Examination of Pelvic Floor Muscle Elasticity in Patients with Interstitial Cystitis/Bladder Pain Syndrome Using Real-time Tissue Elastography

Yui Abe-Takahashi[1,2], Takeya Kitta[1], Mifuka Ouchi[1,3], Hiroki Chiba[1], Madoka Higuchi[1], Mio Togo[1], Nobuo Shinohara[1]

1. Department of Renal and Genitourinary Surgery, Graduate School of Medicine, Hokkaido University, Sapporo, Japan.
2. Department of Physical Therapy, Faculty of Health Sciences Hokkaido University of Science, Sapporo, Japan.
3. Department of Physical Therapy, School of Rehabilitation Sciences, Health Sciences University of Hokkaido, Tobetsu, Japan.

Corresponding author: Takeya Kitta, MD, PhD

kitta@fb3.so-net.ne.jp

Department of Renal and Genitourinary Surgery, Graduate School of Medicine, Hokkaido University Sapporo 060-8638, Japan

Phone: +81-11-716-1161 (5949)

Fax: +81-11-706-7853

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Madoka Higuchi: Manuscript writing/editing

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Abbreviations

ANOVA, analysis of variance

BMI, body mass index

IC/BPS, interstitial cystitis/bladder pain syndrome

ICPI, Interstitial Cystitis Problem Index

MPQ, McGill Pain Questionnaire

SF-36, MOS 36-Item Short-Form Health Survey

ICSI, O'Leary-Sant Interstitial Cystitis Symptom Index

PFM, pelvic floor muscle

RTE, real-time tissue elastography

SR, strain ratio

SWE, shear wave elastography

SUS, striated urethral sphincter

VAS, Visual Analogue Scale

2D, 2-dimensional

Abstract

Introduction and hypothesis

The aim was to compare pelvic floor muscle (PFM) elasticity between interstitial cystitis/bladder pain syndrome (IC/BPS) patients and healthy women using real-time tissue elastography.

Methods

The subjects were 17 IC/BPS female patients (IC/BPS group; age 34-84 years), 10 healthy middle-aged women (Middle-aged group; 50-80), and 17 healthy young adult women (Young group; 23-37). The target sites of elastography were the striated urethral sphincter (SUS) and adipose tissue as the reference site; muscle elasticity was calculated as the strain ratio (SR) of the SUS to the reference site. Evaluations were performed at rest and during PFM contraction. The IC/BPS group completed lower urinary tract symptom and pain questionnaires. SUS SR was compared among the three groups. SUS SR at rest and during PFM contraction was compared among the three groups with the *t*-test and the Wilcoxon test. Associations between questionnaire results and SUS SR were evaluated by correlation analysis.

Results

There was no significant difference in age between the IC/BPS and Middle-aged groups, but the Young group was significantly younger than the other groups (p<0.001). SUS SR at rest was significantly higher in the IC/BPS group than in the Middle-aged (p=0.014) and Young groups (p=0.002). Furthermore, in the IC/BPS group, there was no significant difference in SUS SR between at rest and during PFM contraction. SUS SR was not significantly correlated with questionnaire results for lower urinary tract symptoms.

Conclusion

SUS SR at rest was significantly higher in the IC/BPS group than in the Young and Middle-aged groups.

Key words

Elasticity, Strain ratio Interstitial Cystitis/Bladder Pain Syndrome, Pelvic floor muscles, Real-time tissue elastography

Brief summary

Pelvic floor muscle strain ratio was significantly higher in the interstitial cystitis/bladder pain syndrome group than in the young and middle-aged groups

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a collective term for a chronic debilitating condition characterized by chronic urologic pelvic pain, bladder pain, frequency, and urgency associated with lower urinary tract symptoms [1]. A previous study reported that the best estimate of the prevalence of clinically confirmed probable IC/BPS in women was 300 cases per 100,000 [2]. Furthermore, the incidence of IC/BPS has been shown to be higher in women, with a male to female ratio of 1:5.8 [3]. However, the etiology of IC/BPS is not fully understood, so no treatment has yet been established [4].

In IC/BPS patients, transvaginal palpation reveals increased pelvic floor muscle (PFM) tone [5,6]. Pain arising from PFMs with myofascial trigger points is believed to result from an excessive release of acetylcholine from neuromuscular junctions after chronic muscle hyper contraction. Pelvic floor hypertonicity, characterized by an increase in the tonic activity of a pelvic floor muscle, is present in up to 85% of patients with IC/BPS [7]. According to a previous report, 78% of IC/BPS patients have pain in the PFMs [8], and it has been reported that manual stretching of the PFMs, such as the pubococcygeus muscle, significantly improved the pain and symptoms [5]. The American Urological Association guidelines report that stretching of the PFMs with manual physical therapy techniques for IC/BPS patients is evidence strength grade A [1]. Therefore, PFM elasticity may affect lower urinary tract symptoms and pain.

Recently, ultrasound elastography has received much attention as a novel imaging technique that is non-invasive and easily accessible. In the field of oncology, this technique has been reported to be useful for the diagnosis of cancer [9]. Ultrasound elastography can be used to quantify tissue elasticity, and there are two types of ultrasound elastography: real-time tissue elastography (RTE) and shear wave elastography (SWE). RTE is the most widely used technique to evaluate tissue elasticity. In RTE, the sonographer manually compresses the ultrasound transducer against the patient's body surface. Tissue deformation, represented by strain, is measured in a 2-dimensional (2D) region under the transducer (typically the full field of view) and is displayed as an elastogram. Given the same amount of applied stress, softer tissue in the elastogram has more deformation and therefore experiences greater strain than stiffer tissue [10]. SWE is an ultrasound elastography technique that uses shear waves to measure tissue stiffness quantitatively. Shear waves are tracked by pulse-echo ultrasound and can be used to quantitatively calculate the tissue modulus (i.e., stiffness); as the stiffness of underlying tissue increases, shear-wave speed increases [11].

In recent years, there have been reports on the quantification of muscle elasticity by SWE using the target PFM as a striated urethral sphincter (SUS) [12]. SUS provides a capacity is considered a major contributor to urinary incontinence [13]. Aljuraifani et al. [12] showed the relationship between muscle activity and SUS stiffness obtained by needle electromyography of the levator ani muscle in healthy women has been shown. The results show that SWE could remove barriers to widespread functional assessment of SUS caused by the need to use invasive recording methods.

Quantitative assessment of PFM elasticity in IC/BPS patients has not yet been reported. We hypothesized that PFM stiffness would be higher in IC/BPS patients than in healthy adult women, and furthermore, that it would be significantly correlated with pain and lower urinary tract symptoms. Therefore, the primary objective of this study was to compare PFM elasticity between IC/BPS patients and healthy women using RTE, which is widely used in clinical practice. The second objective was to investigate the relationship between PFM elasticity and lower urinary tract symptoms.

Materials and methods

Subjects

This was a prospective, observational study. A convenience sample of 17 IC/BPS female patients (IC/BPS group), 10 healthy middle-aged women (Middle-aged group), and 17 healthy young adult women (Young group) was recruited for this study. This study was conducted at the Department of Urology in our University. Seventeen IC/BPS patients diagnosed with IC/BPS who visited the urologist from October 2018 to July 2019 were included, and 27 healthy middle-aged and young adult women volunteered. The inclusion criterion for the IC/BPS group was a diagnosis of IC/BPS in accordance with European and East Asian clinical guidelines on IC/BPS [14]. The differential diagnosis of IC/BPS is made by cystoscopy to determine the presence of Hunner lesions (reddish mucosal lesions accompanied by abnormal radial capillary structures) and glomerulations (mucosal bleeding after bladder distension). All IC/BPS patients underwent cystoscopic hydraulic dilatation under anesthesia. IC/BPS was categorized into two subtypes based on these cystoscopic findings: IC/BPS with and without Hunner lesions. Participants were excluded if they had stress urinary incontinence or pelvic organ prolapse. Given this was a proof of concept study with no a priori data available for sample size estimation, the sample size was based on a sample of convenience. This was a prospective, observational study. The present study was approved by the Scientific Ethics Committee of Hokkaido University (#018-0404), and all patients provided their informed consent.

Procedure

The target PFM was the SUS in accordance with previous studies [12]. Clinically, it is important to objective and quantitatively assess pelvic floor dysfunction in IC/BPS to better understand the etiology of pelvic floor hypertonicity and ensure complete symptom resolution. Activation of SUS has been reported in conjunction with levator ani muscle during voluntary pelvic floor contractions [15]. Although ultrasound imaging enables assessment of levator ani muscle function via movement of ano-rectal junction and bladder neck, it cannot assess levator ani muscle of elastography. New methods are required. Therefore, in this study, the target PFM was the SUS. The elasticity of the SUS was quantified using a real-time ultrasound imaging device with RTE functionality (ARIETTA 70, HITACHI, Aloka, Japan). Measurements were performed with the patients in the supine position with an empty bladder in all cases. A linear probe (frequency range: 3-7 MHz) was placed on the perineum in the mid-sagittal plane such that the urethra and pubic symphysis were in view (Fig. 1, 2a).

First, the SUS was located by transperineal ultrasound. Transperineal elastography was carried out immediately after the conventional gray-scale ultrasound image was acquired. Therefore, gray-scale ultrasound and elastography images were shown simultaneously. Images were obtained by applying repetitive light pressure on the skin of the perineum, two or three times per second, with the probe, positioned perpendicular to the skin when applying pressure. The examiner manually and rhythmically pressed the transducer to the muscle while monitoring the strain graph of the pressing force shown on the ultrasonic apparatus to ensure consistency (Fig. 3). During the measurement, the amplitude of the up-and-down movement of the probe was set to about 1-2 mm, and the speed of the probe movement was set to 1-2 times per second. In this study, the ultrasound manipulation of all subjects was performed by a single examiner. Measurements were taken in two conditions: at rest and during PFM contraction. They were measured three times each.

The tissue elasticity information was displayed in color, with blue indicating hard tissue, green indicating medium tissue stiffness, and red indicating soft tissue.

Elastic parameters used strain ratio (SR) values. Based on the principle that less elastic tissue deforms more than more elastic tissue, a higher strain ratio indicates less elasticity [16]. Muscle elasticity was calculated using the SR, and the region of interest (ROI) was set with the SUS as the target site (A) and adipose tissue as the reference site (B), and the value (B/A) was calculated by dividing the reference site by the target site. The anatomical location of the SUS has been confirmed to be in the area surrounding the anterior aspect of the urethra from the bladder neck [17]. The location of the reference site was set in the adipose tissue, referring to previous reports [18] on the anatomy of the female pelvic floor. Referring to previous studies [12], ROI A was set 10 mm anterior to the urethra and 15 mm above the pubic bone (1.5 mm × 1.0 mm), and ROI B was set 5-10 mm below ROI A (Fig. 2b).

The following questionnaires for lower urinary tract symptoms and pain were selected: O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI), McGill Pain Questionnaire (MPQ), the Visual Analogue Scale (VAS), and the MOS 36-Item Short-Form Health Survey (SF-36). These questionnaires were completed only by the IC/BPS group. The ICSI and ICPI has been proposed as a treatment outcome measure in IC/BPS. In this study, these questionnaires were not administered to the Middle-aged and Young groups because they were healthy, and no patients had lower urinary tract symptoms or pain. Data on age, body mass index (BMI), and duration of illness for the IC/BPS group were collected from hospital medical records.

Statistical analysis

Comparisons among the three groups in age, BMI, and SUS SR (at rest and during

PFM contraction) were analyzed using the Kruskal-Wallis test, one-way analysis of variance (ANOVA), and multiple comparative studies. A nonparametric test and the Mann-Whitney U test were performed by applying the appropriate significance level (0.05/3 = 0.016), which was adjusted by post hoc Bonferroni testing. Within-group comparisons of SUS SR (at rest and during PFM contraction) for the IC/BPS group, Middle-aged group, and Young group were performed using the *t*-test and the Wilcoxon test. Correlations between SUS SR (at rest and during PFM contraction) and each of the questionnaires' (ICSI, ICPI, MPQ, VAS, and SF-36) results were examined using Pearson's product-moment correlation coefficient or Spearman's rank correlation coefficient. Statistical analyses were performed using the free statistical analysis software R, version 2.8.1, with the level of significance set at 5%.

Results

Sample characteristics

The characteristics of three groups are presented in Table 1. A total of 44 participants volunteered for this study, with median (range) ages of 74 years (34 to 84 years) for the IC/BPS group, 63 years (50 to 80 years) for the Middle-aged group, and 26 years (23 to 37 years) for the Young group. The results of the Kruskal-Wallis test of age showed a significant difference among the three groups ($p < 0.05$). Further analysis via post hoc multiple comparisons showed no significant difference in age between the IC/BPS group and the Middle-aged group. The young group was significantly younger than the IC/BPS group ($p < 0.001$) and the Middle-aged group ($p < 0.001$). The one-way ANOVA results for BMI showed a significant difference among the three age groups ($p < 0.05$). However, further analysis by post hoc multiple comparisons showed no significant differences among the groups ($p > 0.05$).

Comparison of SUS SR among the groups

The results of the Kruskal-Wallis test of SUS SR at rest showed a significant difference among the three groups ($p < 0.05$). SUS SR at rest was significantly higher in the IC/BPS group than in the Middle-aged group ($p = 0.014$) and the Young group ($p = 0.002$). There was no significant difference between the Middle-aged and Young groups ($p = 0.036$). SUS SR during PFM contraction was not significantly different among the three groups ($p > 0.05$) (Fig. 4).

Comparison of SUS SR within a group

In the IC/BPS group, there was no significant difference in SUS SR between at rest and during PFM contraction (p = 0.120). In the Middle-aged group, SUS SR was significantly higher during PFM contraction than at rest (p=0.018). In the Young group, SUS SR was significantly higher during PFM contraction than at rest (p=0.003) (Fig. 4).

Correlation between SUS SR and each lower urinary tract symptom questionnaire in the IC/BPS group

SUS SR (at rest and during PFM contraction) was not significantly correlated with any of the ICSI, ICPI, MPQ, VAS, and SF-36 questionnaire results (Table 2).

Discussion

The primary objective of this study was to compare PFM elasticity between IC/BPS patients and healthy women using the RTE. In this study, the IC/BPS group showed significantly higher SUS SR at rest than the Young and Middle-aged groups. In addition, there was no significant association between SUS SR and lower urinary tract symptoms and pain in the IC/BPS group. To the best of our knowledge, this is the first study investigating SUS elasticity measured using RTE in IC/BPS patients. The female SUS provides an important contribution to urinary continence by compression of the mid-urethra [18]. However, most methods to assess the function or dysfunction of the SUS are highly invasive [e.g. needle electromyography (EMG) [19], intra-urethral surface EMG [20], urethral pressure [21]]. Aljuraifani et al [12] reported that SWE has the potential to be a non-invasive, real-time method for assessing SUS functionality. The present results may provide a non-invasive, real-time method using RTE to evaluate SUS function of the idiopathic patient.

In the present study, SUS SR at rest was significantly higher in the IC/BPS group than in the Young and Middle-aged groups. It has been reported that the muscle stiffness of the lumbar multifidus muscle at rest is significantly higher in low back pain sufferers than in asymptomatic individuals [22]. This follows the common clinical notion of “hypertonicity”. A previous study reported that MRI showed that IC/BPS patients have pelvic floor hypertonicity, which may contribute to or amplify pelvic pain [23]. In general, tissue damage causes skeletal muscles to become hypertonic by exciting alpha motor neurons and stimulating muscle contraction when pain occurs [24]. Based on the above, we speculated that PFM tone and SUS SR were increased in IC/BPS patients due to bladder pain and the pain of organs in the pelvis. Furthermore, SUS SR at rest was not significantly different between the Middle-aged and Young groups in the present study. Previous studies have reported that the stiffness of limb skeletal muscles is affected by aging. In the lower extremity muscle groups of the quadriceps and hamstrings, aging is related to the decrease in muscle stiffness [25]. However, in the biceps of the upper extremity, muscle stiffness has been reported to increase with age, and furthermore, muscle stiffness has been shown to decrease more in women than in men [26]. The effects of aging on muscle elasticity are controversial, depending on location and muscle type. In the present study, there was no relationship between the SUS SR and aging. There is no previous report on the relationship between SUS and age in the present study. We believe that this result requires further study.

Comparison of SUS SR within the groups showed that the Middle-aged and Young groups had significantly higher SR during PFM contraction than at rest, but no significant difference was observed in the IC/BPS group. In a report examining SUS stiffness using SWE in healthy adult females, it was found that SUS stiffness was significantly increased with PFM contraction [12]. In the present study using RTE, SUS SR was also found to increase in healthy adult women with PFM contraction. A previous study showed concomitant pelvic floor muscle dysfunction in over 90% of IC/BPS subjects [7]. Furthermore, it has been reported that in women with PFM dysfunction, correct contraction is difficult in about 24% of cases [27]. This study confirmed the movement of the PFM during PFM contraction on B-mode images during SUS elasticity measurement. Therefore, correct contraction of the PFM was thought to have been performed. The fact that there was no significant difference in SUS SR between resting and PFM contraction in the IC/BPS group suggests that the PFM tone at rest was higher in IC/ BPS patients, regardless of whether they had pain or not.

The second objective was to investigate the relationship between PFM elasticity and lower urinary tract symptoms and pain. SUS SR at rest and during PFM contraction was not significantly correlated with any of the ICSI, ICPI, MPQ, VAS, and SF-36 questionnaire results. We had expected that SUS SR would be significantly correlated with pain and interstitial cystitis symptoms. However, the present results differed from our hypothesis. There was no correlation with the pain and lower urinary tract symptoms questionnaires in the IC/BPS group with and without Hunner lesions. Previous reports examining the relationship between other skeletal muscle stiffness and pain symptoms reported that those with pain in the shoulder and lumbar area and those without symptoms had higher muscle stiffness than those without pain, but there was no correlation with pain [22, 28]. The reason for this is that the perception of pain is a highly subjective experience and can be affected by differences in individual susceptibility, as well as personality. The mechanisms of pain development are clearly multi-faceted, and despite the numerous studies in healthy subjects and in pathological conditions, the precise underlying neural processes are still uncertain [29].

The results of this study suggest the following clinical applications: it may be possible to evaluate the stretching effect on SUS elasticity before and after treatment.

There was a limitation in this study. The linear probe used in this study can only observe a depth of 4.0 cm from the body surface. Therefore, it may be difficult to measure SUS elasticity in the case of obese people. The RTE used in this study also detects and displays the relative stiffness of the tissue. On the other hand, SWE is a technology to quantify the elasticity of the tissue as an absolute value. The relationship between RTE and SWE needs to be examined.

Conclusion

The present study showed that SUS SR at rest was significantly higher in IC/BPS patients than in healthy young adult and middle-aged women. The results of this study suggest that it may be possible to evaluate the stretching effect on SUS elasticity before and after treatment.

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Figure Legends

Figure 1

A linear probe placement on the perineum.

Figure 2

Method for analysis of real-time tissue elastography images. a: B mode image, b: Elastography image. Images are shown at rest. The region of interest (ROI) is set with the SUS as the target site (A) and adipose tissue as the reference site (B); ROI A is set 10 mm anterior to the urethra and 15 mm above the pubic bone (1.5 mm x 1.0 mm), and ROI B is set 5 to 10 mm below ROI A.

Figure 3

The strain graph shows the average strain in the tissue as a function of pressure.

Figure 4

The comparison of striated urethral sphincter (SUS) strain ratio (SR) at rest and during pelvic floor muscle (PFM) contraction is shown. White represents the Interstitial cystitis/bladder pain syndrome (IC/BPS) group, gray represents the Middle-aged group, and shaded lines represent the Young group. Comparisons among the three groups in SUS SR were analyzed using the Kruskal-Wallis test, one-way analysis of variance, and multiple comparative studies. A nonparametric test and the Mann-Whitney U test were performed by applying the significance level adjusted by post hoc Bonferroni testing (* $p < 0.016$). SUS SR at rest is significantly higher in the IC/BPS group than in the Middle-aged group and the Young group. In the Middle-aged group, SUS SR during PFM contraction is significantly higher than at rest. In the Young group, SUS SR during PFM contraction is significantly higher than at rest.

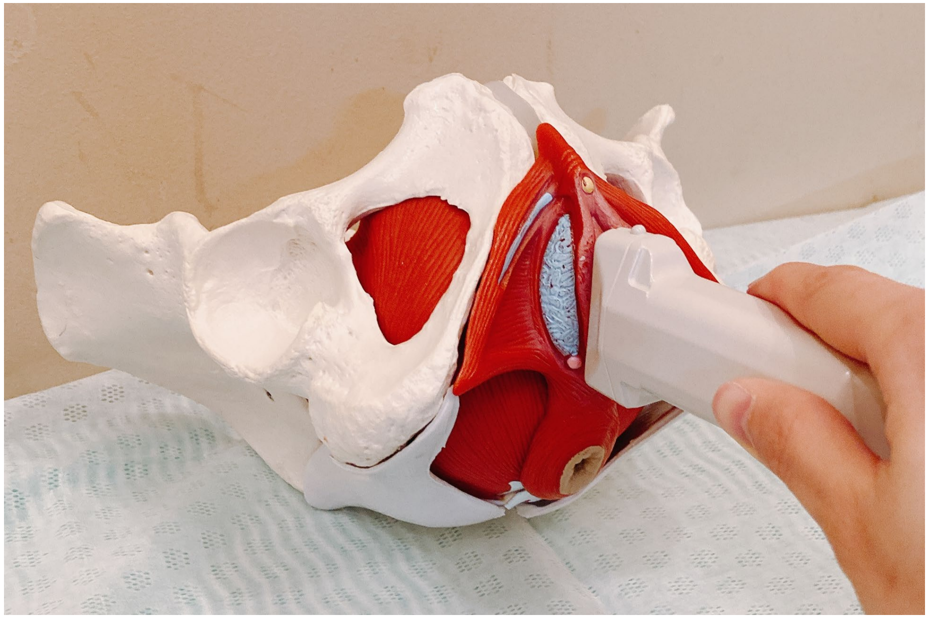


Figure 1

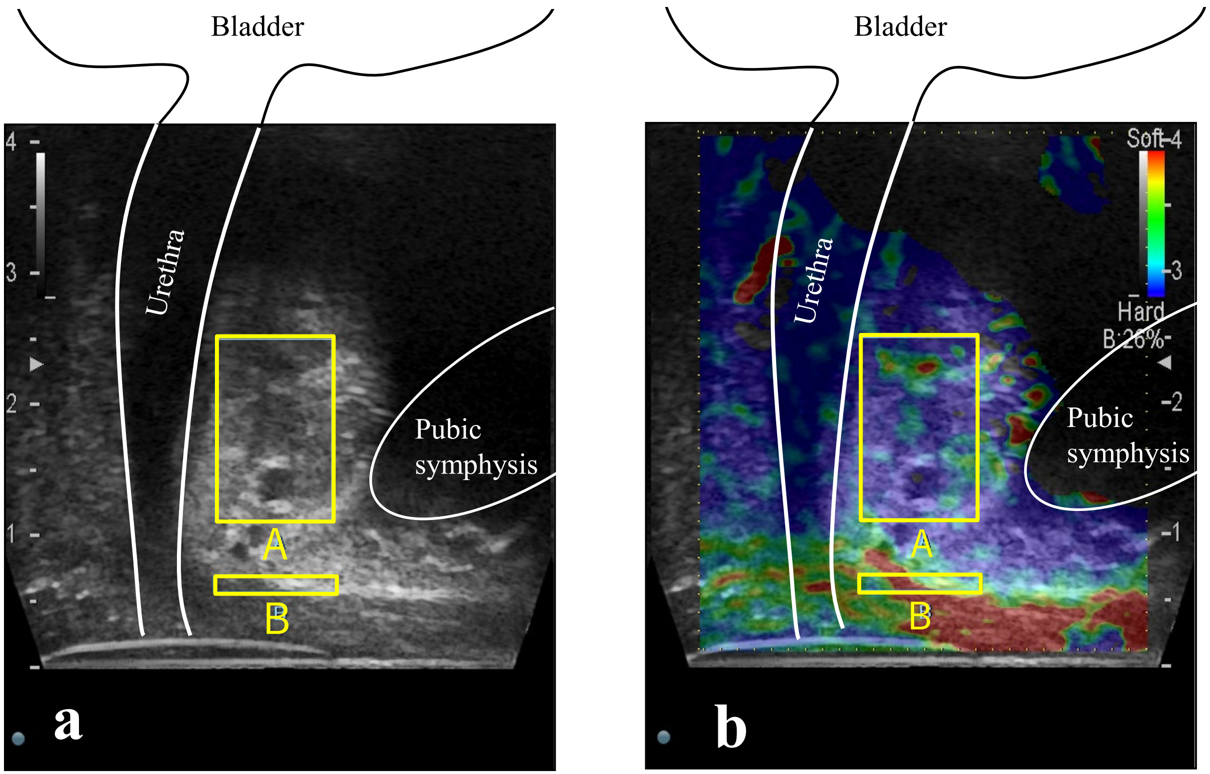

Bladder
Urethra
Pubic symphysis
A
B
a
Bladder
Urethra
Soft
Hard
B:26%
Pubic symphysis
A
B
b

Figure 2

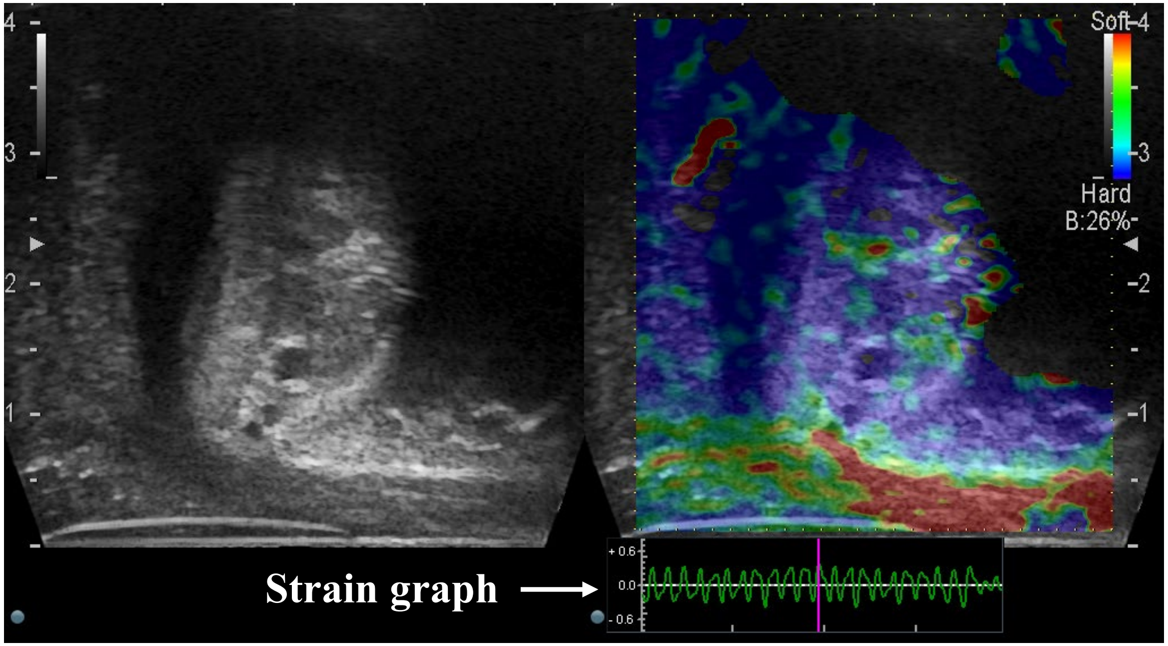
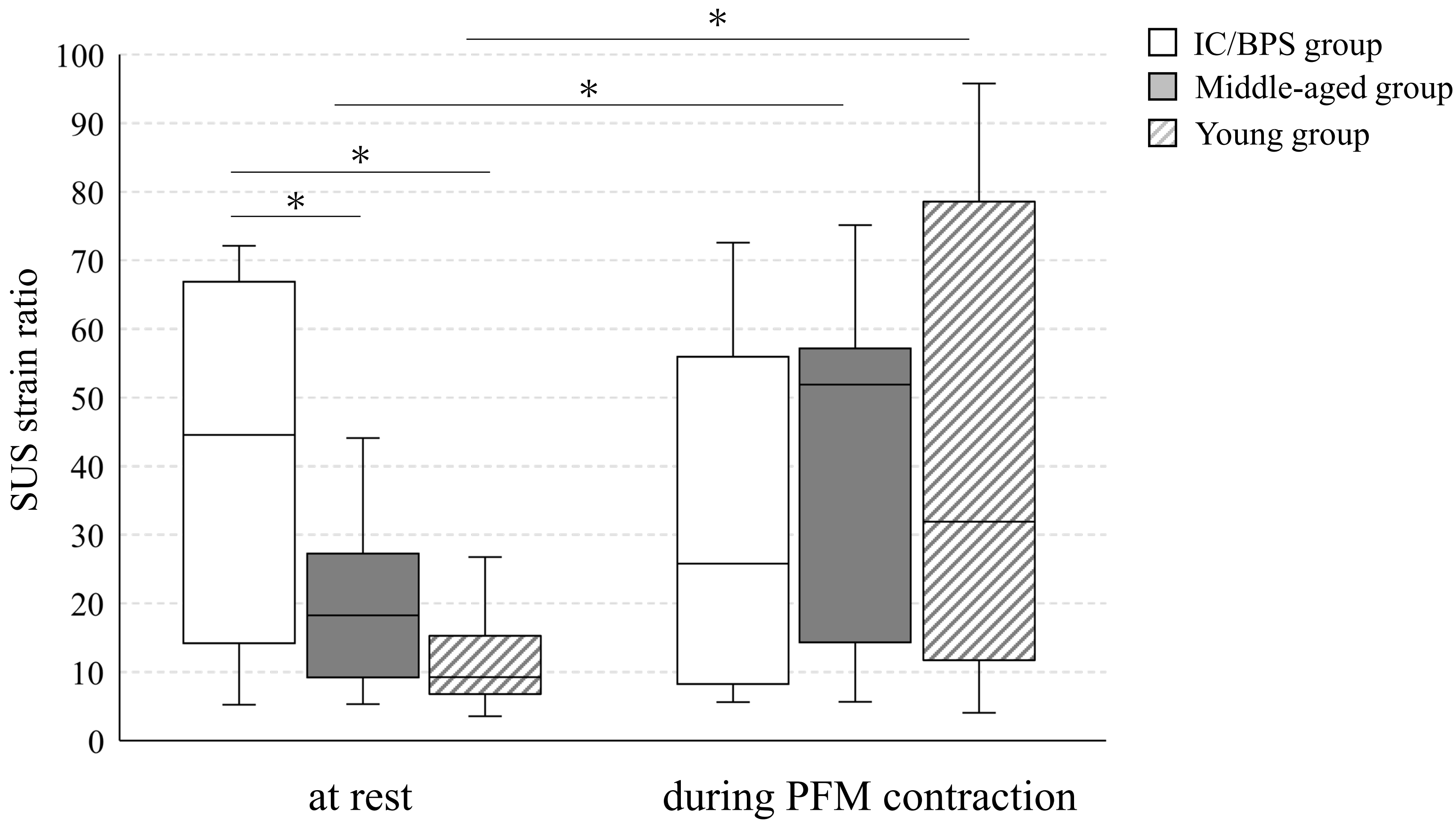


Figure 3



IC/BPS group
Middle-aged group
Young group
SUS strain ratio
100
90
80
70
60
50
40
30
20
10
0
*
*
*
*
at rest
during PFM contraction

Figure 4

Table 1. Characteristics of the participants prior to the start of data collection

Characteristic	IC/BPS group (n = 17)	Middle-aged group (n = 10)	Young group (n = 17)	P value	Post hoc[a]
Age (y)	74 (34-84)	63 (50-80)	26 (23-37)	< 0.001	a, b > c
BMI (kg/m^2)	21.4 (17.6-28.3)	21.7 (20.0-26.4)	19.6 (17.5-23.4)	p = 0.04	> 0.05
Duration of illness (days)	1378 (77-5259)	—	—	—	—

Data are shown as medians (range).

BMI: body mass index, IC/BPS group: Interstitial cystitis/bladder pain syndrome female patients, Middle-aged group: healthy middle-aged women, Young group: healthy young adult women.

[a]Results of the post hoc Mann-Whitney test with a significance level of 0.05/3 = 0.016, which was adjusted by post hoc Bonferroni testing.

Table 2. Correlation between SUS SR and each lower urinary tract symptom questionnaire in the IC/BPS group

		SUS SR (at rest)		SUS SR (during PFM contraction)	
		r or ρ	p value	*r* or ρ	p value
Interstitial cystitis symptom score		0.16	0.53	0.33	0.18
Interstitial cystitis problem score		0.29	0.24	0.33	0.18
MPQ	Sensory	0.27	0.28	0.35	0.16
	Affective	-0.09	0.71	-0.19	0.45
	Evaluative	0.12	0.63	0.11	0.65
	Mixed	-0.03	0.88	0.14	0.58
	Total	0.12	0.62	0.24	0.34
Visual Analog Scale		0.18	0.47	0.31	0.21
SF-36	Physical functioning	-0.31	0.22	-0.41	0.09
	Role physical	-0.18	0.48	-0.14	0.57
	Bodily pain	-0.25	0.31	-0.10	0.67
	General health	-0.21	0.41	-0.37	0.14
	Vitality	-0.25	0.33	-0.33	0.18
	Social functioning	0.07	0.77	0.04	0.86
	Role emotional	-0.14	0.57	-0.08	0.74
	Mental health	-0.36	0.14	-0.48	0.05

SUS: striated urethral sphincter, SR: strain ratio, IC/BPS: interstitial cystitis/bladder pain syndrome, PFM: pelvic floor muscle.

SF-36: MOS Short-Form 36-Item Health Survey, MPQ: McGill Pain Questionnaire.

Pearson’s product moment correlation coefficient or Spearman’s rank correlation coefficient