

## The Relationship Between Testosterone-Replacement Therapy and Lower Urinary Tract Symptoms: A Systematic Review



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<b>OBJECTIVE</b>	To systematically review prospective trials evaluating the clinical effects of testosterone-replacement therapy on lower urinary tract symptoms and prostate volume.
<b>MATERIALS AND METHODS</b>	We performed a literature review through PubMed, Embase, and Cochrane Library from 1994 to 2015 for prospective trials of hypogonadal men with benign prostatic hyperplasia or lower urinary tract symptoms treated with testosterone-replacement therapy. We evaluated the abstracts for outcomes related to International Prostate Symptom Score, prostate volume, and urodynamic parameters.
<b>RESULTS</b>	An original cohort of 3079 abstracts was reviewed. Thirty-five trials were selected for inclusion. The majority of trials reviewed found no significant prostate growth due to testosterone-replacement therapy. Studies of men with baseline mild lower urinary tract symptoms demonstrated either no change or an improvement in symptoms after treatment. There was a lack of relevant urodynamic studies. Trials of men with the metabolic syndrome demonstrated uniform improvement in lower urinary tract symptoms. Forty-six percent of all the trials identified included exclusion criteria for baseline severe-range lower urinary tract symptoms or other signs of obstructive lower urinary tract symptoms.
<b>CONCLUSION</b>	The current literature demonstrates scant support for a causative relationship between testosterone-replacement therapy, de novo or worsening lower urinary tract symptoms, and prostate volume. Furthermore, our review found an absence of high quality evidence that would support guideline recommendations that testosterone-replacement therapy is relatively contraindicated in men with severe-range lower urinary tract symptoms. Future clinical trials with more inclusive voiding criteria are needed. UROLOGY 88: 22–32, 2016. © 2016 Elsevier Inc.

The overall prevalence of symptomatic hypogonadism among men 30-79 years old is 5.6%, according to the Boston Area Community Health Survey.<sup>1</sup> The prevalence of bothersome lower urinary tract symptoms (LUTS) is 26.5% among men in their 60s and 25.5% among men in their 70s.<sup>2</sup> Increasing use of testosterone-replacement therapy (TRT) among men at risk for LUTS has raised concerns about potential adverse effects of TRT on LUTS and benign prostatic hyperplasia (BPH), including the development of de novo LUTS.<sup>3</sup>

The proposed pathophysiological relationship between TRT and LUTS relates to the integral role of androgens in the development and continued growth of the prostatic epithelium.<sup>4</sup> However, the clinical effects of physiological or exogenous androgens on the development of benign prostatic enlargement remain controversial. Physiological testosterone levels have not been consistently associated with the development of LUTS in longitudinal studies, after accounting for age.<sup>5</sup> However, in a trial of men undergoing surgical correction for benign prostatic enlargement, high levels of physiological testosterone were associated with an increased risk of severe LUTS.<sup>4</sup>

Severe LUTS is listed as a relative contraindication to the initiation of TRT by the Endocrine Society due to concerns over possible exacerbation of symptoms.<sup>6</sup> However, several of the recommendations pertaining to TRT made by the Endocrine Society have recently been critically reexamined.<sup>7</sup> We performed a systematic review of

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prospective clinical trials to evaluate the clinical relationship between TRT and prostate volume or LUTS to address this issue.

## MATERIALS AND METHODS

We queried PubMed, Embase, and the Cochrane Library for articles, from January 1, 1994, to February 1, 2015, using the following search terms: “testosterone” AND “International Prostate Symptom Score” OR “prostate volume” OR “benign prostatic hyperplasia” OR “safety” OR “adverse events” OR “quality of life.” The search was performed using criteria presented in the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.<sup>8</sup> Our query was limited to prospective human trials published in English. There was no restriction on follow-up duration.

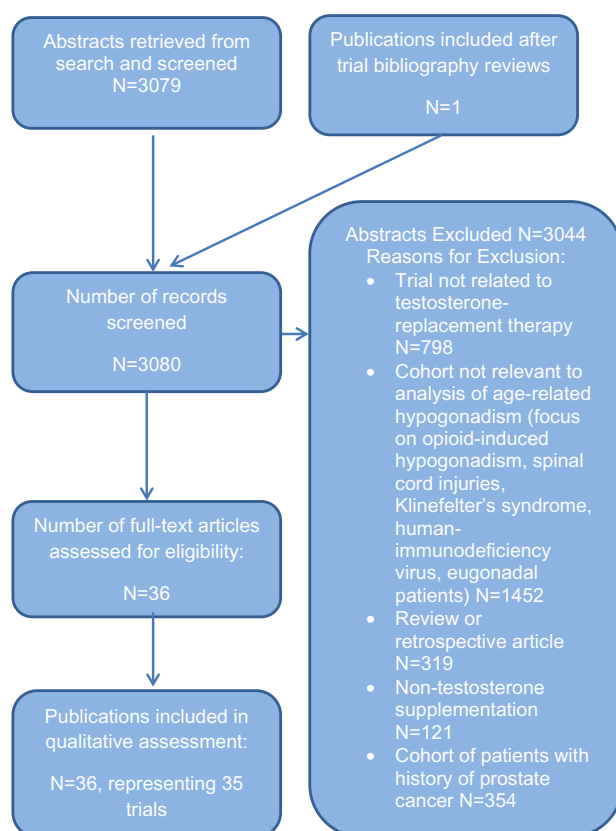
Patient population, intervention, comparator, outcome, and study design (PICOS) criteria were used to select individual trials for inclusion (Appendix).<sup>9</sup> The summary measures examined included differences in outcomes related to International Prostate Symptoms Score (IPSS), prostate volume, or urodynamic parameters, reported as end-point differences between treatment and placebo or absolute differences after treatment versus placebo. Ninety-five percent confidence intervals and standard deviation were reported when available. Two reviewers selected the studies for their relevance to the topic after discussion.

## RESULTS

Out of an original cohort of 3079 abstracts, 35 prospective trials were selected for inclusion (Fig. 1). The level of evidence was assessed for all included trials.<sup>10</sup> Study details, exclusion criteria relating to baseline LUTS, and outcomes are presented in Table 1. The level of bias was assessed for randomized placebo-controlled, double-blind trials<sup>46</sup> (Table 2). We present an analysis of the published literature as it pertains to TRT and (1) prostate size, (2) bladder physiology, (3) and IPSS.

### TRT and Prostate Size

**Level I Evidence.** LUTS may be classified as a dysfunction of bladder emptying, storage, or both.<sup>47</sup> Worsening bladder outlet obstruction due to benign prostatic enlargement induced by TRT has been hypothesized. However, Marks et al, in a randomized, double-blind, placebo-controlled trial of 44 hypogonadal (HG) men with moderate-severity LUTS, treated with short-term depot injectable testosterone enanthate (TE) for 6 months, demonstrated no effect on prostate size as measured by magnetic resonance imaging. Although the prostate transition zone did not show any trend toward increasing size, the whole prostate volume showed a nonsignificant trend toward increasing prostate size. Importantly, the authors did not find a strong correlation between serum and intraprostatic levels of testosterone ( $r = 0.35$ ,  $P = .13$ ) or dihydrotestosterone ( $r = 0.01$ ,  $P = .99$ ).<sup>11</sup> Two large randomized, double-blind, placebo-controlled trials of men treated with long-acting depot testosterone undecanoate (TU) for approximately 6 months also failed to demonstrate any change in prostate volume as measured by ultrasound.<sup>12,13</sup>



**Figure 1.** Diagram of phases of trial selection for systematic analysis. (Color version available online.)

**Level II Evidence.** Six prospective, observational open-label studies, with treatment durations ranging from 6 months to 7 years, did not identify any significant increase in prostate volume.<sup>14-19</sup> However, other level IIb studies have demonstrated a significant increase, however modest, in the prostate volume of HG men after TRT. Nieschlag et al and Minnemann et al, in open-label studies of injectable TU, revealed small but significant increases in prostate volume after a 24 week and a 4-year trial, respectively.<sup>20</sup> Snyder et al demonstrated a significant increase in prostate volume after 3 years of treatment with testosterone patch, albeit in a small cohort.<sup>21</sup> Arver et al performed an open-label trial of HG men previously treated with TE, followed by an 8-week “washout” period and subsequent treatment with transdermal testosterone for 1 year. The cohort demonstrated a reduction in prostate volume after the “washout” followed by prostate regrowth during patch treatment.<sup>22</sup>

Studies comparing eugonadal controls with HG men undergoing TRT have been useful in elucidating both the relationship between physiological testosterone levels, prostate volume, and the effects of TRT. Francomano et al studied HG men treated with injectable TU for 60 weeks and found no change in prostate volume when compared with eugonadal age-matched controls in an open-label observational trial.<sup>23</sup> In a cross-sectional trial, HG men treated with TE showed similar end-treatment prostate volume

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