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Obesity associated low testosterone levels: Role of adiponectin

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Abstract:
Obesity is an increasing worldwide health problem, which linked to many health consequences as diabetes mellitus, hypertension and male infertility. Obesity is associated with low testosterone levels in men. Several mechanisms are involved in decreasing testosterone levels in obese men such as dyslipidemia, inflammation, oxidative stress and low adiponectin levels. Adiponectin, an adipokine secreted from adipose tissue and its level is decreased in obese subjects. It may play a role in decreasing testosterone levels in obese subjects. This review article, discusses causes of low testosterone levels associated with obesity, causes of decreased adiponectin levels in obesity and its association to testosterone.

***Key Word**: Obesity; testosterone; adiponectin*

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I. Introduction

Obesity is a major health problem. Its rate is increasing all over the world [1]. It is mainly caused by a positive energy balance in the form of increased energy intake levels than energy expenditure levels [1]. It is related to many health problems affecting several body systems [2]. Cardiovascular diseases, hypertension, dyslipidemia, Diabetes mellitus, cancer, arthritis, gastrointestinal diseases, respiratory diseases, male infertility, and mortality are linked to obesity [3,4]. Obesity may affect all male fertility parameters including semen parameters and hormonal levels. Obesity is associated with lower semen volume, sperm count, sperm motility, and a higher percentage of abnormal sperms [5]. Lower testosterone levels are found associated with obesity [6]. Many mechanisms are involved in lowering testosterone levels in obese subjects, However, the exact mechanism is still unclear [7].

II. Effect of obesity on testosterone levels

An inverse relationship between testosterone levels and Body mass index (BMI) in men was detected by several studies. **Rastrelli et al**[8] detected that obesity is predisposed to testosterone deficiency that can be reversed by weight loss**. Eriksson et al**[9] and **Amjad et al**[6] observed that increased BMI was associated with decreased serum testosterone levels in men.

Testosterone deficiency predisposes to infertility, in addition, it is considered a biomarker for mortality and morbidity in men[10]. Decreased muscle mass, decreased bone mineral density[11], high triglycerides (TG) levels, low high-density lipoprotein cholesterol (HDL-c) levels, hypertension, atherosclerosis, myocardial infarction, increased insulin resistance, and increased risk of diabetes mellitus are related to low testosterone levels [12]**.**

Mechanisms of how obesity affects testosterone levels

Obesity can alter testosterone levels by either acting peripherally on the gonads or centrally through its effect on the hypothalamic-pituitary-gonadal (HPG) axis[13]**.**

The direct effect of obesity on male gonads

Oxidative stress associated with obesity can directly damage testicular tissues decreasing testosterone secretion [14,15]**.** Another way of how obesity can directly affect testosterone levels is through causing obstructive sleep apnea[16]**.** Obstructive sleep apnea increased in obesity, reduces circulating serum testosterone levels and the degree is related to the severity of hypoxia during sleep [17,18]**.**

Effect of obesity on HPG axis

Under normal conditions, gonadotropin-releasing hormone (GnRH) is secreted from the hypothalamus which influences the pituitary gland to secrete follicle-stimulating hormone (FSH) and leutinizing hormone (LH) that act on testicles to stimulate spermatogenesis and steroidogenesis, respectively[19].

Obesity can decrease testosterone levels by affecting the HPG axis through many mechanisms:

1- Obesity through high aromatase enzyme expression in adipocytes converts testosterone to estradiol so decreasing testosterone levels[20]. Estradiol then acts on the HPG axis to negatively inhibit GnRH and LH release which contributes to the reduction in gonadal testosterone release[21].

2- Obesity is a pro-inflammatory state that predisposes to systemic chronic low-grade inflammation[22]. Macrophages infiltrating hyperplastic adipose tissues will induce more Pro-inflammatory cytokines (as TNF-α) and chemokines (as monocyte attractant protein-1) attracting more monocytes which are converted to macrophages inducing more TNF-α production creating a self-intensifying cycle with a systemic chronic low-grade inflammation [23]. These increased TNF- α levels associated with obesity can directly inhibit LH [16,24].

3- Several adipokines released from adipose tissues may influence the HPG axis as Leptin and adiponectin [22]. Leptin stimulates the expression of GnRH from the hypothalamus as well as increasing LH secretion[25]. However, Obesity generates a leptin-resistant state with high leptin levels and low testosterone levels [26]. Adiponectin levels are decreased in obesity [27]. It directly affects the HPG axis at all levels[22,28].

In addition, dyslipidemia associated with obesity may affect testosterone production. Low testosterone levels were found associated with low HDL-c and high TG levels in men[12]. TG levels were described as a significant risk factor for decreased serum testosterone levels in men [29]. Insulin resistance related to obesity also can alter testosterone levels, since insulin resistance increases TG levels by decreasing their clearance[30], which could lower testosterone levels.

III. Adiponectin hormone

Adipose tissues not only act as energy stores but also they are considered endocrine organs. They secrete different types of adipokines, cytokines, and chemokines. Adipokines as adiponectin secreted from adipose tissues act as hormones affecting glucose and lipid metabolism while their secretions are altered in obesity affecting body metabolism[31].

Scherer et al[32] first discovered adiponectin describing it as a new protein produced in adipocyte and released in the circulation. Skeletal and cardiac muscles are also capable of producing adiponectin[33,34]**.** It performs its function through binding to Adiponectin receptor 1 (Adipo R1) and Adipo R2 [35]. Adiponectin receptors are expressed in many tissues as in the pituitary gland, the hypothalamus, skeletal muscles, the liver, the testis, macrophages, and the pancreas [36,37,38]**.**

Adiponectin stimulates insulin secretion thus it has a hypoglycemic effect [39]. It also enhances glucose uptake and increases insulin sensitivity in both adipocytes and muscles [34,40]**.**

Adiponectin levels in obesity

Low adiponectin levels are found associated with obesity, these levels increase after weight loss[27,41]. Adiponectin levels are inversely associated with BMI [42,43]. Adipo R1 and Adipo R2 are downregulated in obesity and are increased after weight loss [44]**.**

Obesity negatively influences adiponectin levels through many possible mechanisms. In obesity, adipocytes develop a chronic inflammatory state with the secretion of multiple inflammatory cytokines as TNF-α and interleukin- 6 (IL-6) which negatively influence adiponectin [45]. TNF-α and IL-6 act on adipocyte and decrease adiponectin mRNA stability and mRNA expression thus decreasing adiponectin formation, glucose uptake, and insulin sensitivity [46,46]. Suppression of TNF-α increased adiponectin levels again[48]**.** Fetuin-A, a glycoprotein secreted by the liver and increased in high-fat diet intake, decreases adiponectin levels, it is also upregulated by TNF-α[49]. In addition, Chronic inflammatory conditions associated with obesity and its complications as metabolic syndrome and diabetes mellitus are associated with increased oxidative stress that decreases adiponectin formation[50].

The relation between obesity and adiponectin runs in a vicious circle, increased visceral fat mass and the inflammatory state developed in obesity lower adiponectin levels[45]. Low adiponectin further induces an insulin resistance state[34], and which further stimulates glucose and glycogen conversion into fats to be taken by organs increasing fat accumulation in organs like the liver and skeletal muscles[51]**.** Visceral fat accumulation further inhibits adiponectin production and so on[51].

Adiponectin relation to testosterone in obesity

Serum adiponectin levels show a statistically significant positive correlation with serum testosterone in obese adult men [52]. **Riestra et al**[53] detected a significant positive correlation between adiponectin and sex hormone-binding globulin (SHBG) in adolescent males and females while no significant correlation between adiponectin and testosterone. While, in old men, **Song et al**[54] detected no significant correlation between adiponectin and testosterone. Different testosterone levels in these different age groups might explain these different results.

Adiponectin can regulate testosterone secretion possibly through acting on the HPG axis [55, 56], Since Adipo R1 and R2 are expressed in human pituitary and hypothalamus glands[38]**.** Adiponectin inhibits GnRH secretion from the hypothalamus and LH release from the pituitary gland [57]. It can directly affect testosterone levels as adiponectin receptors were identified in testis [37]. Adiponectin administration in rats reduced testosterone at a testicular level[58].

Adiponectin levels are decreased in obesity[27]**,** which decreases adiponectin inhibition on GnRH and LH secretion and increases testosterone levels. However, adiponectin can also affect testosterone through other possible ways:

1- Low adiponectin levels associated with obesity increase TG levels by decreasing TG catabolism [59]. High TG levels are considered a significant risk factor of low testosterone levels in men [29].

2- Adiponectin decreases hepatic TNF-α production, so with low adiponectin levels, TNF-α production is increased [60]. TNF-α can directly inhibit LH secretion from the pituitary gland[16,24]**.** In addition, TNF- α induces lipolysis in adipose tissues and stimulates hepatic *de novo* fatty acid synthesis and TG production[61]**,** which could affect testosterone levels.

3-Insulin resistance associated with low adiponectin levels[62] could affect testosterone through increasing TG levels[30]**.**

4- High oxidative stress levels are associated with low adiponectin which decreases testosterone levels through acting directly on the testicles[15].

Although low adiponectin levels when acting directly on the hypothalamus, the pituitary and the testis could increase testosterone levels, it also could decrease testosterone levels by causing insulin resistance, increasing TG levels, and increasing TNF-α levels. The net effect of adiponectin on testosterone could be the sum of all these mechanisms.

IV. Conclusion

Obesity is a worldwide problem that is linked to many health problems as low testosterone levels. Several mechanisms can explain low testosterone levels in obesity. One of them could be adiponectin, its level is decreased in obesity and can affect testosterone levels in several ways either directly on the pituitary, the hypothalamus, and the testis or indirectly through altering insulin sensitivity, TG, and TNF-α levels.

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