REVIEW PAPER

FUNCTIONAL UROLOGY

Co-treatment of lower urinary tract symptoms and cardiovascular disease – where do we stand?

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Introduction The relationship between cardiovascular disease (CVD) and lower urinary tract symptoms (LUTS) is well established. A healthy lifestyle with a good quality diet and regular physical activity is important for reducing the severity of LUTS.

Material and methods A literature search was performed on the subject of association between LUTS and cardiovascular risk.

Results The recent data indicates that therapy for cardiovascular risk reduction might also reduce the severity of LUTS (e.g. statins reduce the risk of benign prostatic hyperplasia [BPH] and slow down the progression of LUTS in patients with hyperlipidaemia). Hypertensive patients treated with angiotensin II receptor blockers have a lower severity of LUTS. This paper shortly discusses the relationship between the occurrence of LUTS and CVD and the potential clinical implications regarding the management of the patients.

Conclusions Patients with lower urinary tract symptoms require a holistic approach and cooperation of a urologist and cardiologist to diagnose concomitant cardiovascular diseases as early as possible and implement appropriate treatment. Antihypertensive, antithrombotic, hypolipemic therapies and healthy lifestyles reduce not only cardiovascular mortality, but also might reduce the severity of LUTS.

Key Words: lower urinary tract symptoms ‹› cardiovascular disease ‹› adjuvant ‹› cardiovascular risk

INTRODUCTION

In recent years, there have been several articles published suggesting a correlation between cardiovascular disease (CVD) and lower urinary tract symptoms (LUTS). Gacci et al. conducted a meta-analysis of 15 studies concerning this topic and showed that patients with moderate to severe LUTS have an increased risk of major adverse cardiac events [1]. A positive association between metabolic syndrome and greater prostate size and LUTS was demonstrated in most of the US and European population-based studies [2]. The pathophysiological mechanisms underlying this relationship are still under investigation, but it seems that the following factors might play an important role:

- metabolic syndrome,
- chronic inflammation,
- atherosclerosis-induced pelvic ischemia,
- increased Rho-kinase activation,
- impaired nitric-oxide synthase pathway in the endothelium,
- autonomic hyperactivity with sympathetic dysregulation,
- declining testosterone levels [3] (Figure 1).

Furthermore, it has been suggested that therapy for cardiovascular risk reduction might also reduce the severity and slow down the progression of LUTS. This paper discusses the effect of cardiovascular pharmacotherapy on the occurrence and progression of LUTS.

Therapies for cardiovascular risk reduction

Statins

The recent studies indicate that statins use is connected with a lower risk of incidence and development of LUTS [4, 5, 6]. In the study conducted by Sauver et al. statin users had a lower cumulative incidence of moderate/severe LUTS. Moreover, researchers observed that longer duration of statin use was associated with a decreased risk of development of moderate/severe LUTS and prostate volume ($p < 0.001$). [4]. In another study, the patients with metabolic syndrome after 12 months of treatments with statins (40 mg of simvastatin, 20 mg of atorvastatin daily) have a statistically significant reduction of prostate volume ($p = 0.000$) and International Prostate Symptom Score (IPSS) ($p = 0.012$) compared to the control group [5]. After statin treatment, the prostate volume was decreased to a greater extent in obese patients than in the normal-weight patients and in the hyperlipidaemia patients than in the normal-lipid patients. The statin treatment was correlated to the decrease in the levels of total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6) [5]. The results of the newest meta-analysis (49 128 participants) conducted by Yang and al. suggest that statins reduce the risk of benign prostatic hyperplasia (BPH) for patients over 60 years old (OR = 0.35 (0.22, 0.55), $p < 0.0001$) and slow down the progression of LUTS in patients taking statins for more than one year (standardized mean difference, SMD = 0.32 (-0.54, -0.10), $p = 0.004$) [6].
The pathophysiological mechanisms underlying the relationship between statin therapy and BPH/LUTS have yet to be established. Statins significantly reduce prostate volume, the severity of LUTS and slow down the clinical progression of BPH possibly by lowering cholesterol and anti-inflammatory factors, especially interleukin 6. High triglycerides and cholesterol levels seem to have a detrimental effect on prostatic cells, boosting prostate inflammation, which is associated with the development of BPH/LUTS. High levels of interleukin 6 (observed in metabolic syndrome) accelerate the proliferation of prostatic tissues and might contribute to the progression of BPH/LUTS. Additionally, high dose statin therapy have anti-angiogenesis effects, inhibit the capillary formation and reduce the release of vascular endothelial growth factor.

Renin-angiotensin-aldosterone system inhibitors

Studies concerning the use of the renin-angiotensin-aldosterone system (RAAS) inhibitors in the treatment of hypertension in patients with concomitant LUTS provided information on the potential role of these drugs in reducing the severity of LUTS. One of the largest studies, was conducted by Ito and al. in a group of 769 men with hypertension and LUTS [7]. They found that the IPSS was significantly lower in patients treated with angiotensin II receptor blockers (ARBs) than in hypertensive patients who were not receiving any medication (16.8 ± 6.8 vs. 18.3 ± 6.6, $p < 0.01$). The baseline IPSS in patients treated with angiotensin-converting enzyme inhibitor, calcium channel blockers and without treatment were respectively 18.3, 19.6, and 18.1, and were significantly higher than in patients treated with ARBs. Besides, it has been observed, that the voiding-symptoms score was significantly lower in patients treated with ARBs ($p < 0.01$ for ARB monotherapy and $p < 0.05$ for combination therapy with ARBs) and there was a tendency for the lower storage-symptoms score in ARB-treated patients.
Explanations for these results might be the existence of angiotensin II receptors in the bladder wall, basal layer of the epithelium, stromal smooth muscle and pronounced contractile effects of angiotensin II on the detrusor muscle. The recent studies reported hyperactivity of the renin-angiotensin system and elevated levels of angiotensin II in the prostate of patients with BPH. It has been suggested that angiotensin II mediates paracrine functions on cellular growth and smooth muscle tone in the human prostate and increase the noradrenaline release from the sympathetic nerve in the prostatic tissue. ARBs improve voiding and storage symp-

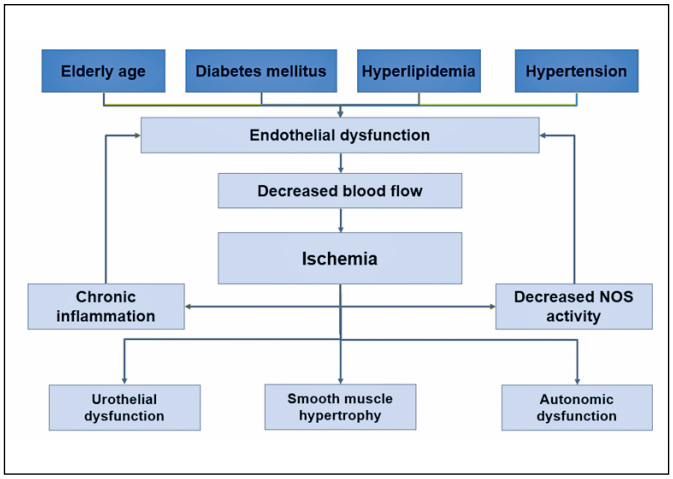

Figure 1. *Potential mechanisms underlying the relationship between cardiovascular risk factors and lower urinary tract symptoms (LUTS).*
NOS – nitric-oxide synthase

Table 1. *Perioperative Non-Vitamin K Antagonist Oral Anticoagulant (NOAC) Management Protocol*

Procedure		Prostate or bladder biopsy		Transurethral prostate resection	
NOAC		Preoperative NOAC Interruption Schedule	Postoperative NOAC Resumption Schedule	Preoperative NOAC Interruption Schedule	Postoperative NOAC Resumption Schedule
Dabigatran	(CrCl ≥50 ml/min)	-1	+1	-2	+2
	(CrCl <50 ml/min)	-2	+1	-4	+2
Apixaban		-1	+1	-2	+2
Edoxaban		-1	+1	-2	+2
Rivaroxaban		-1	+1	-2	+2

NOAC – non-vitamin K antagonist oral anticoagulants; -1 – stop one day before the procedure; -2 – stop two days before the procedure;-4 – stop four days before the procedure; +1 – start the first day after the procedure; +2 – start the second day after procedure; CrCl – creatinine clearance

toms by suppressing the noradrenaline release in the prostate.

Healthy lifestyle

The protective role of weight loss, regular physical activity and a healthy diet in cardiovascular disease prevention are obvious. Due to recent data reporting the connection between LUTS and cardiovascular risk, the important question seems to be: is there any relationship between lifestyle and LUTS? So far, there are only a few studies, in most cases- epidemiological data, concerning this topic. Pao-Hwa Lin and Stephen J. Freedland sums up the results of these studies and they focus on three main factors: obesity, diet and physical activity [8]. They conclude that obesity and increased total energy intake have been associated with LUTS. Based on a prospective study of 1740 elderly men at least 65 years old they found that being overweight was associated with a significantly higher risk for symptomatic progression of LUTS (assessed on the IPSS). The next topic, dietary factors also have been associated with LUTS. It has been observed that higher intake of red meats and fat, and a lower intake of fruits and vegetables have been associated with greater self-reported LUTS among men aged at least 40 years [8]. Also, alcohol intake is associated with LUTS – in another study, it has been observed that modest consumption of alcohol (0–10 g/day) compared to heavy or no consumption has been connected with the lowest odds of moderate or severe LUTS [8]. No association has been found between caffeine and tobacco use [9]. Increased physical activity was connected with decreased risk of LUTS. A meta-analysis of 11 studies with about 43 000 men demonstrates that moderate-to-vigorous physical activity reduced the risk of LUTS by 25% compared with a sedentary lifestyle, with stronger effects seen with higher levels of activity [8].

Non-vitamin K antagonist oral anticoagulant

Hu and Lin demonstrated that BPH patients are at significantly higher risk of atrial fibrillation compared with non-BPH patients, regardless of age (adjusted HR = 1.19, 95% CI = 1.11–1.28) [10]. Due to the high prevalence of atrial fibrillation, a very important issue is antithrombotic treatment. Nowadays, the use of a non-vitamin K antagonist oral anticoagulants (NOAC) is becoming increasingly common. The knowledge of the appropriate time to stop and restart NOAC treatment before and after urology procedures is crucial for reducing the risk of complications [11, 12]. Based on current guidelines, prostate or bladder biopsy is an intervention with a low risk of bleeding, while transurethral prostate resection is an intervention with a high risk of bleeding [11]. The perioperative NOAC management protocol is presented in Table 1.

CONCLUSIONS

Patients with lower urinary tract symptoms require a holistic approach and cooperation of a urologist and cardiologist to diagnose concomitant cardiovascular diseases as early as possible and implement appropriate treatment. Antihypertensive therapy with angiotensin II receptor blockers, statins or healthy lifestyles reduce not only cardiovascular mortality but also might reduce the risk and severity of lower urinary tract symptoms.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

References

1. Gacci M, Corona G, Sebastianelli A, et al. Male Lower Urinary Tract Symptoms and Cardiovascular Events: A Systematic Review and Meta-analysis. Eur Urol. 2016; 70: 788-796.

2. Sebastianelli A, Gacci M. Current Status of the Relationship Between Metabolic Syndrome and Lower Urinary Tract Symptoms. Eur Urol Focus. 2018; 4: 25-27.

3. Fusco F, D'Anzeo G, Sessa A, et al. BPH/LUTS and ED: Common Pharmacological Pathways for a Common Treatment. J Sex Med. 2013; 10: 2382-2393.

4. Sauver JL, Jacobsen SJ, Jacobson DJ, et al. Statin use and decreased risk of benign prostatic enlargement and lower urinary tract symptoms. BJU Int. 2011; 107: 443–450.

5. Zhang X, Zeng X, Dong L, Zhao X, Qu X. The effects of statins on benign prostatic hyperplasia in elderly patients with metabolic syndrome. World J Urol. 2015; 33: 2071-2077.

6. Yang X, Zhang Q, Jiang G, et al. The effects of statins on benign prostatic hyperplasia and the lower urinary tract symptoms: A Meta-analysis. Medicine 2019; 98: e15502.

7. Ito H, Taga M, Tsuchiyama K, Akino H, Yokoyama O. IPSS is lower in hypertensive patients treated with angiotensin-II receptor blocker: posthoc analyses of a lower urinary tract symptoms population. Neurourol Urodyn. 2013; 32: 70-74.

8. Lin Pao-Hwa, Freedland SJ. Lifestyle and LUTS: what is the correlation in men? Curr Opin Urol. 2015; 25: 1-5.

9. Bradley CS, Erickson BA, Messersmith EE, at al. Evidence of the Impact of Diet, Fluid Intake, Caffeine, Alcohol and Tobacco on Lower Urinary Tract Symptoms: A Systematic Review. J Urol. 2017; 198: 1010-1020.

10. Hu WS, Lin CL. Increased risk of atrial fibrillation in patients with benign prostatic hyperplasia: A population-based cohort study. Clin Cardiol. 2018; 41: 1374-1378.

11. Steffel J, Verhamme P, Potpara TS, et al. ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018; 39: 1330-1393.

12. Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant. JAMA Intern Med. 2019. doi:10.1001/jamainternmed.2019; 2431. [Epub ahead of print] ■