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Late Onset Hypogonadism and Lower Urinary Tract Symptoms: New Insights

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= Abstract =

Late onset hypogonadism was originally perceived as an academic topic. In the course of two decades it has become an issue impacting on everyday urology. For long time clinical conditions, such as cardiovascular disease, diabetes mellitus type 2, sexual dysfunction and urological complaints affecting the aging male, were regarded as independent clinical entities, treated by a number of medical specialists. Over the last decade their close interrelationship could be convincingly demonstrated. Declining testosterone levels in elderly appear to be central to the above pathologies. Epidemiological studies show that prostate disease occurs at an age when serum testosterone levels decline. It is now clear that erectile dysfunction is a local expression of endothelial dysfunction of the cardiovascular system. Testosterone deficiency is associated with an increased incidence of cardiovascular disease and diabetes mellitus, sequels of the metabolic syndrome. There is a relationship between the metabolic syndrome and lower urinary tract symptoms (LUTS). The pathophysiology of LUTS has much in common with the pathological substrate of erectile dysfunction with regard to vascular factors and the role of nitric oxide, explaining why phosphodiesterase type 5 inhibitors have often a beneficial effect on LUTS. It must be regarded an omission not to include testosterone measurements in the work-up of the LUTS, erectile dysfunction, cardiovascular disease and diabetes mellitus type 2. These conditions hinge on testosterone deficiency, and if testosterone deficiency can be proven, testosterone treatment can improve these conditions. There are many sites in the lower urinary tract where testosterone exerts effects.

Key Words: Hypogonadism, Prostate, Urological Menifestations, Urination Disorders, Nitric Oxide, Metabolic Syndrome X

Professor Alex Vermeulen from Gent/Belgium started his pioneering work on the decline of testosterone levels in aging men in the 1970-ies.[1] Then his work seemed to most professionals only of theoretical interest. But further studies have substantiated that, with age, a significant percentage of men over the age of 60 years have serum testosterone levels below the lower limits of normal for young adult men (aged 20 ~ 30 years).[2] Now, 30 ~ 40 years later, the pathophysiological implications of this decline, sometimes amounting to outright testosterone deficiency, have become clearer.

Until a decade ago the ailments of elderly men, such as atherosclerosis, hypertension, diabetes mellitus, lower urinary tract symptoms and erectile dysfunction, were regarded as distinct diagnostic/therapeutic entities but there is a growing evidence that these entities are not disparate and, to improve the health of the aging male, require an integral approach. There is an interdependence between the metabolic syndrome, erectile

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dysfunction, lower urinary tract symptoms on the one hand and patterns of testosterone in aging men on the other.[3] The main features of the metabolic syndrome are abdominal obesity, insulin resistance, hypertension and dyslipidemia, significant factors in the etiology of erectile functions. The metabolic syndrome is associated with lower-than-normal testosterone levels. Testosterone is a determinant of glucose homeostasis and lipid metabolism[4] and plays also a significant role in the development and maintenance of bone and muscle mass. Testosterone is not only a factor in libido but exerts also essential effects on the anatomical and physiological substrate of penile erection.[5] The effects of phosphodiesterase type 5-inhibitors are suboptimal in the presence of hypogonadal values of circulating testosterone.[5] A relationship between lower urinary tact symptoms (LUTS) and circulating levels of testosterone has been difficult to prove but the association of LUTS with the metabolic syndrome and with erectile dysfunction is well established in the literature.[6] Testosterone treatment of hypogonadal men not only improves features of the metabolic syndrome but also improves LUTS.[7] This was conformed in two other studies,[8,9] the latter a randomized controlled study (Fig. 1). With these recent insights, the health problems of elderly men must be placed in a context that allows an integral approach. On the basis of recent insights, diagnosis of testosterone deficiency should be part of the diagnostic work-up of the above conditions. It certainly would be an exaggeration to claim that testosterone is a cure-all for the health problems of the aging male. But ignoring the role testosterone plays in the above pathologies would equally be a disservice to our patients. The literature on the role of declining levels of testosterone in aging men has grown explosively and this review, necessarily, must be selective in the choice of issues to address. For a readership of mainly urologists, it is probably interesting to address the relationship between testosterone and its decline in old age and a number of common conditions the urologist meets in daily practice.

Benign Prostatic Hyperplasia (BPH)

BPH is an age-related and progressive neoplastic condition of the prostate gland. Its definition is histological. BPH in the clinical setting is characterised by lower urinary tract symptoms (LUTS). There is no causal relationship between benign and malignant prostatic hypertrophy. Clinically apparent BPH represents a considerable health problem for older men, due to the negative effects it has on quality of life. A recent study has demonstrated an overall prevalence of 10.3%, with an overall incidence rate of 15 per 1,000 man-years, increasing with age (3 per 1,000 at age 45～49 years, to 38 per 1,000 at 75～79 years). For a symptom free man at age 46, the risk of clinical BPH over the coming 30 years, if he survives, is 45%.[10] The true prevalence and incidence of clinical BPH will vary according to the criteria used to describe the condition. BPH presents itself clinically as lower urinary tracts symptoms (LUTS), but LUTS can exist without signs of BPH - as the symptoms can be caused by variations in the sympathetic nervous stimulation of

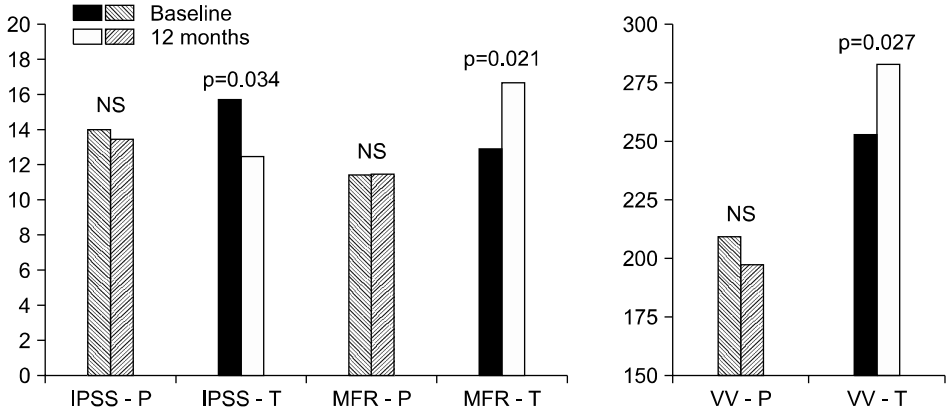

Fig. 1. Effect of 12 months treatment with testosterone in 46 men with LOH on LUTS parameters. MFR: maximal flow rate (ml/sec), VV: voiding volume (ml), P: placebo, T: testtosterone.[9] MFR: maximal flow rate, IPSS: International Prostate Symptom Score, NS: Not Significant.

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 demonstrating the fact that clinical BPH is a progressive disease. The Olmsted county study[11] showed that with each year there were deteriorations in symptom scores, peak flow rates, and increases in prostate volumes based on transrectal ultrasound scanning.

Epidemiological Studies on the Relationship Between Androgens and Benign Prostate Hyperplasia

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 benign prostate hyperplasia. Rather the opposite appeared to be the case. Men with low serum androgens had more often BPH/LUTS.[12]

Indirect Actions of Androgens on the Lower Urinary Tract

As indicated above, the occurrence of prostate disease with aging 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 inter-related 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.[13] 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 may be demonstrable over relatively short periods of observation. Throughout a 4-year follow-up in elderly patients with erectile dysfunction there was a steady decrease in testosterone levels.

Many studies have tried to establish a relationship between sex steroids and benign prostate hyperplasia, and a few studies have analyzed the relationship between circulating testosterone and LUTS symptoms. One study found that hypogonadism was seen in approximately one fifth of elderly men with LUTS, but it had no impact on symptom status. Another study found a relation between symptoms of LUTS and plasma total and bioavailable testosterone but this relationship disappeared after statistical adjustment for age.[14] No consistent correlations were found between total and calculated free testosterone and symptoms of LUTS in another study.[13] On univariate analysis, the total International Prostate Symptoms Score was significantly associated with age, DHEA-S, and free testosterone.[13] But a recent study found that low testosterone levels in clinical bladder outlet obstruction correlated negatively with detrusor pressure at urethral closure and detrusor pressure at maximum flow, while promoting detrusor overactivity.[15] 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.[16] But it is of note that, 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 may be (in part) explained by properties of the androgen receptor (the CAG repeat polymorphism in exon 1 of the androgen receptor gene). But more likely is that the role of testosterone is indirect.

The Relationship between the Metabolic Syndrome and LUTS

Trying to explain the epidemiological relationship between the metabolic syndrome and LUTS it has been hypothesized that the metabolic syndrome is associated with an overactivity of the autonomic nervous system for which hyperinsulinemia, 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.[17] 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, and age, 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. Inflammatory infiltrates are frequently found in and around nodules in benign prostate hyperplasia (BPH) in 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 non-specific 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.[18,20] (Central) Obesity is a hallmark of the metabolic syndrome of which the other components are: dyslipidemia, 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 prostate specific antigen.[21] The severity of LUTS was significantly correlated with waist circumference, blood pressure, and fasting blood glucose.[22] Insulin resistance is associated with hyperinsulinemia and insulin, particularly in excess, has due to its biochemical similarities with insulin-like growth factor, growth promoting properties. This might apply to the prostate.[23]

All the above elements of the metabolic syndrome are conducive to the development of erectile dysfunction but also of LUTS. Risk factors and medical co-morbidities of erectile dysfunction were prevalent among patients with LUTS, and it is, therefore, not surprising that a larger number of studies have established a relationship between LUTS and erectile dysfunction,[6,24,25] particularly since an underlying vascular association between LUTS and erectile dysfunction could be demonstrated.[26] Diet-induced weight loss significantly and rapidly improved sexual function, and reduced LUTS, in obese middle-aged men with or without diabetes.[27,28]

As indicated above, with a more integrative approach to the ailments of the aging male, 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 proven successes of 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.

Effects of Testosterone 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 may 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.[29] In a recent study bladder capacity and smooth muscle/collagen content improved with testosterone therapy in orchiectomized rats.[30] The presence of androgen receptors was confirmed in another study but the study concluded that estrogens, derived from androgens through aromatization, might be more significant for the RhoA/Rho-kinase pathway inducing overactivity.[31] The role of testosterone and its metabolites in maintaining the reflex activity in the pelvic part of the autonomic nervous system has been demonstrated.[32] Others have postulated the influence of testosterone on postsynaptic non-genomic receptors

which are suppressing detrusor activity.[33,34] Castration resulted in significant alterations in the activities of citrate synthase-thapsigargin sensitive Ca^{2+} ATPase (Sarco/Endoplasmic Reticulum Ca^{2+}-ATPase [SERCA]), 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.[35]

Not only the penis but also in other parts of the urogenital tract nitric oxide (NO) acts as a non-adrenergic non-cholinergic neurotransmitter in the urogenital tract and the action of testosterone on the urogenital tract may be mediated by this system.[36] 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 NOS/NO theory, and the autonomic hyperactivity.[37] Studies treating one condition (e.g. ED) and measuring the impact on the other (e.g. LUTS) should further contribute to support this common link. But as yet it is not possible to provide a comprehensive picture of the impact of testosterone (and its deficiency) on the lower urinary tract.

Nitric Oxide Production is Androgen Dependent in Urinary Tract

Nitric oxide (NO) acts as a non-adrenergic non-cholinergic neurotransmitter not only in genital structures but also in the urinary tract and exerts 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.[38] There is NO-dependent signaling in the control of smooth muscle function in the human prostate.[39] In humans 72～96% of neurons in the wall of the bladder appear to contain nitric oxide synthase. Nitric oxide synthase-immunoreactive nerve terminals provide a moderate innervation to the detrusor muscle of the bladder body, and a denser innervation to the urethral muscle. Nitric oxide may be an inhibitory transmitter involved in the relaxation of the bladder neck.[40] Cyclic nucleotides are important secondary messengers of nitric oxide involved in modulating the contractility of various smooth muscles.

Phosphodiesterases (PDE) play important roles in this process by modulating the levels of cyclic nucleotides and their duration of action. Their presence in the urinary bladder could be identified in studies of the rat and the human.[41] Phosphodiesterase 5 is an inhibitor of nitric oxide/cGMP signalling. A recent study, investigating PDE5 expression and activity in the human bladder, elegantly demonstrated that PDE5 regulates smooth muscle tone of the bladder. Vardenafil appeared to block PDE5 activity, and therefore, may be a possible therapeutic option for bladder dysfunction by ameliorating irritative lower urinary tract symptoms. The study also found that castration decreased, and testosterone supplementation restored, PDE5 gene expression in rat bladder.[36]

As a further substantiation of the role of androgens in the urogenital tract, NO-synthase in an earlier study appeared to be androgen dependent in the urogenital tract of the rat.[42] Meanwhile a large number of clinical studies have convincingly shown that phosphodiesterase inhibitors have a beneficial effect on LUTS.[43,44] 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 aging contributes to the discomfort elderly men experience with micturition.

Effects of Testosterone on LUTS

The first mention of effects of testosterone on bladder function was reported by Holmäng et al[45] finding an increase in peak urinary flow and mean urine volume voided in a testosterone treated group of men compared to placebo treatment. But 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 have shown that normalisation of testosterone levels has a positive effect on LUTS in men with BPH and LOH. The pos-

itive effects of testosterone treatment on bladder functions is exerted by increasing bladder capacity and compliance and decreasing detrusor pressure at maximal flow in men with symptomatic LOH.[46] In a series of papers we have tested the effects of testosterone administration on a number of variables relating to the ailments of the aging male. The studies were not specifically designed to investigate the effects of testosterone administration to elderly men on symptoms of LUTS but effects of testosterone treatment on the International Prostate Symptoms Score (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 analyzed.[47] There were positive clinical effects of administration of TU on the IPSS and also on parameters of the metabolic syndrome, progressive over the 12 month study period. When the men in this study were shifted to treatment with parenteral testosterone undecanoate after 9 months of administration of T gel, plasma T levels rose to higher levels than with T gel and further improvements were noted with the higher concentrations of T.[48] These findings were confirmed in a pilot study in 30 men receiving either testosterone gel or testosterone undecanoate injections. In both groups, IPSS improved.[49] In a larger study hypogonadal, mainly elderly men were treated with parenteral testosterone undecanoate whereupon both variables of the metabolic syndrome and symptoms of LUTS improved.[7] Recently, the first placebo-controlled trial has confirmed beneficial effects of testosterone on LUTS using both subjective (IPSS) and objective parameters.[9]

Inflammation and LUTS

Inflammatory infiltrates are frequently found in and around nodules in benign prostate hyperplasia (BPH).[18] There is an association between C-reactive protein (CRP) levels and LUTS in both men and women.[20] A dose-response relationship between increased CRP levels and an increased odds of LUTS supports the hypothesized role of inflammatory processes in the etiology of LUTS.[20] In men with CRP levels of >or =3.0 mg/l were more likely to have rapid increases in irritative LUTS.[50] The presence of the metabolic syndrome might be a mediator of this association because it is associated with elevated serum CRP concentrations, a non-specific marker of inflammation.[19] Thus the metabolic syndrome might be linked to LUTS and elevated CRP concentrations as an indicator of intraprostatic inflammation in symptomatic BPH.[18,19] CRP levels showed a quantitatively significant decline upon testosterone administration to men with features of the metabolic syndrome and elements of LUTS.[7]

CONCLUSIONS

The traditional assumption that the prostate is an exquisitely sensitive organ to androgen action still holds true but there are a number of new insights. 1) 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 impact on the prostate; 2) this has relevance for prostate disease (prostate cancer and benign prostate hyperplasia) usually occurring at an age when circulating levels of testosterone are declining. These diseases cannot be attributed to an excess of testosterone; 3) 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 nitric oxygen for the relaxation of smooth muscle structures, having this in common with the biological substrate of erectile function. This explains why phosphodiesterease type 5 inhibitors benefit erectile function and symptoms of the lower urinary tract as well. Testosterone augments the action of nitric oxide, and therefore, may be helpful in men with lower urinary tract symptoms 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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