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Testosterone Deficiency Linked to Lower Urinary Tract Symptoms

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1. Introduction

Over the past decade, it has become clear many of the age-related health problems of men, that have hitherto been treated using different medical disciplines, are actually inter-related and require a more integrative approach in the aging male. Lower urinary tract symptoms (LUTS) may serve as an example. LUTS consists of storage, voiding, and post micturition symptoms affecting the lower urinary tract. Storage symptoms (daytime frequency, nocturia, urgency, incontinence) are experienced during the storage phase of the bladder. Voiding symptoms (weak stream, splitting or spraying, abdominal straining, hesitancy, intermittency, terminal dribble) are experienced during the voiding phase. Post-micturition symptoms (feeling of incomplete emptying, post micturition dribble) are experienced immediately after micturition. Individuals with LUTS often experience urinary incontinence (UI) or overactive bladder (OAB) symptoms. OAB is a subset of storage LUTS defined as urgency, with or without urgency UI, usually with frequency and nocturia. Men may report one or any combination of the symptoms and LUTS, including UI and OAB, have detrimental effects on health-related quality of life.

The prevalence of LUTS increases from 8% in the fourth decade of life to more than 70% in the seventh decade. In a large population-based cross-sectional survey the prevalence of storage LUTS (men, 51.3%; women, 59.2%) was greater than that for voiding (men, 25.7%; women, 19.5%) and post micturition (men, 16.9%; women, 14.2%) symptoms combined (Irwin et al., 2008).

Once symptoms arise, their progress is variable and unpredictable with about one third of patients improving, one third remaining stable and one third deteriorating. LUTS may point to serious pathology of the urogenital tract but are often nonspecific and large studies of patients have failed to show any correlation between LUTS and a specific diagnosis. An all-encompassing view of LUTS that focuses on the lower urinary tract as an integrated functional unit, but simultaneously reflects pathophysiology in the body as a whole, is more likely to improve a clinician's ability to manage the symptoms and therefore improve patient outcomes. Benign prostatic hyperplasia (BPH), which occurs more frequently with aging, is the most common cause of LUTS in middle-aged and elderly men, although many other diseases such as detrusor muscle weakness and/or instability, urinary tract infection, chronic prostatitis, urinary stone, prostate cancer, bladder cancer, neurological disease, e.g. multiple sclerosis, spinal cord injury, cauda equina syndrome, and cardiac and renal diseases may accompany LUTS.

The role of testosterone in voiding function remains obscure, although it plays a definite role in the etiopathogenesis of BPH. The indirect relation could obscure an interrelation between circulating levels of testosterone and symptoms of LUTS at a statistically significant level which nevertheless is biologically plausible. This chapter will discuss possible relationships between androgens and LUTS

2. Sex hormone involvement in the etiopathognesis of BPH

The two factors that are generally accepted to play a role in the etiopathogenesis of BPH are aging and androgen. While serum testosterone level steadily decreases after 40 years of age, the prevalence of histologic BPH in autopsy studies rises from approximately 20% in men aged 41-50 to 50% in men aged 51-60, and to over 90% in men older than 80 (Berry et al., 1984). An enlarged prostate (BPE) is detectable in approximately on half of the patients with histologic evidence of BPH. The gradual reduction of plasma testosterone in middle-aged and older men from mid-life onwards coincides paradoxically with the time when there is progressive growth of the prostate, a highly androgen-dependent organ. In the prostate, testosterone is converted into the more potent androgen, dihydrotestosterone (DHT) by 5α reductase. It is thought that DHT has a central role in BPH development and maintenance because the inhibition of 5α reductase activity is associated with decreased serum DHT concentration and decreased prostate size (Figure 1).

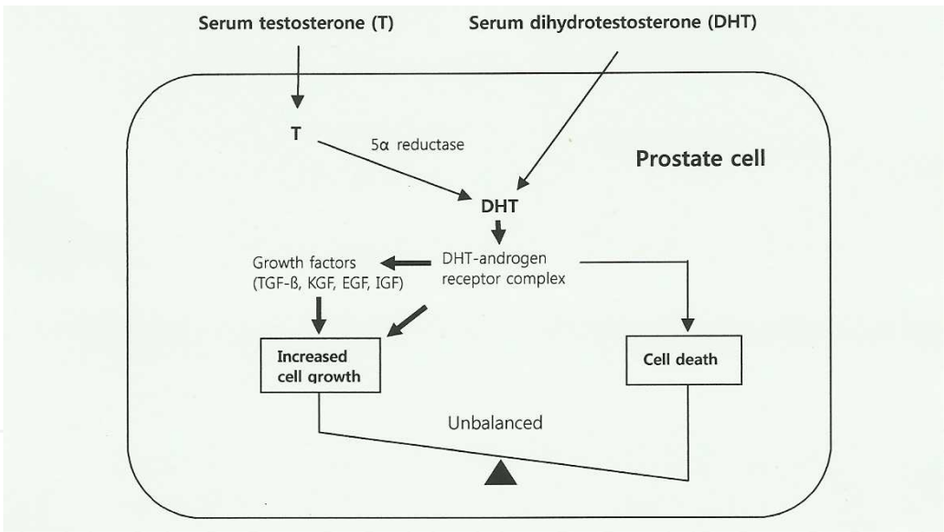


Fig. 1. Androgen regulation of cell growth in the prostate cell

Observations and clinical studies in men have clearly demonstrated that BPH is under endocrine control. Men castrated before puberty (eunuchs) develop neither BPH nor BPE, and individuals with an inherited deficiency of 5α reductase have only a vestigial prostate gland. Castration results in the regression of established BPH and improvement in urinary symptoms. Administration of a gonadotropin releasing hormone (GnRH) analog in men reversibly shrinks established BPH, resulting in objective improvement in urinary flow rate and subjective improvement in symptoms. Finally, clinical experience with finasteride, a 5α reductase type II inhibitor has documented the relevance of DHT on prostate size (Marberger, 1998). Despite these convicting data, the correlation between androgens and

prostate volume in elderly men is less pronounced. Joseph et al. (2002) reported that a large prostate volume was marginally associated with increased total testosterone level in African-American men, but Meikle et al. (1997) found an inverse correlation between prostate volume and total testosterone level in 214 male twins based on white populations. Others have not found a significant association between total testosterone level and prostate volume. Partin et al. (1991) correlated 23 hormonal factors, including total testosterone/free testosterone to BPH volume assessed histologically. After correcting for age, the BPH volume correlated significantly with free testosterone, but not total testosterone. If not corrected for age, neither testosterone nor free testosterone correlated with BPH volume.

It has been demonstrated that 5 alpha-reductase activity (Bruchovsky et al., 1998), and androgen receptor levels (Barrack et al., 1983) increase with aging, which means that prostatic cells may gradually become more sensitive to DHT during aging, and that this stimulates cell replication in the prostate. Estradiol has been hypothesized to potentiate the effects of androgens in inducing BPH by inducing the androgen receptor, which thereby sensitizes the prostate to free testosterone. In dogs, estrogens have been shown to induce the androgen receptor, alter steroid metabolism resulting in higher levels of intraprostatic DHT, inhibit cell death when given in the presence of androgens, and stimulate stromal collagen production. Schatzl et al. (2000) found hypogonadism in approximately one fifth of elderly men with LUTS but it had no impact on LUTS status, PSA level, prostate volume, uroflowmetry, or endocrine parameters. In contrast to testosterone, they observed an age-related increase in estradiol (+0.86 pg/mL per decade), the only hormone to correlate with prostate volume, thus suggesting its significance for BPH and BPE. Gann et al. (1995) assessed the relation of steroid hormone levels with subsequent surgical treatment for BPH among participants in the Physicians Health Study and found a strong correlation for increasing risk and serum estrogen levels. The relevance of estrogens is underscored by the fact that, within the prostate, the highest concentrations have been detected in the stroma, the predominant tissue found in BPH. The rate-limiting step in estrogen biosynthesis is the conversion of androgens to estrogens, which is catalyzed by the enzyme aromatase. This enzyme is expressed in the human prostate and is regulated by follicle-stimulating hormone (FSH). The recent demonstration of a coexpression of gonadotropin hormones and their corresponding receptors in the human prostate suggests that FSH receptor activation acts in an endocrine fashion by way of age-dependent, elevated FSH (Schatzl et al., 2000). Alternatively, FSH might act in a para-autocrine fashion by way of locally produced FSH, potentially stimulating aromatase activity.

From the above mentioned facts, the age-related growth of the prostate cannot be explained by a mere increase or decrease in serum androgens. Schultheiss et al. (2004) reviewed previous studies and concluded that the link between androgens and age-related growth of the prostate might be explained by a shift of the hormonal ratio (e.g. the androgen/estrogen ratio), the changing intraprostatic hormonal level, or a modified action of hormones and their respective receptors, as well as of intraprostatic enzymes (e.g. 5α reductase). Additional large studies are needed to evaluate the above mechanisms.

3. Testosterone deficiency linked to LUTS

Historically, bladder outlet obstruction (BOO), LUTS, and BPH has been considered to be almost synonymous, however, an increasing number of studies now demonstrate that the correlations between these parameters are weak and symptoms may arise from many

different etiologies. Although LUTS is commonly attributed to BOO caused by BPE, LUTS is not associated with BOO in a third to a half of men (Figure 2) and furthermore, the severity of LUTS secondary to BPH is not necessarily correlated with prostate volume (Chang et al., 2009). Some men with greatly enlarged glands may have little obstruction and few symptoms while others with prostate glands less enlarged have more outlet obstruction and severe symptoms. Asian men have a smaller prostate than Caucasians, but may have similar or higher symptom scores and a more impaired quality of life (Homma et al., 1997).

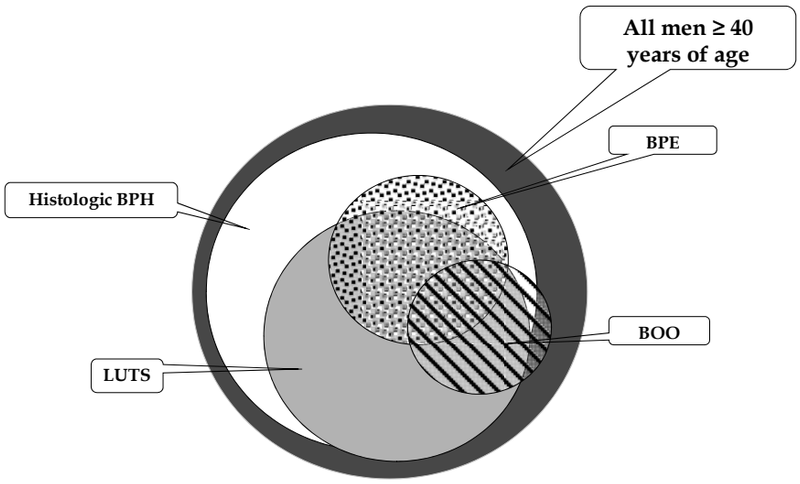


Fig. 2. Correlation between lower urinary tract symptoms (LUTS) and histologic benign prostatic hyperplasia (BPH), benign prostatic enlargement (BPE) and bladder outlet obstruction (BOO)

Many studies have tried to establish a relationship between sex steroids and BPH, but a few studies have analyzed the relationship between circulating testosterone and LUTS. At the epidemiological level, an association between central obesity in adulthood, the metabolic syndrome, erectile dysfunction (ED) and LUTS has been established (Rohrmann et al., 2007). A common denominator of the ailments is lower-than-normal testosterone levels occurring in a significant proportion of elderly men. However, there is no consensus on possible effects of testosterone on LUTS. Schatzl et al. (2003) found that hypogonadism was seen approximately one-fifth of elderly men with LUTS, but it had no impact on symptom status. Litman et al. (2007) found an inverse correlation between symptoms of LUTS and plasma total and bioavailable testosterone but this relationship disappeared after statistical adjustment for age. Roberts et al. (2004) reported a negative association between total testosterone and American Urological Association Symptom Index (AUA-SI) but not with bioavailable testosterone. Miwa et al. (2008) noted an inverse association of free testosterone, but not total testosterone, to International Prostate Symptom Score (IPSS). Recently, author (2009) found free and bioavailable testosterone had significant negative relationships with IPSS total scores and subscores for voiding symptoms even after adjusting for age, prostate total volume and transitional zone volume, high sensitivity C-reactive protein (CRP) and homeostasis model assessment of insulin resistance (HOMA-IR). In addition, free and bioavailable testosterone were significantly related to the presence of severe LUTS (IPSS

≥20) even after adjusting for confounding factors (Figure 3). However, the odds ratio of bioavailable testosterone was lower than that of free testosterone on multivariable analysis (Figure 4).

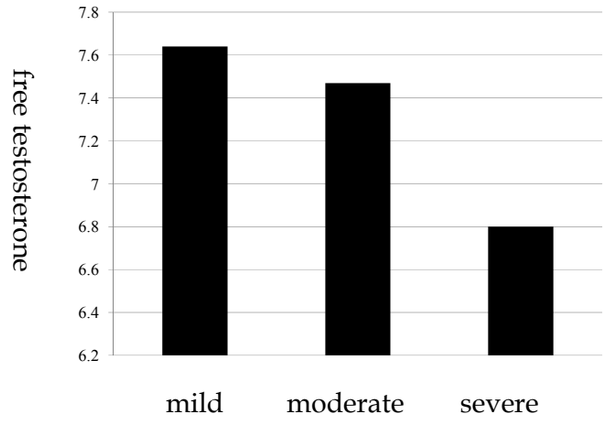


Fig. 3. Blood levels of free testosterone (pg/ml) depending on degree of LUTS severity (Adopted from Chang, et al., 2009)

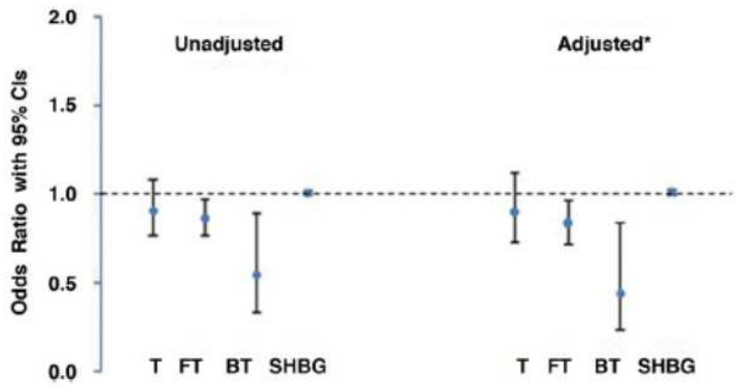


Fig. 4. Odds ratios (95% Cl) of total (T), free (FT) and bioavailable (BT) testosterone, and sex hormone binding globulin (SHBG) on log scales for prediction of severe LUTS (Adopted from Chang, et al., 2009)

A few studies have investigated serum DHT and LUTS. Of the studies examining this association, DHT has not been related with LUTS or BPH in prospective (Meigs et al., 2001; Gann et al., 1995) or cross sectional studies (Platz et al., 1999; Litman et al., 2007). Trifiro et al. (2010) found there was a weak (and unadjusted) association only, suggesting an increase in mean serum DHT concentration among men with LUTS compared with those without. However, serum DHT may not be an ideal measurement of intraprostatic androgen concentrations, as serum DHT does not necessarily correlate to prostate tissue concentrations of DHT. Because of this observation, the serum DHT metabolites 17 beta-diol-glucuronide and androrstanediol glucuronide (AAG) are often used to estimate DHT activity. A cross sectional and a prospective study showed higher levels of the DHT

metabolites and testosterone to DHT metabolite ratios to be directly associated with LUTS or BPH (Kristal et al., 2008; Platz et al., 1999). Kristal et al (2008) showed stronger associations as a ratio suggesting that the testosterone : DHT metabolite or testosterone : DHT ratio may therefore be a more sensitive marker of LUTS/BPH than either hormone individually. Platz et al. (1999) estimated the risk of BPH and severe LUTS in relation to testosterone, DHT, estradiol and AAG in 300 men with severe LUTS. There was a positive relation with AAG and an inverse one with estradiol for the risk of BPH surgery/LUTS, the correlations persisting even after adjusting for steroid hormones and sex hormone binding globulin (SHBG).

A study showed at the 105th Annual Scientific Meeting of the AUA that as testosterone levels decreased, LUTS severity increased and maximum flow rate decreased, while prostate volume remained the same as hormone levels decreased (Sauver, et al., 2010). In another study to determine the relationship between androgens, LUTS and urodynamic variables of BOO in patients with LUTS/BPH, free testosterone was negatively correlated with detrusor pressure at the end of urinary flow (closure detrusor pressure) and pressure at the maximum urinary flow rate (Qmax) (Koritsiadis et al., 2008). Mean closure detrusor pressure and detrusor pressure at Qmax differed significantly between patients with low and normal free testosterone levels. Detrusor overactivity (DO) was noted in patients who had significantly lower free testosterone levels than those with no DO. Although several cross-sectional and prospective studies showed no consensus of association of testosterone with LUTS or BPH, it is notable that no studies have as yet reported an increased risk of LUTS with higher testosterone.

In the rabbit bladder outlet obstruction study, bladder dysfunction is mainly mediated by three cellular processes; 1) progressive denervation, 2) cellular mitochondria malfunction, 3) dysregulation of intracellular calcium storage and release from the sarcoplasmic reticulum (SR). Biomarkers for these three functions are calcium adenosine triphosphatase (ATPase) for calcium release, citrate synthase for mitochondrial function, and choline acetyl-transferse for cholinergic innervations (Juan et al., 2007). Bladder contraction can be divided into phasic and tonic period. The phasic response depends on the adenosine triphosphate (ATP) concentration in the bladder wall, whereas the tonic phase requires mitochondrial oxidative activity to generate energy. Castration of adult male rabbits resulted in a significant decrease in the activities of the mitochondria specific enzyme, citrate synthase of the bladder body and base, muscle and mucosa, urethra and corpora, while choline acetyl-transferse activity and calcium ATPase activity showed different responses depending on the sites (Juan et al., 2007).

Preliminary evidence indicates that men with LUTS benefit from testosterone treatment, and pilot studies have also shown that testosterone therapy has a positive effect on LUTS in late-onset hypogonadism. A study found that the higher plasma levels of testosterone generated with oral testosterone undecanoate than with testosterone gel (50mg/day) were more effective in reducing the score on the IPSS, probably indicating that there is a relationship between plasma levels of testosterone and their effects on LUTS (Yassin et al., 2008). Although this inverse association is contrary to the commonly held clinical opinion that higher serum androgen levels may worsen clinical LUTS and BPH, the risk would not applicable to normalization of the serum testosterone levels in late onset hypogonadism. Clinical trials are needed to confirm that testosterone replacement therapy in older men does not increase the risks of LUTS or clinical BPH. It would also be significant to explore whether normalization of plasma testosterone has an adjunctive therapeutic effect to the more established

pharmacological treatment modalities of LUTS as in an adjunctive therapeutic effect of testosterone supplement to phosphodiesterase type 5 (PDE5) inhibitors for ED treatment accompanied by the testosterone deficiency (Buvat et al., 2011; Blute et al., 2009).

There is ample evidence from many epidemiological studies that LUTS and ED are strongly linked, independently of age. ED assessed by a questionnaire, International Index of Erectile Function (IIEF) score was strongly related to LUTS severity. When controlling for age, LUTS severity was by far the strongest predictor of erectile function, with an odd ratio for severe vs mild LUTS of 8.99 followed by diabetes, 3.01; cardiac disease, 2.17; hypertension, 1.83 and hyperlipidemia, 1.57 (McVary., 2006). The fact that LUTS severity is the strongest predictor of ED suggests that LUTS and ED may share their underlying causes and the underlying causes may explain the reasons why severity of LUTS does not correlates with prostate size. Although a direct causal relationship is not established yet, four pathophysiological mechanisms can explain the relationship. These include 1) insulin resistance and autonomic hyperactivity, 2) alteration in nitric oxide bioavailability, 3) Rho-kinase activation/endothelin pathway, 4) pelvic atherosclerosis, all of which are known to be androgen-dependent.

4. Insulin resistance and autonomic hyperactivity

It was proposed that LUTS is a part of the metabolic syndrome which includes hyperglycemia, obesity, dyslipidemia and hypertension. Recently, testosterone deficiency has captured attention to be a possible risk factor of metabolic syndrome. The basis of this concept came from increased insulin resistance found in both hypergonadotropic and hypogonadotropic hypogonadism. Patients of un-treated Klinefelter's syndrome, compared with control subjects, showed a significantly higher prevalence of metabolic risk factors (Bojesen et al., 2006). GnRH agonist-treated men with prostate cancer also showed significantly decreased insulin sensitivity (Smith et al., 2006). Long-term survivors of testicular cancer have an increased risk for cardiovascular events 10 or more years after chemotherapy (Huddart et al., 2003). Nuver et al. (2005) found lower testosterone associated with a higher body mass index (BMI) pretreatment and a larger BMI increase during follow-up in testicular cancer survivors following cisplatin–based chemotherapy than controls, suggesting testosterone may play a role in the development of the metabolic syndrome.

Plasma testosterone levels decline with aging in healthy men and features of the metabolic syndrome also show age-related deteriorations, suggesting that testosterone is an important regulator of insulin sensitivity in men. There are lots of evidences that late onset hypogonadism is associated with metabolic syndrome. Blouin et al. (2006) investigated whether this decline or the aging process per se accounts for the risk of metabolic syndrome. They observed that patients with a high testosterone level were more likely to have fewer than three components of metabolic syndrome than those with a low testosterone level. Author (2009) also found that HOMA-IR correlated negatively with serum total, free and bioavailable testosterone. Studies showed that blood levels of insulin and metabolic risk factors increased with lower testosterone levels in middle aged men (Laaksonen, et al., 2003). And patients with metabolic syndrome had significantly lower serum testosterone level than those without metabolic syndrome. Men who developed both metabolic syndrome and diabetes mellitus at 11-year follow-up were especially likely to have low testosterone levels already at baseline (Laaksonen, et al., 2004). Pitteloud et al (2005a)

demonstrated men with hypogonadal testosterone levels were twice as insulin resistant as their eugonadal counterparts and 90% fulfill criteria for the metabolic syndrome.

Recent studies provide insight into the role of mitochondrial function in the pathogenesis of insulin resistance. Mitochondria have a critical role in Ca^{2+} buffering in bladder smooth muscle. Pitteloud et al. (2005a) demonstrated testosterone levels were positively correlated not only with insulin sensitivity but also with genetic (oxidative phosphorylation gene expression) and functional (maximal aerobic capacity) markers of mitochondrial function, suggesting a novel molecular mechanism whereby testosterone might modulate insulin sensitivity in men. Pitteloud et al. (2005b) found in another study that insulin resistance was associated with a decrease in Leydig cell testosterone secretion by evaluating the hypothalamic-pituitary-gonadal axis in men with a spectrum of insulin sensitivity.

The most common cause of ED is penile vascular insufficiency. This is usually part of a generalized endothelial dysfunction and is related to several conditions, including type 2 diabetes mellitus, hypertension, hyperlipidemia, and obesity, of which conditions underlie the pathophysiology of metabolic syndrome. There is evidence from multiple epidemiological studies that LUTS and ED are correlated, independent of age or comorbidities as diabetes or hypertension. The prevalence of LUTS was 72% in men with ED versus 38% in those without ED. And the presence of LUTS was a risk factor of ED. Therefore, men seeking care for one condition should always be screened for complaints of the other condition.

Metabolic risk factors induce testosterone deficiency. Obesity-related conditions such as obstructive sleep apnea, insulin resistance and type 2 diabetes mellitus are independently associated with decreased plasma testosterone. Possible mechanisms include decreased LH pulse amplitude, inhibitory effects of estrogen at the hypothalamus and pituitary and the effects of leptin and other peptides centrally and on Leydig cells. Diabetes induces testicular oxidative stress and damage,

Summing up, metabolic syndrome is a risk factor of LUTS and ED and may reduce the blood level of testosterone. Contrariwise, testosterone deficiency may be a causative factor of metabolic risk factors and may accompany LUTS and ED. LUTS is a risk factor of ED and vice versa. This interrelationship suggests that these ailments may be a symptom complex and may share the underlying causes (Figure 5).

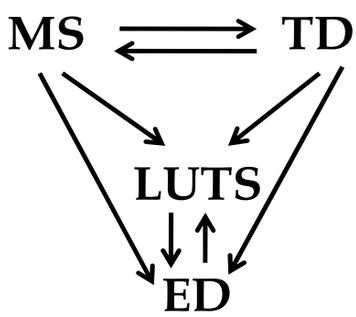


Fig. 5. Interrelationship between metabolic syndrme (MS) testosterone deficiency (TD) lower urinary tract symptom (LUTS) and erectile dysfunction (ED)

However, previous studies on the relationship between androgens and insulin sensitivity in men gave conflicting results depending on whether total or free testosterone levels were

used. One explanation for this discrepancy is the SHBG is mediating the link between testosterone and insulin sensitivity. Proponents of the use of free testosterone argue that it is the best index of androgenicity in insulin-resistant men given the low SHBG levels that pertain in this setting (Plymate et al., 1988). Another explanation is that the assays used to measure free testosterone have serious methodological limitations (Matsumoto & Bremner, 2004).

In a recent study of the epidemiological relationship between metabolic syndrome and LUTS, it was hypothesized that metabolic syndrome is associated with overactivity of the autonomic nervous system, and that insulin resistance, a key element of metabolic syndrome, might be responsible. Hyperinsulinemia promotes endothelin-1 (ET-1) secretion through mitogen-activated protein (MAP)-kinase pathway leading to increase in smooth muscle contraction. In addition, it activates sympathetic nerve system contributing to further increase in the contraction. Overactivity of the autonomic nervous system is supposedly not responsible for the development of LUTS, but rather is believed to play a key role in increasing LUTS severity above an intrinsic basal intensity (McVary et al., 2005; Kasturi et al., 2006).

The studies of Meusburger & Keast (2001) and Keast et al. (2002) have provided elegant demonstrations on the potential role of androgens in maintaining the structure and function of many pelvic ganglion neurons. Giuliano et al. (1993) suggested that testosterone acting peripherally to the spinal cord enhances the erectile response of the cavernous nerve. Traish et al. (2007) showed that testosterone treatment of castrated animals restored the cavernosal nerve fibers and myelin sheath structure, similar to that observed in the sham group. Considering these reports and the hypothesis that noradrenaline and α1-AR that mediate adrenergic contraction of smooth muscles in the prostate, bladder neck, urethra and corpus cavernosum, contribute to the common link, testosterone deficiency could be a causative factor of LUTS via autonomic hyperactivity.

Another possible mechanism includes a direct relaxation effect of testosterone on smooth muscle cells, a change in the number of receptors for sympathetic affecter molecules or a change in sensitivity of smooth muscle cell α-adrenergic receptors (ARs). Comparative binding and functional studies of lower genitourinary tissues have demonstrated that α1-ARs are abundant in the bladder base and prostate but spare in the bladder body (Lepor & Shapiro, 1984). In certain human arteries, α1-AR expression increases and the relative proportion of α1-AR subtypes is modulated by aging (Rudner et al., 1999). These changes might be happening as well in the human prostatic, bladder and erectile tissue. The contractile response of the cavernosal strips of older men with ED was greater than for those isolated from younger men with ED, suggesting that aging has a role in adrenergic sensitivity in patients with ED (Christ et al., 1991). It has also been suggested that α1-ARs are up-regulated in patients with LUTS associated with BPH, resulting in increased smooth muscle tone in the prostatic capsule and bladder neck (Medina et al., 1999).

Theoretically, selective α1-AR antagonists are ideally suited for the treatment of the dynamic component of bladder outlet obstruction, because the resistance along the bladder outlet can be selectively reduced without impairing detrusor contraction. Virtually, α1-AR antagonists have been widely used in practice for treating symptomatic BPH/LUTS. Despite the clinical availability of α1-AR antagonists for treating LUTS, as yet it is not possible to provide a comprehensive picture of the impact of testosterone on α1- ARs. While androgen effect on central and peripheral nervous system are well known, the local effect of androgen on bladder and urethra has not been extensively studied. Even reports on the density of α1-ARs after castration are not consistent. Takyu (1993) found the density of α1-ARs in rabbit

proximal urethra decreased after castration and testosterone supplementation restored the densities of α1-ARs to control levels. Morita et al. (1992) reported that α1-adrenergic and muscarinic cholinergic receptor densities decreased significantly after castration. Yono et al (2006) found the density of α1-ARs in the rat prostate decreased with aging. Because the percent of muscle density shows no significant change throughout life in the rat prostate (Moriyama et al., 1995), the age related decrease in the density of α1-ARs appears to result from direct down-regulation of α1-AR protein. Auger-Pourmarin et al. (1998) presented that testosterone administration produced a 23% decrease of α1-AR density, likely by an increase of prostatic glandular epithelium and a decrease in the relative proportion of smooth muscle, thus of α1-AR density. Lacey et al. (1996) found there was an apparent increase in α1-AR density in dog prostate after castration which returned to baseline with testosterone replacement. However, the increase in α1-ARs density resulted from relative increases in the ratio of smooth muscle to epithelium rather from direct up-regulation of α1-AR protein.

Lastly, recent studies provided an evidence that the inflammatory infiltrates, which are frequently found in and around nodules of BPH (Rohrmann et al, 2005), elevate serum CRP concentration, a non-specific marker of inflammation. Furthermore, the presence of metabolic syndrome might mediate intraprostatic inflammation because of its association with an elevated serum CRP concentration, which would link metabolic syndrome to symptomatic BPH (Rohrmann et al., 2005).

5. Alteration in nitric oxide bioavailability

It is widely accepted that NO, which is synthesized from its precursor L-arginine via NO synthase (NOS), is important in the relaxation of corpus cavernosum smooth muscle and vasculature. By activating gualnylate cyclase, with resultant elevation of cyclic guanylate monophosphate (cGMP), NO results in a lowering of intracellular calcium and smooth muscle relaxation. cGMP is an important secondary messenger of NO involved in modulating the contractility of various smooth muscles. It stimulates protein kinase G, which in turn initiates phosphorylation of membrane-bound proteins at the potassium channels. This leads to potassium ion outflow into the extracellular space resulting in hyperpolarization. Hyperpolarization leads to closure of the L-type calcium channels subsequently resulting in a decrease in the intracellular Ca^{++} ion concentration and consequent smooth muscle cell relaxation. PDE plays important roles in this process by modulating the levels of cGMP and their duration of action (Traish et al., 2007) (Figure 6).

NO is also present in the human prostate and bladder and putatively modulates smooth muscle tone. NOS activity has been reported to be highest in the prostatic urethra, intermediate in the bladder neck, and less pronounced in detrusor muscle. It has been reported that NOS expression, and thus NO production, of the prostate is reduced in the transition zone of the prostate in BPH compared with normal prostate (Bloch et al., 1997). The proposed reduction in expression of NOS isoforms results in increased smooth muscle cell contractile forces at the bladder neck and prostatic urethra leading to the subsequent development of LUTS or LUTS without BPH. On the other hand, reduced NOS/NO results in smooth muscle cell proliferation and may result in structural changes in the prostate and simultaneously increased contraction and affects outlet resistance and bladder compliance (Figure 7). Histochemical staining and immunohistochemistry confirmed dense nitrinergic innervations of glandular epithelium, fibromuscular stroma and blood vessels in the normal human prostate. The nitrinergic innervations is also less in hyperplastic human prostate

than in normal prostate, and this may also contribute to affect voiding function (Podlasek et al., 2003).

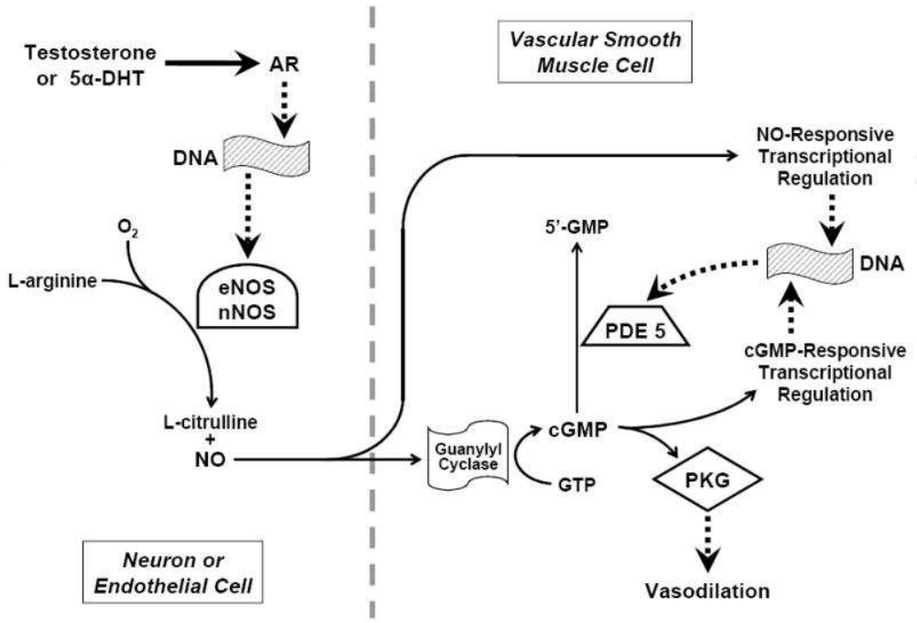


Fig. 6. Potential regulation of nitric oxide synthase (NOS) and hosphodiesterase type 5 (PDE5) by androgens (Adopted fromTraish, et al., 2007)

It is known that the lower urinary and genital tracts are embryologically and anatomically closely related, and that both are sensitive to sex steroids. A preponderance of evidence reports a role for androgens in regulating the expression and activity of NOS isoforms in the corpus cavernosum in animal models. In castrated animals, testosterone and DHT administration restored the erectile response and NOS expression in penis. It can be speculated that if testosterone participates in erectile mechanisms by modulating NOS and phosphodiesterase type 5 (PDE5), a similar interaction might be found in the lower urinary tract, given that the same enzymes and androgen receptors are also present.

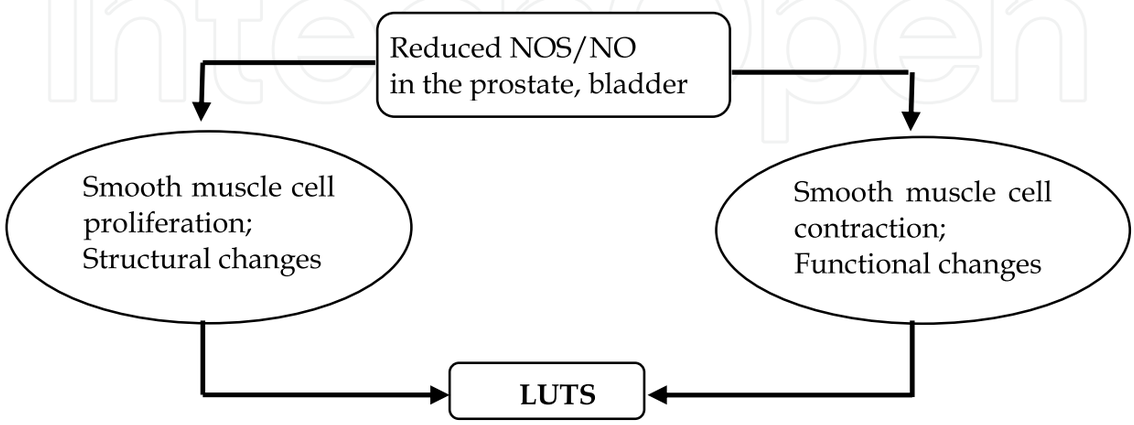


Fig. 7. NOS/NO theory for LUTS/ED (Adopted from McVary, et al., 2006)

Jones & Schoenberg (1985) suggested that aging itself might be an underlying cause of DO, besides BOO. In experimental studies, the inhibition of NO production causes bladder hyperactivity in rats in vivo (Persson et al., 1992), indicating a possible relation with changes in NOS activity in the lower urinary tract. Koritsiadis et al. (2008) found men with no DO had higher free testosterone levels, and all hypogonadal patients had DO, providing evidence that a decline in androgen levels might be a causative factor in DO, by triggering overactivity in an otherwise pathological bladder.

PDE5 hydrolyzes cGMP in vascular and cavernous smooth muscle into GMP. Activation of PDE5 terminates NO-induced, cGMP-mediated smooth muscle relaxation. In penile tissue, the balance between the intracellular levels of cGMP and GMP is primarily regulated by the activities of NOS and PDE5. Thus, it is likely that any disruption in the expression or activity of these enzymes will lead to pathophysiology. Castration has been shown to induce the expression and activity of PDE5 in rabbits and rats, and androgen supplementation has been shown to up-regulate the expression and activity of PDE5 (Zhang et al., 2005; Morelli et al., 2004). Further, administration of PDE inhibitor to castrated animals has little effect on the intracavernosal pressure in response to pelvic nerve stimulation (Zhang et al., 2005), suggesting that androgens are critical not only for regulating NOS activity, but also in modulating PDE5 activity. The presence of PDE in the urinary bladder was identified in studies of the rat (Qiu, et al., 2001) and the human (Werkstrom, et al., 2006).

A recent study, investigating PDE5 expression and activity in the human bladder, elegantly demonstrated that PDE5 regulates smooth muscles tone of the bladder. Vardenafil appeared to block PDE5 activity, and therefore, may 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 (Morelli, et al., 2009). Meanwhile, a large number of clinical studies have convincingly shown that PDE inhibitors have a beneficial effect on LUTS. Sairam et al (2002) found the overall trend in the IPSS was towards improvement after treatment with sildenafil. In a recent 12-week global dose-finding study conducted in 1058 men with BPH-LUTS, tadalafil was associated with statistically significant and clinically meaningful improvements in multiple measures of LUTS, including quality of life and ED improvement, compared to placebo (Roehrborn et al., 2008). Kim et al (2011) reported men with BPH-LUTS treated with tadalafil 5 mg once daily experienced a reduction in BPH-LUTS which was comparable to tamsulosin.

6. Rho-kinase activation/endothelin activity

Smooth muscle contraction has been attributed to an increase in the intracellular calcium concentration. However, some regulatory mechanisms can modify the sensitivity of contractile and regulatory proteins to calcium, leading to a smooth muscle contraction without changing intracellular calcium concentration (Somlyo A.P. & Somlyo A.V., 2000). One of these mechanisms is the Rho-kinase pathway, which is thought to be a major calcium-sensitizing mechanism in smooth muscle. The Rho-kinase is activated by a G-protein, RhoA, thought to be coupled to excitatory α1-adrenoceptors. The major contractile process in bladder is under acetylcholine control, through the activation of M3 muscarinic receptors. RhoA/Rho-kinase calcium sensitization pathway plays a major role in maintaining the contractile actions in bladder smooth muscle tone. Rees et al. (2003) found that a specific inhibitor of Rho-kinase, Y-27632, decreased the proliferation of human and rat

prostatic smooth muscle cells, and inhibited noradrenergic contractions elicited by electrical field stimulation and exogenous phenylephrine in rat prostatic tissue.

In many pathological cases, hyperactivity of Rho/Rho-kinase signaling has been observed. Increased Rho-kinase activity, and consequently increased calcium sensitivity of the contractile machinery, can be found in the detrusor of rabbits with partial BOO (Bing et al., 2003) and in the corpus cavernosum smooth muscle of rabbits with partial BOO (Chang et al., 2005). Increased smooth muscle myosin basal phosphorylation necessary for smooth muscle contraction in the corpus cavernosum smooth muscle of partial BOO, mediated via an increase in Rho-kinase expression/activity, would be expected to make the corpus cavernosum smooth muscle more difficult to relax, which suggests that the RhoA/Rho-kinase pathway as being involved in the mechanism for LUTS-associated ED.

In various animal species estrogen receptors are shown to be expressed in central nervous structures involved in micturition (VanderHorst et al., 2001), as well as in the bladder and urethra (Williams & Papka, 1996; Makela et al., 2000). Chavalmane et al. (2010) found that estrogen supplementation significantly increased the relaxing response of carbacol-precontracted rat bladder strips to Y-27632, an inhibitor of Rho-kinase. On the contrary, testosterone administration in the same animal model did not increase responsiveness to Y-27632, but even reduced it. This was in apparent contrast with the observation in isolated human bladder cells, where testosterone mimicked estrogen effects. However, in human bladder cells co-incubation with letrozole, an inhibitor of aromatase, reverted all the testosterone-induced effects. In addition, DHT, a non-aromatizable androgen, did not substantially stimulate smooth muscle gene expression and cell motility. These findings suggest that active aromatization is operating in human bladder cells and that estrogen and not androgen receptors are involved in stimulating cell migration and expression of genes related to the smooth muscle phenotype. In contrast to human bladder, rat bladder does not express aromatase/CYP19A1 mRNA and testosterone presumably acts only through the androgen receptors. These data indicate that estrogen, more than androgen, receptors up-regulate Rho/Rho-kinase signaling and might have a role in calcium sensitization in human male bladder and androgens have the opposite effect. Clinical studies showing that androgen deficiency is associated with male bladder instability are in keeping with this view. Since an altered estrogen/androgen ratio characterizes several physiological and pathological conditions, often associated to bladder hyperactivity and LUTS, it is possible that a relative hyperesterogenism might induce bladder overactivity, through an activation of the Rho/Rho-kinase pathway.

The actions of several factors beside noradrenaline (e.g. endothelin-1, angiotensin II), possibly involved in the increased smooth muscle activity found in both LUTS/BPH and ED, are dependent on Rho-kinase activity that acts downstream from these receptors (Anderson, 2003). Although the exact mechanisms by which angiotensin II elicits its cellular effects are not known, the mechanism of action of angiotensin II in the cells is related to the Rho/Rho-kinase pathway. While estradiol did not change the number of human aortic endothelial cells secreting endothelin-1 but decreased the number of secreting cells stimulated with angiotensin-II, testosterone induced an increase in the number of cells secreting endothelin-1 and up-regulated endothelin-1 mRNA, indicating that testosterone, estradiol and angiotensin-II have parallel effects on the production of endothelin-1 (Pearson et al., 2008).

7. Pelvic atherosclerosis

Various studies show that bladder dysfunction can be caused by ischemia and suggest that atherosclerosis and hypercholesterolemia might be associated with LUTS. Ischemia in rabbit urinary bladder caused a marked reduction in the compliance and capacity of the bladder (Gill et al., 1988). Azadzoi et al. (1999) found that atherosclerosis-induced chronic bladder ischemia increased transforming growth factor-β1 expression in the bladder leading to fibrosis, smooth muscle atrophy and non-compliance. Hypercholesterolemia also interfered with bladder structure and compliance but to a significantly lesser extent compared with chronic bladder ischemia. It is known atherosclerosis and hypercholesterolemia are associated with low serum androgen levels. Bladder outlet obstruction results in bladder hypertrophy which induces ischemia. Levin et al. (1997) hypothesized that this leads to a release of intracellular calcium, leading to activation of specific enzymes and generation of free radicals. These then attack the membranes of nerves, sarcoplasmic reticulum and mitochondria.

In two cross-sectional studies of elderly men, intima-media thickness (IMT), an indicator of general atherosclerosis, was associated with lower testosterone levels (Hak et al., 2002; van den Beld et al., 2003). In a prospective population-based study, free but not total, testosterone levels were inversely related to IMT (Muller et al., 2004). In a logistic regression model adjusted for the confounding effect of cardiovascular risk factors, men with testosterone levels in the lowest quintile (<9.0 nmol L-1) had an independent OR =1.51 (P=0.015) of being in the highest IMT quintile (Svartberg et al., 2006). Besides the possible modulating effect of testosterone on cardiovascular disease risk factors, a few other possible explanations for the association between testosterone and atherosclerosis have been suggested. A direct beneficial effect of testosterone on plaque development, probably mediated by the vascular androgen receptor has been reported in an animal study (Hanke et al., 2001). Testosterone has also been shown to enhance endothelium-independent and endothelium-dependent vasodilation (Kang et al., 2002)

8. Conclusion

Many studies have tried to establish a relationship between sex steroids and BPH, but a few studies have analyzed the relationship between circulating testosterone and LUTS. Although there is no consensus on possible effects of testosterone on LUTS, endogenous testosterone may have a beneficial effect on the lower urinary tract function, and testosterone deficiency may provide a pathophysiologic basis for the link between LUTS. Preliminary evidence indicates that men with LUTS benefit from testosterone treatment. Four pathophysiological mechanisms can explain the relationship; insulin resistance and autonomic hyperactivity, alteration in NO/NOS/PDE activity, Rho-kinase activation/endothelin pathway, pelvic atherosclerosis, all of which are known to be androgen-dependent.

9. References

Andersson, KE. (2003). Erectile physiological and pathophysiological pathways involved in erectile dysfunction. *Journal of Urology*, 170:S6-S14.

Auger-Pourmarin, L.; Roubert, P. & Chabrier, PE. (1998). Alpha1-adrenoceptors in testosterone-induced prostatic hypertrophy. *European Journal of Pharmacology*, Vol.341, No.1, pp. 119-126.

Azadzoi, KM.; Tarcan T.; Siroky, MB. & Krane, RJ. (1999). Atherosclerosis-induced chronic ischemia causes bladder fibrosis and non-compliance in the rabbit. *Journal of Urology*, Vol.161, No.5, pp. 1626-1635.

Barrack, ER.; Bujnovszky, P. & Walsh, PC. (1983). Subcellular distribution of androgen receptors in human normal, benign hyperplastic, and malignant prostatic tissues: characterization of nuclear salt-resistant receptors. *Cancer Research*, Vol. 43, No. 3, pp. 1107-1116.

Berry, SJ.; Coffey, DS.; Walsh, PC. & Ewing, LL. (1984). The development of human benign prostatic hyperplasia with age. *Journal of Urology,* Vol. 132, No. 3, pp. 474-479.

Bing, W.; Chang, S.; Hypolite, JA.; DiSanto, ME.; Zderic, SA.; Rolf, L.; Wein, AJ. & Chacko, S. (2003). Obstruction-induced changes in urinary bladder smooth muscle contractility: a role for Rho kinase. *American Journal of Physiology- Renal Physiology*, Vol. 285, No. 5, pp. F990-997.

Bloch, W.; Klotz, T.; Loch, C.; Schmidt, G.; Engelmann, U. & Addicks, K. (1997). Distribution of nitric oxide synthase implies a regulation of circulation, smooth muscle tone, and secretory function in the human prostate by nitric oxide. *Prostate*, Vol. 15, No. 1, pp. 1-8.

Blouin, K.; Richard, C.; Brochu, G.; Hould, FS.; Lebel, S.; Marceau, S.; Biron, S,; Luu-The, V. & Tchernof, A. (2006). Androgen inactivation and steroid-converting enzyme expression in abdominal adipose tissue in men. *Journal of Endocrinology*, Vol. 191, No. 3, pp. 637-649.

Blute, M.; Hakimian, P.; Kashanian, J.; Shteynshluyger, A.; Lee, M. & Shabsigh, R. (2009). Erectile dysfunction and testosterone deficiency. *Frontiers of Hormone Research*, Vol. 37, pp.108-122.

Bojesen, A.; Kristensen, K.; Birkebaek, NH.; Fedder, J.; Mosekilde, L.; Bennett, P.; Laurberg, P.; Frystyk, J.; Flyvbjerg, A.; Christiansen, JS. & Gravholt, CH. (2006). The metabolic syndrome is frequent in Klinefelter's syndrome and is associated with abdominal obesity and hypogonadism. *Diabetes Care*, Vol. 29, No. 7, pp. 1591-1598.

Bruchovsky, N.; Rennie, PS.; Batzold, FH.; Goldenberg, SL.; Fletcher, T. & McLoughlin, MG. (1988). Kinetic parameters of 5 alpha-reductase activity in stroma and epithelium of normal, hyperplastic, and carcinomatous human prostates. *Journal of Clinical Endocrinology and Metabolism,* Vol. 67, No. 4, pp. 806-816.

Buvat, J.; Montorsi, F.; Maggi, M.; Porst, H.; Kaipia, A.; Colson, MH.; Cuzin, B.; Moncada, I.; Martin-Morales, A.; Yassin, A.; Meuleman, E.; Eardley, I.; Dean, JD. & Shabsigh, R. (2011). Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). *Journal of Sexual Medicine,* Vol. 8, No. 1, pp. 284-293.

Chang, IH.; Oh, SY. & Kim, SC. (2009). A possible relationship between testosterone and lower urinary tract symptoms in men. *Journal of Urology,* Vol. 182, No. 1, pp. 215-220.

Chang, S.; Hypolite, JA.; Zderic, SA.; Wein, AJ.; Chacko, S. & Disanto, ME. (2005). Increased corpus cavernosum smooth muscle tone associated with partial bladder outlet obstruction is mediated via Rho-kinase. *American Journal of Physiololgy- Regulatory, Integrative and Comparative Physiology,* Vol. 289, No. 4, pp. R1124-1130.

Chavalmane, AK.; Comeglio, P.; Morelli, A.; Filippi, S.; Fibbi, B.; Vignozzi, L.; Sarchielli, E.; Marchetta, M.; Failli, P.; Sandner, P.; Saad, F.; Gacci, M.; Vannelli, GB. & Maggi, M. (2010). Sex Steroid Receptors in Male Human Bladder: Expression and Biological Function. *Journal of Sexual Medicine,* Vol. 7, No. 8, pp. 2698-2713.

Christ, GJ.; Stone, B. & Melman, A. (1991). Age-dependent alterations in the efficacy of phenylephrine-induced contractions in vascular smooth muscle isolated from the corpus cavernosum of impotent men. *Canadian Journal of Physiology and Pharmacology,* Vol. 69, No. 7, pp. 909-913.

Gann, PH.; Hennekens, CH.; Longcope, C.; Verhoek-Oftedahl, W.; Grodstein, F. & Stampfer, MJ. (1995). A prospective study of plasma hormone levels, nonhormonal factors, and development of benign prostatic hyperplasia. *Prostate,* Vol. 26, No. 1, pp. 40-49.

Gill, HS.; Monson, FC.; Wein, AJ.; Ruggieri, MR. & Levin, RM. (1988). The effects of short-term in-vivo ischemia on the contractile function of the rabbit urinary bladder. *Journal of Urology,* Vol. 139, No. 6, pp. 1350-1354.

Giuliano, F.; Rampin, O.; Schirar, A.; Jardin, A. & Rousseau, JP. (1993). Autonomic control of penile erection: modulation by testosterone in the rat. *Journal of Neuroendocrinology,* Vol. 5, No. 6, pp. 677-683.

Hak, AE.; Witteman, JC.; de Jong, FH.; Geerlings, MI.; Hofman, A. & Pols, HA. (2002). Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. *Journal of Clinical Endocrinology and Metabolism,* Vol. 87, No. 8, pp. 3632-3639.

Hanke, H.; Lenz, C.; Hess, B.; Spindler, KD. & Weidemann, W. (2001). Effect of testosterone on plaque development and androgen receptor expression in the arterial vessel wall. *Circulation,* Vol. 103, No. 10, pp. 1382-1385.

Homma, Y.; Kawabe, K.; Tsukamoto, T.; Yamanaka, H.; Okada, K.; Okajima, E.; Yoshida, O.; Kumazawa, J.; Gu, FL.; Lee C.; Hsu, TC.; dela Cruz, RC.; Tantiwang, A.; Lim, PH.; Sheikh, MA.; Bapat, SD.; Marshall, VR.; Tajima, K. & Aso, Y. (1997). Epidemiological survey of lower urinary tract symptoms in Asia and Australia using the international prostate symptom score. *International Journal of Urology,* Vol. 4, No. 1, pp. 40-46.

Huddart, RA.; Norman, A.; Shahidi, M.; Horwich, A.; Coward, D.; Nicholls, J. & Dearnaley, DP. (2003). Cardiovascular disease as a long-term complication of treatment for testicular cancer. *Journal of Clinical Oncology,* Vol. 21, No. 8, pp. 1513-1523.

Irwin,DE.; Abrams, P.; Milsom, I.; Kopp, Z.; Reilly, K.& EPIC Study Group. (2008). Understanding the elements of overactive bladder: questions raised by the EPIC study. *British Journal of Urology International.* Vol. 101, No. 11, pp. 1381-1387.

Jones, KW. & Schoenberg, HW. (1985) Comparison of the incidence of bladder hyperreflexia in patients with benign prostatic hypertrophy and age-matched female controls. *Journal of Urology,* Vol. 133, No. 3, pp. 425-426.

Joseph, MA.; Wei, JT.; Harlow, SD.; Cooney, KA.; Dunn, RL.; Jaffe, CA.; Montie, JE. & Schottenfeld, D. (2002). Relationship of serum sex-steroid hormones and prostate volume in African American men. *Prostate,* Vol. 53, No. 4, pp. 322-329.

Juan, YS.; Onal, B.; Broadaway, S.; Cosgrove, J.; Leggett, RE.; Whitbeck, C.; De, E.; Sokol, R.& Levin, RM. (2007) Effect of castration on male rabbit lower urinary tract tissue enzymes. *Molecular and Cellular Biochemistry,* Vol. 301, No. 1-2, pp. 227-233.

Kang, SM.; Jang, Y.; Kim, JY.; Chung, N.; Cho, SY.; Chae, JS. & Lee, JH. (2002). Effect of oral administration of testosterone on brachial arterial vasoreactivity in men with coronary artery disease. *American Journal of Cardiology,* Vol. 89, No. 7, pp. 862-864.

Kasturi, S.; Russell, S. & McVary KT. (2006). Metabolic syndrome and lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Current Urology Report,* Vol. 7, No. 4, pp. 288-292.

Keast, JR.; Gleeson, RJ.; Shulkes, A. & Morris, MJ. (2002). Maturational and maintenance effects of testosterone on terminal axon density and neuropeptide expression in the rat vas deferens. *Neuroscience.* Vol. 112, No. 2, pp. 391-398.

Kim, SC.; Park, JK.; Kim, SW.; Lee, SW.; Ahn, TY.; Kim, JJ.; Paick, JS.; Park, NC.; Park, K.; Min, KS.; Kraus, SR.; Secrest, RJ.; Elion-Mboussa, A. & Viktrup, L. (2011). Tadalafil administered once daily for treatment of Asian men with lower urinary tract symptoms secondary to benign prostatic hyperplasia: Results from a placebo-controlled pilot study using tamsulosin as an active comparator. *Lower Urinary Tract Symptoms, in press*

Koritsiadis, G.; Stravodimos, K.; Mitropoulos, D.; Doumanis, G.; Fokitis, I.; Koritsiadis, S. & Constantinides, C. (2008). Androgens and bladder outlet obstruction: a correlation with pressure-flow variables in a preliminary study. *British Journal of Urology International,* Vol. 101, No. 12, pp. 1542-1546.

Kristal, AR.; Schenk, JM.; Song, Y.; Arnold, KB.; Neuhouser, ML.; Goodman, PJ.; Lin, DW.; Stanczyk, FZ. & Thompson, IM. (2008). Serum steroid and sex hormone-binding globulin concentrations and the risk of incident benign prostatic hyperplasia: results from the prostate cancer prevention trial. *American Journal of Epidemiology,* Vol. 167, No. 12, pp. 1416-1424.

Laaksonen, DE.; Niskanen, L.; Punnonen, K.; Nyyssönen, K.; Tuomainen, TP.; Salonen, R.; Rauramaa, R. & Salonen, JT. (2003). Sex hormones, inflammation and the metabolic syndrome: a population-based study. *European Journal of Endocrinology,* Vol. 149, No. 6, pp. 601-608.

Laaksonen, DE.; Niskanen, L.; Punnonen, K.; Nyyssönen, K.; Tuomainen, TP.; Valkonen, VP.; Salonen, R. & Salonen, JT. (2004). Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care,* Vol. 27, No. 5, pp. 1036-1041.

Lacey, JP.; Donatucci, CF.; Price, DT.; Page, SO.; Bennett, SA.; Tenniswood, MP. & Schwinn, DA. (1996). Effects of androgen deprivation on prostate alpha 1-adrenergic receptors. *Urology,* Vol. 48, No. 2, pp. 335-341.

Lepor, H. & Shapiro, E. (1984). Characterization of alpha1 adrenergic receptors in human benign prostatic hyperplasia. *Journal of Urology,* Vol. 132, No. 6, pp. 1226-1229.

Levin, RM.; Levin, SS.; Zhao, Y. & Buttyan, R. (1997). Cellular and molecular aspects of bladder hypertrophy. *European Urology,* Vol. 32, Suppl 1: pp. 15-21.

Litman, HJ.; Bhasin, S.; O'Leary, MP.; Link, CL. & McKinlay, JB. (2007). BACH Survey Investigators. An investigation of the relationship between sex-steroid levels and urological symptoms: results from the Boston Area Community Health survey. *British Journal of Urology International,* Vol. 100, No. 2, pp. 321-326.

Mäkelä, S.; Strauss, L.; Kuiper, G.; Valve, E.; Salmi, S.; Santti, R. & Gustafsson, JA. (2000). Differential expression of estrogen receptors alpha and beta in adult rat accessory sex glands and lower urinary tract. *Molecular and Cellular Endocrinology,* Vol. 170, No. 1-2, pp. 219-229.

Marberger, MJ. (1998). Long-term effects of finasteride in patients with benign prostatic hyperplasia: a double-blind, placebo-controlled, multicenter study. PROWESS Study Group. *Urology,* Vol. 51, No. 5, pp. 677-686.

Matsumoto, AM.& Bremner, WJ. (2004). Serum testosterone assays--accuracy matters. *Journal of Clinical Endocrinology and Metabolism,* Vol. 89, No. 2, pp. 520-524.

McVary, K. (2006). Lower urinary tract symptoms and sexual dysfunction: epidemiology and pathophysiology. *British Journal of Urology International, Vol.* 97, Suppl 2, pp. 23-28.

McVary, KT.; Rademaker, A.; Lloyd, GL. & Gann, P. (2005). Autonomic nervous system overactivity in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Journal of Urology,* Vol. 174, No. 4 Pt 1, pp. 1327-1433.

Medina, JJ.; Parra, RO. & Moore, RG. (1999). Benign prostatic hyperplasia (the aging prostate). *Medical Clinics of North America,* Vol. 83, No. 5, pp. 1213-1229.

Meigs, JB.; Mohr, B.; Barry, MJ.; Collins, MM. & McKinlay, JB. (2001). Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. *Journal of Clinical Epidemiology,* Vol. 54, No. 9, pp. 935-944.

Meikle, AW.; Stephenson, RA.; Lewis, CM. & Middleton, RG. (1997). Effects of age and sex hormones on transition and peripheral zone volumes of prostate and benign prostatic hyperplasia in twins. *Journal of Clinical Endocrinology and Metabolism,* Vol. 82, No. 2, pp. 571-575.

Sauver, J.; Jacobson, D.; McGree, M.; Girman, C.; Hill, C.; Lieber, M. & Nehra, A. (2010). Correlations between rates of decline in testosterone level and rates of change in lower urinary tract symptoms, prostatic enlargement, and maximum urinary flow rate. *Proceeding of the 105th Annual Scientific Meeting of the AUA*, #1633, San Francisco, May 2010.

Miwa, Y.; Kaneda, T. & Yokoyama, O. (2008). Association between lower urinary tract symptoms and serum levels of sex hormones in men. *Urology,* Vol. 72, No. 3, pp. 552-555.

Morelli, A.; Filippi, S.; Sandner, P.; Fibbi, B.; Chavalmane, AK.; Silvestrini, E.; Sarchielli, E.; Vignozzi, L.; Gacci, M.; Carini, M.; Vannelli, GB. & Maggi, M. (2009). Vardenafil modulates bladder contractility through cGMP-mediated inhibition of RhoA/Rho kinase signaling pathway in spontaneously hypertensive rats. *Journal of Sexual Medicine,* Vol. 6, No. 6, pp. 1594-1608.

Morelli, A.; Filippi, S.; Mancina, R.; Luconi, M.; Vignozzi, L.; Marini, M.; Orlando, C.; Vannelli, GB.; Aversa, A.; Natali, A.; Forti, G.; Giorgi, M.; Jannini, EA.; Ledda, F.& Maggi, M. (2004). Androgens regulate phosphodiesterase type 5 expression and functional activity in corpora cavernosa. *Endocrinology,* Vol. 145, No. 5, pp. 2253-2263.

Morita, T.; Tsuchiya, N.; Tsujii, T. & Kondo, S. (1992). Changes of autonomic receptors following castration and estrogen administration in the male rabbit urethral smooth muscle. *Tohoku Journal of Experimental Medicine,* Vol. 166, No. 403-405.

Moriyama, N.; Kurimoto, S.; Nagase, Y.; Inagaki, O.; Takanashi, M. & Kawabe, K. (1995). Age-related changes in alpha 1-adrenoceptors in rat prostate. *Urological Research,* Vol. 22, No.6, pp. 389-392.

Muesburger, SM. & Keast, JR. (2001).Testosterone and nerve growth factor have distinct but interacting effects on structure and neurotransmitter expression of adult pelvic ganglion cells in vitro. *Neuroscienc*e, Vol.108, No. 2, pp. 331-340.

Muller, M.; van den Beld, AW.; Bots, ML.; Grobbee, DE.; Lamberts, SW. & van der Schouw, YT. (2004). Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. *Circulation,* Vol. 109, No. 17, pp. 2074-2079.

Nuver, J.; Smit, AJ.; Wolffenbuttel, BH.; Sluiter, WJ.; Hoekstra, HJ.; Sleijfer, DT. & Gietema, JA. (2005). The metabolic syndrome and disturbances in hormone levels in long-term survivors of disseminated testicular cancer. *Journal of Clinical Oncology.* Vol. 23, No. 16, pp. 3718-3725.

Partin, AW.; Oesterling, JE.; Epstein, JI.; Horton, R. & Walsh, PC.(1991). Influence of age and endocrine factors on the volume of benign prostatic hyperplasia. *Journal of Urology,* Vol. 145, No. 2, pp. 405-409.

Pearson, LJ.; Yandle, TG.; Nicholls, MG. & Evans, JJ. (2008) Regulation of endothelin-1 release from human endothelial cells by sex steroids and angiotensin-II. *Peptides*, Vol. 29, No. 6, pp.1057-1061.

Persson, K.; Igawa, Y.; Mattiasson, A. & Andersson, KE. (1992). Effects of inhibition of the L-arginine/nitric oxide pathway in the rat lower urinary tract in vivo and in vitro. *British Journal of Pharmacology,* Vol. 107, No. 1, pp. 178-184.

Pitteloud, N.; Mootha, VK.; Dwyer, AA.; Hardin, M.; Lee, H.; Eriksson, KF.; Tripathy, D.; Yialamas, M.; Groop, L.; Elahi, D. & Hayes, FJ. (2005). Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. *Diabetes Care,* Vol. 28, No. 7, pp. 1636-1642.

Pitteloud, N.; Hardin, M.; Dwyer, AA.; Valassi, E.; Yialamas, M.; Elahi, D. & Hayes, FJ. (2005). Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. *Journal of Clinical Endocrinology and Metabolism,* Vol. 90, No. 5, pp. 2636-2641.

Platz, EA.; Kawachi, I.; Rimm, EB.; Longcope, C.; Stampfer, MJ.; Willett, WC. & Giovannucci, E. (1999). Plasma steroid hormones, surgery for benign prostatic hyperplasia, and severe lower urinary tract symptoms. *Prostate Cancer and Prostatic Disease,* Vol. 2, No. 5/6, pp. 285-289.

Plymate, SR.; Matej, LA.; Jones, RE. & Friedl, KE. (1988). Inhibition of sex hormone-binding globulin production in the human hepatoma (Hep G2) cell line by insulin and prolactin. *Journal of Clinical Endocrinology and Metabolism,* Vol. 67, No. 3, pp. 460-464.

Podlasek, C.; Zeiner, DJ. & McKenna, KE. (2003). Morphological changes and altered NOS isoform distribution in the BB/WOR diabetic rat prostate. *Journal of Urology,* Vol. 169, Suppl, pp. 285, A1108.

Qiu, Y.; Kraft, P.; Craig, EC.; Liu, X. & Haynes-Johnson, D. (2001). Identification and functional study of phosphodiesterases in rat urinary bladder. *Urological Research.* Vol. 29, No. 6, pp. 388-392.

Rees, RW.; Foxwell, NA.; Ralph, DJ.; Kell, PD.; Moncada, S. & Cellek, S. (2003). Y-27632, a Rho-kinase inhibitor, inhibits proliferation and adrenergic contraction of prostatic smooth muscles. *Journal of Urology,* Vol. 170, No. 6 pt 1, pp. 2517-2622.

Roberts, RO.; Jacobson, DJ.; Rhodes, T.; Klee, GG.; Leiber, MM. & Jacobsen, SJ. (2004). Serum sex hormones and measures of benign prostatic hyperplasia. *Prostate,* Vol. 61, No. 2, pp. 124-1231.

Roehrborn, CG.; McVary, KT.; Elion-Mboussa, A. & Viktrup, L. (2008). Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study. *Journal of Urology,* Vol. 180, No. 4, pp. 1228-1234.

Rohrmann, S.; Nelson, WG.; Rifai, N.; Kanarek, N.; Basaria, S.; Tsilidis, KK.; Smit, E.; Giovannucci, E. & Platz, EA. (2007). Serum sex steroid hormones and lower urinary tract symptoms in Third National Health and Nutrition Examination Survey (NHANES III). *Urology,* Vol. 69, No. 4, pp. 708-713.

Rohrmann, S.; De Marzo, A.; M., Smit, E.; Giovannucci, E. & Platz, EA. (2005). Serum C-reactive protein concentration and lower urinary tract symptoms in older men in the Third National Health and Nutrition Examination Survey (NHANES III). *Prostate,* Vol. 62, No. 1, 27-33.

Rudner, XL.; Berkowitz, DE.; Booth, JV.; Funk, BL.; Cozart, KL.; D'Amico, EB.; El-Moalem, H.; Page, SO.; Richardson, CD.; Winters, B.; Marucci, L. & Schwinn, DA. (1999). Subtype specific regulation of human vascular alpha(1)-adrenergic receptors by vessel bed and age. *Circulation,* Vol. 100, No. 23, pp. 2336-2343.

Sairam, K.; Kulinskaya, E.; McNicholas, TA.; Boustead, GB. & Hanbury, DC. (2002). Sildenafil influences lower urinary tract symptoms. *British Journal of Urology International,* Vol. 90, No. 9, pp. 836-839.

Schatzl, G.; Madersbacher, S.; Temml, C.; Krenn-Schinkel, K.; Nader, A.; Sregi, G.; Lapin, A.; Hermann, M.; Berger, P. & Marberger, M. (2003). Serum androgen levels in men: impact of health status and age. *Urology,* Vol. 61, No. 3, pp. 629-633.

Schatzl, G.; Brössner, C.; Schmid, S.; Kugler, W.; Roehrich, M.; Treu, T.; Szalay, A.; Djavan, B.; Schmidbauer, CP.; Söregi, S. & Madersbacher, S. (2000). Endocrine status in

elderly men with lower urinary tract symptoms: correlation of age, hormonal status, and lower urinary tract function. The Prostate Study Group of the Austrian Society of Urology. *Urology,* Vol. 55, No. 3, pp. 397-402.

Schultheiss, D.; Machtens, S. & Jonas, U. (2004). Testosterone therapy in the ageing male: what about the prostate. *Andrologia,* Vol. 36, No. 6, pp. 355-65.

Smith, MR.; Lee, H. & Nathan, DM. (2006). Insulin sensitivity during combined androgen blockade for prostate cancer. *Journal of Clinical Endocrinology and Metabolism,* Vol. 91, No. 4, pp. 1305-1308.

Somlyo, AP. & Somlyo, AV. (2000). Signal transduction by G-proteins, Rho-kinase and protein phosphatase to smooth muscle and non-muscle myosin II. *Journal of Physiology,* Vol. 522, No. Pt 2, pp. 177–185.

Svartberg, J.; von Mühlen, D.; Mathiesen, E.; Joakimsen, O.; Bønaa, KH. & Stensland-Bugge, E. (2006). Low testosterone levels are associated with carotid atherosclerosis in men. *Journal of Internal Medicine,* Vol. 259, No. 6, pp. 576-582.

Takyu S. (1993). Effects of testosterone on the autonomic receptor-mediated function in lower urinary tract from male rabbits. *Nippon Hinyokika Gakkai Zasshi.* Vol. 84, No. 2, pp. 330-338.

Trifiro, MD.; Parsons, JK.; Palazzi-Churas, K.; Bergstrom, J.; Lakin, C. & Barrett-Connor, E. (2010). Serum sex hormones and the 20-year risk of lower urinary tract symptoms in community-dwelling older men. *British Journal of Urology International.* Vol. 105, No. 11, pp. 1554-1559.

Traish, AM.; Goldstein, I. & Kim, NN. (2007). Testosterone and erectile function: from basic research to a new clinical paradigm for managing men with androgen insufficiency and erectile dysfunction. *European Urology*, Vol. 52, No. 1, pp. 54-70.

van den Beld, AW.; Bots, ML.; Janssen, JA.; Pols, HA.; Lamberts, SW. & Grobbee, DE. (2003). Endogenous hormones and carotid atherosclerosis in elderly men. *American Journal of Epidemiology,* Vol. 157, No. 1, pp. 25-31.

VanderHorst, VG.; Meijer, E. & Holstege, G. (2001). Estrogen receptor-alpha immunoreactivity in parasympathetic preganglionic neurons innervating the bladder in the adult ovariectomized cat. *Neuroscience Letters,* Vol. 298, No. 3, pp. 147-150.

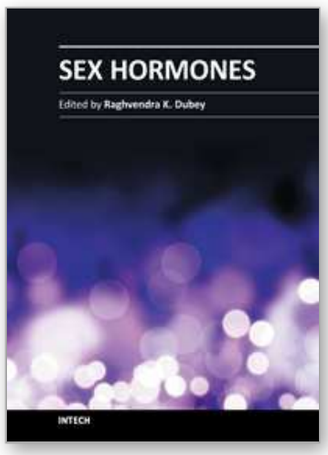
Werkström, V.; Svensson, A.; Andersson, KE. & Hedlund, P. (2006). Phosphodiesterase 5 in the female pig and human urethra: morphological and functional aspects. *British Journal of Urology International,* Vol. 98, No. 2, pp. 414-423.

Williams, SJ. & Papka, RE. (1996). Estrogen receptor-immunoreactive neurons are present in the female rat lumbosacral spinal cord. *Journal of Neuroscience Research,* Vol. 46, No. 4, pp. 492-501.

Yassin, AA.; El-Sakka, AI.; Saad, F. & Gooren, LJ. (2008). Lower urinary-tract symptoms and testosterone in elderly men. *World Journal of Urology,* Vol. 26, No. 4, pp. 359-364.

Yono, M.; Foster, HE Jr.; Weiss, RM. & Latifpour, J. (2006). Age related changes in the functional, biochemical and molecular properties of alpha1-adrenoceptors in the rat genitourinary tract. *Journal of Urology,* Vol. 176, No. 3, pp. 1214-1219.

Zhang, XH.; Morelli, A.; Luconi, M.; Vignozzi, L.; Filippi, S.; Marini, M.; Vannelli, GB.; Mancina, R.; Forti, G.& Maggi, M. (2005). Testosterone regulates PDE5 expression and in vivo responsiveness to tadalafil in rat corpus cavernosum. *European Urology.* Vol. 47, No. 3, pp. 409-416.



Sex Hormones

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Sex Hormones not only regulate reproductive function, but they also play a prominent role in the biology and physiology of several organs/tissues and in the pathophysiology of several diseases. During the last two decades, the information on the mechanisms of action of sex hormones, such as estrogens and androgens, has rapidly evolved from the conventional nuclear receptor dependent mechanisms to include additional non-nuclear, non-genomic and receptor-independent mechanisms. This highlights the need to update the current knowledge on sex hormones and their mode of action. Increasing evidence that exogenous/epigenetic factors can influence sex hormone production and action highlights the need to update our knowledge on the mechanisms involved. This book provides a systematic and updated overview of the male/female sex-hormones and their impact in the biology and physiology of various organs. Additionally, the book discusses their positive and negative association with the pathophysiology of various diseases (e.g. osteoporosis, cardiovascular-disease, hypogonadism, reproduction, cancer) and their therapeutic potential.

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