Erectile Dysfunction — A Missed Part of Benign Prostate Hyperplasia

Shang-Sen Lee, M.D.
Department of Urology, Tri-Service General Hospital, Taipei, Taiwan

INTRODUCTION

Lower urinary tract symptoms (LUTS) are common in aging individuals, with benign prostatic hyperplasia (BPH) being the primary cause of LUTS in men over 50 years of age. The presence of histological BPH at autopsy is approximately 8% in men aged 31-40 years, 50% in those aged 51-60 years, 70% in those aged 61-70 and 90% in those aged 81-90 [1]. The Massachusetts Male Aging Study (MMAS) results demonstrated an erectile dysfunction prevalence of 52%, with nearly 35% reporting moderate/severe erectile dysfunction. The prevalence of complete erectile dysfunction was dependent on age, increasing from 5% for men aged 40 years to 15% for those aged 70 years. Erectile dysfunction was also significantly associated with various age-independent comorbidities, including diabetes, depression, hypertension and heart disease.

In the last decade, numerous epidemiological studies have investigated the prevalence of erectile dysfunction, ejaculatory dysfunction and the specific risk factors associated with LUTS conditions. The data from these studies have demonstrated consistent and compelling evidence for an association between LUTS/BPH and sexual dysfunction in aging men that is independent of the effects of age, other comorbidities and various lifestyle factors. As a result of this association, new approaches have been recommended for the evaluation and management of LUTS/BPH and male sexual dysfunction, and for the selection of treatment options.

RELATIONSHIP BETWEEN LUTS/BPH AND MALE SEXUAL DYSFUNCTION

Studies of both population-based and clinic-based samples have examined the relationship between different types of male sexual dysfunction and LUTS/BPH using multiple logistic regression analysis to determine the independent effect of LUTS after controlling for age and other known risk factors. The National Health and Social Life Survey [2] in the United States indicated that LUTS were a significant predictor for erectile dysfunction after controlling for demographic characteristics, and health and lifestyle factors. The Cross National Study [3] assessed the prevalence of erectile dysfunction in relatively healthy men (no previous diagnosis of cardiovascular disease, prostate disease or surgery, diabetes, ulcer or depression, and not taking hormones) in Brazil, Italy, Japan and Malaysia. In these healthy men, multivariate analyses that controlled for age and other erectile dysfunction risk factors (depression, smoking, physical activity, body mass index (BMI) and education level) indicated that moderate and severe LUTS were the most significant predictors for erectile dysfunction. This study provides convincing evidence for the association between LUTS and erectile dysfunction, independent of the role of other comorbidities.

The Multinational Survey of the Aging Male (MSAM-7) [4], one of the largest population-based studies of aging men to date, evaluated the association between age, LUTS, concomitant comorbidities and male sexual dysfunction in 12,815 men in the United States and six European countries. The results of this study strongly confirmed the relationship between LUTS and sexual dysfunction in men, independent of the effects of age, medical comorbidities and various lifestyle factors. The overall prevalence of LUTS was 90%, with the prevalence of moderate/severe LUTS significantly related to age. The overall prevalence of erectile dysfunction was 49%, with 10% reporting complete or total erectile dysfunction. The prevalence of ejaculatory dysfunction in men able to achieve erections was 46%, with 5% of the men reporting a complete absence of ejaculation. The rates of both erectile dysfunction and ejaculatory dysfunction were significantly dependent on age and highly correlated with the severity of LUTS. In multivariate analyses, which controlled for age, medical comorbidities (diabetes, hypertension, cardiac disease and hypercholesterolemia), tobacco use, alcohol consumption, age and the severity of LUTS were independ-ent risk factors for both erectile dysfunction and ejaculatory dysfunction. In this large, multinational study of aging men, LUTS were a stronger predictor of erectile dysfunction and ejaculatory dysfunction than diabetes, hypertension, heart disease or hyperlipidemia.

In a health-screening study of Austrian men aged 20-80 years [5, 6], the prevalence of LUTS was 84% and the prevalence of erectile dysfunction was 32%, with both conditions significantly related to age. In multivariate analyses that controlled for age, comorbidities (diabetes, hypertension and hyperlipidemia) and lifestyle factors (smoking, alcohol consumption, physical activity and stress), moderate/severe LUTS were an independent risk factor for erectile dysfunction. Interestingly, the results indicated that obstructive symptoms, nocturia and problems associated with LUTS were primarily responsible for the association between LUTS and erectile dysfunction [5].

In a recent longitudinal analysis from the Olmsted County Study [7] of 1,547 men aged 40-70 years in Olmstead County, Minnesota, all sexual function domains assessed (sex drive, erectile function, ejaculatory function, problem assessment and overall satisfaction) and LUTS worsened with increasing age. After adjusting for age, significant correlations were demonstrated between LUTS severity and the domain scores for erectile function and ejaculation function. Interestingly, age stratification analyses showed that the correlation between LUTS and ejaculatory function was significant for men under 70 years of age, whereas the correlation between LUTS and erectile function was only significant for men under 60 years of age. Significant age-adjusted correlations were demonstrated between sexual function domains and

Received: February 12, 2007 Accepted: March 2, 2007
Address correspondence to: Dr. Shang-Sen Lee, Department of Urology, Tri-Service General Hospital, 325, Section 2, Chenggong Road, Taipei, Taiwan
E-mail: johnson@ndmctsgh.edu.tw

all obstructive symptoms, urgency and nocturia.

MECHANISM OF INTERACTION BETWEEN ERECTILE DYSFUNCTION AND LUTS

α_1-Adrenergic receptors

An imbalance in the autonomic control of smooth muscle contraction and relaxation may play an important role in both LUTS and sexual dysfunction. α_1-adrenergic receptors are known to play an important role in mediating the tone of smooth muscle cells in various tissues. Various α_1-adrenergic receptor subtypes have been identified in the lower urinary tract, including α_{1A}- and α_{1D}-receptors in prostatic stromal cells [8,9], α_{1B}-receptors in epithelial cells, α_{1A}- and α_{1B}-receptors in vascular smooth muscle, α_{1A}- and α_{1D}-receptors in the urethra and bladder, and α_{1D}-receptors in the detrusor muscle [10]. It has been suggested that α_1-adrenergic receptors are up-regulated in patients with LUTS associated with BPH, resulting in increased smooth muscle tone in the pro-static capsule and bladder neck [11]. This is supported by the fact that α_1-adrenergic receptor antagonists, which relax the smooth muscle of the prostate and bladder, are effective first-line medications for the treatment of LUTS associated with BPH.

Penile detumescence and erection are dependent on the balance between contraction and relaxation of the corpus cavernosum smooth muscle. In erectile dysfunction, the balance favors contraction (detumescence) rather than relaxation (erection). Noradrenaline is involved in the contraction of penile tissues via activation of α_1-adrenergic receptors in the penile vasculature and corpus cavernosum smooth muscle, with androgens possibly regulating the responsiveness of these receptors [12]. With α_{1D}- and α_{1A}-adrenergic receptors identified as the receptor subtypes in the human vas deferens and prostate gland, activation of α_1-adrenergic receptors is a possible mechanism for both emission and ejaculation. Any impairment in the activation of the α_1-adrenergic receptors of the seminal tract may theoretically result in ejaculatory dysfunction.

The contraction and growth of vascular smooth muscle cells is also mediated by α_1-adrenergic receptors. In certain human arteries, α_1-receptor expression increases and the relative proportion of α_1-adrenergic receptor subtypes is modulated by aging [13]. In mammary arteries from healthy individuals aged <55 years, α_{1A}-adrenergic receptors were identified as the main subtype, whereas the α_{1B}-adrenergic receptor subtype predominated in individuals aged ≥ 65 years. Tissue-specific regulation of α_1-adrenergic receptor subtypes may also occur in various disease states, especially those that are age-dependent. Interestingly, the mean efficacy of phenylephrine-induced contractions of vascular smooth muscle strips, mediated by activation of α_1-adrenergic receptors, was significantly greater for those isolated from the corpus cavernosum of older (≥ 60 years) men with erectile dysfunction than for those isolated from younger (<60 years) men with erectile dysfunction, without an alteration in phenylephrine affinity. Kinetic studies indicated that the maximal rate constant for the onset of these contractions was significantly greater in older versus younger men with erectile dysfunction [14].

Adrenergic-mediated contraction of smooth muscle may also be regulated by Rho and Rho-associated kinase [15], which have been found in human prostatic smooth muscle cells and the vas deferens of the mouse. The results of other studies have suggested a possible role for the Rho/Rho kinase pathway in the mechanism of penile smooth muscle contraction [16,17]. Thus, alterations in α_1-adrenergic receptor-mediated smooth muscle tone and its regulators may be a common component involved in LUTS associated with BPH, erectile dysfunction and ejaculatory dysfunction.

Endothelial dysfunction

Another mechanism that may link the pathophysiology of LUTS with male sexual dysfunction is endothelial dysfunction, which refers to impaired endothelium-dependent vasodilation (i.e. relaxation) resulting from the decreased bioactivity of nitric oxide (NO) [18]. Endothelial dysfunction has been associated with aging, cardiovascular disease, diabetes, hypertension and hypercholesterolemia. Possible mechanisms responsible for endothelial dysfunction include accelerated breakdown of NO by reactive oxygen species, alterations in antioxidant defense systems and alterations in the activity or expression of the endothelial NO synthase (eNOS) enzyme. In aging men, decreasing levels of testosterone and reductions in the conversion of testosterone to estradiol by the aromatase enzyme may contribute to the deficits in eNOS-derived NO. In an animal model of age-related erectile dysfunction, endothelial dysfunction of the corpus caver-nosum was associated with up-regulation of eNOS and alterations in intracellular calcium flux. Endothelial dysfunction has been suggested as the common component linking erectile dysfunction and cardiovascular disease. Furthermore, in prostatic tissue from men with BPH, nitrergic innervation was demonstrated to be decreased compared with that in normal prostate tissue [19], which suggests a possible role for NO in the pathophysiology of BPH. Studies in animals also suggest that NO plays a role in preventing bladder contractions that result in bladder hyperactivity, as observed in LUTS [20]. Thus, alterations in vascular endothelium function may be responsible for various age-related conditions, including LUTS associated with BPH and male sexual dysfunction.

Sex hormones

The development and growth of the normal prostate gland is known to be dependent on an intact sex hormone-signaling axis. Dihydrotestosterone (DHT), which is more potent than testosterone and demonstrates a higher affinity for androgen receptors, is predominantly produced peripherally from testosterone via the enzyme 5α-reductase. Androgen receptors, which are present in both the stroma and epithelium of the prostate as well as in most blood vessel endothelial cells, smooth muscle cells and fibrocytes, may play a role in the interaction between the stroma and the epithelium of the prostate.

Age-related changes in circulating hormone levels and an imbalance in the testosterone/estrogen ratio may play a role in the pathophysiology of BPH and sexual dysfunction. Longitudinal data from the MMAS indicated that serum levels of total testosterone, dehydroepiandrosterone (DHEA), DHEA-sulfate, cortisol and estrone declined, whereas levels of DHT, sex hormone binding globulin, luteinizing hormone, follicle-stimulating hormone and prolactin increased in men who were aged 40 to 70 years of age at baseline and followed for 7 to 10 years. It was suggested that higher levels of DHT with aging may be an adaptation to compensate for decreased testosterone levels. With sex hormones primarily produced from precursors in peripheral tissues in humans, each target tissue has the ability to modulate hormone metabolism and signaling processes through the regulation of tissue enzyme activities [21,22] and hormone receptor subtypes. Ad-

ditional studies are needed to assess whether alterations in sex hormone levels and their receptors play a role in the pathophysio-logy of BPH and sexual dysfunction.

Impact of alpha-blockers on erectile dysfunction

If LUTS and erectile dysfunction are causally linked, then treatment of LUTS with alpha-blockers may improve erectile dysfunction. What is the impact on erectile function when patients are treated with alpha-blockers? Alpha-blockers might contribute to the improvement of erectile dysfunction by altering the balance of penile vasoconstrictive and vasorelaxant forces in favor of the proerectile mechanisms. Conversely, α_1-blockers with excessive hypotensive effects may be anti-erectile by reducing penile filling pressure. Oral α-receptor antagonists exert their effects by blocking the actions of norepinephrine at α_1-adrenoceptors on cavernosal smooth muscle cells. Norepinephrine released from sympathetic nerve terminals ordinarily acts at postjunctional α_1-receptors to produce smooth muscle contraction and detumescence, and is a likely candidate for a mechanism of action in the autonomic hyperactivity model. This neurotransmitter also acts at presynaptic α_2-receptors on the ends of nerve terminals to reduce norepinephrine release. It is not likely that the alpha-blockers used for LUTS would affect the presynaptic α_2-receptors given the selectivity profile [23]. There are few reports detailing the impact of alpha-blocker use on erectile dysfunction improvement. Lukacs et al reported patients' self-perceived sense of sexual satisfaction as significantly improved from baseline, with the degree of improvement correlating to age, while being treated with alfuzosin [24]. The biggest improvement was noted in middle-aged men with moderate to severe LUTS at baseline. Similarly, the effect of a once dayly treatment with alpha-blocker for one year, alfulzosin has been shown to improve sexual function in men with lower urinary tract symptoms and concomitant sexual dysfunction [25]. Comparison of mean weighted scores using the DAN-PSS sex score showed improvement of the erectile function domain by 36% over baseline(2.5 (2.2) decreased to 0.9(2.0), p <0.001). Improvement was most marked in those with the most severe LUTS. The open labeled nature of these latter two studies is problematic.

As the addition of alpha-blockers may have a beneficial effect on patients with erectile dysfunction, Kaplan et al investigated the synergistic effects of doxazosin and intra-cavernosal therapy (ICI) in those for whom ICI alone failed to induce an erection. Overall, 22 (57.9%) of 38 patients with the combined regimen had a significant (more than 60% improvement in International Index of Erectile Function (IIEF) score) therapeutic response [26]. The synergistic effects of vascular dilation and blockade of sympathetic inhibition is one explanation for this response. In general, the improvement of erectile dysfunction in conjunction with alpha-blocker treatment is not as robustly affected as the improvement of LUTS.

CONCLUSION

Research during the past decade has firmly established that erectile dysfunction and ejaculatory dysfunction are highly prevalent conditions in aging men, particularly those with LUTS/BPH. Large-scale epidemiological studies have demonstrated that LUTS are an independent risk factor for male sexual dysfunction. The underlying mechanisms responsible for the relationship between LUTS and male sexual dysfunction are not fully elucidated. With our knowledge of the relationship between LUTS and sexual dysfunction, we have gained new insights into the evaluation and management of patients with these conditions. It is now recommended that men presenting with LUTS should be evaluated for sexual dysfunction and those presenting with sexual dysfunction should be evaluated for LUTS. Furthermore, because some oral therapies for LUTS/BPH can adversely affect sexual function in patients who are already at increased risk of sexual dysfunction, healthcare providers should discuss sexual function with their patients both before and during treatment. Further studies of combination therapy for LUTS/BPH, sexual dysfunction and other age-associated comorbidities may provide new approaches to the optimal management of these conditions in aging men.

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