Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia and Cardiovascular Diseases in Japan — What Is the Next Step? —

Tetsuya Ohira, MD, PhD

The frequency of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) and erectile dysfunction (ED) increases with age, and the number of men with these symptoms is climbing in Japan as the population continues to age. The pathogenesis of LUTS/BPH and ED remains unclear because of the multiple factors involved. However, risk factors for cardiovascular disease (CVD), including obesity and diabetes mellitus, have been also identified as risk factors for LUTS/BPH and ED, and their association with CVD has been reported mainly in Europe and the USA.¹ However, this association has not been examined much in Japan.

In this issue of the Journal, Tanaka et al² present a cross-

Article p2092

sectional study on LUTS in Japanese community-dwelling men during their health examinations, reporting that moderate-to-severe LUTS were associated significantly with coronary artery disease and stroke. Although the causal relationship is unclear, this study did clarify the association between LUTS/BPH and CVD, even in Japan, where the incidence of obesity is lower than in Western countries. The proportions of patients with moderate or severe LUTS were 38.4% and 6.5%, respectively, among men in the general population aged 55–75 years (mean age, 67 years).

According to a patient survey in 2017 by the Japanese

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.

Received August 6, 2021; accepted August 6, 2021; J-STAGE Advance Publication released online September 17, 2021

Department of Epidemiology, Fukushima Medical University School of Medicine, Fukushima, Japan

Mailing address: Tetsuya Ohira, MD, PhD, Department of Epidemiology, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima 960-1295, Japan. E-mail: teoohira@fmu.ac.jp

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

ISSN-1346-9843

Ministry of Health, Labor, and Welfare, the number of patients with BPH was estimated to be 473,000,³ but the actual number of patients may be much higher. According to a 2021 population estimate, 23.35 million men aged ≥ 55 years old were living in Japan. If the percentage of those with severe LUTS (6.5%) were applied to this figure, the number of men with LUTS would be 1.5 million, and if those with moderate symptoms were added, the number would be 10.5 million. Therefore, a more detailed study of the association between urological disease and CVD may be important for prevention.

Two points must be addressed in future research on the relationship between urological disease and CVD. The first is to elucidate the pathophysiology involved. As Tanaka et al point out,² although stroke and heart failure may affect urological disease, LUTS/BPH may be an important predictor of CVD. Previous epidemiological studies have reported that CVD risk factors such as obesity and diabetes also are associated with BPH.^{4,5} Prospective studies have shown that men who are obese or have a greater abdominal circumference have a higher risk for developing LUTS/BPH than do men without these health issues.^{6,7} Furthermore, a systematic review and a meta-analysis for LUTS and cardiovascular events has shown that the presence of moderate-to-severe LUTS was associated with an increased incidence of major adverse cardiac events as compared with the rest of the sample (odds ratio, 1.68; 95% confidence interval, 1.13–2.50; $P=0.01$).¹

BPH is characterized by an enlarged prostate gland and increased smooth muscle tone, which leads to urinary symptoms. The prostate and prostatic urethra are surrounded by adipose tissue, which is thought to play a paracrine role in prostate growth and reactivity by releasing growth factors and anti-inflammatory, antioxidant, contractile, and anticontractile substances.⁵ As shown in the **Figure**, the prostatic microenvironment, including angiogenesis, proliferation, and inflammation, can be influenced by substances present in the systemic circulatory system or released from the periprostatic adipose tissue.⁵ Microscopic evaluation of local atherosclerosis in prostatic arteries removed during prostatectomy has shown a dose-response relationship between the degree of atherosclerosis and prostatic enlargement, which may be mediated by chronic inflammation and oxidative stress, such as lectin-like oxidized low-density lipoprotein receptor-1 and macrophages.^{8,9} Therefore, a detailed study of the relationships among perivascular adipose tissue, systemic adipose tissue including prostate and periprostatic fat, and LUTS/BPH will enable an approach to CVD prevention that also includes a urological perspective.

A second point to be considered is the treatment of LUTS/BPH. A treatment that can alleviate symptoms and also prevent CVD would be ground-breaking. One medication that can be expected to have this effect is the phosphodiesterase type 5 (PDE5) inhibitor, a typical treatment for ED. The pathophysiological mechanisms of ED and LUTS/BPH are similar, and tadalafil, a PDE5 inhibitor, is now available in Japan for the clinical treatment of urinary dysfunction associated with BPH. PDE5 inhibitors are known to have pharmacological effects on the lower urinary tract, including inhibition of bladder outlet obstruction and improvement of bladder blood flow, as well as providing vascular endothelial protection and

anti-inflammatory and antioxidant effects.¹⁰ Therefore, they also can have a protective effect on the cardiovascular system.

In an observational study of 5,956 men with type 2 diabetes aged 40–89 years in the UK, those who had taken a PDE5 inhibitor at baseline had a 31% lower risk of death during a mean observation period of 7.5 years as compared with those who had not.¹¹ These associations were similar after adjusting for confounding factors such as age, serum lipids, renal function, smoking history, and medication use, and also were similar when the analysis was limited to those men with a history of myocardial infarction. Therefore, future interventional studies of PDE5 inhibitors on cardiovascular events are warranted to clarify the causal relationship.

The associations of LUTS/BPH and ED with CVD are still unclear in many respects, including pathophysiology and causality. However, the prevalence of LUTS/BPH and ED is high, and their attribution to CVD also is high. Further studies, including interventional trials, are necessary to determine a new approach from a urological perspective to prevent CVD.

Disclosures

Conflicts of interest: none.

References

- Gacci M, Corona G, Sebastianelli A, Serni S, De Nunzio C, Maggi M, et al. Male lower urinary tract symptoms and cardiovascular events: A systematic review and meta-analysis. *Eur Urol* 2016; **70**: 788–796.
- Tanaka Y, Matsuyama S, Tada H, Hayashi K, Takamura M, Kawashiri M, et al. Association of lower urinary tract symptoms based on the International Prostate Symptom Score and Cardiovascular Disease. *Circ J* 2021; **85**: 2092–2099.
- The Japanese Ministry of Health, Labor, and Welfare. A patient survey 2017. <https://www.mhlw.go.jp/toukei/saikin/hw/kanja/10syoubu/01/> (accessed July 28, 2021).
- Calogero AE, Burgio G, Condorelli RA, Cannarella R, La Vignera S. Epidemiology and risk factors of lower urinary tract symptoms/benign prostatic hyperplasia and erectile dysfunction. *Aging Male* 2019; **22**: 12–19.
- Passos GR, Ghezzi AC, Antunes E, de Oliveira MG, Mônica FZ. The role of periprostatic adipose tissue on prostate function in vascular-related disorders. *Front Pharmacol* 2021; **12**: 626155. doi:10.3389/fphar.2021.626155.
- Penson DF, Munro HM, Signorello LB, Blot WJ, Fowke JH, Urologic Diseases in America Project. Obesity, physical activity and lower urinary tract symptoms: Results from the Southern Community Cohort Study. *J Urol* 2011; **186**: 2316–2322.
- Mondul AM, Giovannucci E, Platz EA. A prospective study of obesity, and the incidence and progression of lower urinary tract symptoms. *J Urol* 2014; **191**: 715–721.
- Haga N, Akaiha H, Hata J, Aikawa K, Yanagida T, Matsuoka K, et al. The association between local atherosclerosis of the prostatic artery and benign prostatic enlargement in humans: Putative mechanism of chronic ischemia for prostatic enlargement. *Prostate* 2018; **78**: 1001–1012.
- Haga N, Akaiha H, Hata J, Hiraki H, Honda R, Tanji R, et al. The association between local arteriosclerosis of the prostatic arteries and chronic inflammation in human benign prostatic enlargement. *Prostate* 2019; **79**: 574–582.
- Hackett G. Should all men with type 2 diabetes be routinely prescribed a phosphodiesterase type 5 inhibitor? *World J Mens Health* 2020; **38**: 271–284.
- Anderson SG, Hutchings DC, Woodward M, Rahimi K, Rutter MK, Kirby M, et al. Phosphodiesterase type-5 inhibitor use in type 2 diabetes is associated with a reduction in all-cause mortality. *Heart* 2016; **102**: 1750–1756.