Bladder wall thickness in the assessment of neurogenic bladder: a translational discussion of current clinical applications

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Abstract: The prospective trial by Kim *et al*. "Can Bladder Wall Thickness Predict Videourodynamic Findings in Children with Spina Bifida?" published in *Journal of Urology* investigated the measurement of bladder wall thickness (BWT) as a non-invasive assessment tool for lower urinary tract changes in neurogenic bladder (NGB). In this study, no significant association was observed between BWT and high-risk urodynamic parameters. This editorial discusses the basic science of bladder wall thickening as well as prior studies relating wall thickness to clinical parameters. Although Kim *et al*. provide a unique literature contribution in terms of assessment of BWT at defined percent cystometric capacity, specific aspects of study methodology and population may have contributed to a lack of correlation with high-risk urodynamic findings. The application of non-invasive modalities to lower urinary tract assessment of NGB remains a promising and relevant area of future research to prevent progression to end stage lower urinary tract changes for all individuals with spina bifida.

Keywords: Urinary bladder; neurogenic; spinal dysraphism; ultrasonography

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Introduction

The urologic sequelae of neurogenic bladder (NGB) have historically been a major cause of morbidity and mortality for individuals with spina bifida (1,2). Fortunately, current management strategies have decreased early risk of progression to renal failure (3). However, the neurologic lesion of spina bifida is dynamic and changes may be reflected in unanticipated deterioration of urologic function in formerly stable individuals (4). One focus of urologic management then has been prevention of upper urinary tract deterioration through timely identification of elevated bladder storage pressures that, in turn, may be reflective of alterations in bladder wall architecture and a decrease in capacity and compliance (2). As a result, children with spina bifida often undergo frequent urodynamic and radiologic testing to aid in early detection of bladder functional changes (2).

Measurement of bladder wall thickness (BWT) by ultrasonography is promising as a non-invasive, readily available screening tool to evaluate for early bladder wall changes without radiation exposure. However, BWT has been limited in its application due to a lack of standardized measurement criteria and reference values in children with NGB as well as varied reports of correlation with clinically meaningful outcomes.

Kim *et al*. (5) examined the utility of BWT measurement in a cohort of children with NGB secondary to spina bifida to predict the outcome of urodynamics, the current gold standard clinical evaluation of lower urinary tract function. In this study, BWT did not correlate with high-risk urodynamic parameters but did correlate with bladder trabeculation. This editorial will discuss the basic science of bladder wall thickening and prior studies relating wall thickness to clinical parameters. Specifically, we will discuss how varied assessment criteria and exclusion of the most severe phenotypes in the children evaluated may have contributed to the lack of association in this study between BWT and changes in bladder function.

Background/basic science

Of numerous etiologies resulting in bladder wall thickening, models of partial bladder outlet obstruction (pBOO) (6,7) and NGB (8) have been most extensively studied. An increase in BWT and altered tissue morphology may decrease bladder compliance through effects on smooth muscle, connective tissue, innervation and tissue hypoxia (9). Histologic studies of the thickened bladder wall have demonstrated both smooth muscle hypertrophy as detrusor smooth muscle is replaced with non-muscle isoforms and fibrosis with altered composition of elastin and type I to III collagen in the detrusor layer (9,10). In pBOO, neurologic changes include neuronal hypertrophy and an increase in muscarinic receptor density followed by progressive, patchy denervation of muscle fibers. Ongoing ischemic damage can be observed in varied cell types including myocytes, nerve axons, fibroblasts and endothelial cells (11). In NGB, early changes in contractility and innervation also occur, likely reflective of denervation and ischemia in the presence of recurrent mechanical stretch on mechanosensitive myocytes and urothelium (12-15). In human histologic studies, an increase in the ratio of connective tissue to muscle fibers is likewise observed in dysfunctional bladders at time of augmentation cystoplasty, a urologic procedure performed in bladders with severely decreased compliance (16).

The ultrasonographic assessment of the bladder wall as a clinically meaningful outcome, however, requires not only the occurrence of histologic changes but also a corollary increase in thickness or weight that precedes irreversible bladder decompensation. In animal models of pBOO, both compensated and decompensated phases of bladder wall changes have been observed with rapid increase in bladder mass occurring early during the initial compensated phase in association with increased intravesical pressures. Following this initial compensated phase, the majority of SM cells display characteristic hypertrophy (11). Animal models of NGB have likewise linked worsening neurologic disability to increased bladder weight and wall thickness in association with the histopathologic changes of hypertrophy (17,18). To date in human studies, an increase in the degree of bladder wall thickening has been correlated with the symptoms and severity of pBOO (19) and, albeit less consistently, with decreased compliance in NGB (8).

Primary and secondary insults likely exist along a continuum that may be reflected in measurable bladder wall changes, the first of which is partially reversible but the second leads to an end stage bladder with irreversible, severe fibrosis and loss of compliance. Fortunately, animal data supports that the potential exists for collagen infiltration of the bladder wall to decrease when a denervated bladder is emptied regularly and remains free of infection (20). Additionally, animal and human studies of pBOO in which the obstruction is relieved have demonstrated decreases in bladder weight and thickness in association with a decrease in detrusor myocyte hypertrophy and in the volume of collagen present in the bladder wall (18,19,21). From a basic science perspective then, the measurement of a secondary change such as detrusor wall thickness (DWT) in a non-invasive manner may be promising if it can detect early bladder wall changes and evaluate for an adequate response to therapeutic interventions. If these changes could be measured clinically such as Kim *et al.* evaluated in this study (5), it may then be possible to prevent ongoing hypoxia, denervation and tissue remodeling before changes become irreversible (7,22).

Clinical assessment strategies for BWT

Understanding the sensitivity and specificity of BWT measurements to assess changes that precede irreversible decompensation is paramount to utilization of BWT as a clinical measure. To date, the utility of this measurement has been limited due to a lack of consistent correlation between BWT and clinically meaningful functional bladder changes. This is potentially due to a couple of factors. First, as described above, an increase in wall thickness is a secondary measurement of the downstream effects of denervation and ischemia. Additionally, inconsistencies in assessment methods are present throughout the literature and limit comparison between studies. For example, there are three measurements of wall hypertrophy that are referred to as 'bladder wall thickness': DWT, BWT or calculated bladder weight. Although standardization of type, location, number and plane of measurements obtained has been recommended by the International Consultation on Incontinence, threshold values of wall thickness and optimal filling volume at time of assessment in individuals with NGB remain to be established (23). Although the study by Kim *et al.* (5) was planned overall in accordance with formerly published methodology, there are variations from prior publications that should be noted. For one, measurements from the ventral wall rather than ventral and dorsal walls may affect the outcome as these measurements have been demonstrated to vary with location (24). Secondly, it is important to note that the thickness reported by Kim

et al. (5) is of the entire bladder wall. It is possible that BWT may have decreased specificity as compared to DWT due to potential alterations such as inflammatory changes in the urothelial layer that may affect the measurement rather than pathologic alterations within the detrusor layer alone that may directly alter compliance. Standardization of these measurement methods for future studies may improve the application of these studies to clinical practice (23).

One measure that requires further standardization is optimal volume at time of bladder wall assessment. Oelke *et al*. reported DWT in a healthy adult cohort, first noting the importance of filling volume to these measurements by observation of a rapid decrease in DWT followed by a plateau occurring beyond a volume of 250 mL (25). Although in healthy children standard formulas may be utilized to estimate bladder capacity, in children with NGB standard age-based formulas may not be accurate (26). The selection of bladder volumes for measurements in the analyzed study reflects this challenge. In a subset, maximum cystometric capacity was assessed individually by urodynamic criteria based on either maximal filling volume tolerated or at the point of ongoing incontinence. Although this may be the most accurate predictor of EBC on a urodynamic evaluation and is a uniquely valuable aspect of this study, it may under or overestimate this volume in certain children.

Additionally, for improved applicability once assessment parameters are standardized, reference ranges would be valuable. As in adults, normal reference values for the wall thickness of healthy children have been published. In a series of healthy children, the overall reference ranges in bladder thickness at estimated bladder capacity (EBC) were 0.4 to 2.3 mm for ventral wall measurements (24). In comparison to these values, even though Kim *et al*. (5) reported the thickness of the entire bladder wall which would be anticipated to be greater than DWT alone, the ranges of BWT observed do not reflect significant overall bladder wall thickening. Mean BWT at capacity was 1.7±0.5 mm for all children, within the reference range above for DWT in healthy children. Furthermore, even in studies that have reported a significant correlation between wall thickness and parameters posing potential risk for upper tract changes, their applicability has been limited by a lack of a cutoff values proposed due to the overlap in the ranges between cohorts. A cutoff of 3.3 mm, greater than the majority of the cohort by Kim *et al*., was proposed with a specificity of 75.0% and sensitivity of 95.1% to detect unfavorable urodynamic parameters (27). In summary then, variability in current assessment methods and a lack of overall increased wall thickness by Kim *et al*. may have contributed to the lack of correlation between BWT and changes in compliance observed in the study cohort.

Clinical effectiveness of ultrasonographic measurement of BWT

To further place the lack of correlation observed by Kim *et al*. between BWT and high-risk urodynamic findings including maximal detrusor pressure >40 cmH_2O during filling or at leak, bladder compliance <10 mL/cmH_2O, detrusor overactivity or vesicoureteral reflux into the context of prior studies evaluating the clinical applicability of BWT to NGB, it is important to note that this article joins a body of conflicting results. In a corollary study of children with NGB, the DWT of children and young adults was measured. The participants were managed at a single center with close follow-up, frequently scheduled imaging and aggressive management with the majority treated with CIC since infancy. Similar to the results of Kim *et al*., the authors reported no correlation between wall thickness in age-matched children and degree of bladder dysfunction, bladder wall trabeculation or changes in renal function (28). Of note, the majority of individuals evaluated also had only mild to moderate bladder dysfunction and demonstrated a lack of severe compliance changes (28). Thus, both this study and the study by Kim *et al*. (5) potentially only report that increased BWT was absent in a population representative of minimal risk to the upper urinary tract and one in which the most severe phenotypes were excluded due to prior bladder augmentation.

On the other hand, there are other studies with contrasting results in terms of the clinical applicability of BWT in the neurogenic population. The observations of these studies may be in populations with less aggressive, expectant management or include more severely affected children with a higher proportion having poor bladder compliance. One such study evaluated BWT in children with MMC of whom more than a quarter were found to have high-risk urodynamic changes. These children were indeed found to have significantly increased BWT as compared to those with 'safe' urodynamic parameters (27). Similarly, in a study that evaluated wall thickness in relation to both upper and lower tract changes, a significant association was observed between DWT in children with NGB and presence of scarring on DMSA scan, the presence of vesicoureteral reflux or poor bladder compliance (8).

Put together, an association has been demonstrated between either increased BWT or DWT and both upper and lower urinary tract pathology. However, the current data is insufficient to suggest that these measurements may currently replace evaluation with urodynamic studies for NGB. In synthesizing these results, it is reassuring to note that those studies with minimal observed changes in BWT such as the publication by Müller *et al.* (24) or Kim *et al.* (5) occurred in well-managed patients with the majority representative of 'safe' bladders based on compliance criteria.

Conclusions

In summary, the study by Kim *et al.* (5) observed a correlation between BWT and bladder trabeculation but no other high risk urodynamic parameters in a study cohort with closely monitored and managed NGB secondary to spina bifida. Taken together, basic science and clinical literature point to a role for regular emptying and maintenance of a compliant reservoir in prevention of detrusor hypertrophy and the associated neurologic and ischemic changes that may lead to irreversible damage to the bladder wall. The authors are congratulated for their overall description of utilized criteria to allow comparison with reference values and in the publication of a method to assess BWT in relation to the individualized capacity of each child's bladder. However, this study's ability to assess an association between wall thickness and urodynamic findings may be limited due to both the lack of standardized assessment criteria in prior literature and an overall exclusion of the most severe phenotypes in the children evaluated.

Future directions

The application of non-invasive, safe and accessible monitoring methods for early ultrastructural bladder changes is an exciting area of future research. Novel imaging technologies currently under evaluation include magnetic resonance or ultrasonographic elastography to evaluate for early tissue composition changes and near infrared spectroscopy or Doppler ultrasonography for detrusor blood volume and oxygenation. Although BWT may provide a secondary measure of bladder wall changes, further longitudinal testing and standardization is required to improve its utility in the assessment of NGB. The goal of these assessment methods must be to detect and prevent progression to end stage lower urinary tract changes for all individuals with spina bifida, thus preserving a compliant reservoir, improving continence and preventing potential renal damage associated with prolonged elevated intravesical pressures.

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Footnote

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