

Commentary

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Exploring the role of testosterone upon adiposity and cardiovascular risk markers in men with severe obesity

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How to cite this article: Armeni E. Exploring the role of testosterone upon adiposity and cardiovascular risk markers in men with severe obesity. *Metab Target Organ Damage* 2024;4:4. <https://dx.doi.org/10.20517/mtod.2023.40>

Received: 23 Oct 2023 **First Decision:** 5 Dec 2023 **Revised:** 25 Dec 2023 **Accepted:** 3 Jan 2024 **Published:** 9 Jan 2024

Academic Editors: Angelo Cignarelli, Amedeo Lonardo **Copy Editor:** Dan Zhang **Production Editor:** Dan Zhang

Abstract

A prominent endocrine disorder linked to unhealthy lifestyle behaviors and increased visceral adiposity is Male Obesity Secondary Hypogonadism (MOSH). The pathogenesis of MOSH remains under investigation. However, recent evidence supports a direct role of leptin in affecting Leydig cells, reducing testosterone production, and increasing appetite. Conversely, testosterone deficiency is associated with comorbidities like hypertension, diabetes, and nonalcoholic fatty liver disease. A recently published study entitled "Relationship between sex hormones, markers of adiposity and inflammation in male patients with severe obesity undergoing bariatric surgery" describes evidence supportive of an inverse association between testosterone and serum leptin as well as levels of c-reactive protein (CRP) and IL-6, as well as a correlation between body mass index and CRP. The same study also provides novel insight retrieved from their *in vitro* findings, which reveal that testosterone exposure influences the expression of genes associated with adiposity, like fatty acid binding protein 4, peroxisome proliferation-activated receptor γ (PPAR γ), leptin, and adiponectin, as well as von Willebrand factor, in human-derived adipocytes. Overall, the latest evidence highlights the importance of early identification of hypogonadism in obese males and the potential benefits of testosterone supplementation in alleviating complications associated with obesity, particularly chronic inflammation. These observations underscore the need for a holistic approach to managing severe obesity, addressing hormonal and inflammatory factors to reduce its overall burden on health.

Keywords: Testosterone, male obesity secondary hypogonadism, adipocytes, von Willebrand factor



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Obesity and metabolic syndrome are medical conditions linked to an array of hormonal irregularities, often underestimated but significantly impacting the well-being of affected individuals^[1,2]. The predominant endocrine disorder associated with unhealthy lifestyle behaviors and increased visceral adiposity prevalence often manifests as temporary gonadal dysfunction^[3-5]. This condition, known as MOSH, may resolve in parallel with the resolution of metabolic disorders and the amelioration of insulin resistance after a significant and enduring weight loss^[2,6,7]. The hormonal imbalance in cases with MOSH is characterized by organic hypothalamic-pituitary-testicular axis suppression with the ensuing presence of low testosterone levels and elevated 17- β -estradiol concentrations^[8].

As per the latest guidelines of the European Academy of Andrology (EAA), secondary hypogonadism can be classified as organic or functional, while it can also be related to altered testosterone bioactivity^[7]. Functional testicular failure can occur in individuals aged over 70 years, particularly when accompanied by concurrent health conditions^[7]. In any case, comorbidities such as acute or critical illness, malnutrition, and obesity, and drugs like opioids, glucocorticoids, and androgens or anabolic-androgenic steroids are known to be associated with secondary hypogonadism^[7,9]. In this context, MOSH also represents a subgroup of secondary hypogonadism^[10].

While the exact mechanisms at play remain to be clarified, the role of aromatase as a cause of hypogonadism is still not fully understood, and inflammatory activity may be the main player^[11,12]. This enzyme, predominantly found in adipocytes, enhances the conversion of circulating testosterone into 17- β -estradiol, ultimately contributing to the development of MOSH^[13,14]. However, this hypothesis has limitations, as it does not consistently explain why a decrease in testosterone is not invariably accompanied by an increase in 17- β -estradiol levels in clinical practice^[13,14]. Elevated estrogen levels diminish the pulse amplitude of luteinizing hormone (LH) and potentially promote adipogenesis directly, resulting in heightened accumulation of subcutaneous, ectopic, and visceral fat^[15]. Consequently, the heightened expression of aromatase due to obesity could contribute to additional peripheral fat buildup, both by amplifying estrogen levels and diminishing testosterone production induced by LH^[15,16]. Heightened estrogen is exerting an adverse effect on erectile function, leading to increased vascular permeability in the mature penis, and a reported increase in the prevalence of erectile dysfunction^[17].

Recent evidence highlighted the role of leptin, a well-documented regulator of gonadotrophin-releasing neurons^[18], typically produced by the white adipose tissue. This hormone mediator acts directly on Leydig cells, downregulating their steroidogenic capacity^[19]. On the other hand, hyperleptinemia and the ensuing leptin resistance further decrease testosterone production, a hormonal alteration that contributes to increasing food intake and appetite^[20]. On the contrary, a growing body of evidence also supports the role of hypogonadism in regulating body fat accumulation. Testosterone deficiency is likely attributed to comorbidities such as hypertension, diabetes mellitus, visceral obesity, and metabolic syndrome^[21,22]. Data from patients treated with androgen deprivation therapy for prostate cancer highlighted that antiandrogen treatment increases the body mass index and consequently contributes to the development of obesity^[23]. Testosterone deficiency is also associated with the risk of developing nonalcoholic fatty liver disease (NAFLD) and obstructive sleep apnea^[24,25].

The recent study by Di Vincenzo *et al.*, published in this journal, aimed to investigate the intricate connection between obesity and hypogonadism and the role of low-grade inflammation as a possible mediator of this relationship^[26]. The findings offer valuable insights into the potential factors contributing to obesity-related complications in males. The clinical arm of the study was conducted on a small cohort of 24 patients with grade III obesity undergoing bariatric surgery (mean age of 43 ± 8 years). The *in vitro* arm of

the study involved differentiated human adipocytes, which were incubated in a testosterone environment, after which the expression of markers related to adiposity was evaluated. The results of the clinical arm of the study^[26] described a strong correlation between the body mass index (BMI) and high-sensitivity C-reactive protein (hsCRP). More importantly, the investigators described an inverse association between levels of testosterone and hsCRP, HOMA (homeostasis model assessment) index, leptin, and von Willebrand factor concentrations^[26]. Furthermore, the *in vitro* arm of the study demonstrated that exposure to testosterone can influence the gene expression of markers associated with adiposity, such as fatty acid binding protein 4 (FABP-4), PPAR γ , leptin, and adiponectin, in human-derived adipocytes. This effect was partially reversed when the antiandrogen flutamide was introduced.

The finding of an association between obesity and low-grade chronic inflammation, as reported in the study by Di Vincenzo *et al.*, is in line with earlier observations^[26]. Results retrieved from *in vitro* studies described that in states of increased energy storage, white adipocytes react with abnormal expansion, leading to hypoxia and remodeling-induced senescence^[27]. These states of hypoxia and senescence play a pivotal role in initiating and perpetuating a state of chronic, low-grade inflammation. In such circumstances, adipocytes encounter endoplasmic reticulum stress and heightened production of reactive oxygen species (ROS)^[27]. Dysfunctional adipocytes further exacerbate the situation by releasing inflammatory cytokines while compromising the production of protective adipokines, such as adiponectin^[27]. These adipocytokines can mediate the adverse effects of obesity, particularly on the cardiovascular system and endothelial function, further underscoring the intricate relationship between hormonal changes and the broader health implications associated with obesity^[28,29].

The association between endogenous testosterone levels and metabolic markers described in the study by Di Vincenzo *et al.* is supported by clinical data retrieved from observational studies^[26]. A meta-analysis of 37 observational studies (43,041 participants, mean age of 63.5 years, follow-up of 333 weeks) reported that low levels of testosterone were significantly associated with a 1.26-times higher risk of predicted overall mortality, 1.54-times higher risk of cardiovascular mortality, and 1.17-times higher risk of cardiovascular morbidity^[30]. Furthermore, low testosterone levels affect 30% of patients with type 2 diabetes^[31]. In any case, a large number of studies described that the link between testosterone deficiency and diabetes mellitus is bidirectional^[32,33].

A growing body of evidence also supports an association between exogenous testosterone administration and parameters of the metabolic profile. The T4DM trial (Testosterone for Diabetes Mellitus), a randomized, double-blind, placebo-controlled phase 3b trial, suggests that implementing a lifestyle program alongside two years of testosterone supplementation in overweight men with low testosterone levels, yet no signs of pathological hypogonadism has the potential to reverse type 2 diabetes (T2DM)^[33]. Furthermore, a mediation analysis of the same population showed that a significant portion of the impact of testosterone treatment was attributed primarily to changes in fat mass, skeletal muscle mass, and grip strength^[34]. Furthermore, testosterone treatment is improving body composition by increasing the total fat-free mass in hypogonadal men, and the effect is more pronounced in those with testosterone levels below the diagnostic cut-off for the diagnosis of hypogonadism (< 264 ng/dL)^[35]. In a very long-term observational registry study, exogenous testosterone administration has been demonstrated to achieve remission of T2DM^[36] and completely prevent progression from prediabetes to T2DM^[37]. The body composition and musculoskeletal parameters adversely affected by low testosterone levels may mirror sarcopenia, which is also known to be associated with NAFLD^[38]. Moreover, the link between steatotic liver disease and low testosterone levels has been described in human and animal studies. In fact, studies in castrated rodents showed that testosterone supplementation can sufficiently ameliorate the proportion of hepatic steatosis induced by a high-fat diet.

Moreover, low testosterone levels in males have been linked with steatotic liver disease, independently of type 2 diabetes mellitus, insulin resistance, and BMI^[39].

The link between androgenicity and prothrombotic parameters has been supported by the results of earlier *in vivo* and human evidence. The earlier *in vivo* study by Alqahtani *et al.* assessed the effect of testosterone deficiency and replacement upon prothrombotic and antifibrinolytic parameters^[40]. This study showed that TD induces hypercoagulation and inhibits platelet aggregation and fibrinolysis, effects that can be reversed by testosterone supplementation^[40]. Similar results were reported in a human study when lower androgenicity was related to higher levels of prothrombotic factors such as fibrinogen and factor VII concentrations. At the same time, men with low levels of sex hormone-binding globulin were found to have higher levels of plasminogen activator inhibitor-1, both antigen and activity^[41]. The clinical arm of Di Vincenzo *et al.*'s study reported a significant inverse association between testosterone levels and von Willebrand factor levels^[26]. Considering the role of heightened von Willebrand factor levels during acute coronary events^[42], treatment with testosterone appears even more encouraging in states where cardiovascular protection is desired.

A growing body of evidence describes the role of molecules involved in adipogenesis, which appear to regulate adipocyte differentiation and activity, including leptin, adiponectin, PPAR γ , and FABP-4. Leptin regulates the intracellular signaling in both preadipocytes and adipocytes, fostering adipogenesis and influencing the release of inflammatory mediators. Additionally, leptin reinstates adipogenesis even in the absence of insulin^[43]. Adiponectin is a well-accepted biomarker of adipocyte differentiation in human mesenchymal stromal cells. The effect of adiponectin appears to be mediated by PPAR γ , which modulates its activation^[44-46]. PPAR γ is one of the major adipogenic transcription factors, which works together with other epigenomic regulators and transcription factors, aiming to activate the adipocyte genes required to regulate the terminal differentiation of preadipocytes^[47]. FABP-4 has been demonstrated to act as the downstream regulator of PPAR γ which plays an important role in the regulation of β cell function^[48,49].

Additionally, the *in vitro* arm of Di Vincenzo *et al.*'s study (2023) highlighted that testosterone incubation can downregulate the gene expression of various markers, such as leptin and adiponectin, but also transcription factors like PPAR γ and FABP-4, in human differentiated adipocytes^[26]. These observations concerning the effect of testosterone and the regulation of adipocyte gene expression are not surprising. Earlier data showed that testosterone administration can stimulate the expression of the two salmon leptin-a genes in a dose-dependent manner, as observed in Atlantic salmon parr hepatocytes^[50]. The expression of androgen receptors has been demonstrated by *in vitro* studies of human preadipocytes and mature adipocytes^[51-53]. Earlier evidence from differentiated preadipocytes retrieved from male rat fat pads also showed that the density of androgen receptors is regulated by testosterone^[52]. On the contrary to the above, mature SGBS (Simpson-Golabi-Behmel syndrome) preadipocytes incubated in testosterone did not result in a higher expression and secretion of adiponectin mRNA or higher synthesis of intracellular adiponectin multimer proteins^[54].

The study by Di Vincenzo *et al.* has significant implications, as their findings explain various interactions between testosterone and cardiometabolic risk markers, which include insulin resistance, chronic inflammation, and predisposition towards a more thrombotic profile^[26]. In more clinical terms, this study highlights the importance of early identification of males affected by hypogonadism, including those affected by states of obesity and early initiation of testosterone supplementation. By addressing this hormonal imbalance, it may be possible to alleviate some of the complications related to obesity, particularly the chronic inflammatory state. These findings emphasize the need for a holistic approach to managing severe obesity, considering hormonal and inflammatory factors to reduce the disease's overall burden.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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