

Review Article

Late-Onset Hypogonadism Syndrome and Lower Urinary Tract Symptoms

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Androgen replacement therapy (ART) is a widely accepted form of treatment worldwide for aging men with late-onset hypogonadism (LOH) syndrome. Concurrent with the progressive decline in testosterone from middle age, there is a gradual increase in prostate volume, reflecting the development of benign prostatic hyperplasia (BPH). Prostate growth is dependent on the presence of androgens, and conversely, anti-androgen agents or orchidectomy can decrease prostate volume in patients with BPH. Thus, it is important to investigate whether ART could have any negative effects on prostatic disease or lower urinary tract symptoms (LUTS). Although only limited amounts of information on the correlations between androgen levels in aging men and clinical manifestations of LUTS are available, a few recent studies have suggested that testosterone levels may have some beneficial effects on various urinary functions in men. Androgen receptors are found in the urothelium, urinary bladder, prostate, and urethra, and testosterone could have an impact on the autonomic nervous system, bladder smooth muscle differentiation, nitric oxide synthase, phosphodiesterase-5 and Rho/Rho-kinase activities, and pelvic blood flow. In addition, some previous studies demonstrated that ART had little effect on LUTS or urinary function in aging men with LOH syndrome. Furthermore, some recent randomized controlled trials indicated that short-term ART may be effective in the improvement of LUTS in hypogonadal men with mild BPH. However, only limited information is available regarding the effects of longer-term ART or the safety of ART in men with severe BPH and LUTS, and further studies are required to reach more definitive conclusions.

Key Words: Hypogonadism; Prostatic hyperplasia; Testosterone; Urination disorders

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INTRODUCTION

Currently, the number of individuals over 65 years of age has increased more than 10-fold compared with the 1990s, and the number of elderly people will continue to increase worldwide in the future. In women, ovarian hormone production decreases from about 50 years of age, which often results in various menopausal symptoms. Hormone replacement therapy can contribute to maintenance of quality of life in older women. On the other hand, biologically active free testosterone levels are known to decline with age by 2% to 3% annually in men, which may result in andropause symptoms [1]. The clinical condition associated

with low levels of serum testosterone with specific symptoms is called late-onset hypogonadism (LOH) syndrome. The Massachusetts Male Aging Study demonstrated that the prevalence of hypogonadism in men ranges from 6.0% to 12.3% between the ages of 40 and 69 years and estimated that 2.4 million men in the United States have androgen deficiency [2]. The widely recognized clinical signs of LOH syndrome are decreases in libido and sexual desire, decreases in muscle mass and strength, a decrease in bone mineral density, an increase in visceral fat, loss of memory, anemia, and deterioration of insulin resistance [3-5]. Furthermore, some studies indicated that low T levels are associated with increased risk for the development of type

2 diabetes mellitus or cardiovascular disease [3,6,7]. Therefore, LOH syndrome is considered to be a clinical condition that could affect the functions of multiple organ systems, and LOH syndrome itself is an important sign of many potentially serious conditions. Androgen replacement therapy (ART) is a widely accepted form of treatment to prevent and ameliorate many of the symptoms and conditions associated with LOH in aging men. According to practical industry estimates, more than 1.8 million prescriptions for testosterone products were issued in the United States in 2002, representing a 30% increase over the previous 5 years [8].

On the other hand, there is a gradual increase in prostate volume concomitant with the progressive decline in testosterone from middle age, reflecting the evolution of benign prostatic hyperplasia (BPH), a common disease of later life affecting older men [9]. Several studies have shown the frequency of lower urinary tract symptoms (LUTS) caused by BPH to be from 8% to 31% in men in their fifties, increasing to 27% to 44% of men in their seventies [10]. Prostate growth is dependent on the presence of androgens, and androgens play an important role in the development of BPH. Conversely, administration of antiandrogen agents and orchidectomy can decrease prostate volume in patients with BPH [11]. These observations suggest that ART may potentially worsen LUTS by increasing prostate volume, and potential concerns regarding the effects of testosterone on prostate disease and LUTS must be addressed. Because LUTS is also associated with an increased risk of falls, diminished quality of life, depression, and sadness, similar to LOH syndrome [12], it is important to investigate the effects of hypogonadism or ART on prostatic disease and LUTS.

At present, little is known about the correlations between androgen levels in aging men and clinical manifestations of LUTS [10]. Furthermore, there are no compelling data suggesting that ART contributes to exacerbation of LUTS or promotion of urinary retention [3]. Therefore, we reviewed the relationship between LOH syndrome and LUTS and the effects of ART on LUTS in hypogonadal men.

SERUM SEX HORMONES AND LOWER URINARY TRACT SYMPTOMS

Many studies have established the potential relationship between testosterone levels and erectile dysfunction (ED) or metabolic syndrome, whereas there have been few studies of the relationship between testosterone and LUTS [3]. There are several similarities in the etiologies of ED and LUTS, such as metabolic syndrome, autonomic nervous activity, nitric oxide (NO) activity, arteriosclerosis, pelvic ischemia, and Rho-kinase activity [13]. Furthermore, recent studies suggested that BPH and LUTS are significantly associated with metabolic syndrome, and that patients with LUTS may share the same metabolic abnormalities as those with metabolic syndrome [14-16]. These findings suggest a relation between declines of testosterone and

LUTS.

Several reports have been published regarding the relationships between various serum sex hormones and LUTS. Schatzl et al reported that hypogonadism was detected in 22.1% of 312 men with LUTS but had no impact on International Prostate Symptom Score (IPSS), maximum flow rate (MFR), prostate volume, or prostate-specific antigen (PSA) level [17]. One large population study indicated that circulating levels of sex hormones are generally not significant predictors of LUTS in men after adjustment for age, and the pathophysiology of LUTS is complex and probably includes factors other than circulating sex steroid levels [18]. Also, no consistent correlations were shown between testosterone or free testosterone and LUTS in another cross-sectional study [19].

On the other hand, some studies have indicated inverse associations between total testosterone, bioavailable testosterone, and free testosterone with LUTS. One prospective study investigating serum sex hormones and the 20-year risk of LUTS in 185 men with a mean age of 58 years revealed a significant inverse association between dihydrotestosterone and LUTS and indicated that men with higher concentrations of bioavailable testosterone had a 56% decreased risk of LUTS compared with those with hypogonadal concentrations. However, this study demonstrated no relationship between total testosterone and LUTS [20]. Miwa et al noted that LUTS were not associated with serum levels of total testosterone and free testosterone, but storage symptom scores of the IPSS could be affected by the serum dehydroepiandrosterone sulfate level in older men [21]. Furthermore, Tan et al reported that the decrease in serum free testosterone concentrations with a relative rise in serum estradiol levels with advancing age may be an important factor in the development of BPH in a population of 61 men aged 60 to 69 years [22]. These findings indicated that the relationships between sex hormone levels and the development or severity of LUTS are conflicting, and further studies in large populations of men with and without LUTS and with various severities of BPH are required to reach more definitive conclusions.

TESTOSTERONE LEVELS MAY AFFECT URINARY FUNCTION AND LOWER URINARY TRACT SYMPTOMS

As described above, the results of a few studies have suggested that testosterone levels may have an effect on LUTS. Some interesting reports have also provided some insights into the mechanism of this effect (Fig. 1).

Androgen receptors were found in the urothelium of the urinary bladder and urethra or autonomic neurons of pelvic ganglia in some experimental studies in rabbits and rats [23-25]. These neurons show remarkable sensitivity to androgens, and testosterone appears to play an important role in the morphology of pelvic autonomic neurons supplying the urinary bladder and urethra [26]. Indeed, one study demonstrated that castration decreased the

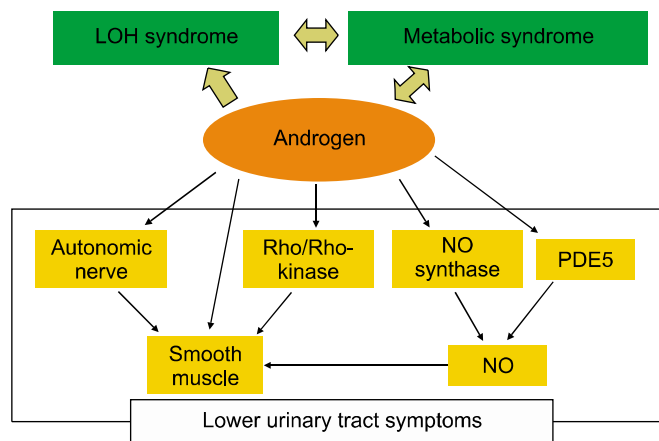


FIG. 1. Hypotheses regarding the effects of testosterone level on lower urinary tract symptoms. The testosterone level is likely to have effects on the autonomic nervous system, Rho-kinase, and activities of nitric oxide (NO) synthase and phosphodiesterase-5 (PDE5) through the androgen receptors localized on the lower urinary tract and may be associated with urinary functions. LOH: late-onset hypogonadism.

function of alpha 1-adrenergic and muscarinic cholinergic receptors in the urinary bladder, and testosterone replacement restored these functions, indicating that testosterone has an effect on autonomic receptor function in the smooth muscle of the lower urinary tract [27]. Furthermore, androgen stimulates stromal precursor cells to differentiate into smooth muscle cells. Cayan et al reported that in rats testosterone treatment resulted in a significantly higher bladder smooth muscle/collagen ratio than that in controls, suggesting that androgen interacts directly with the androgen receptors localized in the urinary bladder [28]. Madeiro et al also reported that the bladders of castrated rats receiving androgen therapy for 28 days showed larger numbers of vessels, greater epithelial thickness, and larger quantities of muscular fibers than in untreated controls [27].

The Rho and Rho-associated kinase pathway is also involved in the autonomic system. Increased Rho-kinase activity results in increased smooth muscle contraction, which leads to impaired erectile function and changes in bladder outlet tone [29]. Testosterone has been shown to have an effect on Rho-kinase activity, and Rho-kinase activity in the urinary tract may be at least in part dependent on testosterone [10]. Rho-kinase plays a central role in the regulation of smooth muscle contraction of the urinary bladder and is associated with calcium sensitivity of the contractile machinery in prostate smooth muscle of BPH or in the detrusor of bladder outlet obstruction in experimental animal models [30]. Increased Rho-kinase activity coincides with the development of LUTS in aging men with BPH, and inhibition of Rho-kinase in the rat model is considered to decrease prostatic smooth muscle cell proliferation and to decrease adrenergic contractions [31].

As further substantiation of the relationship between

testosterone levels and LUTS, testosterone regulates not only cyclic guanosine monophosphate formation through NO synthase stimulation but also its catabolism through phosphodiesterase-5 (PDE-5) activity. NO induces vasodilation and is the basis for using PDE-5 in the treatment of erectile dysfunction. NO is also one of the mediators of dilatation of the urethra and bladder neck. NO synthase gene expression is reduced with aging in rat prostate tissue and may be a factor involved in the increased smooth muscle tone associated with LUTS [30]. Chamness et al reported that testosterone had an effect on NO synthase in the urinary tract and suggested the possibility of improving urinary symptoms by increasing NO production [32]. Moreover, the presence of PDE-5 was identified in the urinary bladder [33], and PDE-5 appeared to regulate the smooth muscle tone of the bladder. Indeed, it has been clinically demonstrated that PDE-5 inhibitors have a beneficial effect on LUTS [34-36]. Alternatively, elevated testosterone levels or testosterone replacement also activate endothelial NO synthase and consequently increase NO concentration in the tissue of the vessels, resulting in dilation of pelvic vessels and alleviation of pelvic ischemia. A decrease in bladder blood flow has been suggested in BPH patients [37], and decreased bladder blood flow and ischemia caused by aging and arterial sclerosis are associated with the development of detrusor overactivity and LUTS [38, 39]. Chronic bladder ischemia is attributable to bladder distention induced by bladder outlet obstruction [40].

EFFECTS OF ANDROGEN REPLACEMENT ON LOWER URINARY TRACT SYMPTOMS

The relationships between ART and the risk of progression of BPH or LUTS have been discussed in the literature (Table 1). First, Franchi et al noted that oral testosterone undecanoate replacement for 8 months at doses from 40 to 160 mg/day resulted in no subjective increase in prostate size or deterioration of voiding symptoms [41]. A placebo-controlled study using weekly injection of 100 mg of testosterone enanthate for 3 months did not significantly increase prostate volume or postvoiding residual (PVR) volume [42]. Another double-blind controlled study demonstrated that ART resulted in an increase of 12% in volume of the prostate gland after 8 months of treatment but did not affect uroflowmetry (UFM) data, PVR, or IPSS [43]. Behre et al reported a comparison of prostate volume measured by transrectal ultrasonography, serum levels of PSA and sex hormones, and UFM parameters in a controlled cross-sectional study [44]. There were no significant differences in UFM data between 78 hypogonadotropic hypogonadism patients who received ART for > 6 months, 75 normal age-matched men, and 47 untreated hypogonadotropic hypogonadism patients. Furthermore, no significant differences in prostate volume or PSA value were detected between hypogonadism patients who received ART and normal controls. Marks et al reported an interesting double-blind placebo-controlled study and noted that 6

TABLE 1. The previous reports regarding the effects of androgen replacement therapy on lower urinary tract symptoms

Study	Design	N	Treatment regimen	Results	Reference
Franchi (1978)	CS	34	Oral T undecanoate (40-160 mg; daily for 8 months)	ART had no subjective increase in prostate size or deterioration of voiding symptoms.	41
Tenover (1992)	RCT	13	IM T enanthate (100 mg; weekly for 3 months) vs placebo	There were not significant increase in prostate volume or PVR, and a sustained increase in serum PSA levels.	42
Holmång (1993)	RCT	23	Oral T undecanoate (160 mg; daily for 8 months) vs placebo	ART resulted in an increase of 12% in volume of the prostate gland after 8 months of treatment, but did not affect UFM data, PVR.	43
Gooren (1994)	CS	33	Oral T undecanoate (80-200 mg; daily for 10 years)	Urine flow showed a slight decrease, but no increase was shown in prostate size.	50
Behre (1994)	CS	Group 1 (N=47) Group 2 (N=78) Group 3 (N=75)	Group 1: untreated hypogonadotropic hypogonadism Group 2: ART-received patients Group 3: age-matched normal controls	There was no significant difference in UFM data of the three groups. Furthermore, no significant difference was detected in PSA value and prostate volume between ART group and normal age-matched controls.	44
Sih (1997)	RCT	32	T cypionate (200 mg; biweekly for 12 months) vs placebo	There were not significant increase in PSA, and no patients who had worsening of urinary symptoms.	46
Kenny (2001)	RCT	67	Transdermal T patch (5 mg; daily for one year) vs placebo	Testosterone resulted in a modest increase (not significantly) in PSA levels but resulted in no change in signs or symptoms of prostate hyperplasia	47
Perchersky (2002)	DRS	207	Oral T undecanoate (80-120 mg; daily for 6 months)	ART resulted in a decrease of approximately 30% in prostate volume and a significant decrease of IPSS score	51
Marks (2006)	RCT	44	IM T enanthate (150 mg; biweekly for 6 months) vs placebo	ART had little effect on prostatic tissue androgen levels, such as those of testosterone and DHT, or on their urinary symptoms and UFM data.	45
Saad (2008)	DRS	Group 1 (N=28) Group 2 (N=27)	Group 1: IM T undecanoate (1,000 mg for 9 months) Group 2: T gel (50 mg; daily for 9 months)	Plasma PSA values remained stable for 9 months with both T gel and T undecanoate, whereas the scores on the IPSS improved slightly (not significantly) in both groups.	48
Karazindi- yanoğlu (2008)	CS	25	T gel (50-100 mg; daily for one year)	ART contributed to a significant increase in prostate volume, but had an improvement in IPSS score. ART significantly increased maximal bladder capacity and compliance, and decreased detrusor pressure at maximal flow based on PFS.	52
Kalinchenko (2008)	DRS	Group 1 (N=10) Group 2 (N=20)	Group 1: T gel (50 mg; daily for 26 weeks) Group 2: IM T undecanoate (1000 mg for 26 weeks)	ART improved total IPSS score, irritable symptoms, obstructive symptoms, and nocturia. But total PSA value did not change significantly.	53
Takao (2009)	CS	21	T enanthate (125 mg; triweekly for 3 months) or hCG (5000 IU for 3 months)	ART had no short-term effects on IPSS and QOL-index.	49
Amano (2010)	CS	41	Glowmin (6 mg; daily for 3 months)	ART was effective in the improvement of IPSS and its subscores.	54
Shigehara (2011)	RCT	46 (ART: 23, Control 23)	IM T enanthate (250 mg; monthly for 12 months)	ART for the patients with LOH and mild BPH had improvement in IPSS score, MFR and VV, but had no effects on PVR and PSA.	55

RCT: randomized controlled study, CS: case series, DRS: dose-response study, IM: intramuscular, T: testosterone, ART: androgen replacement therapy, PVR: post-voiding residual volume, PSA: prostate specific antigen, UFM: uroflowmetry, IPSS: international prostate symptom score, DHT: dihydrotestosterone, PFS: pressure flow study, BPH: benign prostate hyperplasia, QOL: quality of life, MFR: maximum flow rate, VV: voided volume

months of testosterone administration normalized serum androgen levels in aging men with hypogonadism but had little effect on prostatic tissue androgen levels, such as those of testosterone and dihydrotestosterone, or on the patients' urinary symptoms and UFM data [45]. Furthermore, no ART-related changes were observed in prostate histology or tissue biomarkers, such as androgen receptor, Ki-67, and CD34, in the biopsy samples. Other studies demonstrated many beneficial systemic effects of ART but failed to show a significant exacerbation of LUTS during ART, and complications, such as urinary retention, did not occur at higher rates than in controls [46-49]. These studies have demonstrated that ART for a short period of within 1 year has little negative effect on urinary function or prostate volume.

On the other hand, a long-term clinical study using oral testosterone undecanoate for 10 years in 33 men demonstrated a slight decrease in urine flow but no increase in prostate size and no evidence of cancer development [50]. However, there have been few studies including populations with long-term observation of ART and with severe BPH or LUTS. Clearly, further long-term observational trials including patients with varying severities of BPH are required to clarify the possible effects of ART on the prostate or LUTS due to BPH.

ANDROGEN REPLACEMENT CAN CONTRIBUTE TO IMPROVEMENT OF LOWER URINARY TRACT SYMPTOMS IN HYPOGONADAL MEN

As described above, the potential relationship between LUTS and LOH syndrome has been addressed, and some recent studies also demonstrated that ART improved LUTS in hypogonadal men (Table 1). An uncontrolled study indicated progressive reduction of prostate volume and improvement of urinary symptoms among 207 middle-aged and older men who were treated with oral testosterone undecanoate at a dose of 80 to 120 mg daily for 6 months [51]. This previous report indicated that ART resulted in a decrease of approximately 30% in prostate volume and a significant decrease in IPSS. On the other hand, they also reported that 20 patients had no suppression of plasma luteinizing hormone, which reflects defects in hypothalamic-pituitary regulation in testicular function, suggesting failure to demonstrate a consistent increase in plasma testosterone level, and did not show a decrease in prostate volume. These findings suggest that successful ART could improve urinary symptoms and BPH directly. Karazindiyanoglu et al mentioned that ART with transdermal testosterone gel (50 to 100 mg) per day for 1 year in 25 men with LOH syndrome improved the IPSS, although mean prostate volume showed a significant increase [52]. Furthermore, according to the results of pressure-flow analysis, this study demonstrated that ART significantly increased maximal bladder capacity and compliance and decreased detrusor pressure at maximal flow. Kalinchenko et al also reported that two types of testoster-

one administration (testosterone gel or testosterone undecanoate) improved many LUTS, such as irritative symptoms, obstructive symptoms, and nocturia, in men with LOH syndrome [53]. Amano et al noted that ART by administration of testosterone ointment (Glowmin) 6 mg/day for 3 months contributed to elevation of serum testosterone levels observed within the normal range and was effective in improving not only ED and LOH symptoms but also LUTS (especially voiding disturbance) in 41 patients with LOH [54].

Recently, we reported a randomized controlled study regarding the effects of ART on LUTS in 52 hypogonadal men with mild BPH [55]. Fifty-two patients were randomly assigned to receive testosterone (ART group 26 patients) as 250 mg of testosterone enanthate every 4 weeks or to the untreated control group (26 patients), and IPSS, UFM data, and PVR at baseline and 12 months after treatment were compared. Finally, 46 patients (ART group, n=23; control group, n=23) who completed this trial over 12 months were included in the analysis. At the 12-month visit, IPSS showed a significant decrease compared with baseline in the ART group (15.7 ± 8.7 vs. 12.5 ± 9.5 ; $p < 0.05$), whereas no significant changes were observed in the control group (14.0 ± 10.1 vs. 13.5 ± 9.8 ; $p = 0.345$). The ART group also showed improvement in MFR (from 12.9 ± 5.6 to 16.7 ± 9.5 ml/s, $p < 0.05$) and voided volume (VV: from 253 ± 120 to 283 ± 145 ml/s, $p < 0.05$), whereas no significant improvements were observed in the controls. Furthermore, IPSS subscores showed improvements in categories associated with MFR (Q5: "Over the past month, how often have you had a weak urinary stream?") and VV (Q2: "Over the past month, how often have you had to urinate again less than two hours after you finished urinating?") in the ART group. PVR showed no significant changes in either group. This was the first randomized controlled study suggesting that ART may improve LUTS in hypogonadal men with mild BPH by increasing MFR and VV. During this study period, there were no patients who required prostate biopsy or had a diagnosis of prostate cancer. With regard to the safety of ART for 1 year, no other severe adverse events occurred that resulted in withdrawal from the trial. Urinary complications, such as severe exacerbation of voiding symptoms or urinary retention, did not occur in either group. Furthermore, no patients required additional medication or changed drugs because of worsening urinary symptoms during the period of this trial. However, the limitations of the present study included the small sample size and the lack of data based on urodynamic study. Moreover, the severity of BPH in the target population was mild, and the present results may not necessarily be applicable to patients with severe BPH. Therefore, further studies including long-term observations and many patients with severe BPH or LUTS are required to reach more definitive conclusions regarding the associations between testosterone therapy and urinary function.

CONCLUSIONS

Many previous studies have demonstrated that ART has few negative effects on urinary function, LUTS, or prostate volume among aging men for at least about 1 year. There are many benefits of ART for hypogonadal aging men regarding many general conditions, such as loss of muscle mass and strength, bone mineral density, enhanced memory, sexual function, insulin resistance, improvement of metabolic syndrome and visceral fat, and general sense of well-being. As an additional benefit, ART may also be effective for improving LUTS in aging men. However, currently, ART is generally a relative contraindication in severe BPH and LUTS with an IPSS of more than 19. Furthermore, only limited information is available regarding the effects of ART in men for longer periods, and further studies including long-term observations and many patients with varying severities of BPH or LUTS are required to reach more definitive conclusions.

Conflicts of Interest

The authors have nothing to disclose.

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