Testosterone Supplementation and Sexual Function: A Meta-Analysis Study

Giovanni Corona, MD,* Andrea M. Isidori, MD,† Jaques Buvat, MD,‡ Antonio Aversa, MD,† Giulia Rastrelli, MD,§ Geoff Hackett, MD,¶ Vincenzo Rochira, MD,** Alessandra Sforza, MD,* Andrea Lenzi, MD,† Edoardo Mannucci, MD,†† and Mario Maggi, MD§

*Endocrinology Unit, Medical Department, Azienda USL Bologna, Maggiore-Bellaria Hospital, Bologna, Italy; †Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy; ‡Centre ETPARP, Lille, France; §Sexual Medicine and Andrology Unit, Department of Biomedical, Clinical and Experimental Sciences, University of Florence, Florence, Italy; ¶Good Hope Hospital, Sutton Coldfield, UK; **Chair of Endocrinology, Department of Biochemical, Metabolic and Neural Sciences, University of Modena & Reggio Emilia & Azienda USL of Modena, Italy; ††Diabetes Agency, Careggi Hospital, Florence, Italy

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ABSTRACT

Introduction. The role of testosterone supplementation (TS) as a treatment for male sexual dysfunction remains questionable.

Aim. The aim of this study was to attempt a meta-analysis on the effect of TS on male sexual function and its synergism with the use of phosphodiesterase type 5 inhibitor (PDE5i).

Methods. An extensive Medline, Embase, and Cochrane search was performed.

Main Outcome Measures. All randomized controlled trials (RCTs) comparing the effect of TS vs. placebo or the effect of TS as add on to PDE5is on sexual function were included. Data extraction was performed independently by two of the authors (A. M. Isidori and G. Corona), and conflicts resolved by the third investigator (M. Maggi).

Results. Out of 1,702 retrieved articles, 41 were included in the study. In particular, 29 compared TS vs. placebo, whereas 12 trials evaluated the effect of TS as add on to PDE5is. TS is able to significantly ameliorate erectile function and to improve other aspects of male sexual response in hypogonadal patients. However, the presence of possible publication bias was detected. After applying "trim and fill" method, the positive effect of TS on erectile function and libido components retained significance only in RCTs partially or completely supported by pharmaceutical companies (confidence interval [0.04–0.53] and [0.12; 0.52], respectively). In addition, we also report that TS could be associated with an improvement in PDE5i outcome. These results were not confirmed in placebo-controlled studies. The majority of studies, however, included mixed eugonadal/hypogonadal subjects, thus imparting uncertainty to the statistical analyses.

Conclusions. TS plays positive effects on male sexual function in hypogonadal subjects. The role of TS is uncertain in men who are not clearly hypogonadal. The apparent difference between industry-supported and independent studies could depend on trial design more than on publication bias. New RCTs exploring the effect of TS in selected cases of PDE5i failure that persistently retain low testosterone levels are advisable. **Corona G, Isidori AM, Buvat J, Aversa A, Rastrelli G, Hackett G, Rochira V, Sforza A, Lenzi A, Mannucci E., and Maggi M. Testosterone supplementation and sexual function: A meta-analysis study. J Sex Med 2014;11:1577–1592.**

Key Words. Testosterone; Erectile Dysfunction; Libido; PDE5i; Orgasm

Introduction

Although erectile dysfunction (ED) is a common medical condition [1–4], it remains an often undiagnosed and untreated problem [5]. It is generally accepted that androgens modulate erectile function (EF) acting on different aspects of the male sexual response [6,7].

Despite this evidence, the widespread screening for hypogonadism in ED subjects and the role of testosterone supplementation (TS) as a possible treatment still remain questionable [6]. Current European Association of Urology (EAU) guidelines gave a level of evidence (LE) of 4 and grade of recommendation (GR) B for the assessment of testosterone (T) in all subjects complaining of ED [8]. Similar considerations have been released by The Endocrine Society [9] and the standard operating procedures of the International Society for Sexual Medicine (ISSM) [10].

The effects of TS on male sexual functions in ED subjects are still more controversial. The EAU guidelines indicated an LE 1b (at least one randomized controlled trial [RCT]) and a GR of B to the need to treat at first any "curable cause of ED," including hypogonadism [8]. Similar LEs were released by the ISSM [10]. Conversely, The Endocrine Society emphasized the concept that androgen deficiency and ED are two independently distributed clinical disorders with distinct pathophysiology, which may coexist in middle-aged and older men [9].

Another controversial issue is the effect of TS on phosphodiesterase type 5 inhibitor (PDE5i) outcomes [6,11–15]. A substantial improvement in the response to PDE5s was seen in 37.5–92% of these men following combination of T therapy with PDE5i [6,11,16]. However, data on randomized placebo controlled studies are more conflicting [6,17–20].

The aim of present study is to meta-analyze available data evaluating the effect of TS on male sexual function and its therapeutic synergism with the combined use of PDE5i.

Methods

A meta-analysis was performed including all RCTs enrolling men comparing the effect of TS vs. placebo on sexual function or the effect of TS as add on to PDE5i on EF.

An extensive Medline, Embase, and Cochrane search was performed including the following words: "testosterone" (MeSH terms) OR "testosterone" (all fields) AND "erectile dysfunction" (MeSH terms) OR "erectile" (all fields) AND "dysfunction" (all fields) OR "erectile dysfunction" (all fields). The search, which accrued data from January 1, 1969 up to July 1, 2013, was restricted to RCT. The identification of relevant studies were performed independently by two of the authors (A.M. Isidori and G. Corona), and conflicts resolved by the third investigator (M. Maggi). The quality of RCTs was assessed using the Cochrane criteria [21]. Completed but still unpublished trials were identified through a search of the http://www.clinicaltrials.gov website.

A trial was considered partially or completely supported by pharmaceutical companies when declared by the authors and/or when at least one author belongs to any industry company.

Several sexual-related components were evaluated. In particular, overall EF component included the evaluation of TS outcome on all spontaneous erection in awaking state and/or sexual-related erections (including frequency and/or erection quality, according to the different studies; see also Table 1) but not nocturnal erections. Conversely, sexual-related EF component dealt only on the effect of TS on sexual-related erection improvement. In addition, because sexual function was evaluated using different tools, a sensitivity analysis considering all those studies applying International Index of Erectile Function (IIEF) was also performed (see also Table 2). For each study, a treatment–effect size and the 95% confidence interval (CI) for the effect size were calculated using the method of Hedges and Olkin [21].

Statistical Analysis

Heterogeneity across studies of effect size of TS vs. placebo or PDE5i in comparison with PDE5i + T on EF was assessed using I^2 statistics. Considering that I^2 was 87.73 and 96.41, respectively, a random effect model was used for the calculation of standardized mean differences. This choice is also justified by the heterogeneity in the methods used for the assessment of the principal outcome (i.e., sexual function). In order to reduce ecological bias, meta-regression analyses were performed using both mean and categorical variables referred to patients' enrollment criteria (hypogonadal vs. mixed, eugonadal). Several sensitivity analyses or regression linear adjusted models were performed whenever appropriate. All analyses were performed using Comprehensive Meta-analysis Version 2 (Biostat, Englewood, NJ, USA). Multivariate