



ENDOCRINE FUNCTION IN OBESITY

Chapter 12 - Yasser Ousman, M.D., and Kenneth D. Burman, M.D.

August 21, 2002

[Contents](#)
[Contributors](#)
[Search](#)

INTRODUCTION

This chapter will discuss the endocrine changes or alterations that can occur in association with obesity. We will discuss the endocrine role(s) of adipose tissue, alterations in the hypothalamic-pituitary-endocrine axis, and the possible changes that can occur in each of these axis in association with obesity.

At this point, it is important to emphasize several issues that are relevant.

- The first question is whether the endocrine changes that can be seen in obesity are secondary to obesity or could, some of them at least, 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, changes in thyroid function tests, testosterone, and growth hormone concentrations are commonly seen in response to acute and chronic illnesses, and starvation. These alterations are typically transient and resolve as the subject recovers from the offending insult. These changes are, therefore, thought to be secondary and reflective of a homeostatic mechanism. It is, however, also important to mention that these "adaptive" changes in hormonal dynamics may not necessarily be appropriate and that therapeutic measures aimed at restoring "normal" serum level of perturbed hormones may hasten recovery and improve patient outcome. So far though, such interventions have not shown to be successful.
- Obesity is a straightforward term, which is defined by an increase in body mass index. Different phenotypes of obesity have different health implications. Abdominal or visceral obesity is considered to be a more hazardous condition than gluteofemoral or gynecoid obesity. Some also distinguish between subcutaneous abdominal obesity where most of the abdominal fat is under the skin and visceral abdominal obesity where the majority of the fat is in the omentum. The latter having even more health implications than the former. Therefore, when discussing complications of and metabolic abnormalities associated with obesity, one has to remember that different phenotypes of obesity exist and may carry different degrees of risk, in particular cardiovascular risk.
- Our understanding of the physiology of adipose tissue has improved in the last decade and extensive research has been dedicated to the study of the interactions between the adipose tissue and other body systems, in particular the central nervous system. New hormones and substances with important potential roles in energy balance and food intake have been discovered and our understanding of their action continues to expand. Some of the newly discovered hormones have not had their role 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 rather limited pharmacological arsenal.

ENDOCRINE FUNCTION OF THE ADIPOSE TISSUE

Adipose tissue has an important role in storing energy in the form of fat for subsequent use by various body organs. Lipid metabolism depends on the integration of a number of signals that include hormones, neuronal pathways and nutrients. The details of how these different signals influence fat metabolism is beyond the scope of this chapter. 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 can act on distant targets in an endocrine fashion or act locally in a paracrine or autocrine fashion.

The hormone leptin is one of these "messengers" and its discovery has greatly influenced our understanding of how the adipose tissue "communicates" with other systems in the body, in particular with the central nervous system(1,2). Leptin is clearly a major link between fat and not only the CNS but also other body components³. The physiologic roles of leptin are numerous; besides its important role as an anti-obesity hormone⁴, leptin has important metabolic effects: It has been shown to be implicated in glucose and lipid metabolism(4-6). It has an important role in reproduction and can exert actions on the different hypothalamic-pituitary-endocrine axes(4-6). Leptin is also formed in the placenta and is widely expressed in the fetal tissues. It stimulates hematogenesis and angiogenesis indicating a possible role in development. Leptin may also be involved in brain development as evidenced by the decreased brain weight and impaired myelination in mice with leptin deficiency(4-6). Leptin increases sympathetic nerve activity in the brown adipose tissue, adrenal gland, kidney, and hindlimb skeletal muscle. It is speculated, therefore, that leptin may have a role in the etiology of hypertension, cardiovascular, and renal changes associated with obesity⁷.

Besides leptin, the adipose tissue secretes a number of other substances, which can have systemic or local actions. These include cytokines such as tumor necrosis factor alpha (TNF- α), which may play a role in fat metabolism and insulin resistance(8-10). Adipocytes also produce IL-6^{10,11}. Which stimulates C-reactive protein. C-reactive protein, a systemic marker of inflammation, is increased in obesity. IL-6 and its subsequent Inflammation has been postulated to play an etiologic role in the increased risk of thromboembolism observed in obese patients. The adipose tissue is capable of producing plasminogen activator inhibitor-1 (PAI-1)¹². Several components of the renin-angiotensin system (renin, angiotensinogen, angiotensin-converting enzyme and angiotensin II receptors) are expressed by the adipose tissue^{13,14}. Elevations in the levels of PAI-1 and angiotensin II could explain at least partly the increased cardiovascular risk associated with obesity. Other proteins such as complement factors, adiponectin, and adiponectin that are expressed by fat tissue may also have a role in the pathophysiology or the progression of coronary artery disease(15-20).

Finally, adipocytes can metabolize sex steroids and glucocorticoids²¹. Adipocytes convert androgens to estrogens under the influence of the enzyme aromatase. Another hormone present in the adipose tissue, 11-beta hydroxysteroid dehydrogenase-1 (11beta-HSD1), converts cortisone to cortisol and its overactivity in obesity has been suggested to result in increased local concentrations of cortisol in the adipose tissue²².

The adipose tissue is a target for the action of sex steroids and cortisol through interaction with their nuclear receptors present in adipocytes(23-27).

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

TESTIS

Most of the circulating testosterone is bound to transport proteins; Sex Hormone Binding Globulin (SHBG), and albumin. SHBG is produced by the liver. Only about 2% of circulating testosterone is unbound or free, and this is thought to represent the vast majority of the bioactive fraction of the hormone. Some believe that at least part of the bound testosterone is readily available for use by the body target cells. Total testosterone, therefore, reflects the bound and unbound hormone and is greatly dependent on the serum concentration of SHBG. Table 1, shows some common conditions that can affect the serum concentration of SHBG:

Table 1.	
Increase SHBG	Decrease SHBG
Estrogens Hyperthyroidism Cirrhosis	Androgens Glucocorticoids Growth hormone Hypothyroidism Obesity

Testosterone should be measured in the morning when its serum concentration is at its peak and we recommend repeating an abnormal measurement for confirmation. It is an unresolved question whether total testosterone, free testosterone, or both should be routinely measured. In most patients, we prefer to assess both free and total.

Obesity itself is one of several conditions that can result in a low SHBG. As a result total testosterone is frequently low normal or below the normal range in obese men²⁸. The free testosterone and bioavailable testosterone (total testosterone minus SHBG bound testosterone), however, are generally normal in this situation. Men with massive obesity can also manifest low levels of free testosterone²⁹. These changes in total and free testosterone concentrations are reversible with weight loss indicating that they are secondary to obesity^{30,31}.

The reduction in free testosterone seen in massive obesity is not accompanied by a reciprocal increase in luteinizing hormone (LH) suggesting a central rather than gonadal mechanism behind this change⁽³⁰⁻³²⁾.

In obese patients, the serum concentration of pituitary gonadotropins, LH and FSH, is normal. The response of gonadotropins to gonadotropin releasing hormone, GnRH, or to clomiphene was reported to be normal in previous studies indicating a normal hypothalamic-pituitary responsiveness to stimuli⁽³³⁻³⁶⁾.

Serum levels of testosterone rise in response to human chorionic gonadotropin (HCG), administration which suggests normal gonadal function in obese individuals. In a study by Isidori et al, however, the response of testosterone to LH/HCG stimulation in obese men was reduced in comparison to the response in nonobese men³⁷. Testosterone response to LH/HCG stimulation correlated negatively with serum leptin levels. The authors suggested that elevated levels of leptin may contribute to the development of reduced androgens in male obesity.

Fewer data are available on the effect of obesity on sperm count and fertility in men. Studies have not shown impaired fertility or oligospermia in relation to obesity.

Some studies found increased serum levels of estradiol and estrone in obese men(35,38). This may result from increased peripheral conversion of androgens to estrogens through the action of the enzyme aromatase present in the adipose tissue³⁹. This increase in serum estrogen concentration is, however, not typically accompanied by signs of feminization.

Several randomized studies assessed the impact of testosterone administration in elderly men with low normal testosterone values (levels usually in the range of 250 to 400 ng/dl) on several metabolic and anthropometric measures. Testosterone given intramuscularly or topically results in mild but significant increase in lean body mass and reductions in fat mass and may have a favorable effect on glucose homeostasis⁴⁰. The impact of such an intervention on mortality and cardiovascular event rates is not known. This type of therapy is not approved by the FDA for the treatment of obesity per se. Careful attention must be given to the causes and significance of a low serum total and free testosterone in an obese patient and treatment options must be carefully considered. Rarely would exogenous testosterone therapy be indicated and this would only be when a definable etiology can be specifically identified.

In conclusion, obesity can result in low total testosterone levels due to reduced levels of SHBG. The free testosterone is generally normal except in some men with massive obesity in whom it may be reduced. These changes are secondary to obesity and do not by themselves indicate hypogonadism nor the need for testosterone supplementation. In this regard it is also worthwhile remembering that when evaluating men for erectile dysfunction, the same observations apply whether or not obesity exists; hypogonadism is not a common cause for erectile dysfunction, which often has a vasculogenic etiology. Therefore, one should not rush to the conclusion that an obese man with erectile dysfunction and a low total but normal free and bioavailable testosterone has hypogonadism as a cause for his erectile difficulties. Testosterone administration in these circumstances rarely improves erectile function.. Interpretation of serum testosterone levels must always be placed in the corresponding clinical context and the decision to utilize testosterone therapy has to be made carefully.

OVARY

Obesity is a common feature of PCOS. Nearly 50% of women with PCOS are obese(41-44).

As in men, obesity in women is associated with decreased levels of Sex Hormone Binding Globulin (SHBG) but here the concentration of free testosterone is increased^{39,45}. The increase in free testosterone concentration is usually moderate but some women with PCOS can have much higher testosterone levels which need to be differentiated from other causes of hyperandrogenism in women, such as androgen producing ovarian tumors.

Hyperandrogenism and anovulation are the hallmarks of PCOS. The association between obesity and hyperandrogenism is seen mainly in women with visceral obesity^{45,46}. Women with PCOS also have insulin resistance and are at a high risk for developing impaired glucose tolerance and diabetes mellitus.

The precise etiology of PCOS is not known but insulin resistance and hyperinsulinemia are thought to play an important role. Hyperinsulinemia decreases the levels of SHBG and increases the ovarian production of androgens^{47,48}. Administration of metformin to women with PCOS may reduce free testosterone and increases SHBG levels⁴⁹.

Anovulation and menstrual irregularities are also major features of PCOS. Again, metformin appears to result in improved fertility in women with the syndrome, implicating

hyperinsulinemia as a direct or indirect cause for the menstrual irregularities^{50,51}. These improvement in fertility and hyperandrogenism can also be achieved with weight loss. The use of metformin therapy in this situation must be evaluated carefully, in consultation with the patient with discussion of pros and cons. The drug is not approved by the FDA for this indication.

Obesity in women is also accompanied with enhanced estrogen production as a result of increased aromatization of adrenal androgens into estrogens in the adipose tissue^{52,53}. Obesity is a known risk factor for endometrial cancer⁵⁴. Given the lower levels of SHBG seen in obese women, free estradiol levels are elevated and there is increased conversion of estradiol to estriol along with decreased conversion of estradiol to 2-hydroxyestradiol⁵⁵.

Gonadotropin levels are normal in obese premenopausal women. In women with PCOS, an increased ratio of serum LH to FSH may be seen^{56,57}.

Leptin levels are higher in obese women with PCOS than in normal weight women with PCOS. Higher leptin levels in obese women with PCOS are inversely correlated with basal LH levels⁵⁸. Leptin may have a modulatory effect on GnRH. Other studies in normal weight women with PCOS found a significant correlation between insulin resistance compared with free testosterone and LH.

In conclusion, 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.

THYROID

More than 99% of T4 and T3 circulate bound to transport proteins. Only a very small, less than 1%, amount of thyroid hormone is unbound or free and represents the biologically active fraction of the hormone. Thyroxin Binding Globulin (TBG) is the major transport protein. The serum concentration of TBG is influenced by several conditions (Table 2) which can result in a significant increase or decrease in total T4 concentration. Therefore, when evaluating thyroid function we measure TSH and free T4. Free T3 can also be measured in selected circumstances, such as hyperthyroidism.

Table 2.	
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, it is not surprising that the dynamics of the hypothalamic-pituitary-thyroid axis in obesity have been studied in detail.

In obesity, the serum concentration of T4, T3 and thyroid stimulating hormone, TSH are normal if the subject is in a neutral energy balance state(59-61). Some have reported elevations in serum T3 in obese subjects but this has not been confirmed and is likely related to enhanced carbohydrate intake⁶². An important point in this case is whether the subject(s) were in positive energy balance state. Increased caloric intake can, in fact, result in increased T3 and decreased reverse T3 concentrations^{63,64}. Inversely, caloric restriction in obese subjects results in a low T3 and increased reverse T3 concentrations(64-67). These changes in T3 and rT3 levels normalize upon achievement of a steady state from an energy balance standpoint. Therefore, when evaluating thyroid function in a patient with obesity, it is important to consider this possibility.

The TSH response to Thyrotropin Releasing Hormone, TRH, has been found to be increased in patients with obesity although this was not significantly different from control subjects(66-69). Obese subjects in whom TSH values are slightly elevated but who have normal T4 and T3 concentrations display increased TSH response to TRH in comparison to obese subjects with normal TSH. In this case the exaggerated TSH response to TRH probably reflects a mild degree of thyroid failure or "subclinical hypothyroidism" which is not an uncommon finding particularly in elderly women. Subclinical hypothyroidism, however, is not more common in obese subjects than in subjects of normal weight. Treatment of subclinical hypothyroidism does not result in significant weight loss. This is important as some patients with obesity may attribute their failure to lose weight to "slow metabolism" and not infrequently the thyroid gland is looked at as the culprit, even when the thyroid function tests are perfectly normal.

As mentioned above, T3 levels fall during fasting or caloric restriction. This fall in T3 results from decreased T3 production. Simultaneously reverse T3 levels increase due to decreased reverse T3 clearance. Overfeeding has the opposite effects with resulting increase in T3 and decrease in reverse T3. No effects are seen on T4 in these situations. These changes in T3 levels are not related to the adipose tissue mass since they also occur in normoweight individuals, but are thought to be related to dietary components.

In conclusion, the function of the hypothalamic-pituitary-thyroid axis in obesity is normal. Overfeeding and caloric restriction can affect the concentrations of T3 and reverse T3 with return to normal when a steady state of the caloric balance has been reached.

Synthetic thyroid hormones as well as various other thyroid hormone preparations have been and are being used as adjunctive measures to induce or facilitate weight loss. It is clear that supraphysiologic doses of thyroid hormones are not only associated with loss of fat, but also lean tissue. Some authors have suggested that small doses of T3 (20 μ g a day) may be helpful when used in conjunction with very low caloric diets(70-72). The argument is that such doses can facilitate weight loss and are rarely associated with adverse side effects. The long term benefits and side effects of such therapy are not known, therefore we do not recommend such an intervention at this point. Further studies may better define the role of thyroid hormone supplements in the treatment of obesity.

ADRENAL GLANDS

Cortisol is mainly bound to Cortisol-Binding Globulin (CBG 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 3) and this should be kept in mind when interpreting the results of adrenal function.

Table 3.	
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 or syndrome X. These features include abdominal obesity, 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.

The serum concentration of cortisol is essentially normal in obesity. Some have reported a decrease in the morning cortisol in obese subjects as compared with normal weight subjects (73-76). The 24 hour urine free cortisol excretion is also normal or sometimes mildly elevated in obesity. If complicated by conditions such as depression and/or alcoholism it may also be slightly elevated⁷⁵.

Adipose tissue is involved in the metabolism of cortisol. The enzyme 11 Beta-hydroxysteroid dehydrogenase-1 (11beta-HSD-1) which converts cortisone to cortisol, is expressed in adipose tissue⁷⁷. 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 fat mass⁷⁸. Urine studies in obesity also show an increase in the ratio of tetrahydrocortisol to tetrahydrocortisone indicating an relative increase in the pathways leading to cortisol formation⁷⁸ (through the action of 11Beta-HSD-1).

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. This hypothesis is purely speculative at present.

The cortisol response to a variety of stimuli such as corticotropin releasing hormone, CRH, or meal ingestion is increased in obesity⁷⁹. An increase in cortisol response to ACTH has also been seen in obese men and obese premenopausal women, but not in obese postmenopausal women, indicating a possible role for estrogens in that response⁸⁰.

ACTH secretion in obesity may be altered with increased pulsatile frequency but decreased pulse amplitudes. It is not clear whether this has an influence on cortisol release from the adrenal glands⁷⁹.

Dexamethasone is used in different dosages to study the suppressibility of cortisol secretion in the diagnosis of Cushing's syndrome. Obese individuals have decreased suppression with small doses of dexamethasone (0.5 or 1mg) but they do typically suppress normally with higher doses⁸⁰.

Pasquali et al, summarized the main abnormalities of the hypothalamic-pituitary-adrenal axis

seen in abdominal/visceral obesity phenotype as follows (81):

Table 4.	
Urine free cortisol	Normal or increased
Cortisol suppression with 1mg dexamethasone	Decreased
Cortisol clearance rate	Increased
Peripheral production of cortisol	Increased
ACTH and cortisol response to stimuli	Increased
ACTH pulse amplitude	Decreased
ACTH pulse frequency	Increased

These subtle alterations in the HPA axis could result from peripheral and/or central mechanisms. We have previously mentioned the action of 11Beta-HSD-1 in the fat tissue and subsequent increase in local cortisol production. This, however, does not lead to increased total cortisol and should not be expected to inhibit the central release of ACTH and or CRH. There could be a central defect in the glucocorticoid receptor sensitivity to cortisol. The glucocorticoid receptor is located in the hippocampus. Alternatively, there could be a decrease in the HPA sensitivity to the inhibitory effect of the sympathetic nervous system which is exerted through alpha-2 adrenergic receptors leading to a state of HPA axis "excitation"⁸².

In a recent cross-sectional designed study, Bjørntorp et al, assessed HPA axis function through measurements of salivary cortisol, which is a reasonable reflection of serum free cortisol, and dexamethasone suppression test. They also examined a number of other parameters such as BMI, Waist to hip ratio, testosterone, IGF-1 and lipids⁸³. The authors found that there was an association between increased BMI, increased waist to hip ratio, low testosterone, low IGF-1, abnormal glucose metabolism, increased insulin, low HDL, and elevated triglycerides, all of which are features of the metabolic syndrome. An abnormal HPA axis dynamic characterized by low morning cortisol, poor cortisol response to feeding and poor dexamethasone inhibition was also seen. The authors concluded that a primary abnormality of the HPA axis is likely to result in visceral fat accumulation and the resultant endocrine and metabolic changes that may be associated. It would be interesting to reevaluate these subjects following weight loss. The question here again is whether the observed HPA abnormalities in this subgroup of obese men reflect an initial alteration in the HPA axis that might have been brought forward or exaggerated due to some genetic factor (s), or whether they represent bystander effects that happen to accompany visceral obesity as it develops.

A decrease in the mineralocorticoid receptor response to circulating corticosteroids was suggested by Jessop et al as an explanation for the decreased HPA axis to glucocorticoid feedback in obesity⁸⁴.

In conclusions, obesity is accompanied by alterations in the HPA axis characterized mainly by an increased sensitivity to stimuli and decreased sensitivity to inhibition. An increase in the local production of cortisol in the adipose tissue, abnormal central control of the HPA axis by the sympathetic nervous system, and abnormal glucocorticoid-receptor response may all

contribute to the altered HPA axis described in obesity. From the general internist or the clinical endocrinologist standpoint, however, there is little direct clinical impact of such findings. The main clinical question here is whether the patient with obesity has a subtle form of Cushing's syndrome. The laboratory tests commonly used by practitioners to rule out Cushing's syndrome, such as urine free cortisol and salivary cortisol are not increased in obesity. Occasionally a patient with a pseudo-Cushing's may present with slight elevations of the UFC and abnormal suppression with the 1mg overnight dexamethasone test. For these patients a combined CRH/Dexamethasone diagnostic test can be used. This test is relatively accurate in distinguishing pseudo-Cushing's from true Cushing's syndrome.

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). 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.

Several conditions may affect the concentration of GH (Table 4). 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 percent fat mass. Another major determinant of GH level is age⁸⁵; GH levels fall with increasing age and recombinant human growth hormone, rhGH, has been studied as a supplement to counteract the effects of aging on body composition.

Table 5.	
Increase GH	Decrease GH
Starvation	Obesity Aging Hyperthyroidism Hypothyroidism

The reduction in GH levels in obesity is believed to result from decreased pituitary release of the hormone. In animal models of genetic obesity there is a decrease in the number of somatotroph cells in the pituitary gland. GH responses to a variety of stimuli such stimuli included GHRH, Arginine, and GHRPs (growth hormone releasing peptides) have also been shown to be reduced in obesity^{86,87}. Cordido et al, on the other hand, found a normal growth hormone response in obese men after combined administration of GH-releasing hormone and GHRP-6, a growth hormone releasing peptide, suggesting a normal pituitary growth hormone reserve⁸⁸. Exercise is a known physiologic stimulus of GH secretion. A recent study by Holt et al found no difference in GH response to exercise between young obese and nonobese men⁸⁹. A decreased response was seen between elderly obese and nonobese men. However, on multivariate analysis, only age and physical fitness, as reflected by oxygen consumption (VO₂ max), predicted GH response. Obesity did not. These findings are in contrast to those by Kanaley et al who examined GH response to exercise in women

with and without obesity⁹⁰. They found a significantly higher GH response in the group of nonobese women compared to the group of obese ones. The increased response was attributed to increased GH pulse amplitude. Interestingly, after 16 weeks of aerobic training, the GH response did not improve in the group of obese women in spite of a significant improvement in VO₂ max. Weight loss is associated with improved GH response to stimuli, however there is uncertainty on how much weight loss is required to completely normalize GH secretion^{91,92}.

In spite of the reduced GH levels seen in obesity, IGF-1 levels do not appear to be significantly different between obese and non obese subjects^{93,94}.

Individuals with visceral obesity, even in the absence of total body obesity, may, on the other hand, have lower IGF-1 levels than comparable individuals with no abdominal obesity. The serum concentration of unbound or free IGF-1 is increased in obese subjects. Similarly it has been found that GHBP levels are increased in obesity. This suggests that lower levels of GH are accompanied by increased peripheral sensitivity to GH accounting for the normal IGF-1 levels. Increased peripheral sensitivity to GH in obesity 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 subjects⁹⁵. 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 in normal⁹⁶. Hyperinsulinemia, frequently found in the obese could help explain these findings. Insulin could result in increased peripheral sensitivity to GH, reduced IGF-1 levels and increased (to within normal range) 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. This hypothesis supports a peripheral rather than a central mechanism by which GH release is decreased in obesity.

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 hormone⁹⁷. 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 level⁹⁸.

Finally, it is important to remember that in children, obesity is also accompanied by reduced basal and stimulated GH. Nevertheless, linear growth is normal in obese children who reach a final height comparable to that of nonobese controls.

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. Therefore it is unlikely that obesity represents a condition of GH deficiency that is reflected at the tissue level. The use of recombinant growth hormone in elderly and in subjects with visceral obesity has resulted in a number of mild to moderate, but significant positive anthropometric and metabolic effects such as reduced fat mass, increased lean mass, and improved lipid profile. The role of GH replacement/supplementation 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. Further studies need to be performed in order to determine if there is a role, at all, for rhGH in the management of visceral obesity.

PANCREAS

Obesity is strongly associated with insulin resistance and is a risk factor for type 2 diabetes⁹⁹. Recently available data from the diabetes prevention program (DPP) showed that life style modifications including weight loss and exercise, and metformin, lower the risk of developing diabetes in patients with impaired fasting plasma glucose and impaired post-glucose load plasma glucose. In these individuals at high risk for developing diabetes, both life style modification and metformin use reduced the incidence of diabetes by 58% and 31% respectively as compared to no intervention. The follow up was for 2.8 years¹⁰⁰.

Visceral abdominal obesity is associated with increased hepatic glucose production and reduced peripheral glucose uptake. A significant correlation exists between waist to hip ratio and insulin sensitivity. Visceral abdominal fat is inversely correlated with insulin sensitivity^{101,102}.

Insulin levels are elevated in obese individuals and a high correlation exists between insulin secretion and BMI. The hyperinsulinemia seen in obese subjects is mainly due to increased insulin secretion. In some patients, decreased insulin clearance can also contribute to the elevated insulin levels. Insulin release in lean and obese subjects who have normal glucose homeostasis, is pulsatile. The pulse amplitude is greater in the obese. The insulin response to mixed meals is also normal in this case. When impaired glucose tolerance develops, the insulin secretory dynamics are altered with progressive decrease in the ability of the pancreas to maintain normal glucose homeostasis, initially in response to glucose load, and ultimately in the basal state¹⁰³.

The exact mechanism(s) by which obesity contributes to the development of insulin resistance is the subject of extensive research. In animal models insulin resistance itself and hyperinsulinemia can precede the development of obesity.

Substances originating in the adipose tissue and capable of exerting distant or local actions may explain the link between obesity and insulin resistance. Free fatty acids (FFA) are released in excess by abdominal fat⁽¹⁰⁴⁻¹⁰⁶⁾. Increased concentrations of FFA cause insulin resistance and decreased glucose uptake by impairing insulin mediated glucose transport. Impairment at the level of the insulin receptor and insulin receptor substrate-1 (IRS-1) are likely reasons for the impaired insulin mediated glucose uptake¹⁰⁷.

Tumor necrosis factor- α (TNF- α) is another potential link between obesity and insulin resistance^{108,109}. Although TNF- α has been shown to alter basal and glucose stimulated insulin secretion and to produce insulin resistance in isolated cell lines, the contribution of TNF- α to insulin resistance in humans is uncertain^{110,111}. Similar conclusions can be drawn in regard to leptin. Leptin in vitro is capable of inhibiting insulin release but its role in the pathogenesis of insulin resistance in humans has not been confirmed¹¹².

Resistin, a peptide isolated from the mouse, is produced by the adipose tissue and its expression is decreased by PPAR gamma agonists¹¹³. Serum levels of resistin are elevated in obese mice. Immunoneutralization of this peptide improves insulin sensitivity in the mouse. mRNA levels of resistin in freshly isolated human adipocytes are very low but the role of resistin in human obesity and insulin resistance is unclear at this point¹¹⁴.

Ghrelin, a potent growth hormone secretagogue, is produced mainly by the stomach. Administration of ghrelin results in increased GH release, hyperglycemia, and decrease insulin concentrations¹¹⁵. Tschöpp et al, found a negative correlation of circulating ghrelin levels with insulin, leptin levels, and percent body fat¹¹⁶. Ghrelin is yet another peptide which may turn out to have a role in the pathogenesis of insulin resistance accompanying

obesity117.

In conclusions, obesity, in particular abdominal or visceral obesity, is strongly associated with insulin resistance, and increases the risk for type 2 diabetes. The link between obesity and insulin resistance continues to be explored. Weight loss as well as metformin use improve insulin resistance and lowers the risk of developing type 2 in individuals with impaired glucose tolerance. As our understanding of the interaction between obesity and insulin resistance improves we should be able to develop new therapeutic strategies to treat insulin resistance and prevent or delay the development of type 2 diabetes in subjects at a high risk for the disease.

RECOMMENDATIONS:

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-adrenal axis and the possibility that some "subclinical" alterations in this axis 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 thought, 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 underdiagnosed in the general population. Routine screening of patients who present with obesity with a sensitive TSH assay and free T4 is mandatory. As previously mentioned, subclinical hypothyroidism does not appear to be a contributor to obesity. There is debate on whether or not to treat subclinical hypothyroidism. The presence of anti-thyroid antibodies in these patients increases the risk of progressive thyroid failure. Treatment of subclinical hypothyroidism decreases cholesterol levels. In the presence of mildly elevated TSH and normal Free T4 and T3 concentrations, we generally recommend to repeat these tests after a few weeks and if the TSH elevation persists, to treat with thyroid hormones. The benefits and potential disadvantages of this approach should be discussed with the patient.

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. However, if there is a reasonable suspicion that it may be present, the patient should be screened. Attention should be focused on these symptoms and signs that are more specific to Cushing's such as proximal muscle weakness, purple striae, thin, bruised skin, hypokalemia, and osteopenia... In these circumstances we recommend a 24 hour urine free cortisol (UFC) measurement. Repeatedly normal UFC are highly accurate in helping to rule out Cushing's syndrome. An overnight dexamethasone suppression test (1 mg) may also be helpful although false positive results can occur due to obesity. In patients with obesity and depression or alcoholism, who may have an elevated UFC, we recommend a CRH/Dexamethasone test which has good discrimination power to separate patients with "Pseudocushing's" from patients with true Cushing's. Occasionally, even the most

sophisticated testing may not be sufficient to make a definitive diagnosis of Cushing's disease and it may be necessary to closely follow a patient with repeated examination. Referral to a specialist is indicated in these more difficult cases.

Insulinomas are rare neuroendocrine tumors. They typically present with symptoms and signs of hypoglycemia and perhaps weight gain. The diagnosis requires confirmation of the hypoglycemia usually through a fasting test with measurement of glucose, insulin and C-peptide. A referral to an endocrinologist is indicated.

Hypogonadism and growth hormone deficiencies can both lead to abdominal obesity. The latter is usually suspected in the setting of surgery or disease of the hypothalamus-pituitary axis, the former is not very common but 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. An estimate of bioactive testosterone can be determined by measuring a morning free or bio-available testosterone (and total testosterone), and repeating the measurement at least once. LH should be measured if the testosterone is clearly low to distinguish between primary versus central hypogonadism. Ruling out GH deficiency requires dynamic testing and is indicated in the appropriate setting.

► [Go to OBESITY Index](#)