



# The Complex Relationship Between Lower Urinary Tract Symptoms and Sexual Health

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## Abstract

**Purpose of Review** Lower urinary tract symptoms (LUTS) and sexual health have common links. Medical and surgical treatments for LUTS can significantly affect various domains of sexual health including erectile function, ejaculatory function, and libido. This review summarizes recent findings.

**Recent Findings** Current literature demonstrates a strong association between LUTS, sexual health, and metabolic syndrome. The role of miRNA is also being investigated. Combination medical therapy with phosphodiesterase 5 inhibitors (PDE5-I) shows promise but needs further investigation. Newer surgical therapies for benign prostatic hyperplasia (BPH) aim to preserve sexual function without sacrificing efficacy and durability.

**Summary** Although we are beginning to acknowledge the link between LUTS and sexual health, a better understanding of the underlying biochemistry is needed. Only then can more effective therapies be developed. Further prospective studies should focus on the long-term durability and safety of treatments for both conditions.

**Keywords** Benign prostatic hyperplasia · Lower urinary tract symptoms · Sexual health · Erectile dysfunction · Metabolic syndrome

## Introduction

The relationship between lower urinary tract symptoms (LUTS) and various aspects of men's sexual health including erectile dysfunction (ED), ejaculatory dysfunction, and libido is increasingly important to understand. Individually, LUTS and sexual dysfunction each has a tremendous impact on a man's quality of life (QoL) [1]. The severity of both conditions is strongly and independently correlated to lower QoL [2, 3]. Large epidemiological surveys have found an association between LUTS and sexual dysfunction, and the prevalence of both rises with advancing age. Importantly for providers and patients, there is a better understanding of how

medical and surgical treatments of LUTS can significantly impact sexual health and conversely, how treatment for ED can have a dual benefit for LUTS [1, 4].

While the biochemistry underlying benign BPH/LUTS and sexual dysfunction are individually well described, there are now several theories connecting the two molecular pathways. This connection has been aided by investigative work into the action of PDE5-Is. These pathways provide a better understanding of the complexities of the genitourinary system and may give insight into future treatment options.

Macroscopically, LUTS and sexual dysfunction are markers of an individual's overall health. Both have been strongly associated with the metabolic syndrome (MetS) and may be valuable tools for addressing the patient's cardiovascular and general medical well-being [5, 6]. For these patients with LUTS, sexual dysfunction, and evidence of MetS, their symptoms provide an opportunity for the urologist to encourage a more holistic approach to treatment with lifestyle modifications.

Medical and surgical treatments for BPH/LUTS are evolving. Alpha-adrenergic blockers (ABs) and 5 $\alpha$ -reductase inhibitors (5AR-Is) remain the gold standard of medical therapy.

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Recent studies have renewed the focus on the short- and long-term impacts of these medications on sexual function. Now that PDE5-Is have also been incorporated into the treatment algorithm, the efficacy and side effects of various treatment combinations need to be investigated. New surgical treatments have focused on minimizing sexual side effects but their long-term durability on BPH/LUTS is yet unknown.

The aim of this article is to provide an overview and explore recent developments in the relationship between LUTS and sexual dysfunction.

## Pathophysiology

Several biochemical pathways are hypothesized to associate LUTS and sexual dysfunction, including the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway, RhoA/Rho-kinase pathway, autonomic nervous system hyperactivity, and pelvic atherosclerosis [1, 7]. Furthermore, these pathways seem to be related to systemic disorders including chronic inflammation, metabolic syndrome, diabetes, and hypertension (Fig. 1).

The NO-cGMP pathway has been widely acknowledged given the success of PDE5-Is [8]. Nitric oxide is created from the conversion of L-arginine to L-citrulline and activates guanylyl cyclase (GC) [8]. GC then synthesizes guanosine monophosphate (cGMP) to activate protein kinase G (PGK) and inhibit calcium release, ultimately leading to smooth muscle relaxation [9]. This action is terminated by GMP phosphodiesterase. The NO-cGMP pathway has been well studied in the corpus cavernosum, and NO and NO synthase has been found in the prostate, bladder neck, prostatic urethra, and urothelium [10–12].

The RhoA/Rho-kinase pathway also modulates smooth muscle contraction. Rho-kinase acts to inhibit myosin light

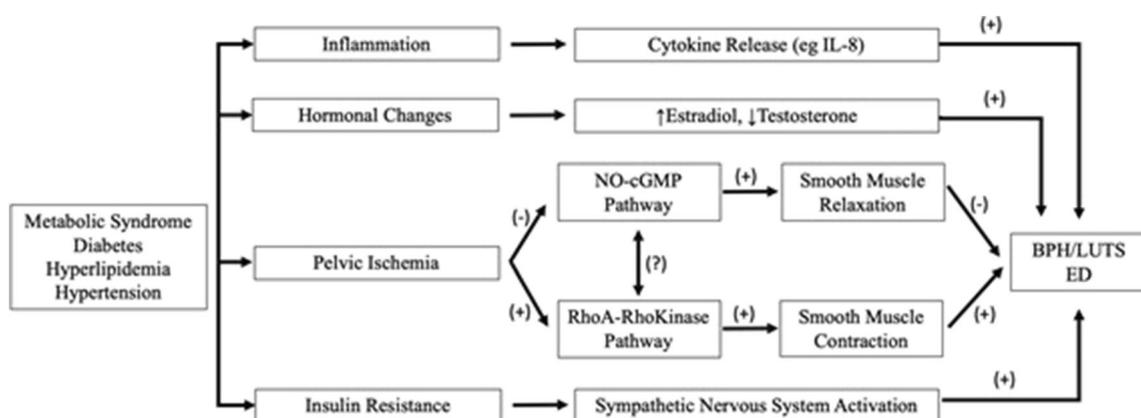
chain phosphatase [13, 14]. Increasing levels of phosphorylated myosin light chain lower the calcium sensitivity and promote smooth muscle contraction [13]. Conversely, inhibition of Rho-kinase will lead to smooth muscle relaxation [14, 15]. The Rho-kinase pathway appears to be stimulated by alpha-adrenoceptors [15].

Alterations in either pathway can result in worsening LUTS and ED [14]. Endothelial dysfunction and poor circulation decrease NO levels and are hypothesized to cause poor relaxation of the bladder neck and prostatic urethra [10, 16]. In addition, alpha-adrenoceptors are upregulated in men with LUTS, and patients with metabolic syndrome and insulin resistance have elevated sympathetic tone and increased smooth muscle contraction in the lower urinary tract and corpora [1, 17].

Recent studies have also investigated the role of miRNA or microRNA in LUTS and ED. miRNAs are small RNA molecules between 19 and 25 nucleotides long that can target and modulate various genes. They are involved in almost every cellular process. The impact of miRNAs on oncologic diseases is widely acknowledged, but now there is evidence of their impact on benign urologic diseases. A recent review by Grego et al. identified 64 different miRNAs that may act as biomarkers or potential therapeutic targets for BPH [18]. In addition, miRNAs have been investigated in ED. They have been found to inhibit nitric oxide synthase activation, regulate endothelial and smooth muscle functions, and downregulate the androgen receptor [19–22].

## Relationship with Metabolic Syndrome

Metabolic syndrome (MetS) is defined as a cluster of commonly co-existing conditions including hypertension, diabetes, abdominal obesity, elevated serum triglycerides, and low serum high-density lipoprotein [23]. The prevalence of MetS



**Fig. 1** Proposed biochemical mechanism of the relationship between metabolic syndrome, diabetes, hyperlipidemia, and hypertension and BPH/ED. IL, interleukin; NO-cGMP, nitric oxide-cyclic guanosine monophosphate; BPH/LUTS, benign prostatic hypertrophy, lower

urinary tract symptoms; ED, erectile dysfunction. Image adapted from De Nunzio et al., “Erectile Dysfunction and Lower Urinary Tract Symptoms,” *European Urology Focus* 2017

is nearly 35% in the USA [24]. A meta-analysis of 21 studies found that individuals with metabolic syndrome compared with those without had an increased all-cause mortality and cardiovascular mortality (relative risk 1.35 and 1.74, respectively) [25]. These individuals also had significantly increased risks of cardiovascular disease (RR 1.53; 95% CI, 1.26–1.87), coronary heart disease (RR 1.52; 95% CI, 1.37–1.69), and stroke (RR 1.76; 95% CI, 1.37–2.25) [25].

The relationship between MetS and ED has been well established [26, 27]. High adipose stores lead to decreased total testosterone levels due to decreased levels of sex hormone-binding globulin and increased conversion of testosterone to estrogen via aromatase activity. This hypogonadal state can cause poor libido and ED. Diabetes, hyperlipidemia, and hypertension lead to microvascular disease via endothelial and nitrenergic dysfunctions, and ultimately result in local tissue hypoxia, nerve ischemia, and smooth muscle dysfunction [28]. In fact, early onset of ED is considered to be a harbinger of future cardiovascular events and requires further medical evaluation [29].

LUTS and MetS are closely related [27, 30, 31]. While male LUTS is conventionally attributed to BPH and urethral obstruction, current literature suggests additional systemic factors. MetS has been associated with a pro-inflammatory and oxidative state [30]. Patients with MetS have elevated markers of inflammation including interleukins, C-reactive protein, and tumor necrosis factor alpha. Some of these markers like IL-8 have been shown to stimulate abnormal prostatic growth and correlate strongly to prostatic inflammation [32, 33]. In turn, the prostatic stromal cells secrete their own inflammatory chemokines to perpetuate the process [30]. This is why some prostate tissue specimens in BPH contain inflammatory infiltrates [34]. This process does not appear to be limited to the prostate, as animal models of metabolic syndrome have demonstrated histological effects on the bladder including fibrosis, hypoxia, and inflammation [35].

Large population studies have shown that the severity of LUTS inversely correlates to the level of physical activity. In a survey of 106,435 Australian men aged 45 years or older, increasing physical activity was found to be associated with a decreased risk for severe LUTS (OR = 0.83, 95% CI 0.76–0.91) while the presence of smoking, obesity, heart disease, and erection dysfunction was associated with increased risk of severe LUTS [36]. In addition, changes in body weight can significantly impact LUTS [37, 38]. A prospective study of 18,055 men found that men with increasing body mass index, higher waist circumference, or weight gain were more likely to develop LUTS or experience progression of disease [37]. The authors attributed this to several biologic mechanisms including elevated levels of estrogen, larger prostates, and increased sympathetic nervous system activity in men with obesity. Diet may also have a factor in the progression of LUTS. In a cross-sectional analysis of 1545 men from the

Boston Area Community Health study, Maserejian et al. found that greater total energy and sodium intake were positively associated with LUTS [38]. Nevertheless, a recent systemic review of the evidence associating LUTs and diet, caffeine, alcohol, and tobacco found that the literature is sparse and mostly consists of observational and lower quality studies [39]. While further prospective clinical studies are needed, urologists should be aware of the impact of MetS, exercise, and diet on two very common urologic conditions.

## PDE5 Inhibitors

Although PDE5-Is have been used for ED for over 20 years, more recently they have been used to treat LUTS [40]. Large randomized, placebo-controlled studies have demonstrated a significant improvement in urinary symptom scores and quality-of-life measures with various PDE5-Is vardenafil, sildenafil, tadalafil [41–44]. At 8 weeks, 10 mg of vardenafil taken twice daily improved International Prostate Symptom Scores (IPSS) compared with placebo (−5.9 vs. −3.6,  $p = 0.0013$ ) [41]. At 12 weeks, 50 mg sildenafil also significantly improved IPSS compared with placebo (−6.32 vs. −1.93,  $p < 0.0001$ ) [42]. Tadalafil also has been shown to significantly improve IPSS, and in a dose-finding study, 5 mg was shown to have the best risk to benefit ratio at 12 weeks compared with placebo (−4.9 vs. −2.3,  $p < 0.001$ ) [43, 44]. Interestingly, these medications appear to have minimal effects on objective measures of urinary flow such as Qmax, voiding efficiency, detrusor pressure, and bladder capacity, leading to further questions on their targets of action [45–47].

Phosphodiesterase enzymes have been found throughout the lower urinary tract, in the prostate, urethra, bladder, and the surrounding vasculature [48–51]. They appear to be expressed in both smooth and striated muscles [48, 50]. There are several proposed mechanisms as to how PDE5-I can improve urinary symptoms. PDE5-Is relax detrusor muscle tone, improve lower urinary tract oxygenation, suppress prostatic stromal cell proliferation, and reduce markers of inflammation [52–54, 55]. In a decerebrated mouse model, low-dose sildenafil was shown to increase bladder compliance, increase the bursting activity of the external urethral sphincter, and raise pelvic afferent nerve activity [56].

It is not clear where PDE5-Is fit in the treatment algorithm for BPH/LUTS. Multiple systematic reviews and meta-analyses have demonstrated a significant improvement in urinary symptoms, erectile function, and quality of life for PDE5-Is compared with placebo [55]. A recently published Cochrane review of 16 different randomized trials summarized the benefits of PDE5-Is [57]. Compared with placebo, PDE5-Is result in a small improvement in IPSS (mean difference 1.89 lower, 95% CI 1.50 to 2.27). The combination of PDE5-I and AB appears to result in a small improvement in

IPSS compared with either PDE5-I alone (mean difference 2.4 lower, 95% CI 1.67 to 6.47) or AB alone (mean difference 2.56 lower, 95% CI 1.19 to 3.92) [57]. However, these studies were limited by a small number of patients and short follow-up.

In a large, randomized double-blind study of 695 patients, Casabe et al. found that the combination of tadalafil and finasteride resulted in a significant improvement in the IPSS at 4, 12, and 26 weeks compared with placebo and finasteride (least squares mean changes of  $-4.0$  vs.  $-2.3$ ,  $-5.2$  vs.  $-3.8$ , and  $-5.5$  vs.  $-4.5$  at 4, 12, and 26 weeks, respectively;  $p < 0.022$  for all visits) [58]. There was also an improvement in erectile function with an increase of 4.7 points in the erectile function domain of the International Index of Erectile Function (IIEF) of the tadalafil/finasteride group compared with 0.0 points for the placebo/finasteride group at 26 weeks ( $p < 0.001$ ) [58]. While there is clearly a role for PDE5-Is in the treatment of BPH/LUTS, further research will better identify the patients who would benefit the most from this drug class. Furthermore, questions about long-term effects, disease progression, and cost-effectiveness still need to be answered.

## Medical Therapies for LUTS

ABs and 5AR-Is are well established medical treatments for BPH/LUTS. However, they have variable effects on sexual function.

ABs appear to have mixed but overall positive effect on erectile function [59]. The  $\alpha$ -adrenergic blockade may help relax penile smooth muscle to promote erections [60]. The improvement in LUTS and quality of life may lead to better sexual function [60]. ABs negatively impact ejaculatory function, although this appears to be dependent on the specific type and uroselectivity of the AB [7]. The more uroselective ABs such as tamsulosin and silodosin have up to an 18% risk of ejaculatory dysfunction, depending on the dosage [61, 62].

5AR-Is appear to have higher rates of sexual side effects including ED, loss of libido, and ejaculatory dysfunction [63–65]. There does not appear to be any differences between finasteride and dutasteride [64, 65]. Interestingly, patients who have worse baseline urinary symptoms or flow rates appear to be more negatively impacted by the sexual side effects of 5AR-Is [64]. Patients should be counseled about potential sexual adverse effects of 5AR-Is prior to initiating therapy. Fortunately, the sexual side effects of 5AR-Is appear to be temporary for many patients as longitudinal analysis has shown a diminishing negative impact over time [64, 66]. In a meta-analysis of 17 randomized trials, Corona et al. found that the risk of hypoactive sexual desire and ED for 5AR-Is decreased as a function of trial duration [64].

It should be noted that the sexual side effects for ABs and 5AR-Is that have been previously described have generally

been reported as adverse events from clinical trials [67]. These adverse events are spontaneously reported and difficult to quantify and may not represent the true incidence of sexual dysfunction. Recently, Roehrborn et al. sought to better understand the true quantitative impact of ABs and 5AR-Is in various domains of sexual function [68••]. In this double-blind trial, 489 patients were randomized to dutasteride 0.5 mg and tamsulosin 0.4 mg (DUT-TAM) or placebo, and changes in the various domains of sexual function were assessed by the Men's Sexual Health Questionnaire (MSHQ). At 12 months, the DUT-TAM group had significantly worse total MSHQ scores ( $-8.7$  vs.  $-0.7$ ; standard error [SE] 0.81, 0.78;  $p < 0.001$ ). The DUT-TAM group also had worse outcomes in the ejaculation ( $-7.5$  vs.  $-0.6$ ; SE 0.56, 0.55;  $p < 0.001$ ) and satisfaction ( $-0.6$  vs.  $+0.3$ ; SE 0.3, 0.29;  $p = 0.047$ ) domains, but not the erection domain ( $-1.0$  vs.  $-0.5$ ; SE 0.19, 0.19;  $p = 0.0961$ ). Sexual adverse events in the DUT-TAM group included ED (9%), ejaculation disorder (8%), ejaculation failure (6%), decreased libido (8%), and decreased semen volume (8%) [68••]. This study highlights the need to better characterize the risks of sexual dysfunction with LUTS treatments [69, 70]. More data is needed on long-term effects of these medications, especially on libido and sexual desire.

## Surgical Therapies for LUTS

Transurethral resection of the prostate (TURP) has been the gold standard for surgical management of BPH. The adverse effects of TURP are well described, including retrograde ejaculation in over 50% of patients and ED in 13 to 35% [71]. Newer, more minimally invasive therapies have attempted to reduce sexual side effects including retrograde ejaculation while maintaining improvements in objective and subjective measures of voiding [72].

The Prostatic Urethral Lift (PUL) (NeoTract Inc., Pleasanton, CA) procedure uses permanent implants to hold apart the obstructive prostatic lobes [73]. As there is no physical resection of prostatic tissue, ejaculatory function should be preserved. In 2017, the 5-year follow-up data of 140 patients was published, demonstrating a durable improvement in IPSS, QOL, and Qmax [74]. At 5 years, there was no significant change in the IIEF-5 or Men's Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) from baseline [74]. This preservation of ejaculatory function is consistent with other multi-institutional studies and systematic reviews on PUL [75–77].

The Rezum system (Boston Scientific, Marlborough, MA) uses heated water vapor thermal energy to ablate prostate tissue [78]. Three-year outcomes were recently published which also demonstrated a persistent improvement in IPSS, QOL, and Qmax. There were no changes in the IIEF-EF and MSHQ-EjD scores from baseline at 3 years, and the

ejaculatory bother score actually improved from baseline [79]. Aquablation (PROCEPT BioRobotics, Redwood City, CA) is another water-based ablation therapy that uses real-time ultrasonic guidance to direct a high-velocity saline stream. While the phase III trial is ongoing, preliminary results on 15 patients demonstrated no cases of ED [80].

Prostate artery embolization (PAE) is another minimally invasive therapy under investigation. Abt et al. recently reported on an open-label non-inferiority trial of 103 patients who were randomized either to PAE or to TURP [81]. While both treatments similarly improved the primary endpoint of IPSS, non-inferiority of PAE could not be established. There was no difference in IIEF score at 12 weeks between TURP and PAE. Of the patients with assessable ejaculatory function, 56% (14/25) patients after PAE had postoperative ejaculatory dysfunction [81]. Other studies have been retrospective in nature, and any changes in IIEF or ejaculatory function may be confounded by changes in BPH medication [82].

For men with very large prostates, laparoscopic and robotic simple prostatectomies have replaced the traditional open procedure [83]. However, there is limited data on ejaculatory and erectile function as the current literature has mainly focused on operative and urinary outcomes [84]. A prostatic urethra-sparing approach has been described to preserve antegrade ejaculation. Wang et al. published a series of 28 patients and found no change between preoperative and postoperative IIEF scores (18.5 vs. 17.5,  $p = 0.685$ ) [85]. Of the 15 patients who were sexually active in the series, only 1 patient developed retrograde ejaculation [85]. Simone et al. described using indocyanine green to assist in urethral-sparing dissection during robot-assisted simple prostatectomy to help preserve the prostatic urethra and ejaculatory function. In their series of 12 patients, there was no difference between preoperative and postoperative IIEF and MSHQ-Ejd scores at 1 year [86]. Eight patients (67%) reported satisfactory antegrade ejaculation [86].

Other options are currently being investigated, including intraprostatic injectables and implantable nitinol devices [72, 87, 88]. Preservation of sexual function is a key goal for new surgical therapies for LUTS. While initial results are promising, more data are needed to prove the long-term durability and safety of these treatments.

## Approach to Treatment and Future Directions

There are more medical and surgical options than ever before. Because the risk of sexual dysfunction varies with individual treatment options, shared decision-making is important during the preoperative consultation. However, a recent survey of 245 specialists (199 urologists) found that 30% do not routinely discuss the risk of ejaculatory dysfunction before prescribing ABs and 20% do not discuss the risk of ejaculatory dysfunction before TURP [89]. Of note, urologists with a higher surgical volume

were less likely to discuss alternative therapies for the risk of sexual dysfunction [89]. This study suggests that despite the data in the literature of how sexual health relates to LUTS, clinicians are not always relaying this information to patients. Solely treating LUTS represents a missed opportunity to address sexual health and further improve the patient's quality of life. Potential sexual adverse effects deserve more acknowledgment during the consenting process for LUTS therapy.

There are many questions to explore in future studies. Due to increased life expectancies, many men could potentially continue medical therapy for LUTS for decades. The risks of prolonged treatment are not well understood. For example, Duan et al. used Medicare data to find that tamsulosin may increase the risk of dementia in elderly men with BPH [90]. Although these results were recently refuted by Tae et al. in an analysis of National Health Insurance Claims for the entire Korean population, these studies highlight the need to better understand the long-term effects of these medications [91]. Likewise, the durability of the newer surgical therapies is still largely unknown. Even well-proven treatments like TURP lose effectiveness over time, and some men undergo multiple procedures over the course of their lives. It is not known whether more than one LUTS treatment results in a cumulative risk to sexual function. Finally, the costs of treatment will be an important topic to explore. Because of the complex relationship between LUTS and sexual function, cost/benefit analyses of treatment are more difficult to assess and warrant further attention.

## Conclusion

The relationship between LUTS and sexual health for men is an exciting one for both clinical and investigational urology, ripe with opportunities for basic science research, drug development, and innovative surgical approaches to improving quality of life. PDE5-Is are one example of targeted therapy that benefits both clinical conditions, representing not only a therapeutic opportunity, but also an eloquent example of the bidirectional flow of data between the laboratory and the clinic. Further investigation into the biochemical pathways between the two conditions may lead to other targeted therapies. Clinically, providers need to recognize the connection between MetS and sexual health/LUTS. Urologists and patients need to understand that medical and surgical treatments for BPH/LUTS can significantly impact erectile function, libido, and ejaculation. As we expand our array of treatment options and better understand their long-term benefits and risks, we move closer to providing patients with personalized and tailored treatments for their LUTS and sexual health.

## Compliance with Ethical Standards

**Conflict of Interest** Hanson Zhao and Howard H. Kim each declare no potential conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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