

Hypotestosterone in Male with Obesity

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ABSTRACT

Obesity can be defined as the excess of body fat. The prevalence of obesity worldwide increases in the last decades and causes a higher risk of cardiovascular diseases. Male subjects tend to develop visceral (abdominal) obesity, which produces pro-inflammatory adipokines. Obesity in males is associated with low testosterone levels. Several mechanisms have been proposed to explain the link between male obesity and hypotestosterone, including increased aromatization of testosterone to form estradiol, suppressing the Hypothalamus-Pituitary (HPT) axis due to pro-inflammatory adipokines, and decrease of Sex Hormone Binding Globulin (SHBG) production. Because hypotestosterone in males with obesity is a functional but reversible condition, it is essential to screen testosterone levels in obese males for early intervention and treatment.

Keywords: Male, obesity, visceral, testosterone, hypotestosterone

INTRODUCTION

Population with overweight and obesity is growing in these last decades. It is estimated worldwide that overweight subjects are around 1.2 billion people, with 300 million obese.¹ The prevalence of obesity in Indonesia increases in the last two decades. The proportion of adults with obesity in 2007 was 10.5% and increased to 21.8% in 2018. The prevalence is higher in males than female children but is higher in females than male adolescents. The prevalence of obesity is also higher in urban areas and high-income and highly educated people.² Obese males often have low testosterone levels than non-obese subjects even though they do not have recognizable hypothalamic-pituitary-testicular axis disorder. Several mechanisms have been proposed to explain the association between obesity and hypotestosteronemia. Hypotestosteronemia caused by obesity is a non-permanent yet functional condition and may be reversible by marked weight loss.³

Obesity

Obesity can be simply defined as excess body fat. Measurement of body fat can be calculated by Body Mass Index (BMI). The disadvantage of BMI is that it cannot be used directly to estimate the exact amount of body fat because some individuals have a high

BMI not because of the large amount of fat but because of the large muscle mass. A better way to assess obesity is to measure the percentage of total body fat. Obesity term in male is used if total body fat is more or equal to 25%, while in female more or similar to 35%.^{4,5}

Central obesity is caused by an increase in the amount of intra-abdominal fat associated with the progression of cardiometabolic risk factors. Obesity in the upper body (android/apple shape) is more common in males. Upper body fat comes from subcutaneous and intra-abdominal fat. Intra-abdominal fat (visceral) is defined as the fat found around the viscera and in the peritoneum, the intestine's dorsal border, and the kidney's ventral border. The accumulation of intra-abdominal fat can be found in males and females. The use of BMI does not provide an ultimate indication of intra-abdominal fat.⁶

Adipose tissue is also an endocrine organ. Several hormones and chemical compounds are produced by adipose tissue (adipokine). Central obesity triggers the secretion of several biologically active metabolites and substances such as glycerol, Free Fatty Acids (FFA), pro-inflammatory mediators such as Tumor Necrosis Factor- α (TNF- α), Interleukin 6 (IL-6), Plasminogen Activator Inhibitor-1 (PAI-1), and C-Reactive Protein (CRP) shown in Table 1. Decreased secretion of cardioprotective adiponectin is also found in central obesity.⁶

Table 1. Role of adipokine and its secretion in central obesity⁶

Adipokine	Key properties	Secretion in abdominal obesity
Adiponectin	Anti-atherogenic, reduces risk of developing diabetes ↓ Differentiation of macrophages into foam cells ↓ Atherogenic vascular remodelling ↓ Hepatic glucose output ↑ Insulin sensitivity	↓
IL-6	Promotes inflammation, pro-atherogenic, promotes diabetes ↑ Vascular inflammation ↑ Hepatic C-reactive protein production ↓ Insulin signaling	↑
TNF α	Pro-atherogenic / pro-diabetic Paracrine role in the adipocyte ↓ Insulin signaling ↑ Secretion of other pro-inflammatory mediators	↑
C-reactive protein	Promotes inflammation, pro-atherogenic Marker of chronic low-grade inflammation Predicts adverse cardiovascular outcomes	↑
PAI-1	Pro-atherogenic, pro-coagulant ↑ Atherothrombotic risk	↑
Resistin	Exacerbates insulin resistance ↓ Insulin signaling ↓ Endothelial function ↑ Vascular smooth muscle proliferation	↑

Testosterone: Synthesis, Physiology, and Role

The testes secrete several sex hormones that are collectively called androgens (with a masculinizing effect), including testosterone, dihydrotestosterone (DHT), and androstenedione (Figure 1). Testosterone is a steroid hormone consisting of 19 carbons (C₁₉H₂₈O₂). Testosterone is the main hormone of androgen. This hormone has an essential role in developing external genitalia and secondary sexual characteristics in males and as a precursor of estrogen in females.⁷⁻⁹

Testosterone metabolism involves cholesterol. It is a steroid hormone derived from cholesterol. Cholesterol via desmolase activity will produce pregnenolone, converted to 17- α -hydroxyprogesterone, to dehydroepiandrosterone, to 4-androstene-3,17-dione, and finally to testosterone. Alternative pathway to produce testosterone is via conversion of cholesterol to progesterone, to 17- α -hydroxyprogesterone, to 4-androstene-3,17-dione, to testosterone (Figure 2).¹⁰

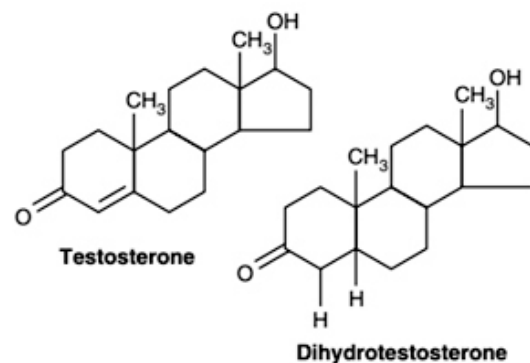


Figure 1. Structure of testosterone and dihydrotestosterone⁹

This hormone generally plays a role in the formation of masculine characteristics of the body. In the fetal phase, Human Chorionic Gonadotropin (HCG) from the placenta stimulates the testes to produce enough testosterone for up to 10 weeks after birth; then, there is no testosterone production during childhood until the age of 10-13 years and

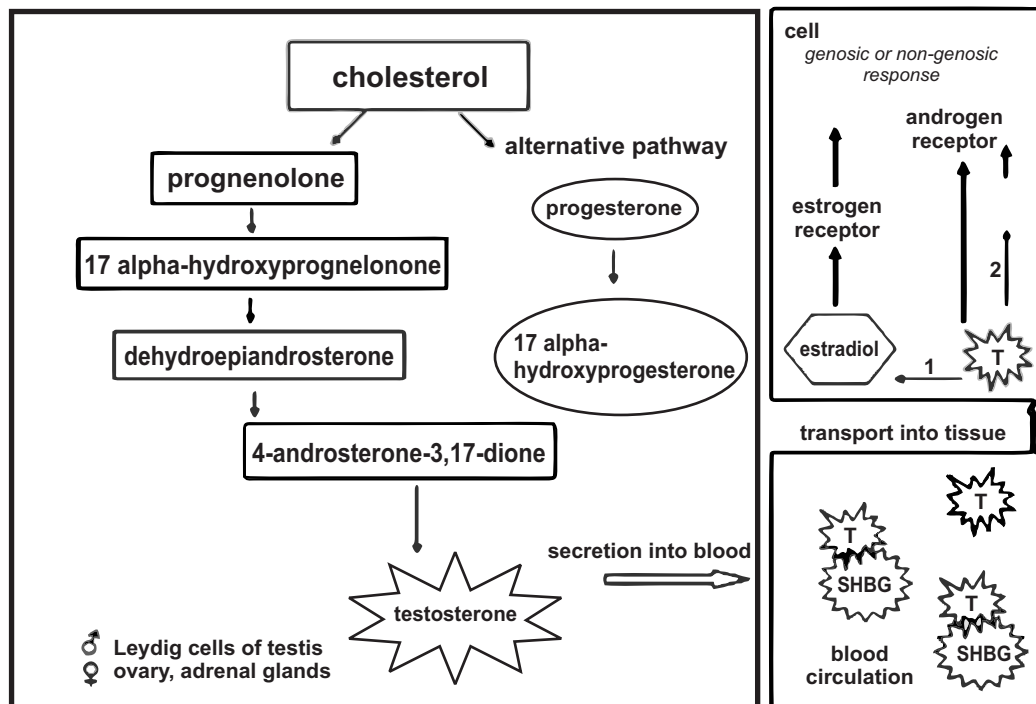


Figure 2. Metabolism of testosterone¹⁰

after puberty. Testosterone is secreted rapidly, thus causing the enlargement of the penis, scrotum, and testes. The effects of testosterone are pubic hair growth, hypertrophy in the laryngeal mucosa and enlargement of the larynx, causing a distinctive voice in male, increases protein and muscle formation, increases bone matrix and calcium deposits in bones, increases the body's basal metabolic rate, and increases the number of erythrocytes.⁹

Testosterone in males is secreted mainly by testicular Leydig cells and in small amounts by the adrenal cortex and Sertoli cells. In non-menopause females, testosterone is mainly produced by the ovaries and a small part by the adrenals and peripheral tissues. This ovarian production of testosterone decreases significantly after menopause.⁸ In a male, low testosterone level is found at the time of pre-puberty, increases at the age of 11 years, and reaches a peak at the age of 19 years, then will slowly decline until the age of 40.¹¹

After secreted by the testis, about 97% of testosterone will be bound to plasma albumin or SHBG and circulates in the blood for 30 minutes to several hours. This hormone will enter the tissue or be degraded into an inactive form that will be excreted. Most testosterone in the tissues will be converted to DHT, especially in target organs such as the prostate gland in adult males and the external genitalia in the fetus. Testosterone, which is not

bound to tissue, will be rapidly converted by the liver to androsterone and dehydroepiandrosterone, then conjugate with glucuronide and excreted into the intestine through the bile duct or into the urine through the kidneys.⁹

Testosterone circulates in plasma both as free testosterone or bound to plasma proteins. Sex hormone-binding protein is a specific protein, which binds testosterone, whereas albumin is a non-specific protein that binds testosterone. About 44-65% of testosterone circulating in males is bound tightly to SHBG, 33-50% is bound to albumin, and 1-3% of testosterone is unbound (free), which remains metabolically active (Figure 2).^{12,13} The biological effects of testosterone are mediated by free testosterone or testosterone, bound to easily released albumin; therefore, these two forms are called bioavailable testosterone. Hepatocytes synthesize sex hormone-binding globulin, and its production is influenced by estrogen, thyroid, androgen, and insulin.^{9,14}

Testosterone in the blood is transferred to the tissue or degraded into an inactive product, then excreted. Most testosterone in the tissues will be converted to DHT. In contrast, those that are not bound to the tissue will be converted rapidly by the liver to androsterone and dehydroepiandrosterone and simultaneously conjugated and excreted into the intestine bile and the urine through the kidneys.⁹

Sex hormone-binding globulin is a homodimer-shaped glycoprotein with a molecular weight of 90,000-100,000 dalton synthesized in the liver. As transport molecules of sex hormones, these glycoproteins play an essential role in the physiology of testosterone.¹⁵ The active part of the binding unit is a homodimer, which has three different oligosaccharide chains. Every one mole of homodimer binds to one mole of steroids.¹⁶

Sex hormone-binding globulin has a low capacity for steroids but binds to very strong affinity, whereas albumin has a high capacity but low affinity. Sex hormone-binding globulin binds to testosterone, dihydrotestosterone, and estradiol. The affinity of SHBG is the highest for DHT and lowest for estradiol. Sex hormone-binding globulin binds to DHT five times stronger than testosterone and 20 times stronger than estradiol.¹⁷

The high testosterone affinity for SHBG causes this fraction to be biologically inactive because lipophilic testosterone cannot diffuse through cell membranes if it is bound to SHBG. The non-SHBG-bound testosterone fraction is a biologically active steroid hormone. This fraction is vital in metabolic and biological activity on target cells. It causes SHBG to be the primary regulator in

determining the availability of steroid hormones for tissue uptake. The relationship between testosterone and SHBG has essential value in clinical practice. Because SHBG-bound testosterone is the most fraction of total testosterone measured, it is a standard test to identify male with testosterone deficiency (hypogonadism).¹⁶

Testosterone secretion by testicular Leydig cells only occurs when stimulated by Luteinizing Hormone (LH) from the anterior pituitary, leading to increased secretion of testosterone in proportion to the amount of LH level. Testosterone secretion by the testis gives negative feedback to the hypothalamus to reduce Gonadotropin-Releasing Hormone secretion (GnRH) and to the anterior pituitary to inhibit LH synthesis. Therefore, if testosterone levels increase, the negative feedback effect will run automatically through the hypothalamus and pituitary, making the Testosterone levels return to normal. Contrastingly, suppose testosterone levels are too low. In that case, it will stimulate the hypothalamus to secrete large amounts of GnRH, which increases the synthesis of LH by the anterior pituitary and ultimately increases the secretion of testosterone by the testes.⁹ This process is shown in Figure 3.

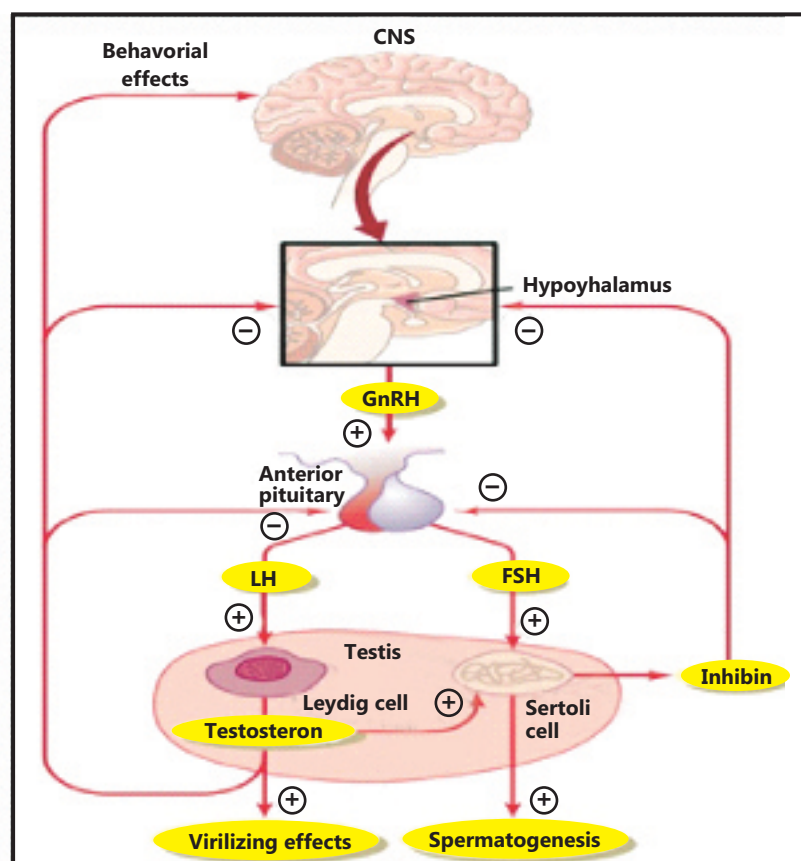


Figure 3. The feedback mechanism of hypothalamic-pituitary-testicular axis in male⁹

Hypotestosterone is defined as abnormally low testosterone or decreased testosterone levels in males, which indicates partial or total hypogonadism caused by primary or secondary/tertiary abnormalities. Primary failure in the testis can be caused by genetic abnormalities, developmental abnormalities, testicular trauma, infections, autoimmune diseases, and orchidectomy. Secondary/tertiary hypogonadism or congenital abnormalities can cause hypogonadotropic hypogonadism in the hypothalamus and pituitary, tumors, head trauma, and drugs. The manifestation of hypotestosteronemia can be erectile dysfunction, decreased libido, osteoporosis, decreased energy and quality of life, and depression. Testicular or adrenal tumors can cause increased testosterone levels.^{7,9,12}

Testosterone and Insulin Sensitivity in Male Obesity

Several studies have reported a relationship between serum testosterone levels and insulin sensitivity. Testosterone levels are reported to be positively correlated with insulin sensitivity.¹⁸ Low testosterone levels are also associated with an increased risk of type 2 Diabetes Mellitus (DM) in males. Administration of testosterone in middle-aged males with low testosterone levels improves insulin sensitivity and lowers plasma insulin levels.¹⁹

Endogenous androgens such as testosterone have a protective effect on obesity and metabolic syndrome. In males with hypotestosterone, an increased incidence of metabolic syndrome is reported. In the older male, serum testosterone

levels were reported to correlate negatively with the metabolic syndrome components such as abdominal circumference, high sensitive CRP (hsCRP), insulin and High-Density Lipoprotein (HDL).²⁰

Hypotestosterone in Male Obesity

Male obesity is often associated with a decrease of testosterone levels both in free and bound form. Several studies have reported the association between obesity and testosterone levels. The reduction of testosterone levels along with the increase of BMI has been reported.²¹ In pubertal and post-pubertal males with obesity, the testosterone levels are lower in obese than in non-obese.²² Endogenous androgen such as testosterone seems to have a protective effect against obesity and metabolic syndrome. In males with low testosterone, the incidence of metabolic syndrome is higher.²⁰ Low testosterone levels in obese males with type 2 DM also contribute to sexual dysfunction and risk of cardiovascular disease.²³ It is also reported that low testosterone is associated with insulin resistance and mitochondrial dysfunction.¹⁸

Mechanism of Low Testosterone in Male Obesity

Low testosterone levels in obese male can be caused by several mechanisms such as aromatization of testosterone to estradiol, impaired secretion of hypothalamic GnRH and pituitary and Follicle Stimulating Hormone (FSH) LH (suppression of the HPT axis), reduced testosterone synthesis in testicular Leydig cells, and insulin resistance associated reductions in SHBG production.^{3,24} This mechanism is shown in Figure 4.

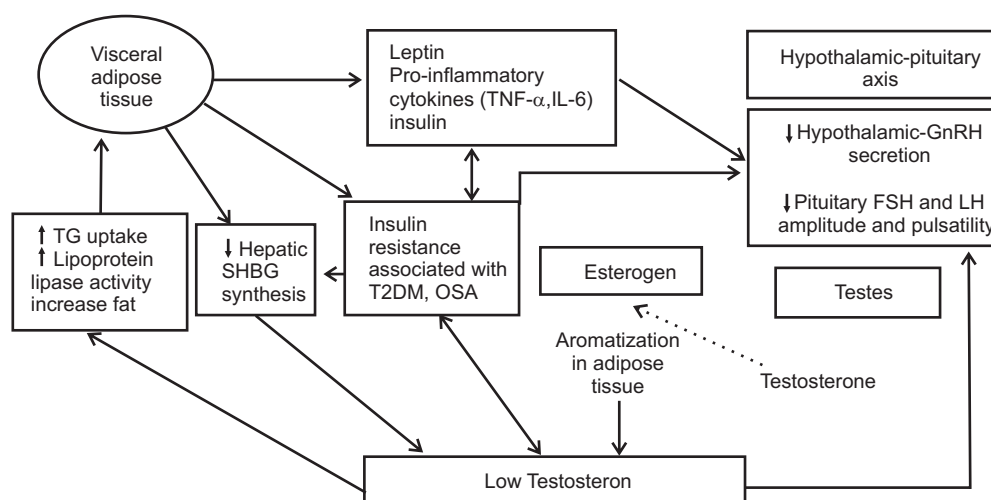


Figure 4. Association between obesity and hypotestosterone²³

Obesity can interfere with hypothalamic and pituitary functions. Testosterone aromatization, which forms estradiol in adipose tissue, binds to hypothalamic receptors, reducing the frequency of GnRH release resulting in reduced LH and pituitary secretion, leading to reduced production of testosterone by testicular Leydig cells. Reduced GnRH, which causes reduced LH secretion, will cause reduced expression of LH receptors in Leydig cells, causing Leydig cells to be less responsive to LH.^{3,24}

Hormones, growth factors, and cytokines produced by adipose tissue in obesity also reduce testosterone production directly by inhibiting Leydig cell steroidogenesis. Excessive leptin in the circulation binds to leptin receptors in Leydig cells and inhibits LH stimulation's effects on Leydig cells. This process will cause a blockade of the conversion of the steroid 17-hydroxyprogesterone precursor to testosterone. Local cortisol production, which is increased in visceral adipose tissue, also suppresses the Leydig cell steroidogenesis. Central obesity will cause a reduction in the nuclear transcription factor: hepatocyte nuclear factor 4 alpha (HNF-4 α), which causes reduced SHBG synthesis. Sex hormone-binding reduction will cause a decrease in total testosterone levels in obese males.^{3,24}

The association of hypogonadism and obesity is complex. It has a bidirectional effect because obesity is correlated with low testosterone and decreased SHBG levels, while hypogonadism and decreased circulating SHBG levels may also lead to the accumulation of abdominal fat. This results in increased adiposity and low testosterone levels that are interrelated and aggravate each other.^{3,24}

CONCLUSION

The prevalence of obesity worldwide is increased nowadays. Male subjects tend to have visceral obesity and have a higher risk of developing hypotestosterone conditions than non-obese ones. Several mechanisms have been proposed to link visceral obesity and hypotestosterone in obese males. Increased aromatization of testosterone to form estradiol, suppression of HPT axis due to production of pro-inflammatory adipokines, and decreased SHBG production are several mechanisms that can explain the development of hypotestosterone in obese males, typically visceral obesity. It is important to screen testosterone levels in males with obesity for early intervention and treatment.

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