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Endothelial dysfunction, abnormal vascular structure and lower urinary tract symptoms in men and women

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ABSTRACT

Background: Lower urinary tract symptoms (LUTS) is not only common symptoms in elderly men and women but also risk of future cardiovascular events. The purpose of this study was to evaluate the relationships of vascular function and structure with LUTS in men and women.
Methods: We investigated flow-mediated vasodilation (FMD) and nitroglycerine-induced vasodilation (NID) as vascular function, brachial-ankle pulse wave velocity (baPWV) as vascular structure, and LUTS assessed by International Prostate Symptom Score (IPSS) in 287 men and 147 women.
Results: IPSS was significantly correlated with traditional cardiovascular risk factors, Framingham risk score, FMD, NID and baPWV. Moderate to severe LUTS was associated with the prevalence of coronary heart disease in men but not in women. In men, FMD and NID were significantly lower in the moderate to severe LUTS group than in the none to mild LUTS group (2.1 ± 2.0% vs. 4.0 ± 3.0% and 9.3 ± 6.1% vs. 12.8 ± 6.6%, $P < 0.001$, respectively). baPWV was significantly higher in the moderate to severe LUTS group than in the none to mild LUTS group (1722 ± 386 cm/s vs. 1509 ± 309 cm/s, $P < 0.001$). In multivariate analysis, FMD was independently associated with a decrease in the odds ratio of moderate to severe LUTS in men (OR: 0.83, 95% CI, 0.72–0.95; $P = 0.008$) but not in women. NID and baPWV were not independently associated with moderate to severe LUTS either in men or women.
Conclusions: These findings suggest that endothelial dysfunction is associated with LUTS in men. LUTS in men may be useful for a predictor of cardiovascular events.
Clinical trial registration information: URL for Clinical Trial: http://UMIN; Registration Number for Clinical Trial: UMIN000003409.

1. Introduction

Lower urinary tract symptoms (LUTS) is common symptoms in elderly men and women and impairs quality of life (QoL) [1–3]. Recently, several lines of evidence have shown that atherosclerosis plays a critical role in the maintenance and development of LUTS [4–7]. Indeed, coexistence of LUTS and atherosclerotic status such as aging, diabetes mellitus, hypertension, dyslipidemia, smoking and metabolic syndrome is generally found [8–10]. It is clear that LUTS per se is a risk factor for cardiovascular events, especially in men [7,11,12]. In addition, it has been reported that nocturia is independently associated with increased all-cause mortality [13].

Endothelial dysfunction is established as an initial step of atherosclerosis, leading to cardiovascular diseases [14,15]. Measurements of flow-mediated vasodilation (FMD) of the brachial artery as an index of

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endothelium-dependent vasodilation and nitroglycerine-induced vasodilation (NID) as an index of endothelium-independent vasodilation are useful for assessing vascular function [16,17]. In addition, both FMD and NID are useful predictors of future cardiovascular events [18–20]. It is well known that pulse wave velocity (PWV) is an index of vascular structure assessed by arterial stiffness [21]. Several investigators have shown that PWV reflects cardiovascular risk factors and cardiovascular diseases and is a predictor for future cardiovascular events [21,22].

Previous studies demonstrated that vascular dysfunction and abnormal vascular structure subsequent to chronic bladder ischemia contribute to the pathogenesis, maintenance and development of LUTS, suggesting a strong relation between atherosclerosis and LUTS [4,5,23–26]. However, there is little information on the relationships of vascular function and structure with LUTS in a clinical setting. Therefore, we evaluated the associations of vascular dysfunction and abnormal vascular structure with LUTS in men and women.

2. Methods

2.1. Subjects

This study was a single center cross-sectional study. A total of 434 subjects (mean age, 63 ± 16 years) were recruited from people who underwent a health checkup at Hiroshima University Hospital between April 2016 and June 2017. Subjects with urologic cancer, neurologic disease and previous pelvic surgery were excluded from the study. Urinalysis was performed in all patients for excluding urinary tract infection. Subjects receiving antidepressants, sleep medication or anti-arrhythmic drugs were also excluded. Subjects with hypertension were defined as those taking oral antihypertensive agents or with systolic blood pressure of >140 mm Hg or diastolic blood pressure of >90 mm Hg measured in a sitting position on at least 3 different occasions. Diabetes mellitus was defined according to the American Diabetes Association recommendation [27]. Dyslipidemia was defined according to the third report of the National Cholesterol Education Program [28]. Smokers were defined as those who had ever smoked. One pack-year was equivalent to 20 cigarettes per day for 1 year. Insomnia was defined in accordance with Athens Insomnia Scale, which is a self-rating scale designed for quantifying sleep difficulty based on the basis of the Tenth Revision of the International Classification of Disease and Related Health Problems [29,30]. Framingham risk score was calculated in accordance with risk factors: age, total cholesterol level, high-density lipoprotein cholesterol level, systolic blood pressure, and smoking status [31]. Peripheral artery disease was defined as current intermittent claudication with ankle-brachial index <0.9 or chronic ischemic rest pain or a history of previous angioplasty and bypass graft. Coronary heart diseases included angina pectoris, myocardial infarction, and unstable angina. Cardiovascular diseases were defined as peripheral artery disease, coronary heart disease, and stroke including ischemic stroke, hemorrhagic stroke, and transient ischemic attack.

2.2. Study protocol

Vascular function was assessed in all subjects using measurements of FMD and NID in brachial artery, and vascular structure was assessed in all subjects using measurement of brachial-ankle PWV (baPWV) as an index of arterial stiffness. The subjects fasted overnight for at least 12 h and the study began at 08:30 h. The subjects remained in a supine position in a quiet, dark, air-conditioned room (constant temperature of 22 °C to 25 °C) throughout the study. A 23-gauge polyethylene catheter was inserted into the left deep antecubital vein to obtain blood samples. After 30 min of maintaining a supine position, baPWV, FMD and NID were measured. The observers were blind to the form of examination.

2.3. Assessment of LUTS

All subjects completed the International Prostate Symptom Score (IPSS) questionnaire, a clinically validated questionnaire (seven symptom questions and one QoL question) for assessing the presence and severity of LUTS [1,32,33]. LUTS was classified as none (IPSS of 0), mild (IPSS of 1–7), moderate (IPSS of 8–19) and severe (IPSS of ≥20). LUTS was also subclassified as storage symptoms (frequency, urgency, and nocturia) and voiding symptoms (incomplete emptying, weak stream, intermittency, straining). In men, benign prostate hyperplasia (BPH) was defined as a previous history or prostate enlargement assessed by transabdominal ultrasound and computed tomography [1,34].

2.4. Measurements of FMD and NID

We evaluated the vascular response to reactive hyperemia in the brachial artery for assessment of endothelium-dependent FMD. A high resolution linear artery transducer was coupled to computer assisted analysis software (UNEX18G, UNEX Co, Nagoya, Japan) that used an automated edge detection system for measurement of brachial artery diameter. A blood pressure cuff was placed around the forearm. The brachial artery was scanned longitudinally 5–10 cm above the elbow. When the clearest B-mode image of the anterior and posterior intimal interfaces between the lumen and vessel wall was obtained, the transducer was held at the same point throughout the scan by a special probe holder (UNEX Co) to ensure consistency of the image. Depth and gain settings were set to optimize the images of the arterial lumen wall interface. When the tracking gate was placed on the intima, the artery diameter was automatically tracked, and the waveform of diameter changes over the cardiac cycle was displayed in real time using the FMD mode of the tracking system. This allowed the ultrasound images to be optimized at the start of the scan and the transducer position to be adjusted immediately for optimal tracking performance throughout the scan. Pulsed Doppler flow was assessed at baseline and during peak hyperemic flow, which was confirmed to occur within 15 s after cuff deflation. Blood flow velocity was calculated from the Doppler data and was displayed as a waveform in real time. The baseline longitudinal image of the artery was acquired for 30 s, and then the blood pressure cuff was inflated to 50 mm Hg above systolic pressure for 5 min. The longitudinal images of the artery were recorded continuously until 5 min after cuff deflation. Pulsed Doppler velocity signals were obtained for 20 s at baseline and for 10 s immediately after cuff deflation. Changes in brachial artery diameter were immediately expressed as the percentage change relative to the vessel diameter before cuff inflation. FMD was automatically calculated as the percentage change in peak vessel diameter from the baseline value. Percentage of FMD [(Peak diameter–Base line diameter)/Baseline diameter] was used for analysis. Blood flow volume was calculated by multiplying the Doppler flow velocity (corrected for the angle) by the heart rate and vessel cross-sectional area ($-r^2$). Reactive hyperemia was calculated as the maximum percentage increase in flow after cuff deflation compared with baseline flow.

The response to nitroglycerine was used for assessment of endothelium-independent vasodilation [35]. After acquiring baseline rest image for 30 s, a sublingual tablet (nitroglycerine 75 μg) was given and imaging of the artery was done continuously for 5 min. NID was automatically calculated as a percentage change in peak vessel diameter from the baseline. Percentage of NID [(Peak diameter–Baseline diameter)/Baseline diameter] was used for analysis.

2.5. Measurement of baPWV

The measurement of baPWV, which is used for assessing aortic stiffness, was determined by two pressure sensors, placed on the right ankle and left brachial arteries to record each pulse wave simultaneously, and the time lag (t) between the notches of the two waves, using a pulse wave velocimeter (Form PWV/ABI, model BP-203RPE, Colin Co.). The distance (D) between the two recording sensors was calculated automatically by inputting the value of individual height. The PWV value was calculated as PWV = D/t. PWV was measured for five consecutive pulses, and averages were used for analysis.

2.6. Statistical analysis

Results are presented as means ± SD for continuous variables and percent (%) for categorical variables. A probability value of <0.05 was considered statistically significant. Categorical values were compared by means of the $\chi 2$ test. Continuous variables were compared by using ANOVA for multiple groups. Receiver operating characteristic (ROC) curve analysis was performed to assess the sensitivity and specificity of IPSS for predicting a previous history of cardiovascular disease. Multiple logistic regression analysis was performed to identify independent variables associated with moderate to severe LUTS. Age, gender, presence of insomnia, hypertension, diabetes mellitus and smoking history, and use of diuretics were entered into the multiple logistic regression analysis. As sensitivity analysis, we investigate the association between LUTS and vascular function using a propensity score-matched population. A logistic regression model was used to estimate the propensity of moderate to severe LUTS in men or women based on variables associated with LUTS, including age, body mass index, presence of insomnia, hypertension, diabetes mellitus and smoking history, and Framingham risk score. Subjects with moderate to severe LUTS were matched 1:1 with those with none or mild LUTS in accordance with propensity scores using a caliper width of 0.2 standard deviations of the logit of the propensity score. The data were processed using the software package Stata version 9 (Stata Co, College Station, TX, USA).

3. Results

3.1. Baseline clinical characteristics

Baseline clinical characteristics of all subjects are summarized in Table 1. Of the 434 subjects, 287 (66.1%) were men, 147 (33.9%) were women, 85 (19.6%) had coronary heart disease, and 55 (12.7%) had stroke. Twenty-three subjects (5.3%) were being prescribed medication for LUTS. In men, 20.6% had BPH. On the basis of IPSS, all of the subjects were categorized into two groups as follows: none or mild LUTS (IPSS of 0–7) and moderate to severe LUTS (IPSS of >7). In men, there were significant differences in traditional cardiovascular factors, including age, prevalence of hypertension, diabetes mellitus, dyslipidemia, and smoking history, and cardiovascular diseases between the two groups (Table 1). In women, there were significant differences in age, prevalence of insomnia, hypertension, and stroke, and percentage of subjects receiving diuretics between the two groups (Table 1).

3.2. Cardiovascular risk factors, cardiovascular diseases and LUTS

IPSS was significantly correlated with traditional cardiovascular risk factors including age, body mass index, total cholesterol, low-density lipoprotein cholesterol, glucose, and Framingham risk score (Supplementary Table S1). After adjusting for conventional cardiovascular risk factors, moderate to severe LUTS was significantly associated with prevalence of cardiovascular disease (OR: 1.79, 95% CI, 1.08–2.96; $P = 0.02$) and coronary heart disease (OR: 1.83, 95% CI, 1.02–3.30; $P = 0.04$) (Supplementary Table S2). Moderate to severe LUTS was independently associated with an increased odds ratio of coronary heart disease in men (OR: 2.54, 95% CI, 1.31–4.99; $P < 0.001$) but not in women (Supplementary Table S2). The ROC curve of IPSS to diagnose cardiovascular diseases in men is shown in Supplementary Fig. S1. Area under the curve values of ROC curves for IPSS to diagnose cardiovascular disease and coronary heart disease were 0.70 and 0.71, respectively ($P < 0.001$) (Supplementary Fig. S1A and S1B).

3.3. Vascular function and structure and LUTS

Vascular function assessed by FMD and NID and vascular structure assessed by baPWV were significantly correlated with conventional cardiovascular risk factors including age, glucose, and Framingham risk score (Supplementary Table S3). IPSS were

Table 1
Clinical Characteristics of the Subjects.

Variables	Total ($n = 434$)	Men		Women	
		None/mild LUTS ($n = 191$)	Moderate/severe LUTS ($n = 96$)	None/mild LUTS ($n = 112$)	Moderate/severe LUTS ($n = 35$)
Age, yr	63 ± 16	54 ± 18	70 ± 8**	68 ± 12	74 ± 10**
Body mass index, kg/m^2	24.3 ± 3.9	24.5 ± 4.1	25.0 ± 3.6	23.5 ± 4.1	23.8 ± 3.3
Systolic blood pressure, mm Hg	128.6 ± 18.0	127.2 ± 17.3	127.6 ± 19.0	130.4 ± 16.6	133.7 ± 22.7
Diastolic blood pressure, mm Hg	75.8 ± 11.2	77.1 ± 11.8	75.6 ± 11.0	74.6 ± 10.6	72.7 ± 10.0
Heart rate, beats/min	69.6 ± 12.0	69.3 ± 12.7	69.5 ± 12.4	69.5 ± 10.7	71.1 ± 11.3
Creatinine, μmol/L	75.1 ± 25.6	80.4 ± 26.5	86.6 ± 24.8	61.0 ± 15.0	69.8 ± 34.5
Uric acid, μmol/L	345.0 ± 83.3	362.8 ± 77.3	368.8 ± 89.2	303.4 ± 77.3	315.2 ± 77.3
Total cholesterol, mmol/L	4.97 ± 1.03	4.91 ± 0.93	4.65 ± 1.02	5.33 ± 1.13	5.02 ± 0.95
Triglycerides, mmol/L	1.52 ± 1.04	1.61 ± 1.12	1.72 ± 1.25	1.30 ± 0.73	1.28 ± 0.65
HDL-cholesterol, mmol/L	1.52 ± 0.41	1.44 ± 0.40	1.42 ± 0.39	1.68 ± 0.39	1.64 ± 0.38
LDL-cholesterol, mmol/L	2.90 ± 0.91	2.84 ± 0.91	2.66 ± 0.79	3.13 ± 0.99	2.90 ± 0.81
Glucose, mmol/L	6.27 ± 2.27	6.11 ± 1.67	7.05 ± 3.34**	5.88 ± 1.87	6.16 ± 1.73
Hemoglobin A1c, %	6.1 ± 1.2	6.1 ± 1.2	6.3 ± 1.7	5.9 ± 0.7	6.0 ± 0.7
Medical history, *n* (%)					
BPH		28 (16.5)	31 (32.3)**		
Insomnia	26 (6.0)	11 (5.8)	8 (8.3)	3 (2.7)	4 (11.4)*
Hypertension	342 (78.8)	131 (68.6)	90 (93.8)**	88 (78.6)	33 (94.3)*
Diabetes mellitus	115 (26.5)	44 (23.0)	37 (38.5)**	24 (21.4)	10 (28.6)
Dyslipidemia	300 (69.1)	111 (58.1)	73 (76.0)**	88 (78.6)	28 (80.0)
Peripheral artery disease	20 (4.6)	6 (3.1)	11 (11.5)**	2 (1.8)	1 (2.9)
Coronary heart disease	85 (19.6)	32 (16.8)	41 (42.7)**	9 (8.0)	3 (8.6)
Stroke	55 (12.7)	22 (11.5)	20 (21.1)*	4 (3.6)	9 (25.7)**
Cardiovascular disease	122 (28.1)	48 (25.1)	49 (51.0)**	13 (11.6)	12 (34.3)**
Smoking, *n* (%)	219 (50.5)	125 (65.5)	78 (81.3)**	10 (8.9)	6 (17.1)
Medications, *n* (%)					
Calcium channel blockers	247 (56.9)	88 (46.1)	67 (70.0)**	69 (61.6)	23 (65.7)
RAS inhibitors	218 (50.2)	85 (44.5)	58 (60.4)*	53 (47.3)	22 (62.9)
Diuretics	77 (17.7)	26 (13.6)	21 (21.9)	16 (14.3)	14 (40.0)**
Statins	193 (44.5)	62 (32.5)	60 (62.5)**	51 (45.5)	20 (57.1)
Medically treated diabetes mellitus					
Any	80 (18.4)	35 (18.3)	23 (24.0)	14 (12.5)	8 (22.9)
Insulin-dependent	18 (4.1)	8 (4.2)	4 (4.2)	3 (2.7)	3 (8.6)
Medications for LUTS					
α1-blockers	18 (4.1)	4 (2.1)	13 (13.5)**	1 (0.9)	0
5α-reductase inhibitors	4 (1.0)	0	4 (4.2)**	0	0
PDE5 inhibitors	2 (0.5)	1 (0.5)	1 (1.0)	0	0
Antimuscarinic drugs	5 (1.2)	0	1 (1.0)	0	4 (11.4)**
β3-adrenoceptor agonists	2 (0.5)	0	0	0	2 (5.7)*
Total IPSS	5.9 ± 5.7	3.0 ± 2.4	13.5 ± 5.5**	2.7 ± 2.1	11.3 ± 3.7**
Storage subscore	3.0 ± 2.7	1.8 ± 1.6	5.5 ± 2.9**	2.0 ± 1.7	6.1 ± 2.6**
Voiding subscore	2.9 ± 3.9	1.2 ± 1.6	8.0 ± 4.4**	0.8 ± 1.4	5.3 ± 3.2**
QoL index	1.8 ± 1.6	1.3 ± 1.4	3.2 ± 1.3**	1.3 ± 1.3	3.3 ± 0.9**
Framingham risk score	6.3 ± 4.3	5.1 ± 4.3	8.1 ± 2.6**	6.6 ± 4.6	7.7 ± 4.0
FMD, %	3.3 ± 3.0	4.0 ± 3.0	2.1 ± 2.0**	3.6 ± 3.4	2.3 ± 2.6*
NID, %	11.4 ± 6.5	12.8 ± 6.6	9.3 ± 6.1**	11.6 ± 6.5	8.7 ± 4.2*
baPWV, cm/s	1610 ± 349	1509 ± 309	1722 ± 386**	1633 ± 318	1748 ± 377

LUTS indicates lower urinary tract symptoms; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BPH, benign prostatic hyperplasia; RAS, renin-angiotensin system; PDE5, phosphodiesterase type 5; IPSS, International Prostate Symptom Score; QoL, quality of life; FMD, flow-mediated vasodilation; NID, nitroglycerine-induced vasodilation; baPWV, brachial-ankle pulse wave velocity.

* $P < 0.05$.

** $P < 0.01$ versus none/mild LUTS group.

significantly correlated with FMD, NID and baPWV in men (Fig. 1A, B and C), and IPSS were significantly correlated with FMD and NID but not baPWV in women (Fig. 1D, E and F).

FMD and NID were significantly lower in men with moderate to severe LUTS than in men with none or mild LUTS (2.1 ± 2.0% vs. 4.0 ± 3.0% and 9.3 ± 6.1% vs. 12.8 ± 6.6%, $P < 0.001$, respectively),

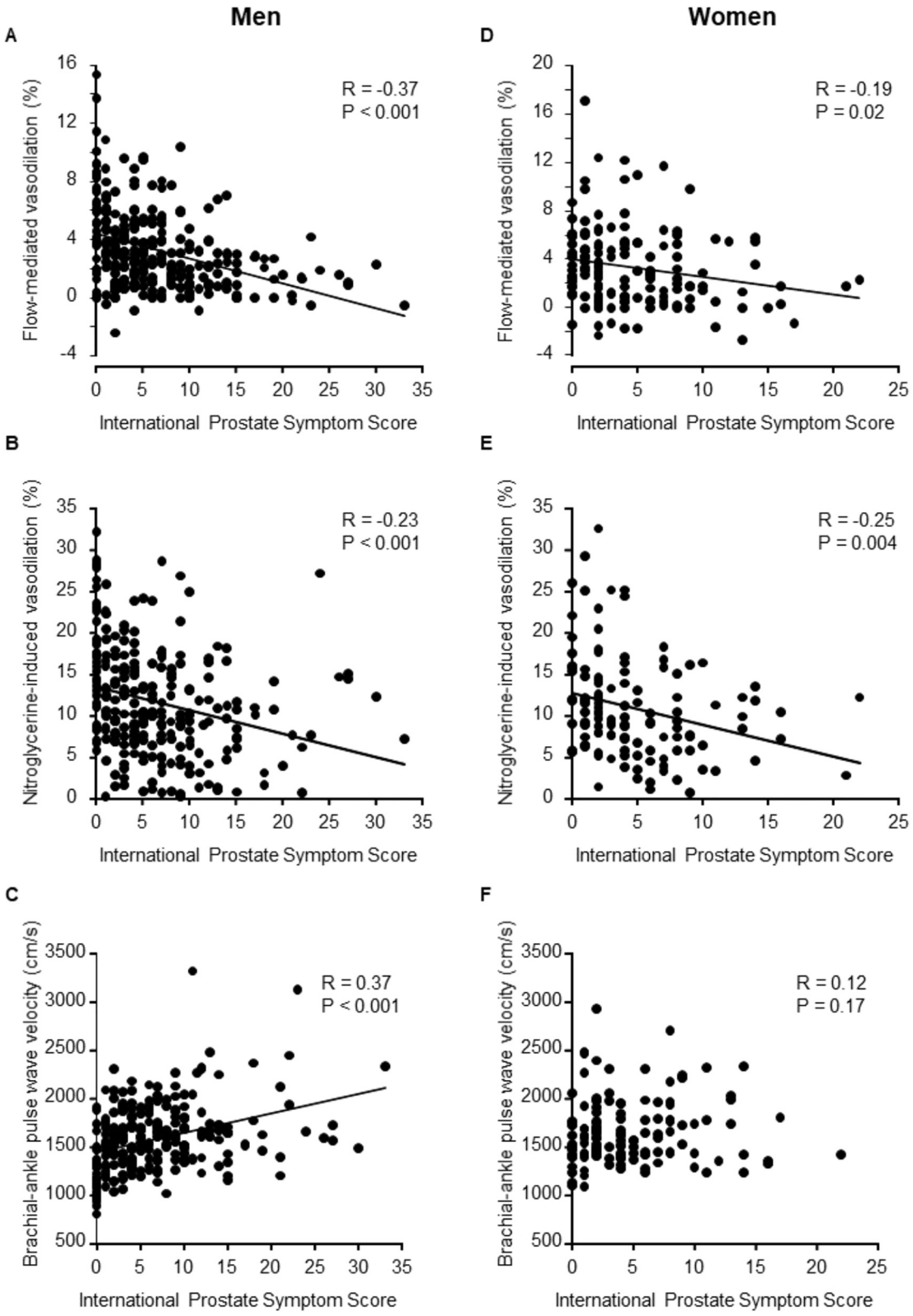

Fig. 1. Scatter plots show the relationship between flow-mediated vasodilation (A), nitroglycerine-induced vasodilation (B), and brachial-ankle pulse wave velocity (C) and international prostate symptom score in men and the relationship between flow-mediated vasodilation (D), nitroglycerine-induced vasodilation (E), and brachial-ankle pulse wave velocity (F) and international prostate symptom score in women.

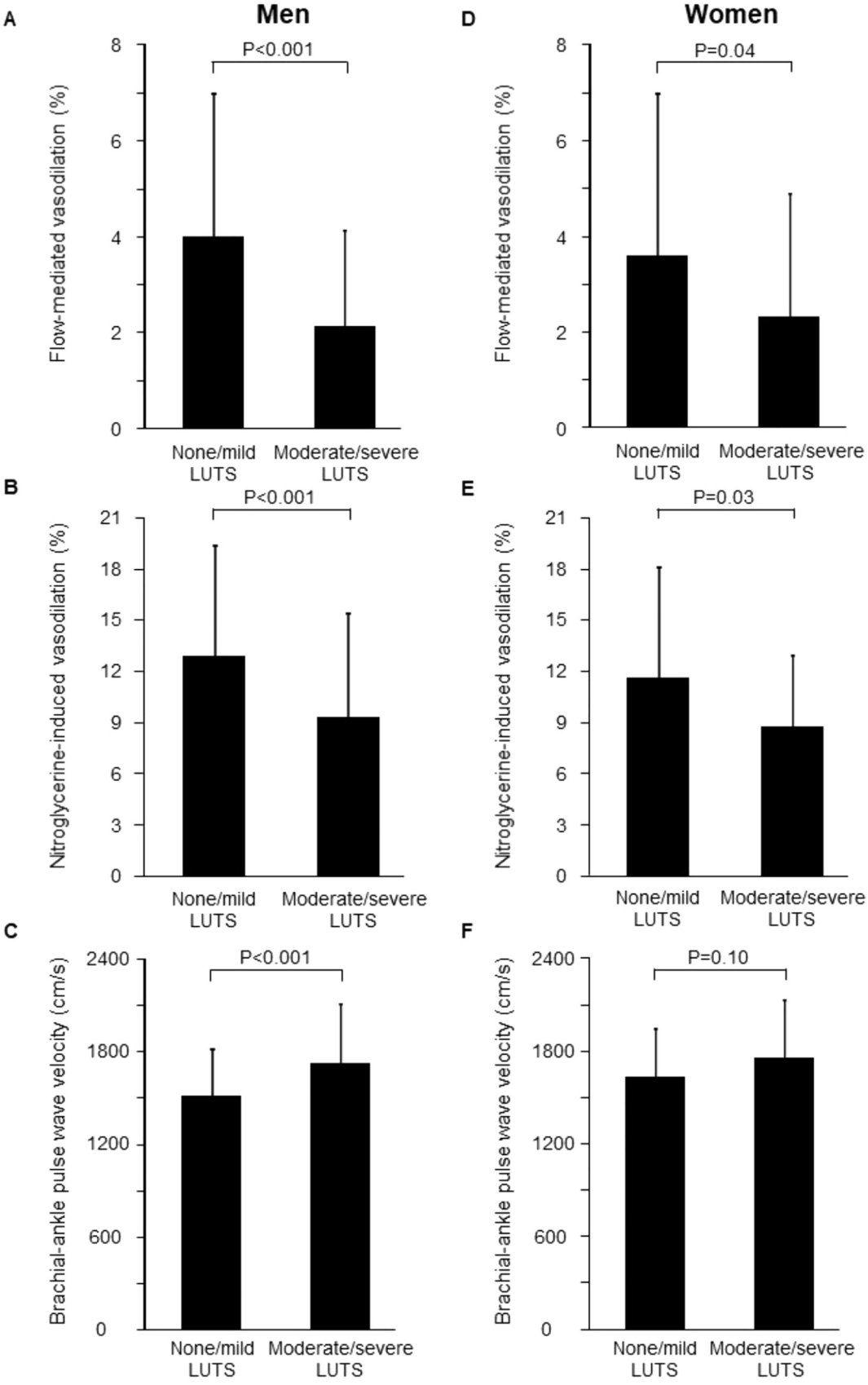

Fig. 2. Bar graphs show flow-mediated vasodilation (A), nitroglycerine-induced vasodilation (B) and brachial-ankle pulse wave velocity (C) in the none or mild lower urinary tract symptoms (LUTS) group and moderate to severe LUTS group in men and flow-mediated vasodilation (D), nitroglycerine-induced vasodilation (E) and brachial-ankle pulse wave velocity (F) in the none or mild LUTS group and moderate to severe LUTS group in women.

and baPWV was significantly higher in men with moderate to severe LUTS than in men with none or mild LUTS (1722 ± 386 cm/s vs. 1509 ± 309 cm/s, $P < 0.001$) (Table 1 and Fig. 2A, B and C). FMD and NID were significantly lower in women with moderate to severe LUTS than in women with none or mild LUTS (2.3 ± 2.6% vs. 3.6 ± 3.4%, $P = 0.04$, and 8.7 ± 4.2% vs. 11.6 ± 6.5%, $P = 0.03$, respectively), but there was no significant difference in baPWV between the two groups (Table 1 and Fig. 2D, E and F).

Multivariate analysis revealed that FMD was independently associated with a decrease in the odds ratio of moderate to severe LUTS in men (OR: 0.83, 95% CI, 0.72–0.95; $P = 0.008$) but not in women (Table 2). In men, FMD was significantly associated with decreasing IPSS ($\beta = -0.15$, $P = 0.01$), storage subscore ($\beta = -0.13$, $P = 0.03$) and voiding subscore ($\beta = -0.13$, $P = 0.04$) after adjusting for confounding factors (Supplementary Table S4). NID and baPWV were not independently associated with moderate to severe LUTS in men (Table 2). In women, there was no independent association of FMD, NID or baPWV with LUTS assessed by IPSS including storage and voiding subscore (Supplementary Table S4).

We next evaluated the associations of LUTS with vascular function and structure in propensity score-matched population in men. There were significant differences in the prevalence of coronary heart disease, use of statins, and medication for LUTS between men with none or mild LUTS and men with moderate to severe LUTS (Supplementary Table S5). There were no significant differences in other baseline variables between the two groups. After matching for confounding factors, FMD was significantly lower in men with moderate to severe LUTS than in men with none or mild LUTS, while there were no significant differences in NID and baPWV between the two groups (Supplementary Table S5). In women, FMD, NID and baPWV were not significantly different between the none or mild LUTS group and the moderate to severe LUTS group after propensity score matching (Supplementary Table S6).

4. Discussion

We demonstrated for the first time that endothelial dysfunction assessed by FMD was independently associated with LUTS assessed by IPSS in men but not in women after adjusting for confounding factors of LUTS and that endothelial dysfunction was independently associated with holistic urological symptoms including storage and voiding dysfunction. Moderate to severe LUTS was associated with the prevalence of coronary heart disease in men but not in women.

Recently, atherosclerosis has been focused on as one of the causes of LUTS. Several lines of evidence have shown the coexistence of LUTS and atherosclerotic disease [8–10,36]. In addition, it has been reported that LUTS is an independent predictor of cardiovascular events [7,11–13]. Gacci et al. revealed that moderate to severe LUTS in men is strongly related to an increase in the risk of major cardiovascular events [7]. In contrast, Bouwman et al. reported that LUTS in men is not a predictor of cardiovascular events [37]. In the present study, cardiovascular risk factors such as age, body mass index, glucose and Framingham risk score showed significant relationships with IPSS. Moreover, men with moderate to severe LUTS had a high prevalence of a history of cardiovascular diseases compared with men with none or mild LUTS. These findings suggest that atherosclerotic diseases contribute to vascular dysfunction and abnormal vascular structure, leading to not only cardiovascular diseases but also LUTS.

It is well known that a variety of factors including bladder outlet obstruction, neurological disease, sleep disorder, and pelvic surgery contribute to the development and progression of LUTS. A decrease in blood flow of the bladder has been shown to lead to detrusor dysfunction in elderly rats and humans [23,26]. Nomiya et al. showed that atherosclerosis-induced bladder ischemia caused detrusor dysfunction in male rats through oxidative stress and inflammatory reaction [4]. Several pharmacotherapies for LUTS/BPH improve bladder dysfunction through an increase in bladder blood flow [38–40]. These findings suggest that chronic bladder ischemia induced by atherosclerosis plays a critical role in the development of voiding and storage dysfunction.

In the present study, we investigated, for the first time, the associations of vascular smooth muscle function and vascular structure with LUTS. Endothelium-dependent vasodilation as an index of endothelial function is impaired in the early stage of atherosclerosis, and vascular smooth muscle function and vascular structure are gradually impaired in relation to the advanced atherosclerosis [15]. In the present study, endothelial function was independently associated with LUTS in men, while vascular smooth muscle function and vascular structure were not related to LUTS, suggesting that endothelial dysfunction has a critical role in the pathogenesis of male LUTS. Interestingly, a previous study indicated a link between FMD and nocturia in patients with BPH [41]. LUTS in men may be an early phenotype of atherosclerosis, indicating that the presence of LUTS is useful as a predictor of cardiovascular events.

In the present study, a significant association between LUTS and vascular dysfunction was found in men but not in women. A significant relationship between LUTS and cardiovascular events was also confirmed only in men in previous studies [7], being consistent with our results. It is well known that LUTS in women is associated with menopause, pelvic floor disorder, and sleep disorder, indicating a gender difference in the pathogenesis of LUTS [42,43]. In the present study, age, insomnia, use of diuretics and smoking independently contributed to an increase in IPSS in women. It is likely that non-atherosclerotic conditions as well as atherosclerosis play an important role in the pathogenesis and development of LUTS in women.

4.1. Study limitations

There are a number of limitations in the present study. First, the cross-sectional design of the study did not allow us to establish definitive causal relations between LUTS, vascular function and structure, and cardiovascular disease. In addition, the relatively small number of subjects may result in a discrepancy of relationships of vascular failure and LUTS between men and women. Future prospective studies are needed to determine whether LUTS is associated with vascular dysfunction, abnormal vascular structure and cardiovascular events in a large population. Second, although the association between male LUTS and vascular dysfunction remained significant after adjustment for confounding factors, there were significant differences in cardiovascular risk factors between the two groups. As sensitivity analysis, we confirmed the relationship between LUTS and endothelial function in a propensity score-matched population. It is likely that endothelial dysfunction contributes to the coexistence of LUTS and atherosclerotic

Table 2
Multivariate analysis of the relations between moderate to severe LUTS and vascular function and structure.

Variables	All subjects	Men	Women
	Adjusted[a] OR (95% CI) *P* value	Adjusted[b] OR (95% CI) *P* value	Adjusted[b] OR (95% CI) *P* value
FMD, %	0.88 (0.79–0.98) 0.01	0.83 (0.72–0.95) 0.008	0.97 (0.82–1.14) 0.72
NID, %	0.97 (0.92–1.01) 0.15	0.97 (0.92–1.02) 0.25	0.97 (0.87–1.07) 0.55
baPWV, cm/s	1.00 (0.99–1.00) 0.66	1.00 (0.99–1.00) 0.99	1.00 (0.99–1.00) 0.27

LUTS indicates lower urinary tract symptoms; OR, odds ratio; CI, confidence interval; FMD, flow-mediated vasodilation; NID, nitroglycerine-induced vasodilation; baPWV, brachial-ankle pulse wave velocity.

[a] Adjusted for age, gender, and the presence of insomnia, hypertension, diabetes mellitus, smoking history, and use of diuretics.

[b] Adjusted for age, and the presence of insomnia, hypertension, diabetes mellitus, smoking history, and use of diuretics.

risk factors. Third, baPWV has recently been used for the assessment of arterial stiffness as well as carotid-femoral PWV (cfPWV), which is used as the gold standard for non-invasive assessment of central arterial stiffness. It has been shown that baPWV correlates closely with directly measured aortic PWV and cfPWV [44,45]. Measurement of baPWV using a separate oscillometric cuff for each of the four extremities is easier than measurement of cfPWV, which requires a skilled technique and exposure of the inguinal region during measurement [44,45]. It has been reported that baPWV is not only an index of atrial stiffness but also a predictor of cardiovascular events [22]. Fourth, we did not measure oxidative stress markers and inflammatory markers in the present study. Further studies including measurements of these markers are needed to obtain a more specific conclusion as to whether inflammation is asscociated with the pathogenesis of endothelial dysfunction and LUTS.

5. Conclusions

In conclusion, we evaluated LUTS from the aspect of vascular medicine, including vascular function and vascular structure. Endothelial dysfunction, which initially occurs in the pathogenesis of atherosclerosis, was associated with LUTS in men. LUTS in men should be focused on as the early phenotype of atherosclerosis. Further studies are needed to determine whether LUTS can predict future cardiovascular events in a large population.

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Conflict of interest/disclosures

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.02.041.

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