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Chapter

Lower Urinary Tract Symptoms (LUTS) and Sexual Function and Dysfunction

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Abstract

In recent years, the coexistence of sexual dysfunction (SD) and lower urinary tract symptoms (LUTS) has become a popular topic for researchers. Numerous clinical epidemiologic studies have been planned for this reason and have evaluated the relationship between these seemingly irrelevant urological conditions. The connection between SD and LUTS has already been acknowledged, and common pathophysiological pathways have been recognized. In this chapter was attempted to evaluate the impact on patient's quality of life (QoL), common pathophysiological pathways and therapy aspects of this condition. SD and LUTS are common problems among the general population and affect a great percentage of urological patients. It is a subject that affects the community in social, financial, and psychological terms. In this case, research for new treatment options has been triggered as phosphodiesterase type 5 inhibitors established their role as the widely approved combination therapy.

Keywords: lower urinary tract symptoms (LUTS), sexual dysfunction (SD), PDE5i

1. Introduction

In recent years, the coexistence of sexual dysfunction and lower urinary tract symptoms has become a popular topic for researchers. Numerous clinical epidemiologic studies have been planned for this reason and have evaluated the relationship between these seemingly irrelevant urological fields of study. In this chapter, an approach to these two fields, their impact on patients' quality of life (QoL), common pathophysiological pathways and therapy aspects are attempted. Both are common problems among the general population and affect a great percentage of urological patients. In this case, research for new treatment options has been triggered as phosphodiesterase type 5 inhibitors established their role as the widely approved combination therapy.

2. Lower urinary tract symptoms

Lower urinary tract symptoms (LUTS) are a common complaint in adult men and women with a major impact on quality of life (QoL) [1–4]. They can be divided into storage, voiding, and postmicturition symptoms [5]. LUTS are strongly associated with aging [1, 2] and also with a number of modifiable risk factors, suggesting

potential targets for prevention (e.g., metabolic syndrome) [6]. Most elderly men have at least one LUTS [2], which is often mild or not very bothersome [4, 7, 8]. LUTS progression is a dynamic procedure. LUTS may persist and upscale over long time periods, or they may retreat [2]. LUTS have usually been related to bladder outlet obstruction (BOO), which is often caused by an increase of prostatic volume, as a result of benign prostate hyperplasia (BPH) [3, 5]. On the contrary, numerous studies have shown that LUTS are often not related to the BPH [2, 9]. Bladder dysfunction may also cause LUTS, such as detrusor overactivity or overactive bladder syndrome (OAB), detrusor underactivity, and structural or functional abnormalities of the urinary tract and its surrounding tissues [9]. Prostatitis may also cause the appearance of LUTS [10, 11]. Furthermore, there are some nonurological conditions that may be related to urinary symptoms, mainly to nocturia [2].

The definitions of the most common conditions related to LUTS are presented below:

- Acute retention of urine is defined as a painful and palpable bladder when the patient cannot urinate [5].

- Chronic retention of urine is defined as a nonpainful bladder, which remains palpable even though the patient has urinated. It may also be accompanied by incontinence [5].

- Bladder outlet obstruction (BOO) is characterized by reduced urine flow rate and increased detrusor pressure. It can be diagnosed by studying the synchronous values of detrusor pressure and urine flow rate [5].

- Benign prostatic obstruction (BPO) is a form of BOO, diagnosed when the cause of outlet obstruction is known to be BPH [5].

- Detrusor overactivity (DO) is a urodynamic observation characterized by involuntary detrusor contractions during the bladder filling phase [5].

- Overactive bladder (OAB) syndrome is characterized by urinary urgency, with or without urinary incontinence, usually with increased daytime frequency and nocturia, and in this case, there is no proven infection or other obvious pathology [12].

Patient's history must be assessed thoroughly [13–15]. A medical history aims to identify relevant comorbidities and potential causes, including medical and neurological diseases. Lifestyle habits, medication, emotional, and psychological factors must also be reviewed. When relevant, the sexual function should be assessed, preferably with validated symptom questionnaires such as the International Index for Erectile Function (IIEF). The literature recommends, for male LUTS assessment, the use of validated symptom score questionnaire [13, 15]. Several questionnaires have been developed, which are sensitive to symptom changes. In this case, they are helpful in monitoring treatment approaches [16–22]. Symptom scores are helpful in quantifying LUTS and identifying the predominant symptoms. Nevertheless, they are not disease- or age specific.

3. Sexual dysfunction

It is difficult to identify the prevalence of sexual dysfunction in men, because there is no standard definition of sexual dysfunction (SD). Erectile dysfunction

(ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [23]. Penile erection is a complex phenomenon, which implies coordination among the neurological, vascular, and smooth muscle compartment. It includes arterial dilation, trabecular smooth muscle relaxation, and activation of the corporal veno-occlusive mechanism [24]. ED may affect physical and psychosocial health. It might have a significant impact on the QoL of sufferers and their partners' as well [25–27]. Therefore, ED should not be regarded only as a QoL issue, but also as a potential warning sign of cardiovascular disease (CVD), as it can be an early manifestation of coronary artery and peripheral vascular disease [28–30].

The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced, and/or psychogenic [24]. Usually, many pathophysiology pathways can be comorbid and concomitant, negatively impacting on erectile function. In most cases, ED is the result of more than one organic pathophysiological element and, very often, a psychological component. ED was initially classified into three categories based on its etiology. These include organic, psychogenic, and mixed ED. Nowadays, these are recognized as two categories: the psychogenic and the mixed one, as any organic ED has an additional psychogenic impact that interferes with the pathophysiology of ED and causes additional distress to the patient.

Epidemiological data have shown a high incidence and prevalence of ED worldwide. The Massachusetts male aging study (MMAS) [25] reported, in noninstitutionalized men aged 40–70 years in the Boston area, an overall prevalence of 52% ED. Prevalence for minimal, moderate, and complete ED was 17.2, 25.2, and 9.6%, respectively. In the Cologne study of men aged 30–80 years, the prevalence of ED was 19.2% [65]. The incidence rate of ED (new cases per 1000 men annually) was 26 in the long-term data from the MMAS study [66] and 19.2 (mean follow-up of 4.2 years) in a Dutch study [31].

ED shares common risk factors with CVD (e.g., obesity, diabetes mellitus, dyslipidemia, metabolic syndrome, lack of exercise, and smoking) [27, 32–34]. The association among ED and age, diabetes mellitus, body mass index (BMI) [35, 36], obstructive sleep apnea, and hyperhomocysteinemia has been established [37–39]. A number of studies have shown evidence that lifestyle modification [29, 40] and pharmacotherapy [40, 41] for CVD risk factors may also improve sexual function in men with ED. Epidemiological studies have also demonstrated consistent evidence for an association between LUTS and sexual dysfunction, regardless of age, other comorbidities, and behavioral factors [42]. The multinational survey on the aging male (MSAM-7) study (performed in France, Germany, Spain, Italy, the Netherlands, the USA, and the UK) investigated the relationship between LUTS and sexual dysfunction in over 12,000 men aged 50–80 years. From 83% of sexually active men, the prevalence of LUTS was 90%, with the prevalence of ED being 49%. The complete absence of erection was reported in 10% of patients. The prevalence of ejaculatory disorders has been reported in 46% of patients [43]. Association between chronic prostatitis or chronic pelvic pain syndrome (CP/CPPS) and ED is confirmed [44].

Surgical interventions to the prostate also have an impact on erectile function according to the type of surgery that was performed [45]. Epidemiologically, there are other risk factors that potentially associate to ED, including psoriasis [46–48], gouty arthritis [49, 50], ankylosing spondylitis [51], nonalcoholic fatty liver [52], chronic liver disorders [53], chronic periodontitis [54], open-angle glaucoma [55], inflammatory bowel disease [56], and complications following transrectal ultrasound (TRUS) guided prostate biopsy [57].

World Health Organization (WHO) and International Classifications of Diseases-10 (ICD-10) define female sexual dysfunction as "the various ways in

which an individual is unable to participate in a sexual relationship as she would wish" [58]. There are three categories of sexual dysfunction: female sexual interest-arousal disorder, female orgasmic disorder, and genito-pelvic pain-penetration disorder [59]. It is estimated that 10% of women suffer from female sexual interest-arousal disorder and 3.5–35% present orgasmic problems [60].

Validated psychometric questionnaires, such as the International Index for Erectile Function (IIEF) [61] or the sexual health inventory for men (SHIM) [62], are the assessment tools needed in different sexual function domains (i.e., erectile function, sexual desire, intercourse, orgasmic function, and overall satisfaction), as well as for the potential impact of a specific treatment modality. The use of the erectile hardness score for the assessment of penile rigidity in practice and in clinical trial research is supported by psychometric analyses [63]. Patients should be screened for symptoms of possible hypogonadism (testosterone deficiency), libido, fatigue, cognitive impairment, and LUTS. Even though LUTS does not represent a contraindication to treat a patient for late-onset hypogonadism, screening for LUTS severity is clinically relevant [64].

4. The relationship between ED and LUTS

A lot of epidemiological studies demonstrate the coexistence of ED and LUTS. It is also proven that the existence of LUTS is a risk factor for ED. The patient's age and the severity of LUTS are independent prognostic factors for ED, as well. Although it is not clear if LUTS lead to ED, or ED results to LUTS, or these conditions are just coexisting, their relation is very narrow and clear, especially in older patients. Therefore, men who suffer from LUTS should be checked for ED and men who present ED should be evaluated for LUTS. There are four theories that try to correlate LUTS with ED. These theories include deregulation of NO/NOS system, increased sympathetic tone (autonomic hyperactivity (AH)), up-regulation of Rho-kinase, and chronic hypoxia. Common vascular risk factors can combine and support these theories.

4.1 Alteration in nitric oxide (NO)

The role of nitric oxide (NO) in erectile function is well known as the main regulator of penile corporal smooth muscle relaxation and resultant erection. The decrease in NO/cyclic guanosine monophosphate (cGMP) has the effect of reduction in NO synthase (NOS) due to endothelial dysfunction. Luck or reduction of smooth muscle relaxation of the bladder neck, prostate and urethra may lead to LUTS. The NO system has been shown to be down-regulated in the transition zone of the prostate in BPH when compared with normal controls [67, 68].

4.2 Autonomic hyperactivity (AH)

AH, as a component of the metabolic syndrome, refers to dysregulation of sympathetic and parasympathetic tone. Increased sympathetic tone results in flaccidity and antagonizes penile erection, due to vasoconstriction. Parasympathetic activation can lead to prostate smooth muscle contraction (due to activation of the M2 receptors), so nonrelaxing bladder neck, prostatic urethra, and pelvic floor may lead to LUTS [67, 68].

4.3 RhoA/rho-kinase-calcium-sensitizing pathway

Smooth muscle tone is adjusted commonly not only through the calcium-dependent mechanism, but also through the activity of RhoA/ROCK calcium

pathway. Activation of RhoA-ROCK pathway can affect smooth muscle relaxation and finally increase ED and LUTS. Therefore, penile RhoA/ROCK signaling was increased in pathologic situations associated with ED, like diabetes and involuntary bladder contractions were associated with increased signaling of the muscarinic receptor-activated RhoA/ROCK pathway. Increase in RhoA/ROCK was demonstrated in corpora cavernosa and bladder of spontaneously hypertensive rats (SHR), a rat strain genetically prone to develop BPH and OAB. The inhibition of ROCK reduces bladder hyperactivity, limits contractions in bladder strips from SHR, and improves erectile function [67, 68].

4.4 Pelvic atherosclerosis

Atherosclerosis of the bladder, prostate, and penis serves an extra assumption linking LUTS with ED. The theory claims that the risks for ED (smoking, hypertension, hypercholesterolemia, and diabetes mellitus) also affect on LUTS. An epidemiologic study was published that supports this theory, all men and women who had two risk factors of atherosclerosis (diabetes mellitus, hypertension, hyperlipidemia, and nicotine use) and had a statistically higher International Prostate Symptom Score (IPSS) compared with those with one or no risk factors at all. Smooth muscle changes in the prostate, bladder, and penis of animal models of hypercholesterolemia and pelvic ischemia are quite similar. Hypoxia drives to overexpression of TGFb1, and converted prostanoid production has been suggested as potential mechanisms. Similarly, penile ischemia leads to smooth muscle loss in it and ends up with ED. Likewise, the loss of smooth muscle in the bladder may decrease compliance and increase the symptoms of LUTS. Additionally, bladder ischemia either from BOO or pelvic vascular disease would result in bladder smooth muscle loss with the resultant replacement of collagen deposition and fibrosis as well as loss of compliance, overactivity, and impaired contractility. Loss of smooth muscle in the prostate can induce a less distensible urethra, a decreased urinary flow rate, increased flow resistance, and worsening LUTS. Pelvic atherosclerosis associated with the previously described theories, as pelvic ischemia/atherosclerosis is a component of the metabolic syndrome/AH, up-regulates Rk activity, and reduces NOS expression. [35, 67, 68].

5. Multifactorial interaction between LUTS and ED

LUTS are significant indicators of a disease when the patient, caregiver, or partner realizes it, and change of them may lead him/her to find help from professionals. It is also known (from the 6th International Consultation on Incontinence 2016) that from overall world's population, 46% (of the adults >20 years) experience LUTS, 11.8% suffer from OAB symptoms, 8% complain of some type of urinary incontinence (UI), and 4% of severe stress urinary incontinence (SUI). Urinary incontinence is associated with reduced QoL, higher rates of depression, reduced work productivity, and decreased enjoyment of sexual activity [35, 69].

It is well known that sexual life, behavior, and relationships are very important for a good and healthy life, and they are affected by attitudes, social models and overall health. For sexual health many aspects are necessary and not only the absence of infirmity, disease or dysfunction. Sexual practice and habits have changed a lot over the last years, it is over also known that the sexual frequency and different practices are reducing with age. On the other hand, some sexual behaviors are more common in our days, like anal sex. These changes are more likely to be attributed to educational status, rather than economic status [69].

From a physiological prospect, the functions of pelvic organ functions are related as there is a direct relationship with the neuronal network of the pelvis that includes bladder, bowel, and sexual functions. Furthermore, vascular, hormonal, cellular, and other factors comprehensively affect pelvic organ functions. LUTS and ED in males share common pathophysiological pathways [4].

6. Effects of LUTS/incontinence on male sexual function: epidemiological data

Many large studies over the last years have proved the coexistence of SD in men with storage and voiding LUTS. Statistics from the Health Improvement Network database showed that from 11,327 men in the UK, there was a rise in the overall prevalence of recorded SD from 1.7% in 2000 to 4.9% in 2007. The odds ratio (OR) for ED was 3.0 (2.6–3.4) for storage LUTS, 2.6 (2.4–2.7) for voiding LUTS, and 4.0 (3.4–4.8) for voiding and storage LUTS. The EpiLUTS study (a cross-sectional, population-representative survey in the UK, Sweden, and the USA with 6326 men) show off an impact of OAB on sexual health. Both OAB wet and OAB dry were associated with poor sexual health, diminished enjoyment of sex ($P < 0.0001$), and decreased sexual activity. OAB dry/wet was very significant predictors of ED and ejaculatory dysfunction (EjD) in men. According to a study by Rosen et al., the attendance and severity of LUTS are independent risk factors for SD in older men [69].

LUTS are common in older men. While LUTS have a multifactorial etiology, BOO/BPH has traditionally been considered as one of the most common causes of LUTS. These symptoms, which include dribbling and urgency with leaking, nocturia, and difficulty in urinating, can also impact the sexual function, probably due to impact on QoL [70].

7. Medical and surgical therapy for LUTS and its impact on sexual function

The efficacy of all currently available treatments for LUTS is well studied. However, the negative impact of them on erectile function is under evaluation. Behavior modification therapies and phytotherapies seem to have minimal or no impact on sexual function, and even less efficacy on LUTS treatment. On the other hand, α-blockers, 5α-reductase inhibitors, and prostatic surgery are associated with improvement in LUTS, but they usually have a negative impact on the sexual function [68]. Many clinical trials have reported on the efficacy of chronic treatment with phosphodiesterase type 5 inhibitors (PDE5-Is), either alone or in combination with other therapies, in treating LUTS in men with or without ED [71].

α-Blockers such as alfuzosin, doxazosin, tamsulosin, and silodosin have shown similar efficacy, but their effect on sexual function is variable. They seem to have a slightly positive impact on erectile function. However, they can have a negative impact on orgasmic function and ejaculation [72]. Originally, the abnormal ejaculate was thought to be retrograde. However, it seems likely to be due to a decrease or absence of seminal fluid, possibly by a central effect. α-Blockers decrease the prostate secretion and inhibit the contraction of seminal vesicles as both effects are mediated by the sympathetic adrenergic system.

5α-Reductase inhibitors (5-ARIs) are usually offered to men with LUTS who have a prostate estimated to be larger than 40 ml and who are considered to be at high risk of progression [73–75]. Compared to α-blockers, 5-ARIs have a greater

impact on sexual function. The side effects most frequently notified are reduced libido, ED, and ejaculation disorders such as dry orgasm, ejaculation failure, or decreased semen volume [76–78]. It must be mentioned that the effect of 5-ARIs on ejaculatory function is currently poorly studied.

Regarding surgical options, transurethral resection of the prostate (TURP) and transurethral incision of the prostate (TUIP) are the gold standard surgical techniques for BPH/BOO treatment. Dry orgasm after these operations ranges from 30.4 to 96.9% and 6.1 to 55.1%, respectively. Heterogeneous data are reported, mainly because only a few studies analyzed these rates [79–81] in a prospective fashion. ED has been found ranging from 3.4 to 32.4% [80, 81] after TURP.

Laser procedures, such as GreenLight photoselective vaporization of the prostate (PVP) and holmium laser enucleation of the prostate (HoLEP) are widely offered for BOO/BPH as well. The impact of GreenLight on sexual function seems to be close to that of TURP. One single study, comparing these two prostatic surgery techniques, reported no significant difference in the rate of retrograde ejaculation [82]. There is also no difference reported between TURP and PVP for erectile function [83, 84]. HoLEP seems to have comparable results. Specifically, the incidence of retrograde ejaculation and erectile dysfunction is comparable between HoLEP and TURP [85, 86]. It is reported that almost 75% of sexually active patients have retrograde ejaculation after HoLEP. Currently, both GreenLight and HoLEP surgeons are trying to develop ejaculation preserving techniques [87, 88].

Transurethral thermotherapy and microwave techniques such as transurethral needle ablation (TUNA) seem to have lower rates of retrograde ejaculation comparing to TURP. A few studies report that the incidence of retrograde ejaculation seems to be much lower compared to TURP, with no reported cases in the TUNA cohort, compared to the 45% of the TURP arm [89–91]. Urolift/prostatic urethral lift (PUL) is an alternative option and has shown positive results in terms of sexual function [92].

Currently, because of the increase in life expectancy, patients with LUTS often wish to preserve or to improve their sexual function according to their treatments. Physicians may focus on the symptoms without considering patients' wishes and expectations. In those cases, despite successful treatment, many patients still complain about their QoL due to the procedure or medication side effects.

8. Medical therapy for ED and its impact on LUTS

Phosphodiesterase type 5 (PDE5) is expressed in the whole of the lower urinary tract, including the urethra, prostate, and bladder. All these organs are targets of PDE5-Is [93–96]. PDE5 is prominently localized in the stroma and in the vascular bed (endothelial and smooth muscle cells), suggesting the action of PDE5-I on smooth muscle contraction and blood flow.

McVary et al. [97], in 2007, evaluated the safety and efficacy of tadalafil for the treatment of LUTS in men with or without ED, for the first time. A total of 479 patients were screened. After a 4-week washout and 4-week placebo run-in period, 281 were randomly assigned to a 6-week treatment with once-daily placebo or tadalafil 5 mg. After 6 weeks, the remaining 261 patients were assigned to continue with placebo for another 6 weeks (a total of 12 weeks of once-daily placebo treatment) or to dose escalate tadalafil to 20 mg once daily. Of 143 placebo-assigned patients, 121 (84.6%) were sexually active, 84 (59.2%) had no erectile dysfunction, and 76 (53.1%) were sexually active despite ED. On the other hand, 138 men treated with 5 or 20 mg tadalafil, 107 (77.5%) were sexually active, 99 (71.7%) had normal sexual function, and 80 (58.0%) were sexually active despite ED. The IPSS

(including the IPSS-QoL question) and BII questionnaires were used in order to evaluate LUTS. Maximum urinary flow rate (Q_{max}) and average urinary flow rate (Q_{ave}) of free uroflowmetry were record and post-void residual urine (PVR) was measured by ultrasound after uroflowmetry. The erectile function (EF) domain of the International Index of Erectile Function (IIEF) questionnaire (questions 1–5 and 15) was used to estimate the sexual function.

Since 2007, numerous studies proved the safety and efficacy of PDE5s as a medical therapy for both LUTS and ED. Bora Irer et al. [98] studied LUTS, nocturia, SD, and the status of QoL in men with obstructive sleep apnea syndrome (OSAS). Patients applied continuous positive airway pressure (CPAP) treatment, which is one of the most effective treatments for OSAS, supplying positive air pressure for the opening of the respiratory tract and keeping high saturation of oxygen. Changes in IPSS, IIEF, Overactive Bladder Syndrome Score (OABSS), International Consultation on Incontinence Questionnaire for Male LUTS (ICIQ-MLUTS), Neuro-quality of life score (Nqol), 36-item Short Form Health Survey (SF-36), and Benign Prostatic Hyperplasia Impact Index (BII); the frequency of nocturia; and night-time urine volume were reported. After CPAP treatment, significant changes and improvements on these symptoms and QoL were observed. It has been shown that the frequency of nocturia decreases and erectile function and QoL improves in patients with OSAS under CPAP treatment [99, 100].

9. Conclusion

SD and LUTS are confirmed to have a strong connection. It is implied by common pathophysiological paths that seem to link these two complications, which have a great impact on a significant percentage of urological patients. For men, PDE5s inhibitors are the milestone of medical treatment for ED and LUTS. Their safety and efficacy are widely accepted. More studies need to support this relatively new field of research for both LUTS and SD, and new treatments may be used as an alternative in near future.

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