The Association between Severity of Atherosclerosis and Lower Urinary Tract Function in Male Patients with Lower Urinary Tract Symptoms

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Objectives: The present study was undertaken to investigate the association between the severity of atherosclerosis and lower urinary tract function in male patients with lower urinary tract symptoms.

Methods: Male patients with lower urinary tract symptoms were examined with routine investigation. The severity of atherosclerosis was assessed by ultrasound examination of carotid artery. Patients were divided into two groups: control group and atherosclerosis group. The voiding function and storage function were compared between the two groups.

Results: A total of 50 men (69.9 ± 9.1 years [mean ± standard deviation]) entered the study. There was no significant difference in age distribution (control group: 68.7 ± 7.6 years; atherosclerosis group: 72.5 ± 9.7 years) and prostate volume (control group: 26.5 ± 17.3 mL; atherosclerosis group: 22.2 ± 11.0 mL) between the two groups. In the voiding parameters, maximum flow rate in the atherosclerosis group (13.4 ± 5.5 mL/s, P < 0.05) was significantly lower than that in the control group (16.7 ± 7.7 mL/s). Postvoid residual urine volume showed no significant difference between the two groups. In the storage parameters, voided volume was significantly reduced in the atherosclerosis group (161.8 ± 46 mL, P < 0.05), as compared to control group (201.1 ± 78 mL). Moreover, daytime frequency was 7.13 ± 3.02 times in the control group, and significantly higher in the atherosclerosis group (8.75 ± 2.50 times, P < 0.05).

Conclusion: Development of atherosclerosis impairs both voiding and storage function independently of age, suggesting atherosclerosis leads to lower urinary dysfunction.

Key words atherosclerosis, lower urinary tract dysfunction, male lower urinary tract symptoms

1. INTRODUCTION

Male lower urinary tract symptoms (LUTS) are among the most bothersome problems for which elderly men suffer. The main cause of male LUTS has been considered to be prostatic pathology such as bladder outlet obstruction (BOO) and prostatic enlargement. Currently, epidemiological studies show that LUTS and overactive bladder (OAB) occur commonly in both men and women, with an age-related increase in both sexes.1–3 Thus, male LUTS cannot be simply characterized as a prostate specific disease.

Recent studies suggest that arterial occlusive disease such as atherosclerosis may cause lower urinary tract dysfunction via ischemia, hypoxia and oxidative stress in the bladder. Ponholzer et al. reported the association of four major vascular risk factors (diabetes mellitus, hyper tension, nicotine abuse and hyperlipidemia) and LUTS in both sexes.4 According to their study, in men, the International Prostate Symptom Score (IPSS) was identical in those with no or one vascular risk factor, yet significantly increased in those with two or more risk factors. This study shows the possibility that atherosclerosis plays an important role in the development of male LUTS. Although the association between vascular risk factors and LUTS has been demonstrated, direct effects of atherosclerosis on lower urinary tract function remains to be elucidated.

Measurement of intima-media thickness (IMT) of the carotid artery by ultrasound examination, which can assess severity of atherosclerosis by calculating thickness of plaques, is widely used as a screening for cardiovascular diseases. O’Leary et al. reported that plaques in the

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carotid artery were strongly associated with the presence of peripheral arterial disease. Thus, by using ultrasound examination of carotid artery, the present study was undertaken to investigate the association between severity of atherosclerosis and lower urinary tract function in the male patients with LUTS.

2. METHODS

From December 2008 to April 2009, male patients with LUTS aged 50 or older, were enrolled in this prospective study. All participants were assessed for detailed medical history and current medical therapies. A physical examination, including age, weight, height, blood pressure (BP), digital rectal examination and serum prostate specific antigen test, was carried out.

Exclusion criteria were diabetes mellitus, neurogenic bladder, prostate cancer and/or bladder cancer and treatment history of LUTS using α1-adrenoceptor antagonists and/or antimuscarinics. Each patient was examined with routine investigation including measurement of prostate volume (mL) using transabdominal ultrasound, free uroflowmetry (UFM), and postvoid residual urine volume (PVR) measurement. In addition, a two-day frequency volume chart (FVC), which records the voiding times, volumes, and urgency episodes, was also evaluated. Urgency was diagnosed as presence of urgency episodes at least once during a 2-day FVC. The whole prostate volume was estimated by using an ellipsoid formula (width × height × length × π/6). All participants were asked to complete the validated Japanese version of IPSS. Moreover, the IPSS subscores, such as voiding symptom score (the summation of intermittency score, weak stream score and straining score) and storage symptom score (the summation of frequency score, urgency score and nocturia score), were also assessed as individual scores.

The severity of atherosclerosis was assessed by IMT in the carotid artery. It was measured by recording ultrasonographic images of both the left and the right carotid artery with an 11-MHz linear array transducer (SSA-770A, Toshiba, Japan). The upper limit of normal for IMT is 1.0 mm, and lesions with a focal IMT > 1.0 mm are defined as atheromatous plaques. The total carotid plaque score was defined as the summation of thickness of plaques (mm) at both the left and the right carotid artery. The atherosclerosis severity was graded as follows: no plaque (score 0), mild plaque (score 1–5), moderate plaque (score 5.1–10), and severe plaque (score over 10).

Patients were then divided into two groups, normal–mild atherosclerosis group (control group, plaque score 0–5) and moderate–severe atherosclerosis group (atherosclerosis group, plaque score more than 5.0). The voiding parameters (maximum flow rate [Qmax] and PVR) and the storage parameters (voided volume in daytime, daytime frequency and number of nocturia) were compared between the two groups.

All values were expressed as mean ± standard deviation. Statistical significance was determined by unpaired t-test or Fisher’s test. P < 0.05 was considered statistically significant.

### Table 1. Patients’ characteristics and objective parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control group</th>
<th>Atherosclerosis group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.7 ± 7.6</td>
<td>72.5 ± 9.7</td>
</tr>
<tr>
<td>Plaque score</td>
<td>2.0 ± 1.5</td>
<td>10.6 ± 3.9**</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>126 ± 17</td>
<td>130 ± 15</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79 ± 10</td>
<td>77 ± 13</td>
</tr>
<tr>
<td>Prostate volume (mL)</td>
<td>26.5 ± 17.3</td>
<td>22.2 ± 11.0</td>
</tr>
<tr>
<td>Total IPSS score</td>
<td>11.7 ± 7.0</td>
<td>13.5 ± 7.7</td>
</tr>
<tr>
<td>Voiding symptom score†</td>
<td>4.8 ± 4.4</td>
<td>4.6 ± 4.5</td>
</tr>
<tr>
<td>Storage symptom score‡</td>
<td>6.8 ± 3.7</td>
<td>7.3 ± 3.7</td>
</tr>
<tr>
<td>Urgency (%)</td>
<td>17.4 (4/23)</td>
<td>44.4 (12/27)*</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.01 compared to control group. Values are mean ± standard deviation. †The summation of intermittency score, weak stream score and straining score. ‡The summation of frequency score, urgency score and nocturia score. BP, blood pressure.

3. RESULTS

3.1. Patient characteristics and objective parameters of the two groups

A total of 50 men (69.9 ± 9.1 years) entered the study. The characteristics of the two groups are shown in Table 1. Average age and number of patients in each group were as follows: control group, 68.7 ± 7.6 years (n = 23); atherosclerosis group, 72.5 ± 9.7 years (n = 27). Systolic and diastolic BP of the control group and the atherosclerosis group were 126 ± 17 mmHg versus 130 ± 15 mmHg and 75 ± 10 mmHg versus 77 ± 13 mmHg, respectively. Average prostate volume of control group and atherosclerosis group were 26.5 ± 17.3 and 22.2 ± 11.0 mL, respectively. Mean score points of IPSS in control group and atherosclerosis group were 11.8 ± 7.0 and 13.9 ± 7.7, respectively. Moreover, voiding symptom score and storage symptom score in control group and atherosclerosis group were 4.8 ± 4.4 versus 4.6 ± 4.5 and 6.8 ± 3.7 versus 7.3 ± 3.7, respectively. There was no significant difference in age distribution, BP, prostate volume and IPSS points (total IPSS score, voiding symptom score and storage symptom score) between the two groups. In the atherosclerosis group, 44.4% of patients (12/27) complained of urgency, and only 17.4% of patients (4/23) in the control group had urgency episodes (P < 0.05).

3.2. Voiding function

In the voiding parameters, Qmax in the control group and atherosclerosis group were 16.7 ± 7.7 and 13.4 ± 5.5 mL/s, respectively (Fig. 1). It was significantly lower in the atherosclerosis group than in the control group (P < 0.05). PVR showed no significant difference between the two groups (control group 62.5 ± 72.8 mL, atherosclerosis group 74.9 ± 88.8 mL).

3.3. Storage function

In the storage parameters voided volume in daytime, daytime frequency and number of nocturia were evaluated (Fig. 2). These parameters were derived from the 2-day FVC. Comparison of the mean total urine volume in daytime between the two groups demonstrated no
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Fig. 1 Effect of atherosclerosis on the voiding function. Data are mean ± standard deviation. *P < 0.05 compared to control group. PVR, postvoid residual urine volume; Qmax, maximum flow rate.

Fig. 2 Effect of atherosclerosis on the storage function. Data are mean ± standard deviation. *P < 0.05 compared to control group.

Fig. 1 Effect of atherosclerosis on the voiding function. Data are mean ± standard deviation. *P < 0.05 compared to control group. PVR, postvoid residual urine volume; Qmax, maximum flow rate.

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4. DISCUSSION

Recently, an international population-based survey (the EPIC study) was conducted using the 2002 International Continence Society definition for LUTS. This study showed that LUTS were, to a similar extent, highly prevalent in both men and women. The prevalence of storage LUTS of men and women were 51.3 and 59.2%, respectively. The voiding LUTS were 25.7 and 19.5%, respectively. The EPIC study confirmed that OAB was equally common in men and women and that its prevalence increased with age. The overall prevalence of OAB reported was 11.8% (men, 11%; women, 13%). In Japan, an epidemiologic population-based study was also conducted and showing similar results.

Other studies have showed that detrusor overactivity (DO) and OAB symptoms often occur independently of BOO, since many men with LUTS (approximately 50%) do not have BOO. These findings demonstrated that all LUTS, including OAB, were not sex specific and increased with age, suggesting that male LUTS cannot be attributable exclusively to the prostate.

One possible mechanism contributing to bladder dysfunction with age might be atherosclerosis of the pelvic vascular system. In humans, several studies have investigated the influence of vascular risk factors on LUTS. More interestingly, Ponholzer et al. showed that the
IPSS increased significantly in men and women with two or more risk factors, suggesting the potential role of atherosclerosis in the development of LUTS in both sexes. This observation seems to provide new information about our understanding of the pathogenesis of LUTS. Supporting these observations, many investigations have been carried out in animal models. These studies showed that arterial obstructive disease induced pelvic ischemia and hypoxia, which caused functional and structural alteration of the detrusor, leading to DO.

Whereas several studies have demonstrated strong influence of cardiovascular disease on LUTS, there is no direct clinical evidence showing the association between atherosclerosis and lower urinary tract dysfunction in humans. It has long been recognized the objective assessment of LUTS based on a case history alone, such as IPSS, is relatively inaccurate to evaluate the lower urinary tract function, since it relies on the patient’s vocalization of the symptoms. The parameters derived from FVC and UFM have been found to be more consistent and accurate. Bryan and Chapple reported that a FVC is recommended with a view to obtaining objective data to patients’ voiding and storage dysfunction. Hence, in the present study we investigated the influence of arterial obstructive conditions on lower urinary tract function by using FVC and UFM. The ultrasound examination of carotid artery was used to measure the severity of atherosclerosis. Then using this parameter, the effect of atherosclerosis on both voiding and storage function was estimated.

With regard to the ultrasound examination of carotid artery, it is commonly used for the screening of atherosclerosis in most hospitals and clinics because of its non-invasiveness and accuracy. It is well known that the severity of carotid atherosclerosis is closely related to the presence of cardiovascular disease and the risk of cardiovascular events. Several indices, such as IMT and plaque score (summation of total plaque thickness) have proved valuable to estimate the relations between carotid atherosclerosis and cardiovascular disease. HANDA et al. established the plaque score as an index of the severity of carotid atherosclerosis and reported the relationship of plaque score with traditional factors of cardiovascular disease. Therefore in the present study, we used the plaque score derived from the carotid ultrasonography to evaluate the severity of atherosclerosis.

In this study, we divided the patients into two groups according to the plaque score. There was no difference in the age distribution between the two groups. In the storage parameters, reduced bladder volume and increased daytime frequency were observed in the patients with severe atherosclerosis. Additionally, the prevalence of urgency was significantly higher in the atherosclerosis group. Regarding the voiding parameters, Qmax was significantly lower in the atherosclerosis group than that in the control group. These findings implied that atherosclerosis plays a role in the development of both voiding and storage dysfunction independently of age. Whereas voiding and storage dysfunction were shown in the atherosclerosis patients, mean IPSS was almost identical in both groups. Our findings are in apparent disagreement with the results of Ponholzer et al. The reason for the discrepancy in results between their study and the current study are unclear but it may depend on the difference in the methods, number and characteristics of the participants, and inaccuracy of IPSS.

The exact mechanism by which arterial occlusive disease leads to lower urinary dysfunction is not fully understood. There are several possibilities to explain this hypothesis. Currently, it is thought that bladder dysfunction following pelvic vascular disease may in part be caused by ischemia/reperfusion injury. Whenever the bladder contracts, the increased intra-wall pressure leads blood vessels to be compressed, resulting in decreased blood flow and tissue hypoxia. This cyclical ischemia-hypoxia would be enhanced in the patient with atherosclerosis.

Masuda et al. have recently reported that oxidative stress mediates DO in the bladder of rats. This study indicated that oxidative stress induced by H2O2 activates capsaicin-sensitive C-fiber afferent pathways partly mediated via stimulation of the cyclooxygenase pathway, resulting in DO. It is therefore, assumed that long-term arterial insufficiency such as atherosclerosis can cause storage dysfunction via ischemia, hypoxia and oxidative stress in the bladder.

Another study suggested that arterial insufficiency leads to denervation in the bladder via ischemia, hypoxia and oxidative stress. As a result of denervation, detrusor muscle shows increased sensitivity to acetylcholine and other antagonists, suggesting that denervation supersensitivity may be the basis for DO following ischemia and hypoxia as well as BOO. Moreover, denervation of the efferent neuron may be the cause of deteriorated detrusor contraction, leading to voiding dysfunction.

Our data demonstrated strong association between the severity of atherosclerosis and the lower urinary tract dysfunction. Arterial occlusive disease may play a potential role in the development of both voiding and storage dysfunction via ischemia, hypoxia and oxidative stress in the bladder. Further investigations are needed to understand deeply the contribution of atherosclerosis to the development of lower urinary tract dysfunction.

Treatment of cardiovascular risk factors, such as hypertension, diabetes mellitus and hyperlipidemia, would therefore also contribute to the prevention of LUTS.

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Declaration

There is nothing to declare.

REFERENCES


