

Serum Testosterone Level and Obesity

Zarchi Theint Theint Hlaing^{1*}

¹*Department of Physiology, University of Medicine, Magway, Myanmar.*

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Obesity has been proposed to affect male fertility both directly and indirectly, by inducing hormonal profiles. Male factor infertility is associated with a higher incidence of obesity. The link between obesity and low testosterone levels is found in men at all ages, even in young men and teenagers. The relationship between obesity and testosterone level in men is complex and bidirectional. This article is aimed to share the information about the cause and effect of obesity on serum testosterone level.

Keywords: Male; obesity; serum testosterone level.

1. INTRODUCTION

Testosterone has 19 carbon atoms and is produced from cholesterol, mainly by Leydig cells in the testes. The majority of testosterone is inactivated by the liver and excreted by the kidneys. Only approximately 2 percent of testosterone is "free" and available for biological activity by target organs. The remaining testosterone in the serum is bound to carrier proteins, with most bound to sex hormone-

binding globulin and a lesser extent to albumin. Male sex hormones are also known to fluctuate along the day and throughout life [1]. Young men also experience a diurnal variation in serum testosterone levels, which peak around 08:00 A.M. and are at their lowest in the late afternoon. Before puberty, the testosterone level is usually low in males. However, after puberty, testosterone level increases and reaches its peak around the age of 20-25 in men. As aging occurs, testosterone levels decline. Normal adult

*Corresponding author: Email: zarchi.tth@gmail.com;

testosterone level is 10.4 – 34.7 nmol/L or 300 – 1000 ng/dL or 3-10 ng/mL [2]. Testosterone and its derivatives are well known for their androgenic properties and anabolic effects [3].

2. OBESITY AND SERUM TESTOSTERONE LEVEL

Central or abdominal obesity, measured as waist circumference (WC), is a classical feature of metabolic syndrome and is associated with reduced total testosterone levels [4]. Pasquali et al. [5]; Khaw & Barrett-Connor, [6]; Vaidya et al. [7] stated that the decrease in testosterone levels appears to be more pronounced in men with abdominal adipose fat distribution since waist circumference, indirect measurements of visceral body fat distribution, have been negatively associated with both total and free testosterone and sex hormone-binding globulin (SHBG) levels [5,6,7]. Low testosterone and sex hormone binding globulin (SHBG) levels predict the development of central obesity and are associated with a higher mortality rate for cardiovascular disease.

There are some studies relating to obesity and serum testosterone level. Isidori et al. [8] studied testosterone level in non-obese (BMI ≤ 30 kg/m²), moderately obese (BMI 30 – 40 kg/m²) and massively obese men (BMI ≥ 40 kg/m²). It was found that serum testosterone level of the massively obese group was significantly lower than that of the moderately obese and non-obese group (p < 0.05 and p < 0.01, respectively) [8].

Fogari et al. [9] studied the association of serum testosterone level and BMI in 356 men. It was found that serum testosterone levels had a highly significant negative correlation with BMI (p < 0.001) [9].

In the study of Osuna et al. [10], significant negative correlations between testosterone level and BMI (r = - 0.447, p < 0.01) as well as WC (r = - 0.464, p < 0.01) were observed in 77 men with age range between 20 and 60 years [10].

A cross-sectional study done by Aggerholm et al. [11] recruited the total of 2139 men and they were divided into normal weight group (BMI 20.0 to 25.0 kg/m²), overweight group (BMI 25.1 to 30 kg/m²) and obese group (BMI > 30 kg/m²). It was shown that serum testosterone levels were 25–32% lower in obese men than in normal-weight men [11].

Dhindsa et al. [12] conducted a population-based cross-sectional comparative study in 1451 men. Subjects were categorized into lean (BMI < 25 kg/m²) and obese (BMI ≥ 30 kg/m²) and serum testosterone level was measured. The serum testosterone level of the obese group was lower than that of the lean (p < 0.001) [12].

Allan et al. [13] conducted a cross-sectional study of 207 men (age 54-86 years). It was found that serum testosterone level was inversely correlated with BMI (r = -0.16, p < 0.02) and WC (r = - 0.32, p < 0.001) [13].

Table 1. Results of some previous studies on serum testosterone level

Study	Subjects					Serum testosterone level (ng/mL) (Mean ± SD)	p value
	No.	Sex	Age (yrs)	BMI(kg/m ²)	WC (cm)		
Isidori et al. [8], UK	10	M	37.8 (23-58)	24.5±0.47	–	5.5±0.43	
	14	M	42 (27-58)	32.7±0.65	–	3.9±0.38	<0.05
	14	M	40.7 (18-58)	45.7±1.25	–	3.0±0.30	<0.01
Laaksonen et al. (2005), Finland	70	M	52±7	27.5±3.4	92.8± 9.5	4.3±0.17	
Dhindsa et al. [12], USA	275	M	62.8±11.5	23±3.2		3.9±1.67	<0.05
	489	M	57.9±9.1	34.6±3.2		3.5±1.33	
Bekaert et al. [16], Belgium	25	M	49 (43-64)	24±4		4.71±1.94	<0.001
	24	M	41 (32-49)	41±6		3.12±1.47	
Zarchi Theint	30	M	22.23±1.76	22.99±1.08	75.27±4.09	5.81±2.35	
Theint Hlaing et al. [17], Myanmar	30	M	23.77±2.93	30.92±0.89	83.63±2.91	4.55±1.24	<0.001
	30	M	23.47±1.66	31.81±2.54	97.00±3.47	3.41±1.31	<0.05

Khan et al. [14] done a cross-sectional study of 50 men and found that serum testosterone level was significantly and negatively correlated with BMI ($r = -0.334$, $p < 0.05$) as well as WC ($r = -0.443$, $p < 0.001$) [14].

Shoujun et al. [15] conducted in 188 male consecutive hypertensive patients and 31 healthy men. In this study, plasma total testosterone level was significantly and negatively correlated with BMI ($r = -0.34$, $p < 0.001$) [15].

Bekaert et al. [16] studied the changes of serum testosterone level between normal (age: 43 – 64 years; BMI: 24 ± 4 kg/m²; $n = 25$) and obese male (age: 32 – 49 years; BMI: 41 ± 6 kg/m²; $n = 24$) subjects. It was noted that serum testosterone level of obese men was significantly lower than that of normal men ($p < 0.001$) [16].

Zarchi-Theint-Theint-Hlaing et al. [17] conducted a cross-sectional study in 30 non-obese male subjects and 60 obese male subjects. It was found that serum testosterone level of obese subjects was significantly lower than that of non-obese subjects ($p < 0.0001$). The reduced serum testosterone level was more pronounced in men with central obesity. Risk of developing testosterone deficiency among centrally obese subjects was 4.3 times greater than that of generally obese subjects (Odd ratio= 4.33; 95% CI -1.2 to 15.61). There was also significant negative correlation between serum testosterone level and BMI ($r = -0.473$, $p < 0.001$, $n = 90$) as well as WC ($r = -0.567$, $p < 0.001$, $n = 90$) [17].

3. MECHANISM OF REDUCED SERUM TESTOSTERONE LEVEL IN OBESITY

According to the previous studies, the decrease in testosterone levels appear to be more pronounced in men with abdominal adipose fat distribution. Pasquali et al.[5]; Khaw & Barrett-Connor, [6] and Vaidya et al.[7] also state that there was a negative association between waist circumference and both total and free testosterone and sex hormone-binding globulin (SHBG) levels. Low testosterone and sex hormone-binding globulin levels predict the development of central obesity and are associated with a higher mortality rate for cardiovascular disease [5,6,7].

Wozniak et al. [18] indicated that white adipose tissue plays a much more integral role in maintaining physiological homeostasis. It is made up of adipocytes, preadipocytes,

macrophages and lymphocytes, making it an important mediator of inflammation and metabolism [18]. Ahima,[19] composed that visceral fat tissues is associated with an increased in adipokines and cytokines (TNF α , IL-6,IL-8) which play an important role in local and generalized low-grade inflammatory state [19]. These cytokines, as well as adipokines, may influence testosterone level by directly interfering with the hypothalamic-hypophyseal-gonadal axis and indirectly by insulin transduction pathway [20]. *In vitro* studies done by Russell et al. [21] and Watanobe & Hayakawa, [22] have shown that TNF- α and IL-6 influence on gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) secretion and consequently reduction of serum testosterone level [21,22]. Elevated TNF- α and IL-6 in adipose tissue are known to contribute to insulin resistance by inhibiting insulin receptor transduction in tissues [23]. Amery & Natrass [24] have done animal study and found that insulin act synergistically with LH on steroidogenesis in the rat testes [24]. Gautier et al. [25] have also shown that IL-6 is associated with low testosterone level in metabolic syndrome [25].

Schneider et al. [26]; Giagulli et al. [27] indicated that obesity can increase aromatase enzyme which is secreted by adipose tissue especially visceral adipose tissues. High levels of estrogens in obese males result from the increased conversion of androgens into estrogens due to the high bioavailability of these aromatase enzymes. They concluded that estrogen production rate is closely related to body weight as the increase in adipose tissue mass leads to increased aromatase activity [26,27]. This increase in circulating estradiol levels may, in turn, lead to an inhibition of the hypothalamic GnRH secretion and LH pulsatility which results in a reduction of gonadal testosterone production [28]. Moreover, estrogen excess may also directly inhibit gonadal 17- α hydroxylase and thus inhibiting Leydig cell steroidogenesis [29].

There is also a relationship between serum leptin level and testosterone level. Leptin is secreted by adipocytes. Isidori et al. [8] found that there was an inverse correlation between serum leptin and serum testosterone levels. Leptin affects testosterone production by directly inhibiting the conversion of 17-OH-progesterone into testosterone in the Leydig cell and indirectly, at the hypothalamic level [8,30,31,32]. Cioffi et al.

[33] studied the possible role of leptin in reproduction and reported that high-level leptin receptors ob gene was expressed at the adult reproductive organ [33]. In vitro animal study done by Caprio et al. [34] demonstrated the functional leptin receptor isoform from rat Leydig cells in culture and leptin directly inhibits human chorionic gonadotropin (hCG)-stimulated testosterone secretion [34]. Similarly Tena-Sempere et al. [35] has shown that leptin inhibits basal and hCG-stimulated testosterone secretion from incubations of rat testicular samples [35].

There is an increased turnover and production of glucocorticoids in obesity. This increased glucocorticoid flux has been suggested to reflect an abnormal control of the hypothalamic – pituitary- adrenal axis in obese patients, which may determine inhibition of the hypothalamic-pituitary-gonadal axis [36]. In addition, it has been shown that patients with excess cortisol

secretion have an increased BMI, WC, and WHR, potentially mediated through the suppression of testosterone production via the hypothalamic-pituitary axis [37].

With the discovery of the hypothalamic peptide (kisspeptin), it is now recognized as a crucial regulator of the onset of puberty, sex hormone-mediated secretion of gonadotrophins and control of fertility as shown in Fig 1. It acts directly on gonadotrophin-releasing hormone (GnRH)-expressing neurones determining the pulse amplitude and pulse frequency of LH. Oestrogen exerts its negative feedback action by inhibiting the release of kisspeptin and therefore GnRH secretion. The increased oestrogen in obese men will decrease the pulsatile frequency of LH and hence decreased testosterone production [38]. Low level of inhibin B in obesity is also associated with seminiferous tubule dysfunction and decrease testosterone production [39].

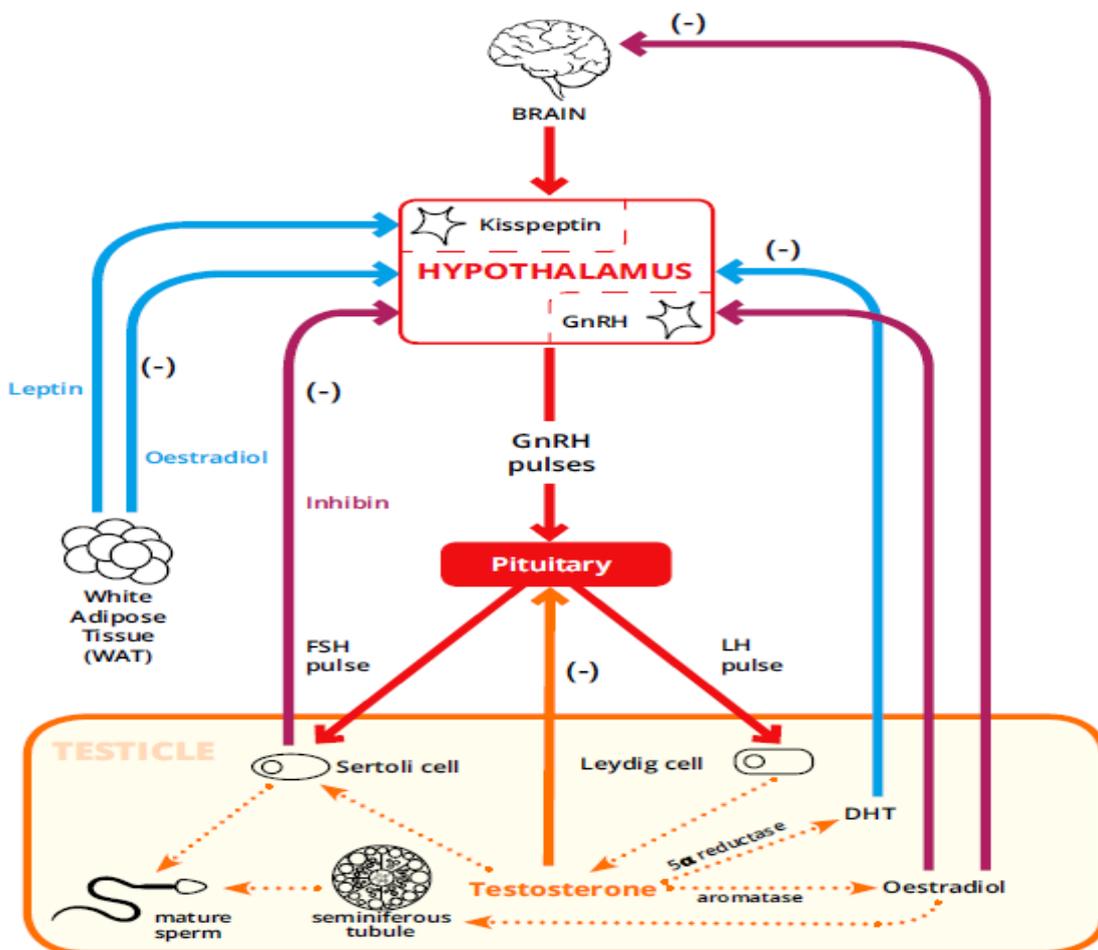


Fig. 1. The effect of obesity on male reproductive hormones [39]

Testosterone is a fat-reducing hormone. In particular, testosterone inhibits lipid uptake and lipoprotein-lipase (LPL) activity in adipocytes and stimulates lipolysis [40]. Men with visceral obesity are in a vicious cycle as testosterone deficiency leads to reduced lipolysis, reduced metabolic rate, visceral fat deposition, and insulin resistance [37].

Chen et al. [41] investigated the effect of androgen deprivation (surgical or medical treatment) on total body fat mass after 5 years of treatment in 62 men with prostate cancer. There was a significant increase in total body fat mass and a reduction in lean body mass after androgen deprivation therapy [41].

Smith et al. [42] compared the changes in body composition of men at baseline and after androgen deprivation therapy for prostate cancer for a period of 12 to 48 weeks. It was observed that a significant increase in fat mass, BMI, and total body weight and reduced in lean body mass after treatment [42].

Yassin and Doros [43] done a prospective study to evaluate long term effects of normalizing testosterone levels in 261 hypogonadal obese men (Mean age 59.5 ± 8.4 years). Subjects received parental testosterone (undecanoate 1000 mg) at baseline and 6 weeks and thereafter every 12 weeks for up to 60 months. It was found that there was a continuous weight loss over the full observation period (5 years) [43].

In accordance with the findings of previous studies, it can be assumed that the relationship between obesity and low testosterone level in men is complex and bidirectional.

Feeley & Saad, [37] indicated that men with visceral obesity are in a vicious cycle as testosterone deficiency leads to reduced lipolysis, reduced metabolic rate, visceral fat deposition, and insulin resistance [37]. Testosterone is fat-reducing hormone. In particular, testosterone inhibits lipid uptake and lipoprotein-lipase (LPL) activity in adipocytes, and stimulates lipolysis [40]. The lipolytic activity of testosterone is mediated by increasing the number of lipolytic β -adrenergic receptors, adenylate cyclase, protein kinase A and hormone-sensitive lipase activity [44,45,46]. Lastly, testosterone inhibits differentiation of adipocyte precursor cells. An indirect proof of the lipolytic effect of testosterone is represented by the experimental finding that the treatment of

male rats with an anti-androgen (cyproterone acetate) decreases the ratio between triglyceride degradation and free fatty acid (FFA) re-esterification in the adipose tissue, a metabolic short-circuit producing heat and possibly, regulating body weight. In particular, cyproterone acetate administration induces a decrease of catecholamine-stimulated lipolysis, but it does not modify the activity of the fatty acid esterifying enzymes [47].

Lipolysis activity of testosterone is confirmed by a study done by Bouloumie et al. [46]. Adipose precursor cells from male hamsters were exposed to testosterone in primary culture. It was concluded that androgens act directly on fat cells by upregulating alpha 2-adrenoceptor expression. The effects are not mediated by aromatization into estrogens and probably involve androgen receptor interactions [46].

Lipoprotein lipase (LPL) supplies the adipocytes with free fatty acids for intracellular esterification by hydrolyzing triglyceride-rich lipoproteins in the circulation, and it has been suggested that the abnormal activity of the enzyme may be the cause of obesity. Incubation of human adipose tissue with testosterone inhibits the expression of lipoprotein lipase [40]. A study by Iverius and Brunzell [48] demonstrated that abdominal and femoral lipoprotein lipase activity decreased one week after parenteral testosterone administration in obese men [48]. In contrast, an oral testosterone preparation administered four times daily for 6 weeks caused significant suppression of abdominal lipoprotein lipase activity [49]. Chronic testosterone treatment of hypogonadism men is responsible for a marked decrease of both lipoprotein lipase activity and FFA uptake in abdominal, but not in femoral subcutaneous fat [50].

Stoch et al. [51] studied that in a patient with prostate cancer who were treated with GnRH agonist (n=19) or untreated (n = 41), for 6 months, and demonstrated that total lean mass decreased and fat mass increased in men with GnRH agonist [51].

Chen et al. [41] investigated the effect of androgen deprivation (surgical or medical treatment) on total body fat mass after 5 years of treatment in 62 men with prostate cancer. There was a significant increase in total body fat mass and a reduction in lean body mass after androgen deprivation therapy [41].

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Yassin and Doros [43] done a prospective study to evaluate long term effects of normalizing testosterone levels in 261 hypogonadal obese men (Mean age 59.5±8.4 years). Plasma testosterone levels for each subject were measured and the subjects were found to have subnormal plasma testosterone levels. Subjects received parental testosterone (undecanoate 1000 mg) at baseline and 6 weeks and thereafter every 12 weeks for up to 60 months. It was found that there was a continuous weight loss over the full observation period (5 years). The mean percent weight loss was 3.2±0.3% after 1 year, 5.6±0.3% after 2 years, 7.5±0.3% after 3 years, 9.1±0.3% after 4 years and 10.5±0.4% after 5 years. Waist circumference declined from 107.7±10 cm to 99.0±9 cm with a mean reduction of 9.4±0.3 cm (p< 0.001). Body mass index was also found to decline from 31.7±4.4 to 29.4±3.4 kg/m² after 5 years [43].

4. CONCLUSION

Based on the findings of present studies, it can be concluded that central or visceral adipose tissue is a major risk factor for testosterone deficiency.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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