

Original Article

Atherosclerosis is associated with erectile function and lower urinary tract symptoms, especially nocturia, in middle-aged men



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ABSTRACT

Background: Atherosclerosis is a systematic disease in which plaque builds up inside the arteries that can lead to serious problems related to quality of life (QOL). Lower urinary tract symptoms (LUTS), erectile dysfunction (ED), and late-onset hypogonadism (LOH) are highly prevalent in aging men and are significantly associated with a reduced QOL. However, few questionnaire-based studies have fully examined the relation between atherosclerosis and several urological symptoms.

Materials and methods: The study comprised 303 outpatients who visited our clinic with symptoms of LOH. Several factors influencing atherosclerosis, including serum concentrations of triglyceride, fasting blood sugar, and total testosterone measured by radioimmunoassay, were investigated. We also measured brachial-ankle pulse wave velocity (baPWV) and assessed symptoms by specific questionnaires, including the Sexual Health Inventory for Men (SHIM), Erection Hardness Score (EHS), International Prostate Symptom Score (IPSS), QOL index, and Aging Male Symptoms rating scale (AMS). Stepwise associations between the ratio of measured/age standard baPWV and clinical factors including laboratory data and the scores of the questionnaires were compared using the Jonckheere–Terpstra test for trend. The associations between the ratio of measured/age standard baPWV and each IPSS score were assessed in a multivariate linear regression model after adjustment for serum triglyceride, fasting blood sugar, and total testosterone.

Results: Regarding ED, a higher level of the ratio of measured/age standard baPWV was associated with a lower EHS, whereas no association was found with SHIM. Regarding LUTS, a higher ratio of measured/age standard baPWV was associated with a higher IPSS and QOL index. However, there was no statistically significant difference between the ratio of measured/age standard baPWV and AMS. A multivariate linear regression model showed only nocturia to be associated with the ratio of measured/age standard baPWV for each IPSS score.

Conclusion: Atherosclerosis is associated with erectile function and LUTS, especially nocturia.

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1. Introduction

Because androgen plays many physiological roles in various organs and tissues, such as the skin, muscle, liver, bone and bone marrow, brain, and sexual organs, the concept of late-onset

hypogonadism (LOH), defined as “a clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels,” has recently gained increased attention. The Japanese guidelines for LOH include seven typical symptoms: erectile dysfunction (ED) in sexual dysfunction, changes in mood and depression, sleep disturbances, decrease in lean body mass, increase in visceral fat, decrease in body hair and skin alterations, and decreased bone mineral density. Although lower urinary tract symptoms (LUTS) are not included in the LOH symptoms in these guidelines, it is usual for

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middle-aged patients with LOH symptoms to complain at least somewhat of LUTS clinically. Indeed, LUTS, ED, and LOH are highly prevalent in aging men and are significantly associated with a reduced quality of life (QOL).^{1,2} Furthermore, LUTS and ED are considered to be risk factors for cardiovascular disease (CVD) based on several previous studies. Because we already reported that a lower level of serum testosterone level was associated with a higher carotid artery intima-media thickness in middle-aged Japanese men,³ LOH might also be related with CVD caused by the progression of atherosclerosis. Atherosclerosis is a systematic disease in which plaque builds up inside the arteries that can lead to serious problems relating to QOL. However, with respect to the relation between atherosclerosis and several urological symptoms, few questionnaire-based studies have been fully conducted. Pulse wave velocity (PWV) is known to be an indicator of arterial stiffness and a marker of atherosclerosis.^{4,5} Presently, a simpler method of measuring brachial-ankle PWV (baPWV) has been used clinically, instead of carotid-femoral PWV, as the gold standard measurement of arterial stiffness.⁶

In the present study, we measured baPWV to evaluate atherosclerosis and assessed several urological symptoms of LOH by specific questionnaires to clarify the relation between urological symptoms and atherosclerosis in men with LOH.

2. Materials and methods

2.1. Patients

This study comprised 303 men with some of the LOH symptoms listed above who visited our clinic between April 2012 and March 2014. Several factors influencing atherosclerosis, including abdominal circumference, serum concentrations of triglyceride, fasting blood sugar (FBS), and total testosterone measured by radioimmunoassay, were investigated. We assessed several urological symptoms by specific questionnaires including the Sexual Health Inventory for Men (SHIM) and Erection Hardness Score (EHS) for erectile status, International Prostate Symptom Score (IPSS) and QOL index for LUTS, and the Aging Male Symptoms rating scale (AMS) for LOH.

As the index of arterial stiffness, baPWV was calculated from measurements of pulse transmission time and the distance between the brachial artery and ankle artery by a validated non-invasive and automated waveform analyzer (VP2000, Omron, Kyoto, Japan). Because a previous large-scale study already reported the age standard baPWV according to the following formula,

$$\text{age standard baPWV} = 0.20 \times \text{age}^2 - 12.13 \times \text{age} + 1,341.34,^7 (1)$$

we used the ratio of measured/age standard baPWV to analyze the relation between atherosclerosis and several symptoms in the present study to eliminate the factor of aging. Informed consent was obtained from all patients. The study protocol was approved by the Ethical Committee of the Men's Health Clinic Tokyo, Tokyo, Japan.

2.2. Statistical analysis

Continuous variables and scores of the questionnaires are expressed as mean \pm standard error. Stepwise associations between the ratio of measured/age standard baPWV and clinical factors, including abdominal circumference, laboratory data, and the scores of the questionnaires, were compared using the Jonckheere–Terpstra test for trend. To identify the contributors of LUTS to the ratio of measured/age standard baPWV, the associations between the ratio of measured/age standard baPWV and each IPSS score

were assessed in a multivariate linear regression model after adjustment for serum triglyceride, FBS, and total testosterone. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Patients' characteristics are summarized in Table 1. The mean age and abdominal circumference of the patients was 50.3 years and 88.0 cm, respectively, and the mean concentrations of serum triglyceride, FBS, and total testosterone were 128.9 ± 5.5 mg/dL, 94.7 ± 1.1 mg/dL, and 5.3 ± 0.1 ng/mL, respectively. The severities of LUTS, ED, and LOH were all moderate as evaluated by the IPSS, SHIM, and AMS, respectively. The ratio of measured/age standard baPWV was 1.1, indicating that our patients were members of the group with slightly hard arterial stiffness.

No association between the ratio of measured/age standard baPWV and abdominal circumference was found (Table 2). As expected, men with a higher level of the ratio of measured/age standard baPWV had statistically higher concentrations of serum triglyceride ($P_{\text{trend}} = 0.010$) and FBS ($P_{\text{trend}} = 0.001$) and a lower level of serum testosterone ($P_{\text{trend}} = 0.017$; Table 2). Regarding ED, a higher level of the ratio of measured/age standard baPWV was associated with a lower EHS ($P_{\text{trend}} = 0.012$), whereas no association was found between the ratio of measured/age standard baPWV and the SHIM score. As the ratio of measured/age standard baPWV increased, the EHS decreased (Fig. 1A). Regarding LUTS, a higher level of the ratio of measured/age standard baPWV was associated with a higher IPSS ($P_{\text{trend}} = 0.036$) and QOL index ($P_{\text{trend}} = 0.016$; Table 2). However, there was no statistically significant difference between the ratio of measured/age standard baPWV and the AMS scale. A multivariate linear regression model after adjustment for serum triglyceride, FBS, and total testosterone showed only nocturia to be associated with the ratio of measured/age standard baPWV (Table 3). As the ratio of measured/age standard baPWV increased, the nocturia score also increased (Fig. 1B).

4. Discussion

It is well known that atherosclerosis is one of the major causes of ED because erectile status is maintained by adequate blood flow

Table 1
Patient background.

Age (yr)	50.3 (22–86)
Abdominal circumference (cm)	88.0 (62.0–126.0)
Triglyceride (mg/dL)	128.9 (25.0–714.0)
FBS (mg/dL)	94.7 (65.0–213.0)
Testosterone (ng/mL)	5.3 (0.4–13.3)
IPSS total	7.7 (0–33)
Post voiding	1.2 (0–5)
Voiding	3.0 (0–15)
Storage	4.7 (0–20)
QOL index	2.6 (0–6)
SHIM	10.4 (0–25)
EHS	2.3 (0–4)
AMS total	38.3 (0–69)
Somatovegetative	14.9 \pm 0.3 (0–31)
Psychological	10.3 (0–26)
Sexual	13.1 (0–23)
baPWV (cm/sec)	1,448.2 (961.0–2,469.0)
Measured/age standard baPWV	1.1 (0.80–1.86)

Values are expressed as mean (minimum–maximum).

AMS, Aging Male Symptoms rating scale; baPWV, brachial-ankle pulse wave velocity; EHS, Erection Hardness Score; FBS, fasting blood sugar; IPSS, International Prostate Symptom Score; QOL, quality of life; SHIM, Sexual Health Inventory for Men.

Table 2
Clinical characteristics of the association between atherosclerotic and metabolic factors, serum testosterone level, and questionnaire scores.

	Measured/Age standard baPWV (Mean ± SE)					P _{trend}
	0.80–1.00 (0.94 ± 0.01)	1.00–1.07 (1.03 ± 0.00)	1.08–1.17 (1.13 ± 0.00)	1.18–1.27 (1.23 ± 0.00)	1.28–1.86 (1.41 ± 0.01)	
Case	61	61	60	61	60	–
Abdominal circumference (cm)	87.3 ± 1.2	87.3 ± 0.9	87.4 ± 1.4	88.9 ± 1.2	88.9 ± 1.2	NS
Triglyceride (mg/dL)	105.0 ± 8.7	120.0 ± 9.0	137.6 ± 14.3	136.2 ± 12.0	146.0 ± 15.5	0.010
FBS (mg/dL)	89.8 ± 1.3	91.0 ± 1.6	95.0 ± 2.6	99.0 ± 2.8	98.8 ± 3.0	0.001
Testosterone (ng/mL)	5.4 ± 0.3	5.5 ± 0.2	5.6 ± 0.3	5.0 ± 0.2	5.0 ± 0.3	0.017
SHIM	10.5 ± 0.8	10.7 ± 0.7	10.3 ± 0.8	10.4 ± 0.8	10.4 ± 0.8	NS
EHS	2.6 ± 0.1	2.4 ± 0.1	2.2 ± 0.1	2.0 ± 0.2	2.2 ± 0.1	0.012
IPSS	7.2 ± 0.9	6.9 ± 0.8	7.5 ± 0.8	8.2 ± 0.9	8.9 ± 0.9	0.036
QOL index	2.4 ± 0.2	2.3 ± 0.2	2.5 ± 0.2	2.6 ± 0.2	3.0 ± 0.2	0.016
AMS	35.8 ± 1.3	38.7 ± 1.6	39.6 ± 1.5	36.4 ± 1.3	41.3 ± 1.6	NS

AMS, Aging Male Symptoms rating scale; baPWV, brachial-ankle pulse wave velocity; EHS, Erection Hardness Score; FBS, fasting blood sugar; IPSS, International Prostate Symptom Score; NS, not significant; QOL, quality of life; SHIM, Sexual Health Inventory for Men.

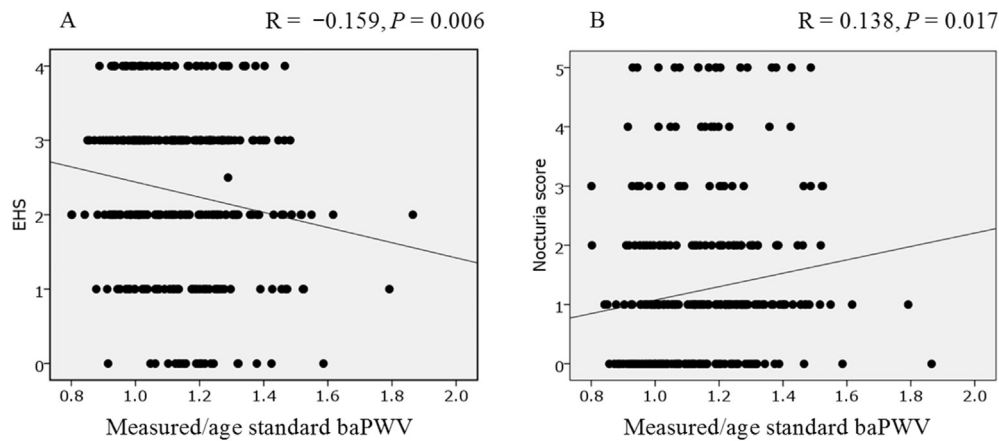


Fig. 1. Relation between measured/age standard brachial-ankle pulse wave velocity (baPWV) and Erection Hardness Score (EHS) score (A) and nocturia score (B).

Table 3
Contributors of IPSS score to measured/age standard baPWV.

	Regression coefficient	95% CI		P
		Lower	Upper	
Incomplete emptying	0.117	-0.034	0.281	NS
Frequency	0.096	-0.052	0.233	NS
Intermittency	0.116	-0.062	0.336	NS
Urgency	-0.106	-0.320	0.065	NS
Weak stream	-0.099	-0.233	0.053	NS
Straining	-0.067	-0.276	0.120	NS
Nocturia	0.126	0.001	0.247	<0.05

baPWV, brachial-ankle pulse wave velocity; CI, confidence interval; NS, not significant.

into the corpus cavernosum. Recently, an interesting concept has been raised that ED may precede the onset of clinical CVD because the diameter of the cavernosum artery is much smaller than that of the coronary arteries. Indeed, several clinical studies have shown that ED is an independent predictor of CVD events.^{8–10} Conversely, it was recently reported that the early detection of subclinical coronary calcification and carotid plaque can provide an opportunity for predicting the onset of subsequent vascular ED.¹¹ Thus, the evaluation and control of atherosclerosis is very important for the prevention and management of both ED and CVD. The intima-media thickness (IMT), which reflects structural changes in the arterial wall as measured by high-resolution B-mode ultrasound, has been used for the noninvasive assessment for atherosclerosis. A

previous study with sexually active hypertensive men aged 50–70 years showed that the carotid IMT was significantly greater in patients with ED than in control patients. In that study, the erectile function domain score of the International Index of Erectile Function Questionnaire correlated negatively with the carotid IMT.¹² It was also reported that the carotid IMT correlates strongly with the presence and extent of CVD.^{13,14} Another diagnostic procedure for the assessment of atherosclerosis is the measurement of PWV, which indicates aortic stiffness as an early sign of atherosclerosis. The baPWV was already reported to be a marker of atherosclerotic vascular damage and cardiovascular risk.¹⁵ Furthermore, a Japanese study with 280 healthy male volunteers already showed that baPWV is an independent risk factor for ED.¹⁶ Because the measurement of baPWV is easier and more objective than that of conventional IMT by high-resolution B-mode ultrasound, we evaluated the atherosclerotic factor by baPWV in the present study. We showed that a higher ratio of measured/age standard baPWV was associated with a statistically lower level of serum testosterone (Table 2). This close relation between atherosclerosis and low testosterone is consistent with previous studies including ours, in which we evaluated with IMT.³ Unexpectedly, the SHIM score was not associated with the ratio of measured/age standard baPWV in the present study. SHIM, which was developed and validated as a patient-reported diagnostic tool, has high sensitivity and specificity, moderate-to-high correlations with a single-item self-assessment of ED severity, and tangible correlations with improvement in erections and with treatment satisfaction for both the patient and his partner.^{17,18} However, SHIM includes questions

regarding confidence and satisfaction judged by patients, which may be affected by individual and psychological conditions. By contrast, EHS is a simple, reliable, and specific questionnaire including questions only regarding erection hardness of the penis. This means that the evaluation by EHS may be more sensitive to the present vessel condition in the penis than that by SHIM. With respect to this point, we showed that a higher level of the ratio of measured/age standard baPWV was associated with a lower EHS score in the model adjusted for other factors such as serum triglyceride, FBS, and total testosterone concentrations in Japanese patients with LOH symptoms. These findings may indicate that even subclinical atherosclerosis can worsen erectile function because of reduced blood flow.

In the present study, we also found an association between the ratio of measured/age standard baPWV and LUTS. Because the pathogenesis of LUTS is multifactorial, atherosclerosis and endothelial dysfunction may have a significant role. Furthermore, there is recent growing evidence of the association of metabolic syndrome, whose main components are central obesity, insulin resistance, dyslipidemia, and hypertension, and the initiation and clinical progression of benign prostatic hyperplasia (BPH).¹⁹ Metabolic syndrome is also associated with microvascular dysfunction and increased arterial stiffness as measured by several examinations including PWV in both African Americans and white patients.²⁰ Thus, a cross-relation between atherosclerosis and BPH/LUTS has been speculated. Indeed, it has been reported that age-related impairment of the blood supply to the lower urinary tract due to atherosclerosis is important in the development of BPH.²¹ First, atherosclerosis of the pelvic vessels may cause prolonged chronic ischemia in the bladder and prostate. This chronic phenomenon subsequently causes the generation of oxidative stress in the bladder wall and mild hypoxia in the prostate, resulting in injury to the neural pathways responsible for micturition. The hypothesis of this process was confirmed in an animal model.²² In humans, it was reported that there was a significant increase in the severity of the IPSS in accordance with the severity of plaque size detected by carotid ultrasound, which may indicate carotid artery atherosclerosis.²³ A previous study of 110 men aged 55–75 years who presented with LUTS evaluated by uroflowmetry showed that the maximal flow rate of the men with carotid artery atherosclerosis was decreased compared with that of the men without it (12.5 ± 6.3 mL/s vs. 17.6 ± 6.5 mL/s).²⁴ In that study, daytime frequency and nocturia were also significantly higher in men with carotid artery atherosclerosis than in those without it (3.1 ± 1.2 times vs. 1.92 ± 1.12 times). Another study that measured the PWV showed that carotid-femoral PWV was significantly higher in men with LUTS after adjustment for age and glucose level.²⁵ A study with Japanese patients showed similar findings in that the maximum flow rate in men with atherosclerosis assessed by ultrasound examination of the carotid artery was significantly lower than that in the men without it (13.4 ± 5.5 mL/s vs. 16.7 ± 7.7 mL/s). This Japanese study also showed the daytime frequency of urination to be significantly higher in the men with atherosclerosis than in those without it (7.13 ± 3.02 times vs. 8.75 ± 2.50 times), although nocturia was not evaluated.²⁶ These findings indicate that atherosclerotic disease may play a significant role in the impairments of both voiding and storage function in male patients.

We also showed that a higher level of the ratio of measured/age standard baPWV is associated with a higher IPSS and QOL index. In particular, the most interesting finding in the present study is that only the nocturia score of the IPSS was associated with the ratio of measured/age standard baPWV by multivariate linear regression model after adjustment for serum triglyceride, FBS, and total testosterone concentrations. This means that atherosclerosis may be cross-related with nocturia in middle-aged men. A previous

study of patients with BPH showed that the frequency and duration of nocturia were significantly and inversely associated with endothelial dysfunction as measured by flow-mediated dilatation of the brachial artery.²⁷ As we already reported,²⁸ nocturia disturbs sleep quality because of interrupted sleep duration. It is speculated that poor sleep quality causes an imbalance of sympathetic and parasympathetic activity and subsequently disturbs the circadian rhythm of blood pressure. Indeed, nocturia is a strong independent predictor of prevalent hypertension in obstructive sleep apnea.²⁹ We speculated that hypertension caused by nocturia might finally result in atherosclerosis.

Some limitations of the present study need to be mentioned. First, although a relation between atherosclerosis and erectile function and LUTS was clearly shown, the number of patients was too small to derive definitive conclusions. Second, we excluded blood pressure from the variables analyzed because blood pressure is highly associated with baPWV, although we included serum triglyceride and FBS as metabolic factors, and total testosterone based on our previous study. Third, there is a possibility of an effect of prostate enlargement on nocturia in our patients because their mean age was 50.3 years. However, prostate volume and the information by uroflowmetry were not evaluated in all patients participating in this questionnaire-based study.

In conclusion, we found that a higher level of the ratio of measured/age standard baPWV was associated with erectile function and LUTS. Particularly, only nocturia was found to be associated with the ratio of measured/age standard baPWV by multivariate linear regression model after adjustment for serum triglyceride, FBS, and total testosterone concentrations. A larger-scale study that includes the evaluation of prostate volume will be necessary to assess these relations.

Conflicts of interest

All authors have no conflict of interest to declare.

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