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Review

Lower urinary tract symptoms in elderly men: a simple yet comprehensive approach

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Lower urinary tract symptoms (LUTS) are common among elderly men and they may be linked to benign and malignant diseases of prostate and bladder, because of their shared inflammatory pathophysiology involving also the immune system. Actually the prostate should not be considered the only target of treatment in the management of male LUTS: it is necessary to treat bladder outlet obstruction, but also bladder and urethra. LUTS (particularly when refractory to therapy) often represent the starting point for identifying such conditions, requiring a specific and comprehensive approach. In this review, LUTS have been analysed with their association to the most frequent urological diseases as benign prostatic hyperplasia, prostate cancer, bladder cancer, and detrusor overactivity/underactivity, in a complex system of the elderly men.

Key words: Lower urinary tract symptoms, Benign prostatic hyperplasia, Prostate cancer, Bladder cancer, Detrusor overactivity, Detrusor underactivity, Elderly

INTRODUCTION

Lower urinary tract symptoms (LUTS) are common among elderly men and are highly widespread with significant effects on male wellness [1-3]. Extensive population studies estimate the overall prevalence of LUTS as 62.5% of men over the age of 40 and 80.7% of men over the age of 60 [4].

LUTS have been related to higher morbidity and mortality [5] and billions of dollars in USA annual health care expenditure [6]. LUTS are present in > 50% of men aged > 60 year and nearly 100% of men aged ≥ 90 year [7 8].

LUTS are usually associated with benign prostatic hyperplasia (BPH), and although BPH can produce LUTS, they can be complained without BPH. Moreover, both BPH [9] and LUTS [10] have been linked to the consequent risk of prostate cancer (PCa).

LUTS, BPH, and PCa are age-dependent processes [7 11]. Both a hormone-dependent pathway [12 13] and inflammation may have a key function in the development of these processes [14 15]; accordingly, they can be treated with antihormone drugs [16 17].

LUTS may occur independently of BPH [18]. Refractory LUTS are a well-recognized initial presenting symptom in a small percentage of patients with newly diagnosed bladder cancer (BC) [19]. Like LUTS, BPH and PCa, also BC is significantly associated with aging.

Sometime men with mixed voiding and storage LUTS after initial treatment for LUTS/BPH, show only voiding symptoms improvement, with storage symptoms persistence: in these cases the symptoms are related to bladder dysfunctions as detrusor overactivity (DO) or detrusor underactivity (DU), and deserve different approaches [20].

In this review, LUTS have been analysed with their association to the most frequent urological diseases as

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BPH, PCa, BC, and DO/DU in a complex system of the elderly men.

LUTS AND BPH

LUTS are traditionally classified into storage, voiding and post micturition symptoms [21]. They are most generally correlated with an increasing incidence of bladder outlet obstruction (BOO), which mainly results from age-related BPH [21 22]. Conversely BPH does not describe symptoms, but it is a histologic diagnosis with a micronodular hyperplasia and a macroscopic nodular enlargement causing BOO, partially responsible for male symptoms [23]. In this scenario another part of responsibility is kept by the bladder and its complex neural network [22]. As elderly women complain storage LUTS caused by DO, also men can suffer from the same storage symptoms which are the most troublesome with deep impact on quality of life (QoL) [24].

Actually the prostate should not be considered the only target of treatment in the management of male LUTS: it is necessary to treat BOO, but also bladder and urethra. The recommended medical therapy in men affected by BPH suggests α1-antagonists, 5α-reductase inhibitors and phytotherapy [25]. Despite full dose treatment, some patient continues to be symptomatic or may show BPH progression, with recurrent urinary infections, acute urinary retention (AUR), or may need surgery [26]. Furthermore, patient's adherence to pharmacological therapy may be reduced because of adverse effects and patients stop taking drugs [27]. For this reason investigators are proposing new medical strategies in the management of BPH-related LUTS: more selective α1-antagonists, phosphodiesterase 5 (PDE5) inhibitors, anticholinergics, and beta-3 adrenoceptor agonist have been introduced in clinical management of BPH, particularly in the elderly.

The most recent silodosin has equivalent efficacy compared to tamsulosin, with a lower risk of cardiovascular side effect; it may be considered a good alternative to common non-selective α1-antagonists, especially in the older patients where blood pressure modifications may cause important clinical troubles and ejaculatory dysfunctions are not really relevant [22].

Among PDE5 inhibitors, tadalafil 5 mg is an effective and well tolerated treatment for BPH-related LUTS as well as for concomitant erectile dysfunction; it reduces significantly International Prostate Symptom Score (IPSS) score improving patients' QoL, with no significant increase in Qmax. In case of PDE5 inhibitor's prescription, physician should consider carefully the risk of systemic vasodilation and cardiac failure in elderly patients with pre-existing cardiac insufficiency [28]. Likewise concomitant treatment with nitroderivates is an absolute contraindication to PDE5 inhibitor's use.

Recently, bladder dysfunctions such as DO and DU have been revealed to play important roles in LUTS especially in the elderly men [29].

Several studies have established that atherosclerosis and consequent chronic pelvic ischemia of the bladder may be a reason of LUTS in evolving age [30]. Experimental models with rabbits and rats have proved that chronic pelvic ischemia produces bladder ischemia; when this process is protracted, morphological and functional alterations in bladder innervation, urothelium, detrusor muscle, and the endothelium of local microvessels may occur [31]. Remarkably, studies with these models reveal that the duration and grade of organ ischemia are important to the kind of bladder dysfunction: moderate ischemia is associated with DO, while severe and long-term ischemia would result in DU [32-35].

The IPSS voiding to storage subscore ratio has been proposed as a guide for initial treatment of men with mixed voiding and storage symptoms [36]. In order to achieve the real pathophysiology for the persistent storage LUTS, a urodynamic study is mandatory [29 37 38].

The AUA and EAU guidelines recommend pressure flow studies as an optional test if patients with LUTS and BPH are planning to undergo surgery; similarly antimuscarinic drugs should be prescribed in men with BPH with residual storage symptoms after treatment with α1-antagonists [39 40].

Jiang et al. [20] studied 614 men $\geq$ 40 years of age with LUTS and an IPSS of $\geq$ 8 and evidenced that LUTS does not correlate with bladder or bladder outlet dysfunction, and prostate size does not relate to symptoms or BOO sufficiently, especially in men with persistent storage LUTS after initial treatment for LUTS/BPH. In these cases an antimuscarinic drug or beta-3 adrenoceptor agonist is recommended for treatment of DO or DO+DU [41 42]. Video-urodynamic studies should be always performed for determining the specific differential diagnosis causing LUTS when patients still have storage symptoms. Only men who do not respond to the combination medical treatment and that are verified to have BOO should be referred for surgery [20].

It is possible that storage symptoms may occur primarily or secondarily to BOO or BPH; therefore, combined treatment is favourable and can reduce LUTS after the initial medical treatment [43].

Numerous trials have investigated the efficacy and safety of an antimuscarinic drug in patients with persistent storage symptoms already in treatment with an α1-antagonist [44-46]. The TIMES study [44] included 879 men with symptoms of BPH and OAB: patients were randomized and received either tolterodine 4 mg ER + tamsulosin, one of the two drugs alone or placebo

and after 12 weeks, in the combination arm the patients showed significant reduction in urgency incontinence episodes (-0.88 *vs* -0.31, p = 0.005), frequency (-2.54 *vs* -1.41, p < 0.001) and an improvement of QoL. The rate of AUR was low for the combination (0.4%) and the tolterodine arm alone (0.5%), though higher than for placebo and for tamsulosin alone [44]. MacDiarmid et al. [45] reported a significant improvement of both storage and voiding symptoms (p = 0.006) in men affected by BPH treated with tamsulosin + oxybutinin 10 mg, with a non-significant increase in post-residual volume (PVR) in treated patients compared to placebo. Analogously, in the VICTOR study [46], 398 men were randomized and received tamsulosin plus either solifenacin 5 mg or placebo: in the solifenacin group, patients demonstrated a significant reduction of urgency episodes (-2.18 *vs* -1.10, p = 0.001) but a non-significant decrease of frequency (-1.05 *vs* -0.67, p = 0.135) [46]. In the first two trials the most recurrent adverse event related to antimuscarinics was xerostomia; increased PVR, although statistically significant in many studies, often did not result in a significant rise in the risk of AUR requiring catheterization [44 45].

As a matter of fact, during antimuscarinic therapy, BPH patients (particularly in the elderly) should be closely monitored for PVR [25] and in the elderly great care by physician is crucial, as cognitive deterioration may be a severe side-effect of these drugs, considering that 16% of patients > 70 years already show cognitive impairment [47]. In this regard, cholinergic activity of the brain (in particular M1 and M2 receptors which characterize over 60% of the brain cholinergic receptors) is fundamental in cognitive function [48].

The only antimuscarinic which was given a favourable safety profile in the elderly is fesoterodine, since this drug was investigated particularly in the aging population [49-51]. In the SOFIA trial 581 patients > 65 years (of which 33% were > 75 years old and under several drugs) were included in a 3 month double-blind randomized trial of fesoterodine versus placebo [49]. At 12 weeks, patients in the treatment group showed decreased urgency (-3.8 episodes), frequency and nocturia (-0.55 episodes) (all p < 0.001) compared to placebo. Fesoterodine presented an equivalent rate of adverse events compared to placebo (39.8 *vs* 36.1%), mainly mild xerostomia; about the cognitive function (assessed by the mini-mental status examination) no clinically significant modifications were reported in both groups. This result may be due to the high affinity of fesoterodine for the M3 receptor and its incapacity to pass the blood-brain barrier [52].

LUTS and prostate cancer

Prostate cancer (PCa) is the most frequent solid malignant neoplasm among men in the United States [53], and one of the most common in the world [54]. The incidence rises in an age-dependent way and with evidence of PCa at autopsy of almost every man in advanced age [55].

Researchers have long investigating whether there is a biologic association between BPH, LUTS and PCa or not [56-58]. BPH and LUTS have not been considered risk factors for development of PCa [9 10]. Actually, the Prostate Cancer Prevention Trial (PCPT) pointed out there was no association between LUTS and PCa [59].

On the other hand, a large recent population-based European study established a clear association between LUTS and the subsequent risk of PCa with hazard ratios (HR) ranging from 2.2 to 4.5 [10]. These numbers of relative risk (RR) are as high or higher than more traditional risk factors such as family history (RR: 2-4), race (African American vs white, RR: 1.3), prostatitis (RR: 1.5), obesity (RR: 1.05), and sexually transmitted diseases (RR: 1.5) [60]. Nevertheless the European study did not use a standardized measurement of LUTS and was not capable to assess whether the association between clinical LUTS and PCa incidence was related to detection bias or not.

If an association between LUTS and PCa exists, a relevant number of men would develop PCa independently on treatment of LUTS. Weight J et al. [61] evaluated the effect of LUTS on subsequent PCa testing and diagnosis, studying prospectively a cohort of 1922 men (aged 40-79 years) with interviews, questionnaires, and abstracts of medical records for prostate outcomes. They pointed out that a possible cause of the association between LUTS and PCa is the increased “diagnostic intensity” among men whose LUTS attract the attention of physicians; however, augmented symptoms alone were not associated with intensity of testing or diagnosis [61].

A recent study pointed out that the IPSS is an independently inverse predictor of the risk of being diagnosed with PCa [62]. Similarly, other LUTS-related parameters have been investigated. Prostate volume, which is directly correlated to BPO, has been shown to be inversely correlated with the risk of harboring PCa [63 64]. We recently demonstrated that peak flow rate (PFR) and post-void residual (PVR) independently predicted the risk of being diagnosed with PCa [65 66] and constructed a novel nomogram based on such BPO-related parameters providing significant predictive accuracy for overall PCa (0.768) and clinical significant PCa (0.8002) [67].

It is therefore intuitive that LUTS prompts not only PSA testing but also evaluation of easily available BPO-related parameters. In clinical practice, however, physicians tend to be reluctant to advise PSA testing in men > 75 years as well as to recommend prostate biopsy for increased PSA levels; this is even more true for those

with PSA in the grey zone (4-10 ng/ml) who suffer from LUTS. Such reluctance is likely due to the perception of most PCas in the elderly being clinically insignificant. Therefore, together with improvements in prostate biopsy technique [68-70], great efforts are currently made to identify novel markers that can improve the detection of clinically significant PCa [71-73]. Indeed, PCa overdiagnosis may lead to too aggressive treatments with their risk of procedure-related complications [74]. Therefore, like for other common benign urological conditions, the final clinical decision has to rely on wise clinical judgment [75-77].

LUTS and bladder cancer

Bladder cancer (BC) is the ninth neoplasm in worldwide cancer incidence and the seventh most common malignancy in men and seventeenth in women [78 79]. The worldwide age standardized incidence rate (ASR) is 10.1 per 100,000 for males and 2.5 per 100,000 for females [78]. Worldwide differences in exposure to risk factors are largely responsible for the observed variability in incidence in different geographic areas. Cigarette smoking, accounting for 50% of BC in males and 35% in females, and occupational carcinogens are the most principal risk factors for BC in Western countries [80]. Both genders have the highest risk to develop BC within 10 years at the age of 75; for males this risk is 2.32% and for females 0.560% [81]. In Europe, mortality rates show a substantial reduction over the last decade of ~16% in men and ~12% in women [82]; in the USA, BC mortality rates show decreasing trends for men already since 1975 as confirmed by the SEER (Devcan 6.7.6, April 2018, National Cancer Institute, https://surveillance.cancer.gov/devcan/) [83].

When LUTS are complained, the presence of PVR in the bladder exposes urothelium to a prolonged time contact of potential carcinogens usually contained in urine [84 85]. Zhou J et al. [86] examined prospectively the risk of BC associated to severity of LUTS among 30,183 men; among them, 476 new cases of BC were diagnosed. They pointed out that males with LUTS (voiding dysfunctions, especially urinary hesitancy) had a significantly higher risk of BC (RR: 1.60, 95% confidence interval: 1.00, 2.56). Moreover, they reported a stronger association between LUTS and early stages of bladder cancer instead of later stages, which further excludes the possibility that in this study the observed positive associations were all due to reverse causation [86].

Usually, the majority of patients affected by BC present with gross painless hematuria [87 88], but the remaining newly diagnosed BC patients complain refractory LUTS. Up to one fourth of patients with carcinoma in situ could present with irritative storage symptoms including frequency, urgency and dysuria [89]. In a study on 1,000 patients, frequency and dysuria (6.0%), difficult or poor stream (3.5%) and AUR (4.0%) were reported as presenting symptoms for BC though with significant co-existing (35-41%) hematuria in each of these groups [90]. Stower et al. pointed out that the “cystitis” symptoms were referred as the primary symptoms for patients with newly diagnosed BC in 12% of patients (12/100) and “obstructive symptoms” were mentioned in 3% of patients (3/100) [91]. However in these studies no data was provided about oncological outcomes.

Dobbs RJ et al. [19] evaluated the prevalence and clinical characteristics of 14/340 (4.1%) newly diagnosed BC patients who presented with LUTS in the absence of gross or microscopic hematuria. In this study the majority of patients with LUTS presented with Ta lesions, notwithstanding a higher incidence of carcinoma in situ compared to patients with other presenting symptoms. In high risk populations with significant smoking exposure and other risk factors (included elderly patients), physicians should consider a cystoscopy in patients with refractory LUTS [19]. In a study by Weiss et al. assessing patients for refractory overactive bladder without hematuria, 8 patients were identified with bladder cancer from a total of 1,420 patients undergoing cystoscopy for a diagnostic yield of 0.6% [92].

However, in asymptomatic patients (included elderly), no screening for BC is currently considered mandatory by the American Association of Family Physicians (AAFP), European Association of Urology (EAU) or The American Cancer Society (ACS) [93].

Question remains whether the presence of LUTS, like other clinical variables such as cigarette smoking [94], may impact on treatment outcome. To our knowledge, this issue has not been specifically address in BC whereby attention is mainly focused on molecular markers [95-103].

FINAL REMARKS

There is increasing evidence for a link between inflammation and development and progression of benign and malignant diseases of prostate and bladder [104], and this seem to be particularly true in the elderly, whereby senesce of the immune system [105] may further contribute to such events. While this may open perspective to immune modulation of such tumors, like in other urological cancers [106 107], LUTS often represent the starting point for identifying such conditions, requiring a specific and comprehensive approach.

Conflict of Interest

The authors declare no conflict of interest.

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