

ORIGINAL RESEARCH—ENDOCRINOLOGY

Effects of Testosterone Supplementation on Depressive Symptoms and Sexual Dysfunction in Hypogonadal Men with the Metabolic Syndrome

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ABSTRACT

Introduction. Low testosterone levels in men are associated with the metabolic syndrome (MetS) as well as with depressive symptoms, low vitality, and sexual dysfunction.

Aim. To assess the effects of testosterone administration on these subjective symptoms, which have not extensively been studied in hypogonadal men with the MetS.

Main Outcome Measures. The Beck Depression Inventory (BDI-IA), Aging Males' Symptoms (AMS) scale, and International Index of Erectile Function 5-item (IIEF-5) scale at baseline, 18 and 30 weeks were analysed using multilevel analysis.

Methods. In a randomized, placebo-controlled, double-blind, phase III trial (ClinicalTrials.gov identifier: NCT00696748), 184 men suffering from both the MetS and hypogonadism were included. They were treated for 30 weeks with either parenteral testosterone undecanoate (TU; 1,000 mg IM TU, at baseline, and after 6 and 18 weeks; Nebido®) or placebo injections, 105 (92.9%) men receiving TU and 65 (91.5%) receiving placebo completed the 30-week trial.

Results. The 184 men were aged mean 52.1 years old (standard deviation [SD] 9.6; range 35–69), with a mean body mass index of 35.5 kg/m² (SD 6.7; range 25.1–54.8), and a mean total testosterone level of 8.0 nmol/L (SD 4.0). There were significant improvements in BDI-IA (mean difference vs. placebo after 30 weeks: –2.5 points; 95% confidence interval [CI]: –0.9; –4.1; $P = 0.003$), AMS (–7.4 points; 95% CI: –4.3; –10.5; $P < 0.001$), and IIEF-5 (+3.1 points; 95% CI: +1.8; +4.4; $P < 0.001$). The effects on the BDI-IA, AMS, and IIEF-5 were strongest in men with baseline total testosterone levels <7.7 mmol/L (i.e., median value).

Conclusions. TU administration may improve depressive symptoms, aging male symptoms and sexual dysfunction in hypogonadal men with the MetS. The beneficial effects of testosterone were most evident in men with the lowest baseline total testosterone levels. **Giltay EJ, Tishova YA, Mskhalaya GJ, Gooren LJG, Saad F, and Kalinchenko SY. Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome. J Sex Med 2010;7:2572–2582.**

Key Words. Randomized Trial; Testosterone Administration; Metabolic Syndrome; Depression; Placebo-controlled; Sexual Dysfunction

Introduction

Testosterone levels fall progressively with increasing age. In healthy young men (aged 20 to 30 years) morning levels of serum total testosterone vary between 12 and 35 nmol/L (i.e., 350 and 1,000 ng/dL) [1,2]. This laboratory reference range for young men may also be applicable to elderly men [1,2]. Low androgen status has been associated with symptoms of irritability and dysphoria, declining vigor and vitality, erectile dysfunction, and diminished libido and orgasm [2–6], and an increased risk of depressive symptoms and depression [7–10]. Depression may even further deteriorate sexual function [6]. In a large community sample of almost 4,000 elderly men, free testosterone concentration in the lowest quintile was associated with more depressive symptoms [9]. Likewise, androgen deprivation therapy in men treated for prostate cancer induces mood disturbances, anxiety, fatigue, lack of drive, and listlessness [11,12]. The syndrome associated with hypogonadism in elderly men is often called late-onset hypogonadism (LOH) or testosterone deficiency syndrome of the aging male. There is a substantial overlap between the phenomenology of hypogonadism and depressive symptoms. In middle-aged and elderly men, total and free testosterone levels are inversely and independently associated with depressive symptoms and also with sexual dysfunction [3,13].

The metabolic syndrome (MetS) is characterized by the presence of central obesity, a high blood pressure, dyslipidemia (i.e., high triglycerides and low high-density lipoprotein [HDL] cholesterol), and hyperglycemia according to the International Diabetes Foundation (IDF) [14] or National Cholesterol Education Program (NCEP) criteria [15]. The MetS is not only associated with an increased risk of cardiovascular disease and type 2 diabetes mellitus [14,15], but may also predispose to hypogonadism, sexual dysfunction, low vitality, and depressive symptoms [2,16–19]. In a prospective study, nondepressed men with the MetS at baseline were at an increased risk of depressive symptoms at follow-up [17]. In a study of twins, the association seemed to be largely attributable to environmental, nongenetic factors [20]. Obesity—which is often present in the MetS—predicts depressive symptoms in cross-sectional and longitudinal studies [19–21]. Thus, the MetS is linked to poor psychological and sexual well-being.

Several randomized placebo-controlled trials with testosterone treatment arms included ques-

tionnaires on depressive symptoms, sexual function, and other scales of quality of life. Several of these individual randomized trials failed to demonstrate a beneficial effect of testosterone or dihydrotestosterone on the above subjective measures [22–36]. A crossover trial of 24 hypogonadal men with type 2 diabetes mellitus found that intramuscular testosterone improved subjective symptoms in the questionnaire for Androgen Deficiency in Aging Males (ADAM) [37]. Moreover, some trials did [38,39] and some trials did not [23,31] find beneficial effects of parenteral testosterone on depression rating scales compared with placebo in men with a major depressive disorder. In a recent meta-analysis of trials with depressed patients, testosterone replacement did increase the response rate to testosterone treatment vs. placebo [40]. The duration of the included trials ranged from 6 to 12 weeks. Randomized trials also found in general moderate beneficial effects on sexual interest, sexual satisfaction and erectile function in hypogonadal men [23,26,29,32,35,41], which were confirmed in meta-analyses [42,43].

In this trial we assessed the effects of intramuscular testosterone undecanoate (TU) on depressive, aging male and sexual symptoms during 30 weeks [44,45]. TU is a depot testosterone ester with a long fatty acid side chain. As previous studies found evidence for beneficial effects of testosterone treatment in hypogonadal men with obesity and type 2 diabetes [37,46], this study was designed to examine whether normalization of testosterone in hypogonadal men with the MetS would improve features of the MetS. The results for the effects of TU on components of the MetS and prostate safety will be published elsewhere. We are not aware of other studies that examined the effects of testosterone on these subjective measures in hypogonadal men with the MetS. Our hypothesis was that testosterone supplementation would significantly decrease depressive and aging male symptoms, and would significantly improve sexual function.

Methods

Participants

This study was a 30-week, randomized, double-blind, placebo-controlled trial of parenteral TU or matching placebo. Hypogonadal male out-patients with the MetS were recruited through our outpatient academic center (department of Andrology and Urology, Moscow, Russia). The study was conducted from October 2005 until October 2008.

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