrease ovarian steroidogenesis in vitro by inhibition of the cytochromes CYP17A1 and CYP11A1 [18]. Interestingly, adiponectin receptors are also expressed in the hypothalamus. Experimental data suggest that short-term administration of adiponectin inhibits GnRH, and subsequently LH, secretion. Because high LH levels induce adiponectin release from the ovaries, this mechanism resembles a classic feedback loop [19]. Interestingly, the effect of adiponectin on steroidogenesis in the testes is the opposite of that in the ovary: it increases testosterone synthesis, which is accompanied by increased anti-oxidative enzyme activity [20]. A similar gender-dependent effect on steroidogenesis in the gonads is observed for visfatin. In the ovaries, visfatin, by activation of sirtuin 1 gene expression, can promote steroidogenesis, and it leads to increased estradiol secretion by granulosa cells in vitro [21]. However, it exerts the opposite effect on the testes by inhibiting testosterone synthesis [22].

The hypothalamic–pituitary–thyroid axis

Leptin also plays an important role in the regulation of the hypothalamic-pituitary-thyroid (HPT) axis by controlling thyrotropin-releasing hormone (TRH) gene expression in the paraventricular nucleus and by regulating thyrotropin (TSH) release from the pituitary gland [23]. Moreover, the HPT axis is indirectly regulated by the interaction of leptin with the melanocortin pathway, because alpha-MSH (melanocyte-stimulating hormone) stimulates and AgRP (agouti-related protein) blocks TRH release [24]. In addition, leptin can increase the ex-

pression of prohormone convertases PC1/3 and PC2, responsible for the activation of TRH from proTRH [25]. These phenomena occur in a dose-dependent [26]. Even though leptin deficiency is usually not associated with abnormal thyroid hormone levels, it interrupts the circadian rhythm of TSH [27].

The effects of other adipokines on HPT axis function are less well investigated. However, clinical studies suggest a positive association between circulating adiponectin levels and free thyroxine (fT4) [28]. Even though this relationship may be partly secondary to the effect of thyroid hormones on insulin sensitivity, the carboxy-terminal globular structure of adiponectin was shown to have an affinity for the gC1q receptor in the mitochondria of thyrocytes, and thus adiponectin may regulate thyroid hormone production [29]. There has also been much controversy about studies suggesting a protective role for adiponectin in thyroid cancer risk. However, based on existing data, it is not clear whether adiponectin plays a protective role in thyroid cancer alongside or independently of nutritional status [30]. In turn, resistin has been found to regulate the activity of iodothyronine deiodinase type I, and its serum levels may correlate positively with fT4 concentrations [16], while chemerin concentrations correlate positively with the risk of thyroid autoimmunity [31]. In contrast, data on the effects of visfatin and vaspin on HPT axis function, TSH, and thyroid hormone levels are inconsistent and depend on the type of study population and the co-occurrence of autoimmune thyroid disease in study participants [reviewed in 32].

Of note, the physiological relation between the HPT axis and adipose tissue is bidirectional, because adipocytes express receptors for thyroid hormones and TSH, which can subsequently modulate adipose tissue metabolism [31, 33]. Indeed, TSH was found to stimulate the expression of leptin and proinflammatory cytokines including interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-α) [34].

The hypothalamic–pituitary–adrenal axis

The hypothalamic-pituitary-adrenal (HPA) axis is also subject to the modulating effect of adipokines. Leptin can inhibit glucocorticoid synthesis, both centrally in the paraventricular nucleus of the hypothalamus [35] and peripherally in the adrenals [36]. During starvation, leptin levels decrease, which triggers a counter-regulatory increase in cortisol, activating brain circuits that drive motivation to eat [37]. Moreover, leptin induces the adrenal production of aldosterone, and its deficiency is associated with hypotension [6, 38]. Similarly, adiponectin, via activation of its receptors in the adrenal cortex, was found to inhibit corticosterone and aldosterone secretion, which was accompanied by decreased expression of the key genes involved in steroidogenesis [39]. The effects of other adipokines on adrenal steroidogenesis are currently the subject of numerous basic and clinical studies.

It should also be noted that glucocorticoid hormones are important regulators of lipid metabolism in adipose tissue, promoting lipolysis in acute conditions but lipogenesis with chronic exposure. This differential effect of glucocorticoids on lipid metabolism is mediated by different receptors. Stimulation of the glucocorticoid receptor (GR) type α has a lipolytic effect. In contrast, the receptor for mineralocorticoids, also activated by cortisol, appears to be the main stimulator of adipogenesis. GRβ, on the other hand, can be regulated by both glucocorticoids and insulin, resulting in the promotion of lipogenesis [40]. The final effect is influenced not only by the pool of circulating glucocorticoids but also by those produced locally in adipocytes, as described in the next section.

Adipose tissue as a site of hormone synthesis and metabolism

Adipose tissue is an important site for the synthesis and metabolism of steroid hormones (Fig. 1). Classical steroidogenic tissues (e.g. adrenals, gonads, and placenta) are able to synthesize steroid hormones de novo from cholesterol, whereas steroidogenesis in other tissues mainly involves the conversion of various precursors obtained from the circulation [2]. This rule applies to adipose tissue, although the early stages of steroid synthesis can also take place in adipocytes [41].

The primary steroid metabolism occurring in adipose tissue concerns the conversion of androgens to oestrogens. Aromatase (CYP19A1) is a key enzyme for oestrogen synthesis; however, the effect of its activity depends on the local availability of its substrates, the androgens. While in the ovary (where the main androgen available is testosterone) CYP19A1 activity results in the synthesis of estradiol (E2), in adipocytes [where the main substrate is androstenedione synthesized from dehydroepiandrosterone (DHEA) and its sulphate produced in the adrenals] aromatization leads to the synthesis of estrone (E1) [2]. An alternative pathway for E1 synthesis in adipose tissue is the oxidation of E2 in a reaction catalysed by the 17β-hydroxysteroid dehydrogenases (17βHSD) types 1, 7, and 12. E1 formed by both types of reactions can be converted by steroid sulfotransferase (STS) to estrone sulphate, which is the most important component of the circulating oestrogen pool. Another enzyme regulating the local availability of sex steroids is hormone-sensitive lipase (LIPE), which hydrolyses the fatty acyl esters (FAEs) of DHEA and E2. E2 esterified with fatty acyl esters is its storage form, in-

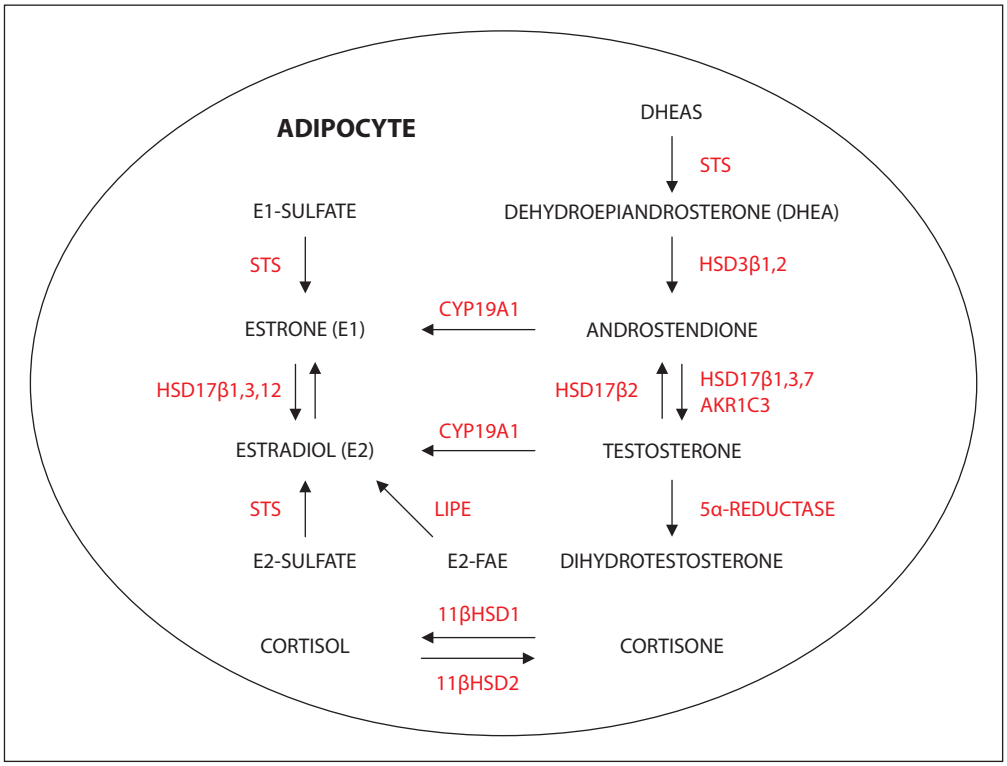

Figure 1. *Simplified diagram of adipocyte steroidogenesis. DHEA — dehydroepiandosterone; DHEAS — dehydroepiandrosterone sulfate; STS — steroid sulfotransferase; E1 — estrone; E2 — estradiol; HSD17β — 17β-hydroxysteroid dehydrogenase; AKR1C3 — aldo-keto reductase family 1 member C3; LIPE — hormone-sensitive lipase; FAE — fatty acyl esters*

REVIEW

capable of exerting its biological functions. Therefore, the balance between esterification and hydrolysis of E2 is an important mechanism regulating the levels of biologically active steroids [42].

The pool of steroid hormones accumulated in adipose tissue is significant: in pre- and postmenopausal women, progesterone, DHEA, androstenedione, and E1 are 5-20 times higher in subcutaneous and visceral adipose tissue than in serum [43]. Irrespective of gender, the most abundant steroids in adipose tissue are DHEA and androstenedione. However, in women, E2 concentrations in subcutaneous adipose tissue are higher than in men, which correlates with higher expression of genes encoding oestrogen-converting enzymes [42]. Importantly, the course of steroidogenesis in adipose tissue may depend on menopausal and nutritional status. Conversely, cortisol in adipose tissue and cortisone in women is reportedly only 10–20% of the concentrations found in serum [43]. Glucocorticoid metabolism in adipocytes is primarily regulated by 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1), an enzyme converting inactive 11β-ketoglucocorticoid metabolites (e.g. cortisone) to active 11β-hydroxylated metabolites (e.g. cortisol). 11βHSD1 is highly expressed in human adipose tissue, particularly in the visceral depot; however, adipocyte-specific cortisol synthesis amplifies its local concentrations without affecting circulating levels [44].

Obesity-related adipose tissue dysfunction

Up to 60% of the European adult population is overweight and obese, which is associated with more than 200 complications affecting virtually all tissues and organs in the human body [45]. Many obesity-related complications are caused by phenomena within the adipose tissue itself.

Hypertrophy in response to excess nutrients causes profound changes in adipocyte metabolism. The primary mechanism involved in this process is mitochondrial dysfunction, manifested by decreased activity of cellular pathways of fatty acid oxidation, ketone body metabolism, and the tricarboxylic acid cycle, together leading to adipocyte apoptosis, defective differentiation of preadipocytes into mature cells, and adipose tissue fibrosis (reviewed in [46]). These phenomena result in increased expression of genes encoding cytokines, chemokines, and adhesion molecules that attract immune cells (mainly macrophages and various subpopulations of lymphocytes), which further contribute to the synthesis of pro-inflammatory mediators. Pro-inflammatory cytokines (such as IL-1β, IL-6, or TNF-α) impair

adipocyte metabolism in an auto- and paracrine manner but also affect the function of distant tissues and organs, including endocrine glands [47].

Notably, the excess of nutrients not only induces the adipocyte to synthesize pro-inflammatory mediators but also alters the physiological secretion of adipokines. This applies, for example, to adiponectin, the levels of which, measured in the serum and adipose tissue of obese individuals, are significantly lower compared to normal-weight individuals [48]. Conversely, obesity is accompanied by increased leptin secretion and the subsequent development of leptin resistance. As a result, in obese individuals, leptin does not exert an anorectic effect, but through modulation of macrophage and T cell function, it enhances the production of several inflammatory cytokines (including TNF-α, IL-6) [49].

The phenomena described above are referred to as adipose tissue dysfunction and have systemic consequences.

Endocrine consequences of obesity-related adipose tissue dysfunction

The hypothalamic–pituitary–insulin-like growth factor 1 axis

Obesity is associated with reduced spontaneous and stimulated GH secretion that is reversible after weight loss [50]. There are several hypotheses explaining the suppression of GH secretion in obesity. The chief role in this process is played by hyperinsulinaemia resulting from peripheral insulin resistance caused by excessive fat mass accumulation and related metabolic inflammation. This hypothesis provides that in human obesity, insulin sensitivity is preserved in some tissues (e.g. in the hypothalamus and pituitary gland). By inhibiting pituitary GH secretion, insulin suppresses hepatic synthesis of IGF-1 binding protein (IGFBP-1) and subsequently increases free IGF-1 availability and feedback inhibition of GH secretion [50, 51].

The hypothalamic–pituitary–gonadal axis

In both men and women, obesity leads to severe disruption of the HPG axis. In a recent meta-analysis, the prevalence of hypogonadism in obese men [assessed by a decrease in total testosterone (TT)] was estimated at 43.8%. However, among severely obese patients referred for bariatric surgery, low TT concentrations affect up to 75% of men [52]. Several underlying mechanisms are responsible for the development of obesity-related hypogonadism in men. Firstly, obesity is associated with increased cytochrome P450 aromatase activity in adipose tissue, which results in enhanced conversion of testosterone to estradiol. Subsequently, higher concentrations of estradiol, via stimulation of oestrogen receptor β, result in the downregulation of glucose transporter (GLUT) 4 in muscle and adipose tissue, exacerbating insulin resistance [53]. The metabolic inflammation associated with obesity also induces insulin resistance in the liver, resulting in decreased synthesis of sex hormone-binding globulin (SHBG), which translates into more TT available for conversion to estradiol in adipose tissue. In turn, high levels of oestrogen inhibit the secretion of gonadotropins from the pituitary gland. Therefore, obesity also impairs sperm concentration, motility, and morphology [54]. In addition, the HPG axis is modulated by adipokines. For example, elevated leptin levels inhibit testosterone production by Leydig cells, while low adiponectin levels contribute to hepatic insulin resistance, thus further affecting SHBG synthesis [53, 55]. Moreover, the obesity-related HPA axis dysfunction resulting in functional hypercortisolaemia described below may contribute to the inhibition of gonadotropin secretion and subsequent reduction in testosterone levels [56].

In contrast to obese men who are testosterone deficient, the most common manifestation of obesity-related HPG axis dysfunction in women is hyperandrogenism, often associated with hyperinsulinaemia and infertility. The exact prevalence of biochemical hyperandrogenism in obese women is difficult to assess because most epidemiological studies have focused on the prevalence of polycystic ovary syndrome (PCOS), the diagnosis of which in adult women does not always require the presence of clinical/biochemical androgen excess. The prevalence of PCOS in obese women is similar to that in the general population (25–29%), but increases with greater body mass index (BMI) [52]. In turn, obesity is present in 40–70% of PCOS patients [57].

In obese women, metabolic inflammation-related insulin resistance in the liver, as in men, results in a decrease in SHBG synthesis leading to a relative increase in oestrogen concentrations, which stimulates pulsatile LH secretion and subsequent steroidogenesis in theca cells. Similarly, high levels of insulin and IGF-I influence higher 17α-hydroxylase activity in theca cells and increased ovarian androgen synthesis and secretion [58]. A significant part of circulating androgens in obese women originates from the adrenals due to the abnormal HPA axis function (see the following sections). In contrast, the adipose tissue of obese women is characterized by a higher 5α-reductase activity, which converts testosterone into the much more active androgen dihydrotestosterone [59]. Obesity also disrupts the physiological balance between the oestrogens produced in adipose tissue, e.g. causing enhanced conversion of androstenedione to the less active oestrogen — estrone. The rate of conversion of androstenedione into estrone

increases with age and body fat volume and is higher in women with gynoid obesity than in women with android obesity [2]. The result of the phenomena described above is clinical hyperandrogenism (most commonly hirsutism) and menstrual and/or ovulatory disorders. Therefore, excess adiposity in women with PCOS exacerbates not only metabolic but also hormonal dysfunction [reviewed in 60].

Abnormal adipokine secretion also plays its part in the obesity-related disruption of ovarian steroidogenesis and ovulation. Low levels of adiponectin in obese women with PCOS negatively increase LH secretion in the pituitary gland, resulting in a high LH and androgen level and ovulation dysfunction [61]. Similarly, high concentrations of leptin, which, through its receptors in the ovary, inhibit follicle maturation as well as steroidogenesis, are also implicated in the occurrence of ovulatory disorders in obese women [8]. In addition, proinflammatory cytokines secreted due to adipose tissue dysfunction contribute to impaired pituitary gonadotropin secretion [62]. Consequently, the percentage of ovulatory cycles decreases with BMI, reaching only 12% in those with a BMI ≥ 35 kg/m^2, and obese women, even when eumenorrheic, have reduced fertility and poorer in vitro fertilization (IVF) outcomes [63]. It is also important to note that metabolic inflammation has a negative impact on oocyte and embryo development, as manifested by impaired meiotic spindle formation and mitochondrial function. In addition, pro-inflammatory cytokines have toxic effects on reproductive tissues, including the endometrium, which is characterized by impaired stromal decidualization and thus reduced receptivity. All these factors contribute to an increased incidence of miscarriage, stillbirth, and pre-eclampsia in obese women [64].

In conclusion, hyperandrogenism and infertility appear to be the main manifestations of obesity-related HPG axis dysfunction in women, and in both cases weight control should be considered as first-line therapy.

The hypothalamic–pituitary–thyroid axis

Both overt and subclinical hypothyroidism are more prevalent in obese individuals than in normal-weight subjects, and they can affect up to 15.0% of patients [65]. The pathogenesis of obesity-related changes in thyroid hormone levels is complex [34]. The increase in TSH levels in obese patients may be explained by a central resistance to locally produced triiodothyronine (T3), and it represents an adaptive process to increase basal energy expenditure. TSH concentrations correlate positively with BMI and leptin levels, which in turn can directly stimulate TRH and TSH secretion [23, 31]. In addition, leptin has been found to activate deiodinases, enzymes responsible for increasing the conversion of fT4 to free T3 (fT3), which is thought to be another mechanism to increase basal metabolism and energy expenditure [66]. However, obesity-related increases in TSH levels are usually accompanied by normal fT4 and fT3 concentrations (corresponding to central hypothalamic and pituitary resistance) in contrast to subclinical hypothyroidism, in which thyroid hormone levels are usually low normal [67].

Nevertheless, when TSH and fT4 levels in obese patients suggest a diagnosis of subclinical hypothyroidism, screening for autoimmune thyroiditis (AITD) should be performed, especially because elevated leptin levels predispose to thyroid autoimmunity [68]. In this case, the determination of thyroid antibodies is helpful not only in the diagnosis of AITD but also in identifying individuals at risk of developing overt hypothyroidism. Importantly, both subclinical and overt hypothyroidism are risk factors for impaired glucose metabolism, and the fT3/fT4 ratio was found to correlate positively with insulin resistance [69]. Of note, individuals with grade III obesity (BMI ≥ 40 kg/m^2) are characterized by a higher prevalence of autoimmune thyroiditis compared to subjects with a BMI of 30–39.9 kg/m^2 [31].

The ultrasound diagnosis of AITD in obese patients is challenging because they more often present with a hypoechoic thyroid parenchymal picture. The hypoechoic thyroid image in obese patients is due to increased permeability of the thyroid blood vessels caused by pro-inflammatory cytokines secreted by dysfunctional adipose tissue. A fine-needle thyroid biopsy performed in an obese person with a hypoechoic thyroid gland usually does not show lymphocyte infiltration, ruling out Hashimoto's disease. Therefore, the correlation of a suggestive ultrasound image of the thyroid with AITD can be found in only 20% of obese individuals compared to 85.7% in normal-weight controls [70].

In conclusion, the majority of obese individuals are in a euthyroid state although their TSH levels tend to exceed the values observed in normal-weight individuals. Furthermore, obesity is associated with reduced echogenicity of the thyroid gland on ultrasound, which does not reflect the presence of autoimmune thyroid disease. Regardless, obesity increases the risk of thyroid autoimmunity. While several studies (described in the following sections) have found that weight loss leads to the normalization of TSH in most obese individuals, the effect of weight normalization on thyroid echogenicity remains unknown.

The hypothalamic–pituitary–adrenal axis

Obese patients are a highly heterogeneous group in terms of HPA axis function [71]. Whilst in some of them the HPA axis acts normally, in others it is hyper-activated and leads to 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 (resulting from the activation of the 11βHSD1 enzyme) and the increased number of glucocorticoid receptors in peripheral tissues [72]. Although increased 11βHSD1 gene expression and enzyme activity in adipose tissue correlate with BMI in humans, it is unclear whether this phenomenon is a cause or consequence of obesity [72]. Adipose-specific overexpression of 11βHSD1 in experimental animals results in a significant increase in intra-adipose cortisol levels and subsequent development of visceral obesity and its metabolic complications [73]. Otherwise, overexpression of 11βHSD2 (responsible for the inactivation of cortisol to cortisone) in adipose tissue protects from the development of high-fat diet-induced obesity [74]. Similar phenotypes represent mice with knockout of the gene encoding 11βHSD1: they are resistant to diet-induced visceral obesity, with an enhanced lipid metabolism and a decreased adipose tissue inflammation profile [75]. These findings suggest that reduced cortisol levels in adipose tissue may counteract the development of metabolic diseases. This hypothesis was confirmed in a clinical trial, in which 12-week administration of a selective 11βHSD1 inhibitor to patients with type 2 diabetes or metabolic syndrome resulted in a decrease in glycosylated haemoglobin level, blood pressure, and body weight [76].

In healthy subjects, adipose-specific glucocorticoid metabolism amplifies local glucocorticoid concentrations without significantly altering circulating levels. Therefore, it is difficult to assess the extent to which an increase in 11βHSD1 activity in adipose tissue contributes to obesity-related functional hypercortisolism manifesting as increased nocturnal cortisol levels and increased urinary excretion of cortisol metabolites [77]. This hypercortisolism is characterized also by an increased nocturnal adrenocorticotropin (ACTH) release and enlargement of adrenal glands in imaging studies, which suggests also hyperactivation of the corticoliberin (CRH) pathway in the hypothalamus [77]. Irrespective of the pathogenesis, the abnormal HPA axis function is associated with a worse metabolic profile in obese individuals, including higher waist-to-hip ratio (WHR), total and low-density lipoprotein cholesterol, and blood pressure. In addition, obesity-associated HPA axis overactivity may inhibit the secretion of sex steroids and growth hormone and in this way contribute to the development of other hormonal dysfunctions [71].

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.

The role of obesity treatment in the restoration of hormonal homeostasis

Both clinical and preclinical studies show that weight reduction constitutes an effective treatment for obesity-related adipose tissue dysfunction. Lifestyle interventions based on diet combined with exercise lead to the suppression of metabolic inflammation (measured, e.g., as a decrease in C-reactive protein [CRP], IL-6, and TNF-α levels) and the restoration of normal adipokine secretion (e.g. a decrease in leptin and increase in adiponectin concentrations) [78]. Supporting the treatment of obesity with pharmacotherapy or metabolic surgery yields even better results in this field [79, 80]. Restoring the proper function of adipose tissue in terms of both adipokine secretion and steroidogenesis has a beneficial effect on the endocrine system.

Behavioural interventions

Behavioural interventions constitute a basic therapeutic strategy for weight management, regardless of whether they are supported by pharmacotherapy and/or surgery, and even applied alone they have a beneficial effect on the endocrine system.

Lifestyle interventions are efficient in the reduction of obesity-associated thyroid dysfunction. Dietary restriction exerts an inhibitory role on the HPT axis, resulting in a net decrease in circulating TSH and thyroid hormones, thus contributing to a reduction in energy expenditure to compensate for the reduction in energy intake [81]. A 20% energy deficit results not only in a decrease in BMI and percentage body fat but also leptin and TSH serum concentrations with a subsequent increase in fT3/fT4 index. Of importance, an increase in energy deficit from 20% to 50% provokes a greater decline in thyroid hormone plasma concentration, which could hinder further mass reduction [82]. However, a moderate calorie restriction results in a decrease in the number of individuals with TSH levels above the normal range (from 17.2% to 6.2%) [83]. These findings strongly suggest that obesity-associated hyperthyrotropinaemia is transient and resolves after weight loss. The decrease in TSH level during weight loss can be explained by a restoration of normal leptin secretion and sensitivity. However, body weight reduction results in a parallel decline in the peripheral conversion of fT4 to fT3, suggesting that the effects of leptin on the HPT axis do not fully explain the changes in thy-

roid hormone homeostasis observed during weight loss, and this phenomenon requires further research [84].

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 the gene encoding 11βHSD1 in subcutaneous adipose tissue [85]. Although this observation needs to be confirmed by sufficiently powered studies, the concept of an effect of caloric restriction on 11βHSD1 activity is plausible because animal studies suggest that a hypercaloric, high-sugar/fat diet stimulates unfavourable changes in cortisol metabolism that can be restored by a calorie restriction and proper macronutrient composition [86].

Lifestyle interventions are also a first-line therapy for women with obesity-related hyperandrogenism, regardless of the presence of PCOS [60, 87]. Calorie restriction combined with a low glycaemic index/low carbohydrate regimen was shown to be effective in the restoration of the ovulatory function of ovaries and reduction of androgen level [88]. Moreover, in a study of obese women with PCOS, a 20-month lifestyle intervention aiming at weight loss resulted in a complete recovery from all PCOS features (normal androgen blood levels, hirsutism score below 8, and normal menses and ovarian morphology) in 37% of participants, while 48% of patients showed partial improvement [89]. However, it has to be underlined that the restoration of the HPG axis in obese women in response to lifestyle modifications only is highly heterogenous and unpredictable [90].

Because obesity can lead to functional male hypogonadism, which, in a vicious circle, can further promote obesity, the first-line therapy should also be focused on weight management. However, non-invasive approaches focused on lifestyle modification aiming at 5% weight loss are frequently insufficient to normalize testosterone levels [91]. 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.

Pharmacological treatment

Unfortunately, lifestyle interventions are seldom effective in the long run, and most patients regain weight and fail to maintain a normal BMI. Moreover, the probability of successful and sustainable weight loss is adversely proportional to the BMI value [92]. Therefore, contemporary guidelines of obesity management advise the introduction of pharmacological treatment in individuals with BMI ≥ 30 kg/m^2 and in those with BMI ≥ 27 kg/m^2 in whom overweight is associated with at least one obesity-related complication [93, 94].

The choice of the therapeutic option depends on the patient's clinical characteristics. In those with an emotional background in which weight gain seems to dominate in the clinical picture, a combination of bupropion with naltrexone is recommended. Conversely, if the metabolic complications of obesity and/or cardiovascular risk are of therapeutic priority, glucagon-like peptide 1 receptor agonists (GLP-1RAs e.g. liraglutide 3 mg/day or semaglutide 2.4 mg)/week) are the therapy of choice [93, 94]. The cardiometabolic complications of obesity are closely related to adipose tissue dysfunction, and the utility of GLP-1RAs, in this case, is justified by their favourable impact on the metabolic inflammation and restoration of normal adipokine secretion and action, including downregulation of resistin, TNF-α, IL-1β, and IL-6 serum level with a parallel increase in adiponectin concentrations and leptin sensitivity [95, 96, 97]. The abovementioned GLP-1RAs introduced changes that translate also to the improved function of the endocrine system. Moreover, GLP-1RAs may have a direct, drug-specific impact on the endocrine glands' function.

GLP-1 provides a permissive signal to support fertility when metabolic homeostasis is adequate, and its analogues help to restore HPG axis function impaired by obesity [98]. A 16-week administration of liraglutide to obese, hypogonadal patients resulted in a significant enhancement of gonadotropins and testosterone levels [99]. Moreover, in obese, hypogonadal men with type 2 diabetes (T2D) chronic liraglutide treatment was more effective in increasing testosterone levels than testosterone replacement and metformin alone [100]. The impact of GLP-1RA treatments on ovarian steroidogenesis was extensively studied in hyperandrogenic women. A meta-analysis including studies published from 2008 to 2015 revealed that liraglutide treatment in women diagnosed with PCOS resulted in a significant decrease in testosterone levels without influencing SHBG and androstenedione concentrations [101]. The validity of the use of GLP-1RA analogues for the treatment of overweight/obesity in patients with PCOS has been confirmed in several clinical trials. The effect of GLP-1RA therapy is not only weight loss but also an improvement in insulin sensitivity and a reduction in hyperandrogenaemia. This treatment may also increase spontaneous and in vitro pregnancy rates. Therefore, in obese women with PCOS, GLP-1RAs offer an opportunity not only to lose weight but also to improve metabolic, hormonal, and fertility parameters [60].

However, it is still unclear whether GLP-1RAs have a beneficial effect on the HPG axis in the absence of weight loss. In rodents, activation of GLP-1Rs increas-

es hypothalamic levels and stimulates GnRH secretion in a normal energy balance state; however, it does not rescue LH inhibition during negative energy balance [102]. In nonobese, eugonadal men administration of intravenous infusion of GLP-1 reduced food intake but did not alter serum levels of reproductive hormones, including LH and testosterone pulsatility [103]. This finding suggests that weight loss and associated restoration of proper adipose tissue function play the primary role in the GLP-1RAs' induced improvement of HPG axis function in men. However, clinical studies did not address whether the impact of GLP-1 RAs on hyperandrogenism in women is due to a reduction in weight or reflect a direct action of GLP-1RAs at the ovaries [98].

GLP1-RAs therapy has been of concern in terms of increased risk of thyroid disease, as suggested by preclinical studies in rodents. Nevertheless, a recent meta-analysis showed that GLP-1 analogues have no significant influence on the risk of thyroid cancer, hyperthyroidism, hypothyroidism, thyroiditis, thyroid mass, and the prevalence of goitre [104]. Moreover, liraglutide treatment, parallel to weight loss, leads to a decrease in TSH accompanied by restoration of impaired TRβ expression and in this way may improve obesity-associated thyroid hormone resistance [105].

Bariatric surgery

Even though appropriately selected pharmacotherapy enables the achievement of significant weight reduction, bariatric surgery remains the only treatment option for some patients. New guidelines of the American Society of Metabolic and Bariatric Surgery and the International Federation for the Surgery of Obesity and Metabolic Disorders recommend bariatric surgery in patients with BMI ≥ 35 kg/m^2. Surgical treatments should also be considered in individuals with obesity-related complications and a BMI of 30–34.9 kg/m^2, while in the Asian population, as early as BMI ≥ 27.5 kg/m^2 [106]. As well as leading to significant weight loss, bariatric surgery is also effective in restoring proper adipose tissue function. A decrease in pro-inflammatory cytokines (e.g. TNF-α, IL-6, IL-8) and acute-phase protein serum levels are systematically reported in bariatric patients [107]. This phenomenon is associated with morphological changes in adipose tissue (reduction in adipocyte size and the number of infiltrating macrophages) and favourable changes in secretion of adipokines, which translate to the improvement of endocrine gland function [108].

The influence of bariatric procedures on the HPT axis has been investigated in several prospective and observational studies, with controversial results; however, meta-analyses consistently report that surgically-induced weight loss leads to a decrease in TSH and FT3 levels [109]. These phenomena correlate with a decline in inflammatory parameters and changes in vaspin and leptin concentrations and may contribute to the compensatory reduction of energy expenditure and catabolism that typically accompany weight loss [110].

The effect of bariatric surgery on improving HPG axis function in both sexes has also been widely reported. Despite some differences in results between individual studies, meta-analyses confirmed that sustained weight loss induced by bariatric surgery leads to a significant improvement of reproductive hormones: an increase in gonadotropins, total testosterone, and SHBG levels and, conversely, a decrease in DHEA and E2 concentrations in males, while in females: increase in gonadotropins and SHBG and decrease in androstenedione and testosterone levels [111, 112]. Subsequently, significant resolution of hirsutism is observed in 53% of women with PCOS after bariatric surgery, while the resolution of menstrual dysfunction is seen in 96% [113].

There are also data showing that bariatric surgery, by reducing metabolic inflammation, leads to the restoration of the GH-IGF-1 axis [114].

Conclusions

The increasing incidence of obesity confronts physicians with the need to diagnose and treat this group of patients. In selecting appropriate management, it is crucial to distinguish which endocrine abnormalities observed in obese individuals are a manifestation of primary endocrine gland disease and which are functional and secondary to obesity-related adipose tissue dysfunction. In the case of obesity-induced functional endocrine system impairment, weight loss management is crucial. Weight loss by ceasing metabolic inflammation and restoring normal steroidogenesis and adipokine secretion in adipose tissue can be an effective and causative treatment for obesity-related endocrine dysfunction. Furthermore, a purely symptomatic approach (e.g. levothyroxine supplementation for obesity-induced hyperthyrotropinaemia or testosterone administration to obese men with functional hypogonadism) may not only fail to produce clinical effects but potentially expose the patient to complications associated with unwarranted therapy [65].

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Conflicts of interest

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References

1. Cypess AM, Cypess AM. Reassessing Human Adipose Tissue. N Engl J Med. 2022; 386(8): 768–779, doi: 10.1056/NEJMra2032804, indexed in Pubmed: 35196429.
2. Li J, Papadopoulos V, Vihma V. Steroid biosynthesis in adipose tissue. Steroids. 2015; 103: 89–104, doi: 10.1016/j.steroids.2015.03.016, indexed in Pubmed: 25846979.
3. Morrison CD. Leptin signaling in brain: A link between nutrition and cognition? Biochim Biophys Acta. 2009; 1792(5): 401–408, doi: 10.1016/j.bbadis.2008.12.004, indexed in Pubmed: 19130879.
4. Watanobe H, Habu S. Leptin regulates growth hormone-releasing factor, somatostatin, and alpha-melanocyte-stimulating hormone but not neuropeptide Y release in rat hypothalamus in vivo: relation with growth hormone secretion. J Neurosci. 2002; 22(14): 6265–6271, doi: 10.1523/JNEUROSCI.22-14-06265.2002, indexed in Pubmed: 12122085.
5. Saleri R, Giustina A, Tamanini C, et al. Leptin stimulates growth hormone secretion via a direct pituitary effect combined with a decreased somatostatin tone in a median eminence-pituitary perifusion study. Neuroendocrinology. 2004; 79(4): 221–228, doi: 10.1159/000078103, indexed in Pubmed: 15153755.
6. Ozata M, Ozdemir IC, Licinio J. Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects. J Clin Endocrinol Metab. 1999; 84(10): 3686–3695, doi: 10.1210/jcem.84.10.5999, indexed in Pubmed: 10523015.
7. Witkowska-Sędek E, Rumińska M, Stelmaszczyk-Emmel A, et al. The associations between the growth hormone/insulin-like growth factor-1 axis, adiponectin, resistin and metabolic profile in children with growth hormone deficiency before and during growth hormone treatment. Acta Biochim Pol. 2018; 65(2): 333–340, doi: 10.18388/abp.2018_2601, indexed in Pubmed: 29913483.
8. Childs GV, Odle AK, MacNicol MC, et al. The Importance of Leptin to Reproduction. Endocrinology. 2021; 162(2), doi: 10.1210/endocr/bqaa204, indexed in Pubmed: 33165520.
9. Jin L, Burguera BG, Couce ME, et al. Leptin and leptin receptor expression in normal and neoplastic human pituitary: evidence of a regulatory role for leptin on pituitary cell proliferation. J Clin Endocrinol Metab. 1999; 84(8): 2903–2911, doi: 10.1210/jcem.84.8.5908, indexed in Pubmed: 10443698.
10. Cioffi JA, Shafer AW, Zupancic TJ, et al. Novel B219/OB receptor isoforms: possible role of leptin in hematopoiesis and reproduction. Nat Med. 1996; 2(5): 585–589, doi: 10.1038/nm0596-585, indexed in Pubmed: 8616721.
11. Tena-Sempere M, Manna PR, Zhang FP, et al. Developmental and hormonal regulation of leptin receptor (Ob-R) messenger ribonucleic acid expression in rat testis. Biol Reprod. 2001; 64(2): 634–643, doi: 10.1095/biolreprod64.2.634, indexed in Pubmed: 11159367.
12. Boutari C, Pappas PD, Mintziori G, et al. The effect of underweight on female and male reproduction. Metabolism. 2020; 107: 154229, doi: 10.1016/j.metabol.2020.154229, indexed in Pubmed: 32289345.
13. Reverchon M, Cornuau M, Ramé C, et al. Resistin decreases insulin-like growth factor I-induced steroid production and insulin-like growth factor I receptor signaling in human granulosa cells. Fertil Steril. 2013; 100(1): 247–55.e1, doi: 10.1016/j.fertnstert.2013.03.008, indexed in Pubmed: 23548939.
14. Munir I, Yen HW, Baruth T, et al. Resistin stimulation of 17alpha-hydroxylase activity in ovarian theca cells in vitro: relevance to polycystic ovary syndrome. J Clin Endocrinol Metab. 2005; 90(8): 4852–4857, doi: 10.1210/jc.2004-2152, indexed in Pubmed: 15886251.
15. Maillard V, Elis S, Desmarchais A, et al. Visfatin and resistin in gonadotroph cells: expression, regulation of LH secretion and signalling pathways. Reprod Fertil Dev. 2017; 29(12): 2479–2495, doi: 10.1071/RD16301, indexed in Pubmed: 28672116.
16. Ziora KT, Oswiecimska JM, Swietochowska E, et al. Assessment of serum levels resistin in girls with anorexia nervosa. Part II. Relationships between serum levels of resistin and thyroid, adrenal and gonadal hormones. Neuro Endocrinol Lett. 2011; 32(5): 697–703, indexed in Pubmed: 22167129.
17. Raeisi T, Rezaie H, Darand M, et al. Circulating resistin and follistatin levels in obese and non-obese women with polycystic ovary syndrome: A systematic review and meta-analysis. PLoS One. 2021; 16(3): e0246200, doi: 10.1371/journal.pone.0246200, indexed in Pubmed: 33740002.
18. Lagaly DV, Aad PY, Grado-Ahuir JA, et al. Role of adiponectin in regulating ovarian theca and granulosa cell function. Mol Cell Endocrinol. 2008; 284(1-2): 38–45, doi: 10.1016/j.mce.2008.01.007, indexed in Pubmed: 18289773.
19. Rodriguez-Pacheco F, Martinez-Fuentes AJ, Tovar S, et al. Regulation of pituitary cell function by adiponectin. Endocrinology. 2007; 148(1): 401–410, doi: 10.1210/en.2006-1019, indexed in Pubmed: 17038552.
20. Choubey M, Ranjan A, Bora PS, et al. Role of adiponectin as a modulator of testicular function during aging in mice. Biochim Biophys Acta Mol Basis Dis. 2019; 1865(2): 413–427, doi: 10.1016/j.bbadis.2018.11.019, indexed in Pubmed: 30471430.
21. Reverchon M, Rame C, Bunel A, et al. VISFATIN (NAMPT) Improves In Vitro IGF1-Induced Steroidogenesis and IGF1 Receptor Signaling Through SIRT1 in Bovine Granulosa Cells. Biol Reprod. 2016; 94(3): 54, doi: 10.1095/biolreprod.115.134650, indexed in Pubmed: 26792944.
22. Jeremy M, Gurusubramanian G, Roy VK. Localization pattern of visfatin (NAMPT) in d-galactose induced aged rat testis. Ann Anat. 2017; 211: 46–54, doi: 10.1016/j.aanat.2017.01.009, indexed in Pubmed: 28163205.
23. Ortiga-Carvalho TM, Oliveira KJ, Soares BA, et al. The role of leptin in the regulation of TSH secretion in the fed state: in vivo and in vitro studies. J Endocrinol. 2002; 174(1): 121–125, doi: 10.1677/joe.0.1740121, indexed in Pubmed: 12098670.
24. Kim MS, Small CJ, Stanley SA, et al. The central melanocortin system affects the hypothalamo-pituitary thyroid axis and may mediate the effect of leptin. J Clin Invest. 2000; 105(7): 1005–1011, doi: 10.1172/JCI8857, indexed in Pubmed: 10749579.
25. Nillni EA. Regulation of prohormone convertases in hypothalamic neurons: implications for prothyrotropin-releasing hormone and proopiomelanocortin. Endocrinology. 2007; 148(9): 4191–4200, doi: 10.1210/en.2007-0173, indexed in Pubmed: 17584972.
26. Radwanska P, Kosior-Korzecka U. Effect of leptin on thyroid-stimulating hormone secretion and nitric oxide release from pituitary cells of ewe lambs in vitro. J Physiol Pharmacol. 2014; 65(1): 145–151, indexed in Pubmed: 24622839.
27. Mantzoros CS, Ozata M, Negrao AB, et al. Synchronicity of frequently sampled thyrotropin (TSH) and leptin concentrations in healthy adults and leptin-deficient subjects: evidence for possible partial TSH regulation by leptin in humans. J Clin Endocrinol Metab. 2001; 86(7): 3284–3291, doi: 10.1210/jcem.86.7.7644, indexed in Pubmed: 11443202.
28. Fernández-Real JM, López-Bermejo A, Casamitjana R, et al. Novel interactions of adiponectin with the endocrine system and inflammatory parameters. J Clin Endocrinol Metab. 2003; 88(6): 2714–2718, doi: 10.1210/jc.2002-021583, indexed in Pubmed: 12788878.
29. Soltys BJ, Kang D, Gupta RS. Localization of P32 protein (gC1q-R) in mitochondria and at specific extramitochondrial locations in normal tissues. Histochem Cell Biol. 2000; 114(3): 245–255, doi: 10.1007/s004180000191, indexed in Pubmed: 11083468.
30. Zhou Y, Yang Y, Zhou T, et al. Adiponectin and Thyroid Cancer: Insight into the Association between Adiponectin and Obesity. Aging Dis. 2021; 12(2): 597–613, doi: 10.14336/AD.2020.0919, indexed in Pubmed: 33815885.
31. Walczak K, Siemińska L. The relationships between selected serum adipokines and thyroid function in patients with obesity. Endokrynol Pol. 2022; 73(2): 353–360, doi: 10.5603/EP.a2022.0030, indexed in Pubmed: 35593684.
32. Sotak Š, Schroner Z, Lazúrová I, et al. The Association Between Three Adipocytokines (Adiponectin, Resistin and Visfatin) And Thyroid Status in Patients With Type 2 Diabetes Mellitus and Autoimmune Thyroiditis. Physiol Res. 2021; 70(6): 865–874, doi: 10.33549/physiolres.934701, indexed in Pubmed: 34717061.
33. García-Solís P, García OP, Hernández-Puga G, et al. Thyroid hormones and obesity: a known but poorly understood relationship. Endokrynol Pol. 2018; 69(3): 292–303, doi: 10.5603/EP.2018.0032, indexed in Pubmed: 29952420.
34. Lu S, Guan Q, Liu Y, et al. Role of extrathyroidal TSHR expression in adipocyte differentiation and its association with obesity. Lipids Health Dis. 2012; 11: 17, doi: 10.1186/1476-511X-11-17, indexed in Pubmed: 22289392.
35. Malcher-Lopes R, Di S, Marcheselli VS, et al. Opposing crosstalk between leptin and glucocorticoids rapidly modulates synaptic excitation via endocannabinoid release. J Neurosci. 2006; 26(24): 6643–6650, doi: 10.1523/JNEUROSCI.5126-05.2006, indexed in Pubmed: 16775153.
36. Pralong FP, Roduit R, Waeber G, et al. Leptin inhibits directly glucocorticoid secretion by normal human and rat adrenal gland. Endocrinology. 1998; 139(10): 4264–4268, doi: 10.1210/endo.139.10.6254, indexed in Pubmed: 9751508.
37. Ahima RS, Prabakaran D, Mantzoros C, et al. Role of leptin in the neuroendocrine response to fasting. Nature. 1996; 382(6588): 250–252, doi: 10.1038/382250a0, indexed in Pubmed: 8717038.
38. Faulkner JL, Belin de Chantemèle EJ. Leptin and Aldosterone. Vitam Horm. 2019; 109: 265–284, doi: 10.1016/bs.vh.2018.09.003, indexed in Pubmed: 30678859.
39. Li P, Sun F, Cao HM, et al. Expression of adiponectin receptors in mouse adrenal glands and the adrenocortical Y-1 cell line: adiponectin regulates steroidogenesis. Biochem Biophys Res Commun. 2009; 390(4): 1208–1213, doi: 10.1016/j.bbrc.2009.10.122, indexed in Pubmed: 19878661.
40. John K, Marino JS, Sanchez ER, et al. The glucocorticoid receptor: cause of or cure for obesity? Am J Physiol Endocrinol Metab. 2016; 310(4): E249–E257, doi: 10.1152/ajpendo.00478.2015, indexed in Pubmed: 26714851.

41. Wang L, Li S, Zhao A, et al. The expression of sex steroid synthesis and inactivation enzymes in subcutaneous adipose tissue of PCOS patients. J Steroid Biochem Mol Biol. 2012; 132(1-2): 120–126, doi: 10.1016/j.jsbmb.2012.02.003, indexed in Pubmed: 22381227.
42. Wang F, Vihma V, Soronen J, et al. 17β-Estradiol and estradiol fatty acyl esters and estrogen-converting enzyme expression in adipose tissue in obese men and women. J Clin Endocrinol Metab. 2013; 98(12): 4923–4931, doi: 10.1210/jc.2013-2605, indexed in Pubmed: 24081738.
43. Kinoshita T, Honma S, Shibata Y, et al. An innovative LC-MS/MS-based method for determining CYP 17 and CYP 19 activity in the adipose tissue of pre- and postmenopausal and ovariectomized women using 13C-labeled steroid substrates. J Clin Endocrinol Metab. 2014; 99(4): 1339–1347, doi: 10.1210/jc.2013-3715, indexed in Pubmed: 24456285.
44. Stulnig TM, Waldhäusl W. 11beta-Hydroxysteroid dehydrogenase Type 1 in obesity and Type 2 diabetes. Diabetologia. 2004; 47(1): 1–11, doi: 10.1007/s00125-003-1284-4, indexed in Pubmed: 14652720.
45. Sarma S, Sockalingam S, Dash S. Obesity as a multisystem disease: Trends in obesity rates and obesity-related complications. Diabetes Obes Metab. 2021; 23 Suppl 1: 3–16, doi: 10.1111/dom.14290, indexed in Pubmed: 33621415.
46. Woo CY, Jang JE, Lee SE, et al. Mitochondrial Dysfunction in Adipocytes as a Primary Cause of Adipose Tissue Inflammation. Diabetes Metab J. 2019; 43(3): 247–256, doi: 10.4093/dmj.2018.0221, indexed in Pubmed: 30968618.
47. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017; 542(7640): 177–185, doi: 10.1038/nature21363, indexed in Pubmed: 28179656.
48. Yanai H, Yoshida H. Beneficial Effects of Adiponectin on Glucose and Lipid Metabolism and Atherosclerotic Progression: Mechanisms and Perspectives. Int J Mol Sci. 2019; 20(5), doi: 10.3390/ijms20051190, indexed in Pubmed: 30857216.
49. Abella V, Scotece M, Conde J, et al. Leptin in the interplay of inflammation, metabolism and immune system disorders. Nat Rev Rheumatol. 2017; 13(2): 100–109, doi: 10.1038/nrrheum.2016.209, indexed in Pubmed: 28053336.
50. Kreitschmann-Andermahr I, Suarez P, Jennings R, et al. GH/IGF-I regulation in obesity--mechanisms and practical consequences in children and adults. Horm Res Paediatr. 2010; 73(3): 153–160, doi: 10.1159/000284355, indexed in Pubmed: 20197666.
51. Gleeson HK, Lissett CA, Shalet SM. Insulin-like growth factor-I response to a single bolus of growth hormone is increased in obesity. J Clin Endocrinol Metab. 2005; 90(2): 1061–1067, doi: 10.1210/jc.2004-0501, indexed in Pubmed: 15522943.
52. van Hulsteijn LT, Pasquali R, Casanueva F, et al. Prevalence of endocrine disorders in obese patients: systematic review and meta-analysis. Eur J Endocrinol. 2020; 182(1): 11–21, doi: 10.1530/EJE-19-0666, indexed in Pubmed: 31652416.
53. Cohen PG. Obesity in men: the hypogonadal-estrogen receptor relationship and its effect on glucose homeostasis. Med Hypotheses. 2008; 70(2): 358–360, doi: 10.1016/j.mehy.2007.05.020, indexed in Pubmed: 17825496.
54. Liu Y, Ding Z. Obesity, a serious etiologic factor for male subfertility in modern society. Reproduction. 2017; 154(4): R123–R131, doi: 10.1530/REP-17-0161, indexed in Pubmed: 28747541.
55. Baldelli R, Dieguez C, Casanueva FF. The role of leptin in reproduction: experimental and clinical aspects. Ann Med. 2002; 34(1): 5–18, doi: 10.1080/078538902317338599, indexed in Pubmed: 12014435.
56. Unuane D, Tournaye H, Velkeniers B, et al. Endocrine disorders & female infertility. Best Pract Res Clin Endocrinol Metab. 2011; 25(6): 861–873, doi: 10.1016/j.beem.2011.08.001, indexed in Pubmed: 22115162.
57. Sanchez-Garrido MA, Tena-Sempere M. Metabolic dysfunction in polycystic ovary syndrome: Pathogenic role of androgen excess and potential therapeutic strategies. Mol Metab. 2020; 35: 100937, doi: 10.1016/j.molmet.2020.01.001, indexed in Pubmed: 32244180.
58. Pasquali R, Gambineri A, Pagotto U. The impact of obesity on reproduction in women with polycystic ovary syndrome. BJOG. 2006; 113(10): 1148–1159, doi: 10.1111/j.1471-0528.2006.00990.x, indexed in Pubmed: 16827825.
59. Fassnacht M, Schlenz N, Schneider SB, et al. Beyond adrenal and ovarian androgen generation: Increased peripheral 5 alpha-reductase activity in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2003; 88(6): 2760–2766, doi: 10.1210/jc.2002-021875, indexed in Pubmed: 12788885.
60. Baranowska-Bik A. Therapy of obesity in women with PCOS using GLP-1 analogues - benefits and limitations [Terapia otyłości u kobiet z PCOS przy zastosowaniu analogów GLP-1 - korzyści i ograniczenia]. Endokrynol Pol. 2022; 73(3): 627–643, doi: 10.5603/EP.a2022.0047, indexed in Pubmed: 36059178.
61. Carmina E, Bucchieri S, Mansueto P, et al. Circulating levels of adipose products and differences in fat distribution in the ovulatory and anovulatory phenotypes of polycystic ovary syndrome. Fertil Steril. 2009; 91(4 Suppl): 1332–1335, doi: 10.1016/j.fertnstert.2008.03.007, indexed in Pubmed: 18455165.
62. González F, González F. Inflammation in Polycystic Ovary Syndrome: underpinning of insulin resistance and ovarian dysfunction. Steroids. 2012; 77(4): 300–305, doi: 10.1016/j.steroids.2011.12.003, indexed in Pubmed: 22178787.
63. Best D, Avenell A, Bhattacharya S. How effective are weight-loss interventions for improving fertility in women and men who are overweight or obese? A systematic review and meta-analysis of the evidence. Hum Reprod Update. 2017; 23(6): 681–705, doi: 10.1093/humupd/dmx027, indexed in Pubmed: 28961722.
64. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. Fertil Steril. 2017; 107(4): 840–847, doi: 10.1016/j.fertnstert.2017.01.017, indexed in Pubmed: 28292619.
65. Pasquali R, Casanueva F, Haluzik M, et al. European Society of Endocrinology Clinical Practice Guideline: Endocrine work-up in obesity. Eur J Endocrinol. 2020; 182(1): G1–G32, doi: 10.1530/EJE-19-0893, indexed in Pubmed: 31855556.
66. Zimmermann-Belsing T, Brabant G, Holst JJ, et al. Circulating leptin and thyroid dysfunction. Eur J Endocrinol. 2003; 149(4): 257–271, doi: 10.1530/eje.0.1490257, indexed in Pubmed: 14514340.
67. Janssen IMC, Homan J, Schijns W, et al. Subclinical hypothyroidism and its relation to obesity in patients before and after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2015; 11(6): 1257–1263, doi: 10.1016/j.soard.2015.02.021, indexed in Pubmed: 25868841.
68. Marzullo P, Minocci A, Tagliaferri MA, et al. Investigations of thyroid hormones and antibodies in obesity: leptin levels are associated with thyroid autoimmunity independent of bioanthropometric, hormonal, and weight-related determinants. J Clin Endocrinol Metab. 2010; 95(8): 3965–3972, doi: 10.1210/jc.2009-2798, indexed in Pubmed: 20534769.
69. Štěpánek L, Horáková D, Štěpánek L, et al. Free triiodothyronine/free thyroxine (FT3/FT4) ratio is strongly associated with insulin resistance in euthyroid and hypothyroid adults: a cross-sectional study. Endokrynol Pol. 2021; 72(1): 8–13, doi: 10.5603/EP.a2020.0066, indexed in Pubmed: 33125689.
70. Rotondi M, Cappelli C, Leporati P, et al. A hypoechoic pattern of the thyroid at ultrasound does not indicate autoimmune thyroid diseases in patients with morbid obesity. Eur J Endocrinol. 2010; 163(1): 105–109, doi: 10.1530/EJE-10-0288, indexed in Pubmed: 20453114.
71. Björntorp P, Rosmond R. Obesity and cortisol. Nutrition. 2000; 16(10): 924–936, doi: 10.1016/s0899-9007(00)00422-6, indexed in Pubmed: 11054598.
72. Rask E, Walker BR, Söderberg S, et al. Tissue-specific changes in peripheral cortisol metabolism in obese women: increased adipose 11beta-hydroxysteroid dehydrogenase type 1 activity. J Clin Endocrinol Metab. 2002; 87(7): 3330–3336, doi: 10.1210/jcem.87.7.8661, indexed in Pubmed: 12107245.
73. Masuzaki H, Paterson J, Shinyama H, et al. A transgenic model of visceral obesity and the metabolic syndrome. Science. 2001; 294(5549): 2166–2170, doi: 10.1126/science.1066285, indexed in Pubmed: 11739957.
74. Kershaw EE, Morton NM, Dhillon H, et al. Adipocyte-specific glucocorticoid inactivation protects against diet-induced obesity. Diabetes. 2005; 54(4): 1023–1031, doi: 10.2337/diabetes.54.4.1023, indexed in Pubmed: 15793240.
75. Wamil M, Battle JH, Turban S, et al. Novel fat depot-specific mechanisms underlie resistance to visceral obesity and inflammation in 11β-hydroxysteroid dehydrogenase type 1-deficient mice. Diabetes. 2011; 60(4): 1158–1167, doi: 10.2337/db10-0830, indexed in Pubmed: 21350084.
76. Feig PU, Shah S, Hermanowski-Vosatka A, et al. Effects of an 11β-hydroxysteroid dehydrogenase type 1 inhibitor, MK-0916, in patients with type 2 diabetes mellitus and metabolic syndrome. Diabetes Obes Metab. 2011; 13(6): 498–504, doi: 10.1111/j.1463-1326.2011.01375.x, indexed in Pubmed: 21272190.
77. Pasquali R, Vicennati V, Gambineri A. Adrenal and gonadal function in obesity. J Endocrinol Invest. 2002; 25(10): 893–898, doi: 10.1007/BF03344053, indexed in Pubmed: 12508952.
78. Monzillo LU, Hamdy O, Horton ES, et al. Effect of lifestyle modification on adipokine levels in obese subjects with insulin resistance. Obes Res. 2003; 11(9): 1048–1054, doi: 10.1038/oby.2003.144, indexed in Pubmed: 12972674.
79. Savchenko LG, Digtiar NI, Selikhova LG, et al. Liraglutide exerts an anti-inflammatory action in obese patients with type 2 diabetes. Rom J Intern Med. 2019; 57(3): 233–240, doi: 10.2478/rjim-2019-0003, indexed in Pubmed: 30901315.
80. Kopp HP, Krzyzanowska K, Möhlig M, et al. Effects of marked weight loss on plasma levels of adiponectin, markers of chronic subclinical inflammation and insulin resistance in morbidly obese women. Int J Obes (Lond). 2005; 29(7): 766–771, doi: 10.1038/sj.ijo.0802983, indexed in Pubmed: 15917853.
81. Gajda SN, Kuryłowicz A, Żach M, et al. Diagnosis and treatment of thyroid disorders in obese patients - what do we know? Endokrynol

Pol. 2019; 70(3): 271–276, doi: 10.5603/EP.a2018.0089, indexed in Pubmed: 31290558.
82. Kozłowska L, Rosołowska-Huszcz D. Leptin, thyrotropin, and thyroid hormones in obese/overweight women before and after two levels of energy deficit. Endocrine. 2004; 24(2): 147–153, doi: 10.1385/ENDO:24:2:147, indexed in Pubmed: 15347841.
83. Radetti G, Longhi S, Baiocchi M, et al. Changes in lifestyle improve body composition, thyroid function, and structure in obese children. J Endocrinol Invest. 2012; 35(3): 281–285, doi: 10.3275/7763, indexed in Pubmed: 21623157.
84. Agnihothri RV, Courville AB, Linderman JD, et al. Moderate weight loss is sufficient to affect thyroid hormone homeostasis and inhibit its peripheral conversion. Thyroid. 2014; 24(1): 19–26, doi: 10.1089/thy.2013.0055, indexed in Pubmed: 23902316.
85. Rask E, Simonyte K, Lönn L, et al. Cortisol metabolism after weight loss: associations with 11 β-HSD type 1 and markers of obesity in women. Clin Endocrinol (Oxf). 2013; 78(5): 700–705, doi: 10.1111/j.1365-2265.2012.04333.x, indexed in Pubmed: 22233384.
86. London E, Castonguay TW. Diet and the role of 11beta-hydroxysteroid dehydrogenase-1 on obesity. J Nutr Biochem. 2009; 20(7): 485–493, doi: 10.1016/j.jnutbio.2009.02.012, indexed in Pubmed: 19443197.
87. Gu Y, Zhou G, Zhou F, et al. Life Modifications and PCOS: Old Story But New Tales. Front Endocrinol (Lausanne). 2022; 13: 808898, doi: 10.3389/fendo.2022.808898, indexed in Pubmed: 35498415.
88. Pasquali R. Contemporary approaches to the management of polycystic ovary syndrome. Ther Adv Endocrinol Metab. 2018; 9(4): 123–134, doi: 10.1177/2042018818756790, indexed in Pubmed: 29619209.
89. Crosignani PG, Colombo M, Vegetti W, et al. Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. Hum Reprod. 2003; 18(9): 1928–1932, doi: 10.1093/humrep/deg367, indexed in Pubmed: 12923151.
90. Pasquali R, Gambineri A, Cavazza C, et al. Heterogeneity in the responsiveness to long-term lifestyle intervention and predictability in obese women with polycystic ovary syndrome. Eur J Endocrinol. 2011; 164(1): 53–60, doi: 10.1530/EJE-10-0692, indexed in Pubmed: 20956435.
91. Lotti F, Marchiani S, Corona G, et al. Metabolic Syndrome and Reproduction. Int J Mol Sci. 2021; 22(4), doi: 10.3390/ijms22041988, indexed in Pubmed: 33671459.
92. Fildes A, Charlton J, Rudisill C, et al. Probability of an Obese Person Attaining Normal Body Weight: Cohort Study Using Electronic Health Records. Am J Public Health. 2015; 105(9): e54–e59, doi: 10.2105/AJPH.2015.302773, indexed in Pubmed: 26180980.
93. Canadian Adult Obesity Clinical Practice Guidelines. https://obesitycanada.ca/guidelines/.
94. Bąk-Sosnowska M, Białkowska M, Bogdański P, et al. Zalecenia kliniczne dotyczące postępowania u chorych na otyłość 2022 — stanowisko Polskiego Towarzystwa Leczenia Otyłości. Med Prakt. 2022(Wyd Spec): 1–87.
95. Cariou B. Harnessing the incretin system beyond glucose control: potential cardiovascular benefits of GLP-1 receptor agonists in type 2 diabetes. Diabetes Metab. 2012; 38(4): 298–308, doi: 10.1016/j.diabet.2012.04.003, indexed in Pubmed: 22672960.
96. Lyu X, Yan K, Wang X, et al. A novel anti-obesity mechanism for liraglutide by improving adipose tissue leptin resistance in high-fat diet-fed obese mice. Endocr J. 2022; 69(10): 1233–1244, doi: 10.1507/endocrj.EJ21-0802, indexed in Pubmed: 35705299.
97. Li D, Xu X, Zhang Y, et al. Liraglutide treatment causes upregulation of adiponectin and downregulation of resistin in Chinese type 2 diabetes. Diabetes Res Clin Pract. 2015; 110(2): 224–228, doi: 10.1016/j.diabres.2015.05.051, indexed in Pubmed: 26376464.
98. Jensterle M, Janez A, Fliers E, et al. The role of glucagon-like peptide-1 in reproduction: from physiology to therapeutic perspective. Hum Reprod Update. 2019; 25(4): 504–517, doi: 10.1093/humupd/dmz019, indexed in Pubmed: 31260047.
99. Jensterle M, Podbregar A, Goricar K, et al. Effects of liraglutide on obesity-associated functional hypogonadism in men. Endocr Connect. 2019; 8(3): 195–202, doi: 10.1530/EC-18-0514, indexed in Pubmed: 30707677.
100. Giagulli VA, Carbone MD, Ramunni MI, et al. Adding liraglutide to lifestyle changes, metformin and testosterone therapy boosts erectile function in diabetic obese men with overt hypogonadism. Andrology. 2015; 3(6): 1094–1103, doi: 10.1111/andr.12099, indexed in Pubmed: 26447645.
101. Niafar M, Pourafkari L, Porhomayon J, et al. A systematic review of GLP-1 agonists on the metabolic syndrome in women with polycystic ovaries. Arch Gynecol Obstet. 2016; 293(3): 509–515, doi: 10.1007/s00404-015-3976-7, indexed in Pubmed: 26660657.
102. Heppner KM, Baquero AF, Bennett CM, et al. GLP-1R Signaling Directly Activates Arcuate Nucleus Kisspeptin Action in Brain Slices but Does not Rescue Luteinizing Hormone Inhibition in Ovariectomized Mice During Negative Energy Balance. eNeuro. 2017; 4(1), doi: 10.1523/ENEURO.0198-16.2016, indexed in Pubmed: 28144621.
103. Izzi-Engbeaya C, Jones S, Crustna Y, et al. Effects of Glucagon-like Peptide-1 on the Reproductive Axis in Healthy Men. J Clin Endocrinol Metab. 2020; 105(4): 1119–1125, doi: 10.1210/clinem/dgaa072, indexed in Pubmed: 32052032.
104. Hu W, Song R, Cheng R, et al. Use of GLP-1 Receptor Agonists and Occurrence of Thyroid Disorders: a Meta-Analysis of Randomized Controlled Trials. Front Endocrinol (Lausanne). 2022; 13: 927859, doi: 10.3389/fendo.2022.927859, indexed in Pubmed: 35898463.
105. Ye J, Xu J, Wen W, et al. Effect of Liraglutide on Serum TSH Levels in Patients with NAFLD and its Underlying Mechanisms. Int J Clin Pract. 2022; 2022: 1786559, doi: 10.1155/2022/1786559, indexed in Pubmed: 36311486.
106. Eisenberg D, Shikora SA, Kothari SN, et al. 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): Indications for Metabolic and Bariatric Surgery. Surg Obes Relat Dis. 2022; 18(12): 1345–1356, doi: 10.1016/j.soard.2022.08.013, indexed in Pubmed: 36280539.
107. Hafida S, Mirshahi T, Nikolajczyk BS. The impact of bariatric surgery on inflammation: quenching the fire of obesity? Curr Opin Endocrinol Diabetes Obes. 2016; 23(5): 373–378, doi: 10.1097/MED.0000000000000277, indexed in Pubmed: 27455515.
108. Camastra S, Vitali A, Anselmino M, et al. Muscle and adipose tissue morphology, insulin sensitivity and beta-cell function in diabetic and nondiabetic obese patients: effects of bariatric surgery. Sci Rep. 2017; 7(1): 9007, doi: 10.1038/s41598-017-08444-6, indexed in Pubmed: 28827671.
109. Guan B, Chen Y, Yang J, et al. Effect of Bariatric Surgery on Thyroid Function in Obese Patients: a Systematic Review and Meta-Analysis. Obes Surg. 2017; 27(12): 3292–3305, doi: 10.1007/s11695-017-2965-2, indexed in Pubmed: 29039052.
110. Handisurya A, Riedl M, Vila G, et al. Serum vaspin concentrations in relation to insulin sensitivity following RYGB-induced weight loss. Obes Surg. 2010; 20(2): 198–203, doi: 10.1007/s11695-009-9882-y, indexed in Pubmed: 19506980.
111. Lee Y, Dang JT, Switzer N, et al. Impact of Bariatric Surgery on Male Sex Hormones and Sperm Quality: a Systematic Review and Meta-Analysis. Obes Surg. 2019; 29(1): 334–346, doi: 10.1007/s11695-018-3557-5, indexed in Pubmed: 30382463.
112. Emami MR, Safabakhsh M, Khorshidi M, et al. Effect of bariatric surgery on endogenous sex hormones and sex hormone-binding globulin levels: a systematic review and meta-analysis. Surg Obes Relat Dis. 2021; 17(9): 1621–1636, doi: 10.1016/j.soard.2021.05.003, indexed in Pubmed: 34187743.
113. Escobar-Morreale HF, Santacruz E, Luque-Ramírez M, et al. Prevalence of 'obesity-associated gonadal dysfunction' in severely obese men and women and its resolution after bariatric surgery: a systematic review and meta-analysis. Hum Reprod Update. 2017; 23(4): 390–408, doi: 10.1093/humupd/dmx012, indexed in Pubmed: 28486593.
114. Juiz-Valiña P, Pena-Bello L, Cordido M, et al. Altered GH-IGF-1 Axis in Severe Obese Subjects is Reversed after Bariatric Surgery-Induced Weight Loss and Related with Low-Grade Chronic Inflammation. J Clin Med. 2020; 9(8), doi: 10.3390/jcm9082614, indexed in Pubmed: 32806629.