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Review Article

The promise of bladder wall thickness as a useful biomarker for objective diagnosis of lower urinary tract dysfunction

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Clinical diagnosis of lower urinary tract dysfunction (LUTD), such as bladder outlet obstruction (BOO) or overactive bladder (OAB), is usually based on presenting symptoms. A biomarker for objective diagnosis of these LUTDs is mandatory. Detrusor wall thickness (DWT) has been noted to be increased in men with BOO and children with bladder-induced enuresis. Patients with OAB are also found to have thicker DWT compared with controls. Although clinical studies using transabdominal or transvaginal ultrasound examination have reported a thicker DWT in patients with BOO or OAB, the reported data are not consistent and lack standardization. We believe that DWT is a promising biomarker for objective diagnosis of LUTD, but the examination technique, including sonoprobe frequency, route of scanning, magnification, and landmarks of bladder wall measurement, need standardization before DWT can be widely applied for clinical diagnosis of LUTD.

1. The promise of bladder wall thickness as a biomarker for overactive bladder diagnosis

Lower urinary tract dysfunction (LUTD) is highly prevalent in men and women. Overactive bladder (OAB) is a syndrome based on self-reported symptoms of urgency and frequency with or without urgency urinary incontinence [1]. OAB might be because of detrusor overactivity (DO) or increased bladder sensation. Because patients usually cannot differentiate the sensation of urgency from the urge to void, confusion often exists between these two disease entities [2]. Sometimes, patients with interstitial cystitis/painful bladder syndrome (IC/PBS) also report symptoms similar to OAB. A more objective way to diagnose and assess therapeutic outcomes in patients with OAB or IC/PBS is needed.

Bladder outlet obstruction (BOO) is a commonly diagnosed LUTD for men with lower urinary tract symptoms (LUTS). A high proportion of men with BOO may also have OAB because of DO [3,4]. Diagnosis of BOO can only be made based on invasive urodynamic study, such as pressure flow study or videourodynamic study. A noninvasive method to diagnose BOO is mandatory for more accurate treatment.

Because patients with OAB may have frequent detrusor contractions during the storage phase, it is possible that sustained isometric detrusor contractions could result in increased muscle bulk and hence, increased detrusor wall thickness (DWT). It has been hypothesized that DWT increases in patients with DO [5]. The thickened bladder wall might decrease in response to antimuscarinic treatment, and measurement of DWT might therefore be a useful biomarker for evaluation of disease progression and effectiveness of treatment for OAB.

DWT has been noted to be increased in men with BOO and children with bladder-induced enuresis [6,7]. In patients with OAB, frequent detrusor contractions during bladder filling might result in tetanic detrusor motion and cause hypertrophy of the detrusor muscles. The detrusor is believed to increase in weight after long-term increased workload because of BOO [8]. Therefore, measurement of DWT has been proposed as a useful diagnostic parameter or it could act as a possible biomarker to replace conventional urodynamic pressure flow study in patients with BOO and other types of voiding dysfunction [8–10].

Related studies have not provided consistent findings. Blatt et al [11] and Kuo et al [12] reported that DWT did not differ among healthy controls, patients with BOO, patients with DO, and patients with IBS. These results have challenged previous studies, which showed that an increase in DWT was associated with an increasing degree of BOO and that DWT had a predictive value in the diagnosis of BOO. Thus, further confirmation of the extent of the difference in DWT between patients with OAB and control participants is

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needed. We review the recent advances in using DWT as an objective diagnostic biomarker to assess LUTD.

2. Transabdominal DWT measurement in healthy adults and children

Bladder wall thickness (BWT) has been noted to increase in patients with benign prostatic hyperplasia and BOO as well as in spinal cord injury. The measurement techniques have varied greatly with different sonographic probe frequencies and scanning routes. The bladder wall contains the detrusor muscle wall, mucosal layer, and perivesical fat tissue. If we use a low frequency sonoprobe, these tissues might be involved in the thickness of bladder wall. However, if the scanning frequency increases, we can separate the detrusor wall from the other tissues. Therefore, the true detrusor thickness might be delineated clearly.

Oelke et al [13] found a hyperbolic relationship between an increasing volume and decreasing DWT, with no significant changes in the DWT with increasing bladder volumes beyond 250 mL. In 55 healthy adult volunteers between 15 years and 40 years of age, DWT was measured at the anterior bladder wall with a 7.5-MHz ultrasound probe and with a full bladder. The DWT decreased rapidly during the first 250 mL of bladder filling but, thereafter, remained almost stable until maximal bladder capacity. No statistical difference was found between the DWT at 250 mL and at higher volumes. Men had a greater DWT than women (1.4 mm *vs.* 1.2 mm, $p < 0.001$). The age and body mass index did not have a significant impact on DWT. It seems reasonable to expect that the DWT decreases as the bladder volume increases, and therefore, comparison of the DWT between subgroups requires correction for bladder volumes less than 250 mL [13].

Muller et al [14] have standardized transabdominal ultrasound (TAU) measurement of BWT in children and evaluated its reliability. The thickness of the low echogenic layer of the ventral and dorsal walls was 0.4–2.9 mm (median, 0.9) and 0.4–2.8 mm. (median, 1.1), respectively. The dorsal wall was slightly thicker than the ventral wall. The intra- and interobserver variability of measurements (standard deviation) was estimated to be 0.2 mm. for each wall part.

We have also measured the DWT in three groups of controls in different clinical studies using a high-resolution ultrasound probe [12,15,16]. The mean DWT in the controls was only 1.13 ± 0.30 mm in one study, which compared DWT among controls, patients with OAB, and patients with IC/PBS [12]. However, in another study using an 8-MHz transabdominal sonographic probe (E8 model LOGIQ P5/A5; GE Healthcare, Milwaukee, WI, USA), the DWT in the 28 controls was 0.844 ± 0.294 mm at a bladder volume of 250 mL, 0.646 ± 0.177 mm at bladder capacity and 0.800 ± 0.243 mm with a bladder capacity corrected to 250 mL [15].

In the third study, we measured the transvaginal ultrasound (TVU) DWT in 28 control women using an 8-MHz transvaginal sonographic probe (E8C model LOGIQ P5/A5). The DWT of an emptied bladder was 4.73 ± 0.97 mm at the anterior wall, 3.83 ± 1.06 mm at the posterior wall, 4.67 ± 1.12 mm at the bladder base, and 9.10 ± 2.11 mm at the bladder neck [16] (Fig. 1). When we measured the DWT of the same group of patients from the lower abdomen using an 8-MHz transabdominal sonographic probe (8C model LOGIQ P5/A5), the DWT was 0.926 ± 0.287 mm at a bladder volume of 250 mL, 0.739 ± 0.232 mm at bladder capacity, and 0.925 ± 0.257 mm with the bladder capacity corrected to 250 mL. Putting these data together, it is clear that DWT changes with bladder volume and varies greatly when measured through different scanning routes. Therefore, it is necessary to standardize the technique and scanning frequency in measurement of DWT when comparing DWT between subgroups with different bladder disorders or when performing a longitudinal study of DWT as a biomarker for assessing OAB.

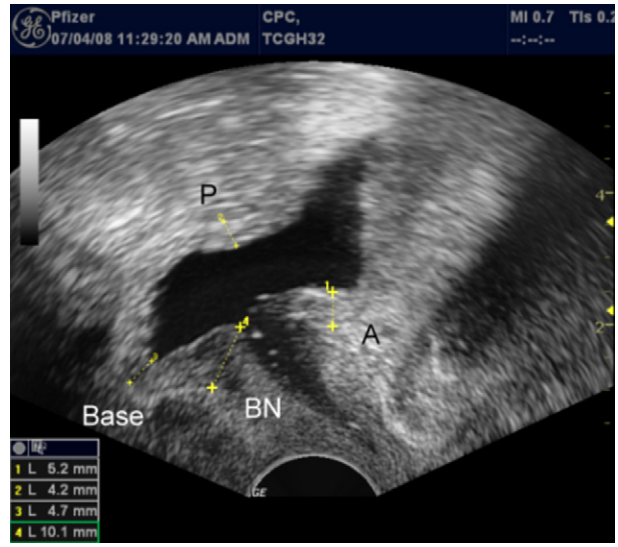

Fig. 1. Transvaginal ultrasound measurement of the detrusor wall thickness at the bladder neck, anterior wall, posterior wall, and bladder base [16]. BN = bladder neck; A = anterior wall; P = posterior wall; Base = bladder base.

3. Transabdominal and transvaginal DWT measurement techniques

The differences in the values of DWT obtained in various previous studies may have been caused by the use of different ultrasound probes with different frequencies as well as by differences in the resolution of images. A review of previous reports found that studies using a higher frequency probe (7.5 MHz) reported a DWT of around 1–2 mm [8,9,11], whereas those using a low frequency probe (2–5 MHz) reported a greater DWT of around 4–5 mm [5,10,17,18]. In our previous studies, we used an 8-MHz high frequency probe to measure the DWT either by TAU or TVU [15,16]. Because the resolution power was able to differentiate the detrusor wall from the posterior rectus fascia, the measured DWT tended to be much less than would have been obtained using a 2–5 MHz low frequency probe (Fig. 2). Although low intra- and interobserver variability has been reported [14], careful identification of the true bladder wall and accurate placement of cursors to measure the landmarks of DWT require experience.

When measuring DWT by TAU, the sonographic probe is placed without pressure on the midline of the lower abdomen and scanning is performed perpendicular to the bladder wall [12,15]. Increasing sonographic magnification is used to obtain a high-resolution picture of the bladder wall. During measurement of the detrusor wall, a careful examination is performed to identify the posterior rectus fascia and distinguish it from the true bladder wall. Using the zoom function, the layers of the bladder wall are apparent. The perivesical tissue, mucosa, and submucosal tissue appear hyperechogenic (bright) and the detrusor appears hypoechogenic (dark). The transducer is manipulated to obtain maximum delineation and ensure the beam is perpendicular to the wall. The bladder wall images are recorded and DWT measurements are made at three different sites along the wall (Fig. 2). The average of these three measurements is used as the DWT value at that bladder volume.

When measuring DWT by TVU, all patients are allowed to void freely, and the postvoid residual (PVR) is recorded, using TAU to

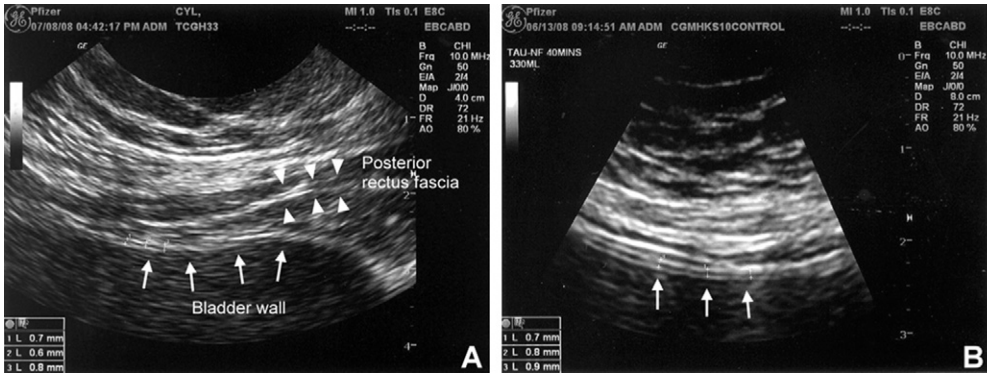

Fig. 2. Transabdominal sonography of the DWT. (A) The bladder wall should be traced laterally to distinguish it from the posterior rectus fascia (arrowheads) and true detrusor wall (arrows). (B) The DWT is determined by measuring the upper margins of the two hyperechoic lines of the bladder wall at three different sites [15]. CF = catheter filling; DWT = detrusor wall thickness; NF = natural filling.

maintain a PVR of less than 50 mL [16]. Then, with the patient in the decubitus position, TVU is performed using an 8-MHz transvaginal sonographic probe (E8C model LOGIQ P5/A5) for the DWT measurement, including the DWT at the bladder neck, anterior wall, posterior wall, and bladder base (Fig. 1).

The measurement of the DWT by TVU is more accurate than that measured by TAU because the high-resolution, high-frequency sonoprobe can delineate the detrusor wall from peritoneal fat and perivesical fat tissue. However, if we do not increase songraphic magnification, the perivesical fat or peritoneal fat might be mistaken for the true detrusor wall, especially when a low frequency probe is used. Khullar et al [5] found that a mean BWT greater than 5 mm with TVU is a sensitive screening method for diagnosing detrusor instability in symptomatic women without outflow obstruction. The data are quite similar to that in our previous study measuring DWT in women with OAB [16]. However, there were still small differences in the DWT between studies, most likely because of lack of standardization in detecting landmarks of the bladder wall (Table 1).

4. Effect of bladder volume on DWT and corrected DWT

We believe the difference in the measured DWT in previous studies is because of different frequencies for the ultrasound probe and resolution of images. In addition, most previous studies used a fixed bladder volume of 200−300 mL to measure DWT [10,19,20]. This was based on the report of Oelke et al [8] showing a hyperbolic relationship between increasing volume and decreasing DWT, with no significant difference in DWT at bladder volumes of 250 mL and beyond. However, we thought the DWT should change as the bladder volume increases. In addition, the volume infused into the bladder might be increased because of the diuretic effect when a patient is lying supine. Under this consideration, the bladder volume should be measured by the voided volume plus PVR urine volume.

Table 1
The detrusor wall thickness in four sites of the bladder wall in symptom and urodynamic subgroups [16]

Subgroup (n)	Anterior wall (mm)	Posterior wall (mm)	Bladder base (mm)	Bladder neck (mm)
Control (28)	4.73 ± 0.97	3.83 ± 1.06	4.67 ± 1.12	9.10 ± 2.11
OAB-dry (28)	4.26 ± 1.41	3.57 ± 0.87	4.51 ± 1.20	8.12 ± 2.20
OAB-wet (25)	4.81 ± 1.45	4.19 ± 1.33	5.11 ± 1.81	9.20 ± 1.98
ANOVA (p)	0.307	0.170	0.327	0.161

ANOVA = analysis of variance; OAB = overactive bladder.

In Fig. 3, we assumed the bladder to be a spherical container and the measured DWT could, therefore, be corrected to a constant volume (250 mL in this study) for comparison among patients with different bladder volumes. Interestingly, we found the statistical difference of a corrected DWT between patients with OAB and controls remained the same as that of the measured DWT [12]. We believed this volume correction method might be a better way of measuring DWT in clinical application when assessing bladder dysfunction.

In addition, the actual bladder volume might be greater than the infused volume because of diuresis when the patient is lying supine. Under these considerations, the bladder volume should be measured as the voided volume plus the PVR to minimize the inaccuracy of sonographic measurement. Interestingly, we found the true bladder capacity was 1.47 and 1.37 times that of the estimated volume measured by TAU or a catheter-filling method [12]. Comparison of DWT at a fixed bladder volume by catheter filling might not be accurate. Based on this corrected method, we measured the DWT in 57 participants without LUTS (controls), including 20 men and 37 women, and found no significant difference in the measured DWT or the corrected DWT (Table 2). The measured DWT in the controls, patients with OAB-dry and patients with OAB-wet decreased with a hyperbaric curve from the emptied bladder to 250 mL, then decreased slowly to bladder capacity [15]. Therefore, 250 mL seems to be an optimal bladder volume in measuring DWT without correction. DWT measured at bladder volumes lower or higher than 250 mL should be corrected to prevent a volume effect on the accuracy of the DWT (Fig. 4).

5. Clinical implication of DWT in children with voiding dysfunction

Yeung et al [20] compared the bladder volume and wall thickness index (BVWI, %) in healthy and enuretic children in correlation with functional bladder capacities. They delineated the BWT and capacity as follows: a BVWI less than 70 indicated a small capacity bladder with a thick wall, a BVWI of 70−130 showed a normal bladder capacity with a normal wall thickness, and a BVWI greater than 130 revealed a large bladder capacity with a thin wall. Patients with good responses to treatment had a normal BVWI, whereas poor responses to treatment were significantly associated with pathological bladder conditions. BWT has also been used in the diagnosis of dysfunctional voiding in children with recurrent urinary tract infection. Yeung et al [21] further evaluated the role of bladder variables measured by ultrasonography in assessing bladder dysfunction in children with urinary tract infections. A high

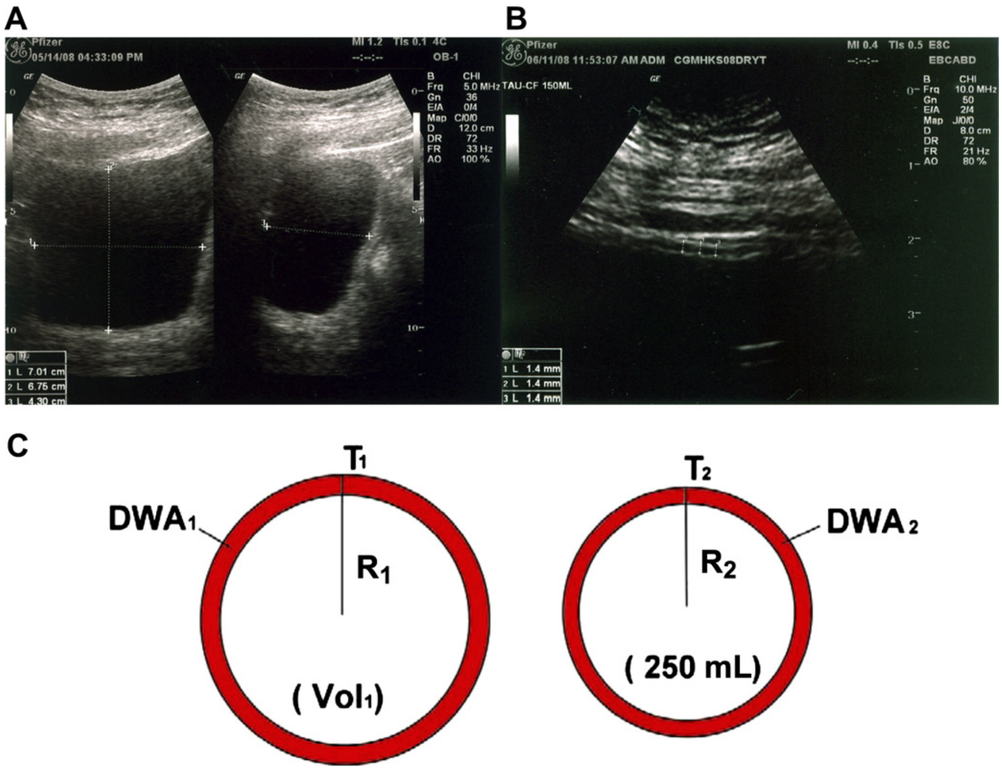

Fig. 3. The method for correcting the DWT to a bladder volume of 250 mL: (A) measurement of the bladder volume; (B) estimation of the DWT by the average of three measurements at different sites; (C) correction of the measured DWT by the equation: $T_1 = R_2/\ R_1 \times T_2$, where T_1 is the thickness of the detrusor wall at volume 1 mL, R_1 is the radius of bladder at volume 1 mL, T_2 is the thickness of detrusor wall at a volume of 250 mL, and R_2 is the radius of bladder at a volume of 250 mL [12]. DWT = detrusor wall thickness.

voiding detrusor pressure was significantly associated with a thick bladder rather than a normal or thin bladder in children, and 92% of patients with a BVWI less than 70 had an OAB. They confirmed the BWT in children can provide useful predictive clues, which may be helpful in differentiating treatment subtypes, guiding clinical management, and minimizing the need for invasive urodynamic studies in children.

Sreedhar et al [7] prospectively evaluated the role of ultrasound measured bladder parameters for assessment of bladder dysfunction and posttreatment bladder functional changes and their correlation with treatment outcome in children with primary nocturnal enuresis. BVWI were calculated based on ultrasound studies and classified as thick (less than 70), normal (70–130), or thin (more than 130). The criteria for diagnosing urodynamic patterns included normal, overactive, and underactive detrusor activity. A total of 96% of patients with an index less than 70 exhibited bladder overactivity on ultrasound. All of the children with a normal index had either a complete or good response to treatment, whereas 62.5% of those with an index less than 70 did not respond to treatment. They concluded that this ultrasound protocol can provide useful predictive clues in differentiating between various treatment subtypes.

Table 2
The DWT in control men and women [12]

Parameters	Men ($n = 20$)	Women ($n = 37$)	Total ($n = 57$)	Statistics
Age (yr)	54 ± 15	49 ± 16	51 ± 16	All NS
Measured DWT (mm)	1.05 ± 0.20	1.17 ± 0.33	1.13 ± 0.3	
Bladder volume (mL)	364 ± 183	361 ± 188	362 ± 185	
Corrected DWT (mm)	1.15 ± 0.24	1.27 ± 0.39	1.23 ± 0.35	

DWT = detrusor wall thickness; NS = not significant.

6. DWT in BOO

OAB is a highly prevalent disorder, affecting 17% of the population and negatively impacting quality of life [22]. Bladder wall hypertrophy and increased bladder weight has been found in animal studies of partial BOO [23,24]. It has been speculated that the detrusor contracts against increased bladder outlet resistance, and muscle hypertrophy and collagen deposition develop [25]. Bladder wall hypertrophy has been correlated with detrusor function. Independent studies have shown that surgical treatment of benign prostatic obstruction results in a significant decrease of bladder mass [26]. Preliminary data suggest the possibility that medical treatment with alpha-adrenergic antagonists might also produce a reduction in bladder wall hypertrophy [27]. Multiple investigators have tried to develop an easier, office-based, noninvasive diagnostic tool for BOO using ultrasound measurement of the DWT [9,10,13,17]. Previous study showed that measurement of the DWT could detect BOO better than free uroflowmetry, PVR, or prostatic volume [8]. An increased BWT and bladder wall mass (BWM) were highly correlated with the degree of BOO. An ultrasonographically assessed DWT of 2.9 mm or greater has a high predictive value for BOO and can replace pressure flow study for the diagnosis of BOO [9].

Oelke et al [6,8] found that the DWT increases depending on the extent of BOO. Both constrictive and compressive BOO lead to an increase in DWT. BOO is found in 95.5% of men with a DWT $\geqq 2$ mm. They proposed a DWT cutoff value of >2.0 mm to predict BOO in men. Kessler et al [9] suggested a DWT cutoff value of

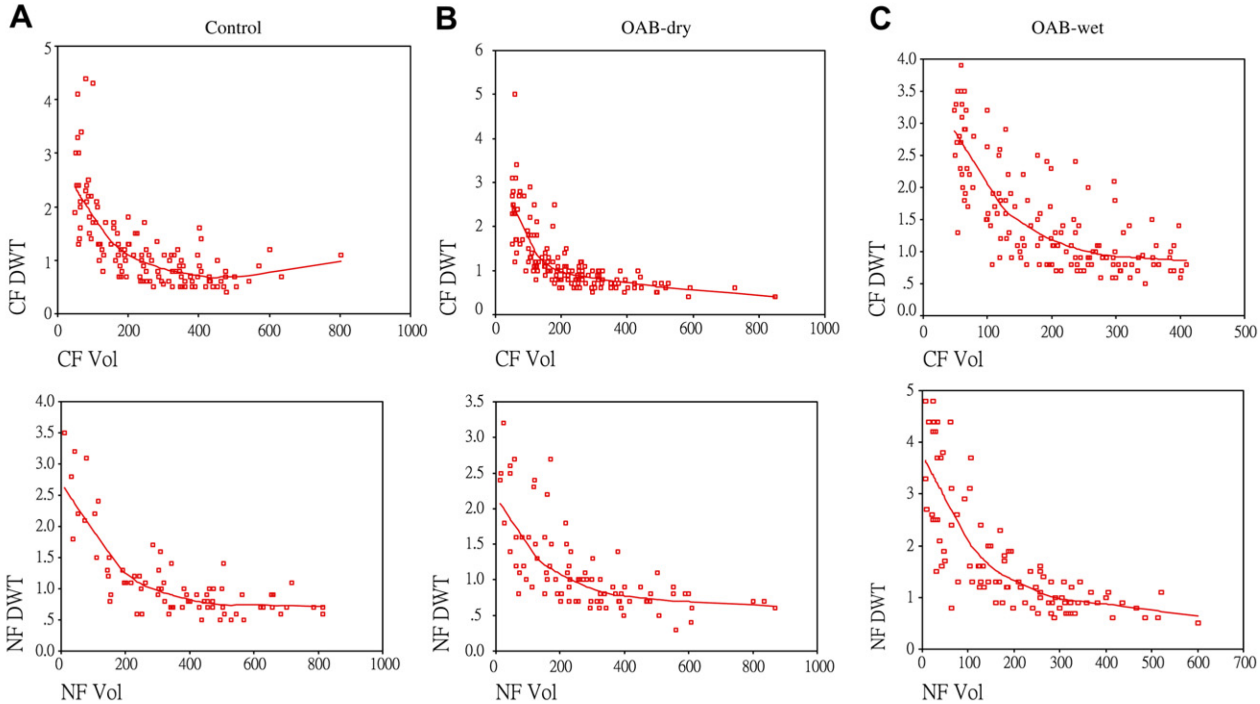

Fig. 4. Nonlinear regression between DWT and bladder volume in (A) controls; (B) patients with OAB-dry; and (C) patients with OAB-wet either by catheter filling (CF) or natural filling (NF) [16]. DWT = detrusor wall thickness; OAB = overactive bladder.

>2.9 mm to diagnose male BOO, which was categorized by a pressure flow study. A BWT of more than 2.9 mm had a positive predictive value of 100% and a sensitivity of 43% in the diagnosis of BOO in men and could replace pressure flow study. However, because many cases of BOO still cannot be detected using the TAU DWT technique, clinical application in screening for male BOO remains limited (Fig. 5).

Hakenberg et al [17] measured the BWT with TAU in 172 men with normal lower urinary tracts, 166 women with normal lower urinary tracts, and 150 men with mild LUTS and clinically benign prostatic enlargement (BPE). The overall mean BWT was 3.35 mm. The mean BWT was 3.04 mm in healthy women, 3.33 mm in healthy men, and 3.67 mm in men with LUTS and BPE. A small increase in BWT with age is seen for both genders, and BWT tends to be greater in men than women. Men with LUTS and BPE show a moderate increase in BWT. Moreover, the resolution of ultrasound and accurate identification of the bladder wall varied greatly in previous ultrasound studies of DWT. The differences in methodology used to measure the DWT resulted in a wide variation of DWT in patients with BOO, with values ranging from 2.0 mm to 5.0 mm [8–10,17].

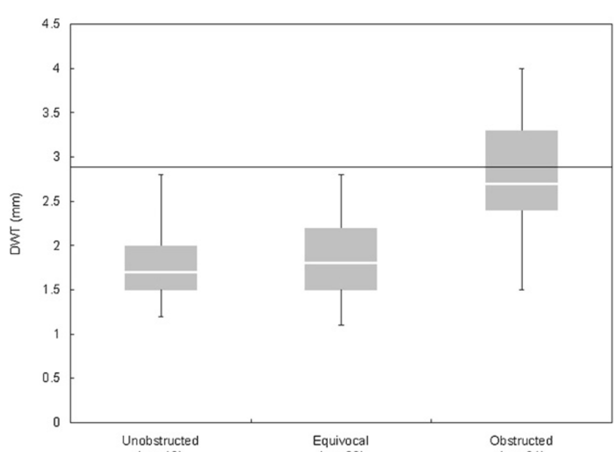

Fig. 5. The measured DWT among unobstructed, equivocal, and obstructed patients. Although the predictive value of BOO is good with a cutoff value of 2.9 mm for the DWT, the sensitivity is only 43% [8]. BOO = bladder outlet obstruction; DWT = detrusor wall thickness.

TAU measurement of BWT or DWT is widely used by most urologists as a tool to assess the bladder condition in patients with LUTS. However, most gynecologists prefer a transvaginal route. Generally, there should be no difference between DWT and BWT. However, TAU measures DWT at a larger bladder volume [9,11,12,15], whereas TVU measures DWT with a nearly empty bladder [5,16]. The bladder volume effect on DWT or BWT varies greatly. The results of previous studies of DWT and BWT in patients with BOO or DO also report discrepant results. The possible causes of these discrepancies might include inconsistent bladder filling conditions or differences in resolution of the ultrasound probe. In fact, the difference between DWT and BWT may be that perivesical tissue is involved in the measurement of BWT using a low frequency sonoprobe, whereas DWT measured by a high frequency probe can delineate the true detrusor wall. The bladder weight, which measures the whole bladder mass, can overcome the problems between BWT and DWT and filling volume. However, the major concern is still the accuracy of DWT measurement, which needs clear standardization.

In addition to measuring DWT in BOO, ultrasound measurement of BWM has also been studied. Kojima et al [28] reported results of the only study to compare ultrasound-estimated bladder width (UEBW) with BOO. They found 94% of obstructed patients had an UEBW greater than 35 g. In another study by Kojima et al [29], BWM was measured by ultrasound in 33 obstructed men before and after prostatectomy for BPE. Results indicated that the bladder weight of the obstructed group was nearly double than that of controls and the BWM of the obstructed group decreased significantly from 52.9 ± 22.6 g to 31.6 ± 15.8 g ($p < 0.05$) after relief of BOO.

7. DWT in OAB and DO

TVU assessment of mean BWT has been found to be a sensitive screening tool, which can detect detrusor instability in women with equivocal laboratory urodynamics. In women who have no evidence of genuine stress urinary incontinence in laboratory studies, a cutoff BWT of 6.0 mm is highly suggestive of detrusor instability [18]. Serati et al [30] compared the ultrasound measurement of BWT in women with different urodynamic diagnoses to correlate BWT with different urodynamic findings of DO. Urodynamics and BWT measurement by TVU were performed. Patients were divided into four urodynamic subgroups, OAB-wet/OAB-dry, urodynamic stress incontinence, mixed incontinence, and normal urodynamics. They found that women with DO had a BWT value significantly higher ($p < 0.0001$) than the other patients. The measured BWT was 5.22 ± 1.17 mm in DO, 4.09 ± 0.86 mm in urodynamic stress incontinence, 4.73 ± 1.27 mm in mixed incontinence, and 4.19 ± 1.14 mm in normal urodynamics. A cutoff of 6.5 mm for BWT had a positive predictive value of 100% for all DO. Although the ultrasound BWT showed a highly significant association with DO, the data showed a high level of overlap and were only reliable in women with DO with a BWT cutoff value greater than 6.5 mm. They concluded that TVU-BWT cannot currently replace urodynamic testing.

Kuo et al [31] recently compared the differences in DWT and urine nerve growth factor (NGF) levels between patients with OAB and controls to evaluate their suitability as biomarkers in OAB. Eighty-one patients, including normal controls ($n = 28$), patients with OAB-dry ($n = 28$), and patients with OAB-wet ($n = 25$) were studied. Urine NGF and DWT measurements were performed at full bladder and urge to void after natural filling or catheter filling during pressure flow study. DWT was measured by TAU. The total bladder volume was calculated as the voided volume plus PVR. These two parameters were compared among different symptomatic and urodynamic subgroups. Key results of this study documented that DWT decreased rapidly from an empty bladder to a bladder volume of 250 mL and slowly to the maximal bladder volume. DWT was not significantly different among subgroups at 250 mL bladder volume. Although patients with OAB-wet had a significantly greater DWT at the maximal bladder volume, this was not significantly different from controls after correction of the volume factor (Table 3). By contrast, urinary NGF levels were significantly increased in patients with OAB-wet and those with urodynamic DO. However, elevated NGF levels in OAB-wet were found only after natural filling and not after catheter filling.

Table 3
TAU measured DWT at 250 mL, final bladder capacity, and corrected DWT in symptom subgroups in natural filling [15]

Subgroups	DWT at 250 mL (mm)	DWT at Bladder capacity (mm)	Corrected DWT (mm)
Control ($n = 28$)	0.926 ± 0.287	0.739 ± 0.232	0.925 ± 0.257
OAB-dry ($n = 28$)	0.904 ± 0.229	0.754 ± 0.203	0.858 ± 0.191
OAB-wet ($n = 25$)	1.048 ± 0.318	0.976 ± 0.379	1.04 ± 0.326
ANOVA	$p = 0.144$	Control *vs.* OAB-wet: $p = 0.008$ OAB-dry *vs.* OAB-wet, $p = 0.007$	OAB-wet *vs.* OAB-dry, $p = 0.048$

ANOVA = analysis of variance; DWT = detrusor wall thickness; OAB = overactive bladder; TAU = transabdominal ultrasound.

Kuo et al [31] concluded that urinary NGF level in natural filling urine samples is a better biomarker for assessment of OAB-wet than DWT. Urine samples from catheter filling do not have detectably high NGF levels. These findings need to be confirmed by other centers, but at this time it appears that urine biomarkers may be superior to ultrasound measurement of the BWT as a biomarker for OAB.

A recent observational study by Lekskulchai and Dietz [32] found a statistically significant correlation between DWT and DO, which indicated that patients with DO have a thicker DWT measured by translabial ultrasound. However, the low sensitivity based on receiver operating characteristic analysis concluded that DWT was not a useful diagnostic tool for DO, which contradicted previously published studies using a cutoff value for DWT [5,18].

Our recent data in measurement of DWT in women with OAB-dry, OAB-wet, and controls also provided further information that measured DWT could be affected by the bladder volume [15]. Current data demonstrated the mean maximal bladder capacity of healthy controls is significantly greater than that of OAB patients. Therefore, although patients with OAB-wet or DO had a significantly greater DWT at maximal volume than controls or patients with IBS, no significant difference was noted among all subgroups after correcting the maximal volume to 250 mL. Although the DWT at 250 mL and the corrected DWT showed no significant difference between patients with OAB and controls, a greater DWT measured at bladder capacity (no matter how small the bladder capacity is) can be considered a biomarker for DO in patients with OAB.

The results of these studies showed that DWT in women with OAB-wet and DO was not significantly greater than that in OAB-dry, controls, patients with IBS, or normal bladders at bladder volumes of 250–300 mL. The DWT at maximal bladder volume, however, was significantly increased in OAB-wet or DO compared with other subgroups. Because the maximal bladder volume in women with OAB-wet or DO was significantly smaller than other subgroups, the significantly increased DWT in patients with OAB-wet or DO at maximal bladder volume is likely to result from a smaller bladder capacity. Because the difference in DWT between OAB and controls, or between DO and non-DO was too small, we suggest the reliability and validity of the diagnosis of DO cannot be established by a cutoff value of the DWT.

Findings have varied in published works on measurement of the DWT or BWT in men and women as a tool to confirm DO as well as BOO. Most published data have confirmed an increased DWT in men with BOO compared with controls [9,11,12,16]. The BWT tends to be greater in men than in women without LUTS. Men with LUTS and BPE show a moderate increase in BWT. A small, significant increase of BWT is noted with age for both men and women [17]. We postulate that the pathophysiology of OAB is quite complicated, especially in women. It has been demonstrated that the incidence of male OAB caused by BOO is much higher than that in women [20,26]. In other words, some men with OAB or DO might have occult BOO, but most women with OAB or DO do not have BOO. This could explain why the DWT of women with OAB was not significantly increased compared with controls. In addition, the exact etiology of detrusor thickening in humans is still obscure.

Although there are statistically significant differences in the DWT at bladder capacity among OAB subgroups and controls, the differences are small. We are not certain of the clinical significance of a 0.2–0.4 mm difference in thickness between controls and patients with OAB or DO. Moreover, whether a 0.2–0.4 mm difference in thickness can be reproduced with repeated measurements by different investigators in different centers using different machines needs further investigation. The DWT at bladder capacity was increased in women with OAB-wet or DO as measured by TAU but not with the TVU approach.

Table 4
The DWT in controls, OAB-dry, OAB-wet, and IC patients [12]

Subgroups	Men	Women	Statistics
Control			
Age	54 ± 15 ($n = 20$)	49 ± 16 ($n = 37$)	All NS
Measured DWT	1.05 ± 0.20	1.17 ± 0.33	
Bladder volume	364 ± 183	361 ± 188	
Corrected DWT	1.15 ± 0.24	1.27 ± 0.39	
OAB-dry			
Age	70 ± 13 ($n = 46$)[a]	61 ± 16 ($n = 41$)	
Measured DWT	1.49 ± 0.30[a]	1.30 ± 0.40	$p = 0.003$
Bladder volume	306 ± 153	319 ± 206	$p = 0.017$
Corrected DWT	1.53 ± 0.32[a]	1.33 ± 0.43	$p = 0.018$
OAB-wet			
Age	73 ± 12 ($n = 17$)[a]	70 ± 14 ($n = 29$)	All NS
Measured DWT	1.70 ± 0.45[a]	1.48 ± 0.43[a]	
Bladder volume	247 ± 127	226 ± 120[a]	
Corrected DWT	1.60 ± 0.51[b]	1.37 ± 0.41	
IC/PBS			
Age		49 ± 13 ($n = 26$)	
Measured DWT		1.23 ± 0.33	
Bladder volume		242 ± 134	
Corrected DWT		1.19 ± 0.29	

DWT = detrusor wall thickness; IC/PBS = interstitial cystitis/painful bladder syndrome; NS = not significant; OAB = overactive bladder.
[a] $p < 0.05$ compared with the controls ($p = 0.001$).
[b] $p < 0.05$ compared with the IC/PBS group ($p = 0.001$).

8. DWT in IC/PBS

IC/PBS is a bladder dysfunction with an undefined pathogenesis. This bladder disorder is usually diagnosed by subjective symptoms. Patients with IC/PBS present with bladder pain and frequency. Cystoscopic hydrodistention has been the gold standard procedure to diagnose IC/PBS; however, not all patients with PBS have cystoscopic findings. Therefore, searching for a biomarker to diagnose IC/PBS has been enthusiastically undertaken by urologists.

We examined the DWT in 26 patients with IC/PBS who visited the urological clinic of a hospital [12]. Control participants were patients who had nonurinary tract disorders and were free of LUTS. Patients with IC/PBS were diagnosed by symptoms of bladder pain and frequency, and their conditions had been proven previously by cystoscopic hydrodistention under general anesthesia. DWT was measured by 8-MHz transabdominal sonography with a full bladder. The measured DWT and corrected DWT (1.23 ± 0.33 mm and 1.19 ± 0.29 mm, respectively) did not show significant differences between women with IC/PBS and female controls (1.13 ± 0.30 mm). However, the corrected DWT was significantly thinner in women with IC/PBS compared with that in women with OAB-dry (1.40 ± 0.36 mm) and OAB-wet (1.56 ± 0.45 mm) ($p = 0.041$ and 0.049, respectively) (Table 4).

This might be the first observation of the DWT in IC/PBS patients. Previously, we thought there could be fibrosis in the bladder wall, which induced a small functional bladder capacity in IC/PBS. However, through ultrasound investigation, we found that the bladder walls in patients with IC/PBS tend to be thinner than those in patients with OAB, and similar to those of controls, suggesting that the main pathophysiology of the decreased capacity of an IC/PBS bladder is inflammation of the bladder wall rather than fibrosis. This finding is also compatible with our clinical findings in IC/PBS bladders during enterocystoplasty for patients with refractory IC/PBS.

9. Conclusions

Ultrasonographic measurement for LUTS is relatively new but shows a promising future. Measurements of BWT, DWT, and UEBW are potentially noninvasive clinical methods of assessing the lower urinary tract. However, a lack of data in healthy asymptomatic participants creates a disparity between studies and hampers the use of ultrasound in routine practice. If methodological discrepancies can be resolved, BWT, DWT, and UEBW will be valuable in assessing LUTS. Studies clearly demonstrate a need for standardized techniques and criteria. The International Consultation on Incontinence-Research Society has recommended all future reports should provide information about the frequency of ultrasound probes, bladder filling volumes at measurement, if the BWT, DWT, or UEBW was measured, enlargement factors for ultrasound images, and one ultrasound image with marker positioning [33]. Only with these quality controls can ultrasonic measurements of urinary bladders be considered suitable to quantify bladder wall hypertrophy because of BOO, DO, or neurogenic bladder dysfunction in adult men, women, and children. Quantification of bladder wall hypertrophy seems to be useful for the assessment of diseases, prediction of treatment outcomes, and longitudinal studies investigating disease development and progression.

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