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## ENDOCRINE CHANGES IN OBESITY

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### ABSTRACT

Obesity can be associated with several endocrine alterations arising from 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, including leptin and adiponectin. Further, obesity is also a common feature of polycystic ovarian syndrome with hyperinsulinemia being the primary etiological factor. Here, we provide an overview of several endocrine syndromes 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 homeostatic responses. 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

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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 obesity phenotypes may have variable health implications. For example, abdominal obesity is considered a more hazardous condition than gluteofemoral, or gynecoid, obesity. In those with abdominal obesity, accumulation of intraperitoneal fat (omental and visceral fat) carries greater health risk than the subcutaneous compartment. Therefore, when discussing complications of and metabolic abnormalities associated with obesity, different obesity phenotypes are recognized to carry different degrees of 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 AS AN ENDOCRINE ORGAN**

### **Adipose Tissue**

Adipose tissue has many important functions other than energy storage that are mediated through hormones or substances synthesized and released by adipocytes. These substances, termed "adipocytokines," act 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. For further characterizations of other types of adipose tissue, including "brown" and "pink" fat, see the Endotext 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 adipose tissue "communicates" with other systems in the body, in particular with the central nervous system (CNS). Following release into the circulation, leptin crosses the blood–brain barrier and binds to presynaptic GABAergic neurons of the hypothalamus of the CNS controlling appetite and energy expenditure (2). One of leptin's key roles is thought to be as a signal of inadequate food intake or starvation. For example, leptin levels decline during fasting, low-calorie dieting, and 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, and in turn leptin levels, to baseline (3,4).

On the other hand, serum concentrations of leptin increase in proportion to increasing adiposity. As a regulatory signal in a homeostatic system, if the leptin receptor is functioning normally, then higher circulating leptin levels should result in decreased energy intake and elevated energy expenditure, but this is not the case when individuals become overweight or obese. Instead, in patients with obesity high leptin levels are associated with low circulating soluble leptin receptors (SLR) consistent with a state of leptin resistance (5). Leptin must cross the blood–brain barrier (BBB) to reach the hypothalamus and

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exert its anorexigenic functions. Decreased transport across the blood-brain barrier (6) and a decreased ability of leptin to activate hypothalamic signaling in diet-induced obesity (7-9) may be crucial in the pathogenesis of leptin resistance.

In addition, anatomical and physiological changes that obesity can cause to the hypothalamus include expression of leptin signaling inhibitors, hypothalamic inflammatory signaling and gliosis, and endoplasmic reticulum stress. Elevated leptin itself may attenuate downstream leptin action, creating a functional ceiling for leptin action (10). These changes, together with the blood-brain barrier alterations, contribute to a failure of rising leptin levels to adequately compensate for the positive energy balance and thus promote the state of unwanted weight gain and obesity. Taken together, evidence points to leptin's primary function as a defense against decreased body weight rather than to limit increases in body weight (10)

Data also suggests that leptin resistance can be a pre-conditioning factor contributing to diet induced obesity. Animal studies show that rats with a pre-existing reduction in leptin sensitivity develop excessive diet-induced obesity without eating more calories or altering their leptin sensitivity (11). 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.

Most people with obesity are hyperleptinemic and show little or no weight loss after leptin treatment. However, recent evidence has indicated that a subset of patients with obesity have low endogenous plasma leptin levels and robustly respond to leptin treatment (12). These findings have led to a proposed classification of obesity based in leptin secretion and action. Type 1 obesity is associated with low leptin levels and leptin replacement can be an effective treatment in these forms of diabetes and obesity.

Examples of patient populations in which this is more likely to be true include children with early onset and severe obesity (congenital leptin deficiency) (13) and those with generalized non-HIV lipodystrophy in whom recombinant methionyl human leptin has been FDA approved (14,15). Type 2 obesity is associated with leptin resistance, in which case leptin replacement is not optimal and other therapeutic approaches should be pursued (12).

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 (16,17). 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 (17). Thus, leptin serves as a putative signal that links metabolic status with the reproductive axis.

Leptin receptors are also 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. For example, leptin has been implicated in glucose and lipid metabolism as an insulin-sensitizer (18). It has been shown to decrease glucagon synthesis and secretion, decrease hepatic glucose production, increase insulin hepatic extraction, decrease lipogenesis in the adipose tissue, and increase lipolysis among multiple other beneficial effects on insulin and lipids metabolism (19).

Other identified links between leptin and biological systems include expression of leptin by placenta and in fetal tissues. In this context, leptin is thought to be important for placentation, maternal-fetal nutrition, and stimulating hematogenesis and angiogenesis in

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the regulation of fetal growth and development (20). On the other hand, the pathological expansion of white adipose tissue during expression of obesity and subsequent increases in cytokines and leptin have been implicated in worsening local and systemic inflammation, sustained proliferative signaling, epithelial-to-mesenchymal transition, angiogenesis, and cellular energetics (21) in association with increased risk of endometrial, kidney, and breast cancers (21,22).

### **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- $\alpha$ , and other yet-unidentified signaling pathways (23). Lower levels of adiponectin in obesity have been associated with insulin resistance (24), dyslipidemia (25), and atherosclerosis (26) in humans. With weight loss, plasma adiponectin levels significantly increase in parallel with improvements in insulin sensitivity (27). In a study with 2258 children with overweight or obesity, independent of the degree of obesity, leptin, adiponectin, and the leptin/adiponectin (L/A) ratio were associated with insulin resistance and other cardiometabolic comorbidities (hyperglycemia and dyslipidemia), but the L/A ratio exhibited stronger associations than the respective adipokines (28).

Genetic analysis of single nucleotide polymorphisms (SNP) in the adiponectin locus have identified in humans a haplotype that, in presence of reduced adiponectin and obesity might alter metabolic profile posing risk towards type 2 diabetes. Presence of +10211T/G and +276G/T SNP are associated with increased fasting plasma glucose, body mass index (BMI), and hypertriglyceridemia (29). Recently,

adiponectin was found to enhance exosome biogenesis and secretion, leading to a decrease in cellular ceramides, the excess of which is known to cause insulin resistance and cardiovascular disease phenotypes (30). Adiponectin has been shown to reduce the action of inflammatory cytokines such as tumor necrosis factor alpha (TNF- $\alpha$ ) (31), favorably modulate natural killer cell function (32) and other immune regulatory molecules (33), and improve dyslipidemia (34) and other risk factors of cardiovascular disease (31).

In addition to an anti-atherogenic effect, adiponectin may also have a variety of anti-tumor effects. This is thought to be mediated, in part, through inhibition of leptin-induced tumor proliferation (35). It retards the aggressiveness of tumors and their metastatic potential. By cancer site and type, high adiponectin levels are associated with a decreased risk of breast, colorectal, and endometrial cancer (22), whereas hypoadiponectinemia has been associated with increased risk for breast, gastric, lung, and prostate cancers (36-39).

A recent study also linked maintenance of the balance between adiponectin and leptin levels with cellular changes in human milk that enhances the protection and decreases the indices of neonatal infection in the breastfeeding infants of women with high BMI values (40).

### **Chemerin**

Chemerin, also known as Retinoic Acid Receptor Responder Protein 2, is a newly discovered adipokine secreted from mature adipocytes thought to play an important role in the regulation of adipogenesis as well as macrophage infiltration into adipose tissue (41,42). Overexpression of chemerin in people with obesity correlates with early vascular damage, as chemerin

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was demonstrated to be a better predictor of intima-media thickening than waist circumference and glycated hemoglobin. Weight loss is associated with a decrease of chemerin level and, like adiponectin, an improvement of all parameters of the metabolic syndrome (43). Also, a decrease of chemerin is independently associated with the reduction of carotid intima-media thickening and the improvement of insulin sensitivity (44).

### **Omentin**

Omentin is an adipokine preferentially produced by visceral adipose tissue that exerts insulin-sensitizing actions (45). Its expression is reduced in obesity, insulin resistance, and type 2 diabetes. Omentin is also positively related with adiponectin and high-density lipoprotein levels, and negatively associated with body mass index, waist circumference, insulin resistance, triglyceride, and leptin levels (46) (47). Apart from obesity, hyperandrogenism and PCOS per se seem to have an additional role in omentin levels since omentin-1 was lower in girls with obesity, PCOS, and hyperandrogenism compared to girls with obesity but not PCOS (48).

Omentin has anti-inflammatory, anti-atherogenic, anti-cardiovascular disease, and anti-diabetic properties (46). 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 (49).

Omentin levels are not significantly different during pregnancy in mothers with diabetes compared to controls. However, significantly lower levels were observed in offspring of the mothers with diabetes,

suggesting an increased risk for the development of insulin resistance in later life (50).

### **Retinol Binding Protein-4**

Retinol binding protein-4 (RBP-4) belongs to the lipocalin family that transports small hydrophobic molecules and is produced primarily in the liver and mature adipocytes (51). Although the relationship between serum RBP-4 and obesity in humans has not been confirmed yet in population studies, several studies have shown positive correlations between the expression of RBP-4 and BMI and glucose concentration (52). RBP-4 levels can be reduced by weight loss, consuming a balanced diet, and exercise in association with increased insulin sensitivity (53,54).

### **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 (55).

### **Fatty Acid-Binding Proteins**

Fatty acid binding protein A (A-FABP) is an isoform expressed in the adipose tissue and macrophages (56). It binds to hydrophobic ligands such as long chain fatty acids and facilitates their transport to specific cell compartments. Several studies have shown positive correlations between A-FABP and proinflammatory factors, such as CRP, and may also have significant importance in predicting insulin resistance (57).



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## **Acylation Stimulating Protein**

Acylation stimulating protein 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 (58). It has been shown to induce glucose-stimulated insulin release from pancreatic beta cells, modulates cytokine synthesis by mononuclear cells, as well as inhibit cytotoxicity of natural killer cells (59).

## **Renin-Angiotensin-Aldosterone System**

Several components of the renin-angiotensin system (renin, angiotensinogen, angiotensin-converting enzyme, and angiotensin 2 receptors) are expressed by adipose tissue (60). Recent studies have shown that adipocyte deficiency of angiotensinogen prevents obesity-induced hypertension in male mice (61). Adipocytes promote obesity-induced increases in systolic blood pressure in male high fat-fed C57BL/6 mice via angiotensin 2 dependent mechanism (62). Adipocyte angiotensinogen deficiency prevents high fat-induced elevations in plasma angiotensin 2 concentrations and therefore in systolic blood pressure (61). These results suggest that adipose tissue serves as a major source of angiotensin 2 in the development of obesity-related hypertension.

## **Other Factors Secreted by Adipose Tissue**

Other proteins secreted by adipose tissue include plasminogen activator inhibitor-1 (PAI-1) (63) 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 (64,65).

Circulating levels of Interleukin-6 (IL-6) are significantly higher in patients with overweight and obesity (66). Interleukin-6 is released by macrophages

and T-cells in the adipose tissue (67) and has been implicated in regulating insulin signaling in peripheral tissues by promoting insulin-dependent hepatic glycogen synthesis and glucose uptake in adipocytes (68). Recent studies show that IL-6 deficient mice develop late-onset obesity as well as disturbed glucose metabolism (69). 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 because 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 (69). It has been suggested that IL-6 potentiates the action of leptin providing a possible mechanism for its anti-obesity effect (70). In addition, IL-6 has been postulated to play an etiologic role in the increased risk of thromboembolism observed in patients with obesity (71).

## **Summary**

Adipose tissue is an extremely active organ with multiple roles, including endocrine, paracrine, and autocrine, in human physiology and disease. How these roles are performed and their contribution to the health or risk of disease 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 HYPOTHALAMIC-PITUITARY AXES**

### **Obesity and Sex Hormones**

Not only is obesity associated with alterations in sex hormone levels but sex hormones may conversely influence expression of 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 (72-74).

SEX STEROID AND SHBG

Most circulating testosterone and estrogen are bound to proteins, SHBG and albumin. Although a portion of

the bound sex hormones may be available for use by the body target cells, only about 2% of circulating sex steroids are unbound, or free, and constitute the bioactive fraction of these hormones. Total hormone levels, therefore, reflect the bound and unbound hormone and are greatly dependent on the serum concentration of SHBG. For example, SHBG levels increase with age and bioactive testosterone levels decrease (Table 1).

Table 1. Common Conditions and Medications that Affect Serum Concentrations of SHBG	
Increased SHBG	Decreased SHBG
Older Age Cirrhosis Hyperthyroidism Estrogens	Obesity Androgens Hypothyroidism Glucocorticoids Growth hormone Insulin

OBESITY AND ANDROGENS IN MEN

Testosterone should be measured in the morning when serum concentrations peak and we recommend repeating an abnormal measurement for confirmation. Evidence indicates that testosterone (T) deficiency in men induces adiposity and, at the same time, increased adiposity induces hypogonadism (72). An obesity-associated decline in SHBG might partially explain the observed fall in T levels (74,75). However, an increased BMI is associated with low measured, or calculated, free- and bioavailable-testosterone levels as well. In a metaanalysis of sixty-eight studies including a total of 19,996 patients with obesity, prevalence of hypogonadism ranged from 22.9 to 78.8% and from 0 to 51.5% depending on whether low total testosterone or low free testosterone was used to define hypogonadism, respectively. Pooled prevalence of hypogonadism when measuring total testosterone or free testosterone was 42.8% and 32.7%, respectively (76).

While the specific pathogenic mechanisms linking obesity with low testosterone levels are not completely understood, both secondary (hypogonadotropic) and, to a minor degree, primary hypogonadism (testicular failure) have been described. Other potentially contributing factors include development of type 2 diabetes, hypertension, and increased adipokines (77,78). Obstructive sleep apnea predisposes to male obesity and secondary hypogonadism (MOSH) through reductions in luteinizing hormone (LH) pulse amplitude and reduced mean serum levels of LH and T in men. Obstructive sleep apnea may also disrupt the association between a rise in serum T levels and the appearance of first REM sleep (79,80).

At the testicular level, studies by Wagner et al have shown that obesity lowers the number of testosterone producing Leydig cells and promotes destruction of existing ones by increasing levels of proinflammatory cytokines (TNF alpha) and cells (macrophages) (81). In both the short and long term, obesity was shown to lower intra testicular levels of testosterone by way of

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increasing serum leptin and estradiol levels and inhibiting the expression of the gene for cytochrome p450 of the cholesterol side chain cleavage enzyme (Cyp11a1) (81).

Whether testosterone treatment in (MOSH) is beneficial has long been controversial. Only those with low free T levels and signs or symptoms of hypogonadism should be considered androgen deficient. Considering the limited number of rigorous testosterone therapy trials that have shown beneficial effects, the modest amplitude of these effects, and unresolved safety issues, testosterone therapy is currently not advocated in the prevention or reversal of obesity-associated metabolic disturbances (82).

On the other hand, true hypogonadism in men can 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 (83,84). 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 (85). This further decreases T levels that in turn further increases the preferential deposition of fat within abdominal depots: a 'hypogonadal-obesity cycle' (86,87). Individuals with obesity retain the capacity to reverse this gonadotrophic response with weight loss, demonstrating that MOSH is a reversible condition. This has been made evident on several studies in which weight loss normalized T levels (88,89).

In summary, obesity is frequently associated with low androgen levels in men and true hypogonadism can worsen adiposity and central fat deposition. The pathogenesis of obesity-related hypogonadism is complex and multifactorial, implicating obesity-related

comorbidities and changes in body fat mass itself with its multiple adipokines and inflammatory mediators. Ultimately, these changes are frequently reversible with weight loss and preferred strategies to manage these conditions target lifestyle, anti-obesity medications, and weight-loss surgeries when indicated.

## OBESITY AND SEX STEROIDS IN WOMEN

Increases in body weight and fat tissue are 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) (90,91). These women have higher total and free testosterone levels than normal-weight woman and lower androstenedione and SHBG levels (91). Some studies examining the co-relationships between the total testosterone levels and phenotypic features of hyperandrogenism, such as hirsutism, found a strong correlation between them, regardless of the assay used for assessment (92).

The timing of menarche is primarily thought to be affected primarily by genetic factors (93,94), but the average age at menarche in US girls has been declining over the past 30 years (95) in conjunction with changes in nutritional status (96). A Mendelian randomization study from the United Kingdom linked a higher BMI with early menarche, suggesting a causal relationship between increasing prevalence of childhood obesity and similar trends in the prevalence of early menarche (97).

Studies have also shown that the earlier the onset of menarche, the higher the risk of developing obesity (98) and other comorbidities in the adult life, independently of BMI, such as: breast cancer,



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cardiovascular disease, cerebrovascular disease, type 2 diabetes, and adolescence at-risk behaviors (99-104). Consequently, all-cause mortality has been linked with early menarche (105). Also, there is evidence that menarche at or before 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 one-year advance in menarcheal age, the probability of having obesity decreased by 22%; interestingly, in this study women with obesity had higher androgens levels (106).

Menarche age also appears to affect offspring. Boys whose mothers with menarche onset  $\leq 13$  years at menarche had an adjusted relative risk of obesity 3-fold greater than sons of mothers with a later menarche onset. The increased obesity risk was not observed in daughters. However, girls who experienced menarche earlier had a less favorable anthropometric profile consisting in a reduced waist and hip circumferences and waist-to-height ratio (107). Early menarche, therefore, has emerged as a risk of later obesity and related 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 (108,109) and directly by stimulating LH and, to a lesser extent, FSH release.

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 (110) of patients with leptin deficiency and several animal studies (111,112).

Kisspeptin play a central role in the modulation of GnRH pulse generator and, thus, downstream regulation of gonadotropins and testosterone secretion in men (113,114). 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 (113).

Serum kisspeptin levels are higher in patients with obesity and tend to decrease after weight loss intervention. (115,116). Also, data suggest a higher concentration of serum kisspeptin in women with PCOS irrespective of their BMI but further data are needed to ascertain the role of kisspeptin in PCOS (116).

Kiss1 neurons appear to transmit the regulatory actions of metabolic cues on pubertal maturation. Recently, it has been documented that AMPK and SIRT1 operate as major molecular effectors for the metabolic control of Kiss1 neurons and, thereby, puberty onset. Alterations of these molecular pathways may contribute to the perturbation of pubertal timing linked to conditions of metabolic stress in humans, such as undernutrition and obesity. As such, it has the potential of becoming a druggable targets for better management of pubertal disorders (117).

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Leptin receptors are also widely expressed in the human ovaries (118) and testes (119) indicating a direct gonadal regulatory role. Studies by Ma et al. have shown that high-fat diet fed mice produce fewer oocytes compared with control mice receiving a normal diet. Leptin has been noted to act locally within the mice ovarian granulosa cells to reduce estradiol production (120). 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 (121). In humans undergoing in vitro fertilization, Ma et al. demonstrated that subjects with higher BMI had higher levels of CART mRNA and peptide in follicular fluid (121). Therefore, in women with obesity, evidence supports a role for leptin as a mediator of infertility at the level of the ovary.

As mentioned above, in men with obesity, intra testicular levels of testosterone are lower due to leptin and estradiol inhibition of the expression of the gene for cytochrome p450 of the cholesterol side chain cleavage enzyme (Cyp11a1) (81). Gregoraszczuk et al exposed porcine ovarian follicles obtained from prepubertal and mature animals to progressively increasing doses of super active human leptin antagonist (SHLA) and measured levels of leptin receptor (ObR), leptin, CYP11A1 and 17 $\beta$ -hydroxysteroid dehydrogenase (17 $\beta$ -HSD), progesterone (P4), and testosterone (T) in the follicles (122). 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. Women with obesity and 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 (123).

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 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 (124). About two thirds of women with PCOS are obese and 50-70% of them have insulin resistance (IR) (125).

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 (126). Visceral adipose tissue (VAT) excess is strongly associated with metabolic disorders such as insulin resistance and dyslipidemia (127). 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 (128,129). 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

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an intrinsic characteristic of this syndrome, independent of obesity (124). Interestingly, in PCOS, despite the insulin resistance in other organs, the ovaries remain sensitive to the stimulatory effect of insulin on androgen production (130). 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 to be the main culprit of its multiple co-morbidities (131).

Anovulation and menstrual irregularities are major features of PCOS in part due to ovarian hyperandrogenism, hyperinsulinemia due to IR, and altered paracrine signaling within the ovary, which can disrupt follicle growth (124). Hyperinsulinemia also decreases hepatic SHBG with a 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 (132,133). 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 (134).

In summary, obesity is a common feature of PCOS and hyperinsulinemia secondary to insulin resistance of the liver and muscle 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 (135,136). Therefore, the role of metformin in improving reproductive outcomes in women with PCOS appears to be limited (137). 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 (138).

A clinical trial in 120 infertile PCOS women showed that when metformin is combined to myoinositol (MI) a significant improvement in live birth rate, menstrual cycle (length and bleeding days), and HOMA index is observed compared to use of metformin alone (139). Treatment with MI has been useful also in in-vitro fertilization (IVF), as it allows a decrease in the amount of recombinant FSH administered, in the duration of the ovulation induction for follicular development (140,141) and an increase in the clinical pregnancy rate (142) [45].

## 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, which is especially important in men and post-menopausal women and increase in proportion to the total body adiposity (143,144).

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 (145,146).

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Estrogens have a positive effect in glucose homeostasis, acting as an insulin sensitizer at multiple levels, including skeletal muscle, liver, and adipocytes (147). Estrogen effects the immune system to decrease inflammation, thus favoring insulin sensitivity (148,149). Pancreatic islet-cells also have estrogens receptors, which when activated improve beta cell function and survival (150). Estrogen deficiency promotes metabolic dysfunction predisposing to obesity, metabolic syndrome, and type 2 diabetes.

In rodent models, estrogen has been shown to 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 (147).

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 (147). Visceral fat is augmented in hypoestrogenic states, as seen in menopause. These changes in body fat composition can be prevented by estrogens replacement (151). 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 (152).

Obesity in both men and women is associated with elevated estrogens levels that result from aromatization of androgens in adipocytes (86). 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 (153), while 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 (154).

## **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 concentrations represent 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 represents the extracellular portion of the GH receptor. IGFs are mostly bound to IGF-Binding Proteins (IGFBPs) with 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 (155). The opposite changes in hormonal concentrations occur during fasting to facilitate lipolysis and hepatic glucose output (156).

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 (157). 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

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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 (158,159). 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 degree of obesity) and an accelerated GH metabolic clearance rate (160).

Since GH has lipolytic and anabolic properties, it has been postulated that the decline of GH seen in elderly and individuals with obesity may be partly responsible for the progression of metabolic diseases (161). 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 (162). 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 (163). 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 (164,165). 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 (166).

Despite the reduced GH levels seen in obesity, IGF-1 serum levels are not significantly different between those with and without obesity. Studies have revealed mostly normal or slightly low IGF-1 serum levels in

individuals with obesity (159,167,168). This suggests that lower levels of GH are accompanied by increased peripheral sensitivity to GH accounting for the relatively normal IGF-1 levels. This is supported by data from Maccario et al., who found that the administration of a low dose of rhGH had an enhanced stimulatory effect on IGF-1 secretion in subjects with obesity compared to normal weight subjects (169). In another study, the same authors showed a normal feedback inhibitory response of the somatotroph to IGF-1 (170). In addition, decreased GH levels 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 subjects with obesity as compared with normal weight individuals (171).

#### PROPOSED MECHANISMS FOR LOWER GH SECRETION IN OBESITY

Hyperinsulinemia that accompanies 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 premenopausal women with obesity (172).

Sex steroid levels may also govern GH activity. It has been shown that testosterone activates the somatotrophic axis in men (173,174) and augments the GH-dependent stimulatory effect on IGF-I production, enhancing protein and energy metabolism (175). Estrogens, in contrast, cause GH resistance in the liver, leading to a relative reduction of IGF-I production per unit of GH secretion (176).



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Other possible mechanisms for 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 subjects with obesity through use of Acipimox leads to increased GH response to GH-releasing hormone (177). 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 (178).

## RECOMBINANT GROWTH HORMONE THERAPY IN PATIENTS WITH OBESITY

The use of recombinant human growth hormone (rhGH) in elderly and subjects with visceral obesity results in several mild to moderate anthropometric and metabolic effects such as reduced fat mass, increased lean mass, and improved surrogate markers of cardiovascular disease (179). Recombinant growth hormone has been extensively studied as a treatment for obesity. A meta-analysis found that rhGH therapy reduces visceral adiposity and increases lean body mass as well as having beneficial changes in lipid profile in adults with obesity, 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 (180). In addition, administration of rhGH was associated with increases in fasting plasma glucose and insulinemia over shorted periods of time (181). However, the dose of rhGH used in these studies was supraphysiological.

Investigations of rhGH in youth have reported favorable outcomes. A pilot study in young adults (18-

29 years old) with obesity and non-alcoholic fatty liver disease suggested that rhGH may have benefits to reduce liver fat content (182). Also, in boys with obesity (8-18 years old) treatment with rhGH for one-year reduced body mass index standard deviation scores and insulin-like growth factor 1 levels increased. GH treatment also reduced low density lipoprotein cholesterol, total cholesterol, triglycerides, and alanine aminotransferase when compared with the baseline. (183). However, further studies of longer duration outcomes, including cardiovascular morbidity and insulin sensitivity, are warranted.

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, other than in those individuals with documented GH deficiency, these are probably not enough (or greater than was is seen with lifestyle) to outweigh potential long-term side effects and the role of GH replacement in patients with obesity and normal GH axis testing, remains controversial.

## Obesity and Adrenal Glands

Cortisol circulates in the bloodstream mainly bound to Cortisol-Binding Globulin (CGB or transcortin) and less to albumin. About 10% of cortisol is free or unbound and this fraction represents the bioactive portion of the hormone. CBG concentrations can be increased or decreased in several conditions and by some medications (Table 2), thus affecting total cortisol levels in these situations.

**Table 2. Medical Conditions and Drugs that Affect Cortisol Binding Globulin (CBG) and Total Cortisol Levels**

<b>Increase CBG</b>	<b>Decrease CBG</b>
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 several 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 accompanying metabolic consequences (184).

The serum concentrations of cortisol are generally normal in obesity (185-188). Salivary cortisol and 24-hour urine free cortisol (UFC) excretion are usually high-normal or sometimes mildly elevated in obesity. A cross-sectional study of subjects with obesity showed a trend to increase salivary cortisol as BMI increased, but the same association was not found with UFC (189). Other studies in which UFC has been shown to be increased in obesity are due to enhanced cortisol clearance (188,190), with maintenance of normal cortisol levels and circadian appearance in those with obesity through subsequent increases in cortisol production rates (188,190,191).

It has been demonstrated that high-normal ACTH and cortisol levels in individuals with obesity are associated with cardiovascular risk factors, such as hypertension, insulin resistance and dyslipidemia

(192,193). On the other hand, depression and/or alcoholism may slightly increase cortisol levels. These conditions have been described as pseudo-Cushing's syndrome (194). 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 (195,196).

Although serum cortisol is not increased in obesity, it is possible that the local production of cortisol in the fat tissue is increased and this, in turn, could lead to increased local action of cortisol with the subsequent metabolic consequences. Adipose tissue is involved in the metabolism of cortisol through action of the enzyme 11 Beta-hydroxysteroid dehydrogenase-1 (11HSD1), which converts cortisone (inactive corticoid) to cortisol (active corticoid) (197). Whole body 11 $\beta$ -HSD1 reductase activity tends to be higher in obesity (~10%) and is further increased by insulin (198). 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. (198).

Some authors provide evidence that cortisol affects zinc metabolism and indicate possible repercussions on insulin signaling that might contribute to the development of resistance to the actions of insulin in

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obesity. Thus, alterations in the biochemical parameters of zinc observed in individuals who are obese contribute to the development of disorders in the synthesis, secretion, and action of insulin (199).

Visceral adipose tissue has higher numbers of glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) than subcutaneous tissue (200,201). 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 (202). Interestingly, blockade of the MR improves these outcomes (203,204). In human adipose tissue, 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 (201). Even though evidence for an increased cortisol concentration within the VAT in human obesity is "possible, but unlikely" (205), it is not surprising that inhibition of 11HSD1 and MR has become a major therapeutic target in metabolic syndrome (206,207).

The cortisol response to a variety of stimuli such as ACTH, CRH, or meal ingestion is altered in obesity and by sex. Animal studies showed that estrogens sensitize and androgens diminish corticotropin-response to ACTH (208). In obesity these sex hormone differences are blunted. One study showed decreased ACTH potency with higher BMI in men (208) 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 (209,210). 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) (211). This pattern is similar to what has been

described in Cushing's syndrome (212). Of note, it is important to mention that older studies have revealed increased responsiveness of adrenal glands to exogenous ACTH pharmacologic stimulation (213), but this finding should not be extrapolated to the effects of endogenous ACTH stimulation.

A decrease in the mineralocorticoid receptor (MR) response to circulating corticosteroids was suggested by Jessop et al as an explanation for the relative insensitivity to glucocorticoid feedback in obesity (214). A more recent study showed that MR represent 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 (215).

The HPA axis is also activated in response to stress along with 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 and therefore well-defined longitudinal studies are needed (216).

Finally, when screening overweight and individuals with obesity 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 (196). A study of 369 overweight or subjects with obesity with at least two features of Cushing's syndrome found that 25% of these subjects had an abnormal screening test result, but none of them had two positive tests, hence none was found to have Cushing's syndrome (217).

In conclusion, obesity is associated with alterations in the HPA axis that may be a manifestation of a causative effect, adaptive changes to a new homeostatic state or, most likely, a combination of both. And although signs and symptoms of hypercortisolism commonly are also found in patients with central obesity, the finding of an actual case of Cushings disease is very rare in the obese population.

**Obesity and the Thyroid**

More than 99% of T4 and T3 circulate bound to transport proteins. Only a very small amount, less than

1%, of thyroid hormone is unbound or free and represents the biologically active fraction of the hormone. Thyroxine Binding Globulin (TBG) is the major transport protein for thyroid hormones and serum TBG concentrations are influenced by several conditions and medications, which result in altered total T4 and T3 concentrations (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 circulation total thyroid hormone activity.

Table 3. Medical Conditions and Drugs that Affect Thyroxine Binding Globulin (TBG) and Total Thyroid Hormone Levels	
Increase TBG	Decrease TBG
Estrogens Pregnancy Hypothyroidism Acute hepatitis	Androgens Corticosteroids Systemic illness Nephrotic syndrome Hyperthyroidism Cirrhosis

Thyroid dysfunction is frequently associated with changes in body weight and composition, body temperature, energy expenditure, food intake, glucose, and lipids metabolism. Hypothyroidism is linked to weight gain and decreased metabolic rate but there is also a positive association across the normal range 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 (218-221). Also, individuals with obesity 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% (222,223). Thyroid-stimulating hormone

concentrations has also been associated with the presence of the metabolic syndrome, even when TSH is within normal levels. In a study of 2,760 euthyroid young woman, those with high-normal TSH (2.6-4.5 mIU/L) had higher prevalence of metabolic syndrome than those with low-normal TSH (0.3-2.5 mIU/L) (224).

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. Contradicting results from different studies illustrate this controversy. For example, a study published by Marzullo et al. supports the idea

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that obesity increases susceptibility for thyroid autoimmunity, since in their group of individuals with obesity they found higher rates of positive anti-thyroid peroxidase antibodies than in controls (225). This finding was not observed in other cross-sectional studies that included individuals with severe obesity (BMI > 40 kg/m<sup>2</sup>). In that study, as compared with controls subjects with severe obesity had higher levels of TSH (but with lower rates of positive thyroid antibodies than control individuals (222,223,226). Data from the NHANES III survey showed no difference in thyroid antibodies positivity among individuals with obesity and the general population (227). However, a recent metanalysis showed that even after stratification, the obese population had increased risks of overt hypothyroidism and subclinical hypothyroidism and was clearly associated with Hashimoto's thyroiditis but not Graves' disease. In patients with Hashimoto's thyroiditis, obesity was correlated with positive thyroid peroxidase antibody (TPOAb) levels but not with positive thyroglobulin antibody (TGAb) levels (228).

In a euthyroid population, when comparing metabolically healthy obese (MHO) with metabolically unhealthy obese (MUO) phenotypes, the following findings were reported: FT4 levels were negatively associated with the MUO phenotype, FT3 levels were positively associated with both the MHO and the MUO phenotypes, and TSH levels were positively associated with the metabolically unhealthy, non-obese phenotype (229).

Also, in population studies higher levels of T3, FT3, T4, and TSH are seen in individuals with obesity, probably the result of the reset of their central thyrostat at higher level (223).

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 individuals with obesity (230) 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 (231). 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 (220). On the other hand, during a hypocaloric diet, serum T3 declines significantly, generating changes in the cardiovascular system like those seen in hypothyroidism, suggesting that the decline in T3 may be an adaptive response for energy preservation (232,233). 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 (234). Subcutaneous and visceral fat showed reduced thyroid gene expression in subjects with obesity, especially TSH Receptor gene expression. These changes were reversed by major weight loss (235).

After weight loss from bariatric surgery, FT3 and TSH levels were significantly reduced and serum thyroperoxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) levels decreased significantly from 79.3 and 177.1 IU/mL to 57.8 and 66.0 IU/mL, respectively, in participants with positive thyroid antibodies (236). Also in patients starting with a subclinical hypothyroidism state, weight loss led to normalization of TSH levels in most patients and none developed overt hypothyroidism (237). Furthermore, in children with obesity and overweight without circulating antithyroid antibodies, BMI reductions uniquely predict reductions in TSH, thyroid volume, and improvement in thyroid structure with an altered parenchymal pattern at thyroid ultrasound (238).



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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 (221,239,240). Not only is the incidence of benign thyroid abnormalities increased in obesity, but a higher rate of malignancy has also been reported (241,242). Pathway analysis has identified 1,036 genes associated with thyroid cancer (TC) and 534 regulated by obesity. Five out of the 358 obesity-specific genes, FABP4, CFD, GHR, TNFRSF11B, and LTF, had significantly decreased expression in TC patients (243). Hyperinsulinemia is a common factor found in most studies linking obesity with increased thyroid cancer incidence (244,245). 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. Even though neck circumference as an index of upper-body adiposity, had a positive correlation with thyroid cancer tumor size and lymph node metastasis (246), other studies do not observe any association between obesity and thyroid cancer aggressive features (247,248). Whether obesity increases the risk of thyroid cancer remains controversial as several authors have concluded that obesity is associated with greater risk of thyroid cancer (249,250), while others do not (251).

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 reported by Kaptein et al (252) recognized 14 randomized controlled trials and prospective observational studies describing the effects of T3 and T4 therapy in comparison with placebo in euthyroid subjects with obesity 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.

Adipose tissue expresses both TRs (253). 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 (254-256).

## CONCLUSIONS AND CLINICAL IMPLICATIONS

As discussed in the previous sections, several endocrine alterations can be identified in association with obesity (Table 4). In most cases, these alterations are reversible with weight loss and, therefore, 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 increased adiposity. At this time 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 patients with obesity 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 patients with obesity. 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, true Cushing's disease (due to excessive endogenous corticosteroids) is rare. Nevertheless, if there is a reasonable suspicion for this condition, 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 former is very common and should be kept in mind in males with other symptoms or signs suggestive of androgen deficiency while the latter is usually suspected in the setting of surgery or disease of the hypothalamus-pituitary axis. 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, not with low-normal levels.

**Table 4. Hormonal Changes in Obesity**

<b>Adipose tissue as an endocrine organ</b>	
	Type 2 obesity with leptin resistance → Leptin increases
	Type 1 obesity with congenital leptin deficiency → Leptin decreases
	Adiponectin decreases
	Chemerin increases
	Omentin decreases
	Retinol Binding Protein increases
	Angiotensin 2 increases
	Plasminogen activator inhibitor-1 (PAI-1) increases
	Interleukin-6 increases
<b>Obesity and the pituitary axes</b>	

	LH pulsatility decreases
	Total testosterone decreases in men
	Free testosterone decreases in men
	SHBG decreases in women and men
	Androgens increase in women
	Free testosterone increases in women
	Androstenedione decreases in women
	Increase in kisspeptin levels
	Aromatization of androgens in adipocytes leads to elevated estrogens levels
	GH level decreases
	GH binding protein increases
	IGF-1 normal or slightly low
	Cortisol normal
	24-hour urine free cortisol (UFC) excretion high-normal
	TSH normal or slightly increased

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