LUTS and BOO

Indenter Study: Associations Between Prostate Elasticity and Lower Urinary Tract Symptoms

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OBJECTIVE
To investigate the associations between prostate elasticity and lower urinary tract symptoms (LUTS).

METHODS
From August 2009 to December 2009, 48 patients with no history of neoadjuvant therapy or previous prostate surgery who underwent robot-assisted radical prostatectomy were included in this study. A novel palpation system was used to measure the tissue elasticity of the prostate specimens. The elasticity of the prostate was defined as the mean elastic modulus (kilopascals [kPa]) of 21 sites from the posterior surface of prostate. All patients completed an International Prostate Symptoms Score questionnaire before surgery, and LUTS was defined as an International Prostate Symptoms Score total of ≥8. Significant voiding symptoms were identified by a score of ≥5 on the basis of patient responses to 4 questions (Q1, Q3, Q5, and Q6), and storage symptoms were identified by a score ≥4 on the basis of patient responses to 3 questions (Q2, Q4, and Q7).

RESULTS
The median elastic modulus of the prostate was 20.8 kPa (interquartile range 15.6-22.9), and the LUTS incidences and voiding symptoms were significantly higher in patients with an elastic modulus >20 kPa. The multivariate logistic regression results indicated that a higher elastic modulus (as a continuous variable) was independently associated with voiding symptoms (odds ratio 1.18, \(P = .038\)) after controlling for age and prostate volume. However, the elastic modulus was not independently associated with LUTS or storage symptoms.

CONCLUSION
Patients with greater prostate stiffness are more likely to develop LUTS. Specifically, prostate elasticity was independently associated with voiding symptoms.

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ower urinary tract symptoms (LUTS) are commonly experienced by older men, and numerous factors have been attributed to their development. Several studies have suggested that there is a correlation between LUTS and lifestyle or metabolic factors. An anatomic change of the lower urinary tract along with aging is also important in LUTS etiology. Prostate has a significant role in LUTS in older men, and microscopic and macroscopic changes of the prostate are related to the development of LUTS. Benign prostatic hyperplasia secondary to unregulated overgrowth of the prostate gland precipitates bladder outlet obstruction and has been associated with an increased risk of LUTS and medical or surgical treatment. However, although prostate volume is an objective and quantitative measure of benign prostatic hyperplasia, the etiology of LUTS related to prostate in older men cannot be fully elucidated by prostate volume alone. Several researchers suggested that the extent to which the prostate protrudes into the bladder or the configuration of the prostate might have clinical significance for predicting bladder outlet obstruction. In addition, the concept of the prostatic urethral angle has also been proposed as an explanation for LUTS etiology.

Recently, Ma et al proposed that prostatic fibrosis could be a potential contributing factor to LUTS. Fibrotic change is associated with dysfunction and disease of the organs, and prostatic fibrosis could increase the mechanical stiffness of the periurethra and might affect urinary outflow.
We previously performed an indenter study with a robotic palpation system; that study measured the prostate tissue elasticity in patients who underwent radical prostatectomy to develop a tissue elasticity map for prostate cancer localization. In this study, we investigated the association between the prostate elasticity and LUTS using posthoc analysis of an indenter study.

MATERIALS AND METHODS

Patients and Data Collection
Between August 2009 and December 2009, 117 consecutive patients underwent robot-assisted radical prostatectomy for localized prostate cancer, which was performed by a single surgeon. Nine patients with neoadjuvant treatment and 5 patients with prostate surgery history were excluded from this study. Ultimately, 48 patients who consented to undergo measurement of prostate elasticity were included in this study. All patients provided written informed consent, and the study was approved by the institutional review board (no.: 4-2009-0140). Preoperative prostate-specific antigen (PSA), age, clinical stage, and the Gleason score from the biopsy were recorded. Pathologic stage, pathologic Gleason score, prostate weight, and tumor volume were determined from the pathologic evaluation. The prostate volume was determined by assuming that the prostatic tissue was primarily composed of water, and the weight was converted from grams to milliliters (1 g H₂O = 1 mL H₂O).

Prostate Elasticity Measurement
The palpation system and the mechanical experiments that were used to measure the prostate elasticity were described in detail in our previous report. The robotic system was designed to measure the tissue behavior against mechanical loading. The system consisted of a force transducer (Kistler Instrument), a hemisphere tip probe (Misumi), a linear motion actuator, a linear position sensor (Piezo-tech), housings, and a connector (Fig. 1). This system was linearly operated, and the reaction force was measured with the force transducer. The experiment was performed on the prostate specimen within 30 minutes after the specimen was extracted and before the specimen being delivered to the pathology department. The probe tip was placed in contact with the tissue, and the tissue was palpated at a rate of 1 mm/s. The reaction force from the deformed tissues was measured by a force transducer and recorded in a data acquisition system.

The experiments were performed at 21 sites across the posterior surface (Fig. 2), and the reaction force against the induced palpations was measured. The mechanical property of the tissue was presented as the elastic modulus (Young’s modulus, E), as calculated using the equation as the following. The Hertz-Sneddon equation was used to estimate the elastic modulus of the tissue. The radius of the probe was designated as R (1 mm), δ was the depth of the indentation (3 mm), f was the measured force, and v was the Poisson’s ratio (an incompressible material is approximately 0.499).

$$E = \frac{3}{4} \times \left(1 - \nu^2\right) \times \frac{f}{\left(R \times \delta^2\right)^{1/2}}$$

LUTS Measurement
The preoperative LUTS were routinely evaluated using the International Prostate Symptoms Score. The presence of LUTS was defined as an International Prostate Symptoms Score total of ≥8. Voiding symptoms were identified by a score ≥5 and were based on patient responses to 4 questions (Q1, Q3, Q5, and Q6). The storage symptoms were determined by a score of ≥4 and were based on responses to 3 questions (Q2, Q4, and Q7).

Statistical Analysis
Patients were divided into 2 groups according to the median prostate elastic moduli value; one group had 26 patients with elastic modulus >20 kilopascals (kPa), and the other group had 22 patients with elastic modulus ≤20 kPa. Age, PSA, prostate weight, the presence of extracapsular extension, tumor volume, and the presence of LUTS, voiding symptoms, and storage symptoms were compared between the 2 groups. Qualitative variables were compared using the Chi-squared test or a Fisher exact test, and quantitative variables were compared using the Mann-Whitney U test. Multivariate logistic regression analysis was conducted to determine whether the elasticity of the prostate was associated with LUTS, voiding symptoms, or storage symptoms. The prostate elasticity was included in the logistic model as the continuous variable in addition to age and prostate volume; only 3 variables were included because the logistic model should be used with a minimum of 10 events per
predictor variable for the rule of thumb. The Statistical Package for Social Science for Windows, version 18.0 (SPSS, Chicago, IL) was used for all statistical analyses. A P value < .05 was considered significant, and all P values were two-sided.

RESULTS

The median age was 66 years (interquartile range, IQR 57-69), and the median prostate volume was 43.4 mL (IQR 33.2-53.5). Five patients (10.4%) were determined to have extracapsular extension, and the median tumor volume was 0.75 mL (IQR 0.44-1.50). The median elastic modulus of the prostate was 20.8 kPa (IQR 15.6-22.9), and the patients were divided into 2 groups according to prostate elasticity (>20 kPa vs ≤20 kPa; Table 1). A prostate with a higher elastic modulus indicated greater prostate stiffness. Patients with higher elastic moduli were older and had higher PSA values, greater prostate volumes, and tumor volumes compared with their counterparts, although the differences were not statistically significant.

The incidence of LUTS (84.6% vs 59.1%, P = .047) and voiding symptoms (84.6% vs 54.5%, P = .022) was significantly higher in patients with higher elastic modulus than in their counterparts. There was no between-group difference when the storage symptoms incidences (80.8% vs 63.6%, P = .183) and storage symptoms scores were compared (4.9 ± 2.4 vs 4.7 ± 3.4, P = .862).

On multivariate logistic analysis which incorporated age, prostate volume, and prostate elasticity, higher elasticity (as a continuous variable) was independently associated with voiding symptoms (odds ratio 1.18, P = .038; Table 2). However, prostate elasticity was not significantly associated with LUTS (P = .242) or storage symptoms (P = .390). Age was independently associated with storage symptoms (odds ratio 1.10, P = .037).

COMMENT

This study investigated the association between prostate elasticity and the development of LUTS. The results indicated that patients with greater prostate stiffness were more likely to have LUTS and voiding symptoms. In addition, a higher elastic modulus was independently associated with voiding symptoms after adjusting for age and prostate volume. On the basis of anatomic considerations, it has been proposed that gland enlargement contributes to the development of LUTS. However, large prostates are not always correlated with LUTS. Warwick et al first explained that the size of the prostate is not the only factor that affects bladder outlet obstruction. Moreover, although prostate volume reduction is clinically useful to relieve LUTS secondary to benign prostatic hyperplasia, studies have indicated that LUTS might result from complex interactions of the bladder, prostate, and urethra. Intravesical prostatic protrusion has been considered a useful predictor for evaluation of bladder outlet obstruction or acute urinary retention. It seems that the protrusion of the median

![Figure 2. Ex vivo experiment of retrieved human prostate specimens using the palpation system (A). The experiments were performed at 21 sites across the posterior surface of the retrieved prostate specimens (B). (Color version available online.)](image)

| Table 1. Characteristic comparisons stratified by elastic modulus (median 20 kPa) |
|-------------------------------|-------------------------------|---------------------------------|
| Variables                      | >20 kPa (n = 26)              | ≤20 kPa (n = 22)                | P Value |
| Age (y), mean ± SD             | 65.8 ± 5.9                    | 61.5 ± 8.7                      | .060    |
| Diabetes, n (%)                | 5 (19.2)                      | 4 (18.2)                        | .926    |
| Body mass index (kg/m²)        | 24.4 ± 1.5                    | 23.4 ± 2.1                      | .073    |
| PSA (ng/mL), mean ± SD         | 10.0 ± 9.0                    | 8.0 ± 6.3                       | .400    |
| Prostate volume (mL), mean ± SD| 47.4 ± 1.45                   | 41.6 ± 16.4                     | .205    |
| Extracapsular extension, n (%) | 3 (11.5)                      | 2 (9.1)                         | .141    |
| Tumor volume (mL), mean ± SD   | 1.29 ± 1.12                   | 0.75 ± 0.56                     | .137    |
| LUTS (IPSS ≥ 8), n (%)         | 22 (84.6)                     | 13 (59.1)                       | .047    |
| Voiding symptoms, n (%)        | 22 (84.6)                     | 12 (54.5)                       | .022    |
| Storage symptoms, n (%)        | 21 (80.8)                     | 14 (63.6)                       | .183    |

IPSS, international prostate symptoms score; kPa, kilopascals; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen; SD, standard deviation.
and lateral lobes of the prostate causes a ball-valve obstruction, which disrupts funneling of bladder neck. In addition, Cho et al suggested that the prostatic urethral angle is a causal factor for LUTS and demonstrated that the prostatic urethral angle significantly affects urinary symptoms and urinary out flow. They conducted a mathematical simulation and demonstrated that energy loss in the bending tube can occur during micturition using fluid dynamics applications.

Considering urinary flow dynamics, we speculated that the mechanical characteristics of the lower urinary tract could affect urinary outflow. However, only a paucity of data is available in published reports in regard to influences of tissue characteristics on LUTS. Ma et al first reported that fibrotic changes of periurethral prostatic tissue are associated with increased stiffness and LUTS, which suggests that prostate fibrosis contributes to LUTS. Gharaei et al subsequently demonstrated that obesity-induced type II diabetes contributed to the acquisition of urinary voiding dysfunction, which was associated with pronounced prostatic and urethral tissue fibrosis in a mouse model. Catiello et al evaluated the extent of periurethral inflammation and showed a correlation between prostate inflammation and obstructive urodynamic findings.

Although previous studies have used periurethral tissue to assess the stiffness and fibrotic changes of the prostate, this present study measured the prostate elasticity in the posterior wall of the retrieved prostate. This study did not demonstrate whether the prostate elasticity measured on the posterior prostate wall could be applied in the urodynamic model that explains the association between periurethral stiffness and urinary outflow. The method used to measure the elasticity of the prostate is a limitation of our study, which results from the nature of a posthoc analysis. However, we measured tissue elasticity on 21 sites of the posterior wall of the prostate and believe that the elasticity measurements obtained by this method can explain the overall characteristics of prostate tissue and the periurethral area.

In this study, patients with higher elastic moduli were more likely to be older, although this finding was not statistically significant. The authors speculate that there is an age-related change of tissue that occurs secondary to inflammation or fibrosis of the prostate, although a histologic analysis was not performed in this study. Several studies have already shown that the aging prostate is characterized by an inflammatory tissue microenvironment, which induces the proliferation of prostate epithelial cells. In the REDUCE (REduction by DUtasteride of prostate Cancer Events) population, the largest database that examined inflammatory changes of the prostate and LUTS, men with chronic inflammation were significantly older and had a greater prostate volume. Although the prostate volume was not included in the multivariate analysis, chronic inflammation and age were significantly associated with LUTS. In addition, the risk of urinary retention because of benign prostate hyperplasia was significantly greater in men with prostate inflammation. These results might be because of increased mechanical stiffness associated with prostate inflammation. The results of our study demonstrated that greater prostate stiffness is independently associated with voiding symptoms after adjustment for age and prostate volume.

This study had several limitations. First, the study included patients with prostate cancer, and the experiments were performed using a specimen that was retrieved after a radical prostatectomy. Although the presence of cancerous tissues might affect the degree of prostate elasticity, the median tumor volume in our series was 0.75 mL, which indicates that there might be only a small influence from cancerous tissues. Second, although prostate elasticity was determined to be independently associated with voiding symptoms, which were assessed by a validated questionnaire, the results were not supported by urodynamic profiles. Finally, histologic analysis was not performed in this study, and we could not determine whether the fibrotic changes in the prostate contributed to the elasticity differences. Although obesity and insulin resistance were previously demonstrated to be closely associated with lower urinary tract fibrosis and voiding dysfunction in a mouse model, the incidence of diabetes and the body mass index values were not significantly different in this study. This result could be because of the small patient population or other undetermined factors that are related to the mechanical characteristics of the prostatic tissues. Additional studies should be conducted to investigate various factors that can affect prostate elasticity.

CONCLUSION
Previous studies have proposed that various anatomic or metabolic factors increase the risk of LUTS. The results of this study demonstrated that patients with greater prostate stiffness are more likely to develop LUTS. Specifically, prostate elasticity was independently associated with voiding symptoms. Additional studies investigating various factors that affect the elasticity of the prostate...
would be helpful. In addition, it is important to consider prostate elasticity when interpreting and managing lower urinary tract dysfunction in clinical practice.

References


EDITORIAL COMMENT

The authors present a study assessing the possibility that prostate elasticity might have some role in lower urinary tract symptoms (LUTS). They describe a novel method for assessing elasticity of the posterior lobe of the gland using a novel palpation system that measures the elastic modulus of various discreet areas of the prostate and then defines the elasticity characteristics of the prostate on the basis of this modulus. They then categorize, on the basis of symptom subscores in the voiding and storage realm, a group of men undergoing prostatectomy. They note that, in general, as prostate stiffness as measured by the elastic modulus increases, there is a higher likelihood that the patients will manifest LUTS. However, this cannot be regarded as a causal relationship and more closely represents an association, or at worst, completely unrelated findings.

Extensive data exist as to the contributors to, and modifiers of, chronic (as opposed to acute) LUTS. The presence of prostatic inflammation, as measured by prostatic biopsy, does appear to influence LUTS presentation (greater degrees of inflammation result in more problematic LUTS).\(^3\) In addition, inflammation has been proposed as being contributory to the pathogenesis and the progression of glandular hypertrophy of the prostate and has also been related to a higher risk of retention in those men with chronic intraprostatic inflammation as compared with those without.\(^3\) Independently, fibrosis (presumably secondary to chronic inflammation) has been shown to be related to LUTS, presumably, because of changes in the elasticity of the urethral wall and parenchyma of the prostate.\(^3\)
Other groups have reported the importance of changes in the elasticity of prostatic tissues and the presence of LUTS, with more stiffness, higher collagen content, and less glandular tissue being noted in men with more significant degrees of LUTS as compared with controls without LUTS.4

Recently, chronic systemic disease has also been described as contributing to LUTS. In a rodent model, prostatic stiffness increased with obesity and type II diabetes mellitus. Therefore, alterations in the systemic milieu must be accounted for as potential modifiers of local changes.5

However, it is important to remember elasticity of the prostate and urethra is only one aspect of urinary storage and bladder contraction. Elastic changes within the bladder associated with aging and common neurologic disease, possibly diabetes, and other chronic illness also affect lower urinary tract storage capabilities and bladder contractile force. These effects might be dramatic and might exist independently of associated prostatic fibrosis and related elasticity phenomena. Therefore, the possibility that field changes within the bladder and the urethra contribute to the development of LUTS must be considered, rather than single organ phenomena. Loss of elasticity has been shown to have significance in other chronic medical conditions (ie, loss of vascular elasticity and hypertension). It is likely that the urinary tract in some way recapitulates this relationship and that change in elasticity plays a significant role in the development of LUTS, especially when superimposed on other chronic effects, such as aging.

This article presents an interesting assessment; however, the longitudinal causality of changes in viscoelastic properties of the lower urinary tract still needs to be determined in large population studies, which also take into account contemporaneous changes in bladder function and generalized comorbidities.

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REPLY
We appreciate the interest and comments regarding our research. Increasing evidence suggests that chronic conditions outside the urinary tract contribute to the development of lower urinary tract symptoms (LUTS). Chronic conditions such as metabolic syndrome, aging, or lifestyle factors are associated with systemic inflammation and oxidative stress, and these might influence not only the prostate but also the entire lower urinary tract system. Thus, as Dmochowski commented, greater stiffness in the prostate might be a surrogate for functional deterioration of the lower urinary tract, subsequent to chronic inflammation, rather than a direct causal factor for LUTS.

LUTS represents a cluster of chronic urinary symptoms, including disorders of storage and emptying. In our study, the authors measured the severity of LUTS using a validated questionnaire, and LUTS were categorized as voiding and storage symptoms. After adjustment for prostate volume and age, the elasticity of the prostate was independently associated with voiding symptoms but not with storage symptoms; age was the only independent factor for storage symptoms. Loss of elasticity of prostate might reflect the inflammatory change and functional deterioration of lower urinary tract. However, the exclusive association between the elasticity of prostate and voiding symptoms indicates the mechanical effect of a stiff prostate on urinary flow. Recently, Cantiello et al also noted that patients with periurethral inflammation showed obstructive urodynamic findings. In a rodent model, lower urinary tract fibrosis increased the chance of acute urinary retention, suggesting voiding dysfunction because of urinary obstruction.

LUTS results from a complex interaction between the prostate, bladder, and urethra. If only the prostate is focused on to explain the development of LUTS, we might miss the forest for the trees. Nevertheless, the prostate has a significant role in male LUTS, and microscopic and macroscopic changes of the prostate contribute to the development of LUTS. Unfortunately, histologic changes of the bladder or prostate were not evaluated in our study. Furthermore, the elasticity of the prostate was not associated with other metabolic components such as body mass index and diabetes incidence in our study. Although we could not figure out what attributes to the changes in the elasticity of the prostate in our study, we speculate that the elasticity of the prostate affects urinary outflow and obstructive symptoms. Greater prostate stiffness might be a direct causal factor for the development of LUTS.

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