available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Andrology
Editorial by XXX on pp. x–y of this issue

Meta-analysis of Results of Testosterone Therapy on Sexual Function Based on International Index of Erectile Function Scores

Giovanni Corona [a], *Giulia Rastrelli* [b], *Abraham Morgentaler* [c], *Alessandra Sforza* [a], *Edoardo Mannucci* [b,d], *Mario Maggi* [b,*]

[a] *Endocrinology Unit, Medical Department, Azienda Usl Bologna Maggiore-Bellaria Hospital, Bologna, Italy;* [b] *Andrology and Sexual Medicine Unit, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy;* [c] *Men's Health Boston, Harvard Medical School, Boston, MA, USA;* [d] *Diabetes Agency, Careggi Hospital, Florence, Italy*

Article info

Article history:
Accepted March 21, 2017

Associate Editor:
Christian Gratzke

Keywords:
Erection
Ejaculation
Erectile dysfunction
Libido
International Index of Erectile Function
Testosterone
Sexual function
Orgasm

Abstract

Context: The interpretation of available clinical evidence related to the effect of testosterone (T) treatment (TTh) on sexual function has been inconsistent, in part due to the use of different and self-reported measures to assess outcomes. The International Index of Erectile Function (IIEF) is the most frequently used validated tool to assess male sexual function.
Objective: To perform a meta-analysis of available data evaluating the effect of TTh on male sexual function using IIEF as the primary outcome.
Evidence acquisition: An extensive Medline, Embase, and Cochrane search was performed including all placebo-controlled randomized clinical trials enrolling men comparing the effect of TTh on sexual function.
Evidence synthesis: Out of 137 retrieved articles, 14 were included in the study enrolling 2298 participants, with a mean follow-up of 40.1 wk and mean age of 60.2 ± 6.5 yr. Using IIEF-erectile function domain (IIEF-EFD) as the outcome, we found that TTh significantly improved erectile function compared with placebo (mean difference = 2.31 [1.41;3.22] IIEF-EFD score, $p < 0.0001$). Patients with more severe hypogonadism (total T < 8 nmol/l) reported greater changes in final IIEF-EFD score when compared with those with a milder T deficiency (total T < 12 nmol/l; 1.47 [0.90;2.03] and 2.95 [1.86;4.03] for total T < 12 nmol/l and <8 nmol/l, respectively, Q = 5.61, $p = 0.02$). The magnitude of the effect was lower in the presence of metabolic derangements, such as diabetes and obesity. Other aspects of sexual function, as evaluated by IIEF subdomains, were also improved with TTh including libido, intercourse satisfaction, orgasm, and overall sexual satisfaction.
Conclusions: TTh significantly improves erectile function and other sexual parameters as measured by IIEF in hypogonadal men. These results argue that sexual dysfunction should be considered a hallmark manifestation of T deficiency, since those symptoms can be significantly improved with normalization of serum T. In addition, these results suggest that TTh alone may be considered a reasonable treatment for hypogonadal men with milder degrees of erectile dysfunction, whereas the addition of other treatments, such as phosphodiesterase type 5 inhibitors, may be more appropriate for men with more severe erectile dysfunction.
Patient summary: We investigated the effect of testosterone treatment on sexual function by performing a meta-analysis of all available studies that used the most frequently used assessment tool, the International Index of Erectile Function. We found that testosterone treatment significantly improves erectile dysfunction, as well as other aspects of sexual function, in men with testosterone deficiency. This treatment may be all that is required for hypogonadal men with milder erectile dysfunction; however, additional treatments may be necessary in more severe cases.

* Corresponding author. Andrology and Sexual Medicine Unit, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Viale Pieraccini 6, Florence 50139, Italy.
Tel. +39-55-4271415; Fax: +39-55-4271413.
E-mail address: m.maggi@dfc.unifi.it (M. Maggi).

http://dx.doi.org/10.1016/j.eururo.2017.03.032
0302-2838/

1. Introduction

The fact that symptoms of testosterone (T) deficiency in adulthood, also termed late-onset hypogonadism, often overlap with those characteristics of the aging process and its associated comorbidities underlies the recent controversy regarding the value of testosterone therapy (TTh) (http://www.fda.gov/downloads/Drugs/DrugSafety/UCM436270.pdf) [1]. In the case of T deficiency (TD), there is uniform consensus among professional medical societies that the diagnosis requires a combination of symptoms/signs together with low serum T concentrations: a reduction of circulating T alone is not enough for diagnosing the condition [1–3]. Symptoms of T deficiency include psychological (ie, depression), physical (ie, fatigue), and sexual concerns [1–3].

A quantitative review by Millar et al [4] on the accuracy and operating characteristics of signs and symptoms for predicting low T in aging men indicates that all relationships are relatively poor in terms of sensitivity and specificity. The European Male Aging Study, a population-based survey performed on more than 3400 men recruited from eight European centers, clearly showed that sexual symptoms—particularly erectile dysfunction (ED) and decreased frequency of sexual thoughts and morning erections—are the most sensitive and specific symptoms in identifying patients with low T [5]. The syndromic association of these sexual symptoms resulted in improved identification of men with T deficiency. Similar results were recently reported by us in a large cohort ($n = 4890$) of patients consulting for ED at the University of Florence [6]. In contrast, psychological and physical symptoms were less informative [5].

Recently, even the association between T deficiency and sexual symptoms has been questioned, because it has been speculated that it is derived from cross-sectional observations and it is conceivable that sexual inactivity drives a reduced testicular function, and not the other way around [1]. However, a longitudinal analysis of the European Male Aging Study cohort showed that the presence of sexual symptoms at baseline is not associated with an incipient high grade, whereas an incipient high grade at follow-up is associated with the development of sexual symptoms [7].

An opportunity to solve the dilemma is offered by the *ex-juvantibus* criterion. If T deficiency is causing sexual symptoms, these symptoms should be improved by T therapy. In our previously published meta-analysis we showed that TTh is superior to placebo in improving all aspects of sexual function [8]. The outcomes observed were independent of age but negatively related to the levels of T at enrolment. In addition, as expected, the effects of TTh were lower in the presence of conditions known to produce vascular damage, such as in the case of diabetes mellitus [8]. It should be recognized that human studies evaluating the effect of T on sexual function are extremely heterogeneous in their assessment, because, quite often, different self-reported measures have been used for the evaluation of the final outcome. To overcome this problem, in our previous meta-analysis we homogenized the effect size by using the method of Hedges and Olkin [9]. However, even this method presents important limitations [10].

Although most studies, including meta-analyses and systematic reviews, have provided supporting evidence that T therapy does in fact improve sexual symptoms in men with TD [11–15], a recent systematic qualitative review on the effect of TTh on several outcomes in controlled trials concluded that TTh did not show consistent benefits for sexual function [16]. That conclusion was based on a subjective interpretation of study results, without considering overall patient population characteristics at baseline, including T levels. Despite those limitations, the question as to whether TTh provides sexual benefits has again resurfaced. For this reason, we have undertaken to perform a new meta-analysis in which we have restricted article inclusion to only randomized controlled trials (RCTs) in T-deficient men in which the same assessment instrument was used, the International Index of Erectile Function (IIEF).

The IIEF is the most frequently used validated tool to assess male sexual function [17]. It has been recommended both as a primary endpoint for clinical trials of ED and for diagnostic evaluation of ED severity. The original version included 15 items encompassing several sexual domains; however, in order to improve its usefulness in clinical practice an abridged 5-item version was developed and is known as the IIEF-5 or Sexual Health Inventory for Men [18]. Another 6-item version of IIEF-15 (IIEF6: the erectile function domain of IIEF-15 [IIEF-EFD]) [19] was separately developed and validated to diagnose the presence and severity of ED.

To better clarify the role of TTh on sexual function, the aim of the present study was to perform a meta-analysis of available data evaluating the effect TTh on male sexual function using IIEF, in its different versions, as the primary outcome.

2. Evidence acquisition

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses checklist (Supplementary data; http://www.prisma-statement.org/).

2.1. Eligibility criteria

All placebo-controlled RCTs enrolling men investigating the effect of TTh on sexual function were included in the analysis.

2.2. Information source and search strategy

An extensive Medline, Embase, and Cochrane search was performed including the following words (“testosterone”[MeSH Terms] OR “testosterone”[All Fields]) AND (“sexual behavior”[MeSH Terms] OR (“sexual”[All Fields] AND “behavior”[All Fields]) OR “sexual behavior”[All Fields] OR “sexual”[All Fields]) AND (“physiology”[Subheading] OR “physiology”[All Fields] OR “function”[All Fields] OR “physiology”[MeSH Terms] OR “function”[All Fields]) AND

Please cite this article in press as: Corona G, et al. Meta-analysis of Results of Testosterone Therapy on Sexual Function Based on International Index of Erectile Function Scores. Eur Urol (2017), http://dx.doi.org/10.1016/j.eururo.2017.03.032