Published in WWW.ENDOTEXT.ORG © 2017

ENDOCRINE CHANGES IN OBESITY

Sharleen Sidhu, MD, Fellow, Medstar Georgetown/Washington Hospital Center
Washington, DC
Tanvi Parikh, MD, Fellow, Medstar Georgetown/Washington Hospital Center
Washington, DC
Kenneth D. Burman, MD, Professor, Department of Medicine, Georgetown University
Chief, Endocrine Section, Medstar Washington Hospital Center, Washington, DC,
e-mail: Kenneth.D.Burman@medstar.net

Updated: 12 October 2017

ABSTRACT

Obesity can be associated with several endocrine alterations arising as a result of changes in the hypothalamic-pituitary hormones axes. These include hypothyroidism, Cushing's disease, hypogonadism and growth hormone deficiency. Besides its role in energy storage, adipose tissue has many other important functions that can be mediated through hormones or substances synthesized and released by adipocytes which include leptin and adiponectin. Further, obesity is also a common feature of polycystic ovarian syndrome with hyperinsulinemia being the primary etiological factor. Here, we provide and an overview of certain endocrine syndromes which are known to result in obesity and discuss the endocrine role of adipose tissue in conjunction to its association with hypothalamic-pituitary-endocrine axes.

INTRODUCTION

This chapter will discuss the endocrine role of adipose tissue and how alterations in each of the hypothalamic-pituitary-endocrine axes can occur in association with obesity. Of particular relevance is the possible bidirectionality of the relationships between endocrine changes and obesity: whether they are secondary to obesity or, in some cases, be a contributive factor to the development and/or perpetuation of obesity.

The endocrine axes of the human body are dynamic systems; they frequently show changes in response to stress, disease or other pathological states. For example, during acute and chronic illnesses, and low calorie or starvation states, levels of thyroid, gonadal, and growth hormone are altered, returning to normal as the subject recovers. These hormonal changes are, therefore, thought to be secondary to the disease state and their recovery is reflective of a homeostatic mechanism. Often these "adaptive" changes in hormonal dynamics may not necessarily be appropriate. Likewise, therapeutic measures aimed at restoring "normal" serum level of

perturbed hormones offered in hopes of hastening recovery and improve patient outcomes have generally not been shown to be beneficial.

The weight gain that leads to obesity is the consequence of a positive energy balance, which can result from an increased energy intake, decreased energy expenditure, or both. This misalignment may be thought of as a failure of the body's homeostatic mechanisms to match energy intake with expenditure. Different phenotypes of obesity may have variable health implications. Abdominal obesity is considered to be a more hazardous condition than gluteofemoral, or gynecoid, obesity. In those with abdominal obesity, accumulation of intraperitoneal fat in the omentum and around viscera carries greater health risk than subcutaneous abdominal obesity. Therefore, when discussing complications of and metabolic abnormalities associated with obesity, different phenotypes of obesity exist and carry different degrees of risk, in particular cardiometabolic risk.

Our understanding of the physiology of adipose tissue has greatly advanced in the last decade and extensive research has been dedicated to the study of the interactions between the adipose tissue and other bodily systems, in particular the central nervous system. New hormones have been discovered with potentially important roles in energy balance and food intake. The roles of many of these newly discovered hormones have not been fully elucidated in humans, but the future holds promise in not only improving our knowledge of the pathophysiology of obesity but also in developing novel therapeutic approaches to complement our currently, rather limited, pharmacological arsenal.

ADIPOSE TISSUE

Besides its role in energy storage, adipose tissue has many other important functions that can be mediated through hormones or substances synthesized and released by adipocytes. These substances, "adipocytokines," are capable of acting on distant targets in an endocrine fashion or locally in paracrine and autocrine fashions. In the following paragraphs, we shall discuss a few of the important adipocytokines secreted from “white" fat. A discussion of "brown" fat, which helps regulate thermogenesis, is beyond the scope of this chapter (1).

Leptin

The hormone leptin (from the Greek word "leptos" meaning "thin") is a 167-amino acid peptide hormone encoded by the *ob* (obesity) gene and secreted by white adipocytes. Its discovery in 1994, has greatly improved our understanding of how the adipose tissue "communicates" with other systems in the body, in particular with the central nervous system (CNS) (2-4). Following release into the circulation, leptin crosses the blood–brain barrier and binds to presynaptic GABAergic neurons to of the hypothalamus of the central nervous system (CNS) to control appetite and energy expenditure (5). One of leptin’s more important roles is thought to be as a signal of inadequate food intake or starvation. For example, leptin levels decline during fasting, low-calorie dieting, or uncontrolled type 1 diabetes. In these situations, the reduced leptin levels stimulate hunger while decreasing energy expenditure and engendering other physiologic adaptations that restore fat stores to baseline (6, 7).

On the other hand, serum concentrations of leptin increase in proportion to increasing adiposity. As a regulatory signal in a homeostatic system, higher circulating levels of leptin should result in decreased energy intake and elevated energy expenditure, but this is not the case when individuals become overweight or obese, suggesting a state of leptin resistance. Obesity is associated with decreasing levels of circulating soluble leptin receptors (SLR) (8). These receptors are proteins that circulate in the blood and contribute directly to leptin function (8, 9). This state of high leptin levels and low SLR may explain in part why obese individuals are resistant to leptin (10). Decreased transport across the blood-brain barrier (9, 11) and also a decreased ability of leptin to activate hypothalamic signaling in diet-induced obesity (12-15) may be crucial mediators in the pathogenesis of leptin resistance that leads to failure to adequately compensate for the positive energy balance leading to unwanted weight gain and obesity. This postulated leptin resistance is a major target in the search for a better understanding of obesity and the development of pharmacological tools to treat this chronic disease.

Leptin not only links fat tissue with the CNS, but also to other tissues in the body. Leptin receptors are present in peripheral organs, such as the liver, skeletal muscles, pancreatic beta cells, and even adipose cells, indicating endocrine, autocrine, and paracrine roles of leptin in energy regulation. Leptin signaling in these organs is thought to mediate important metabolic effects. Leptin has been implicated in glucose and lipid metabolism as an insulin-sensitizer (16, 17). It has been shown to decrease glucagon synthesis and secretion, decrease hepatic glucose production and increase insulin hepatic extraction, decrease lipogenesis in the adipose tissue and increase lipolysis among multiple other beneficial effects on insulin and lipids metabolism (18).

Leptin plays a significant permissive role in the physiological regulation of several neuroendocrine axes, including the hypothalamic-pituitary-gonadal, -thyroid, -growth hormone, and -adrenal axes (19, 20). Leptin regulates reproductive function by altering the sensitivity of the pituitary gland to GnRH and acting at the ovary to alter follicular and luteal steroidogenesis, proliferation, and apoptosis (20). Thus leptin serves as a putative signal that links metabolic status with the reproductive axis.

Leptin is also formed in the placenta and is widely expressed in fetal tissues. It is important for placentation and maternal-fetal nutritional regulating growth and development (21). It stimulates hematogenesis and angiogenesis indicating a possible role in development.

Adiponectin

Adiponectin is another important adipocytokine that influences insulin sensitivity and atherogenesis. Adiponectin mediates its effect through binding to receptors AdipoR1 and AdipoR2, leading to activation of adenosine monophosphate dependent kinase, PPAR-α, and other yet-unidentified signaling pathways (22). Lower levels of adiponectin in obesity have been associated with insulin resistance (23), dyslipidemia (24), and atherosclerosis (25) in humans. With weight loss, plasma adiponectin levels significantly increase in parallel with improvements in insulin sensitivity (26).

Adiponectin also suppresses the action of inflammatory cytokines such as tumor necrosis factor alpha (TNF-alpha) (27), favorably modulates natural killer cell function (28) and other immune regulatory molecules (29), and improves dyslipidemia (30) and other risk factors of cardiovascular disease (27).

In addition to an anti-atherogenic effect, adiponectin may also have a variety of anti-tumor effects. This effect of adiponectin is thought to be mediated, in part, through inhibition of leptin induced tumor proliferation (31). It retards the aggressiveness of tumors and their metastatic potential of tumors and hypoadiponectinemia have been associated with a several cancers including breast, gastric, lung, prostate and others (32-35).

Chemerin

Chemerin, also known as Retinoic Acid Receptor Responder Protein 2, is among the newly discovered adipokines. Chemerin is secreted from mature adipocytes and is thought to play an important role in the regulation of adipogenesis as well as macrophage infiltration into adipose tissue (36). Recently published data suggest that chemerin may serve as an independent marker in diagnosing these conditions even before they become clinically evident (37).

Omentin

Omentin is an adipokine preferentially produced by visceral adipose tissue that exerts insulin-sensitizing actions (38). Its expression is reduced in obesity, insulin resistance and type 2 diabetes. Omentin is also positively related with adiponectin, high-density lipoprotein levels and negatively associated with body mass index, waist circumference, insulin resistance, triglycerides and leptin levels (39). Omentin has anti-inflammatory, anti-atherogenic, anti-cardiovascular disease and anti-diabetic properties (39). Regarding its effects in the cardiovascular system, omentin causes vasodilatation of blood vessels and mitigates C-reactive protein-induced angiogenesis. The ability of omentin to reduce insulin resistance in conjunction with its anti-inflammatory and anti-atherogenic properties makes it a promising therapeutic/diagnostic target (40).

Retinol Binding Protein-4 (RBP-4)

RBP-4 belongs to the lipocalin family transporting small hydrophobic molecules and is produced primarily in the liver and mature adipocytes (41). Although the relationship between serum RBP-4 and obesity in humans has not been confirmed yet in population studies, several studies have shown a positive correlation between the expression of RBP-4 and BMI and glucose concentration (42). RBP-4 levels can be reduced by weight loss, balanced diet and exercise in association with increased insulin sensitivity (43, 44).

Visceral adipose tissue-derived serpin; serpin A12 (Vaspin)

Vaspin is a serine protease inhibitor produced by subcutaneous and visceral adipose tissue. Vaspin is also expressed in the skin, hypothalamus, pancreatic islets, and stomach. Vaspin is considered as an anti-atherogenic insulin-sensitizing factor (45).

Adipocyte Fatty Acid Binding Protein (A-FABP)

A-FABP is one of the fatty acid-binding proteins isoforms expressed adipose tissue and macrophages (46). It binds to hydrophobic ligands such as long chain fatty acids and facilitates their transport to specific cell compartments. Several studies have shown positive correlation between A-FABP and proinflammatory factors, such as CRP, and may also have significant importance in predicting insulin resistance (47).

Acylation Stimulating Protein (ASP)

ASP is synthesized and secreted by adipocytes and plays a major role in fatty acid uptake and triglyceride synthesis in these same cells, including postprandial clearance of triglycerides (48). It has been show to induce glucose-stimulated insulin release from pancreatic beta cells, modulates cytokine synthesis by mononuclear cells, as well as inhibits cytotoxicity of natural killer cells (49).

Renin-Angiotensin-Aldosterone System

Several components of the renin-angiotensin system (renin, angiotensinogen, angiotensin-converting enzyme and angiotensin II receptors) are expressed by the adipose tissue (50). Recent studies have shown that adipocyte deficiency of angiotensinogen prevents obesity-induced hypertension in male mice (51). Adipocytes promote obesity-induced increases in systolic blood pressure in male high fat-fed C57BL/6 mice via angiotensin 2 dependent mechanism (52). Adipocyte angiotensinogen deficiency prevents high fat-induced elevations in plasma angiotensin 2 concentrations and therefore in systolic blood pressure (51). These results suggest that adipose tissue serves as a major source of angiotensin 2 in the development of obesity-related hypertension.

Others Factors Secreted by Adipose Tissue

Other proteins secreted by adipose tissue include plasminogen activator inhibitor-1 (PAI-1) (53) as well as complement factors adipsin, apelin, and pten, which may have roles in the pathophysiology or the progression of coronary artery disease and type 2 diabetes (54-56).

Interleukin-6 (IL-6) is released by macrophages and T-cells in the adipose tissue (57) and has been implicated in regulating insulin signaling in peripheral tissues by promoting insulin-dependent hepatic glycogen synthesis and glucose uptake in adipocytes (58). Recent studies show that IL-6 deficient mice develop late-onset obesity as well as disturbed glucose metabolism (59). The mechanisms underlying the effect of IL-6 on body fat and metabolism are not completely understood. However, IL-6 may exert central effects to decrease fat mass as a result of increased energy expenditure. Administration of IL-6 to the CNS has, for instance, been

shown to induce energy expenditure and reduce fat mass more effectively than peripheral treatment (59). It has been suggested that IL-6 potentiates the action of leptin providing a possible mechanism for its anti-obesity effect (60). In addition, IL-6 has been linked to the increased inflammatory state seen in obesity. IL-6 and its subsequent inflammation have been postulated to play an etiologic role in the increased risk of thromboembolism observed in obese patients (61).

Conclusion

It is clear that the adipose tissue is an extremely active organ with multiple roles, including endocrine, in human physiology and disease. The manner in which these roles are performed and their contribution to the health or risk of disease of the human body will likely be elucidated as more discoveries continue to shed light on the mechanism of the complex interaction between adipocytes and other body tissues.

OBESITY AND PITUITARY HORMONAL AXES

Obesity and Sex Hormones

Not only is obesity associated with alterations in sex hormone levels, sex hormones may conversely influence expression different obesity phenotypes. One of the best examples of this is the relationship between obesity and androgen levels in men and women and the roles played by sex hormone-binding globulin (SHBG) and gonadotropins (62-64).

Sex Steroids and SHBG:

Most of circulating testosterone and estrogen are bound to transport proteins SHBG and albumin. SHBG is produced by the liver. Only about 2% of circulating sex steroids are unbound, or free, and this fraction is thought to represent the vast majority of the bioactive fraction of these hormones. A portion of the bound sex hormones may also be available for use by the body target cells. Total hormone levels, therefore, reflect the bound and unbound hormone and are greatly dependent on the serum concentration of SHBG. With age, SHGB increases and bioactive testosterone decreases. Table 1, shows some common conditions that can affect the serum concentration of SHBG.

Table 1

Increased SHBG	Decreased SHBG
Estrogens	Androgens
Hyperthyroidism	Glucocorticoids
Cirrhosis	Growth hormone
Older Age	Hypothyroidism
	Insulin
	Obesity

Obesity and Androgens in Men:

Testosterone should be measured in the morning when its serum concentration is at its peak and we recommend repeating an abnormal measurement for confirmation. Evidence indicates that testosterone (T) deficiency in men induces increased adiposity and, at the same time, increased adiposity induces hypogonadism (62). It is known that obesity in men is associated with low total T and reduced SHBG levels (64, 65). An obesity-associated decline in SHBG might partially explain the observed fall in T levels. However, an increased BMI is associated with a low measured, or calculated, free- and bioavailable-testosterone. In one study of 160 obese men, more than 40% of those with a BMI ≥ 40 kg/m^2 had a free testosterone level below normal (65).

While the specific pathogenic mechanisms involved in this phenomenon are complex and not completely understood, obesity has been associated mostly with secondary hypogonadism (hypogonadotropic) and, in a minor degree, with primary hypogonadism (testicular failure). Male obesity-associated secondary hypogonadism (MOSH) has been attributed to multiple factors, including obstructive sleep apnea, development of type 2 diabetes, hypertension and also the increased body fat mass itself with its multiple adipokines (66, 67). Obstructive sleep apnea predisposes to MOSH since it reduces LH pulse amplitude and decreases mean serum levels of LH and T in men, and it may also cause disruption of the association between a rise in serum T levels and the appearance of first REM sleep (68, 69).

In addition, studies by Wagner et al have shown that long-term obesity lowers the number of testosterone producing Leydig cells and promotes destruction of existing ones by increasing levels of proinflammatory cytokines and cells such as Tumor Necrosis Factor alpha and macrophages respectively (70). In both the short and long term, obesity was shown to lower intra testicular levels of testosterone by way of increasing serum leptin and estradiol levels and inhibiting the expression of the gene for cytochrome p450 of the cholesterol side chain cleavage enzyme (Cyp11a1) (70) .

Hypogonadism in men can itself worsen obesity and promote increased fat mass, which in turn may worsen the hypogonadal state. Low testosterone levels lead to a reduction in muscle mass and an increase in adipose tissue within abdominal depots, especially visceral adipose tissue (VAT) that can be reversed with testosterone therapy (71-73). As adiposity increases, there is a further raise in aromatase activity that is associated with an even greater conversion of T to estradiol (often termed the 'testosterone-estradiol shunt'), which is thought to decreased GnRH secretion (74). This further decreases T levels that in turn further increases the preferential deposition of fat within abdominal depots: a 'hypogonadal-obesity cycle' (75, 76). Obese individuals retain the capacity to reverse this gonadotrophic response, demonstrating that MOSH is a reversible condition. This has been made evident on several studies in which weight loss normalized T levels (77, 78).

In summary, obesity is frequently associated with low androgen levels in men. The pathogenesis of obesity-related hypogonadism is complex and multifactorial, implicating obese-related comorbidities and changes in body fat mass itself with its multiple adipokines and inflammatory mediators. These changes are frequently reversible with weight loss.

Obesity and Androgens in Women:

It is well known that an increase in body weight and fat tissue is associated with abnormalities of sex steroid levels in both premenopausal and postmenopausal women. It has been shown that women with central obesity have higher circulating androgen levels, even in the absence of a clinical diagnosis of polycystic ovarian syndrome (PCOS) (79, 80). These women have higher total and free testosterone levels than normal-weight woman and lower androstenedione and SHBG levels (80). Measurement of serum testosterone in PCOS by radioimmunoassay (RAI) and liquid chromatography–mass spectrometry (LC/MS) have been found to have comparable precision, however testosterone levels are slightly higher with the RIA than LC/MS assay. Some studies determining the co-relation between the total testosterone levels and a phenotypic feature of hyperandrogenism, such as hirsutism, found a strong co relation between the two, regardless of the assay used for assessment (81).

The timing of menarche is mainly due to genetic factors, but is influenced by environmental factors (82). Age at menarche in US girls has been declining over the past 30 years (83), particularly due to the change in nutritional status (84). A Mendelian randomization study from the United Kingdom found that there might be a causal effect of BMI on early menarche, suggesting that the increasing prevalence of childhood obesity will lead to similar trends in the prevalence of early menarche (85). Other genetic studies have described several adiposity-related gene loci that are associated with age at menarche (86).

Studies have also shown that the earlier the time of menarche, the higher the risk of developing obesity (87) and other comorbidities in the adult life, independently of BMI, such as: breast cancer, cardiovascular disease, cerebrovascular disease, type 2 diabetes and adolescence at-risk behaviors (88-93). Consequently, all-cause mortality has been linked with early menarche (94). Also, there is evidence showing that menarche at <12 years of age is associated with higher androgens levels even during adulthood suggesting that hyperandrogenemia may explain, at least in part, the higher incidence of comorbidities among these women. A recent study demonstrated that with each 1-year increase in menarcheal age, the probability of having obesity decreased by 22%; interestingly, in this study obese women had higher androgens levels (95).

Based on the above evidence, it can be concluded that early menarche may be clinically useful in identifying women who are at risk of later obesity and multiple other medical problems.

Relationship Between Leptin and Sex Hormones:

Leptin participates in the regulation of Hypothalamus Pituitary Gonadal (HPG) axis at multiple levels. Leptin appears to facilitate GnRH secretion indirectly by modulating several interneuron secretory neuropeptides (96), regulates gonadotrophin secretion by the increased expression of leptin receptors on the hypothalamus (97), directly stimulates LH and, to a lesser extent, FSH.

Leptin has a permissive role in timing puberty but is not essential nor is the only trigger for puberty onset, as has been shown in studies of patients with leptin deficiency and several animal studies (98, 99). Kisspeptins play a very important role in the modulation of the hypothalamus-

pituitary-testicular axis in men (100). Kisspeptins are mostly distributed in the hypothalamus, dentate gyrus and adrenal cortex. Inactivating mutations of the kisspeptin receptor have been shown to cause hypogonadotropic hypogonadism in men, while an activating mutation is associated with precocious puberty. Data from studies in animals link kisspeptin expression with hyperglycemia, inflammation, leptin and estrogen, factors known to regulate GnRH secretion. It has been hypothesized that decreased endogenous kisspeptin secretion is the common central pathway that links metabolic and endocrine factors in the pathology of T deficiency observed in MOSH and type 2 diabetes (101).

Leptin receptors are also widely expressed in the human ovaries (102) and testes (103) indicating a regulatory role. Recent studies by Ma et al have shown that mice receiving a high fat diet produce fewer number of oocytes than compared with their counter parts receiving a normal diet. Leptin has been noted to act locally within the mice ovarian granulosa cells to reduce estradiol production (104). These actions are mediated via induction of the neuropeptide cocaine- and amphetamine-regulated transcript (CART) in the granulosa cells (GCs), which in turn detrimentally affects intermediate steps of estradiol synthesis including, intracellular cAMP levels, MAPK signaling, and aromatase mRNA expression (105). In humans undergoing in vitro fertilization, Ma et al demonstrated that subjects with higher BMI had higher levels of CART mRNA and CART peptide in follicular fluid (105). Therefore, in obese women evidence supports a role for leptin as a mediator of infertility at the level of the ovary.

As mentioned above, obesity was shown to lower intra testicular levels of testosterone in men via leptin and estradiol inhibition of the expression of the gene for cytochrome p450 of the cholesterol side chain cleavage enzyme(Cyp11a1) (70). Gregoraszczuk et al exposed porcine ovarian follicles obtained from pre pubertal and mature animals to progressively increasing doses of super active human leptin antagonist (SHLA) and measured levels of leptin receptor (ObR), leptin, CYP11A1 and 17β-hydroxysteroid dehydrogenase (17β-HSD), progesterone (P4), and testosterone (T) in the follicles (106). These experiments showed that SHLA inhibits CYP11A and 17 beta protein expression, subsequently inhibiting leptin, ObR, and hence leptin-mediated follicular P4 and T secretion. Obese women with polycystic ovarian syndrome (PCOS), a condition associated with elevated androgen levels and infertility (see also below), were found to have higher levels of leptin (both bound and free form) and lower levels of s-OBR (soluble Leptin receptors) when compared to lean females with PCOS, after adjusting both groups for age, in studies by Rizk, who hypothesized that lower s-OBR may have been in response to impaired leptin function (107).

Leptin and its soluble receptor are thus implicated in the pathophysiology of PCOS, may act as a mediator of infertility at the level of the ovary and testes, and that leptin antagonists acting peripherally in gonadal tissues may thus be useful in modifying the physiology of reproduction.

Obesity and Polycystic Ovarian Syndrome:

Polycystic ovarian syndrome (PCOS) is a highly prevalent condition of hyperandrogenism frequently associated with obesity. Hence, this disorder has been studied extensively in the context of interactions between sex hormones and obesity. It affects approximately 6-10% of

women in reproductive age (108). About two thirds of women with PCOS are obese and 50-70% of them have insulin resistance (IR) (109).

Adult men have more visceral fat than premenopausal women, in which the body fat is more prominent in the periphery and subcutaneous adipose tissue. This sexual dimorphism is mainly related to the differential effects of androgens and estrogens on adipose tissue (110). Visceral adipose tissue (VAT) excess is strongly associated with metabolic disorders such as insulin resistance and dyslipidemia (111). Women with PCOS manifest what has been called "masculinization of the adipose tissue" characterized by increased VAT and even male pattern adipokine gene expression with its associated metabolic complications (112, 113). Even though increased VAT plays a significant role in the development of insulin resistance in PCOS, it has been suggested that insulin resistance may represent an intrinsic characteristic of this syndrome, independent of obesity (108). Interestingly, in PCOS, despite the insulin resistance in other organs, the ovaries remain sensitive to the stimulatory effect of insulin on androgen production (114). A recent study showed that despite women with PCOS and women with the metabolic syndrome sharing many features, these are different entities, mainly due to the excess of androgens seen in PCOS which seems the be the main culprit of its multiple co-morbidities (115).

Anovulation and menstrual irregularities are major features of PCOS; these are in part due to ovarian hyperandrogenism, hyperinsulinemia due to IR and altered paracrine signaling within the ovary which can disrupt follicle growth (108). Hyperinsulinemia decreases hepatic SHBG with it subsequent increase in free androgens levels. In addition, insulin increases the androgens synthesis stimulated by LH and IGF-1.

An increased ratio of serum LH to FSH may be seen in about 70% of women with PCOS (116, 117). The androgen excess reduces the negative feedback in the hypothalamus causing an enhanced pulsatile release of gonadotropin releasing-hormone (GnRH) which will elevate LH levels and pulse frequency (118).

In summary, obesity is a common feature of PCOS. Hyperinsulinemia is believed to be the main etiological factor behind the development of PCOS. Obesity also leads to hyperestrogenism. Weight loss and/or use of insulin sensitizing agents (mainly metformin) improve insulin sensitivity, reduce insulin levels and improve fertility in women with PCOS but not live births (119, 120). Metformin is associated with improved clinical pregnancy but evidence does not show that metformin improves live birth rates, whether it is used alone or in combination with clomiphene, or when compared with clomiphene (120). Therefore, the role of metformin in improving reproductive outcomes in women with PCOS appears to be limited (121). Letrozole, an aromatase inhibitor, is headed toward replacing clomiphene, a selective estrogen receptor modulator, as the first-choice option for ovulation induction Metabolic treatments such as metformin, troglitazone or d-chiro-inositol have failed to show promise in improving fertility outcomes, further studies are needed of the newer agents to treat type 2 diabetes (122).

Obesity and Estrogens:

Estrogens play an important role in body weight, fat distribution, energy expenditure and metabolism. In healthy premenopausal women, estrogens are mainly synthesized in the ovaries under the regulation of gonadotropins releasing hormones from the pituitary gland. They are also produced in the adipocytes via aromatization from androgenic precursors, this source of estrogens is especially important in men and post-menopausal women and it increases in proportion to the total body adiposity (123, 124).

Most metabolic effects of estrogens are mediated through estrogen receptor (ER) Alpha, whereas most gynecologic actions are exerted through ER Beta. Mice of both sexes with a targeted deletion of the ER Alpha gene manifest obesity-induced insulin resistance with altered plasma adipokines and cytokines levels and increased adiposity, mainly VAT (125, 126). ER Alpha is currently a focus of great interest in the research community.

Estrogens have a positive effect in glucose homeostasis. It is an insulin sensitizer acting at multiple levels, including skeletal muscle, liver and adipocytes (127). Even the immune system is influenced by estrogens decreasing inflammation and thus favoring insulin sensitivity (128, 129). Pancreatic islet-cells also have estrogens receptors which activation improves beta cell function and survival (130). Estrogen deficiency promotes metabolic dysfunction predisposing to obesity, metabolic syndrome, and type 2 diabetes.

It has been shown that estrogens can influence energy intake and energy expenditure via hypothalamic signaling. Estrogen Receptor Alpha is widely expressed in the ventromedial hypothalamus (VMH), area of the brain that controls food intake, energy and body weight homeostasis. In animal models, the lack of ER Alpha in the VMH causes dramatic changes in energy balance leading to increased adiposity (127).

The gynecoid body fat distribution, characterized by increased fat depots into the subcutaneous tissue favoring gluteal/femoral areas and decreased VAT is mediated mainly by estrogens (127). Visceral Fat Tissue is augmented in hypoestrogenic states, as seen in menopause. These changes in body fat composition can be prevented by estrogens replacement (131). Also, estrogen treatment of male-to-female transsexuals significantly increases fat deposition in all subcutaneous fat depots, while having little effect on the visceral fat compartment (132).

Obesity is associated with elevated estrogens levels, as it can be expected due to the aromatization of androgens in adipocytes (75). Increased adiposity is a known risk factor for the development and progression of breast cancer and this hyperestrogenic state is associated with increased risk of cancer, cardiovascular disease and all-cause mortality (133). Weight loss improves prognosis of patients diagnosed with breast cancer and the reduction in estrogens levels may be, at least in part, responsible for this finding (134).

Obesity and Growth Hormone

Growth hormone (GH) is secreted by the pituitary gland. Most of GH-promoting effects are mediated by Insulin- like Growth Factor-1 (IGF-1), but GH also has effects independent of IGF-1. Serum IGF-1 concentration represents the most accurate reflection of growth hormone biologic

activity. The liver is the major, but not exclusive, source of IGF-1. About 50% of circulating growth hormone is bound to binding proteins. These include a high affinity Growth Hormone Binding Protein (GHBP), which actually represents the extracellular portion of the GH receptor. IGFs are mostly bound to IGF- Binding Proteins (IGFBPs). IGF-1 is bound to IGFBP3.

Together GH and IGF-1 influence lipids, protein and glucose metabolism so as to inhibit fat accumulation, promote protein accretion, and alter energy expenditure and body fat/muscle composition. Normally, GH secretion is suppressed as insulin increases in the postprandial period, which permits skeletal muscle glucose uptake promoting glycogenesis and adipogenesis (135). The opposite changes in hormonal concentrations occur during fasting period to facilitate lipolysis and hepatic glucose output (136).

GH secretion from the anterior pituitary is modulated by the hypothalamic GH releasing hormone (GHRH) and follows a pulsatile pattern that is influenced by age, sex, sleep, feeding, physical activity and weight (137). Obesity is typically accompanied by a decrease in GH levels and increase in GHBP levels. This is the opposite picture to starvation in which GH levels are increased and GHBP levels decreased. An inverse relation exists between GH levels and BMI and percent fat mass, particularly VAT, independently of age or sex (138, 139). The reduction in GH levels in obesity is multifactorial and it involves a decreased pituitary release of GH (decreased frequency of GH secretory bursts proportionate to the decree of obesity) and an accelerated GH metabolic clearance rate (140).

Since GH has lipolytic and anabolic properties, it has been postulated that the decline of GH seen in elderly and obese individuals may be partly responsible for the progression of metabolic diseases (141). GH is known to induce insulin resistance (IR). The increased IR seen during puberty and gestational diabetes is, in part, attributed to increased GH action (142). One of the clinical manifestations of acromegaly is glucose intolerance and diabetes mellitus. But interestingly, GH deficiency can also be accompanied by increased IR. A recent general population study in Danish adults revealed that both low and high-normal IGF-1 levels are related to IR (143). There are striking similarities between the metabolic syndrome and untreated adult-onset GH deficiency: increased VAT, IR, non-alcoholic fatty liver disease, dyslipidemia and the associated increased risk of premature atherosclerosis and cardiovascular disease (144, 145). All these observations have led to an increasing interest in investigating the mechanisms behind the decline of GH seen in obesity since it may have important clinical and therapeutic implications. Weight loss is associated with improved stimulated GH response; however there is uncertainty on how much weight loss is required to completely normalize GH secretion (146, 147).

In spite of the reduced GH levels seen in obesity, IGF-1 serum concentration is not significantly different between obese and non-obese subjects. Studies reveled mostly normal or slightly low IGF-1 serum levels in obese individuals (139, 148, 149). This suggests that lower levels of GH are accompanied by increased peripheral sensitivity to GH accounting for the relatively normal IGF-1 levels. This statement is supported by data from Maccario et al. The authors found that the administration of a low dose of rhGH had an enhanced stimulatory effect on IGF-1 secretion in obese subjects compared to normal weight subjects (150). In another study, the same authors

showed a normal inhibitory response of the somatotroph to IGF-1 administration suggesting that the feedback between the somatotroph and IGF-1 is normal (151). In addition, the decreased levels of GH result in up-regulation of GH receptors and increased sensitivity at the liver, as it was shown by higher IGF-1 response to a single GH bolus in obese subjects as compared with normal weight individuals (152).

Multiple mechanisms may explain why GH secretion is decreased in obesity with preservation of near normal serum concentrations of IGF-1:

- Hyperinsulinemia, frequently found in the obesity could be one of the stronger inhibitors of GH secretion by peripheral and central actions. Insulin produces increased peripheral sensitivity to GH, reduced IGFBP-1 levels and increased IGF-1 in spite of decreased GH secretion by the somatotroph. High free IGF-1 levels in this case exert a negative feedback mechanism on GH secretion. Central effects of insulin were shown in a study where the peak GH secretion after GHRH stimulation was inversely associated with fasting insulin in obese premenopausal women (153).
- Androgens may also play a significant role. It has been shown that testosterone activates the somatotrophic axis in men (154, 155) and it augments the GH-dependent stimulatory effect on IGF-I production, enhancing protein and energy metabolism (156). Estrogens, in contrast, cause GH resistance in the liver, leading to a relative reduction of IGF-I production per unit of GH secretion (157).
- Other possible mechanisms included in the altered GH response in obesity are free fatty acids (FFA) and leptin, both of which are increased in obesity. Lee et al showed that reduction in free fatty acids concentrations in obese subjects through use of Acipimox leads to increased GH response to GH-releasing hormone (158). In animals, leptin has an inhibitory role on GH secretion from the pituitary gland through its effects on GHRH and neuropeptide Y (NPY) at the hypothalamus level (159).

The use of recombinant growth hormone in elderly and in subjects with visceral obesity has resulted in a number of mild to moderate anthropometric and metabolic effects such as reduced fat mass, increased lean mass, and improved several surrogate markers of cardiovascular disease (160). Recombinant growth hormone (rhGH) has been extensively studies in the recent era as a treatment for obesity. Studies in the past have shown that, in obesity, rhGH normalized IGF-I levels, induced loss of body weight, mainly body fat, and improved lipid profile without long term effects on insulin sensitivity (161). A meta-analysis indicated that rhGH therapy leads to decrease in visceral adiposity and increase in lean body mass as well as beneficial changes in lipid profile in obese adults, but without inducing significant weight loss. In fact, the observed reductions in abdominal fat mass are modest and similar to what can be achieved by life style interventions (162). Administration of rhGH was associated with increases in fasting plasma glucose and insulinemia over shorted periods of time (163). The dose of rhGH used in these studies was supraphysiological. Further studies of longer duration using closer to physiological doses of rhGH and also determining its effect on cardiovascular morbidity are warranted. The role of GH replacement other than in those individuals with documented GH deficiency as assessed by specific cut off values of GH levels during GH stimulatory testing (using two separate tests), is not clear at this point.

In conclusion, obesity is accompanied by a reduction in basal and stimulated GH secretion by the pituitary gland. The reduction in GH does not appear to translate into similar reduction in IGF-1. While some benefits of GH treatment in obesity are seen in body composition, these are probably not enough (or greater than was is seen with lifestyle) to outweigh potential long-term side effects.

Obesity and Adrenal Glands

Cortisol is mainly bound to Cortisol-Binding Globulin (CGB or transcortin) and less to albumin. About 10% of circulating cortisol is free or unbound and this fraction represents the bioactive portion of the hormone. CBG concentration can be increased or decreased in a number of conditions (Table 2).

Table 2

Increase CBG	Decrease CBG
Estrogens Pregnancy Oral contraceptives Diabetes mellitus Hyperthyroidism	Obesity Cirrhosis Testosterone Nephrotic syndrome Hypothyroidism

The dynamics of the hypothalamic-pituitary-adrenal (HPA) axis in obesity have been examined. Patients with Cushing's syndrome display a number of clinical features that resemble those seen in patients with the metabolic syndrome. These features include redistribution of adipose tissue from peripheral to the truncal region increasing VAT, insulin resistance, impaired glucose homeostasis, hypertension, and lipid abnormalities. These similarities led to the hypothesis that a dysregulation of the HPA axis in the form of "functional hypercortisolism" could potentially be a cause for abdominal obesity and its different metabolic consequences (164).

The serum concentrations of cortisol are generally normal in obesity, several studies over the last several years have tried to unsuccessfully demonstrate the opposite (165-168). The salivary cortisol and 24 hour urine free cortisol (UFC) excretion are usually high-normal or sometimes mildly elevated in obesity. A recent cross-sectional study of obese subjects showed a trend to increase salivary cortisol as BMI increased, but the same association was not found with UFC (169). Other studies in which UFC has been shown to be increased in obesity are due to enhanced cortisol clearance (168, 170), with maintenance of normal cortisol levels and circadian appearance in those with obesity through subsequent increases in cortisol production rates (168, 170, 171).

It has been demonstrated that high-normal ACTH and cortisol levels in obese individuals are associated with cardiovascular risk factors, such as hypertension, insulin resistance and dyslipidemia (172, 173). Other conditions such as depression and/or alcoholism may slightly increase cortisol levels, condition described as pseudo-Cushing's syndrome (174). A pseudo-Cushing's state is characterized by clinical and biochemical features that resemble true

Cushing's syndrome but with resolution of the signs and symptoms once the underlying primary condition is eliminated. It is thought that these primary conditions may stimulate CRH release with subsequent activation of the entire HPA axis (175, 176).

Since serum cortisol is not increased in obesity, it is possible that there is an increase in the local production of cortisol in the fat tissue and this in turn could lead to increased local action of cortisol with the subsequent metabolic consequences known to occur in obesity. Adipose tissue is involved in the metabolism of cortisol. The enzyme 11 Beta-hydroxysteroid dehydrogenase-1 (11HSD1), which converts cortisone (inactive corticoid) to cortisol (active corticoid), is highly expressed in adipose tissue (177). It appears that in obesity more cortisol is derived from cortisone due to the increased activity of this hormone, which could simply be due to increased visceral fat mass (178). Visceral fat cells have higher numbers of glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) than subcutaneous adipocytes (178, 179). Glucocorticoids have higher affinity to MR than to GR. It has been shown that MR activation mediates inflammation and dysregulation of adipokines causing insulin resistance and acceleration of the development of metabolic disorder (180). Interestingly, blockade of the MR improves such changes (181, 182). In human fat, MR mRNA levels increase in direct association with BMI and this augmentation is more significant in VAT, whereas GR mRNA levels had no apparent correlation with BMI or fat distribution (179). Even though evidence for an increased cortisol concentration within the VAT in human obesity is "possible, but unlikely" (183), it is not surprising that, inhibition of 11HSD1 and MR has become a major therapeutic target in metabolic syndrome (184, 185).

The cortisol response to a variety of stimuli such as ACTH, CRH, or meal ingestion is altered in obesity. Sex influences the adrenal glucocorticoid response to ACTH. Animal studies showed that estrogens sensitize and androgens diminish corticotropic-response to ACTH (186). In obesity this sex difference seems to be blunted. One study showed decreased ACTH potency with higher BMI in men (186) and other studies demonstrated ACTH secretion rates comparatively higher than the cortisol secretion rate in centrally obese premenopausal women; suggesting decreased responsiveness of the adrenal gland to the ACTH stimulation in these subjects (187, 188). The same authors showed in a more recent publication, that premenopausal women exhibit diminished ACTH efficacy (maximal cortisol response) and sensitivity (slope of the dose-response curve) (189). This pattern is similar to what has been described in Cushing's syndrome (190). Of note, it is important to mention, that older studies have revealed increased responsiveness of adrenal glands to exogenous ACTH pharmacologic stimulation (191), but this finding should not be extrapolated to the effects of endogenous ACTH stimulation.

A decrease in the mineralocorticoid receptors (MR) response to circulating corticosteroids was suggested by Jessop et al as an explanation for the relative insensitivity to glucocorticoid feedback in obesity (192). A more recent study showed that MR represents an important pro-adipogenic transcription factor that may mediate both aldosterone and glucocorticoid effects on adipose tissue development. Mineralocorticoid receptor thus may be of pathophysiological relevance to the development of obesity and the metabolic syndrome (193).

The HPA axis is also activated in response to stress, as well as the sympathetic nervous system, and the sympathoadrenal system. Whether stress-related obesity due to excess and/or dysfunction of cortisol activity is a distinct medical entity remains unclear and there are contradicting findings in the literature. This topic is evidently difficult to investigate due to multiple confounding variables therefore well-defined longitudinal studies are needed (194).

Finally, when screening overweight and obese individuals for Cushing's syndrome it is imperative to follow the Endocrine Society guidelines which recommend diagnosing the disorder only if two screening tests are abnormal (176). A study of 369 overweight or obese subjects with at least two additional features of Cushing's syndrome found that 25% of these subjects had an abnormal screening test results, but none of them had two positive tests, hence none was found to have Cushing's syndrome (195).

In conclusion, obesity is associated with alterations in the HPA axis which may be a manifestation of a causative effect, adaptive changes to a new homeostatic state or, most likely, a combination of both.

Obesity and Thyroid Hormones

More than 99% of T4 and T3 circulate bound to transport proteins. Only a very small amount of thyroid hormone, less than 1%, is unbound or free and represents the biologically active fraction of the hormone. Thyroxine Binding Globulin (TBG) is the major transport protein. The serum concentration of TBG is influenced by several conditions which can result in a significant increase or decrease in total T4 concentration (Table 3). Therefore, when evaluating thyroid function we measure thyroid stimulating hormone (TSH) and free T4 (FT4). Free T3 (FT3) can also be measured in selected circumstances, such as hyperthyroidism, although it represents only a small fraction of the total thyroid hormone activity.

Table 3

Increase TBG	Decrease TBG
Estrogens Pregnancy Hyperthyroidism Acute hepatitis	Androgens Corticosteroids Systemic illness Nephrotic syndrome Hyperthyroidism Cirrhosis Hyperthyroidism

Given the important role of thyroid hormones in the regulation of thermogenesis and metabolism, it is not surprising that the dynamics of the hypothalamic-pituitary-thyroid axis have been extensively investigated in obesity.

Thyroid dysfunction is frequently associated with changes in body weight and composition, body temperature, energy expenditure, food intake and glucose and lipids metabolism. It is well known that hypothyroidism is linked to weight gain and decreased metabolic rate but, even in

patients with "normal" thyroid function tests, there is a positive association between serum levels of TSH and BMI. Some cross-sectional population studies suggest that even a slightly elevated serum TSH might be important in determining an excess of body weight and it can be considered a risk factor for overweight and obesity (196-199). Also, obese individuals have an increased incidence of subclinical and overt hypothyroidism. Some studies showed a prevalence of these conditions in morbid obesity as high as almost 20% (200, 201). Thyroid-stimulating hormone concentration has also been associated with the presence of the metabolic syndrome showing a positive correlation, even when TSH is within normal levels. In a recent study of 2,760 euthyroid young woman, the subjects with high-normal TSH (2.6-4.5 mIU/L) had higher prevalence of metabolic syndrome than those subjects with low-normal TSH (0.3-2.5 mIU/L) (202).

However, further investigation is needed to determine whether the relationship between TSH and BMI represents causality (mild thyroid failure leading to obesity) or just adaptive changes (physiologic or pathologic) to a new homeostatic state of increased body weight. There are contradicting results from different studies that have tried to elucidate this dilemma:

- A study published by Marzullo et al. supports the idea that obesity increases the susceptibility for thyroid autoimmunity, since in their group of obese individuals they found higher rates of positive anti thyroid peroxidase antibodies than in controls (203). This finding was not observed in other cross sectional studies that included individuals with morbid obesity (BMI > 40 kg/m2). They actually noticed that, as compared with controls, morbidly obese subjects with higher levels of TSH (causing subclinical hypothyroidism or not) but with lower rates of positive thyroid antibodies than control individuals (200, 201, 204). Similar to these 2 studies, observations of data from the NHANES III survey, showed no difference in thyroid antibodies positivity among morbidly obese individuals and the general population (205).
- Also, in population studies higher levels of T3, FT3, T4, and TSH are seen in obese individuals, probably the result of the reset of their central thyrostat at higher level (201).
- The idea that these thyroid function tests (TFTs) changes may reflect a state of thyroid hormone resistance has also been considered. This is supported by the observation of decreased thyroid hormone receptors in circulating mononuclear cells of obese individuals (206) and decreased negative feedback between TSH and peripheral T3 levels.

Fat accumulation increases in parallel with TSH and FT3 levels independently of insulin sensitivity and other metabolic parameters. Also, a positive association has been described between FT3 to FT4 ratio and BMI and waist circumference (207). These findings may result from a high conversion of T4 to T3 due to increased deiodinase activity in the adipose tissue as a compensatory mechanism to increase energy expenditure (198). On the other hand, during a hypocaloric diet, serum T3 declines significantly generating changes in the cardiovascular system similar to those seen in hypothyroidism, suggesting that the decline in T3 may be an adaptive response for energy preservation (208, 209). This adaptive decline in T3 may be mediated, in part, by the fall in leptin levels that accompanies weight loss as it can be reversed with leptin administration (210). Subcutaneous and visceral fat showed reduced thyroid gene expression in obese subjects, especially TSH Receptor gene expression. These changes were reversed by major weight loss (211).

Body mass index is directly associated with thyroid volume and the incidence of thyroid nodules. This association appears to be in positive correlation with the degree of insulin resistance, as it has been shown in several studies (199, 212, 213). Not only the incidence of benign thyroid abnormalities is increased in obesity, even a higher rate of malignancy has been reported (214, 215). Again, hyperinsulinemia is a common denominator found in most studies linking obesity with increased thyroid cancer incidence (216, 217). It is not surprising that particularly high percentage of visceral fat mass has a stronger association with thyroid cancer since VAT is highly metabolically active and associated with increased IR. In a recent study, neck circumference as an index of upper-body adiposity, had a positive correlation with thyroid cancer tumor size and lymph node metastasis (218).

Synthetic thyroid hormones, as well as various other thyroid hormone preparations, have been used as adjunctive measures to induce or facilitate weight loss. A systematic review done by Kaptein el al (219) recognized 14 randomized controlled trials and prospective observational studies describing the effects of T3 and T4 therapy in comparison with placebo in euthyroid obese subjects during caloric deprivation. Most of these studies had a small sample size, ranging from 5 to 12 treated patients. Thyroid hormone treatment resulted in subclinical hyperthyroidism in most patients and there was no consistent effect on weight loss across the studies.

Since the action of thyroid hormone varies depending on the activated receptor, selective thyroid receptor agonists have been developed. In brief, thyroid hormones exert their actions through two major receptors: Thyroid Receptor Alpha (TRA), which mainly mediates T4 effects in bone, skeletal muscle, brain and heart, and Thyroid Receptor Beta (TRB) that regulates TRH/TSH secretion and the metabolic effects of T3 in the liver, such as lowering lipids. The adipose tissue expresses both TRs (220). Selective TRB agonists are promising drugs for treatment of dyslipidemia and obesity without the toxic effects of thyroid hormones analogs on bones or heart in euthyroid patients. This has been tested in animal studies but there are no clinical trials in humans yet (221-223).

CONCLUSIONS AND CLINICAL IMPLICATIONS

As discussed in the previous sections, several endocrine alterations can be identified in association with obesity. In most cases, these alterations are reversible with weight loss and, therefore, they appear to be a consequence of obesity. Emphasis has been focused on the hypothalamic-pituitary hormones axes and the possibility that some "subclinical" alterations in these axes may be at the origin of obesity. At this stage this hypothesis needs further testing. What is true is that the interaction between the adipose tissue and the body is far more complex than once believed, and the future will certainly provide more decisive data on the precise mechanisms of these interactions and their contribution to the development and/or the maintenance of obesity.

Certain endocrine syndromes are known to result in obesity. From the clinical practitioner's perspective it is important to remember these syndromes and to be suspicious should a patient with obesity display one or more of the clinical features seen in these disorders. Hypothyroidism

is a common clinical problem and can, of course, occur in obese patients and could contribute to the presence of symptoms such as fatigue and inability to concentrate. Hypothyroidism is under-diagnosed in the general population and specifically obese patients. Routine screening of patients who present with obesity with a sensitive TSH assay and free T4 is reasonable, although there are no specific guidelines with regards to this. Cushing's syndrome is frequently included in the differential diagnosis of obesity and patients with abdominal obesity have many features in common with patients with authentic Cushing's. However, Cushing's syndrome due to excessive endogenous corticosteroids is rare. Nevertheless, if there is a reasonable suspicion that it may be present, the patient should be screened. Attention should be focused on symptoms and signs that are more specific to Cushing's such as proximal muscle weakness, purple striae, thin and bruised skin, hypokalemia, and osteopenia.

Hypogonadism and growth hormone deficiencies are both associated with abdominal obesity. The latter is usually suspected in the setting of surgery or disease of the hypothalamus-pituitary axis, the former is very common and should be kept in mind in males with other symptoms or signs suggestive of androgen deficiency. The treatment of these two conditions can result directly and indirectly (by improving conditioning, muscle strength, and stamina) in weight loss, improved metabolic profile, and improved bone density but is usually reserved for those with true deficiencies but not with low-normal levels.

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