Testosterone and the Prostate: Artifacts and Truths

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KEYWORDS

• Testosterone • BPH • LUTS • Hypogonadism

KEY POINTS

- Despite a lack of evidence, there have been stated concerns that testosterone replacement therapy (TRT) can pose a risk to men suffering with lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH).
- TRT may improve components of the metabolic syndrome, which is associated with worsening LUTS. Furthermore, the evidence suggests that TRT may decrease prostatic inflammation, which is also associated with worsening LUTS.
- The data on the relationship between TRT and LUTS have never shown worsening of LUTS, often show no change in LUTS, and occasionally show improvement.

INTRODUCTION

As men age, they tend to become burdened with an increasing number of medical illnesses. Many of these illnesses tend to be urologic. Two of these conditions frequently seen by urologist are hypogonadism and benign prostatic hyperplasia (BPH) with its associated lower urinary tract symptoms (LUTS). Testosterone levels begin decline to in men's middle 30s. Shortly thereafter, many men begin to become bothered by LUTS associated with BPH. Understanding the relationship between LUTS/BPH and hypogonadism is increasingly important, as more aging men inquire about testosterone replacement therapy (TRT).

Several safety concerns have been raised about TRT. In 2015, the FDA required a black box warning regarding a possible increased risk for myocardial infarction and cerebrovascular events. Methods from the studies leading to this conclusion have been called into question.[1,2] Additionally, the US Food and Drug Administration (FDA) issued a black box warning regarding TRT in men with BPH. The warning regarding topical androgens included the following statement:

"Patients with BPH treated with androgens are at an increased risk of worsening of signs and symptoms of BPH. Monitor patients with BPH for worsening signs and symptoms. Patients treated with androgens may be at an increased risk for prostate cancer. Evaluation of patients for prostate cancer prior to initiating and during treatment is appropriate."[3]

The data for these recommendations are unclear, and this article will examine the evidence relating to TRT in men with BPH.

Both hypogonadism and BPH become more prevalent with increasing age in men. This article will examine the pathophysiology leading to both processes and the potential impact of TRT in patients suffering from BPH.

NATURAL HISTORY OF TESTOSTERONE/ HYPOGONADISM

Testosterone is the major hormone responsible for male sexual differentiation. It has a short half-life at

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12 minutes. Its secretion begins in utero. It is a cholesterol derivative produced in the adrenal and testes that is 98% bound in the blood. It is loosely bound to albumin and binds tightly to sex hormone-binding globulin. Testosterone that is bound to albumin and testosterone that is free is bioavailable. Its release is pulsatile, and its level fluctuates during the day after peaking in the morning.[4] It appears that these fluctuations become less predominant in men over 45 years of age.[5] Peripheral aromatization results in the conversion of androgens to estrogens. Testosterone binds the androgen receptor (AR), which is translocated to the cell nucleus, and results in the production and secretion of peptide growth factors.

In target organs, testosterone undergoes conversion to 5α-dihydrotestosterone (DHT), a more potent androgen, by the enzyme 5α-reductase. There are 3 isoforms of this enzyme. The 5α-reductase inhibitors (5-ARIs) include finasteride and dutasteride. The type 1 isoenzyme exists primarily in the skin and to a lesser extent the prostate. The type 2 isoenzyme is the dominant form in the prostate although present to a lesser extend in the skin and liver.[6] Finasteride inhibits type 2 5-ARI, with dutasteride inhibiting both type 1 and 2 5-ARI. Dutasteride lowers DHT levels to a greater extent than finasteride. These medications have been used to reduce prostatic volume and LUTS.[7,8]

Increasing awareness of late-onset hypogonadism has made it a frequent subject of discussion among physicians and between physicians and their patients. After a plateau in men in their 20s, testosterone levels begin to decline. Additionally, there is an age-related increase in sex hormone-binding globulin decreasing the bioavailable testosterone.[9–15] In a large cross-sectional study, the European Male Aging Study (EMAS), annually there was a 0.4% decline in serum testosterone and a 1.3% decline in free testosterone.[16] There is controversy concerning whether this decline is physiologic or a pathologic process necessitating treatment.[17] Regardless, there has been a global increase in the prescribing of TRT.[18]

The diagnosis of hypogonadism requires a combination of clinical symptoms and biochemical evidence. There are specific and nonspecific symptoms. Signs and symptoms include: low libido, decrease in muscle mass, anemia, fatigue, decrease in erections, low bone mineral density, and dysthymia. The Androgen Deficiency in Aging Males (ADAM) questionnaire can be helpful in ascertaining this information.[19,20] The Endocrine Society Guidelines published in 2010 do not recommend routine screening.[21] Testing for hypogonadism should consist of a morning total testosterone. A patient with a total testosterone less than 250 is likely to have hypogonadism and should be treated accordingly. Patients with a total T between 250 and 400 should undergo further testing for a free testosterone. Patients with a total testosterone of more than 400 are unlikely to have hypogonadism.[22]

There is no causal link between testosterone therapy and an increased incidence of prostate cancer or LUTS associated with BPH; however, both the International Society of Andrology and the Endocrine society recommend against exogenous testosterone therapy in men who have significant LUTS prior to a urologic evaluation.[23]

NATURAL HISTORY OF BENIGN PROSTATIC HYPERPLASIA

BPH is a technically a histologic diagnosis characterized by the proliferation of prostatic epithelial and stromal cells in the transition zone. Most commonly the diagnosis is made based on clinical symptoms and less commonly radiographic images. Androgen stimulation is required for fetal prostate development. The prostate is small at birth, approximately 1.5 g, and remains stable at this size until puberty. At puberty the gland reaches approximately 10 g. Typically, a prostate reaches its normal weight of 20 g between 21 and 30 years of age.[24] In autopsy studies, the incidence of histologic BPH increases with age, being present in 8% of men 31 to 40 years of age, 42% of those 51 to 60 years of age, and 90% of those older than 90.[25] BPH itself is associated with both erectile and ejaculatory dysfunction. Although contributory, the obstructive effect of hyperplastic nodules does not provide sufficient explanation for the LUTS associated with BPH.

Androgens are necessary but not sufficient for the development of BPH. Animal studies have helped elucidate this role. In a canine study, young castrated dogs only developed BPH after testosterone replacement. BPH regressed in older dogs after the castration but returned following exogenous testosterone administration.[26] Men with primary hypogonadism, who normally do not develop BPH, can now develop BPH after TRT.[27]

Obesity and the metabolic syndrome are both risk factors for LUTS associated with BPH. Obesity is a risk factor for hypogonadism as well. A cross-sectional study examining 100 men with moderate and severe obesity found a negative correlation between androgens (both testosterone/free testosterone) and insulin resistance.[28] It is also interesting to note that multiple studies have demonstrated improvement in hypogonadism after weight loss secondary to bariatric surgery.[29] TRT also is conducive to weight loss.[30] Hyperinsulinemia is associated with increased sympathetic