

Testosterone replacement therapy and voiding dysfunction

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Abstract: Testosterone replacement therapy (TRT) represents an increasing popular treatment option for men with late-onset hypogonadism (LOH). Because of unsubstantiated beliefs of testosterone's effect on the prostate, the FDA has recently placed a warning on testosterone products, stating that TRT may worsen benign prostatic hyperplasia (BPH). Within this review article we have demonstrated the current understanding of the physiology of testosterone and its relationship with prostatic and lower urinary tract physiology. The current evidence suggests that not only does TRT not worsen lower urinary tract symptoms (LUTS), but that hypogonadism itself is an important risk factor for LUTS/BPH.

Keywords: Benign prostatic hyperplasia (BPH); lower urinary tract symptoms (LUTS); testosterone replacement therapy (TRT); hypogonadism

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Introduction

Lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH) represents a spectrum of urinary symptoms including urinary frequency, urgency, weak stream, straining to void, intermittency, and nocturia. These symptoms are not only significant identifiers of overall health, but they also have a major impact on quality of life (1-3). It is a commonly held notion that BPH is the source of LUTS for most men, though in reality BPH is thought to be the source of LUTS in only 8% to 31% of men in their fifties. This number increases with age to 27% to 44% by the time men reach their seventh decade of life (4,5).

Along with LUTS/BPH, hypogonadism is another medical problem that many men deal with during their lifetime. Hypogonadism can be broken down into primary (testicular) or secondary (central) depending on reason for low testosterone (T). This article focuses on "late-onset hypogonadism" (LOH), in which men have low serum testosterone (total T less than 11 nmol/L or free T less than 0.225 nmol/L) and at least three sexual symptoms

(including low libido, impaired erections, and decreased morning erections) (6). It is estimated that the prevalence of hypogonadism ranges from 6.0% to 12.3% in men aged 40 to 69 years of age, and an estimated 2.4 million men in the United States suffer from androgen deficiency (7). Testosterone replacement therapy (TRT) is the gold standard treatment for LOH and is a proven way to help reduce or eliminate these symptoms and lowers the risk of developing associated medical conditions such as obesity and type II diabetes (8,9).

With the known increase in size of the prostate that occurs with age, which is at least partially dependent upon the presence of androgens, there has been a concern raised that androgen replacement therapy could theoretically worsen LUTS by increasing prostate size. This concern resulted in the FDA issuing a warning stating that TRT in men with BPH puts patients "at an increased risk for worsening signs and symptoms of BPH" (10). This review looks to explore the correlation between hypogonadism and LUTS/BPH by reviewing relevant pathophysiology and emerging evidence of TRT's effects on LUTS.

Testosterone and the lower urinary tract

Derived from cholesterol, testosterone is a highly protein bound lipophilic molecule. About 98% of testosterone is bound to albumin and sex hormone binding globulin (SHBG), and only free testosterone and that bound to albumin are biologically active in the body. Beginning in puberty, testosterone levels increase to a peak and plateau as men hit their 2nd and 3rd decades of life. Testosterone is released in an irregular, pulsed fashion (nyctohemeral), causing levels to fluctuate throughout the day, with a peak most often occurring in the early morning (11). Because of this variation it is recommended that testosterone levels be drawn in the morning, as it most accurately represents testosterone peak. With aging comes a blunted diurnal variation of T release, particularly after the age of 45 (12).

After the testosterone plateau in the 2nd and 3rd decade of life there is a steady decline in total testosterone, by approximately 1% per year. There is also an age-related increase in SHBG, which changes in a larger magnitude than testosterone (13,14). This results in the bioavailable testosterone decreasing by approximately 2–3% annually (15). Because of this, 30% of men greater than the age of 70 meet criteria for LOH (16).

The effect of testosterone on the lower urinary tract in men cannot be understated. This effect with the production of testosterone by Leydig cells in utero after gonadal sex has been determined by the presence or absence of sex-determining region Y chromosome (SRY). Lower urinary tract structures derived from the Wolffian duct (seminal vesicles, epididymis, vas deferens, and ejaculatory ducts) develop as the result of testosterone. Via the enzyme 5- α -reductase, testosterone is also converted to dihydrotestosterone (DHT), which is responsible for the development of prostate, penis, and scrotum. In animal models, the urothelium of the urinary bladder as well as autonomic neurons of the pelvic ganglia were found to be important expressers of androgen receptors (17-19). Pelvic ganglia are important modulators of pelvic autonomous neurons supplying smooth muscle of the lower urinary tract, and testosterone has been found to be important in autonomic receptor-mediated function of these pelvic ganglia (5,20).

Testosterone has also been found to be an important modulator of nitric oxide (NO) production as testosterone regulates nitric oxide synthase (NOS) (21-23). Thus, decreased testosterone can lead to decreased NO. With reduced levels of NO, a potent regulator of prostatic

innervation and smooth muscle tone come increased pelvic smooth muscle tone. Interestingly, it is believed that NOS signaling is altered in patients with BPH, and thus lower NO levels result in more severe LUTS (24). Accordingly, NOS expression has been shown to be reduced in the prostates of men with BPH compared to that of normal prostate tissue (25). Pelvic ischemia and chronic hypoxia of the bladder is also believed to be an important factor in the development of LUTS/BPH (26,27). The smooth muscle relaxation properties of NO also applies to pelvic vasculature, as increased NO levels have been found to help relieve pelvic ischemia via pelvic arterial dilation (5).

Phosphodiesterase-5 (PDE-5) inhibitors are effective in the treatment of BPH/LUTS via several mechanisms (28-30). PDE-5 is expressed in numerous tissues in the lower urinary tract including the bladder, prostate, and pelvic vasculature (31). By hydrolyzing cyclic guanosine monophosphate (cGMP) PDE-5 reduces NO production via modulation of NOS. Thus, PDE-5 inhibitors upregulate NO. The interplay of NO, PDE-5, and LUTS offers a scientifically sound explanation as to why daily PDE-5 inhibitors are effective in alleviation of LUTS symptoms, and it is via this pathway of cGMP modulation that testosterone levels can influence LUTS (29).

Hormone levels in the prostate

Serum levels of testosterone and DHT can be manipulated with administration of either agent. However, intra-prostatic levels of both testosterone and DHT appear to be much more recalcitrant to change. Testosterone and DHT levels in normal prostatic tissue vary between 0.26 to 1.8 ng/g tissue for testosterone and 0.7 to 9.3 ng/g for DHT. van der Sluis *et al.* found no difference in the prostatic concentration of T or DHT in patients with or without BPH (32). Other studies by the same author showed stable intraprostatic DHT levels even after castration (33). Marks *et al.* gave hypogonadal men testosterone and produced significant changes in serum T and DHT concentrations at 6 months, however prostate concentrations of both T and DHT remained unchanged (34). Page *et al.* gave men varying concentrations of DHT and found no change in intraprostatic DHT levels despite serum levels of DHT as high as seven times normal (35). Additionally, a prostate saturation model suggests that T levels at about 150 ng/dL produce maximum testosterone effect due to completely utilized androgen receptors (36). If the serum level of testosterone is dropped low enough (castration), intraprostatic levels of T can be lowered and

the prostate becomes hypotrophic (37). In this scenario, return to normotrophic prostate size can occur with T re-administration. When the prostate returns to its genetically inherent size, PSA levels may rise and LUTS may or may not occur. If LUTS do occur, standard LUTS therapy with oral agents may be initiated and T continued (presuming the T is effective in treating the original LOH symptoms). An understanding of the prostate saturation model and the buffered nature of prostate androgen levels helps dispel the assumption that T causes LUTS. This is incorrectly inferred from the fact that castration and 5- α -reductase inhibitors (5ARIs) can decrease prostate size and alleviate LUTS.

Testosterone/DHT and Inflammation

The role of testosterone and DHT as anti-inflammatories is a burgeoning field and warrants special mention within this article. Testosterone's role in inflammation is particularly interesting because of the established role of inflammation with LUTS/BPH (38,39). Several papers have discussed the role of chronic inflammation in the development of BPH, which may be modulated by the hypogonadal state (10). Accordingly, hypogonadism has been shown to result in increased adhesion molecules (ICAM, VCAM, and E-Selectin), CRP, fibrinogens, interleukins, chemotactic proteins (MCP-1), and increased apoptosis (40).

As discussed earlier, testosterone is converted to the more potent DHT via 5- α -reductase, which is highly concentrated in the prostate. It is through the blocking of this enzyme, and ultimately lowering DHT, that 5ARIs such as finasteride work. Blocking 5- α -reductase results in markedly diminished intraprostatic DHT levels, which has been shown to decrease prostatic volume by 25%, and this is believed to be the reason behind the utility of 5ARIs (41,42). However, this does not tell the entire story. There have now been a number of studies which show a link between decreasing DHT levels and increasing inflammation. In a study of prostatic tissue samples obtained at time of TURP for 64 men divided into those taking 5ARIs and those who were not, Fan *et al.* found that 5ARI usage was associated with significantly more CD8⁺ T cell infiltration into the prostate. This study suggested intraprostatic DHT was important in the regulation of the inflammatory response induced by the prostatic epithelial cells (43). This is important for a number of reasons, namely that increased intraprostatic inflammation has been associated with increased total prostatic volume. Wu

et al. examined 105 prostatectomy specimens (either from transurethral resection or suprapubic prostatectomy in men treated for BPH) and gave the specimens an inflammation score based off of the presence of CD4, CD8, and CD20. The study found a strong association between inflammation and total prostatic volume, serum PSA, and AR expression, again suggesting that inflammation may contribute to BPH progression (44). Further research is needed to reconcile why ARIs cause both more prostate inflammation and improvement in LUTS through size reduction. It is possible that the degree of prostate shrinkage trumps increased inflammation. Alternatively, irritative and obstructive voiding symptoms may have different physiologic underpinnings. This theory is supported by the fact that PDE5 inhibitors do not improve urinary flow rates. Or, discrepancies in alteration between serum and prostate androgen levels may offer some explanation. One prospective study of 20 years found that increased serum DHT and testosterone levels in midlife were protective against LUTS (45).

LUTS/BPH and TRT

With the established warning that TRT in men with BPH puts patients "at an increased risk for worsening signs and symptoms of BPH" by the FDA, comes the need for a reexamination of the currently available evidence. The warning issued by the FDA appears to be based a belief that testosterone replacement will increase the size of the prostate, and accordingly worsen symptoms of BPH. There are two main issues with this thinking. The first being that testosterone replacement does not increase prostate size and the second issue being that increased prostate size does not correlate with worsening of LUTS/BPH.

It is a commonly held belief, even amongst physicians, that prostate size and growth is directly correlated with testosterone. This is likely the result of papers published by Huggins *et al.* in the 1940s in which castration caused prostate cancer (PCa) regression, and T administration caused increased PCa growth (46). This sentinel paper in urology revolutionized the way PCa is treated, but we would caution applying this T-dependent model of prostatic growth beyond that of PCa. Certainly, as discussed before, testosterone is important in the development of the prostate, and the prostate has a large number of androgen receptors, but T-dependent growth may not be a foregone conclusion as it was previously believed. Numerous research studies in both animals and humans suggest that these receptors are

completely saturated at near castration serum testosterone levels (approximately 50 ng/dL) (36). As such, young men with the maximum T in their lifetime do not develop large prostates and develop LUTS/BPH (47). Instead, prostatic size steadily increases with age despite lowering levels of testosterone (48,49). In fact, there are numerous interesting studies that have given men testosterone, even resulting in very high supraphysiologic T levels, which resulted in no change in prostate size (50-54). Cui and Zhang did a systematic review on this topic resulting in the inclusion of 16 randomized controlled trials consisting of a total of 1,030 patients. This study found that both short and long term TRT, regardless of route of administration, were not associated with increased prostatic growth (55).

The second major flaw to the FDA warning is the assumption that increased prostate size would result in worsening of LUTS/BPH. As has been shown in numerous studies, prostate size likely has little to no correlation with severity of LUTS/BPH symptoms. Barry *et al.* prospectively enrolled 198 men to study this relationship. This study found that there was no correlation between LUTS symptom severity, uroflowmetry, post-void residual urine volume, or degree of bladder trabeculation with prostate size (56). Instead, LUTS symptom severity was found to be only significantly correlated with lower overall health status which interestingly, has also been associated with decreased testosterone levels in multiple studies (57-60). A lack of correlation between prostatic volume and LUTS symptom severity was also seen in a study of 45 men by Castro *et al.* In this study, prostatic size was correlated with an increase in urethral resistance during micturition, but this did not result in worsening of symptoms (61). In contrast to these studies is a secondary analysis of the Medical Therapy of Prostatic Symptoms (MTOPS) study, in which Crawford *et al.* found that men with a prostate volume of >31 mL had a higher risk of BPH progression than men with prostates <30 mL (62). Of note, this was in a population of men with existing International Prostate Symptom Score (IPSS) ≥ 8 and BPH progression was defined as a ≥ 4 point increase in IPSS, acute urinary retention, incontinence, renal insufficiency, or recurrent urinary tract infections.

The ultimate question becomes, what is the evidence that TRT causes worsening of LUTS/BPH? Fortunately, there have been several studies examining the relationship of prostatic size and LUTS in hypogonadal men receiving TRT, all of which have indicated that there was no significant increase in prostate size or LUTS with testosterone replacement. Kohn *et al.* recently published a

systematic review in which randomized controlled trials of TRT for LOH were compiled. This resulted in inclusion of 14 clinical trials which reported International Prostate Symptom Score (IPSS) data with TRT. These trials showed no significant difference in IPSS scores amongst men receiving TRT versus placebo (63).

While not only has TRT been found not to worsen LUTS, there is evidence that TRT may actually improve LUTS. In a study of 28 men with sexual dysfunction and metabolic syndrome treated for 12 months with long acting testosterone undecanoate, Saad *et al.* found a significant improvement in IPSS scores from 13.4 to 10.5 (64). A significant reduction in IPSS scores was also seen in a study by Yassin *et al.*, in which 261 men with LOH were treated with TRT and followed for 5.5 years (65). Both of these studies saw improvement in obesity amongst patients, which likely contributed to their improvement of LUTS, but there is also the possibility that testosterone induced NO smooth muscle relaxation played a role as well.

Nocturia

Of all the LUTS experienced by men, nocturia is one that probably deserves special mention. Defined as waking during a time of intended time of sleep because of a desire to urinate, nocturia represents a rather common urologic condition that affects patients of all demographics. From the BACH trial, Fitzgerald *et al.* surveyed 5,502 men and women between the ages of 30 and 79 and found the incidence of nocturia (>1 void per night) to be 25.2% in men and 31.3% in women (66). Not only is it relatively prevalent, nocturia is also very bothersome to patients, as it has been associated with increased depressive symptoms, worse sleep, and increased fatigue (67,68).

Nocturia has not only been found to affect quality of life, but it may also affect quantity of life. In a very large study of 15,988 men and women, the third National Health and Nutrition Examination Survey (NHANES III) found nocturia (defined as 2 or more voiding episodes per night) to be a strong predictor of mortality with a hazard ratio of 1.54 in men and 1.28 in women (69). This hazard ratio increased from there with increasing number of voids per night and when stratified by comorbid conditions. In another study following 784 individuals over the age of 70 for 5 years, those with nocturia were significantly more at risk of skeletal fractures and death, even when adjusting for a number of cofounders such as comorbidities and hypnotic usage (70).

As demonstrated by Liu *et al.* in a study of 632 diabetic

men, those men with the lowest testosterone levels (2.21 ± 0.51 ng/dL) had the highest prevalence of nocturia, and it was more likely to be severe (≥ 3 times per night) (71). As expected from the previous discussion, those with severe nocturia had mortality 3 times that of men without severe hypogonadism at 3.5 years follow-up. Interestingly, the relationship between nocturia and testosterone likely goes both ways. In a study of 62 men with LOH, Kim *et al.* found that treating nocturia with desmopressin for 12 weeks actually increased serum testosterone levels significantly (72). It is postulated that the frequent awakenings at night associated with nocturia interferes with the natural circadian rhythm resulting in blunting of nocturnal testosterone production (73).

Given this information, it would stand to reason that TRT may improve nocturia. This was demonstrated in a study of 64 men with nocturia and hypogonadism. Using the IPSS and Aging Male Symptoms (AMS) score, Shigehara *et al.* found that at 6 months, TRT with 250 mg of testosterone enanthate every 4 weeks was associated with decreased nocturia, improved sleep conditions, and improved quality of life (74). Whether or not this improvement in nocturia results in increased survival remains yet to be studied.

Conclusions

The FDA mandates a black box warning on testosterone products stating that TRT in men with BPH increases the risk of “worsening signs and symptoms of BPH”. We have discussed testosterone’s role in the development of the lower urinary tract and physiological effects of testosterone throughout a male’s lifetime. As explained through the saturation model of androgen binding and verified in numerous studies, it has been shown that TRT does not change prostate size. On the contrary, testosterone was shown as an important modulator of lower urinary tract function, and TRT probably exerts a positive effect on LUTS/BPH. Based off of the current evidence, it is likely not harmful to give testosterone to men with LUTS/BPH, but rather, TRT may actually be beneficial.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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