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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.

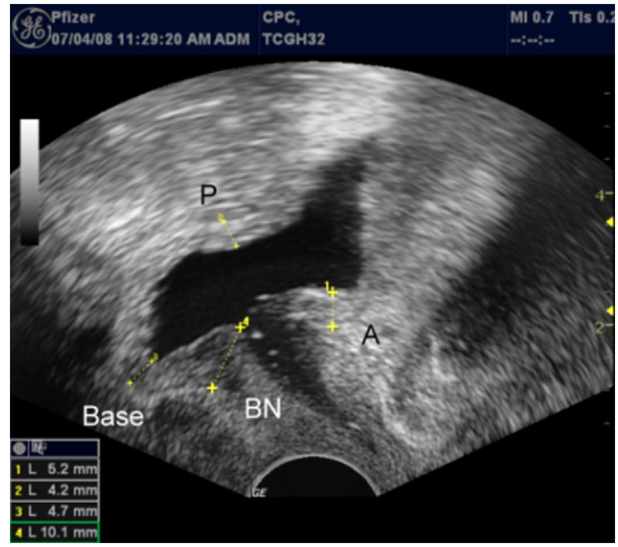

Fig. 1. Transvaginal ultrasound measurement of the detrusor wall thickness at the bladder neck, anterior wall, posterior wall, and bladder base [16]. BN = bladder neck; A = anterior wall; P = posterior wall; Base = bladder base.

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