



Clinical Significance of Periurethral Calcification According to the Location in Men With Lower Urinary Tract Symptoms and a Small Prostate Volume

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Purpose: To assess the impact of periurethral calcification (PUC) according to its location on uroflowmetric parameters and urinary symptoms in patients with small prostate volume (PV).

Methods: Records were obtained from a prospectively maintained database of first-visit men with lower urinary tract symptoms (LUTS). Patients whose PV was > 30 mL were excluded to elucidate more clearly the impact of PUC on LUTS. A total of 539 patients were enrolled in the study. The prostatic urethra was examined by transrectal ultrasonography for PUC, and the location of PUC was divided into 3 areas (proximal, mid, and distal).

Results: The characteristics according to the location of PUC were compared using a 1-way analysis of variance test. The Total International Prostate Symptom Score (IPSS), postmicturition symptoms, and overactive bladder symptom score (OABSS) differed significantly among the groups. In the propensity score matching analysis, the proximal- and distal-PUC groups did not have a significantly different urinary flow rate or symptom score when compared to their matched control groups. However, the mid-PUC group had significantly worse urinary symptoms than its matched control group (total IPSS [P=0.001], voiding symptoms [P=0.002], storage symptoms [P=0.041], and OABSS [P=0.015]). The peak urinary flow rate was also lower in the mid-PUC group with borderline significance (P=0.082). On multivariate linear regression analysis, mid-PUC was independently associated with IPSS and OABSS (P=0.035 and P=0.011, respectively).

Conclusions: Only mid-PUC was associated with symptom severity in men with LUTS and a small PV. Our findings suggest that mid-PUC could be a potential causal factor of LUTS, and the midportion of the prostatic urethra might play a pivotal role in the process of micturition.

Keywords: Urethra; Prostatic hyperplasia; Lower urinary tract symptoms; Calculi; Inflammation

- **Research Ethics:** The study was performed in accordance with applicable laws and regulations, good clinical practices, and ethical principles as described in the Declaration of Helsinki. This study protocol was approved by the Institutional Review Board of Gangnam Severance Hospital (approval number: 3-2016-0149). Written informed consent was obtained from all subjects.
- **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Lower urinary tract symptoms (LUTS) are known to be closely

related to benign prostatic enlargement, benign prostatic obstruction (BPO), and benign prostatic hyperplasia (BPH). Accordingly, the “static” prostate enlargement determined by the

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tone of the prostate and “dynamic” alpha-receptor-mediated smooth muscle tension are regarded as 2 major components connected to male LUTS [1]. However, in clinical practice, approximately half of LUTS patients have a relatively small prostate (30 mL or less) [2] and undoubtedly have a weaker correlation with those volume factors. Moreover, urodynamic findings showed that only half of the patients demonstrated bladder outlet obstruction in LUTS patients with a small prostate volume (PV), indicating the heterogeneity of this disease [3]. For this reason, several anatomical prostatic factors, such as the transitional zone index (TZI) and prostatic urethral angle (PUA), rather than simple volume parameters, have been investigated [4,5].

Male LUTS has a multifactorial etiology, and, recently, a third major hypothetical factor has been proposed, prostatic inflammation [1]. In particular, inflammation of the periurethral area, which ultimately induces periurethral fibrosis, could maximize induction of LUTS [6]. Although the etiology of prostatic calcification remains unclear, calcification of the urethra can, similar to other tissues, result in urethral stiffness [7,8]. Based upon this theoretical hypothesis, we have previously demonstrated the significant impact of periurethral calcification (PUC) on LUTS.

To more clearly elucidate the impact of PUC on LUTS, the volume factor was purely confined in this study ($PV \leq 30$ mL). Herein, we evaluated the association between PUC, urinary symptoms, and uroflowmetric measurements with a small PV and further analyzed the clinical impact of PUC according to its location (proximal, mid, or distal) on the prostatic urethra.

MATERIALS AND METHODS

Patient Cohort

This study is a retrospective analysis of a prospectively maintained database of male patients with LUTS/BPH who had their initial visit at our outpatient clinic between April 2010 and April 2013. During this period, 1,199 patients were registered in our database. A detailed medical history was obtained for patients aged 40 to 80 years after excluding the following conditions that are potential LUTS inducing factors: (1) clinically apparent bladder or prostate cancer, (2) neurologic disease that could influence voiding symptoms, (3) uncontrolled diabetes mellitus, (4) history of a previous lower urinary tract surgery, (5) history of radiotherapy to the pelvis, and (6) urinary tract infections. A total of 1,030 patients were initially enrolled, and those with a

total prostate volume (TPV) > 30 mL were excluded. Finally, 539 patients were eligible for the final analysis.

Good Clinical Practice Protocols

The study was performed in accordance with applicable laws and regulations, good clinical practices, and ethical principles as described in the Declaration of Helsinki. This study protocol was approved by the Institutional Review Board of Gangnam Severance Hospital (approval number: 3-2016-0149). Written informed consent was obtained from all subjects.

Assessment of Urinary Symptoms and Uroflowmetric Measurements

LUTS were evaluated using the International Prostate Symptom Score (IPSS), quality of life score, and overactive bladder symptom score (OABSS). The total IPSS was subcategorized into voiding, storage, and postmicturition symptom scores. For uroflowmetric measurements, maximum urinary flow rate (Q_{max}) and postvoid residual volume (PVR) were evaluated. Both uroflowmetric and PVR measurements were repeated if the voided volume was < 125 mL. The assessment was made using Bluetooth uroflowmetry (Urodyn+; Mediwatch Ltd., Rugby, UK) and a bladder scanner (BioCon-500; MCube Technology Co., Ltd, Seoul, Korea).

Assessment of Prostatic Anatomical Factors

Transrectal ultrasonography (TRUS) was performed on all subjects (Prosound Alpha 5 SV, Hitachi Aloka Medical, Ltd., Tokyo, Japan [between April 2010 and November 2012]; Pro Focus 2202 Ultrasound System, BK-Medical, Herlev, Denmark [between December 2012 and April 2013]). TPV and transitional zone volume (TZV) were measured using the prolate ellipsoid formula ($\text{height} \times \text{width} \times \text{length} \times \pi/6$). The TZI was calculated according to the formula, $TZI = TZV/TPV$ [9].

Prostatic calculi were viewed and scored in both axial and sagittal planes. Two investigators (JHH and JKK) independently determined the degree of prostatic calculi. Disagreement between the 2 investigators was resolved by a discussion with another investigator (KSC). The prostatic urethra was examined along the midsagittal plane. PUC was assessed for all of the sagittal images taken serially on TRUS, and we defined PUC as prostatic calcification that is within 2 mm of the prostatic urethra on the sagittal view of TRUS [10]. According to the classical definition demonstrated by Harada et al. [11], prostatic calcification demonstrating a burden or mass along the prostatic

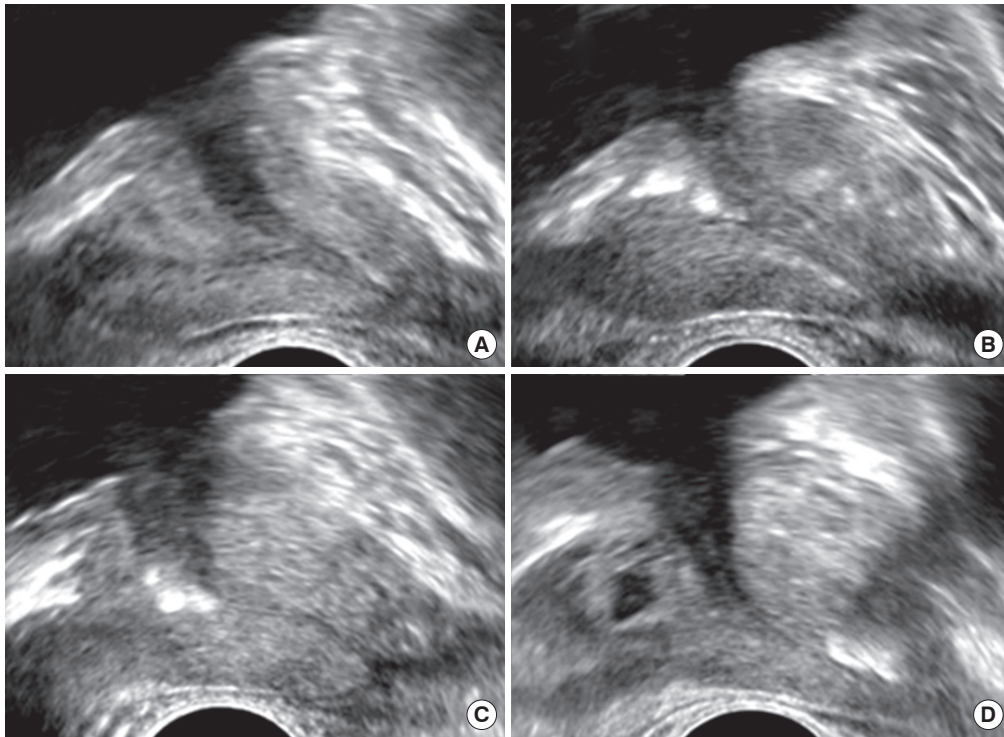


Fig. 1. Representative images of the 3 groups of periurethral calcification (PUC) according to their location on the midsagittal plane during transrectal ultrasonography. Midsagittal plane demonstrating the trace of the urethra without PUC (A), proximal PUC (B), mid-PUC (C), and distal PUC (D).

urethra was considered to be a clinically significant PUC, while the absence of or a small solitary calcification was considered to be an insignificant PUC. Overall PUC was determined based on the proportion of the urethra with significant calcification to the entire prostatic urethral length. The location of the PUC was divided into 3 consecutive nonoverlapping periurethral areas (proximal 1/3, middle 1/3, and distal 1/3) (Fig. 1).

Statistical Analysis

A 1-way analysis of variance (ANOVA) test was applied to compare the clinical characteristics of the 3 different PUC groups according to the location of the PUC. To clarify our comparisons, we targeted the patients that had PUC only in one location (proximal PUC only, mid-PUC only, or distal PUC only). Using a propensity score matching analysis, the volume factor (TPV), age, and voided volume were matched, and each PUC group was sequentially compared to their matched control group using a paired t-test. All statistical analyses were performed using R software (version 3.0.3, R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org>). A P-value <0.05 was considered statistically significant,

and all statistical tests were 2-sided.

RESULTS

As the result of interobserver reliability measurement, we recorded intraclass correlation coefficients for a PUC of 0.981 (95% confidence interval, 0.978–0.983), which indicates an excellent reliability. In terms of the patient baseline characteristics, the mean patient age was 60.03 ± 10.00 years, and the mean TPV and mean TZV were 23.05 ± 4.12 and 9.71 ± 2.88 , respectively. On the midsagittal plane, overall PUC was classified into 3 groups. The numbers of patients with no, mild, and moderate to severe PUC were 351 (65.1%), 126 (23.4%), and 62 (11.5%), respectively. Regarding the distribution of PUC location, the number of patients in the proximal-, mid-, and distal-PUC groups were 79 (14.7%), 124 (23.0%), and 69 (12.8%) (Table 1).

We included 117 out of 539 patients (21.7%) who had only one location with PUC in the 1-way ANOVA test. The proximal-PUC only (p-PUC), mid-PUC only (m-PUC), and distal-PUC only (d-PUC) groups were composed of 35, 63, and 19 patients, respectively. The 3 groups significantly differed in the

Table 1. Clinical features of subjects (n = 539)

Variable	Value
Age (yr)	60.03 ± 10.00
Comorbidities	
Hypertension	179 (33.2)
Diabetes mellitus	91 (16.9)
Serum prostate-specific antigen (ng/mL)	1.29 ± 1.54
IPSS	
Total	16.61 ± 7.22
Voiding symptoms	7.48 ± 3.86
Storage symptoms	6.58 ± 3.40
Postmicturition symptoms	2.55 ± 1.60
Quality of life score	3.90 ± 1.11
OABSS	4.54 ± 3.20
Uroflowmetry	
Qmax (mL/s)	15.25 ± 7.53
Voided volume (mL)	285.33 ± 159.00
Postvoid residual volume (mL)	25.44 ± 39.11
Prostate volume parameters	
Total prostate volume (mL)	23.05 ± 4.12
Transitional zone volume (mL)	9.71 ± 2.88
Transitional zone index	0.42 ± 0.97
Prostatic calcification	
Overall periurethral calcification	
None	351 (65.1)
Mild	126 (23.4)
Moderate to severe	62 (11.5)
Location of periurethral calcification ^{a)}	
Proximal periurethral calcification	79 (14.7)
Mid periurethral calcification	124 (23.0)
Distal periurethral calcification	69 (12.8)

Values are presented as mean ± standard deviation or number (%). IPSS, International Prostate Symptom Score; OABSS, overactive bladder symptom score; Qmax, maximum urinary flow rate.

^{a)}A number of patients have been counted multiple times.

total IPSS, postmicturition symptoms, and OABSS, and the m-PUC group displayed the worst symptom scores in all fields, followed by the p-PUC and d-PUC groups. Total IPSS for the m-PUC group was 19.3 ± 7.5, compared to 16.5 ± 6.0 and 14.7 ± 7.2 for the p-PUC and d-PUC groups, respectively ($P = 0.026$). Postmicturition symptoms were 3.0 ± 1.6 vs. 2.3 ± 1.5 and 2.1 ± 1.4, respectively ($P = 0.016$). OABSS was 5.9 ± 3.8 vs. 4.1 ± 3.3 and 3.8 ± 2.1, respectively ($P = 0.017$). There were no differences in the mean patient age or total PV among the three groups (Table 2).

Propensity score matching analysis was performed for each group (p-PUC, m-PUC, and d-PUC). Neither the p-PUC or d-PUC groups demonstrated any significant impact on urinary symptoms or Qmax when compared to their matched control

group (Tables 3, 4). However, the m-PUC group displayed significantly worse urinary symptoms than its matched control group (Total IPSS [19.3 ± 7.5 vs. 16.2 ± 6.8, $P = 0.001$], voiding symptoms [8.7 ± 4.0 vs. 7.3 ± 3.6, $P = 0.002$], storage symptoms [7.5 ± 3.5 vs. 6.4 ± 3.3, $P = 0.041$], and OABSS [5.9 ± 3.8 vs. 4.2 ± 3.2, $P = 0.015$]). Qmax was also lower in the m-PUC group, with borderline significance (13.7 ± 5.3 and 15.7 ± 7.9, $P = 0.082$) (Table 5).

To confirm the independent clinical power of PUC, we performed univariate and multivariate linear regression analysis following propensity score matching analysis. For the multivariate model, variables proven significant in univariate analysis were taken into account. Multivariate linear regression analysis showed age, TZI, and m-PUC significantly affected IPSS total ($P = 0.002$, $P = 0.016$, and $P = 0.035$, respectively). For the OABSS, only age and m-PUC were independently correlated ($P < 0.001$ and $P = 0.011$, respectively) (Table 6).

DISCUSSION

Male LUTS associated with a small PV represents approximately half of the total LUTS patients [2]. This ratio was also consistent with our data (539 of 1,030, 52.3%). Because the number of LUTS patients has increased over time, there have been several efforts to search for the significant prostatic anatomical parameters capable of predicting male LUTS, such as intravesical prostatic protrusion, TZI, presumed circle area ratio, peripheral zone thickness, and PUA. However, despite the high proportion of patients that have a small PV (< 30 mL), only PUA and TZI have been shown to be independent factors affecting LUTS in this group [4,5].

LUTS in patients with a small PV is being highlighted due to the difference in its characteristics compared to those of general LUTS/BPH. Small PV LUTS patients are not likely to have BPO. The classical dynamic and static components of the prostate cannot explain the exact pathophysiology of small PV LUTS. The 5-alpha-reductase inhibitor finasteride has been shown in large cohort studies to have unsatisfactory results in small PV patients [12]. Alpha blockers play a role in reducing dynamic obstruction; however, outcome data is variable regarding small PV, making achieving a reliable assessment of the effects of medical treatments more difficult [13].

We focused on prostatic inflammation in small PV. For general LUTS/BPH, prostatic inflammation in a previous study was correlated with symptomatic progression, risk for urinary

Table 2. Comparisons of clinical features according to location of periurethral calcification (PUC)

Variable	Total (n = 117)	Proximal-PUC (n = 35)	Mid-PUC (n = 63)	Distal-PUC (n = 19)	P-value
Age (yr)	62.0 ± 9.9	61.7 ± 10.5	61.7 ± 9.7	63.6 ± 10.0	0.752
Serum prostate-specific antigen (ng/mL)	1.2 ± 1.2	1.2 ± 1.1	1.1 ± 1.0	1.6 ± 1.6	0.153
IPSS					
Total	17.7 ± 7.2	16.5 ± 6.0	19.3 ± 7.5	14.7 ± 7.2	0.026
Voiding symptoms	8.0 ± 3.8	7.4 ± 3.5	8.7 ± 4.0	6.8 ± 3.5	0.083
Storage symptoms	7.1 ± 3.6	6.8 ± 3.7	7.5 ± 3.5	5.9 ± 3.1	0.186
Postmicturition symptoms	2.7 ± 1.6	2.3 ± 1.5	3.0 ± 1.6	2.1 ± 1.4	0.016
Quality of life score	4.1 ± 1.1	4.1 ± 1.0	4.1 ± 1.1	3.7 ± 1.0	0.355
OABSS	5.0 ± 3.6	4.1 ± 3.3	5.9 ± 3.8	3.8 ± 2.1	0.017
Uroflowmetry					
Qmax (mL/s)	14.0 ± 6.8	14.1 ± 8.5	13.7 ± 5.3	15.2 ± 7.7	0.696
Voided volume (mL)	254.9 ± 136.9	282.2 ± 141.0	238.1 ± 111.9	260.0 ± 193.9	0.308
Postvoid residual volume (mL)	26.3 ± 45.0	26.4 ± 35.6	28.0 ± 52.8	20.1 ± 31.1	0.801
Prostate volume parameters					
Total prostate volume (mL)	23.1 ± 4.5	22.5 ± 4.4	23.9 ± 4.2	21.6 ± 5.3	0.113
Transitional zone volume (mL)	10.1 ± 3.0	9.6 ± 2.8	10.7 ± 3.1	9.0 ± 2.4	0.036
Transitional zone index	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.394

Values are presented as mean ± standard deviation.

IPSS, International Prostate Symptom Score; OABSS, overactive bladder symptom score; Qmax, maximum urinary flow rate.

Table 3. Matched cohorts of proximal periurethral calcification (PUC) present vs. absent groups using propensity scores

Variable	Total (n = 70)	Matched Cohort		P-value
		Proximal PUC (-) (n = 35)	Proximal PUC (+) (n = 35)	
Age (yr)	62.0 ± 10.8	62.4 ± 11.1	61.7 ± 10.5	0.695
Total prostate volume (mL)	22.7 ± 4.4	23.0 ± 4.3	22.5 ± 4.4	0.688
Transitional zone volume (mL)	9.4 ± 2.7	9.2 ± 2.6	9.6 ± 2.8	0.593
Transitional zone index	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.157
Qmax (mL/sec)	14.2 ± 7.9	14.3 ± 7.2	14.1 ± 8.5	0.929
Voided volume (mL)	279.6 ± 147.1	277.1 ± 155.0	282.2 ± 141.0	0.861
Postvoid residual volume (mL)	28.3 ± 35.5	30.2 ± 35.7	26.4 ± 35.6	0.687
IPSS				
Total	16.8 ± 6.7	17.0 ± 7.4	16.5 ± 6.0	0.780
Voiding symptoms	7.5 ± 3.6	7.6 ± 3.8	7.4 ± 3.5	0.877
Storage symptoms	6.8 ± 3.6	6.8 ± 3.5	6.8 ± 3.7	0.973
Postmicturition symptoms	2.5 ± 1.5	2.6 ± 1.4	2.3 ± 1.5	0.434
Quality of life score	4.0 ± 0.9	4.0 ± 0.8	4.1 ± 1.0	0.681
OABSS	4.7 ± 3.4	5.3 ± 3.4	4.1 ± 3.3	0.180

Values are presented as mean ± standard deviation.

Qmax, maximum urinary flow rate; IPSS, International Prostate Symptom Score; OABSS, overactive bladder symptom score.

retention, and the need for surgery [14]. Complete understanding of the inflammatory process and its pathogenesis is still in progress; however, inflammation is emerging as the new targeted process for male LUTS [15]. Within the prostate's anatomic structure, inflammation of the periurethral region, leading to periurethral fibrosis, was recently highlighted as a LUTS-induc-

ing factor [6,16-18]. Cantiello et al. [19] assessed periurethral tissues from radical prostatectomy specimens and suggested that fibrotic changes in periurethral prostatic tissues induced by prostate inflammation may eventually promote urethral stiffness and LUTS. Kim et al. [16] tested the association between prostate elasticity and LUTS with a novel palpation system (In-

Table 4. Matched cohorts of distal periurethral calcification (PUC) present vs. absent groups using propensity scores

Variable	Total (n = 38)	Matched Cohort		P-value
		Distal PUC (-) (n = 19)	Distal PUC (+) (n = 19)	
Age (yr)	62.8 ± 10.4	62.0 ± 11.1	63.6 ± 10.0	0.449
Total prostate volume (mL)	21.4 ± 5.0	21.2 ± 4.8	21.6 ± 5.3	0.670
Transitional zone volume (mL)	9.3 ± 2.5	9.6 ± 2.6	9.0 ± 2.4	0.360
Transitional zone index	0.4 ± 0.1	0.5 ± 0.0	0.4 ± 0.1	0.110
Qmax (mL/sec)	14.1 ± 7.4	12.9 ± 7.2	15.2 ± 7.7	0.186
Voided volume (mL)	240.1 ± 161.1	220.2 ± 122.2	260.0 ± 193.9	0.436
Postvoid residual volume (mL)	19.3 ± 28.1	18.6 ± 25.6	20.1 ± 31.1	0.857
IPSS				
Total	15.8 ± 7.5	16.8 ± 7.8	14.7 ± 7.2	0.451
Voiding symptoms	7.4 ± 3.8	8.0 ± 4.1	6.8 ± 3.5	0.377
Storage symptoms	6.2 ± 3.2	6.4 ± 3.3	5.9 ± 3.1	0.633
Postmicturition symptoms	2.2 ± 1.5	2.4 ± 1.7	2.1 ± 1.4	0.578
Quality of life score	3.8 ± 1.1	3.9 ± 1.2	3.7 ± 1.0	0.680
OABSS	4.3 ± 2.8	4.8 ± 3.4	3.8 ± 2.1	0.214

Values are presented as mean ± standard deviation.

Qmax, maximum urinary flow rate; IPSS, International Prostate Symptom Score; OABSS, overactive bladder symptom score.

Table 5. Matched cohorts of mid-periurethral calcification (PUC) present vs. absent groups using propensity scores

Variable	Total (n = 126)	Matched Cohort		P-value
		Mid-PUC (-) (n = 63)	Mid-PUC (+) (n = 63)	
Age (yr)	61.4 ± 9.5	61.1 ± 9.3	61.7 ± 9.7	0.755
Total prostate volume (mL)	24.1 ± 3.8	24.3 ± 3.3	23.9 ± 4.2	0.455
Transitional zone volume (mL)	10.5 ± 2.8	10.4 ± 2.6	10.7 ± 3.1	0.499
Transitional zone index	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.369
Qmax (mL/sec)	14.7 ± 6.8	15.7 ± 7.9	13.7 ± 5.3	0.082
Voided volume (mL)	257.9 ± 134.7	277.7 ± 152.5	238.1 ± 111.9	0.124
Postvoid residual volume (mL)	30.3 ± 48.4	32.5 ± 43.8	28.0 ± 52.8	0.611
IPSS				
Total	17.7 ± 7.3	16.2 ± 6.8	19.3 ± 7.5	0.001
Voiding symptoms	8.0 ± 3.9	7.3 ± 3.6	8.7 ± 4.0	0.002
Storage symptoms	6.9 ± 3.5	6.4 ± 3.3	7.5 ± 3.5	0.041
Postmicturition symptoms	2.8 ± 1.6	2.6 ± 0.6	3.0 ± 1.6	0.055
Quality of life score	4.0 ± 1.0	3.9 ± 0.9	4.1 ± 1.1	0.137
OABSS	5.1 ± 3.6	4.2 ± 3.2	5.9 ± 3.8	0.015

Values are presented as mean ± standard deviation.

Qmax, maximum urinary flow rate; IPSS, International Prostate Symptom Score; OABSS, overactive bladder symptom score.

denter) and showed that prostate elasticity was independently associated with voiding symptoms. Based on these studies, periurethral fibrosis can be assumed to be a cause of LUTS through decreased urethral flexibility while compromising the ability of the prostatic urethra to enlarge to adequately accommodate urinary flow during micturition [10,19].

Prostatic calcification has a pathological connection with prostatic inflammation and fibrosis. The etiology of prostatic calcification is not yet fully understood; however, studies at the molecular level have shown that calcifications induced by inflammation generate a microenvironment that drives more inflammatory change, characterized by lymphocyte infiltration,

Table 6. Multivariate linear regression analysis of prostatic parameters for IPSS and OABSS

Variable	International Prostate Symptom Score				Overactive bladder symptom score			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Standardized coefficient β	P-value	Standardized coefficient β	P-value	Standardized coefficient β	P-value	Standardized coefficient β	P-value
Age	0.165	<0.001	0.136	0.002	0.269	<0.001	0.246	<0.001
TPV	-0.017	0.714	-	-	-0.028	0.537	-	-
TZV	0.099	0.027	-0.065	0.383	0.069	0.123	-	-
TZI	0.151	0.001	0.181	0.016	0.109	0.015	0.072	0.097
p-PUC	0.042	0.355	-	-	0.021	0.647	-	-
m-PUC	0.116	0.01	0.094	0.035	0.145	0.001	0.111	0.011
d-PUC	-0.025	0.578	-	-	0.011	0.8	-	-

IPSS, International Prostate Symptom Score; OABSS, overactive bladder symptom score; TPV, total prostate volume; TZV, transitional zone volume; TZI, transitional zone index; p-PUC, proximal periurethral calcification; m-PUC, mid periurethral calcification; d-PUC, distal periurethral calcification.

cytokine activation, and release of reactive oxygen species [20-22]. Prostatic calcification is not synonymous with prostatic fibrosis, but chronic inflammation can eventually lead to fibrosis-related calcification, a proven phenomenon in other tissues [23-25]. If inflammation induces urethral calcification, this process can, as shown in other tissues, affect urethral stiffness [7,8].

In this study, PUC was proposed as an independent risk factor for male small PV LUTS. Notably, this is the first trial to assess PUC according to its location and to demonstrate that PUC is independently associated with worse urinary symptom scores in a small PV. We previously reported that overall PUC was associated with Qmax, total IPSS, and storage symptoms in TPV [10]. However, in the current study overall PUC was only associated with the Qmax when limited to small PV (data not shown). Taking these findings together, we can deduce that periurethral inflammation has a more synergistic effect on male LUTS if accompanied by a larger prostate.

The degree of overall PUC according to TPV in those with a small PV was similar (none, mild, moderate to severe: 63.5%, 22.6%, and 13.9% vs. 65.1%, 23.4%, and 11.5%). The mean age difference between the 2 trials was approximately 2 years, and the mean PV difference was approximately 10 g (i.e., the TPV group was older and had larger prostates).

For the proximal PUC, we considered this presentation to be inflammation and fibrosis of the proximal prostatic urethra and bladder neck, which could hypothetically play a major role in micturition initiation. In clinical practice, primary bladder neck obstruction without BPH is related to a reduced flow rate and higher urinary symptom scores by disturbing bladder neck re-

laxation during the voiding phase. Its etiology varies, and one of the etiologies is known to be an inflammatory-induced fibrotic change [26,27]. However, in this study we failed to prove any clinical relevance of the p-PUC group with the peak urinary flow rate or urinary symptoms. A future study should be undertaken to evaluate the potential relationship between bladder neck calcification and endoscopically proven bladder neck obstruction.

Additionally, the d-PUC group also failed to show any significant impact on the peak urinary flow rate or urinary symptom scores. In the one-way ANOVA test comparing the uroflowmetric measurements and urinary symptom scores among the 3 different PUC groups (p-PUC, m-PUC, and d-PUC), the patient with distal-PUC typically had the best outcomes compared to the p-PUC and m-PUC groups. From this result, conversely, we provisionally conclude that the distal portion of the prostatic urethra has a minimal role in the micturition process compared to the proximal and midportions.

Distinct from the p-PUC and d-PUC groups, the m-PUC group showed a significant impact on most of the urinary symptoms in patients with a small PV. There have been several studies demonstrating urethral movement during the voiding phase. Ukimura et al. [28] reported that the prostatic urethra is pulled upward in a ventral direction toward the pubic bone during voiding. This theory is consistent with PUA mechanics; the urethra tends to reduce its resistance by reducing the PUA by moving ventrally, consequently straightening the urethra. However, if the PUA remains high due to limited movement induced by PUC, energy loss proportional to the PUA could

occur during micturition and could result in a decrease in urine velocity, consequently causing LUTS [4,29]. Theoretically, due to the mid-PUC leading to midperiurethral fibrosis, the PUA could have a fixed tone, causing ineffective voiding, and ultimately causing LUTS. From the urethral dynamic mechanics proven above, we believe these significant findings regarding the mid-PUC indirectly support the idea that the midportion of the prostatic urethra is a clinically important region with respect to male LUTS.

However, our study has some limitations. First, this study included a small number of subjects; thus, further study with a larger cohort is needed to draw a more objective and concise conclusion regarding PUC in patients with a small PV. Although PUC, inflammation, and fibrosis are hypothetically mutually related, it remains unclear whether these 3 factors have the same impact on LUTS or not [10]. Studies on the differences in pathological prostatic tissue according to varying prostate PUC location are warranted. Regarding proximal PUC, further study is required to assess the relationship between the proximal-PUC group and bladder neck fibrosis, accompanied by a pathological and mechanical analysis. Furthermore, a meticulous assessment of the dynamic movement of the urethra is still imperative, and additional controlled prospective studies regarding the effect of urethral stiffness on the 3-dimensional movement of the urethra should be described in future studies.

In conclusion, only mid-PUC was associated with urinary symptom severity in men with LUTS and a small PV. Our findings suggest that the mid-PUC could be a potential causal factor of LUTS, and the midportion of the prostatic urethra might play a pivotal role in the process of micturition.

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