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REVIEW

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Updates on androgen replacement therapy and lower urinary tract symptoms: a narrative review

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ABSTRACT

Lower urinary tract symptoms (LUTS) are caused by higher tension at the bladder neck level (due to fibrosis or stiffness) or benign prostatic hyperplasia, which causes static obstruction of the bladder outlet. Both forms cause a group of symptoms such as hesitancy, intermittency, weak stream, nocturia, urine frequency, and urgency. Additionally, LUTS (obstructive or irritative symptoms) are common in elderly men with hypogonadism, identified as the reduced testes capability in producing sex steroids and sperm, and are categorized as testosterone deficiency. Even though the mode of action (MoA) of testosterone therapy (TTh) on hypogonadal men needs more researched and understanding, the effectiveness of TTh in the development of male genital organs has been reported in several studies. This review shows the latest updates of TTh in LUTS including potential adverse effects, advantages, and disadvantages.

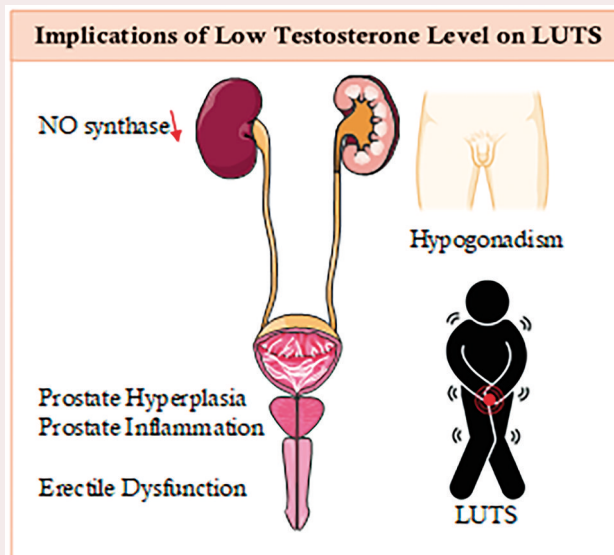
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GRAPHICAL ABSTRACT



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Introduction

The earth's population is indeed aging, and there are many age-related health concerns in men have become obvious over the last two decades. One of the current attracting awareness is the significant incidence of symptoms in aging males with hypogonadism such as weariness, loss of libido, lack of physical strength, erectile dysfunction (ED), depression, and visceral obesity, which are all known to be caused by testosterone deficiency (TD) [1–4]. In aging men, there is a steady reduction in the levels of testosterone [5]. This has shown to lead to many clinical and major biological conditions that have been associated with low levels of testosterone (T) such as ischemic heart disease, hypertension, diabetes mellitus, hypercholesterolemia, and osteoporosis (Figure 1) [6–9].

Lower urinary tract symptoms (LUTS) are sequences of benign prostatic enlargement (BPE), or dynamic tension at bladder neck level leading to symptoms (obstructive, irritative, or both), The symptoms include intermittency, weak stream, hesitancy, urine frequency, nocturia, and urgency [10,11]. Many researchers have investigated testosterone's role in male genital organs in terms of differentiation and development in prolonging good physical health [12].

Even though several investigations were studied on the association between sex hormones and benign prostatic hyperplasia (BPH), few of them have reported the association between LUTS symptoms and circulating testosterone. Hypogonadism was observed in 20% of aging men with LUTS, but without any effect on the status of symptoms [7,13]. For instance, Litman

et al. published a survey study on the possible association between testosterone and LUTS symptoms. Even though they reported good findings in terms of sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEAS), dihydrotestosterone (DHT), and oestradiol (E2), it was concluded that circulating levels of sex hormones are not significant predictors of urological symptoms and perhaps other factors control the pathophysiology of LUTS in hypogonadal men [14]. Furthermore, looking at LUTS and serum sex steroid hormones, there seems to be no associations between LUTS symptoms with total and calculated free testosterone, however, there seem to be some links with androstanediol glucuronide, a dihydrotestosterone metabolite, and estradiol [11].

Low T levels were found to be inversely correlated with urethral closure and detrusor pressure with maximum flow in patients with clinical bladder outlet blockage and also increased detrusor overactivity [15].

Overall, it was proven to be difficult to link plasma testosterone (T) and LUTS. However, it is worth noting that in elderly males, both symptoms and signs of TD do not correlate consistently to testosterone concentrations [16]. This could be explained (in part) by androgen receptor characteristics that were believed to be influenced by the number of CAG repetitions [17].

The side effects of TD and the positive effects of testosterone therapy may be oblique. This review aims to show the latest updates of TTH in LUTS including potential adverse effects, advantages, and disadvantages. It shows the positive effect of regulating levels

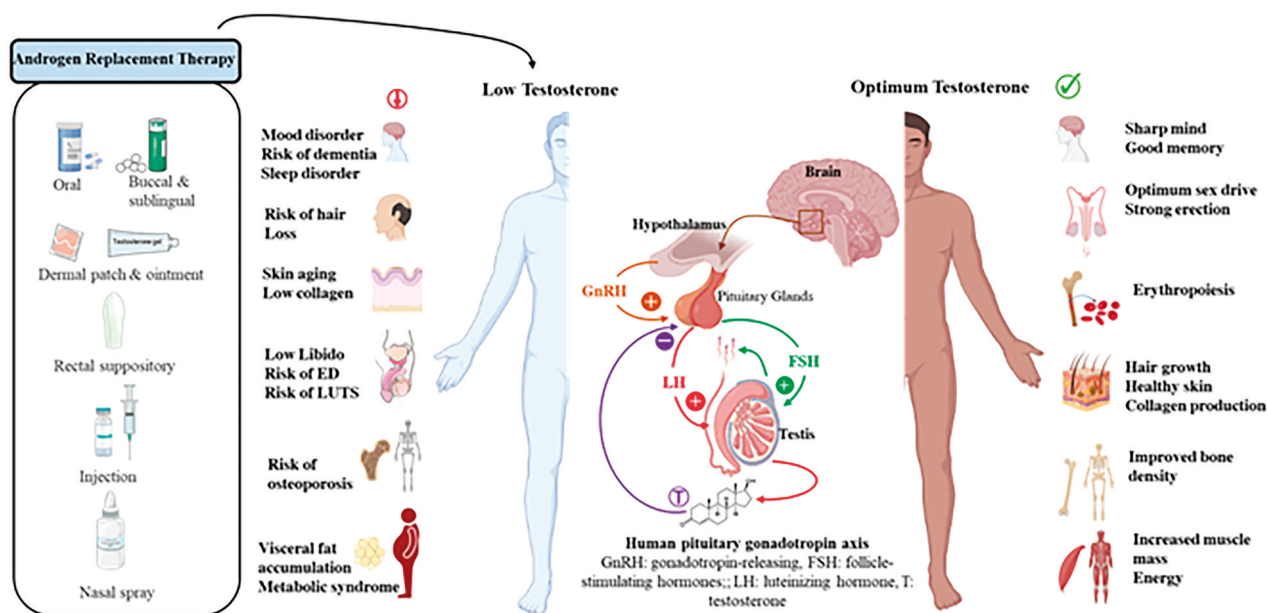


Figure 1. Implication of testosterone in men's health.

of testosterone in elderly men on metabolic syndrome (MetS) variables as well as the International Prostate Symptoms Score (IPSS) [18] scores and with no scientific evidence that TTh could worsen LUTS in men with hypogonadism.

Areas of concentration

Metabolic syndrome and LUTS

Even though the exact association and link between LUTS and MetS is still not completely clear, findings of fast developed LUTS symptoms or normally BPE surgery with men experiencing metabolic alterations support this possible hypothesis.

Pashootan et al. reported an observational cohort study on 4666 European men to investigate the association between MetS and LUTS and revealed a strong association in frequency and severity between LUTS and BPH and metabolic syndrome [19]. Other reports attempted to further clarify some epidemiological relationships between LUTS and MetS and found that metabolic syndrome is linked to autonomic nervous system overactivity [20,21]. Although the vegetative nervous system and its overactivity are perhaps not to be the actual cause of LUTS, it majorly acts in progressing the level of severity in LUTS in addition to the intrinsic basal intensity, which is found to cause LUTS by the pathophysiological characteristics and genitourinary anatomical [22]. In addition, Ullrich et al. published a study and found an association and evidence that stress is mainly associated with the progression of prostatic disease [23]. Accordingly, higher BMI, age, in addition to a greater diastolic blood pressure reactivity were also found to be related to the postvoid residual bladder volume, total prostate gland volume, larger transition zone, in addition to more severity in LUTS [23]. Inflammation penetrates are usually detected around and in the nodules for both benign and symptomatic BPH [24]. Furthermore, metabolic syndrome could be the intermediary of this relationship and is possibly associated with a higher concentration of blood C-reactive protein, a non-specific measure of inflammation [25]. Therefore, the relationship between the higher circulating C-reactive protein concentrations and metabolic syndrome to LUTS may be the direct indication of the symptomatic BPH intraprostatic inflammation [24,25]. Central obesity is also known as the key core of metabolic alterations, and therefore, increased abdominal adiposity contributes to hypertension, insulin resistance, dyslipidemia, type-II diabetes, and impaired glucose metabolism. Moreover, El-Sakka et al. found a solid link

between low total testosterone levels and dehydroepiandrosterone sulfate (DHEA-S) in patients with badly controlled type-II diabetes [26].

In addition, insulin resistance is mainly related to hyperinsulinemia, which contributed to the developing of cancer *via* a growth-promoting effect [27,28]. This could be a contributing factor in aging men's prostate development [27]. Clearly, normalizing T levels have been shown to modulate insulin sensitivity in hypogonadal men with or without noticeable changes in body composition [29].

Although the elements of metabolic syndrome were found to be contributed to more development of LUTS and ED. ED risk factors and medical comorbidities were found to be common among LUTS patients [30]. Consequently, it is not unexpected with the growing number of studies that have been published to find an association between ED and LUTS [31,32]. In addition, a possible underlying association of vascular with LUTS and ED can be also denoted [33]. Other studies reported that a decrease in plasma testosterone levels, which is known as age-related, is found to be central to obesity and ED among aging men improved by restoring T to normal levels [34–38]. Therefore, it is worth looking at the association of LUTS with late-onset hypogonadism (LOH), which is expected to appear, like the other disorders discussed, in the lives of senior men above 65 years at the same time.

Effects of testosterone on LUTS

Testosterone may not be the "primary mover" behind the effects of testosterone on urinary tract systems that are functionally and physically linked to LUTS. The indirect association could obscure the interrelationship between symptoms of LUTS and testosterone levels that is biologically feasible.

Androgen receptors were discovered in considerable quantities in the urethral and bladder epithelial cells [39,40]. Other researchers have assumed that suppressing detrusor activity is the impact of testosterone on postsynaptic non-genomic receptors [41,42].

Juan et al. reported a study on the role of castration (androgen deprivation) on lower urinary tract tissue enzymes of male rabbits and investigated the activities of citrate synthase-thapsigargin sensitive Ca^{2+} ATPase, and choline acetyltransferase as markers [43]. They found that Ca^{2+} ATPase in the control corpora was higher than what was found in the control bladder or urethra. It was concluded that the differences significantly presented within the activities of

Mitochondria, ATPase, and Choline acetyltransferase in the lower urinary tract associated organs. Studies that treated one illness (e.g. ED) in elderly men while also monitoring the role of others (e.g. LUTS) should agree on the consolidation of this link. However, a complete image of the influence of T on the lower urinary tract needs more investigation [44].

The impact of testosterone on the bladder was first reported by Holmäng et al. [45] and found that in the testosterone-treated group, the urinary flow was increased in the mean volume of urine compared to the placebo treated group. There has been initial evidence on LUTS and testosterone benefits for men according to positive results on data recorded on normalizing testosterone levels in hypogonadal males with BPH and LOH [44]. Kalinchenko et al. found that testosterone treatment in men with SLOH positively affects bladder functions, which include decreasing detrusor pressure and increasing bladder capacity and compliance [46]. A pilot study supports these findings as well, the study investigated the impact of testosterone undecanoate (TU) or TTh in hypogonadal men having LUTS with LOH [47].

Even though other reports did not study the direct effect of testosterone therapy and LUTS and looked at testosterone therapy and the International Prostate Symptoms Score (IPSS) [44], their findings showed some great advantages of TTh among the aging male. Accordingly, Saad et al. reported the effects of TU for more than 12 months and showed positive effects on IPSS and metabolic syndrome [48]. Another study reported the testosterone gel (T gel) effectiveness for more than 9 months and revealed that higher plasma levels of testosterone that reduced the IPSS score were shown with T gel (50 mg/day) than with TU/TTh. This can possibly relate to the plasma levels of testosterone on LUTS [49]. Furthermore, Okada et al. reported an improvement in LUTS among Japanese men with LOH after 6 months of taking TTh [50].

All these studies showed that there were great benefits of using TU (50 mg/day) and testosterone gel in metabolic syndrome and in the IPSS. Additionally, there was also a better improvement in the IPSS for hypogonadal patients given TU/TTh after T gel treatment alone for 9 months period [44].

Nitric oxide synthase in the urinary tract

Nitric oxide (NO), known as a non-cholinergic neurotransmitter, is reported to relax smooth muscles in both animals and humans is found in the genital tissues and the urinary tract [44]. According to a human

study by Ehrén et al., NO is reported as a micturition reflex and as an essential nerve-induced mediator of erection that works on the dilatation and erection of the bladder neck and urethral. Moreover, NO is also reported to be part of several other processes such as the human urogenital tract [51].

NOS appears to be presented in up to 96% of neurons in the bladder wall in humans. The bladder body's detrusor muscle has moderated innervation from nitric oxide synthase-immunoreactive nerve terminals, while muscles in the urethral were found to have a stronger innervation. NO could have also a major role in bladder neck relaxation as an inhibitory transmitter [52].

Cyclic nucleotides are key nitric oxide secondary messengers that modulate the contraction of different muscles. Phosphodiesterases (PDEs) have an essential part in the regulating process of cyclic nucleotides, their action length and existence in the urine bladder in human was also reported [53,54].

For instance, Qiu et al. reported a study that looked at PDE5 activity and expression in the bladder. Authors found the role of PDE5 in modulating the bladder smooth muscle tone and accordingly, PDE5 is known as a nitric oxide/cGMP signaling inhibitor [55]. Furthermore, Vardenafil appears to inhibit PDE5 activity, suggesting that it could be used to treat irritative LUTS [55]. In addition, Filippi et al. reported that castration in the rat bladder is found to reduce PDE5 gene expression, but testosterone treatment restored it [56].

NO-synthase proved to be androgen-dependent in the rat urogenital tract, adding to the evidence for androgens' role in the urogenital tract [57]. Meanwhile, several reports have conclusively shown that phosphodiesterase inhibitors help those patients with LUTS [58,59].

From the foregoing, androgens appeared not only important for the prenatal formation of the urogenital tract and puberty development, but also for maintaining the functionality of the urinary tract system in adulthood, like the penis erectile tissue. Therefore, the discomfort experienced by elderly men with micturition may be due to the decrease in testosterone levels as they age.

LUTS, androgens, and prostatic inflammation

Several immune cells exist in the prostate tissue that are immunocompetent such as granulocytes, lymphocytes, and macrophages, which upon activation can introduce a chronic immune response to persisting

inflammations. T is known to help the main cytokines, for example, interleukin (IL)-2 and lymphocytes secrete interferon (IFN)-I, which are known to exist in the early phase of BPH [60]. Furthermore, IL-17 and IFN-c, which are generated by macrophages and Lymphocytes, stimulate chemokine production using stromal cells, and therefore, induce BPH development and prostate cell proliferation [61,62]. The increased IL-6 and IL-8 secretion by prostate stromal cells, which are significant features in prostate hyperplasia, are known to be related to the increased levels of IL-17 [63]. Several reports revealed that men having prostatitis are at a higher risk of LUTS, and therefore, this inflammation could be principal to BPH development [64,65]. For instance, Vignozzi et al. studied prostate inflammation by having low testosterone levels and high estrogen levels in male rabbits with metabolic syndrome (MetS) and concluded that hypogonadism has a major impact on prostate inflammation and its development [66,67]. In line with other reports, testosterone therapy could reduce inflammation and prevent further development of LUTS in men diagnosed with prostate inflammation and hypogonadism [66,68–70].

Temporary interruption of TTh

LUTS are known to be associated with hypogonadism in addition to other common conditions such as obesity, Ed, hypertension, CVD, and depression. Testosterone treatment therapy improves the hypogonadal patient's metabolic factors and the withdrawal, or any interruption converses these benefits [71,72]. Clinical guidelines recommend men with hypogonadism be treated with TTh for a specific period such as 3 months/6 months/12 months and until benefits are achieved [73]. Long-term treatment of testosterone therapy for 12 months may not be enough for achieving the maximum benefits of TTh [72]. In addition, erectile function substantially improved for up to 9 years, although the stabilization of AMS after 2 years of treatment. It is recommended that patients, who were under TTh for up to 12 months and did not gain benefits continue for longer periods.

TTh in hypogonadal men improves residual bladder wall thickness, voiding volume, CRP, AMS, IPSS, and adiposity parameters, however, prostatic enlargement progressed with time, and the PSA also slowly raised accordingly [70]. Interestingly, interruption of TTh replacement caused a deterioration of residual voiding volume, obesity parameters, and bladder wall thickness increased, AMS, and IPSS scores were also worse. It is clear that men are reliant on maintaining a

physiological level of testosterone, and reducing the levels, leads to a deterioration of symptoms and worsening of the obesity state, with its consequences.

Improving LUTS independent of prostate size

Prostatic enlargement secondary to benign hyperplasia is one of the major causes of LUTs. The relationship between LUTs and testosterone is well-documented. Approximately 20% of men with hypogonadism experienced LUTs. If the LUTs severity is related to the levels of testosterone, then the restoration of T levels to the physiological levels using TTh would expect to change enzymes in the urinary tract tissue, and other pathology related to low levels of testosterone such as local ischemia and fibrosis. However, increased prostate volume and worsening urine function remain the main concern with TTh in elderly men and LUTS patients.

A study investigated the impact of TTh on LUTs with hypogonadism [50]. Sixty hypogonadal men were involved in this study and were injected with 250 mg of T. No statistically significant alterations were observed after the TTh treatment in residual urine volume, BMI, and prostate volume. In addition, LUTs and particularly storage symptoms among the control group were significantly improved 6 months after TTh. It was concluded that the improved LUTs parameters appeared to be independent of prostate volume and others such as AMS and IIEF-s scores.

The safety of long-term TTh improves the voiding function, despite the prostatic size, and interruption worsens or reverts the improvement [71,74,75].

Conclusion

Men tend to experience LUTS and other alignments like erectile dysfunction (ED) and metabolic syndrome very commonly and particularly in the aging male population. The association between LUTS and testosterone levels on an epidemiological level may be indirect. However, the autonomic nervous system overactivity may be related to the connection of LUTS to metabolic syndrome. Additionally, LUTS can be related to the genitourinary anatomical/pathophysiological characteristics, which is why it may become severe because of the autonomic nervous system overactivity. Long-term testosterone is found to be effective and safe for males' metabolic outcomes. This review showed the positive effect of normalizing levels of testosterone in aging men on metabolic syndrome variables as well as the IPSS scores and with no

scientific evidence that TTh could worsen LUTS in men with hypogonadism. TTh has been used worldwide as a therapy to treat testosterone deficiency with increasing evidence and benefits. Nevertheless, more randomized and controlled research and clinical trials are needed to further support the use of TTh in treating men with both severe LUTS and testosterone deficiency.

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