

Chapter 8

Minimizing Obesity With Hormone Replacement Therapy

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Obesity is a common disease; its frequency is gradually and progressively increasing. Some 15 years ago, the incidence of obesity in the U.S. was roughly 15 to 16 percent; now it is between 20 and 25 percent. People are more likely to be obese at the end of their lives. The incidence of obesity in boys is about five percent; it is almost eight percent in girls. By the age of 20, however, 25 percent of people are already obese, and 50 percent more will become obese later in life (Figure 1). Thus, a child born today has a 75 percent chance of becoming obese during his or her life. Obesity is a serious health problem, as it increases the risk of several age-related diseases, such as hypertension, myocardial infarction, diabetes, breast cancer, uterine cancer, and prostate cancer. Most importantly, the mortality rate that accompanies moderate obesity is increased by roughly 25 percent.

Why Do We Get Fat?

There are three important questions about obesity. First, is there a mechanism that explains why we get fat? Second, why do we gain back the weight we lose? Most individuals who have been on diets regain the weight or have to make a lifelong effort to control their weight. Possible causes of recurrent weight gain include hormonal deficiencies or imbalances. Third, how do we treat obesity so it does not become chronic? Could an obese person be treated successfully with hormone replacement therapy? To determine what hormones are deficient, a diagnosis should first be made.

It is important to diagnose the parts of the body where obesity—excess fat—predominates. Each hormonal deficiency that favors obesity has its own particular regional fat distribution. One type of hormonal deficiency results in an obesity that predominates on the face, another tends to concentrate fat around the waist, and still another one predominates on the thighs. Consequently, treatment may vary with the regional distribution of fat, and hormone replacement therapies should be adapted to the hormonal deficiency or excess involved. Thyroid deficiency, for example, cannot be treated with cortisone.

OBESEITY INCREASE DURING LIFE SPAN

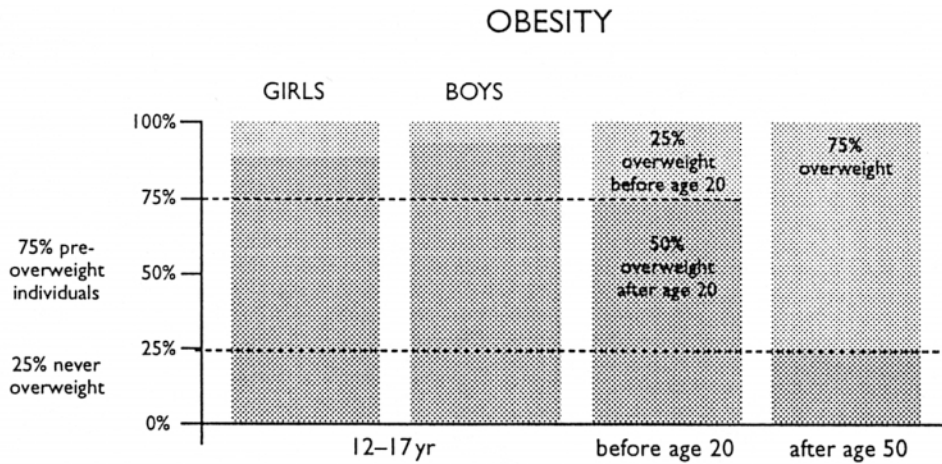


Figure 1. (Troiano RP et al, Arch Pediatr Adolesc Med, 1995, 149; 1085-91; Broy GA Contemporary Diagnosis & Management of Obesity, 1998; New Toun PA, Handbooks in Healthcare: Chapter 4)

THE SOMATOTROPIC AXIS IN OBESE & NON-OBESE WOMEN

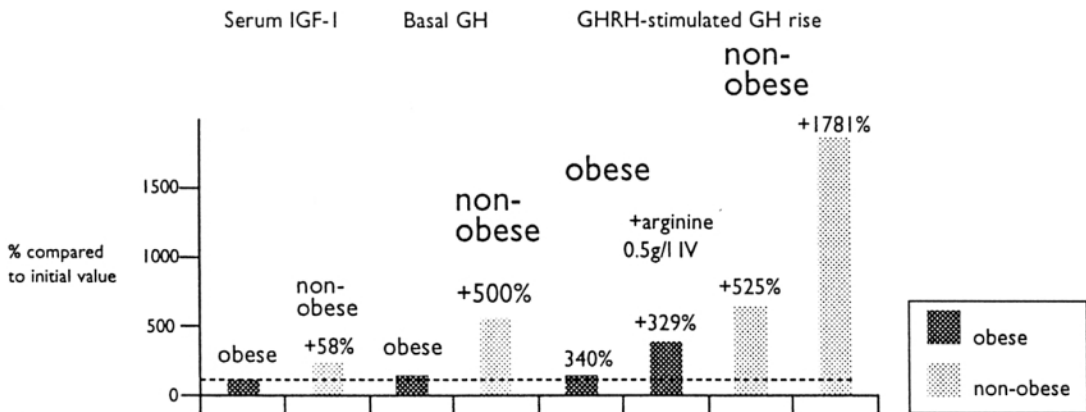


Figure 2. Seven obese women (17-54 yrs) have lower values of the somatotrophic axis compared with 10 healthy control women (22-44 yrs). Short-term (3-4 days) fasting in the obese women has no effect on these values. (Procadio M et al, Elin Endocrinol Oxfr. 1995, 43[6]: 665-9)

This chapter will provide an overview of different parts of the body where excess fat may predominate and also mention some of the possible hormonal deficiencies responsible for those local fat concentrations. Its goal is to give the physician insight into the relationship between obesity and hormonal deficiencies and to give him or her some ideas on how to successfully minimize obesity using hormone replacement therapy.

The Obese Face

Signs of thyroid deficiency are often visible in the face. These signs include:

- Puffy face
- Loss of the outer third of the eyebrow
- Swollen lower eyelids, indicating myxoedema, a sort of non-pitting edema in which waste products accumulate between the cells.
- Dull eyes. On the other hand, people with too much thyroid hormone have extremely bright, shining eyes.
- Flat nose root. The nose of a child who is hypothyroid does not develop fully. A flat nose root in an adult suggests hypothyroidism in youth.
- Swollen lips. This is typical of hypothyroidism.

When people eat a lot, especially a lot of protein, their thyroid function becomes lower, and a lowered thyroid function leads to weight gain. When the thyroid gland is removed from cats, they gain about 11.5 percent extra weight. Thyroid hormones have been proven to speed up lipolysis (the consumption of fat). In euthyroid rats, insulin injections reduce the rate of lipolysis. Thyroid hormones do the opposite. In healthy rats that receive excessive amounts of thyroid hormones, the rate of lipolysis increases dramatically. In humans, insulin depresses the rate of lipolysis. A normal rate can be restored with thyroid hormones. Patients who have been obese and have, through effort, become normal, may have some kind of borderline hypothyroidism. Formerly obese women, for example, have an eight percent lower resting metabolic rate compared with women who have never been obese. These previously obese women are accumulating calories and fat because their thyroid function is low. The free T3 (the active thyroid hormone) is about 30 percent lower in formerly obese women. A reduced T3 level may result from low-calorie dieting, but it is likely that these women previously had a low thyroid function that favored obesity.

Can an obese patient be growth hormone deficient? Facial signs of growth hormone deficiency include:

- Droopy eyelids
- Sagging cheeks
- Thin lips

A growth hormone deficiency results in the atrophy of many tissues in the body, but in an obese man, it means hypertrophy. According to one study, the daily growth hormone production in obese persons is less than 50 percent of normal subjects of the same age. Furthermore, non-obese patients generally respond strongly to stimulation of the secretion of growth hormone, whereas obese patients usually do not (Figure 2). Studies suggest that obese persons

PEAK GH & OBESITY IN MEN

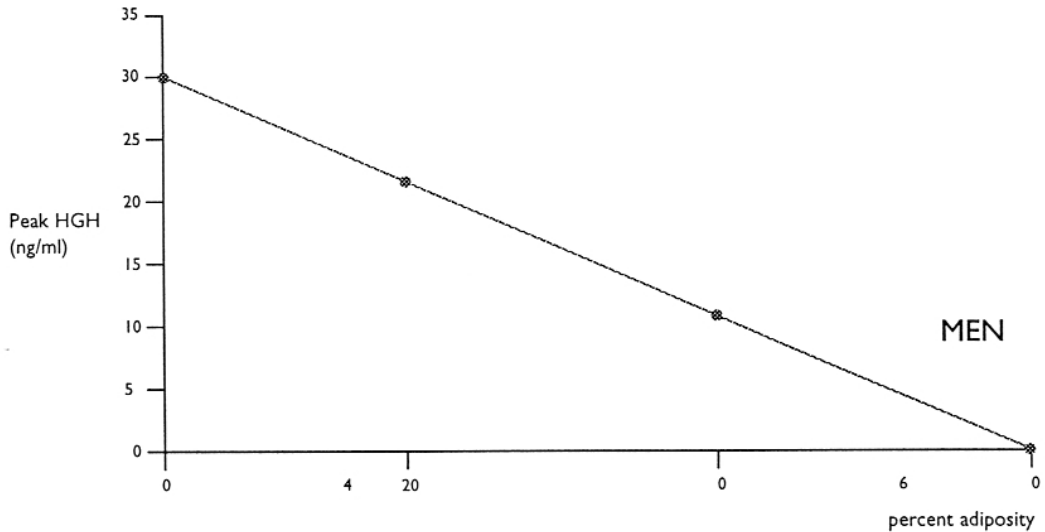


Figure 3. The relationship between adipose mass and peak GH levels in response to arginine infusion in 44 men of varying ages.

(Dudl et al, J Clin Endocrinol Metab. 1973 [37]: 11-16)

PLASMA TESTOSTERONE & LEAN BODY MASS

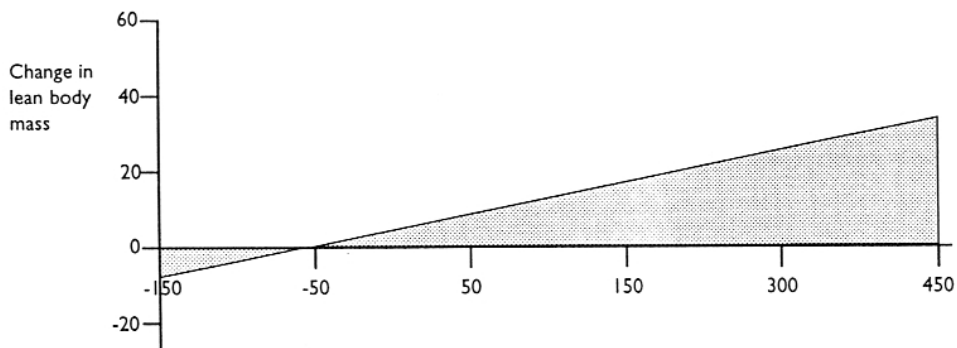


Figure 4. A positive correlation exists between a change in lean body mass and a change in serum testosterone levels during testosterone treatment through a transdermal nonscrotal system (2 patches Androderm® nightly for 12 weeks & in HIV-infected men)

(Bhasin S et al, J Clin Endocrinol Metab, 83: 3155-62)

tend to have a relative growth hormone deficiency compared with normal individuals (Figure 3). Growth hormone treatment may correct this relative deficiency.

There is significantly more subcutaneous fat in growth hormone-deficient adults. With treatment, that fat can be reduced. Dr. Serge Voronoff, one of the early pioneers of anti-aging medicine in the 1920s, did grafting of endocrine glands from monkeys that had the same blood type as his patients. Reports state that patients improved dramatically after endocrine gland grafting, including pituitary grafting. Growth hormone therapy has yielded similar results and therefore is a viable option.

Could the obesity of a patient be due to an androgen deficiency? Historically, Voronoff was one of the first to suspect this. He started grafting his patients with monkey testicles. One year after the graft implantation, the patients were reported to look considerably slimmer and younger. Testosterone treatments lead to similar results.

Facial signs of testosterone deficiency include:

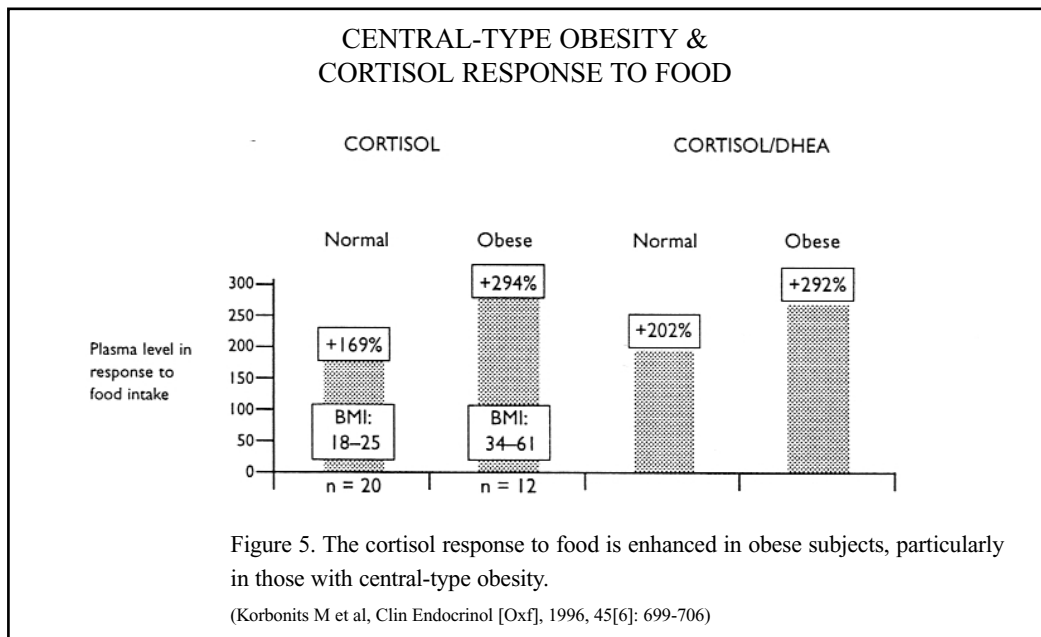
- Obese face
- Dry eyes. The eyes reflect light poorly and appear irritated due to the thinness of the mucous membranes in sexual hormone deficiency, either estrogen or testosterone.
- Pale face. The cheeks should have a rosy or slightly red tint.
- A face lacking firmness

Restoring the serum testosterone to its youthful level leads to a more healthy distribution of fat. The higher the level of plasma testosterone is in men, the more lean body mass they have (Figure 4). When testosterone secretion is chemically blocked by a gonadotropin antagonist in young volunteers, the lean mass decreases by about 2 kg after 10 weeks, while fat mass increases about 1 kg. What is the mechanism at work here? When volunteers ingest fatty milk, about three-quarters of the fat is generally stored in the subcutaneous fat, and most of the rest is stored in the visceral omental and retroperitoneal fat of the abdominal cavity. Those locations are unhealthy for fat accumulation. When volunteers are given testosterone as well, the situation changes. There is much less fat storage inside the abdominal cavity, roughly 10 percent, and the rest is stored under the skin as subcutaneous fat, a far less health-threatening location for fat. Testosterone facilitates better fat distribution and energy expenditure. Carbohydrate oxidation increases when there is a testosterone deficiency, but there is a decrease in protein and lipid oxidation and in energy expenditure. Consequently, testosterone-deficient men accumulate calories in the form of fat more easily and consume them less easily.

Might an obese patient be resistant to insulin? A fatty face and swollen cheeks can be related to too much insulin. Diabetes type II patients often have these features. Can obesity be due to a cortisol excess? Cortisol and other glucocorticoids in high concentrations make the face swell and look moon-like. This is called Cushing's disease or Cushing's syndrome and is characterized by major endogenous cortisol production. Overeating can lead to cortisol excess. When normal people eat, they produce more than 150 percent extra cortisol. Central-type obesity often is associated with excess cortisol. Persons with this condition produce significantly more cortisol, almost a 300 percent increase, when they eat (Figure 5). This increase may not last long, half an hour to two hours after the meal, but it is considerable, almost a tri-fold

increase. The more cortisol there is in the body, the greater the energy level. Cortisol increases considerably the glycogen reserves in the liver and the plasma glucose level in cases of increased need. The increase in energy level in central-type obese persons after a meal may be one of the reasons why obese individuals tend to eat. However, the ratio of cortisol to DHEA is greater, more catabolic, and unfavorable in these obese subjects. Lean subjects maintain a healthy plasma cortisol level compared with the level of DHEA sulfate. Persons with central-type obesity and excessive cortisol are in an imbalanced state (Figure 5).

Other hormonal excesses that may cause a swollen face include estrogen, aldosterone, and insulin excess.



Obesity of the Trunk and Abdomen

Obesity of the trunk and abdomen has an important impact on health. Certain risks are associated with upper-body obesity. The incidence of health complications such as diabetes mellitus, gout, atherosclerosis (arterial hypertension, coronary insufficiency, myocardial infarct), and endometrial cancer is increased in people with upper-body obesity.

A typical patient with adult growth hormone deficiency has a flabby belly. All tissues, including the skin and muscles, have a tendency to sag in adults who have become deficient in growth hormone. Another example of growth hormone deficiency and trunk and abdominal obesity can be seen patients with Prader-Willi syndrome. These individuals accumulate fat on all regions of the body, but mainly on the trunk, abdomen, hips, and thighs.

Growth deficiency also may lead to pseudogynecomastia. In adults who have become growth hormone deficient in adulthood, their breasts are droopy, a sign that the breasts have lost the tonicity of young adulthood. Real gynecomastia may be caused by estrogen excess.

Another result of growth hormone deficiency is kyphosis with hyperlordosis, a bent back. The cause is not only bad posture but also a lack of tonicity of the ligaments and muscles of

the spine around the vertebrae, which is characteristic of a growth hormone deficiency.

With respect to subcutaneous fat and intraabdominal fat (Figure 6), normalizing growth hormone levels with growth hormone treatment results in important reductions of subcutaneous and visceral fat (the fat inside the abdominal cavity). It may take two to three years to obtain a normalization of abdominal fat with growth hormone treatment. In growth hormone deficiency, total body fat, including abdominal fat, is increased, and the volume of adipose cells is increased. Treatment with growth hormone reduces fat mass considerably, although not always completely. About 50 percent of patients who lose weight on a weight-control program produce more growth hormone while at the same time improving their physical appearance.

Might the upper-body obesity of a patient be due to androgen deficiency? The typical signs of androgen deficiency include:

- Obesity
- Gynecomastia, at least if the patient has a relative excess in estrogens.
- Paleness of the skin. A man who is always very pale probably has testosterone deficiency.
- Abdominal fat accumulation and muscle flabbiness. Treatment with androgens and growth hormone makes a dramatic difference in this respect.
- Poor body hair
- Hyperlordosis. The androgens are also very important for the spine. In androgen deficiency, growth hormone may not work efficiently to improve the bone mineral density and muscle tonicity of the spine.
- Bloating belly, which is caused by the loose muscles of the gastrointestinal tract walls.

People with massive obesity tend to have low testosterone levels (Figure 7). With testosterone therapy, one hypogonadal male patient lost 30 percent of his subcutaneous fat and replaced it with lean mass (with an increase in muscle mass). Testosterone reverses the age-related decline in lean mass and increase in fat mass. A person who receives testosterone treatment usually experiences a decrease in abdominal fat. This reduction of fat mass is not the case with all male hormones. Dihydrotestosterone increases intraabdominal fat, so treating obese patients' androgen deficiency with dihydrotestosterone is not the best choice (Figure 8). For these patients, testosterone is a better option. Testosterone decreases protein oxidation and increases lean mass; at the same time, this male hormone increases the oxidation of fat and reduces fat mass. In a study on testosterone treatment, resting energy expenditure did not change. Patients on testosterone therapy consume a similar amount of calories, but they do it in a different way, diverting the calories and food absorbed toward lean tissue, rather than toward the fat tissue. The uptake of lipids in fat cells is decreased during testosterone treatments. Lipoprotein activity is also decreased, which decreases fat accumulation. Lipid and adipose tissue turnover rate decreases, but one study observed no change in femoral fat with testosterone treatment.

GH TREATMENT: EFFECT ON SUBCUTANEOUS & VISCERAL FAT

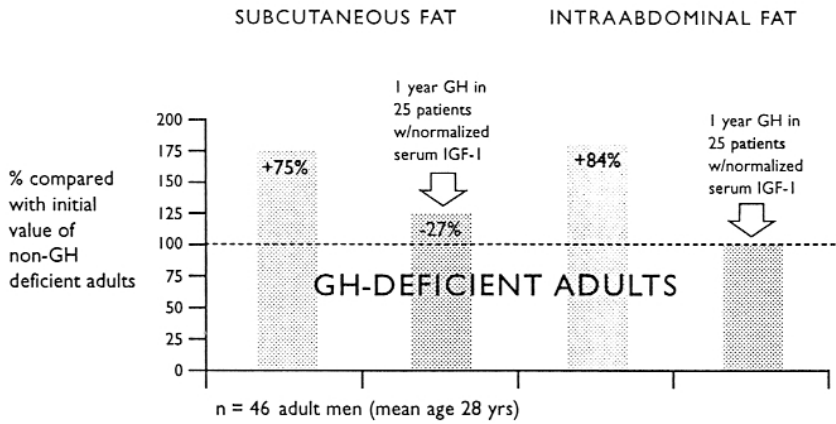


Figure 6. Subcutaneous as well as intraabdominal fat masses were abnormally higher in 46 GH-deficient adult men. GH therapy reduced these fat masses.

(de Boer J et al, Int J Obes Relat Metab Disord, 1996, 20[6]: 580-7)

MASSIVE OBESITY & PLASMA TESTOSTERONE

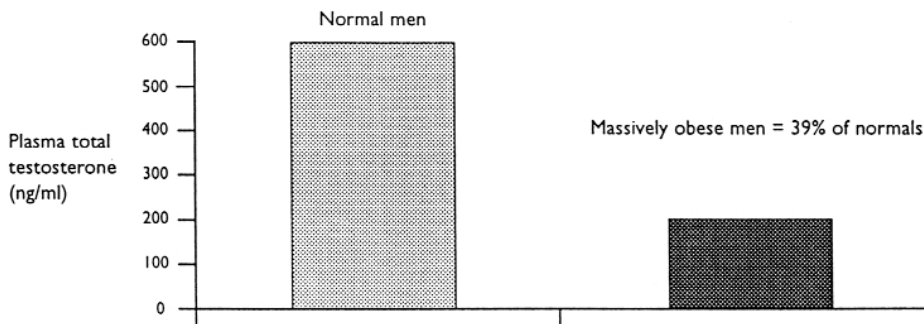
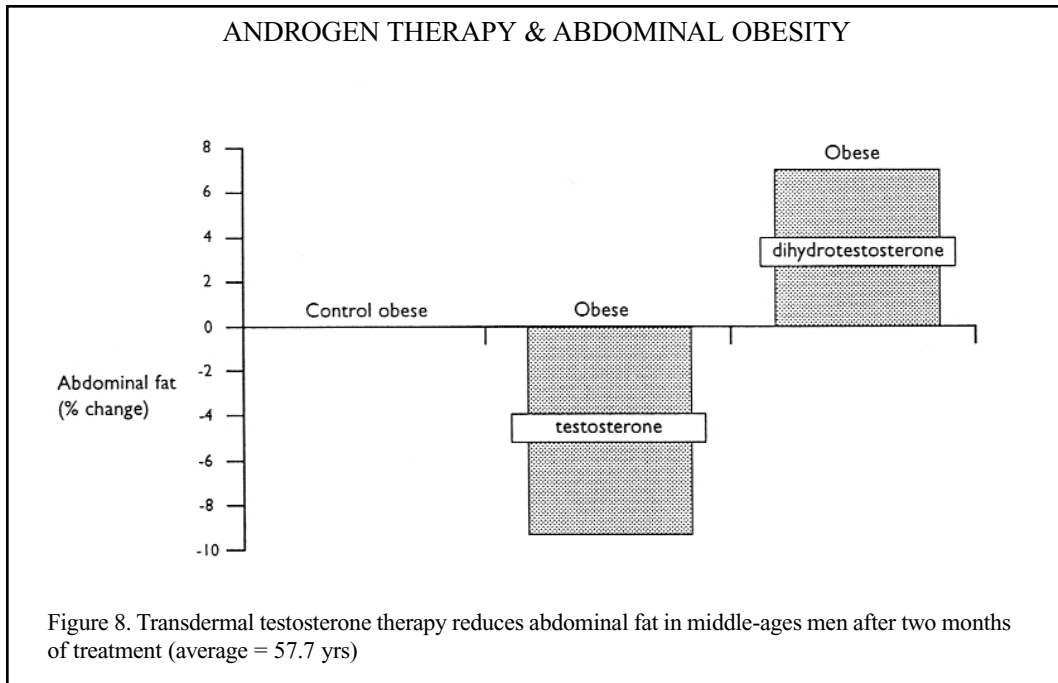


Figure 7. Decreased plasma testosterone in massively obese men (145-238 kg weight or 200% to 380% of ideal body weight, according to Metropolitan Life Insurance Company tables).

(Glass et al, J Clin Endocrinol Metab, 1977, 45[6]: 1209-19)



With respect to estrogen excess, or progesterone deficiency, signs in the upper body area can include:

- Large breasts
- Premenstrual syndrome
- Swollen belly. Excess estrogens slow down the motility and tonicity of the gastrointestinal tract, resulting in abdominal bloating.
- Poor body hair
- Upper-body segment obesity. High levels of receptors in the uterus are usually a sign of estrogen excess and lack of progesterone and are linked to upper-body segment obesity.

Some studies show the opposite, that a person with estrogen and progesterone deficiency may become obese, too. When the ovaries of cats are removed, the body weight of these cats increases about 12 percent. After menopause, an increase in central body fat may be observed that decreases with hormone replacement therapy. A study showed female hormone replacement therapy to have a weight-reducing effect, but with such a treatment, the fluid retention effect of the estrogens must be correctly countered with the administration of sufficient progesterone, androgens, and perhaps thyroid hormones if the thyroid gland is deficient.

The belly may also appear swollen because of thyroid deficiency. In hypothyroidism, bowel movements are slow, resulting in constipation, and the tonicity of the intestinal tract is weak, resulting in dilatation of the intestinal lumen, especially of the colon. The first consequence is abdominal bloating. The second consequence, after years of constipation and hypotonicity of the intestinal tract, is a progressive enlargement and increase in length of the colon, a dolicho-colon. With thyroid hormone therapy, the belly flattens. Other signs of thyroid deficiency are

a swollen chest and dry skin. Cortisol excess in adults can also cause the trunk and the belly to swell, and it may cause thinning of the skin.

Upper-body obesity may result from an excess in insulin production. One variety of excessive insulin production is the metabolic X syndrome, characterized by obesity with insulin resistance, hypertension, and dyslipidemia. The patient with metabolic X syndrome has an increased risk of cardiovascular diseases. Signs of too much insulin include an obese chest and abdomen.

The Enigma of Insulin Resistance

What causes insulin resistance? In the long term, a diet rich in sugars and starches contributes to insulin resistance by stimulating insulin release from the pancreas and increasing the adipose tissue. An excess of fat mass favors the appearance of insulin resistance, as do several hormonal deficiencies. Other factors that may contribute to insulin resistance include trace element deficiencies, lack of physical activity, and aging of the target tissues.

The treatment of insulin resistance depends on the cause. If the suspected cause is a poor diet, changing to a low-calorie, a high-protein diet rich in vegetables is often recommended. When a person with insulin excess follows a diet low in calories but rich in protein, insulin sensitivity increases. Both plasma levels of fasting glucose and insulin are lowered. Consequently, body fat decreases. Diet can improve this sort of condition. Theoretically, toxins in the diet, such as pesticides, may interfere in insulin sensitivity; if this is the case, increasing the consumption of organic foods may help. If a hormonal deficiency is causing the insulin resistance, hormonal deficiencies that cause an increase in fat mass or decrease lipolysis should be suspected. One of these deficiencies is hypothyroidism. Thyroid hormones may facilitate the efficacy of insulin on the target tissues and thus improve the absorption of sugar by myocardial cells, diverting sugar uptake from adipose cells to active muscle and nervous tissue.

When cortisol replacement therapy is used to correct a cortisol deficiency, the dosage should be calibrated carefully. If it is excessive, appetite may increase, eventually resulting in hyperphagia and weight gain. If the dose is insufficient, hypoglycemic episodes may occur, causing sugar cravings and extra starch intake, which lead to weight gain. Insulin resistance may be favored by adult growth hormone deficiency. Growth hormone therapy may improve insulin sensitivity by decreasing fat mass and increasing muscle mass, diverting the uptake of plasma glucose to the active tissues. Deficiencies in androgens, DHEA, estradiol, and progesterone can potentially increase insulin resistance, too. Adequate replacement therapy may improve insulin sensitivity and make weight-loss strategies finally efficient in patients with these deficiencies.

Melatonin deficiency may also lead to weight gain. A patient who is deficient in melatonin does not sleep well and puts on weight. Old rats, for instance, have a lower melatonin level, a higher insulin level, and an increase of visceral fat in the abdomen. Melatonin supplementation restores insulin sensitivity to the level observed in young rats and significantly reduces visceral fat. An increase in production of growth hormone and triiodothyronine with melatonin supplementation may explain the reduction of fat and improvement in insulin sensitivity. Melatonin increases triiodothyronine levels by stimulating the conversion of thyroxine to triiodothyronine.

Fatty Buttocks

Fatty buttocks can be due to several causes. If the person is growth hormone- or androgen-deficient, muscle development or tonicity is relatively poor and fat accumulates. Growth hormone and androgen treatment improves the firmness of the buttocks and reduces subcutaneous fat. In one study, six months of growth hormone treatment reduced gluteal and femoral fat by approximately 30 percent in growth hormone-deficient adults. Fatty buttocks may possibly be due to another endocrine deficiency, leptin deficiency. Levels of leptin are higher in obese persons, but not in proportion with the obesity. Leptin can lower appetite. It is secreted by the adipose cells. Leptin increases if there is more fat, but apparently not in sufficient amounts in obese patients to restore the situation. Fatty buttocks may also indicate insulin excess, because fat increases whenever there is too much insulin.

Cellulite

Accumulation of cellulite may indicate growth hormone deficiency. Sagging inner thighs of a patient may be drastically improved with treatment. Growth hormone makes the skin and bones thicker. With GH treatment, muscles get thicker and firmer, too, while subcutaneous fat decreases, generally around 25 percent and exceptionally up to 75 percent. The change in composition of the thighs decreases cellulite.

Androgen deficiency may also cause development of cellulite. Testosterone treatment increases muscle mass and decreases fat mass (Figure 9). Insulin excess can also cause cellulite development in the thighs.

A low DHEA level may also favor cellulite accumulation. The greater the obesity is in a woman before menopause, the lower her plasma DHEA level. Rats do not increase much in body weight if they receive DHEA treatment. DHEA counters the development of adiposity by increasing fat oxidation. DHEA in male and female rats can increase the fatty acetyl coenzyme A activity, which contributes to fat oxidation in the liver by approximately 1000 percent. When massively obese men follow a diet and lose weight, they may more than double their level of plasma DHEA sulfate (Figure 10).

Fatty Knees

Fatty knees may be a sign of adult growth hormone deficiency, especially if the fat accumulates above the knee. The physical appearance of the knees improves with growth hormone treatment. Thin skin and weak muscles around the knees are additional signs of growth hormone deficiency in an obese patient.

Swollen Calves

Swollen calves with non-pitting edema often indicate a thyroid deficiency. Non-pitting edema is caused by myxoedema. If the thyroid-deficient patient also suffers from pitting edema (caused by water retention), the association of myxoedema and water retention may cause the calves to become very thick. Solely pitting edema at the level of the calves is more likely to be due to aldosterone excess.

TESTOSTERONE THERAPY & MUSCLE SIZE

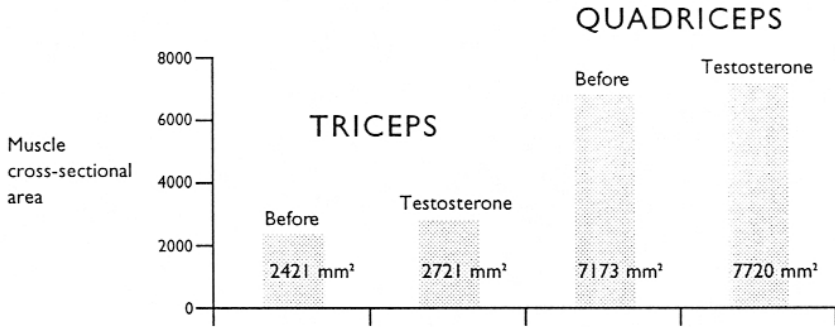


Figure 9. Ten weeks of replacement dose of testosterone enanthate (100 mg/week) increases muscle size in hypogonadal men (ages 19-47 years).

(Bhasin S et al, J Clin Endocrinol Metab, 1997, 82,407-13)

SERUM DHEAs & WEIGHT LOSS

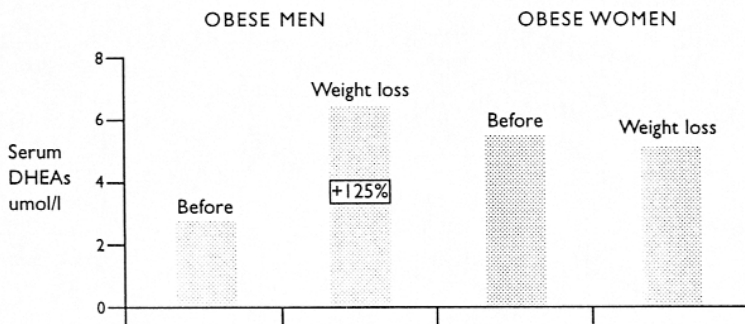


Figure 10. A two-month 1000-1400 kcal diet with weight loss (>3.5 & 3.2kg/m BMI) in obese men & women increases the serum DHEAs only in men.

(Jakubowicz DH et al, J Clin Endocrinol Metab, 1995, 80[11]: 3373-6)

Bulimia

What about bulimia? Isn't the cause of bulimia another medical enigma? Is bulimia caused by hormonal deficiencies? Cravings for sugar and salty foods are two sources of bulimia. Sugar cravings can be related to hypoglycemia. Cravings for salt and salty foods often relate to salt deficiencies, in which the body fails to retain enough sodium. Low blood sugar can be due to several hormonal deficiencies, but the most important one is cortisol deficiency. Cortisol is a glucocorticoid. It increases the blood sugar level. People lacking cortisol easily experience sugar cravings. The most important hormone for salt retention is aldosterone. Patients who lack aldosterone crave salty foods (Figure 11).

The treatment for bulimia caused by sugar cravings is hydrocortisone, 10 mg to 45 mg per day, in combination with DHEA or other anabolic hormones that protect the body from any undesirable catabolic effects. The hydrocortisone should be balanced in physiological doses depending on the deficiency. It should preferably be taken at least twice a day, if not four times daily, because natural cortisol, in contrast with the synthetic derivatives, does not remain in the body very long. It is metabolized more quickly than unnatural synthetic derivatives. The diet of cortisol-deficient patients should include a normal-to-high protein intake. The intake of (animal) protein increases the level of steroid production of the adrenals. Sugars should be avoided.

Bulimia caused by cravings for salty food and by aldosterone deficiency is treated with fludrocortisone (9-alpha-fluoro-hydrocortisone). A once-a-day intake is sufficient, as fludrocortisone's action persists approximately 24 hours. The average dose is about 100 mcg a day, but the dose should be adapted to 50 or 150 mcg a day depending on the severity of the deficiency. Fludrocortisone does not work well if salt intake is poor. The patient must be advised to drink enough water. People low in aldosterone usually have to urinate almost immediately after drinking. They cannot retain salt, so they will not retain water. Water remains in the body when attracted by sodium and other salts. Patients with aldosterone deficiency will feel better lying down rather than standing still or sitting.

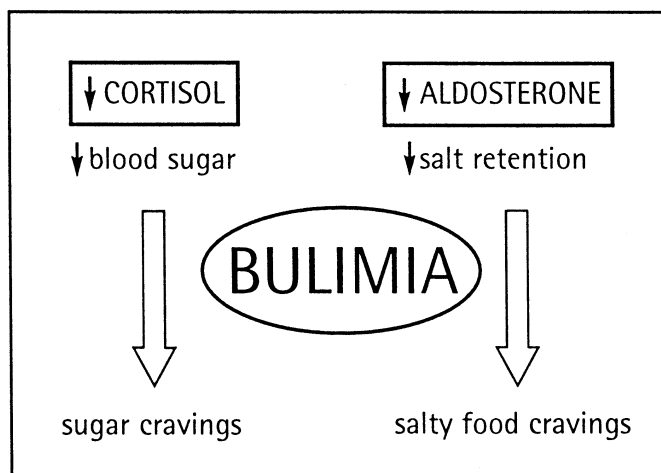


Figure 11 The Role of Hormones in Bulimia

Bulimia may also be due to more straightforward food cravings. In that condition, there are not enough calories available for energy, possibly due to several hormone deficiencies. A high calorie intake increases the production of hormones by most endocrine glands, especially of growth hormone, thyroid hormones, insulin, estrogens, progesterone, and testosterone. The type of calorie is important. The body needs adequate amounts of saturated fat as cholesterol to produce steroid hormones as the adrenal cortex and gonadal hormones. Subjects on high-protein diets generally produce higher amounts of androgens. People on vegetarian diets with milk products have a much lower production of androgens, particularly less adrenal androgens. If these patients want to improve the hormone production of the adrenal cortex, they should avoid milk products.

A woman who is estrogen deficient can improve her plasma estradiol level by six to eight percent by increasing her intake of healthy cholesterol (avoid baking the fat, as baking denatures cholesterol and other fats). A low calorie intake also causes a reduction of plasma androgens. Not all hormones respond the same way. With an increase in calorie intake, a woman's body will produce more progesterone. This suggests that a woman who does not ovulate may need to consume more calories. In the treatment of food cravings, it is very important to correct any thyroid deficiency, as hypothyroidism favors hypoglycemia. For obese individuals, it may be better to treat their hypothyroidism with a combination of T3 and T4, not only T4. The treatment may include the correction of the eventual testosterone deficiency and a diet with normal-to-high protein and normal-to high fat intake. Sugars and processed food should be avoided.

Conclusion

This clinical overview of the regional distribution of different types of obesity suggests the existence of hormonal deficiencies and excesses that increase excessively adipose tissue in different areas of the body. Patients with high levels of hormones such as cortisol, insulin, and possibly estrogen tend to have increased fat mass and gain weight. Aldosterone can lead to swelling and weight gain, but apparently this is through water retention with pitting edema, not through an increase in fat mass. There are also hormonal deficiencies that increase adipose tissue, such as growth hormone, thyroid, testosterone, and progesterone deficiencies. When muscle development is poor, a change in body composition can be obtained through adequate hormone replacement therapy.

The effects of well-adjusted hormone replacement therapy contrast with the consequences of low-calorie diets. Low-calorie diets may aggravate existing hormonal deficiencies or even cause new hormonal deficiencies, so that a patient on a diet loses weight but still does not appear to be healthy. A diet combined with the correct hormone replacement therapy is more likely to result in an attractive, healthy body.

Diagnosis

How do you diagnose hormonal deficiencies? Obesity is, in some cases if not in most, a syndrome caused by multiple hormonal deficiencies. Obesity resembles aging. Most of the hormones decline in obesity, except insulin. The accuracy of an endocrine diagnosis increases

considerably with a 24-hour urine test of hormone or hormone metabolites excretions prior to any treatment. It is important to pay attention to the subjective as well as clinical symptoms of hormonal deficiencies or excesses. A blood analysis of the hormone levels is also essential. When looking for a hormone in the blood, it's important to check, whenever possible, the level of the hormones plasma-binding protein (the protein that transports the hormone from the endocrine gland to the target tissue). Usually, the higher the plasma concentration of a binding protein, the lower the amount of bioavailable hormone there is in the plasma. Indeed, when the level of plasma-binding protein of a hormone is elevated, high amounts of the hormone remain bound to the binding protein, and a low percentage of the hormone gets into the cell. Often, it will not be free on time. Furthermore, the physician should keep in mind that plasma hormone levels fluctuate. A blood test is only a snapshot of the blood at a given time of the day.

The treatment itself is called the therapeutic test and constitutes an additional diagnostic test. If an obese patient reacts well to the treatment, this further confirms the diagnosis. If not, the initial diagnosis may need to be questioned. When interpreting the clinical symptoms and the laboratory tests, it is important to keep in mind that borderline deficiencies exist. The value of a hormone level of a patient may be borderline low, inside the range of reference values but close to the lower reference value. A borderline low hormone level in a patient who has clear clinical symptoms suggestive of hormonal deficiency may consider a trial of hormone replacement therapy. Such borderline low hormone levels often can be evaluated with greater accuracy through the 24-hour urine test.

The 24-Hour Urine Test for Hormone Evaluation

The 24-hour urine test has several advantages over a blood test in evaluating hormones. The hormones or hormone metabolites in 24-hour urine correspond mainly to the free, bioavailable fraction of the urine, as only this fraction of the hormones passes through the glomerular membrane. A small amount may result from secretion by kidney cells. Furthermore, the hormone values obtained in the 24-hour urine test reflect a 24-hour period, eliminating the sometimes frustrating circadian variations and episodic fluctuations during the day. Too often, these variations make blood analyses capable of detecting only gross abnormalities.

If a patient collects the 24-hour urine sample correctly, the values obtained are more stable from day to day and thus more reliable and in accordance with the clinical status. To obtain a urine sample correctly, a patient should collect the urine during a calm period. On the day of the urine collection, and perhaps the day before, only sedentary activities should be allowed. Intense physical activities, such as sports, and major stress increase hormone consumption or production and may give falsely deficient levels (for urinary thyroid hormones) or falsely normal or excessive levels (of the metabolites of the steroid hormones).

Minerals and Peptides in 24-Hour Urine

Analyzing minerals in the 24-hour urine test provides information on food intake that is vital when treating an obese person. Urinary sodium and potassium excretions are worth analyzing, especially when deficiencies or excesses in adrenal cortex hormones are suspected. These hormones retain sodium and excrete potassium. Consequently, deficiencies in cortisol and aldosterone lead to a high urinary sodium excretion and a low potassium excretion in the urine, but the opposite is true in the plasma (high potassium and low sodium plasma levels). If a patient

consumes excessive amounts of salt, urinary sodium is high, too. Urinary sodium is low when salt intake is poor or when there is excessive sodium is lost from intense sweating or increased sodium retention by aldosterone or cortisol excess. For example, if a patient eats at a restaurant on the day of a 24-hour urine collection, sodium intake and urinary excretion are usually high. Therefore, patients should avoid going to a restaurant on the day of the collection. In general, any food excesses or changes on the day of the urine collection should be avoided.

It's important to analyze creatinine in 24-hour urine, because urinary creatinine, a waste product of the muscles, reflects with a certain accuracy the muscle mass of the obese patient. High amounts of creatinine in the 24-hour urine are observed in big-sized and muscled subjects, or in longer than 24-hour urine collections, or with excessively high intake of animal protein. Low urinary creatinine is found in small, thin, or poorly muscled persons, and when the urine collection is incomplete (one or more urine samples have been missed), and when the urine has been collected in a period shorter than 24 hours. The urinary creatinine indicates whether or not the person collected the urine well.

It is important to clearly explain to the patient how to collect the 24-hour urine and to recommend consuming an average amount of meat so as not to interfere with urinary creatinine. If the 24-hour urine has been collected correctly, the urinary creatinine informs on the amount of hormone or hormone metabolite excretion that is necessary for a given patient. The higher the 24-hour urinary creatinine level, the more hormones or hormone metabolites a healthy patient excretes in the 24-hour urine. A borderline low 24-hour urinary hormone excretion in a tall, big-sized, obese person with high creatinine, for example, suggests a deficiency in that hormone, and if clinical symptoms of the hormonal deficiency are clearly observed, a trial of hormone replacement therapy may be recommended.

Urinary phosphorus informs on protein intake. Generally, the more a patient eats, the higher the urinary calcium. High calcium can also result from a high intake of milk products and/or seafood. If a patient consumes significant amounts of vegetables and fruits, urinary potassium excretion will be high. Magnesium will be high if intake of green leaf vegetables is high; if not, the urinary magnesium is usually low.

Hormones and Hormone Metabolites in 24-Hour Urine

The hormone analyses make up the most important part of the 24-hour urine test. Growth hormone can be evaluated in the urine. Clearly too high or too low levels of urinary growth hormone usually indicate growth hormone excess or deficiency. Urinary thyroid hormones are the most important test of the 24-hour urine, because most thyroid hormones eliminated in the urine are obtained by glomerular filtration of the free hormones. In the experience of many physicians, the bioavailable fraction of the thyroid hormones is more closely related to a patient's clinical symptoms and signs.

Evaluating the urinary excretion of the adrenal hormones as cortisol in the urine informs on the cortisol production by the adrenal gland, but analyzing the metabolites of cortisol, the 17-hydroxysteroids, by gas chromatography is even more crucial. Adequate amounts of the total sum of the 17-hydroxysteroids in the 24-hour urine indicate that the cortisol has been used efficiently for metabolic activity. If not, then low levels of these metabolites are observed in the urine, and the obese patient may suffer from cortisol deficiency symptoms such as sugar cravings.

The measurement of the urinary aldosterone is also very important. If the urinary excretion of aldosterone is very low, and salt intake is normal, that individual suffers from an aldosterone deficiency and usually has cravings for salty food.

A 24-hour urine test can measure testosterone. Measuring the urinary excretion of testosterone is important, as testosterone has major anabolic actions in the body. The urinary free testosterone declines sharply with age. The 17-ketosteroids measured by gas chromatography in the 24-hour urine reflect the excretion of adrenal androgen hormones, almost exclusively in women. In men, up to 50 percent of the two major 17-ketosteroids, androsterone and etiocholanolone, are produced by the testicles. Estrogen also can be measured in 24-hour urine.

The 24-hour urine test is important for the hormone evaluation of an obese person, as the values correspond to the free, active fraction of the hormones in the tissue, and hormone metabolites can be measured. The measurement of hormone metabolites evaluates what amount of a hormone has efficiently been used as a hormone for metabolic activity. It gives information on the metabolic activity or efficacy of a hormone. Such an evaluation is often difficult or even impossible with a blood test alone.

Treatment

The following are some practical recommendations for hormone replacement treatments in obese patients. Please note that doses may have to be increased in massively obese patients, as the fat tissue may absorb and sequester an important part of the administered hormones.

Recommended hormonal medications, routes of administration, and dosages are as follows:

Growth hormone

Form: 5 mg to 15 mg/15 ml in injection pen

Dose: 0.05 to 0.6 mg/day

Route of administration: subcutaneous

Comment: beware of cortisol deficiency

Thyroid hormones

Form: synthetic T4-T3, desiccated thyroid

Dose: 25-5 ug to 300-60 ug T3-T4/day; 45 to 360 mg/day

Route of administration: oral

Comment: A slight increase of the dose may be necessary during a diet (hypocaloric diet reduces the T4 to T3 conversion)

DHEA

Form: capsules or tablets of 10 to 50 mg

Dose: 10 to 25 mg/day in women; 25 to 75 mg/day in men

Route of administration: oral

Comment: beware of high serum estradiol levels in men and women, as DHEA may be converted into estradiol

Cortisol

Form: natural hydrocortisone in two to four divided doses per day; synthetic methylprednisolone, if water retention

Dose: 15 to 45 mg/day of hydrocortisone; 2 to 8 mg/day methylprednisolone

Route of administration: oral

Comment: doses may have to be increased during diet (a low-calorie diet decreases steroid hormone production)

Aldosterone

Form: Synthetic 9-alpha-fluorohydrocortisone or, commonly, fludrocortisone

Dose: 50 to 150 ug/day

Route of administration: oral, once a day

Comment: 100 ug corresponds to 1 mg hydrocortisone in glucocorticoid effects

Estradiol

Form: 0.6 mg/g estradiol gel

Dose: 0.5 to 5 g/day

Route of administration: preferably transdermal

Comment: always join progesterone for its diuretic effect; estradiol by transdermal route increases lean mass and decreases fat mass, oral estrogens do not have this effect; doses of estradiol may have to be reduced, as the fat tissue of obese women tends to produce supplementary estrogens

Testosterone

Form: 100 mg testosterone/g liposomal cream

Dose: 0.5 to 3 g/day

Route of administration: preferably transdermal

Comment: beware of high serum estradiol levels in predisposed men

Conclusion

Patients with obesity may suffer more than physicians think they do. It is worth paying attention to the hormonal deficiencies (or excesses) that may cause obesity. A patient with obesity may not be lacking willpower, but suffering from the inadequate production of hormones.