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Review

Non-invasive evaluation of lower urinary tract symptoms (LUTS) in men

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Abstract Lower urinary tract symptoms (LUTS) are common in males over the age of 40 years old and are likely to increase with an aging population. Currently urodynamic studies are the gold standard to determine the aetiology of voiding dysfunction and LUTS. However, due to its invasive nature, a great number of non-invasive ultrasound based investigations have been developed to assess patients with symptomatic LUTS. The clinical application of non-invasive tests could potentially stratify patients who would require more invasive investigations and allow more precise patient directed treatment. A PubMed literature review was performed and we will discuss the non-invasive investigations that have been developed thus far, focusing on bladder wall and detrusor wall thickness (BWT & DWT), ultrasound estimated bladder weight (UEBW) and intravesical prostatic protrusion (IPP).

1. Introduction

Lower urinary tract symptoms (LUTS) are a common group of conditions affecting aging males. LUTS encompass a variety of storage, voiding, and post-micturition symptoms [1,2]. The aetiology of LUTS is multifactorial and can be associated with pathology of the prostate (benign prostatic enlargement (BPE), prostatitis), urethra (urethral stricture), bladder (detrusor under/over activity) and kidney (nocturnal polyuria) [3]. In epidemiological studies, LUTS were present in 57.1% of men and 48% of women [4]. The recorded prevalence of clinically significant LUTS (International Prostate Symptom Score, IPSS $\geq$8) in a community-based study in Singapore was 16.5% and 20.7% in males

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above 40 and 50 years respectively [5]. As populations continue to age, the prevalence and societal impact of LUTS will progressively increase.

Urodynamic studies (UDS) are the most definitive tests available to determine the aetiology of voiding dysfunction. Although considered the current gold standard for the diagnosis of bladder outlet obstruction (BOO), the use of catheters in conventional UDS can cause discomfort to patients and is associated with a 19% risk of adverse events e.g. urinary retention, macroscopic haematuria or urinary tract infection [6,7]. It is also possible that the presence of a catheter in the urethra would influence the reproducibility of the patient's symptoms and the urodynamic readings, despite its small size. There are also cost issues and potential embarrassment to the patient. Hence, a number of non-invasive investigations have been developed. The goal is not to replace, but rather to provide alternatives that may better suit patients and the logistics of different environments (e.g. primary care centres, mobile or remote clinics). These innovations in healthcare enable us to expand our knowledge, modify clinical practice and provide better, more tailored service to patients.

We will discuss these non-invasive investigations that have been developed thus far.

2. Methods

A literature review from 1994–2017 was performed utilizing PubMed using the following MESH terms: non-invasive urodynamics, urodynamic studies, bladder outlet obstruction, LUTS, bladder wall and detrusor wall thickness, ultrasound estimated bladder weight, prostate volume (PV), intravesical prostatic protrusion, resistive index, prostatic urethral angle, and near infrared spectroscopy. We narrowed our search to studies involving male patients. Where possible we focused on studies published within the last 5 years.

2.1. Bladder ultrasound techniques

2.1.1. Bladder and detrusor wall thickness

Chronic BOO results in significant detrusor muscle hypertrophy with thickened or trabeculated bladder wall. It is a well-recognized clinical finding in patients with obstructive LUTS [8]. Studies on animal models have revealed that even with partial urethral obstruction, BOO ensues which results in detrusor muscle hypertrophy and increased bladder weight [9]. There has been an increasing interest in the clinical significance of measurement of bladder wall thickness (BWT) and detrusor wall thickness (DWT). However, to date the clinical value of these parameters remains controversial [10].

DWT and BWT can be measured with transabdominal ultrasound (TAUS). DWT may be superior in this respect as pathologies such as infection and malignancy affect the mucosal layer of the bladder while the detrusor layer is predominately affected in BOO [10]. Oelke et al. [11] found that DWT decreased rapidly during the first 250 mL of bladder filling, but remained almost stable thereafter. 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, $p < 0.001$). Age and body mass index (BMI) did not have a significant impact on DWT [11].

There have been large discrepancies between previous studies regarding the optimal cut-off point of BWT/DWT that should be used to diagnose BOO. Hakenberg et al. [12] assessed the BWT in 3 groups and found 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 [12]. Manieri et al. [8] determined that the best cut-off point for BWT to diagnose BOO was 5 mm. AUC for BWT and uroflowmetry was 0.860 and 0.688, respectively in the receiver operator characteristics analysis. Oelke et al. [13] on the other hand proposed that a cut-off of $\geqq$2.0 mm diagnosed BOO in 95.5% of men with a positive predictive value (PPV) of 94%, negative predictive value (NPV) of 86%, specificity of 95%, specificity of 86% and AUC of 0.93.

Oelke et al. [13] determined that DWT was a more accurate test for BOO compared to uroflowmetry, PVR or prostatic volume. Kessler et al. [14] found a DWT cut-off $>$2.9 mm had a specificity and PPV of 100% and a sensitivity of 43% in the diagnosis of BOO in men, and suggested that this could replace pressure flow studies. Franco et al. [15] investigated men with LUTS and compared a number of parameters, but determined that only intravesical prostate protrusion (IPP) and DWT were associated with obstruction. The AUC for IPP was 0.835 and for DWT, it was 0.845. Combining these two parameters produced the best diagnostic accuracy of 87%.

Although BWT and DWT appear promising in diagnosing BOO, clinical application remains limited. Discrepancies with regards to optimal cut-off may be due to variability in bladder volume, area of bladder measured and differences in resolution of the ultrasound probe. In addition, the difference between DWT and BWT may be that perivesical tissue is involved in the latter. In measurement of BWT, low frequency probes are used, while DWT is measured using high frequency probes, which enable delineation of the true detrusor wall. However, the major concern is still the reporting accuracy of wall thickness measurement, which needs clear standardization. The International Consultation on Incontinence-Research Society has proposed standardization techniques for future research. They recommended that all future reports should provide information about the frequency of ultrasound probes, bladder filling volume, magnification factors, bladder area measured (BWT *vs.* DWT), and one ultrasound image with marker positioning [16]. Using these standardized measures and controls, DWT and BWT may be considered suitable to quantify bladder wall hypertrophy secondary to BOO.

2.1.2. Ultrasound estimated bladder weight

DWT and BWT measurement can be influenced by bladder volume. In order to overcome this, Kojima et al. [17] assessed ultrasound estimated bladder weight (UEBW) to detect slight changes in bladder wall hypertrophy. UEBW is calculated from an applied formula using the BWT and the intravesical volume, assuming a spherical bladder. At autopsy, excised bladder weight correlated well with calculated bladder weight [17]. However another study found that inter- and intra-observer variability in the measurement of BWT resulted in significant differences in UEBW [18]. Kojima et al. [17,19] found that 94% of obstructed patients had an UEBW of >35.0 g; in addition, using this as a cut-off value had a diagnostic accuracy of 86.2% for BOO.

Kojima et al. also found that patients with higher UEBW (UEBW >35.0 g) were 13.4 times more likely to suffer from acute retention of urine (ARU). AUC for UEBW using this cut-off was 0.809. AUC for UEBW was significantly greater than prostate volume (0.631), transitional zone (TZ) volume (0.678) and TZ index (0.641). Thus UEBW would be promising as a non-invasive urodynamic parameter, which is capable of identifying patients at increased risk of ARU [20]. Kojima et al. [21] then investigated the UEBW in 33 obstructed men before and after prostatectomy for BPE. Their results indicated that the bladder weight of the obstructed group was nearly double that of the control group and the UEBW of the obstructed group decreased significantly from 52.9 ± 22.6 g to 31.6 ± 15.8 g ($p < 0.05$) after surgical relief of BOO. Another study of 97 patients with LUTS/BPE showed on multivariate analysis that only UEBW >35 g and a high IPSS score >20 predicted the need for surgery in these patient (TURP or open prostatectomy) [22].

3D ultrasound corrected UEBW (UEBW/bladder surface area) has recently been shown to correlate better than UEBW in diagnosing BOO [23]. Both correlated with urodynamic parameters bladder contractility index (BCI), bladder outlet obstruction index (BOOI) and detrusor pressure at maximal flow rate (Pdet Q_{max}), but UEBW had a weaker correlation [23]. However, in this study the AUC for diagnosing BOO was moderate at best for both parameters with scores of 0.609 *vs*. 0.539 for corrected UEBW and UEBW, respectively [23].

Huang et al. [24] evaluated 202 patients at 6 months follow-up after transurethral resection of the prostate (TURP). The study aimed to assess success of surgery using a variety of parameters between effective and non-effective outcomes following surgery. Significant differences were observed in International Prostate Symptom Score (IPSS), transition zone index (TZI), IPP, resistive index (RI), DWT, UEBW, Q_{max}, PdetQ_{max} and BOOI. On regression analysis, RI, DWT and UEBW were shown to be the most effective at correlating with efficacy and TURP, and AUC scores were 0.816, 0.762 and 0.723, respectively. Used in combination, the PPV and NPV were 96.3% and 75.6%, respectively.

Limitations with UEBW include the fact that majority of the literature with regards to UEBW comes from Asia where prostate size may be smaller compared to white males [25]. Additionally, there are conflicting data with regards to UEBW in the diagnosis of BOO. Bright et al. [26] assessed UEBW in the outpatient setting and found no significant correlation with symptom scores or Q_{max}. Another study revealed similar UEBW in men with mild, moderate and severe BOO. In addition, UEBW did not correlate with IPSS score or BOO as defined by Schafer nomogram in this study [27].

2.2. Prostatic imaging studies

2.2.1. Prostate volume

PV is measured using the ellipsoid formula on the transverse view of the prostate on TAUS [28]. Epidemiological studies had shown that larger prostate glands are more likely to obstruct and develop ARU [29]. A study by Kuo [30] showed that 95% of patients with PV > 40 g had evidence of obstruction on pressure flow studies. However the extent of obstruction is more dependent on the shape of prostate rather than size alone. Thus a protruding median lobe, though small, can cause severe obstruction because of the associated distortion of the funneling effect.

2.2.2. IPP

IPP is measured using TAUS in the sagittal view. The degree of protrusion can be graded by measuring from the tip of the protruding prostate perpendicularly to the bladder circumference at the base of the prostate gland. The IPP can be classified as: grade 1,5 mm or less; grade 2, from >5 mm to 10 mm; and grade 3, >10 mm [31]. The IPP is most reliably measured with bladder volumes between 100 mL to 200 mL and increasing filling volume reduces IPP [28].

In a study correlating IPP and pressure flow on 200 patients, Chia et al. [32] demonstrated that79% of patients with grade 1 IPP were not obstructed, while 94% of grade 3 IPP were obstructed with sensitivity of 76%, specificity 92%, PPV 94%, and NPV 69%. In studies comparing IPP and non-invasive ultrasound urodynamics, IPP was validated as a strong predictor of obstruction [33].

Furthermore, IPP is able to predict successful trial off catheter (TOC). In a study by Tan and Foo [31] where 100 patients with ARU underwent trial without catheter, grade 3 IPP was found to predict a 67% failure rate. Zhang et al. [34] showed concordant results with a failure rate of 31% for grade 1 IPP and 69% for grade 3 IPP. This was validated in studies in Western populations, in which AUC for IPP was 0.833, while that for PV was 0.72 [35].

In addition, IPP has been shown to predict clinical progression. In a study of patients managed conservatively for LUTS secondary to prostate adenoma, 35 patients had clinical progression at follow-up: 7% for Grade 1, 19% for Grade 2 and 49% for Grade 3. Patients with grade 3 IPP were 7 times more likely to progress than those with grade 1 [36]. Higher grades of IPP have been shown to correlate with BOOI index with AUC of 0.835 [15].

Furthermore, IPP may also predict outcomes in patients with LUTS treated medically or surgically. Patients with grade 3 IPP and PV < 40 g showed less improvement in LUTS when treated with alpha blockers compared to lower grade prostates [25,37]. Finally patients with higher grades of IPP (2–3) had better improvements in IPSS symptoms score after TURP [38]. Therefore, IPP in addition to parameters of obstruction can be used to grade and stratify patients with BOO for further individualized management [39].

2.2.2.1. PV and IPP correlation. In a community study in Minnesota, 10% had Grade 3 IPP. It was shown that IPP was significantly related to PV, obstructive IPSS and lower peak flow rates [40]. Prostate adenoma can be graded by the degree of IPP (1, 2 or 3) and sub-classified according to volume (a, b or c). This classification was validated in a study of 408 consecutive patients presenting with LUTS. All patients had IPSS, quality of life index (QoL), uroflowmetry, PVR, IPP and PV measurement performed [41]. A good correlation between PV and IPP ($p < 0.0005$) was demonstrated. Using Q_{max} of 10 mL/s or less at uroflowmetry as a surrogate of obstruction [15], there was significant negative correlation between grading (IPP combined PV) and obstruction. Patients with Grade 1 IPP and a small volume prostate (20 mL or less) usually had flow rates more than 10 mL/s (70% not obstructed), whereas patients with grade 3 IPP and large volume prostate (40 mL or more) usually had flow rates less than 10 mL/s (64% obstructed). However, a small gland, with significant IPP of grade 3 tended to be most obstructive at 82%. These patients with small PV but high grade IPP had prostate adenoma arising from the median lobe, which caused a ball-valve type of obstruction at the bladder neck. These observations suggest that IPP is a better predictor of BOO than PV [41].

2.3. RI

With an enlarging prostate, the transitional zone is thought to compress the artery against the surgical capsule. This is postulated to increase RI. The RI is measured using colour Doppler and calculated with the formula: (peak systolic velocity − end diastolic velocity)/peak systolic velocity. Zhang et al. [42] showed that the RI was significantly higher in patients with BOO and using an RI cut-off of 0.69 predicted BOO with 78% sensitivity and 86.4% specificity. Furthermore, Shinbo et al. [43] in a study of 1962 patients, showed patients with ARU had higher TZI and RI with AUC of 0.860 and 0.867 respectively. In another study by the same center, RI was predictive of outcomes following TURP [44].

2.4. Prostatic urethral angle (PUA)

The anatomical hypothesis behind the PUA describes the prostatic urethra like a bent tube. Thus the PUA may be a causal factor for LUTS and obstruction in BPE [45]. The prostatic urethral angle (PUA) measures the angle between the prostatic urethra and the membranous urethra in the midsagittal plane.

Ku et al. [46] retrospectively studied 260 patients with benign prostatic hypertrophy (BPH)/LUTS and determined that a higher PUA $\geq 35°$ was associated with higher PSA levels, PV, maximal urethral closure pressure and higher BOOI. Another study showed that PUA $\geq 34°$ was associated with higher IPSS and IPSS voiding component [47]. The same study revealed that IPP was associated with both IPSS storage and voiding components [47]. Bang et al. [48] studied 316 patients with LUTS and determined PUA to be independently associated with the IPSS score and Q_{max} with mean PUA of $52.2° \pm 7.3°$, $45.0° \pm 7.9°$ and $39.8° \pm 7.9°$ in those with a Q_{max} of <10 mL/s, 10 mL/s to 20 mL/s, and >20 mL/s, respectively.

2.5. Near infrared spectroscopy (NIRS)

NIRS is a functional imaging technology that measures changes in blood flow that occur during voiding. It enables non-invasive evaluation of oxygen-dependent hemodynamic changes and works on the premise that reactive hyperaemia occurs with voiding.

Oxy-haemoglobin and deoxy-haemoglobin (HHb) respectively represent oxygen supply and consumption of the tissue. The sum of oxy-haemoglobin and HHb represents the total blood perfusion of the tissue [49–51]. NIRS measures changes in the hemoglobin concentration and oxygen consumption in biological tissues, mainly from the venous blood compartment [52,53].

Farag et al. developed a classification model that successfully classified 89% of patients with 89.3% sensitivity, 87.5% specificity, 96.3% PPV and 87.5% NPV for BOO (AUC: 0.96) [54]. However another study showed no significant correlation between NIRS and BOO with an AUC for diagnosing BOO at 0.484 [55].

3. Discussion

In the evaluation of LUTS, although several non-invasive tests are investigated and are available, none have been able to fully replace the gold standard of a pressure flow study. Formal urodynamics evaluation would be able to distinguish between BOO and decreased contractility/ detrusor underactivity in the evaluation of male LUTS.

Ultrasound techniques are operator dependent. Some techniques may require special training and involve a learning curve for the urologist. In addition, not all centers would be able to obtain specialized equipment due to cost and accessibility.

Certain measurement such as IPP, PV and DWT show promise and diagnostic accuracy can be increased when used in combination. UEBW, BWT, DWT and RI all have their limitations and studies can be conflicting. Although RI is promising some limitations include the need for optimal positioning of patients. Variability in pulse rate, arthrosclerosis and use of medications can affect RI. Furthermore patients with median lobe obstruction may have normal RI [44].

Near infrared spectroscopy, while conflicting, appears promising in small studies but further large scale studies are required to validate it use. Studying these modalities in differing populations is required before further conclusions can be made.

A recently published systematic review has made similar observations [56]. A number of non-invasive tests (e.g., DWT, NIRS) have high sensitivity and specificity in diagnosing BOO in men. IPP >10 mm was reported to have similar diagnostic accuracy as Q_{max}<10 mL/s on free-flow testing. IPP can be easily measured by non-invasive ultrasound in the clinic and is useful in the diagnosis of prostate adenoma and also predicts obstruction for further management.

4. Conclusion

Although a combination of investigative techniques is likely to provide better diagnostic accuracy, no one modality so far has been able to replace invasive pressure-flow UDS which remains the gold standard. However, measurement of IPP with simple non-invasive TAUS is promising.

Conflicts of interest

The authors declare no conflict of interest.

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