Lower urinary tract symptoms and erectile dysfunction

Chun-Hou Liao, Han-Sun Chiang, Po-Jen Hsiao*

Division of Urology, Department of Surgery, Cardinal Tien Hospital and Fu-Jen Catholic University, Taipei, Taiwan

1. Introduction

Lower urinary tract symptoms (LUTSs) are comprised of non-gender- and nonorgan-specific symptoms, which include storage, voiding, and postmicturition symptoms.1 The primary cause of LUTSs is benign prostatic hyperplasia (BPH) in men aged ≥50 years. Erectile dysfunction (ED) is defined as the persistent inability to achieve and maintain an erection sufficient for satisfactory sexual performance.2 The relationship between LUTSs and ED has received increasing attention because both conditions are highly prevalent, frequently coassociated in men in the same age group, and significantly contribute to the overall quality of life.3,4

A large body of epidemiological studies demonstrated consistent and compelling evidence for a relationship between LUTSs and ED in aging men using various measurement approaches in different population samples worldwide.5-37 In multivariate analyses that controlled for age, comorbidities (such as hypertension, diabetes, dyslipidemia, and cardiovascular disease), and lifestyle factors, LUTSs were clearly demonstrated to be an independent risk factor for ED. Although the causal link between LUTSs and ED is not well established, four main pathophysiological mechanisms with varying degrees of overlap currently support the relationship. These include the nitric oxide (NO)/NO synthase (NOS) theory, autonomic hyperactivity, the Rho-kinase activation pathway, and pelvic atherosclerosis.38 As a result of these associations, new approaches were recommended to evaluate and manage both conditions and to select treatment options.

2. Epidemiological evidence

Numerous epidemiological studies investigated the association between ED and LUTSs. Although most of these studies were cross-sectional, they demonstrate consistently strong associations, particularly with study consistency and dose-response effects.

2.1. Cross-sectional studies

Large-scale population- (Table 15-19), health screening- (Table 20-23) and clinical-based (Table 24-30) cross-sectional studies summarized here indicate a clear and clinically significant association between LUTSs and ED worldwide. In these studies multivariate logistic regression analyses were used to determine the independent effects of LUTSs on ED after controlling for age and other known risk factors. When viewed together, LUTSs appear to...
be an independent risk factor for ED with an odds ratio (OR) 1.39–7.67. The dose-response effect is well demonstrated by the fact that the severity of LUTSs is significantly associated with the prevalence and severity of ED.7,10,11,13,27 Men with severe LUTSs have a higher OR for ED than those with moderate LUTSs. The baseline data from the placebo arm of the Proscar Long-term Efficacy and Safety Study (PLESS)28 reported that every one-point increase in the LUTS severity score was associated with a 2% increase in ED risk even when controlling for age.

In addition, both storage and voiding LUTSs had significant associations with ED if LUTSs were separated into storage (irritative) and voiding (obstructive) LUTSs.22,29 However, another single-center study reported that obstructive symptoms, not irritative symptoms, were most highly correlated with ED. The data need to be cautiously interpreted due to the small sample size of the study (n = 181).31 On the contrary, two Taiwanese studies demonstrated that irritative symptoms were more related to ED.23,29 The discrepancy may be explained by the different inclusion criteria and adjusted cofactors. Further investigations are needed to clarify the roles of storage and voiding LUTSs in the development of ED.

### 2.2. Longitudinal studies

The preponderance of well-designed longitudinal studies highlights the cause-and-effect relationship. In contrast to numerous cross-sectional studies, only a few longitudinal studies have investigated the association between LUTSs and ED.

Shiri et al32 using population-based data obtained from 1126 Finnish men in the Tampere Aging Male Urological Study reported that obstructive symptoms, not irritative symptoms, were primarily responsible for the association. The dose-response effect is well demonstrated by the fact that the severity of LUTSs is significantly associated with the prevalence and severity of ED.7,10,11,13,27 Men with severe LUTSs have a higher OR for ED than those with moderate LUTSs. The baseline data from the placebo arm of the Proscar Long-term Efficacy and Safety Study (PLESS) reported that every one-point increase in the LUTS severity score was associated with a 2% increase in ED risk even when controlling for age.

In addition, both storage and voiding LUTSs had significant associations with ED if LUTSs were separated into storage (irritative) and voiding (obstructive) LUTSs.22,29 However, another single-center study reported that obstructive symptoms, not irritative symptoms, were most highly correlated with ED. The data need to be cautiously interpreted due to the small sample size of the study (n = 181).31 On the contrary, two Taiwanese studies demonstrated that irritative symptoms were more related to ED.23,29 The discrepancy may be explained by the different inclusion criteria and adjusted cofactors. Further investigations are needed to clarify the roles of storage and voiding LUTSs in the development of ED.

### 3. Possible mechanisms underlying the interaction between LUTSs and ED

A series of hypotheses has been proposed to explain the existence of a common physiopathology for LUTSs and ED. Currently, the relationship between LUTSs and ED is supported by four

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Study name or country (sample size)</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Laumann et al 19997</td>
<td>USA (n = 1410)</td>
<td>LUTSs were a significant predictor for ED (OR, 3.13) after controlling for demographic and lifestyle factors.</td>
</tr>
<tr>
<td>Martin-Morales et al 20018</td>
<td>Spain (n = 2476)</td>
<td>LUTSs were a significant risk factor for ED (age-adjusted OR, 2.67).</td>
</tr>
<tr>
<td>Blanket et al 20019</td>
<td>Krimpen (n = 1688)</td>
<td>ORs of moderate and severe LUTSs for ED were 3.4 and 7.5, respectively.</td>
</tr>
<tr>
<td>Braun et al 200010</td>
<td>Cologne Male Survey (n = 4489)</td>
<td>LUTSs in 72.2% of men with ED vs. 37.7% without ED; the OR of LUTSs for ED was 2.11.</td>
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<tr>
<td>Boyle et al 200311</td>
<td>UK (n = 4580)</td>
<td>The OR of moderate/severe LUTSs for ED was 1.39.</td>
</tr>
<tr>
<td>Nicolosi et al 200312</td>
<td>4 countries (n = 1335)</td>
<td>ORs of moderate and severe LUTSs for ED were 2.19 and 4.91, respectively, in relatively healthy men.</td>
</tr>
<tr>
<td>Rosen et al 200313</td>
<td>MSAM-7 (n = 12815)</td>
<td>ORs of mild, moderate, and severe LUTSs for ED were 1.98, 3.76, and 7.67, respectively.</td>
</tr>
<tr>
<td>Hansen et al 200414</td>
<td>Denmark (n = 3442)</td>
<td>ORs of obstructive, irritative, and mixed LUTSs for ED were 2.07, 1.55, and 2.82, respectively.</td>
</tr>
<tr>
<td>Chung et al 200415</td>
<td>Olmsted County study (n = 1547)</td>
<td>Significant correlation between LUTS severity and domain scores for ED after adjusting for age.</td>
</tr>
<tr>
<td>Laumann et al 200516</td>
<td>29 countries (n = 11205)</td>
<td>The OR of prostate disease for ED was in the range 1.8–2.0.</td>
</tr>
<tr>
<td>Irwin et al 200817</td>
<td>EPIC study (n = 502)</td>
<td>Cases were significantly more likely to have ED than the controls (OR, 1.5).</td>
</tr>
<tr>
<td>Brookes et al 200818</td>
<td>BACH (n = 2301)</td>
<td>ED was significantly associated with LUTSs after adjusting for age; may primarily be due to nocturia, incontinence, and symptoms suggestive of prostatitis.</td>
</tr>
<tr>
<td>Wong et al 200919</td>
<td>China (n = 1566)</td>
<td>Moderate to severe LUTSs (OR, 1.63) were independently associated with increased risk of having ED.</td>
</tr>
<tr>
<td>Wein et al 200920</td>
<td>EPiLUTS (n = 11384)</td>
<td>Men with moderate to severe LUTSs had a statistically significant 40% higher risk of developing subsequent ED than did men without LUTSs.</td>
</tr>
<tr>
<td>Morant et al 200921</td>
<td>UK (n = 11327)</td>
<td>ORs of storage, voiding, and both voiding and storage LUTSs for ED were 3.0, 2.6, and 4.0, respectively.</td>
</tr>
</tbody>
</table>

**BACH** = Boston Area Community Health Survey; **ED** = erectile dysfunction; **LUTSs** = lower urinary tract symptoms; **MSAM-7** = Multinational Survey of the Aging Male; **OR** = odds ratio.

### Table 2

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<thead>
<tr>
<th>Study</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terai et al 200422</td>
<td>Japan (n = 2084)</td>
<td>ORs of moderate and severe LUTSs for ED were 4.49 and 7.34, respectively.</td>
</tr>
<tr>
<td>Ponholzer et al 200523</td>
<td>Austria (n = 2585)</td>
<td>The OR of overall moderate/severe LUTSs for ED was 2.2. Obstructive symptoms and nocturia were primarily responsible for the association.</td>
</tr>
<tr>
<td>Liu et al 200624</td>
<td>Taiwan (n = 141)</td>
<td>ORs of moderate and severe LUTSs for ED were 4.49 and 7.34, respectively.</td>
</tr>
<tr>
<td>Tsa et al 201025</td>
<td>Taiwan (n = 339)</td>
<td>Men with moderate to severe LUTSs were more likely to have ED (age-adjusted OR, 3.27). Irritative symptoms had a more-significant association with ED than did the obstructive symptoms.</td>
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</table>
3.1. NO/NOS theory

The NO system is well characterized as the main regulator of penile corporal smooth muscle relaxation and resultant erection. NO activates soluble guanylate cyclase of smooth muscle cells, which in turn increases cyclic (c)GMP. Increased cellular cGMP is responsible for smooth muscle cell relaxation and resultant tumescence.

The NO pathway is also reported to have a role in the control of human prostatic smooth muscle activity and/or in secretory neurotransmission. Nitricergic innervation has been demonstrated to decrease in human BPH tissues compared to normal prostate tissue, suggesting a potential role for NO in the pathophysiology of BPH. Moreover, the human bladder neck is also innervated by NOS-containing nerves, and their density is higher in the outlet region than in other parts of the bladder.

Furthermore, distinct soluble guanylate cyclase expression and measurement of NO release suggested that the urothelium is also a target structure of NO. Studies in animals also suggest that NO plays a role in preventing bladder contractions that result in bladder hyperactivity, as observed in LUTSs. Taken together, the NO/NOS pathway may have an important regulatory role on lower urinary tract function and erectile function.

3.2. Autonomic hyperactivity

The degree of smooth muscle relaxation is influenced by the balance between sympathetic and parasympathetic tone. Autonomic hyperactivity, which refers to the dysregulation of sympathetic and parasympathetic tone, is a component of metabolic syndrome. Increased sympathetic activity results in penile flaccidity, and it antagonizes penile erection. Hypertension, obesity, and hyperinsulinemia were all claimed to be associated with increased sympathetic activity. Experiments on animal models showed that manipulation of autonomic activity affects prostate growth and differentiation. Special strains of rats that are spontaneously hypertensive can develop increased autonomic activity, prostate hyperplasia, and ED. Brief aggressive treatment of their hypertension can improve their ED. In a different model, hyperlipidemic rats developed simultaneous prostatic enlargement, bladder overactivity, and ED after being fed a high-fat diet.

Autonomic hyperactivity was also reported to be significantly associated with the International Prostatic Symptom Score (IPSS) and BPH impact index score. The prostate size was also significantly correlated with markers for autonomic hyperactivity, such as increased serum norepinephrine levels and an abnormal hypertensive response to tilt-table testing. However, it is yet unclear whether the increase in LUTSs or ED is a consequence of an alteration in the function of the bladder/penis itself leading to increased central activation or the result of a central increase in sensitivity to peripheral signals.

3.3. The Rho-kinase activation pathway

RhoA, a small G-protein, and its downstream target, Rho-kinase, are reported to be possible mediators of α-adrenergic- (norepinephrine) and endothelin-1-triggered smooth muscle contractions. Thus, abnormal upregulation of the Rho-kinase pathway could contribute to a lack of smooth muscle relaxation. Rho-kinase activation may potentiate smooth muscle tone in the corpus cavernosum of the rat via the use of norepinephrine and endothelin. Corpus cavernous smooth muscles from rabbits with partial bladder outlet obstruction are reported to show increased penile smooth muscle contractility, reduced relaxation, modest alterations in total smooth muscle myosin, decreased innervation, and increased smooth muscle bundle size. Another study also showed Rho-kinase dysfunction in the bladder following bladder outlet obstruction. Thus, increased Rho-kinase activity might represent a common link between LUTSs and ED.

3.4. Pelvic atherosclerosis

Diffuse atherosclerosis of the prostate, penis, and bladder is another hypothesis linking LUTSs with ED. Animal models of hypercholesterolemia and pelvic ischemia show similar alterations of smooth muscle in the bladder, prostate, and penis. Hypoxia-induced overexpression of transforming growth factor (TGFB)-β1 and altered prostanoid production are proposed as potential mechanisms.

Bladder ischemia from either bladder outlet obstruction or pelvic vascular disease can induce bladder smooth muscle loss and collagen deposition, leading to loss of compliance, detrusor overactivity, and impaired detrusor contractility. Prostate ischemia can result in a less distensible urethra, which might also worsen LUTSs. Moreover, penile ischemia might result in ED. Pelvic atherosclerosis may be associated with metabolic syndrome, autonomic hyperactivity, upregulated Rho-kinase activity, and reduced NOS expression.

### Table 3

<table>
<thead>
<tr>
<th>Study name or country (sample)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frankel et al 199824</td>
<td>A significant positive association was found between ED and LUTSs after adjusting for age and BPH impact index score.</td>
</tr>
<tr>
<td>Vallancien et al 200325</td>
<td>Age-adjusted ED prevalences were 53%, 62%, and 71% in men with no/mild, moderate, and severe ED, respectively.</td>
</tr>
<tr>
<td>Hoesl et al 200526</td>
<td>Significant association between LUTS severity and ED severity.</td>
</tr>
<tr>
<td>El-Sakka et al 200527</td>
<td>One-point increase in the IPSS was associated with a 2% increase in the ED risk.</td>
</tr>
<tr>
<td>Paick et al 200528</td>
<td>A consistent inverse correlation was found between ED and LUTS severity across age groups.</td>
</tr>
<tr>
<td>Tsao et al 200829</td>
<td>Total IPSS and IPSS bother scores were independent predictors of ED.</td>
</tr>
<tr>
<td>Rosen et al 200930</td>
<td>ED = erectile dysfunction; IPSS = international prostatic symptom score; LUTSs = lower urinary tract symptoms; OR = odds ratio; PLESS = PROscar Long-term Efficacy and Safety Study.</td>
</tr>
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ED = erectile dysfunction; IPSS = international prostatic symptom score; LUTSs = lower urinary tract symptoms; OR = odds ratio; PLESS = PROscar Long-term Efficacy and Safety Study.
3.5. The role of testosterone in the pathogenesis of BPH/LUTSs and ED

Aging, sex hormones, and growth factors are generally considered to play important roles in the pathogenesis of BPH. Although few data describe the relationship between male LUTSs and sex hormones, there are several plausible physiological mechanisms to explain the inverse association of testosterone and LUTSs. Autonomic nervous system overactivity may play a key role in developing and increasing the severity of LUTSs. Others have postulated the influence of testosterone on postsynaptic non-genomic receptors, and NO-mediated bladder neck relaxation. 

Approximately 20% of ED patients have low serum testosterone levels. Serum levels of testosterone are closely related to manifestations of other etiologic factors in ED, such as atherosclerotic disease, diabetes mellitus, and metabolic syndrome, and an inverse relationship exists between serum testosterone and the severity of these symptoms. Consequently, testosterone is becoming recognized as an important factor in ED. A large body of evidence from experimental animal models suggests that androgens beneficially modulate numerous multiple cellular components in the corpus cavernosum, leading to structural and functional integrity of penile erections. It is thought that the primary action of androgens in erectile function in the rat model is via stimulation of NO synthesis.

4. Treatment for LUTSs and ED

α1-Blockers are the most effective monotherapy for LUTSs suggestive of BPH, while phosphodiesterase (PDE)-5 inhibitors are the mainstay treatment for ED. In addition to well-known treatment effects, α1-blockers can also be beneficial in the treatment of ED, while PDE-5 inhibitors can be beneficial in the treatment of LUTSs (Table 4).

4.1. α1-Blockers for ED

The actions of both α1-adrenoceptors and to a lesser extent, α2-adrenoceptors on smooth muscle fibers are functionally important for controlling the contractile tone of erectile tissues. Hence, there is a pharmacological rationale for α1-blockers playing a role in facilitating penile erection by counteracting the contraction (detumescence) of corpus cavernosum smooth muscle fibers when there is sexual stimulation. Supporting this theory, pharmacological experiments conducted on isolated corpus cavernosum of rabbits showed that the selective α1-blocker, alfuzosin, had direct relaxant effects.

Evidence for the beneficial effects of α1-blockers on erectile function was also obtained from studies in patients with BPH/LUTSs associated with ED.

4.2. PDE-5 inhibitors for LUTSs

Because NO was also found to mediate male prostatic and urinary functions in multiple ways, there is increasing interest in using PDE-5 inhibitors to treat concomitant LUTSs. Tinel et al. identified PDE-5 messenger (m)RNA expression in the bladder, followed by the urethra and prostate, confirming that the expression of PDE-5 mRNA in tissues is generally held responsible for LUTSs. They also reported that the inhibition of PDE-5 might decrease obstruction by dilatation of the prostatic urethra and bladder, with effects on the irritative symptoms of LUTSs associated with BPH in rats.

Four randomized, placebo-controlled studies sought to elucidate the relationship between PDE-5 inhibitors and LUTSs using sildenafil, vardenafil, and tadalafil. Regardless of the PDE-5 inhibitor used, these studies generally showed an improvement in IPSS scores, but without a significant change in maximum urinary flow rates (Qmax). The effects of PDE-5 inhibitors on storage symptoms seem to be more marked than on voiding symptoms. However, there is still no direct comparison of the efficacies of PDE-5 inhibitors with α1-blockers.

4.3. Combined treatment with α1-blockers and PDE-5 inhibitors

An alternative management strategy for patients with both LUTSs and ED would be to provide combination therapy with agents that improve LUTSs and/or ED without adversely affecting either condition. α1-Blockers and PDE-5 inhibitors are likely to act via different mechanisms, thereby providing the rationale for combining them to treat LUTSs and ED. Interaction studies confirmed that tadalafil has only marginal effects on blood pressure when coadministered with selective α1-blockers, such as alfuzosin. However, caution is still advised by the US Food and Drug Administration when PDE5 inhibitors are coadministered with α-blocker therapy. In some patients, concomitant use of these two drug classes can significantly lower blood pressure leading to symptomatic hypotension.

Patients should be stable on α-blocker therapy prior to initiating PDE-5 inhibitors. Patients who demonstrate hemodynamic instability on α-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE-5 inhibitors. Even in patients who are stable on α-blocker therapy, PDE-5 inhibitors should be initiated at the lowest dose. In patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Medication</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1-Blockers</td>
<td></td>
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</tr>
<tr>
<td>Kirby et al 2005</td>
<td>680 men with BPH</td>
<td>Doxazosin (4 and 8 mg qd)</td>
<td>Significant improvements in each of the five IIEF domains in men with ED.</td>
</tr>
<tr>
<td>PDE-5 inhibitors (randomized placebo-controlled)</td>
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<tr>
<td>MacVary et al 2007</td>
<td>369 men with ED and LUTSs</td>
<td>Sildenafil (50–100 mg qd)</td>
<td>IPSS improvement of 6.32 vs. a placebo of 1.93.</td>
</tr>
<tr>
<td>Stief et al 2006</td>
<td>222 men with LUTSs</td>
<td>Vardenafil (10 mg bid)</td>
<td>IPSS improvement of 5.9 vs. a placebo of 3.6.</td>
</tr>
<tr>
<td>MacVary et al 2007</td>
<td>281 men with LUTSs</td>
<td>Tadalafil (5–20 mg qd)</td>
<td>IPSS improvement of 2.8 vs. a placebo of 1.2.</td>
</tr>
<tr>
<td>Roehrborn et al 2008</td>
<td>1058 men with LUTSs</td>
<td>Tadalafil (2.5, 5, 10, and 20 mg qd)</td>
<td>IPSS significantly improved with at least a 5-mg dose.</td>
</tr>
<tr>
<td>Combination therapy</td>
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<tr>
<td>Kaplan et al 2007</td>
<td>62 men with LUTSs and ED</td>
<td>Sildenafil (25 mg) + Alfuzosin (10 mg qd)</td>
<td>Combination therapy superior than either agent alone.</td>
</tr>
</tbody>
</table>

BPH = benign prostatic hyperplasia; IIEF = international index of erectile function; IPSS = international prostatic symptom score.
already taking an optimized dose of a PDE-5 inhibitor, α-blocker therapy should be initiated at the lowest dose. Stepwise increases in the α-blocker dose may be associated with further lowering of the blood pressure when taking a PDE5 inhibitor.

The safety of the concomitant use of PDE-5 inhibitors and α-blockers may be affected by other variables, including intravascular volume depletion and other antihypertensive drugs. Sildenafil resulted in transient decreases in supine blood pressure in healthy volunteers (with mean maximum decreases of 8.4 (systolic)/5.5 mmHg (diastolic)), and additional blood pressure reductions of 8 mmHg systolic and 7 mmHg diastolic were noted when combined with antihypertensive medications. Patients older than 65 years, with hepatic or severe renal impairment, and concomitant use of potent cytochrome P450 3A4 inhibitors had higher risks than healthy volunteers.70 Prolonged erections of more than 4 hours and priapism (painful erections of longer than 6 hours in duration) were also infrequently reported after taking PDE5 inhibitors. In addition, alfuzosin and tadalafil show an additive relaxant effect on human detrusor muscle, human prostate tissues, and the human corpus cavernosum in vitro.71 A pilot clinical study also suggested that daily intake of 10 mg of alfuzosin and 25 mg of sildenafil is well tolerated and may be more effective than monotherapy in improving LUTSs and ED.72 Further research is warranted to establish the value of this combination therapy in LUTSs and ED.

5. Conclusions

Both LUTSs and ED are highly prevalent in aging men. LUTSs are an independent risk factor for ED even after controlling for age and other known risk factors. Although four possible pathogeneses were proposed to explain such a relationship, further studies are needed to define the mechanism(s) underlying the association between LUTSs and ED. Additional studies using combination therapy for LUTSs, ED, and other age-associated comorbidities are needed to establish new approaches to achieve optimal management of these conditions in aging men.

References