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Running title. Impact of abdominal aortic calcification and visceral fat obesity on LUTS/BPH.

Keywords. abdominal aortic calcification, visceral fat obesity, lower urinary tract symptoms, benign prostatic hyperplasia

Abstract

Objectives: To investigate the impact of abdominal aortic calcification and visceral fat area on lower urinary tract symptoms (LUTS) and clinical parameters in patients with benign prostatic hyperplasia (BPH).

Methods: We retrospectively studied 250 patients with LUTS associated with BPH. Each participant was examined with routine examination including measurement of various data; 1) voided volume, maximum urinary flow rate on free uroflowmetry 2) postvoid residual urine volume and prostate volume using transabdominal ultrasound, 3) International Prostate Symptom Score (IPSS) and Overactive Bladder Symptom Score (OABSS), 4) aortic calcification index (ACI) and visceral fat area were measured by abdominal CT.

Results: Mean age of the patients was 72.4 ± 9.6 years. ACI significantly correlated with voided volume (P=0.0392) and tended to correlate with maximum urinary flow rate, while ACI did not correlate with subjective symptoms. Visceral fat area significantly correlated with nocturia score of IPSS (P=0.0177) and frequency score of OABSS (P=0.0166), and tended to correlate with urgency score of IPSS and maximum urinary flow rate.

Conclusions: ACI correlated with only objective parameters, while visceral fat area correlated with only storage symptoms. This study suggested that abdominal aortic calcification and visceral fat area have certain influence on LUTS and clinical parameters in patients with BPH.

Introduction

Recently, MetS has been considered to have an important role in LUTS/BPH etiologies [1]. The key factors for MetS are visceral fat obesity, dyslipidemia, hypertension, insulin resistance with secondary hyperinsulinemia [2]. Pathophysiological conditions of MetS involve enhanced sympathetic nervous activity and possibly elevate the risk for atherosclerotic diseases. And, MetS are known to cause autonomic sympathetic overactivity through complex mechanisms [2,3]. It is suggested that overactivity of the sympathetic nervous system takes part in the development of BPH and LUTS [4]. MetS might aggravate systemic vascular factors and disturb blood flow of the lower urinary tract, thus leading to the onset of LUTS and lower urinary tract dysfunction [5]. Ponholzer et al. reported the association of four major vascular risk factors and LUTS in both sexes [6]. Recent studies imply an important role of bladder ischemia and change of bladder blood flow (BBF) in the development and severity of LUTS and lower urinary tract dysfunction. Recent animal studies suggest that arterial occlusive disease such as atherosclerosis may cause lower urinary tract dysfunction via bladder ischemia, hypoxia and oxidative stress in the bladder [5,6-10]. These reports show the possibility that atherosclerosis has a pathophysiological 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 remain to be elucidated.

The preliminary study, the association between visceral fat area (VFA) and LUTS showed a significant correlation of VFA with storage symptoms in

233 patients with BPH [11]. Another study, the association ACI, VFA and LUTS in 24 patients with BPH, poorly controlled by an α_1-antagonist, showed that the ACI significantly correlated with VFA, as well as objective voiding parameters of PV and postvoid residual urine volume (PVR) [12]. From these results, we hypothesized that abdominal aortic calcification and VFA might influence LUTS and lower urinary tract function possibly through bladder ischemia and change of BBF. In this study, we investigated the impact of abdominal aortic calcification and VFA on LUTS and clinical parameters in patients with BPH.

Methods

We retrospectively collected data of male patients, aged 50 or older and diagnosed as LUTS associated with BPH (LUTS/BPH), who visited the urology outpatient clinic of Asahikawa Medical University Hospital and Hokkaido Social Welfare Association Furano Hospital from April 2010 to December 2012. Exclusion criteria included diabetes, neurogenic bladder, prostate cancer, bladder cancer, treatment history of LUTS using α_1-adrenoceptor antagonists, antimuscarinics and other drugs for treatment of voiding dysfunction, and other patients whom the physician considered inappropriate for this study.

Each participant was examined with routine examination including measurement of free uroflowmetry at normal desire to void. The possibility of it having an effect on VV results and the correlation cannot be ruled out., PVR and PV measurement by transabdominal ultrasound. Symptom data were collected from all patients including IPSS and OABSS. The OABSS was developed to detect OAB and assess its severity [13]. The OABSS is a symptom

assessment tool designed to combine OAB symptoms into a single score. It consists of four questions on symptoms: Q1; daytime frequency, Q2; night-time frequency, Q3; urgency, and Q4; urgency incontinence. Patients are asked to rate their symptom severity on a scale with a maximum (worst) score of 2 (Q1), 3 (Q2), 5 (Q3) and 5 (Q4), respectively. According to the clinical guidelines for OAB [13], OAB was defined as urinary urgency once a week or more (Q2 $\geq$ 2) and total score of OABSS $\geq$ 3. Total score of OABSS ranges from 0 to 15, with higher scores indicating increasing symptom severity ($\geq$5, mild; 6–11, moderate; $\geq$12, severe) [14]. All patients were assessed with abdominal CT that was performed as a part of health check and evaluation. ACI and VFA were measured by abdominal CT (Aquillion ^{TM} 64, Toshiba, Tokyo, Japan).

Measurement of Abdominal aortic calcification score

We referred and modified to evaluate abdominal aortic calcification, called ACI, in the previous report [15]. We scanned each subject by 7 slices of 1.5 cm intervals between 0 - 9 cm above the aortic bifurcation and the cross-section of the abdominal aorta on each slice was divided into 12 sectors **(Figure 1)**. ACI was calculated by dividing the total number of sectors with calcification in each CT slice by 84 (7x12).

Measurement of visceral fat area

VFA in each subject was automatically determined by an image at the level of the umbilicus using dedicated software on abdominal CT as described previously [16].

Statistical Analysis

All values were expressed as the mean ± SD (standard deviation).

Spearman's rank correlation coefficient was used to analyze statistical significance. Differences were considered to be significant at a *P*-value < 0.05.

Results

We collected the data of a total of 250 men (age 72.4 ± 9.6 years). The data of the patients are shown in **Table 1**. Mean BMI was 23.5 ± 3.3. Mean IPSS total, quality of life (QOL) index and OBSS total were 13.0 ± 7.4, 4.5 ± 0.9 and 2.6 ± 3.0, respectively. Mean voided volume (VV), maximum urinary flow rate (Qmax) on uroflowmetry and PVR were 168.4 ± 94.3 mL, 11.7 ± 5.0 mL/s and 45 ± 61 mL, respectively. Mean PV, ACI and VFA in CT were 34.1 ± 21.6 mL, 0.17 ± 0.19 and 116.0 ± 63.9 cm^2, respectively.

BMI significantly correlated with age (P=0.0009), ACI (P=0.0243) and VFA (P<0.0001). However, there was no relation among BMI, IPSS, OABSS and clinical parameters (data not shown). ACI significantly correlated with age (P<0.0001) and VV (P=0.0392), and tended to correlate with Qmax (P=0.0508). However ACI did not correlate with IPSS or OABSS (**Table 2**). On the other hand, VFA significantly correlated with age (P=0.0008) and nocturia score of IPSS (P=0.0177) and frequency score of OABSS (P=0.0166), and tended to correlate with an urgency score of IPSS (P=0.0531) and Qmax (P=0.0580) (**Table 3**).

Discussion

Considerable evidence suggests a relationship between LUTS, BPH, OAB, Erectile Dysfunction and MetS. Numerous basic and clinical studies

have focused on the relationships between these risk factors and LUTS/BPH [5]. In the present study, there was no relation among BMI, LUTS and clinical parameters in patients with LUTS/BPH. Significant relation between BMI (overweight men) and male LUTS was reported in some studies [17,18], but not in other studies [19-21]. The study design and the study population differed among these reports. Tomita et al showed no relation between BMI and male LUTS in the Japanese [21]. The result of the present study is similar to the Tomita's report. Interestingly, in the present study, VFA significantly correlated with subjective symptoms, especially storage symptoms (nocturia score of IPSS and frequency score of OABSS). The mean urgency scores of IPSS and OABSS of the subjects were low, and this might be a reason why VFA did not correlate with urgency scores. Visceral obesity is known to cause autonomic sympathetic overactivity through complex mechanisms [3]. Autonomic sympathetic overactivity is one of pathophysiological factors for OAB [4,5]. Our results suggest that VFA could influence storage symptoms possibly through interaction with the sympathetic nervous system.

Atherosclerotic diseases cause bladder ischemia and change of BBF that is one of critical factors for LUTS and lower urinary tract dysfunction. In animal studies, bladder fibrosis and bladder dysfunction were more remarkable in rabbits with experimentally-induced atherosclerosis than in rabbits with hypercholesterolemia alone [7]. Moderate bladder ischemia resulted in detrusor overactivity, whereas severe bladder ischemia was associated with impaired detrusor contraction [7]. Yoshida et al. reported myocardial infarction-prone Watanabe Heritable Hyperlipidemic rabbits, an animal model for human familial

hypercholesterolemia and atherosclerosis, showed detrusor overactivity with decreased detrusor contraction [8]. Another study using the rat model of atherosclerosis-induced chronic bladder ischemia showed that reduction in BBF was associated with detrusor overactivity and urinary frequency [9], and that the levels of oxidative stress markers and proinflammatory cytokines were increased in rats with chronic bladder ischemia [10]. In a clinical study using transrectal color Doppler ultrasonography, chronic ischemia of the lower urinary tract was shown in patients with LUTS/BPH [22]. In an analysis of intrapelvic blood flow using dynamic contrast-enhanced magnetic resonance imaging, men with coronary artery disease had lower intrapelvic blood flow than normal men, showing correlations of intrapelvic blood flow with parameters such as LUTS and Erectile Dysfunction [23]. In a recent clinical study, the bladder vascular resistive index was analyzed using transabdominal enhanced Color Doppler Ultrasonography before and after TURP in LUTS/BPH patients. The bladder vascular resistive index significantly correlated with PV and the severity of obstruction by Schaffer nomogram, and overall significantly reduced after TURP [24]. Tarcan et al showed that one possible mechanism contributing to bladder dysfunction with age might be atherosclerosis of the pelvic vascular system [25]. Takahashi et al investigated the severity of atherosclerosis by measuring the thickness of plaques of the carotid artery by ultrasound, and showed the association between the atherosclerosis and lower urinary tract function in male patients with LUTS [26]. Other studies also investigated the influence of vascular risk factors on LUTS [27,28]. Thus, many previous reports have shown that LUTS and lower urinary tract dysfunction develop if underlying diseases, such as

MetS, cause atherosclerotic changes and disturb BBF. The present study suggests that abdominal aortic calcification might have an influence on bladder capacity (VV). ACI correlated with only objective parameter, while VFA correlated with only storage symptoms. Although abdominal aortic calcification and visceral fat obesity seem to affect the overactivity of the sympathetic nervous system and therefore have an influence on LUTS/BPH, interrelationship among arteriosclerosis, visceral fat obesity and LUTS/BPH remains to be further elucidated. Despite these limitations, the present study suggests that ACI and VFA might affect subjective and objective parameters in patients with LUTS/BPH.

Abbreviations & Acronyms

MetS: metabolic syndrome

LUTS: lower urinary tract symptoms

BPH: benign prostatic hyperplasia

OAB: overactive bladder symptom

ACI: aortic calcification index

VFA: visceral fat area

IPSS: International Prostatic Symptom Score

OABSS: overactive bladder symptom score

PV: prostate volume

BMI: Body mass index

BBF: bladder blood flow

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Conflict of interest. None declared

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Tables Legends

Table 1. Patients' data.

Table 2. Results of correlation with ACI.

Table3. Results of correlation with VFA.

Figure 1. Measurement of ACI by abdominal CT.

Table 1.

		Mean	SD
Age (years)		72.4	9.6
BMI		23.5	3.3
IPSS total		13.0	7.4
	1. Incomplete Emptying	2.2	1.4
	2. Frequency	2.1	1.4
	3. Intermittency	1.5	1.5
	4. Urgency	0.7	1.3
	5. Weak Stream	4.3	1.2
	6. Straining	2.6	1.5
	7. Nocturia	2.5	1.1
QOL index		4.5	0.9
OABSS total		2.6	3.0
	1. Frequency	0.4	0.5
	2. Nocturia	2.4	0.9
	3. Urgency	0.9	1.5
	4. Urge Incontinence	0.4	1.1
UFM	VV (mL)	168.4	94.3
	Qmax (mL/s)	11.7	5.0
PVR (mL)		45.0	60.9
PV (mL)		34.1	21.6
AAC score		0.17	0.19
VFA (cm^2)		116.0	63.9

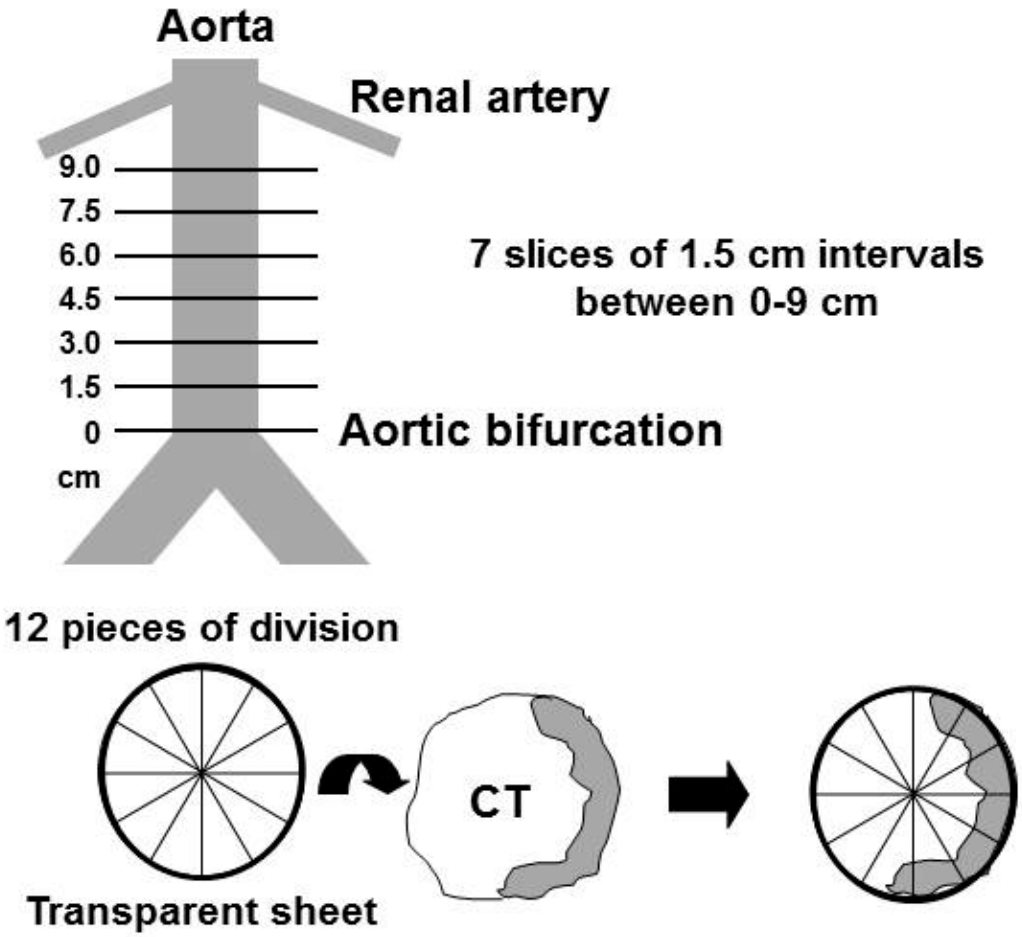
Table 2.

		Spearman's rank correlation coefficient	P-value
Age (years)		0.35637	<0.0001
IPSS total		0.03621	0.5751
	1. Incomplete Emptying	-0.0703	0.3238
	2. Frequency	0.01181	0.8685
	3. Intermittency	0.05941	0.4045
	4. Urgency	0.02511	0.7248
	5. Weak Stream	0.06985	0.3269
	6. Straining	-0.02583	0.7173
	7. Nocturia	0.05883	0.4091
QOL index		0.10303	0.1476
OABSS total		0.07618	0.2338
	1. Frequency	-0.00902	0.9093
	2. Nocturia	0.0573	0.4689
	3. Urgency	0.08762	0.2675
	4. Urge Incontinence	0.11102	0.1596
UFM	VV (mL)	-0.1414	0.0392
	Qmax (mL/s)	-0.13403	0.0508
PVR (mL)		-0.00575	0.9336
PV (mL)		-0.03987	0.5337
VFA (cm2)		-0.01902	0.7666

Table3.

		Spearman's rank correlation coefficient	P-value
Age (years)		-0.2114	0.0008
IPSS total		-0.00597	0.9259
	1. Incomplete Emptying	0.10199	0.1487
	2. Frequency	-0.08706	0.2180
	3. Intermittency	0.0162	0.8190
	4. Urgency	-0.13632	0.0531
	5. Weak Stream	0.08136	0.2497
	6. Straining	0.02017	0.7758
	7. Nocturia	-0.16671	0.0177
QOL index		-0.0802	0.2565
OABSS total		-0.04754	0.4552
	1. Frequency	-0.18796	0.0166
	2. Nocturia	-0.06017	0.4469
	3. Urgency	-0.13843	0.0790
	4. Urge Incontinence	-0.1342	0.0886
UFM	VV (mL)	0.05905	0.3878
	Qmax (mL/s)	0.12918	0.0580
PVR (mL)		0.08192	0.2305
PV (mL)		-0.01401	0.8259
AAC score		-0.01902	0.7666

Figure 1.


Aorta
Renal artery
9.0
7.5
6.0
4.5
3.0
1.5
0
cm
7 slices of 1.5 cm intervals
between 0-9 cm
Aortic bifurcation
12 pieces of division
CT
Transparent sheet