Journal of Andrology, Vol. 25, No. 4, July/August 2004

Review

The Link Between LUTS and ED: Clinical and Basic Science Evidence

JONATHAN D. SCHIFF AND JOHN P. MULHALL

From the James Buchanan Brady Foundation, Departments of Urology, New York-Weill Cornell Medical Center, New York, New York.

Correspondence to: Dr John P. Mulhall, 525 E 68th St, Starr 900, New York, NY 10021 (e-mail: jpm2005{at}med.cornell.edu).

Received for publication September 23, 2003; accepted for publication March 29, 2004.

Lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) are extremely prevalent in aging men. LUTS describes the symptoms that occur with dysfunction of micturition. Both storage and emptying symptoms occur. Storage symptoms refer to urinary frequency, urgency, urge incontinence, nocturia, and dysuria. Emptying symptoms include hesitancy, straining, decreased force of stream, and incomplete emptying of the bladder, including urinary retention (Wein, 1981). BPH refers specifically to the histologic benign proliferation in the prostate gland, which may or may not be associated with LUTS.

Erectile dysfunction (ED) is also an extremely common problem in older men. ED is defined as the consistent inability to maintain a penile erection sufficient for adequate sexual relations (NIH, 1993). The purpose of this review is to explore the link between the 2 conditions. Simply as a result of their predominance in older men, these 2 conditions are very likely to coexist. But is age the only link between LUTS and ED?

Several other hypotheses exist that link LUTS and ED. First, some have postulated that the negative impact that LUTS has on the quality of life causes ED. Second, other studies have examined the role of a hyperadrenergic state in the pelvis associated with LUTS that adversely affects erectile function. Third, pharmacotherapy for BPH may affect erectile function. Finally, in the past, invasive therapy for BPH was thought to cause ED. This paper will explore the pathophysiologic link between LUTS and ED.

Age, LUTS, and ED

Defining BPH and LUTS—BPH is estimated to be present in 40% of men by age 50 and in more than 80% of men older than 80 years (Berry et al, 1984). On the basis of a prostate size in excess of 20 mL and a peak urinary flow rate of less than 15 mL/s, a Scottish study estimated that 14% of men in their 40s have BPH (Garraway et al, 1991). This analysis also estimated that up to 43% of men older

than 60 years have BPH. Definitions are important because, although the pathologic process is present within the prostate, many men are not symptomatically affected. Thus, even though BPH is frequently present in older men, the incidence of LUTS may be lower.

An important contribution to our understanding of the progression of LUTS was provided by the Olmsted County Study. More than 2000 men aged 40–79 years were followed. Peak urinary flow was found to decrease by 2 mL/s each decade, and prostate size was estimated to increase by 0.6 mL/y. Those men with prostates greater than 40 mL were significantly more likely to suffer from LUTS. Men with large prostates were twice as likely to be bothered by their symptoms and also twice as likely to feel that their symptoms interfered with the activities of daily life (Girman et al, 1999). Moderate-to-severe LUTS has been found to occur in 8%–58% of men in the sixth decade, in 15%–64% of men in the seventh decade, and in 26%–90% of men in the eighth decade (Meigs et al, 1999; Collins et al, 2002). The above data and studies demonstrate that prostate size and symptoms increase with age.

Despite this, a worsening of LUTS does not invariably occur with time. A group of 106 men with BPH and LUTS was followed for 5 years, and only 16% of the men thought that their symptoms had deteriorated. Most of the men (52%) considered their symptoms unchanged. Surprisingly, 32% thought their symptoms had improved without treatment (Ball et al, 1981). This implies that LUTS is not a universally progressive condition, in spite of the growth of prostate tissue, and that the symptoms may wax and wane over time. The implications for impact on erectile function are unclear.

Defining ED— ED is defined as the consistent inability to obtain or maintain an erection of sufficient quality to enable satisfactory sexual relations (NIH, 1993). Age is among the most important risk factors for ED in men, although it may not be an independent risk factor. Compared to men in their 40s, men in their 50s have a 2.1-fold increase in their odds ratio of suffering from ED, and this increases to a fivefold increased odds ratio for men in their 60s (Carson et al, 2001).

The prevalence of ED to any degree in 40-year-old men is estimated to be 40% and rises to 70% in 70-year-old men. Overall, 52% of men aged 40–70 years have some degree of ED, and two thirds of these men have moderate-to-severe symptoms (Pearlman and Kobashi, 1972; Feldman et al, 1994). A recent investigation found complete impotence, defined as the inability to attain any erection, in 13.2% of men aged 55–70 years (Green et al, 2001). Braun et al (2000) recently published data from a survey of 4883 men in Cologne. This study used an 18-item validated questionnaire to assess sexual activity, sexual satisfaction, and ED in a population of men with a mean age of 51.8 years (range, 30–80 years). They found that ED increases over time from 2.3% among men younger than 40 years to 53.4% among men older than 70 years, with progressive increases in every decile. ED clearly appears to be associated with advancing age.

Does Aging Provide the Link Between LUTS and ED?— The above data demonstrate the independent relationships of age to LUTS and of age to ED. Blanker et al (2001) surveyed 1600 men using International Prostate Symptom Score (IPSS) and the International Continence Society sexual dysfunction survey (ICSsex) questionnaires to investigate the relationship between age, LUTS, and ED. A multivariate logistic regression analysis of the data found that age, obesity, and urinary tract symptoms were the most important correlates of significant ED. A British study found that rigidity of erection and ejaculate volumes decreased with age. Nine percent of men in their 40s, 79% in their 70s, and 86% in their 80s reported decreases in rigidity of erection ($P < .001$). Reduced ejaculation was also found to be more prevalent with increasing age. Men with LUTS had a significantly higher odds ratio for having sexual dysfunction than did men without urinary symptoms. Overall, there was a strong relationship between LUTS and ED but no relationship between flow rate

and ED (Frankel et al, 1998).

Another recent study from the United Kingdom evaluated 140 men who were referred by general practitioners for treatment of LUTS (Namasivaym et al, 1998). All men completed the IPSS, the BPH impact index (BPHII), and the sexual function index (SFI)—3 validated instruments. Their median age was 68 years, and 59% scored poorly for sexual drive, with two thirds of these men saying they had no or low sexual drive. Age was inversely correlated with sexual drive, erection, and ejaculatory function. Although most correlations were weak, this important study used standardized instruments and prospectively evaluated the men. LUTS did correlate with ED and age again.

The most recent data released from the Multinational Survey of the Aging Male (MSAM-7) study showed a very strong relationship between age, LUTS severity, and ED. The investigators used the IPSS, the Danish Prostate Symptom Score (DAN-PSS), and the International Index of Erectile Function (IIEF) to evaluate LUTS, ED, and a variety of comorbid conditions and demographic characteristics. They found that for every decade, the percentage of men with moderate (IPSS = 8–19) or severe (IPSS > 19) LUTS increased and that for each IPSS grouping (IPSS = 0, 1–7, 8–19, and >19), the frequency of sexual activity declined with age, and the prevalence of ED increased (Rosen et al, 2003). The MSAM-7 provides conclusive data linking age, LUTS, and ED; however, the questionnaire-based nature of this study precludes an establishment of causality.

A recent study analyzed the impact of invasive treatment of BPH on ED (Brookes, 2002). All men completed the ICSsex and IPSS questionnaires pre- and postoperatively. Important data linking age and ED were reported as a secondary endpoint of the data collected. The baseline rates of ED increased dramatically with age and were 38% in men younger than 60 years, 74% in men in their 60s, and 84% in men aged 70 and older. However, with increasing age, anxiety that was related to ED decreased from 95% in men younger than 60 years to 40% in men older than 70 years. Prevalence of ED increases, but distress over this process decreases with time.

Is the Negative Impact on Quality of Life From LUTS a Cause of ED?— Authors have hypothesized that LUTS adversely affects a patient's overall quality of life. Impaired quality of life is associated with ED. Is quality of life the direct link between LUTS and ED?

LUTS is generally not a life-threatening problem to the sufferer. However, many studies have documented a very large negative effect on the quality of life among men suffering from this condition. In the Olmstead County Study, LUTS was associated with significantly worse physical and mental health overall (Roberts et al, 1997). Men with large prostates were twice as likely to be concerned by their symptoms and were also twice as likely to think their symptoms interfered with the activities of daily life (Girman et al, 1999). Among men suffering from LUTS, another study found that 20% reported that urinary dysfunction impaired at least one daily activity most or all of the time (Garraway and Kirby, 1994). More recent data from the Olmsted County Study demonstrate a strong inverse relationship between LUTS and sexual function independent of age (Chung et al, unpublished). These data demonstrate the strongest negative correlation between getting an erection and LUTS severity.

In another study, 20% of men with LUTS were found to have limitations in at least 4 daily routine activities vs only 6% of men without LUTS (Birkhoff et al, 1976). What these data demonstrate is that LUTS affects the global emotional well-being of a man. While they may not be immediately life-threatening problems, other activities such as sexual activity may be adversely affected by LUTS.

ED is also strongly associated with a negative impact on the quality of life. While sexual activity

tends to decrease with age, one survey of men aged 50–88 years found that 42% of men think that sex is important or very important, and another 41% found sex at least occasionally enjoyable. Only 17% of men surveyed said they could live without sex (Burber et al, 1999). The US National Health and Social Life Survey found that men with ED had significantly less physical, emotional, and overall happiness than did men without ED (Laumann et al, 1999). ED is a condition that negatively affects a man's global sense of well-being. Much like LUTS, this condition is not an immediate threat to life, but it appears to adversely affect the emotional health of the sufferer.

Girman et al (1998) compared men from 4 different countries to examine cross-cultural differences in the quality of life among men with LUTS. They found that as the symptom score increased, the overall quality of life decreased. This was particularly evident in the categories of sexual satisfaction and sexual drive, both of which declined significantly as symptom scores increased. They concluded that worsening urinary function causes a global decrease in the quality of life, thereby negatively affecting sexual function. The weakness of this study is that it takes associations found in longitudinal studies and then makes the next logical inference that quality of life is the link between LUTS and ED. However, although associations may imply causation, this direct link cannot be conclusively stated on the basis of this one study.

An important caveat to many studies on BPH is that many used nonstandardized instruments to assess sexual function. More recently, the IIEF and the ICSsex have been used more routinely, both of which allow more meaningful intrastudy comparisons.

Preliminary data from the MSAM-7 study, which used validated instruments exclusively, showed an association between LUTS and ED (Rosen et al, 2003). This study surveyed more than 14 000 men in 7 countries with the IPSS, the DAN-PSS, and the IIEF instruments to assess LUTS and ED. Men ranged in age from 50 to 80 years, and 90% of them reported suffering from LUTS, with 6% classified as severe and 25% as moderate. Only 11% of the men were being medically treated for LUTS. Eighty-three percent of the men were still sexually active, and 71% reported at least 1 episode of intercourse in the preceding 4 weeks. The mean frequency of intercourse for men without LUTS was 8.6 (number of times of intercourse per month) for men aged 50–59 years, dropping to 4.9 for men with an IPSS score greater than 19 (Rosen et al, 2003). Similar decreases in sexual activity were seen across decades. Therefore, worsening LUTS leads to decreased sexual activity, independent of age. Importantly, the frequency of sexual activity per month also declined with increasing age, holding IPSS scores constant. Thus, both age and IPSS scores predict declining sexual activity. This study also found that 49% of men reported erection difficulties, and 46% had ejaculatory disturbance. Overall, sexual activity decreased with age and was strongly associated with the presence and severity of LUTS (Rosen et al, 2003).

An important study linking LUTS and ED included more than 1600 men who were surveyed with the IPSS and ICSsex questionnaires. A multivariate logistic regression analysis of the data found that age, obesity, and urinary tract symptoms were the most important correlates of significant ED in the population of men studied (Blanker et al, 2001). Specifically, men with elevated IPSS scores felt that their voiding symptoms impaired their sex lives. This study is particularly important because of the multivariate logistic regression design: for the first time, we find data in which urinary symptoms strongly predict ED, even after controlling for a variety of other variables, including age. Both age and urinary symptoms were independently linked to ED; hence, both likely play a role in causing ED.

Frankel et al (1998) examined another cohort of men with LUTS. They found that men with LUTS had a significantly higher odds ratio of having sexual dysfunction than did men without urinary symptoms.

Forty-five percent of men felt that LUTS diminished their sex life, and 70% of men surveyed found that the effect of LUTS on their sex life was a problem. Overall, a strong relationship between LUTS and ED was found, but no relation was found between flow rate and ED. This lack of relationship between more objective urodynamic data and ED has been noted in several studies. While the data from this study strongly suggest that LUTS impairs the quality of life and that a poor quality of life leads to sexual dysfunction, causality cannot be confirmed. A deficiency in the current literature is the lack of a prospective longitudinal study of men with baseline sexual function and LUTS surveys who are followed over time to determine if those men suffering from LUTS have a higher risk of developing ED.

A smaller study from the United Kingdom evaluated 140 men who were referred by general practitioners for treatment of LUTS (Namasivaym et al, 1998). All men completed the IPSS, the BPHII, and the SFI. Their median age was 68 years, and 59% scored poorly for sexual drive, with two thirds of these men saying they had no or low sexual drive. The researchers found only a weak correlation between the IPSS score and sexual function. However, scores for the BPHII showed a highly significantly correlation with all aspects of sexual function measured. What these data again suggest is that LUTS decreases a man's quality of life and that the impairment in the quality of life contributes to worsening sexual function. Factors that show a link between specific symptoms of BPH to ED have been difficult to expose, and generally, when relationships are demonstrated, they are weak at best. Overall, it seems that the negative impact on the quality of life contributes to impairment of erectile function but that LUTS itself is less likely to result in a physiologic change that impairs sexual function.

The medical therapy for BPH (MTOPS) trial provided important further evidence that not only linked LUTS to BPH, but that also specifically linked the American Urological Association (AUA) symptom index and flow rates to ED (McVary et al, unpublished). This study evaluated 2912 men with LUTS and found a strong negative relationship on all 5 subscales of sexual function that were surveyed and the AUA symptom index and flow rate. This is one of the few well-performed studies that found a clinically determined value to be related to ED, and it provides compelling evidence for a relationship. What is unclear from this study is what mediates this relationship.

Others have also documented a link between LUTS and sexual dysfunction. Sexual dysfunction worsened as symptoms of hesitancy, straining, reduced stream (voiding symptoms), and incontinence (a storage symptom) worsened (Macfarlane et al, 1996). A French survey showed that both the frequency of sexual intercourse and the intensity of sexual desire declined with increased urinary symptom scores (Richard et al, unpublished). Baniel et al (2000) surveyed 131 men with BPH prior to prostate surgery and found that patients with more severe LUTS, as indicated by higher IPSS scores, had more difficulty engaging in coitus. Among patients with severe LUTS (IPSS score > 18), 44.2% reported an inability to engage in coitus compared to only 13.1% of men with less severe LUTS.

A link between BPH and ED other than that caused by aging is not without controversy. A recent study found no relationship between prostate volume measured by transrectal ultrasound (TRUS), urinary flow rate, and symptoms of ED (Green et al, 2001). In this study of more than 2000 men, age was the only variable that was significantly related to TRUS-measured prostate volume, peak urinary flow rate, and failure to obtain erections. However, other investigators have found no relationship between objective measures of BPH and ED (Frankel et al, 1998). Therefore, it is not surprising that this study did not find a correlation of TRUS volume or flow rate with ED. Again, the most commonly hypothesized link between LUTS and BPH is the impact of LUTS on the quality of life, which then impairs sexual function. Objective measures of BPH often do not correlate with the severity of LUTS; therefore, urodynamic or TRUS measures are unlikely to be predictive of ED.

Most of the evidence suggests that the impact of LUTS from BPH on the quality of life plays a role in exacerbating ED. Perhaps the bothersome symptoms that interfere with everyday activities such as sleep, urinary frequency, and incontinence result in a generally negative state of mind that is not conducive to erectile function. Especially in older men, in whom erectile function is generally not as robust as in younger men, any negative impact on the quality of life could be magnified in its impact. The weight of evidence, including the important data provided by Blanker et al (2001) and the MSAM-7 study, supports a link between LUTS and ED, and this link is likely dependent, to some degree, on the negative impact on the quality of life caused by LUTS.

Linking LUTS and ED—The Metabolic Syndrome?

The metabolic syndrome is a newly described syndrome encompassing systemic dysfunction characterized by glucose intolerance, hypertension, hyperlipidemia, and central obesity (Zimmet et al, 1999). This syndrome is now recognized as a risk factor for ED (Deedwania, 2003). Data have been presented linking endothelial dysfunction to ED, which is likely explained by the link between the metabolic syndrome and ED. All of the above pathologic processes characteristic of the metabolic syndrome are associated with endothelial damage and dysfunction (McVeigh and Cohn, 2003).

Other studies have suggested a link between the elevated insulin levels seen with the metabolic syndrome and the development of BPH (Hammarsten et al, 1998; Hammarsten and Hogstedt, 2001). Prostate growth was found to correlate strongly with the presence of the metabolic syndrome noninsulin-dependent diabetes mellitus; body mass index, hypertension, specifically diastolic; hyperlipidemia; and low levels of high-density lipoprotein. Growth was also positively correlated with plasma insulin levels.

Overall, the metabolic syndrome with its associated endothelial dysfunction and elevated plasma insulin levels provides a good causal link between LUTS and ED. In this case, the 2 conditions are results of the same pathophysiologic process. Patients presenting with BPH and ED should certainly be screened for the presence of insulin resistance, hypertension, and hypercholesterolemia if they are not already under care for these conditions.

Receptors, LUTS, and BPH—A Pathophysiologic Link?

α-Adrenoreceptors—To date, no large-scale studies have been conducted to elucidate the pathophysiologic mechanism that links LUTS and ED. Recent interest in receptor and enzyme populations in both the prostate and corporal smooth muscle has led to a mapping of the smooth muscle populations and has provided a better understanding of the potential pharmacologic manipulations that may be applied. The initial work of Lepor and Shapiro (1984), Hedlund et al (1985), and Lepor et al (1993) established the presence of α-adrenoceptors and muscarinic receptors in the human prostate. These investigators established that α1-adrenergic receptors are present in the prostate smooth muscle in high concentrations, specifically the α1A receptor subtype, but that muscarinic receptors are localized to the glandular portion. α1A receptors appear to be up-regulated in patients with LUTS and BPH (Price et al, 1993; Schwinn, 2001). These and other studies have established that prostate smooth muscle contraction is mediated by α-agonist action at the α1-adrenoreceptors and that the blockade of these receptors relaxes prostate smooth muscle (Lepor et al, 1995). This specific blockade increases flow rates and results in decreased symptom scores (Buzelin et al, 1997).

α-Adrenoreceptors have also been characterized within the corpora cavernosa smooth muscle, and a similar contractile response to α-agonists has been observed (Levin and Wein, 1980; Traish et al, 1995). Notably, muscarinic cholinergic receptors were also identified in corporal tissue, although

their role remains ill-defined (Minorsky et al, 1998).

One hypothesis is that LUTS causes a high sympathetic output state in the pelvis. The elevated sympathetic tone in the pelvis leads to contraction of the prostatic smooth muscle via α-adrenergic receptors. Blockage of these receptors with α-receptor antagonists is often used to treat the symptoms of BPH (Price et al, 1993; Walden et al, 1999). Heightened pelvic sympathetic tone leads to elevated local norepinephrine levels, which act on the α-receptors in the cavernous smooth muscle to stimulate contraction (Levin and Wein, 1980; Traish et al, 2000). The elevated local norepinephrine levels induce both vascular and cavernous smooth muscle contraction, producing an anti-erectogenic state. α-Adrenergic receptor blockers, including phentolamine and phenoxybenzamine, block the effect of norepinephrine and can induce full erections (Brindley, 1983). This provides the rationale for intracavernosal injection therapy with α-blockers.

The impact of α-blockers on ED was carefully evaluated by the Treatment of Mild Hypertension Study (Grimm et al, 1997). This double-blind, randomized trial compared placebo to acebutolol, amlodipine, chlorthalidone, doxazosin, and enalapril in terms of incidence of sexual dysfunction during the study. The incidence of ED among patients was 6%–17% at 24 months and 11%–18% at 48 months. Men taking doxazosin had a lower rate of ED at 24 months (2.8%), but this was not significant. These data demonstrate that α-blockade in the treatment of hypertension certainly does not increase the incidence of ED.

Nitric Oxide and Bladder Outlet Obstruction— Experimental models were created in animals to test the effect of bladder outlet obstruction on cavernosa smooth muscle tissue. A recent study found that in rabbits with partial bladder outlet obstruction, there was impaired nitric oxide (NO)-mediated relaxation of bladder strips in vitro. This group also found that NO synthase was up-regulated on histologic section and by gel electorphoresis densitometry (Calvert et al, 2001). Another group evaluated the partial bladder outlet obstruction model in rabbits with respect to cavernosal smooth muscle contraction. They found that, after partial bladder outlet obstruction, the muscle bundle size was increased in the corpora, and the innervation was decreased on morphologic assessment. They also found that the corporal muscle generated 40%–50% more force in response to procontractile agents and that a high-energy isoform of adenosine triphosphatase (ATPase) was overexpressed in the corpora after partial bladder outlet obstruction. The authors concluded that the change in innervation caused the overexpression of the high-energy ATPase and increased the muscle contractility that makes smooth muscle relaxation more difficult (Chang et al, 2001). A follow-up study from this group confirmed that the relaxation of cavernous smooth muscle is impaired in rabbits with partial bladder outlet obstruction. They also found increased spontaneous cavernosal muscle contractions, increased force generation in response to contractile agents, and decreased neurofilament staining (Chang et al, 2002).

Overall, the experimental receptor mapping studies and animal models of bladder outlet obstruction suggest that increased sympathetic tone does occur in the pelvis after outlet obstruction, leading to a down-regulation of innervation to the corporal muscles as well as an increase in tonic muscle contractility and bulk. These findings support the hypothesis that LUTS associated with BPH partially results from increased norepinephrine in the pelvis. Increased sympathetic tone in the pelvis leads to impaired relaxation of corporal smooth muscle, thus impairing erection. Further studies are necessary to 1) establish a direct causal link between bladder outlet obstruction and elevations in adrenergic compounds locally in the pelvis, and 2) more firmly demonstrate causation of ED in these models.

Rho-kinase Activity—The Link?— ED and LUTS are extremely prevalent conditions in older men,

often beginning to appear in the sixth decade. Since both ED and BPH begin to affect men at roughly the same time in life, temporally, at least, the 2 conditions are related. Recent studies have examined specific molecular pathways that are involved in both LUTS and ED. The Rho-kinase pathway, which mediates smooth muscle contraction, was hypothesized to play a role in ED and also in LUTS.

Rho-kinase inhibits myosin light chain phosphatase and phosphorylates the myosin light chain promoting smooth muscle contraction. This pathway is responsible for the tonic contraction of cavernosal smooth muscle and the normal flaccid state of the penis. Research has demonstrated that inhibition of Rho-kinase leads to erections in rats independently of NO (Chitaley et al, 2001). Furthermore, Rho-kinase inhibition was shown to prevent cavernosal smooth muscle contraction after potent procontractile agents were administered in rats (Mills et al, 2003). Inhibition of Rho-kinase acts synergistically with NO to promote erection (Mills et al, 2002). These data suggest that vasoconstrictors that impair erection operate through the Rho-kinase pathway. Inhibition of this pathway that is responsible for tonic contraction may promote erections.

LUTS may also be affected by Rho-kinase–mediated smooth muscle contraction. In a rabbit partial bladder outlet obstruction, the Rho-kinase pathway was shown to be active in the maintenance of force and the impaired relaxation seen in defunctionalized bladder muscle (Bing et al, 2003). Activation of the Rho-kinase pathway may also contribute to hypertension by promoting vascular smooth muscle contraction. Chronic exposure to vasoconstricting agents such as α-adrenergic, serotonergic, and endothelin-1 agonists may promote cellular remodeling with a tonic up-regulation of Rho-kinase activity (Chitaley et al, 2003). Inhibition of Rho-kinase activity lowered blood pressure in a hypertensive rat model (Sward et al, 2003). In hypertensive humans, treatment with a Rho-kinase inhibitor also lowered vascular resistance (Masumoto et al, 2001).

Chronic exposure to the procontractile endothelins and α-receptor agonists, which are known to be locally up-regulated in the pelvic circulation of men with LUTS, up-regulates the Rho-kinase pathway. This leads to increased tonic smooth muscle contraction that impairs detrusor smooth muscle relaxation and may contribute to LUTS. Furthermore, the increase in tonic activity of Rho-kinase increases tonic cavernosal smooth muscle contraction and impairs erectile function, contributing to ED. This pathway is also active in the development of hypertension, likely via a similar increase in activity in vascular smooth muscles. The Rho-kinase pathway may be a final common denominator linking LUTS and ED, but more work needs to be performed specifically on the role of the Rho-kinase pathway in the development of clinical LUTS.

LUTS Treatment and ED—Cause or Cure?

Medical Therapy—Classic urologic teaching states that BPH therapy can cause ED. Medical and surgical therapy historically was said to promote the development of ED. However, recent evidence has accumulated suggesting that the treatment of LUTS not only does not cause ED, but that it may help improve sexual function.

Tamsulosin is known to cause abnormal ejaculation (ejaculation failure, disorder, and decrease) as well as to increase this condition significantly. This condition occurs in up to 18.1% in patients on 0.8 mg/d (prescribing information). However, when standardized measures of sexual function are used, no increase in ED and no decrease in libido were noted between patients given tamsulosin and placebo-treated groups (Debruyne, 1999; Hofner, 1999).

Alfusozin is another uroselective α-blocker with rates of ED and impaired libido that compare similarly to those with other α-blockers, and retrograde ejaculation has not been reported with this medication to date (Lukacs, 1996, 2000; Debruyne, 1999; Hofner, 1999). Two large studies have

assessed sexual function and health-related quality of life in patients taking alfuzosin. These studies found that sexual function scores improved significantly in all patients with LUTS and BPH on alfuzosin (Lukacs, 1996). A more recent study compared sustained-release alfuzosin with or without finasteride in patients with BPH (Debruyne, 1998). This study found that finasteride alone or in combination with alfuzosin was associated with significantly higher risks of impotence (up to 3.5-fold) and decreased libido (up to threefold) than was sustained-release alfuzosin alone. Again, no cases of ejaculatory failure were noted in patients taking only alfuzosin for LUTS.

Most of the data, especially from more recent studies using standardized and validated instruments to assess erectile function, suggest that treating LUTS from BPH with α-blockers improves sexual function. To resolve this issue, a well-constructed randomized trial is required that compares patients with BPH and some degree of sexual dysfunction who are prescribed different treatments for LUTS; then, patients should be evaluated as to the effect of that treatment on sexual function. Whether the observed improvement in sexual function is related to the overall improvement in the quality of life from symptomatic improvement in LUTS after α-blocker therapy or from a the direct blockade of cavernosal α-receptor level is uncertain, and both factors may play a role.

Surgical/Minimally Invasive Therapy— A variety of invasive therapies exist to remove or alter prostatic tissue in hopes of improving the outlet obstruction that is felt to cause the LUTS from BPH. These include standard electrosurgery of the prostate (transurethral resection [TURP]), thermal ablation, and laser resection of prostatic tissue. In the past, many investigators believed that treating BPH surgically or with minimally invasive techniques actually caused or exacerbated ED. Open prostatectomy is associated with a 3%–5% risk of ED (Osterling, 1998). TURP was found to cause retrograde ejaculation in up to 75% of men and was thought to cause ED in 13% of men after the procedure (US Department of Health and Human Services, 1994). Hypotheses to explain these findings were 1) damage to cavernosal nerves, and 2) patient misunderstanding of questionnaires.

Soderdahl et al (1996) examined the occurrence of ED after TURP in 40 men with a mean age of 66 years. Men were evaluated pre- and post-TURP with a Rigi-scan device and questionnaires. They observed a slight and statistically significant increase in rigidity postoperatively, but 28% of men reported a decrease in sexual function post-TURP. However, of the men who reported post-TURP sexual dysfunction, two thirds of them thought that retrograde ejaculation was sexual dysfunction. This small study suggested that much of the ED reported after TURP is reporting error. The majority of patients who reported ED in this study suffered from retrograde ejaculation and confused this condition with ED.

This small study suggests that TURP does not cause ED. A large, multicenter study was designed to compare the incidence of ED in patients with LUTS who underwent either a watchful waiting protocol or an invasive treatment with TURP or noncontact laser. All men completed the ICSsex and IPSS questionnaires pre- and post-operatively. The baseline rates of ED were 38% in men younger than 60 years, 74% in men in their 60s, and 84% in men 70 and older. As suggested by prior investigation, the prevalence of this symptom decreased from 95% in men younger than 60 years to 40% in men older than 70 years. Importantly, IPSS quality of life scores significantly correlated with ED, ejaculatory dysfunction, and the feeling that sex life was diminished by urinary symptoms. This correlation was significant but weaker for IPSS symptom scores, again underscoring the importance of quality of life issues and ED (Brookes, 2002).

TURP was associated with improved erectile function when compared with watchful waiting and was not significantly different from contact laser therapy. Twenty percent of men noted impaired erections post-TURP (with baseline ED at 38% overall), and nearly 10% of men in the watchful waiting arm

experienced new-onset ED during the 7½ months of the study. Pain on ejaculation was also significantly lower, and ejaculatory dysfunction was higher, all consistent with previous studies (Wasson et al, 1995; Brookes, 2002). The conclusion of this well-designed, randomized trial is that TURP does not cause ED.

TURP was also found at least not to worsen sexual function in men with adequate function preoperatively and possibly to improve sexual function postoperatively in men with ED. Of the 73 patients who were sexually active preoperatively in a cohort of 280 men, all were still sexually active up to 6 months postprocedure. A further 17% of men, all of whom suffered from ED preoperatively, reported improved erectile function after TURP, most likely as a result of improved quality of life (Mishriki, 2001).

Other therapeutic options for BPH include high-energy thick-loop TURP and transurethral needle ablation of the prostate (TUNA). Thick-loop prostatectomy was found not to be associated with increased ED postprocedure, and the only 2 new cases of ED in a follow-up series had reduced potency preoperatively (Talic, 2001). A large multicenter trial evaluated TUNA and found that only 2 patients in 130 reported new-onset ED and that only 1 patient reported retrograde ejaculation after this procedure (Roehrborn, 1998). Another randomized trial compared TUNA to TURP and found that TUNA had a lower effect on sexual function than TURP (Bruskewitz, 1998). Most of these studies evaluated ED secondarily, and until a randomized study is conducted comparing these therapeutic modalities specifically with respect to ED, conclusions will be limited.

Microwave thermotherapy is another minimally invasive therapy used to treat BPH. Compared to TURP, this technique is associated with fewer complications and side effects. While limited follow-up data are currently available, the studies published have not demonstrated an increase in ED postprocedure (Dahlstrand, 1995).

Treating the LUTS associated with BPH with invasive techniques undoubtedly improves a patient's quality of life. This improvement is probably the reason for the improved sexual function noted by many men after invasive treatment for LUTS. Other than the rare surgical complications that occur, ED is not caused by TURP or other minimally invasive therapies that are used to treat BPH.

Summary and Conclusions

LUTS from BPH and ED is a highly prevalent problem among aging men. There is no question that the 2 conditions are linked, at least insofar as age being a very significant risk factor for both conditions. The age relationship between LUTS and ED has been demonstrated repeatedly in population-based surveys across decades and cultures. These associations have also been strengthened by recent multivariate analysis demonstrating independent relationships between age and LUTS and age and ED.

Establishing a direct link between LUTS and ED directly has proven more elusive. A variety of questionnaire studies have linked LUTS and ED, often weakly. Most studies fail to show relationships between specific symptoms of LUTS and ED, though incontinence is often related. Most of the data linking LUTS and ED suggest that LUTS impairs the overall quality of life and that a low quality of life contributes to or causes ED. Important work remains to be done in this arena. We must examine whether improving the quality of life in ways that do not treat prostate obstruction or LUTS directly can improve erectile function. While the multivariate analysis conducted by Blanker et al (2001) demonstrates that the IPSS score is an independent risk factor for ED, these are the only strong data available.

The receptor level and basic science data are still very immature. Small-scale animal models that

may not exactly simulate the physiologic milieu in humans suggest that changes secondary to a hyperadrenergic state induced by bladder outlet obstruction cause changes in smooth muscle characteristics over time and in neural receptors. These changes are felt to cause impaired smooth muscle relaxation and possibly ED. α-Blockade is certainly effective in treating BPH and may at least potentiate erectile function by improving the quality of life and by promoting smooth muscle relaxation. Phosphodiesterase inhibitors definitely improve erectile function by relaxing cavernosal smooth muscle and may have the same effect in the prostate, thus improving LUTS. Randomized trials are needed to directly compare the sexual impact of α-blockers and the effect on LUTS of phosphodiesterase inhibitors prior to making strong claims. However, current evidence suggests that α-blockers at least do not impair erectile function.

Finally, contrary to earlier thought, minimally invasive therapy and TURP do not cause ED and probably improve erectile function. Whether by decreasing the hyperadrenergic state in the pelvis (no real data yet) or by improving the quality of life (minimal data), these therapies do seem to be associated with improving erectile function. The most plausible explanation for now is that an overall improved quality of life improves erectile function. Perhaps animal models that more closely approximate BPH in humans, followed by a simulation of the removal of the outflow obstruction to see if adrenergic tone declines to baseline, are needed.

LUTS is definitely related to ED. The questionnaire and cohort studies establish such a link through aging as well as via the negative impact on the quality of life secondary to LUTS. In that much, LUTS is associated with ED, but without better data, causation is impossible to surmise. We need better prospective data to establish causation between LUTS and ED as well as more basic science data to demonstrate the physiologic and molecular changes that accompany LUTS and probably contribute to ED.

References

Ball AJ, Feneley RCL, Abrams PH. The natural history of untreated "prostatism." *Br J Urol.* 1981; 53: 613 -616.[Medline]

Baniel J, Israilov S, Shmueli J, Segereich E, Livne PM. Sexual function in 131 patients with benign prostatic hyperplasia before prostatectomy. *Eur Urol.* 2000; 38: 53 -58.[Medline]

Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of benign prostatic hyperplasia with age. *J Urol.* 1984; 132: 474 -479.[Medline]

Bing W, Chang S, Hypolite JA, DiSanto ME, Zderic SA, Rolf L, Wein AJ, Chacko S. Obstruction-induced changes in urinary bladder smooth muscle contractility: a role for Rho kinase. *Am J Physiol Renal Physiol.* 2003;285: F990 -F997.[Abstract/Free Full Text]

Birkhoff JD, Wiederhorn AR, Hamilton ML, Zinsser HH. Natural history of benign prostatic hypertrophy and acute urinary retention. *Urology.* 1976;7: 48 -52.[Medline]

Blanker MH, Bohnen AM, Groeneveld FPMJ, Bernsen RMD, Prins A, Thomas S, Rund Bosch JLH. Correlates for erectile and ejaculatory dysfunction in older Dutch men: a community-based study. *J Am Geriatr Soc.* 2001;49: 436 -442.[Medline]

Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. Epidemiology of erectile dysfunction: results of the `Cologne Male Survey.' *Int J Impotence Res.* 2000; 12: 305 -311.[Medline]

Brindley GS. Cavernosal alpha-blockade: a new technique for investigating and treating erectile

impotence. *Br J Psychiatry.* 1983;143: 332 -337.[Abstract/Free Full Text]

Brookes ST, Donovan JL, Peters TJ, Abrams P, Neal DE. Sexual dysfunction in men after treatment for lower urinary tract symptoms: evidence from randomized controlled trial. *BMJ.* 2002; 324: 1059 -1064. [Abstract/Free Full Text]

Bruskewitz R, Issa MM, Roehrborn CG, Naslund MJ, Perez-Marrero R, Shumaker BP, Oesterling JE. A prospective, randomized 1-year clinical trial comparing transurethral needle ablation to transurethral resection of the prostate for the treatment of symptomatic benign prostatic hyperplasia. *J Urol.* 1998;159: 1588 -1593.[Medline]

Burber B, Weidner W, Altwein JE. Prostate and sexuality: an overview. *Eur Urol.* 1999; 35: 177 -184. [Medline]

Buzelin JM, Fonteyne E, Kontturi M, Witjes WP, Khan A. Comparison of tamsulosin with alfuzosin in the treatment of patients with lower urinary tract symptoms suggestive of bladder outlet obstruction (symptomatic benign prostatic hyperplasia). The European Tamsulosin Study Group. *Br J Urol.* 1997;80: 597 -605.[Medline]

Calvert RC, Khan MA, Thompson CS, Dashwood MR, Mikhailidis DP, Morgan RJ. Alterations in nitric oxide signaling provides insight into the pathophysiology of erectile dysfunction associated with benign prostatic hyperplasia. Paper presented at: American Urological Association Annual Meeting; June 2001; Anaheim, Calif.

Carson CC, West SL, Glasser DB, et al. Prevalence and correlates of erectile dysfunction in a United States nationwide population-based sample: phase I results. Paper presented at: American Urological Association Annual Meeting; June 2001; Anaheim, Calif.

Chang S, Hypolite JA, Wein AJ, Chacko S, DiSanto ME. The effect of bladder outlet obstruction on rabbit corpus cavernosum smooth muscle contractility. Paper presented at: American Urological Association Annual Meeting; June 2001; Anaheim, Calif.

Chang S, Hypolite J, Zderic SA, Wein AJ, Chacko S, DiSanto M. Altered contractility of corpus cavernosum smooth muscle: a possible molecular basis for erectile dysfunction associated with partial bladder outlet obstruction resulting from benign prostatic hyperplasia . Paper presented at: American Urological Association Annual Meeting; May 28, 2002; Orlando, Fla.

Chitaley K, Wingard C, Webb RC, Branam H, Stopper VS, Lewis RW, Mills TM. Antagonism of Rho-kinase stimulates rat penile erection via a nitric oxide-independent pathway. *Nat Med.* 2001; 7: 119 -122. [Medline]

Chitaley K, Wingard D, Webb RC. RhoA/Rho-kinase, vascular changes and hypertension. *Curr Hypertens Rep.* 2003; 3: 139 -144.

Collins MM, Meigs JB, Barry MJ, Walker-Corkery E, Giovannucci E, Kawachi I. Prevalence and correlates of prostatitis in the health professionals follow-up study cohort. *J Urol.* 2002; 167: 1363 -1366.[Medline]

Dahlstrand C, Walden M, Geirsson G, Pettersson S. Transurethral microwave thermotherapy versus transurethral resection for symptomatic benign prostatic obstruction: a prospective randomized study with a 2-year follow-up. *Br J Urol.* 1995; 76: 614 -618.[Medline]

Debruyne FM, Jardin A, Colloi D, Resel L, Witjes WP, Delauche-Cavallier MC, McCarthy C, Geffriaud-Ricouard C. Sustained-release alfuzosin, finasteride and the combination of both in the treatment of benign prostatic hyperplasia. European ALFIN Study Group. *Eur Urol.* 1998;34: 169 -175.[Medline]

Debruyne FM, Van der Poel HG. Clinical experience in Europe with uroselective alpha1-antagonists.

Eur Urol. 1999; 36(suppl): 54 -58.

Deedwania PC. Mechanisms of endothelial dysfunction in the metabolic syndrome. *Curr Diabetes Rep.* 2003; 3: 289 -292.

Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, Mckinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol.* 1994; 151: 54 -61. [Medline]

Frankel SJ, Donovan JL, Peters TI, Abrams P, Dabhoiwala NF, Osawa D, Lin ATL. Sexual dysfunction in men with lower urinary tract symptoms. *J Clin Epidemiol.* 1998; 51: 677 -685.[Medline]

Garraway WM, Collins GN, Lee RJ. High prevalence of benign prostatic hypertrophy in the community. *Lancet.* 1991; 338: 469 -471.[Medline]

Garraway WM, Kirby RS. Benign prostatic hyperplasia: effects on quality of life and impact on treatment decisions. *Urology.* 1994;44: 629 -636.[Medline]

Girman CJ, Jacobsen SJ, Rhodes T, et al. Association of health-related quality of life and benign prostatic enlargement. *Eur Urol.* 1999;35: 277 -284.[Medline]

Girman CJ, Jacobsen SJ, Tsukamoto T, et al. Health-related quality of life associated with lower urinary tract symptoms in four countries. *Urology.* 1998;51: 428 -436.[Medline]

Green JSA, Holden STR, Bose P, St George DP, Bowsher WG. An investigation into the relationship between prostate size, peak urinary flow rate and male erectile function. *Int J Impotence Res.* 2001; 13: 322 -325.[Medline]

Grimm RH Jr, Grandits GA, Prineas RJ, et al. Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women. *Hypertension.* 1997; 29: 8 -15.[Abstract/Free Full Text]

Hammarsten J, Hogstedt B, Holthuis N, Mellstrom D. Components of the metabolic syndrome—risk factors for the development of benign prostatic hyperplasia. *Prostate Cancer Prostat Dis.* 1998; 1: 157 -162.

Hammarsten J, Hogstedt B. Hyperinsulinaemia as a risk factor for developing benign prostatic hyperplasia. *Eur Urol.* 2001; 39: 151 -158.[Medline]

Hedlund H, Andersson KE, Larsson B. Alpha-adrenoceptors and muscarinic receptors in the isolated human prostate. *J Urol.* 1985;134: 1291 -1298.[Medline]

Hofner K, Claes H, De Reijke TM, Folkestad B, Speakman MJ. Tamsulosin 0.4 mg once daily: effect on sexual function in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urol.* 1999;36: 335 -341.[Medline]

Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA.* 1999; 281: 537 -544.[Abstract/Free Full Text]

Lepor H, Shapiro E. Characterization of alpha-1 adrenergic receptors in human benign prostatic hyperplasia. *J Urol.* 1984;132: 1226 -1229.[Medline]

Lepor H, Tang R, Kobayashi S, Shapiro E, Forray C, Wetzel JM, Gluchowski C. Localization of the alpha-1A-adrenoceptor in the human prostate. *J Urol.* 1995;154: 2096 -2099.[Medline]

Lepor H, Tang R, Meretyk S, Shapiro E. Alpha-1 adrenoceptor subtypes in the human prostate. *J Urol.* 1993; 149: 640 -642.[Medline]

Levin RM, Wein AJ. Adrenergic alpha receptors outnumber beta receptors in human penile corpus cavernosum. *Invest Urol.* 1980;18: 225 -226.[Medline]

Lukacs B, Grange JC, Comet D, McCarthy C. History of 7,093 patients with lower urinary tract symptoms related to benign prostatic hyperplasia treated with alfuzosin in general practice up to 3 years. *Eur Urol.* 2000;37: 183 -190.[Medline]

Lukacs B, Leplege A, Thibault P, Jardin A. Prospective study of men with clinical benign prostatic hyperplasia treated with alfuzosin by general practitioners: 1-year results. *Urology.* 1996; 48: 731 -740.[Medline]

Macfarlane GJ, Botto H, Sagnier PP, Teilac P, Richard F, Boyle P. The relationship between sexual life and urinary condition in the French community. *J Clin Epidemiol.* 1996; 49: 1171 -1176.[Medline]

Masumoto A, Hirooka Y, Shimokawa H, Hironaga K, Setoguchi S, Takeshita A. Possible involvement of Rho-kinase in the pathogenesis of hypertension in humans. *Hypertension.* 2001; 38: 1307 -1310. [Abstract/Free Full Text]

McVeigh GE, Cohn JN. Endothelial dysfunction and the metabolic syndrome. *Curr Diabetes Rep.* 2003; 3: 87 -92.

Meigs JB, Barry MJ, Biovannucci E, Rimm EB, Stampfer MJ, Kawachi I. Incidence rates and risk factors for acute urinary retention: the health professionals follow-up study. *J Urol.* 1999; 162: 376 -382. [Medline]

Mills TM, Chitaley K, Lewis RW, Webb RC. Nitric oxide inhibits RhoA/Rho-kinase signaling to cause penile erections. *Eur J Pharmacol.* 2002;439: 173 -174.[Medline]

Mills TM, Chitaley K, Wingard CJ, Lewis RW, Webb RC. Effect of Rho-kinase inhibition on vasoconstriction in the penile circulation. *J Appl Physiol.* 2003; 91: 1269 -1273.

Minorsky N, Savage DD, Dail WG. Autoradiographic evidence of muscarinic cholinergic receptors in the corpora cavernosa of penis of the rat. *J Auton Nerv Syst.* 1998; 23: 1 -8.

Mishriki SF, Cohen NP, Mawas A, Gibbons B. TURP can improve your sex life [abstract]. *J Urol.* 2001; 165: 366 .

Namasivaym S, Minhas S, Brooke J, Joyce AD, Prescott S, Eardley I. The evaluation of sexual function in men presenting with symptomatic benign prostatic hyperplasia. *Br J Urol.* 1998; 82: 842 -846. [Medline]

NIH Consensus Conference: ED. NIH Consensus Development Panel on ED. *JAMA.* 1993; 270: 83 -87. [Medline]

Osterling JE. Retropubic and suprapubic prostatectomy. In: Walsh PC, ed. *Campbell's Urology.* 7th ed. Philadelphia, Pa: WB Saunders; 1998: 1529 -1541.

Pearlman CK, Kobashi LI. Frequency of intercourse in men. *J Urol.* 1972;107: 298 -301.[Medline]

Price DT, Schwinn DA, Lomasney JW, Allen LF, Caron MG, Lefkowitz RJ. Identification, quantification, and localization of mRNA for three distinct alpha1 adrenergic receptor subtypes in human prostate. *J Urol.* 1993;150: 546 -551.[Medline]

Roberts RO, Jacobsen SJ, Rhodes T, et al. Natural history of prostatism: impaired health states in men with lower urinary tract symptoms. *J Urol.* 1997;157: 1711 -1717.[Medline]

Roehrborn CG, Issa MM, Bruskewitz RC, Naslund MJ, Oesterling JE, Perez-Marrero R, Shumaker BP, Narayan P. Transurethral needle ablation for benign prostatic hyperplasia: 12-month results of a prospective, multicenter US study. *Urology.* 1998; 51: 415 -421.[Medline]

Rosen R, Altwein J, Boyle P, et al. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). *Eur Urol.* 2003; 44: 637 -649.[Medline]

Schwinn DA. The role of alpha1-adrenergic receptor subtypes in lower urinary tract symptoms. *BJU Int.* 2001; 88(suppl): 27 -34.

Soderdahl DW, Knight RW, Hansberry KL. Erectile dysfunction following transurethral resection of the prostate. *J Urol.* 1996;156: 1354 -1356.[Medline]

Sward K, Mita M, Wilson DP, Deng JT, Susnjar M, Walsh MP. The role of RhoA and Rho-associated kinase in vascular smooth muscle contraction. *Curr Hypertens Rep.* 2003; 5: 66 -72.[Medline]

Talic RF. Erectile function following high-energy thick loop prostatectomy. *Scand J Urol Nephrol.* 2001; 35: 300 -304.[Medline]

Traish A, Kim NN, Huang YH, Goldstein II, Moreland RB. Cyclic AMP regulates mRNA expression of alpha-1d and alpha-2a adrenergic receptors in cultured human corpus cavernosum smooth muscle cells. *Int J Impotence Res.* 2000;12(suppl 1): 41-47.[Medline]

Traish AM, Netsuwan N, Daley J, Padman-Nathan H, Goldstein I, Saenz TI. A heterogeneous population of alpha1 adrenergic receptors mediates contraction of human corpus cavernosum smooth muscle to norepinephrine. *J Urol.* 1995;153: 222 -227.[Medline]

US Department of Health and Human Services. *Benign Prostatic Hyperplasia: Diagnosis and Treatment.* Bethesda, Md: Agency for Health Care Policy and Research; 1994.

Walden PD, Gerardi C, Lepor H. Localization and expression of the alpha1A-1, alpha1B and alpha1D-adrenoceptors in hyperplastic and non-hyperplastic human prostate. *J Urol.* 1999; 161: 635 -640. [Medline]

Wasson JH, Reda DJ, Bruskewitz RC, et al. A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. *N Engl J Med.* 1995; 332: 75 -79. [Abstract/Free Full Text]

Wein AJ. Classification of neurogenic voiding dysfunction. *J Urol.* 1981;125: 605 -609.[Medline]

Zimmet P, Boyko EJ, Collier GR, de Courten M. Etiology of the metabolic syndrome: potential role of insulin resistance, leptin resistance, and other players. *Ann N Y Acad Sci.* 1999; 18: 25 -44.
