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INVITED REVIEW

Male Endocrinology

Testosterone and benign prostatic hyperplasia

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The use of testosterone to treat the symptoms of late-onset hypogonadal men has increased recently due to patient and physician awareness. However, concerns regarding the effect of testosterone on the prostate, in particular any possible effect on the risk of prostate cancer have prompted further research in this regard. Surprisingly, numerous retrospective or small, randomized trials have pointed to a possible improvement in male lower urinary tract symptoms (LUTS) in patients treated with testosterone. The exact mechanism of this improvement is still debated but may have a close relationship to metabolic syndrome. For the clinician, the results of these studies are promising but do not constitute high levels of evidence. A thorough clinical examination (including history, examination and laboratory testing of testosterone) should be undertaken before considering the diagnosis of late-onset hypogonadism or instigating treatment for it. Warnings still remain on the testosterone supplement product labels regarding the risk of urinary retention and worsening LUTS, and these should be explained to patients.

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INTRODUCTION

With an increasing population of aging males, who are living longer and healthier lives, solutions are being sought (and money made) for what were once considered common problems of senescence. Testosterone, inexorably and emotionally linked to male development and sustainment, has come into the spotlight. New proponents champion its replacement in aging men as the panacea of “the andropause”, while more traditional skeptics worry about under-investigated harms.

Urologists have known of testosterone’s importance in prostate development and pathology for some time, but only more recently have we begun to better understand its effects on lower urinary tract symptoms (LUTS); and more importantly, that these symptoms are not always entirely due to bladder outlet obstruction (BOO).

Our understanding of the link between testosterone, benign prostatic hyperplasia (BPH), BOO, and LUTS is slowly improving through research. However, studies that allow clinicians to uphold the vigorous standards of evidence-based medicine in the use of testosterone for LUTS have not yet been forthcoming.

THE PROSTATE AND TESTOSTERONE

Natural history of benign prostatic hyperplasia

The prostate is small at birth (1.5 g) and remains so until early puberty when it increases in size via an androgen-dependent pubescent growth phase¹ from 10 g to an average of 20 g (± 6 g) in young adults.^{2,3} After this initial growth and remodeling phase, which involves the entire prostate gland (peripheral, central and transitional zones), there is a second selective growth phase of the transitional zone that occurs in approximately 50% of men by age 50, and 90% of men older than 80 years. This growth is pathologically recognized as BPH and clinically noted as benign prostatic enlargement (BPE) or benign prostatic

obstruction/BOO. It is thought that the normal interactions between the epithelial and fibromuscular stromal components of the transitional zone prostate tissue are altered leading to a reduced epithelial/stromal ratio and thus micronodular remodeling that characterizes BPH.

Testosterone and benign prostatic hyperplasia

It has long been recognized that the volume of the prostate increases with age in normal men due to BPH but not in their untreated hypogonadal counterparts. This has been clearly demonstrated in animal studies, in which testosterone replacement for younger castrated dogs permits the development of BPH. Furthermore, after initial regression of BPH in older castrated dogs, BPH was restored following testosterone replacement.⁴

Similarly, in human patients with primary hypogonadism, testosterone replacement allows the development of normal prostatic growth and BPH.⁵ It is also well-known that in men with diseases of the prostate (such as prostate cancer or BPH), castration or androgen deprivation treatments leads to decrease prostate size and improvement in urinary function in some patients.⁶

Exactly how testosterone influences BPH is less clear. In a simplified model, an androgen receptor (AR) on prostatic cells is activated inducing growth. This then leads to the AR-dependent transcription of specific target genes resulting in the production and secretion of peptide growth factors, including insulin-like growth factor 1, epidermal growth factor, fibroblast growth factor-related proteins, such as keratinocyte growth factor.³

Wilson⁷ hypothesized that it was dihydrotestosterone (DHT), the highly biologically active metabolite converted from testosterone in the prostate by the isoenzymes 5 α -reductase type 1 (5AR1) and type 2 (5AR2), which was responsible for activating the AR. This local

effect can be reversed clinically by blockade of 5AR1 and/or 5AR2 by 5 α -reductase inhibitors (such as finasteride or dutasteride), which reduce prostate volume by approximately 25%.⁸ Such medications are now used commonly in urological practice and often lead to improvement in voiding symptoms in men with BOO secondary to BPH/BPE.

Effect of aging

Serum testosterone has been shown to decrease in men with age by approximately 2%–3% annually.⁹ The prevalence of hypogonadism (often defined as serum testosterone < 300 ng dl⁻¹) ranges from 6%¹⁰ to as high as 38%¹¹ in some primary practice settings.

The process of BPH, however, continues as men age and despite the fact their serum testosterone decreases. Liu *et al.*¹² demonstrated that in a group of older males (mean age 59.8 years) that there was not a significant correlation of serum testosterone levels (total, free or bioavailable) with either prostate volume or International Prostate Symptom Score (IPSS). This is difficult to explain: Isaacs and Coffey¹³ argue that aging results in an increase in intra-prostatic DHT levels associated with BPH in both animal and human studies. However, Marks *et al.*¹⁴ recently disputed this concept when finding no evidence of increased intra-prostatic DHT with testosterone replacement therapy (TRT) in a small, randomized control trial (RCT).

Benign prostatic hyperplasia is often thought of as the main cause of worsening LUTS as men age.² Although it remains unclear whether there is a close association between aging, hypogonadism and LUTS. While Favilla *et al.*¹⁵ were able to demonstrate an association between LUTS and serum levels of total testosterone in the study of 122 men with symptomatic BPH, they did not find a similar association with BPH/BPE and testosterone.

TRADITIONAL THINKING REGARDING TESTOSTERONE REPLACEMENT THERAPY AND BENIGN PROSTATIC HYPERPLASIA/LOWER URINARY TRACT SYMPTOMS

To this day, there are warning labels on the available testosterone supplements regarding the risk of BPH and urinary retention. These are empirical concerns based on historical studies, which noted that androgens lead to prostatic growth in the post-pubescent male as described in the previous paragraph. In the late-onset hypogonadal male, the addition of testosterone (even to return levels to a “normal” range) was hypothesized by extrapolation to increase prostatic size and thus worsened of LUTS secondary to BOO. Indeed, in eugonadal men, studies have demonstrated that the prostate can increase in volume by approximately 12%¹⁶ with the addition of testosterone, which is thought may be enough to decompensate a significantly obstructed bladder.

Current clinical guidelines reflect these concerns to varying degrees.^{17–19} The European Association of Urology guidelines¹⁷ warn that androgen deprivation therapy (ADT) is contraindicated in men with severe LUTS (IPSS > 21). They note, however, that this assertion is not supported by strong clinical evidence and that once a man's LUTS is appropriately treated there is no longer a contraindication to TRT.

Despite these long-standing warnings, there has been an increase in the use TRT to treat late-onset hypogonadal males for a variety of symptoms and conditions of older age (decreased libido, fatigue, erectile dysfunction, *etc.*).²⁰ Arising more from concerns of other adverse events from this treatment, in particular possible increase the risk of prostate cancer,²¹ a whole body of literature regarding prostate characteristics in late-onset hypogonadal men being treated with TRT was born and is now in early development.

TESTOSTERONE REPLACEMENT THERAPY AND BENIGN PROSTATIC HYPERPLASIA/BENIGN PROSTATIC ENLARGEMENT

There seems to be little doubt that the treatment with testosterone of a young hypogonadal male leads to significant growth of the prostate. This was reported in hypogonadal males with primary hypogonadism who have significant growth in prostate volume with TRT.⁵ Thirteen men between 25 and 32 years old with Klinefelter's syndrome were treated intramuscular testosterone and found to have an increased in prostate size from 9.3 to 19.0 ml, compared with no change in the control volume of 18.7 ml ($P \leq 0.001$). Similarly, Behre *et al.*²² demonstrated increased prostate volume and prostate-specific antigen (PSA) levels in hypogonadal men to those seen in aged-matched normal men after treatment with TRT.

Most studies, however, have shown no effect of exogenous androgens on PSA or prostate volume for older hypogonadal males.²³ In an RCT of 44 late-onset hypogonadal men, Marks *et al.*¹⁴ found that those treated with TRT did not have a significant increase in prostate tissue levels of testosterone or DHT, despite having significantly increased levels of serum testosterone. More recent evidence from placebo-controlled studies of hypogonadal men receiving androgen therapy, indicate that the differences between those men receiving testosterone and those on placebo were insignificant in regards to prostate volume, PSA and BOO.²⁴

These findings are echoed by Jin *et al.*²⁵ who studied 71 aged matched hypogonadal patients. For younger hypogonadal patients, the zonal and total prostate volumes (TPVs) were significantly smaller than their aged matched eugonadal colleagues whether they were treated with TRT or not. However, from mid-life, central, peripheral and TPV increased with age among healthy controls and men with androgen deficiency regardless of TRT. This demonstrated age is a more important determinant of prostate growth than ambient testosterone concentrations maintained in the physiological range for older men.

Through a retrospective review of publications from 1941 to 2008, Morgentaler and Traish²⁶ have theorized a “saturation model” to explain the lack of effect of TRT on prostate volume or PSA in these men. They argue that the prostate is relatively insensitive to changes in androgen concentration at normal levels or in mild hypogonadism because the AR is saturated by androgens and therefore maximal androgen-AR binding is achieved. Conversely, the prostate is very sensitive to changes in androgen levels when testosterone is low (such as castration or androgen ablation). As expected, a similar curvilinear relationship between serum testosterone and PSA has been demonstrated by Rastrelli *et al.*²⁷ with PSA initially increasing, then plateauing in the low hypogonadal range (8 nmol l⁻¹), with no further increase for higher levels of androgens.

These concepts are an important, direct challenge to those traditional safety concerns regarding TRT and BPH outlined above.

There are also numerous other competing theories for the development of BPH in older men that do not rely on the direct action of testosterone, such as the aromatization of androgens to estrogens, which then bind to estrogen receptors in the bladder and prostate.⁶ Supporting this concept was a study of men over 40 with LUTS (IPSS > 7) by Schatzl *et al.*²⁸ that showed increasing estrogens correlated closely to prostate volume, while increasing serum testosterone did not.

Another concept is an inflammatory cause of BPH, which has been known to directly or indirectly contribute to prostate enlargement since described by Kohnen and Drach²⁹ in 1979. The exact molecular

mechanisms of are beyond the scope of this review, however have been clinically revealed in the medical therapy of prostatic symptoms study. Here, men in the placebo arm whose baseline prostate biopsies demonstrate inflammation were significantly more likely to experience BPH progression and a higher rate of acute urinary retention or BPH-related surgery.³⁰ This was similarly demonstrated in a similar analysis of the data of the REDUCE trial.³¹

Finally, Vignozzi *et al.*³ have more recently hypothesized that BPH is a more complex “metabolic” condition, brought about by an initial insult (likely to be an infection) and perpetuated by poor metabolism (in particular features associated with metabolic syndrome, such as dyslipidemia, hypercholesterolemia and hyperinsulinemia) and/or endocrine abnormalities (hypogonadism and hyperestrogenism). This “multi-hit” scenario leads to the overproduction of growth factors, which lead to prostate remodeling and BPE. The theory attempts to reconcile many of the concepts above, but remains to be fully tested.

TESTOSTERONE REPLACEMENT THERAPY AND LOWER URINARY TRACT SYMPTOMS

Lower urinary tract symptoms in men are traditionally considered the ultimate clinical expression of BPH/BPE due to BOO. Nonetheless, LUTS are a set of subjective and objective symptoms, the causes of which are multifactorial and generally not disease specific. In fact, the natural history of LUTS is complex, and symptoms can wax and wane with time even without any treatment.³²

Although there is no double-blinded RCTs to date, current studies seem to demonstrate that either TRT does not worsen LUTS or that it may, in fact, improve symptoms. This is not a new concept; as early as 1939, Walther and Willoughby³³ used testosterone to treat 15 men with “BPH” with the improvement in their LUTS over 2 years; although this treatment seemed to have been dismissed or forgotten for some time.

A recent retrospective review of a prospective database by Pearl *et al.*³⁴ demonstrated a lack of any relationship between IPSS and ADT in 120 men with a median follow-up of 1 year. In fact, there were just as many men who had improvement of their LUTS (change in IPSS > 3) as who had worsening of LUTS. Furthermore, the duration of treatment did not have any effect on IPSS.

These findings correlate with a prospective, observational registry study by Yassin *et al.*³⁵ of 261 hypogonadal men, in which TRT was associated with a significant improvement in LUTS, even when corrected for phosphodiesterase type 5 inhibitors (PDE5I) use and amount of weight loss. The mean IPSS decreased from 10.35 to 6.58, ($P \leq 0.05$) with a median follow-up of 42.3 months.

Ko *et al.*³⁶ investigated a small subset of 17 patients receiving TRT with moderate LUTS and a $Q_{\max} > 10 \text{ ml s}^{-1}$, who were not taking any BPH medication, and found that their IPSS was significantly improved (both voiding and storage components) although mean change was minimal (IPSS 9 to IPSS 7, $P = 0.028$). There was no change in Q_{\max} or post void residual (PVR).

Shigehara *et al.*³⁷ completed a randomized study of 52 patients with BPH and LUTS and showed that treatment with TRT significantly decreased the IPSS from baseline (15.7 ± 8.7 vs 12.5 ± 9.5 ; $P < 0.05$) at 1 year. There was also a significant improvement in Q_{\max} , but not in PVR.

METABOLIC SYNDROME, LOWER URINARY TRACT SYMPTOMS AND TESTOSTERONE REPLACEMENT THERAPY

There is an increased understanding of links between metabolic syndrome and LUTS. Park *et al.*³⁸ investigated a group of 1224 otherwise healthy police officers, 29% of whom were diagnosed with

metabolic syndrome. When compared with those without metabolic syndrome (and corrected for age and serum testosterone), they had a worse IPSS, larger TPV, and larger PVR volume.

Similarly, Kwon *et al.*³⁹ studied risk factors associated with BPH progression (TPV of $> 31 \text{ cm}^3$, PSA level of $> 1.6 \text{ ng ml}^{-1}$, $Q_{\max} < 10.6 \text{ ml s}^{-1}$, or PVR of $> 39 \text{ ml}$) in men with moderate to severe LUTS and demonstrated a significant association with the increasing number of components of metabolic syndrome. These concepts are reinforced by other studies that demonstrate that in obese men (body mass index [BMI] > 25), only age, increasing total testosterone and sex score were related to their worsening LUTS.⁴⁰

Furthermore, in men with Klinefelter’s syndrome (primary hypogonadism) treated with testosterone to eugonadal levels, only men with a waist circumference $> 94 \text{ cm}$ had a significant increase in prostate size;⁴¹ the implication being that visceral obesity (one of the most significant components of metabolic syndrome) is associated with prostate volume and influences prostate growth during TRT.

An intimate relationship between metabolic syndrome, hypogonadism, and LUTS has also been demonstrated in animal models. Vignozzi *et al.*⁴² showed the presence of prostate and bladder inflammation in rabbits with metabolic syndrome; this inflammation was exacerbated when the rabbits were made hypogonadal and returned to baseline when they were treated with testosterone. This hypothesis of inflammation induced LUTS is also argued to be a mechanism for improvement of LUTS with PDE5I.⁴³

The concept, therefore, that treatment with TRT of hypogonadal males with metabolic syndrome might lead to improvement/stabilization of their LUTS, appears to be confirmed in recent work by Francomano *et al.*⁴⁴ They published data in which 20 obese, hypogonadal men with metabolic syndrome were treated with TRT and followed for 5 years. Compared to matched controls, there was no difference between the two groups in terms of IPSS, Q_{\max} , PVR or prostate size. In fact, the TRT group (with moderate baseline LUTS) had stable LUTS throughout the period and had fewer episodes of prostatitis ($P < 0.01$) than the untreated group. There was also an improvement in components of the patient’s metabolic syndrome (such as BMI, waist circumference, hemoglobin A1c [HbA1c], insulin sensitivity, and lipid profile) as well as inflammatory markers and C-reactive protein. They concluded that TRT was safe in this group of men, and hypothesize that TRT mitigates the pro-inflammatory factors associated with metabolic syndrome.

QUALITY OF LIFE AND TESTOSTERONE REPLACEMENT THERAPY

The presence of BPH is known to substantially reduce the quality-of-life.⁴⁵ The treatment of hypogonadal males with testosterone has also been shown to improve health-related quality-of-life,⁴⁶ primarily due to improved erectile function and muscle/joint pain. Unfortunately, in a short term study by Takao *et al.*⁴⁷ there was no difference in quality of life indices or LUTS in 21 men treated with TRT after 3 months.

PATIENT ASSESSMENT

The possibility of a significant relationship between testosterone, testosterone replacement and LUTS/BPH mandate the urologist consider these factors when patients are being investigated for LUTS.

The focused history should enquire for symptoms of hypogonadism, as well as symptoms that may reveal the presence of metabolic syndrome. The physical examination should make note of the patient’s BMI and physical signs of hypogonadism. Obesity in patients with LUTS was found to be significantly prevalent in men with low testosterone.⁴⁸

Investigations to be performed, aside from the usual LUTS workup, may include serum testosterone, HbA1c, and fasting serum glucose. The biochemical diagnosis of hypogonadism should be made carefully, as there are significant intra-individual fluctuations in testosterone levels⁴⁹ and no accepted cut-off that defines “low testosterone”. At least separate two measurements of serum testosterone should be taken to confirm any biochemical diagnosis of hypogonadism.

Finally, testosterone replacement should only be considered for symptomatic hypogonadal men after full clinical assessment and correlation. Despite this obvious caveat, numerous men are still treated for symptoms of hypogonadism with either normal serum levels or without level having been checked at all.⁵⁰

RESEARCH PENDING/OPPORTUNITIES

Unfortunately, the lack of large prospective RCTs makes the application of evidence-based medicine in this area difficult for urologists and their patients.

The challenge for the basic science and clinical researcher is to determine the real effect of TRT on BPH for hypogonadal men, while identifying those patients who may be harmed from such a therapy. Unfortunately, as Francomano *et al.*⁴⁴ point out, the economics of performing such a large RCT in this area are prohibitive.

There is also a need for further basic science research into the exact mechanisms of prostate growth, the effect of testosterone (or lack thereof) and its relationship to LUTS.⁵¹

CONCLUSIONS

While packet warnings still remain, and there is no high-level evidence to support either position, patients should be warned regarding potential worsening of LUTS if treated with testosterone. Despite this, there is emerging evidence that testosterone plays an important part in the role of treating BPH/LUTS in the aging male.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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