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REVIEW

Effects of testosterone on the lower urinary tract go beyond the prostate: New insights, new treatment options

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Abstract   The traditional assumption that the prostate is an organ exquisitely sensitive to androgen action still holds true, but with lower-than-normal circulating levels of testosterone, all androgen receptors are saturated and a further increase in circulating levels of testosterone has no effect on the prostate (saturation model). Prostate disease (prostate cancer and benign prostatic hyperplasia, BPH) usually occur at an age when circulating levels of testosterone are declining, so it is unlikely that they are to be attributed to an excess of testosterone. The bother of BPH is presently subsumed under 'pathology of the lower urinary tract'. Surprisingly, these structures have androgen receptors, and depend for their relaxation on nitric oxide, for which the mechanism, in turn, is aided by androgens. This explains why phosphodiesterase type-5 inhibitors also benefit erectile function and symptoms of the lower urinary tract. Normalisation of testosterone in hypogonadal men favours this action. During the development of the prostate, epithelium and mesenchyme are under the control of testicular androgens, and interact to form an organised secretory organ. Furthermore, many of the disease processes of the prostate have been attributed to androgen action, and consequently, therapies have been aimed at manipulating androgen activity.

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Endocrine control of prostatic growth

Prostatic epithelial cells express androgen receptors. From the beginning of embryonic differentiation to pubertal maturation and beyond, androgens are a prerequisite for the normal development and physiological control of the prostate. Androgens also help to maintain the normal metabolic and secretory functions of the prostate. Androgens do not act in isolation, and other hormones and growth factors are being investigated. Androgens also interact with prostate stromal cells which release soluble paracrine factors that are important in the growth and development of the prostate epithelium. These paracrine pathways may be critical in regulation of the balance between proliferation and apoptosis of prostate epithelial cells in the adult.

Intraprostatic signalling systems are important for the regulation of cell proliferation and extracellular matrix production in prostatic stroma. There is a balance between factors such as TGFβ1, that induces extracellular matrix production, suppresses collagen breakdown and cell proliferation and factors such as fibroblast growth factor 2 and IGF that are mitogenic in the stromal compartment [1]. Other endocrine pathways are being investigated and there are experimental data suggesting an abnormality in the IGF axis playing a role in the pathogenesis of BPH.

Testosterone in the prostate

The metabolism of testosterone to dihydrotestosterone (DHT) and its aromatisation to oestradiol are key events in prostatic steroid response. Testosterone, to be maximally active in the prostate, must be converted to DHT by the enzyme 5α-reductase [2]. DHT has a much greater affinity for the androgen receptor than does testosterone [2]. In studies of rats, DHT is at least twice as potent as testosterone at equivalent androgen concentrations. DHT, due to its greater affinity for the androgen receptor, might have effects intraprostatically independent of serum fluctuations in serum testosterone levels [2].

There is almost no information on the consequences of manipulation of circulating androgen levels on prostate tissue hormone levels in normal men. Studies of men with prostate cancer undergoing androgen deprivation have suggested that, despite a dramatic fall in circulating levels of testosterone, prostatic androgen concentrations are preserved. Rather than circulating levels of androgens, tissue androgens might stimulate prostate growth, producing adverse clinical consequences [3]. In a small study of healthy subjects, despite a 94% decrease in serum testosterone with medical castration, intraprostatic testosterone and DHT levels remained at 20–30% of control values, and biological processes such as prostate cell proliferation, apoptosis and androgen-regulated protein expression were unaffected [3]. Prostate growth is exquisitely sensitive to variations in androgen concentrations at very low concentrations, but becomes insensitive to changes in androgen concentrations at higher levels. This pattern is consistent with the observation that androgens exert their prostatic effects primarily via binding to the androgen receptor, and that maximum androgen-receptor binding is achieved at serum testosterone concentrations well below the physiological range. This could be best explained by a saturation model.

It accounts for the seemingly contradictory results in human prostate cancer studies. Changes in serum testosterone concentrations below the point of maximum androgen-receptor binding will elicit substantial changes in prostate (cancer) growth, as seen with castration, or with testosterone administration to previously castrated men. By contrast, once maximum androgen-receptor binding is reached the presence of additional androgen produces little further effect. This model clearly indicates that there is a limit to the ability of androgens to stimulate the prostate [4]. Therefore DHT concentrations might remain similar to those in young men in the prostate of elderly men, despite serum testosterone levels declining with age [5]. In the prostate, the total level of testosterone is 0.4 ng/g and the total level of DHT is 4.5 ng/g. The total concentration of testosterone in the blood (18.2 nmol/L) is ≈10 times higher than that of DHT. DHT circulates in low concentrations with a tight binding to plasma proteins, and is of minor importance for its effects on prostate growth. These observations are relevant for assessing effects of therapeutic testosterone administration to elderly men. Increasing circulating levels of testosterone is unlikely to increase intraprostatic androgen levels [6].

Oestrogen

Oestrogens, alone or in combination with androgens, are involved in inducing aberrant growth and/or malignant change. Animal models, mainly the dog, have supported this hypothesis. Oestrogens 'sensitise' the ageing dog prostate to the effects of androgen. The evidence is less clear in humans. Oestrogens in the male are predominantly the products of peripheral aromatisation of testicular and adrenal androgens. While the testicular and adrenal production of androgens declines with ageing, levels of total plasma oestradiol do not decline. This has been ascribed to the increase in fat mass with ageing (the primary site of peripheral aromatisation) and to an increased aromatase activity with ageing. However, free or bioavailable oestrogens might decline due to an increase in sexhormone binding globulin, which could translate to lower intraprostatic levels of the hormone. The potentially adverse effects of oestrogens on the prostate might be due to a shift in the intraprostatic oestrogen:androgen ratio with ageing.

Oestrogen, which acts through oestrogen receptors α and β, has been implicated in the pathogenesis of benign and malignant human prostatic tumours [7]. BPH originates in the transitional zone and prostate cancer in the peripheral zone of the prostate. Oestrogen might play a crucial role in the pathogenesis of BPH through oestrogen receptor-β. Investigations are ongoing and could result in a new range of therapies directed against BPH and prostate cancer.

BPH

BPH is an age-related and progressive neoplastic condition of the prostate gland [8]. Its definition is histological; BPH in the clinical setting is characterised by LUTS. There is no causal relationship between benign and malignant prostatic hypertrophy [9]. Clinically apparent BPH represents a considerable health problem for older men, because of its negative effects on quality of life. A recent study showed overall prevalence

of 10.3%, with an overall incidence rate of 15 per 1000 man-years, increasing with age (3 per 1000 at age 45–49 years, to 38 per 1000 at 75–79 years). For a symptom-free man at age 46 years, the risk of clinical BPH over the coming 30 years, if he survives, is 45%. The true prevalence and incidence of clinical BPH will vary according to the criteria used to describe the condition. BPH presents itself clinically as LUTS, but LUTS can exist with no signs of BPH, as the symptoms can be caused by variations in the sympathetic nervous stimulation of prostatic smooth muscle, variability of prostatic anatomy (viz., enlarged median lobe of the prostate), and the variable effects of bladder physiology from obstruction and ageing.

There have been several studies showing that clinical BPH is a progressive disease. The Olmsted County study showed that with each year there were deteriorations in symptom scores, peak flow rates, and increases in prostate volumes based on TRUS scanning.

Epidemiological studies on the relationship between androgens and BPH

As indicated above, the prostate is exquisitely androgen sensitive, and similar to prostate cancer, age is the best predictor of BPH and LUTS. Surprisingly, most problems are encountered when circulating testosterone levels are declining in men. Several investigations have examined whether circulating androgen levels have a predictive value for future development of BPH. Rather the opposite appeared to be the case; men with low serum androgen levels more often had BPH/LUTS [10,11]. It further appeared that androgen receptor CAG repeat length (the shorter the repeat length, the more powerful the biological action of androgens) was not associated with the risk of incident symptomatic BPH.

Clinical conditions and the lower urinary tract with a potential intermediate role for testosterone

As indicated above, the occurrence of prostate disease with ageing is difficult to comprehend from the perspective of direct androgen action alone. Prostate disease manifests itself at an age when men are affected by a much broader range of diseases, and over the last two decades it has become clear that many age-related health problems of men are actually interrelated and require a more integrative approach. At the epidemiological level an association between LUTS, erectile failure, central obesity in adulthood and the metabolic syndrome, has been established [12]. This contribution focuses on the role of testosterone, and a common denominator of the above ailments is lower-than-normal testosterone levels occurring in a significant proportion of elderly men. The decline of serum testosterone might be detectable over relatively short periods of observation. Throughout a 4-year follow-up in elderly patients with erectile dysfunction (ED) there was a steady decrease in testosterone levels.

Many studies have tried to establish a relationship between sex steroids and BPH, and a few have analysed the relationship between circulating testosterone and LUTS. One study found that hypogonadism was seen in about a fifth of elderly men with LUTS, but it had no effect on symptom status. Another study found a relationship between LUTS and plasma total and bioavailable testosterone levels, but this relationship disappeared after statistical adjustment for age [13]. No consistent correlations were found between total and calculated free testosterone level, and LUTS in another study [12]. On univariate analysis, the total IPSS was significantly associated with age, dehydroepiandrosterone sulphate (DHEA-S) and free testosterone levels [12,14]. However, a recent study found that low testosterone levels in clinical BOO correlated negatively with detrusor pressure at urethral closure and detrusor pressure at maximum flow, while promoting detrusor overactivity. In the rabbit, testosterone appeared to have a positive effect on bladder capacity and on compliance (defined as rate of volume change per unit pressure). Notably, within certain limits of testosterone levels, the signs and symptoms of testosterone deficiency in men do not relate in a uniform pattern to testosterone concentrations, which might be (in part) explained by properties of the androgen receptor (the CAG repeat polymorphism in exon 1 of the androgen receptor gene). However, more likely is that the role of testosterone is indirect.

The relationship between the metabolic syndrome and LUTS

In trying to explain the epidemiological relationship between the metabolic syndrome and LUTS it has been hypothesised that the metabolic syndrome is associated with an overactivity of the autonomic nervous system, for which hyperinsulinaemia, a key element of the metabolic syndrome, might be responsible. This overactivity of the autonomic nervous system is supposedly not responsible for the development of LUTS but plays a key role in increasing the severity of LUTS above an intrinsic basal intensity that is determined by the genitourinary anatomical/pathophysiological characteristics of other ailments leading to LUTS [15,16]. Another recent study provided evidence that stress conditions could be associated with the development and aggravation of prostatic disease. It was found that body mass index, age and greater diastolic blood pressure reactivity were associated with a greater transition zone volume, greater total prostate gland volume, greater postvoid residual bladder volume, and more severe LUTS [17]. Inflammatory infiltrates are frequently found in and around nodules in BPH in men with symptomatic BPH [18]. The presence of the metabolic syndrome might be a mediator of this association, because it is associated with elevated serum C-reactive protein concentration, a nonspecific marker of inflammation [19], thus linking the metabolic syndrome to LUTS, and elevated circulating C-reactive protein concentrations might be an indicator of intraprostatic inflammation in symptomatic BPH [18,19]. (Central) obesity is a hallmark of the metabolic syndrome of which the other components are: dyslipidaemia, hypertension, impaired glucose metabolism, with insulin resistance and diabetes type 2. Particularly if poorly controlled, there is a significant association between low level of total testosterone or DHEA-S and indices of poorly controlled type 2 diabetes. In a recent study, body mass index and insulin resistance were negatively correlated with serum levels of PSA. The severity of LUTS was significantly correlated with waist circumference, blood pressure, and fasting blood glucose level [20]. Insulin resistance is associated with hyperinsulinaemia, and insulin, particularly in excess, has (due to its biochemical similarities with IGF) growth-promoting properties. This might apply to the prostate.

All the above elements of the metabolic syndrome are not only conducive to the development of ED but also of LUTS. Risk factors and medical comorbidities of ED were prevalent among patients with LUTS and it is therefore not surprising that more studies have established a relationship between LUTS and ED [21–23], particularly as there is an underlying vascular association between LUTS and ED. Diet-induced weight loss significantly and rapidly improved sexual function, and reduced LUTS, in obese middle-aged men with or without diabetes [24].

As indicated above, with a more integrative approach to the ailments of the ageing man, the age-related decline of plasma testosterone levels has been found to be a feature of erectile failure and central obesity in elderly men, with confirmed success for the administration of testosterone to correct lower-than-normal levels. So, it is timely to pay due attention to the relationship between late-onset hypogonadism (LOH) and LUTS, which like the other ailments mentioned above, manifest themselves concurrently in the lives of elderly men.

Mechanisms of action of androgens on the urinary tract

Testosterone itself might not be the 'prime mover' of the effects of testosterone on those structures of the urinary tract anatomically and functionally related to LUTS. The indirect relation could obscure a demonstrable interrelation between circulating levels of testosterone and symptoms of LUTS at a statistically significant level, even though the relationship might be biologically plausible.

Androgen receptors have been found to be present to a large extent in the epithelial cells of the urethra and the bladder [25]. In a recent study, bladder capacity and smooth muscle/collagen content improved with testosterone therapy in orchidectomised rats [26]. The presence of androgen receptors was confirmed in another study but the study concluded that oestrogens, derived from androgens through aromatisation, might be more significant for the RhoA/Rho-kinase pathway inducing overactivity [27]. The role of testosterone and its metabolites in maintaining the reflex activity in the pelvic part of the autonomic nervous system was reported [28]. Others have postulated the influence of testosterone on postsynaptic nongenomic receptors which are suppressing detrusor activity [29,30]. Castration resulted in significant alterations in the activities of citrate synthase-thapsigargin-sensitive (Ca^{2+})ATPase (sarco/endoplasmic reticulum (Ca^{2+})ATPase), and choline acetyl-transferase as markers for mitochondrial function, sarcoplasmic reticular calcium storage and release, and cholinergic nerve function, in the bladder body, base, urethra and corpora [31].

Not only in the penis but also in other parts of the urogenital tract nitric oxide (NO) acts as a nonadrenergic noncholinergic neurotransmitter in the urogenital tract, and the action of testosterone on the urogenital tract might be mediated by this system [32]. There is increasing evidence for a link between ED and LUTS, the metabolic syndrome, pelvic atherosclerosis with its associated Rho-kinase activation/ endothelin pathway, the NO synthase (NOS)/NO theory, and the autonomic hyperactivity [33]. Studies treating one condition (e.g. ED) and measuring the effect on the other (e.g. LUTS) should further contribute to support this common link. However, as yet it is not possible to provide a comprehensive picture of the effect of testosterone (and its deficiency) on the lower urinary tract.

NO production is androgen-dependent in urinary tract

NO acts as a nonadrenergic noncholinergic neurotransmitter not only in genital structures but also in the urinary tract, and has a smooth-muscle-relaxing effect in both animals and humans. NO is a mediator of erection but also of dilatation of the bladder neck and urethra [34]. There is NO-dependent signalling in the control of smooth muscle function in the human prostate [35]. In humans, 72–96% of neurones in the wall of the bladder appear to contain NOS. NOS-immunoreactive nerve terminals provide a moderate innervation to the detrusor muscle of the bladder body, and a denser innervation to the urethral muscle. NO might be an inhibitory transmitter involved in the relaxation of the bladder neck [36]. Cyclic nucleotides are important secondary messengers of NO involved in modulating the contractility of various smooth muscles.

Phosphodiesterases (PDE) are important in this process by modulating the levels of cyclic nucleotides and their duration of action. Their presence in the urinary bladder was identified in studies of the rat [37] and the human [38].

PDE type 5 is an inhibitor of NO/cGMP signalling. A recent study, investigating PDE5 expression and activity in the human bladder, elegantly showed that PDE5 regulates smooth muscle tone of the bladder. Vardenafil appeared to block PDE5 activity, and therefore might be a possible therapeutic option for bladder dysfunction by ameliorating irritative LUTS. The study also found that castration decreased, and testosterone supplementation restored, PDE5 gene expression in rat bladder [32].

As a further substantiation of the role of androgens in the urogenital tract, NOS, in an earlier study, appeared to be androgen-dependent in the urogenital tract of the rat [39]. Meanwhile many clinical studies have convincingly shown that PDE5 inhibitors have a beneficial effect on LUTS, ascribed to beneficial effects on smooth muscle relaxation, smooth muscle and endothelial cell proliferation, nerve activity, and tissue perfusion which might affect LUTS in men [8,33,40–47].

From the above it would appear that androgens are not only essential for the formation of a male urogenital tract prenatally and its adult development during puberty, but that, similar to erectile tissue in the penis, maintenance of the functionality of the urinary tract in adult life is subserved by androgens. It could be that declining testosterone production with ageing contributes to the discomfort elderly men experience with micturition.

The effects of administration of testosterone on LUTS

In recent years there has been only preliminary evidence that men with LUTS benefit from treatment with testosterone, only in the form of abstracts awaiting peer-reviewed publication. The first data on this subject showed that normalisation of testosterone levels has a positive effect on LUTS in men with BPH and LOH. The positive effects of testosterone treatment on bladder function was by increasing bladder capacity and compliance and decreasing detrusor pressure at maximum flow in men with LOH [48]. In a series of papers we have tested the effects of testosterone administration on several variables relating to the ailments of the ageing male. The studies were not specifically designed to investigate the effects of testosterone administration to elderly men with LUTS, but effects of

testosterone treatment on the IPSS and on residual bladder volume were recorded. In the first study the effects of administration of parenteral testosterone undecanoate (TU) over 12 months were analysed [49]. There were positive clinical effects of administration of TU on the IPSS, and on variables of the metabolic syndrome, progressive over the 12-month study period. When the men in this study were shifted to treatment with parenteral TU after 9 months of administration of testosterone gel, plasma testosterone levels rose to higher levels than with testosterone gel, and further improvements were noted with the higher concentrations of testosterone. These findings were confirmed in a pilot study in 30 men receiving either testosterone gel or TU injections. In both groups, the IPSS improved [50]. In a larger study of hypogonadal (mainly elderly men), they were treated with parenteral TU, whereupon both variables of the metabolic syndrome and LUTS improved [51].

Conclusions

The traditional assumption that the prostate is an exquisitely sensitive organ to androgen action still holds true, but there are several new insights:

- The saturation model: with lower-than-normal circulating levels of testosterone, all androgen receptors are saturated and a further increase in circulating levels of testosterone has no effect on the prostate.
- This has relevance for prostate disease (prostate cancer and BPH) usually occurring at an age when circulating levels of testosterone are declining. These diseases cannot be attributed to an excess of testosterone.
- It is customary now not to attribute the bother elderly men experience with micturition to the prostate only, but to subsume this under pathology of the lower urinary tract. Surprisingly, these structures have androgen receptors and for their functioning they depend on NO for the relaxation of smooth muscle structures, having this in common with the biological substrate of erectile function. This explains why PDE5 inhibitors benefit both erectile function and LUTS. Testosterone augments the action of NO and therefore might be helpful in men with LUTS who are testosterone-deficient.

It becomes apparent that testosterone is not only significant for the formation of male urogenital anatomical structure prenatally, their growth and functioning at the time of puberty but that these structures also need testosterone for maintaining their normal functioning.

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