The Frontiers of Biomarkers in Voiding Dysfunction

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ABSTRCT

The standard measurements for voiding dysfunction include flow rate and pattern in uroflowmetry, postvoid residual urine measurements, and pressure-flow studies in urodynamics. We reviewed the frontiers of biomarkers in voiding dysfunction. There is no single noninvasive biomarker reliable enough to replace the pressure-flow study. For serum biomarkers, C-reactive protein levels are associated with prostate inflammation, and sex hormones may be considered surrogates for developing benign prostatic hyperplasia or lower urinary tract symptoms in men. For urine biomarkers, urinary nerve growth factor levels are associated with overactive bladder and detrusor overactivity but not with voiding dysfunction. Other urine biomarkers have only been used in experimental studies. Ultrasound measurements of bladder wall thickness/detrusor wall thickness, intravesical prostatic protrusion, and prostatic urethral angle can be used as alternative predictors of bladder outlet obstruction. Measurement of isovolumetric bladder pressure requires special equipment, and the results come predominantly from one specific study group.

Keywords: biomarkers, voiding dysfunction

INTRODUCTION

The micturition (voiding) process includes a complex of neural circuits in the brain and spinal cord that coordinate the activity of smooth muscle in the bladder and urethra. The central pathways controlling lower urinary tract function are organized as simple on-off switches that maintain a reciprocal relationship between the urinary bladder and the urethral outlet [1]. Normal bladder filling and urine storage require accommodation of an increasing volume of urine at a low intravesical pressure with appropriate sensation. Bladder emptying requires a coordinated contraction of the bladder smooth muscle with adequate magnitude. Voiding dysfunction is a general term to describe an absolute or relative failure to empty the bladder which results from decreased bladder contractility, increased outlet resistance, or both [2].

The official National Institutes of Health definition of biomarkers is "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [3]. The standard measurements of voiding dysfunction include the flow rate and pattern in uroflowmetry, postvoid residual urine measurements, and pressure-flow studies in urodynamics. Transrectal ultrasonography with measurement of the prostate volume can also be used as a parameter in the evaluation of voiding dysfunction in men.

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A "frontier" means an undeveloped field of study or a topic inviting research and development. We reviewed the frontiers of biomarkers in voiding dysfunction. These biomarkers can be categorized into 4 groups, serum biomarkers, urine biomarkers, ultrasound measurements, and measurement of isovolumetric bladder pressure (Pves.iso).

SERUM BIOMARKERS

C-reactive protein (CRP)

C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation. CRP is synthesized by the liver in response to factors released by fat cells (adipocytes) [4]. The serum CRP level can be used as a nonspecific marker of systemic inflammation. Chronic prostatic inflammation has been hypothesized to be associated with the pathogenesis of benign prostatic hyperplasia (BPH). However, the association between histological prostatic inflammation and lower urinary tract symptoms (LUTS) is relatively weak [5].

Rohrmann et al [6] reported that men with serum CRP levels of >0.30 mg/dL were more likely to show three or four symptoms (i.e., nocturia, incomplete emptying, hesitancy, and weak stream) from the Third National Health and Nutrition Examination Survey. Another report using longitudinal data from the Olmsted County study [7] showed that patients with higher serum CRP levels were approximately twice as likely to exhibit a rapid increase in storage LUTS and almost 2.5 times more likely to show a rapid decrease in the peak flow rate than those with lower CRP levels. Kupelian et al [8] reported a significant association between the serum CRP level and overall International Prostate Symptom Score (IPSS) in both men and women in the Boston Area Community Health survey. We also reported that serum CRP levels are associated with residual urgency symptoms in patients with BPH after medical treatment [9].

However, the serum CRP level is not considered as a good biomarker for voiding dysfunction because of lack of specificity.

Sex hormones

Aging, sex hormones, and growth factors are generally considered important in the pathogenesis of BPH. However, increasing data show that there is no association between serum testosterone concentrations and BPH, regardless of whether total testosterone (TT), free testosterone (FT), or bioavailable testosterone is measured [10]. On the contrary, higher serum dihydrotestosterone (DHT) levels and DHT:TT ratios are associated with larger prostate volumes and higher prevalence of BPH [11]. This significant association may imply that men with higher serum DHT levels or DHT:TT ratios have higher 5α-reductase activity, which increases the likelihood of developing BPH. Another prospective study also reported that higher midlife serum DHT levels were associated with an increased risk of BPH, whereas higher TT:

DHT ratios were associated with a reduced BPH risk [12].

The role of estrogen in BPH pathogenesis is more complex. We also found a significant negative association between total prostatic volume and serum estradiol (E2) levels (and E2:TT ratios) after adjusting for age and body mass index, but the associations disappeared after adjusting for serum DHT levels [11]. DHT may play a major role in prostate growth, and the actual role of estrogens remains elusive.

In one study, serum TT levels were found to be negatively associated with the total IPSS, IPSS storage subscore, weak stream and nocturia on univariate analysis [13]. However, most IPSS items were not associated with serum sex hormone levels after adjusting for age. Two recent studies reported serum TT [14] and FT [15] levels were significantly associated with the severity of LUTS even after adjusting for age. These discrepancies may be explained by variations in study sampling and definitions of LUTS. These data suggest that testosterone is not associated with LUTS, but may be associated with the severity of LUTS. This suggestion was supported by another prospective study showing that mid-life serum TT, E2, and DHT levels were not associated with the development of LUTS [16].

Generally, serum sex hormones may be considered surrogates for developing BPH or LUTS in men, but are difficult to use as predictors of voiding dysfunction.

URINE BIOMARKERS

Nerve growth factor (NGF)

Urine nerve growth factor (NGF) is produced by urothelium and smooth muscle. Clinical and experimental data indicate patients with overactive bladder (OAB) and detrusor overactivity (DO) with or without other clinical conditions had significantly greater urinary NGF/creatinine (Cr) levels than controls [17]. Patients with OAB and DO who were successfully treated had reduced urinary NGF levels. However, the urinary NGF/Cr levels were very low in patients with bladder outlet obstruction (BOO) and without OAB [18]. Urinary NGF is a potential biomarker of OAB and DO, but cannot be used as a biomarker for voiding dysfunction.

Urine adenosine triphosphate (ATP) & Nitric oxide (NO)

Adenosine triphosphate (ATP) & nitric oxide (NO) are released from the urothelium in the bladder. Munoz et al [19] reported that ATP release has a positive correlation while NO release has a negative correlation with the bladder contraction frequency in rats. They suggested that the urinary ATP/NO ratio may be a clinically relevant biomarker characterizing the extent of bladder dysfunction. Sugaya et al [20] found that the improvement in LUTS after treatment with an alpha-1 receptor antagonist or an anti-muscarinic agent was related to a decrease in the urinary ATP/Cr ratio in patients with BPH or OAB. They suggested that measurement of urinary ATP can be used as a marker of pathologic bladder function.

Urine transforming growth factor (TGF)-beta1

Urine transforming growth factor (TGF)-beta1 was negatively associated with detrusor contraction force in a study using detrusor strips stimulated with carbachol [21]. The urine TGF-beta1 level in the 6-week BOO group was significantly higher than in the 2-week BOO and control groups in rats. They suggested the potential role of urine TGF-beta1 as a noninvasive biomarker to predict detrusor contractibility after BOO.

ULTRASOUND MEASUMENTS

Detrusor wall thickness (DWT) / Bladder wall thickness (BWT)

Noninvasive measurements of bladder wall thickness (BWT) and detrusor wall thickness (DWT) have been investigated to replace invasive pressure-flow studies for BOO [22]. BWT and DWT measurements were reported to have a higher diagnostic accuracy in detecting BOO than the maximal flow rate or average flow rate on free uroflowmetry, measurements of postvoid residual urine, prostate volume, or symptom severity [23]. Ultrasound BWT and DWT measurements are also useful in investigating the bladder wall response to surgical or medical treatment of BPH.

Ultrasound measurements of BWT and DWT have several advantages.Types of BOO other than BPH-BOO can be investigated (e.g. bladder neck stenosis, urethral strictures), both men and women can be studied, and voiding is not necessary to make a diagnosis [22]. However, there is still no standardization of threshold values. The results vary with different bladder volumes, and it is unclear if BWT or DWT should be measured. The relationship between BWT and DWT remains to be investigated.

Intravesical prostatic protrusion (IPP)

The prostate median lobe can increase bladder outlet resistance by causing a 'valve ball' type of BOO with incomplete opening and disruption of the funnelling effect of the bladder neck. Ultrasound measurements of intravesical prostatic protrusion (IPP) aim to measure the distance between the tip of the prostate median lobe and bladder neck in the midsagittal plane using a suprapubically positioned ultrasound scanner. IPP has also been used as a diagnostic tool to predict BOO in patients with BPH [24]. In one study, a combination of IPP and DWT produced better diagnostic accuracy than a single method [25].

Prostatic urethral angle (PUA)

Prostatic urethral angle (PUA) had also been reported as a method to assess BOO in men with LUTS and/or BPH. Patients with a PUA> or=35 degrees had higher prostate-specific antigen levels, larger prostate volumes, higher maximal urethral closure pressures, higher detrusor pressures at maximum flow rate, and higher BOO indexes than those with a PUA<35 degrees) [26].

MEASUREMENT OF ISOVOLUMETRIC BLADDER PRESSURE

The condom catheter method and penile cuff test are based on the assumption that there is a continuous fluid column between the bladder and urethra during voiding. Measurement of Pves.iso provides information about bladder pressure during voiding and, when urinary flow is also measured, is able to distinguish between BOO and detrusor underactivity [22].

Condom catheter method

A modified incontinence condom catheter is used for the measurement of the Pves.iso [27]. The condom is connected to tubes, valves, and a pressure transducer; the tubes drain into a flowmeter. During voiding, outflow resistance is gradually increased in the valve until urinary flow ceases. Its advantage is that it is similar to pressure-flow studies. However, special equipment is needed and morbidities such as an unpleasant feeling in the penis and microscopic hematuria have been reported [22].

Penile cuff test

A pneumatic cuff is placed around the penis which automatically inflates in a stepwise increment of 10 cmH_2O per second when voiding commences. The pressure during complete interruption of the urinary flow is determined, which is a valid and reproducible estimate of the Pves.iso [28]. Immediately after flow interruption, the cuff is rapidly deflated again, allowing the flow to resume. The cycle is repeated several times until voiding is complete. However, special equipment is necessary, and the reported results are predominantly from one study group.

CONCLUSIONS

A single parameter from noninvasive tests is not reliable enough to replace pressure-flow study. Uroflowmetry combined with postvoid residual measurement remains the most reliable and applicable noninvasive biomarker. Among serum biomarkers, CRP levels are associated with prostate inflammation, but the specificity is not good enough to be a biomarker for voiding dysfunction. Serum sex hormones may be considered surrogates for developing BPH or LUTS in men, but are difficult to use as predictors of voiding dysfunction. For urine biomarkers, urinary NGF levels are associated with OAB and DO but not with voiding dysfunction. Other urine biomarkers have only been used in experimental studies. Ultrasound measurements of the BWT/DWT, IPP, and PUA can be used as alternative predictors of BOO, and the combination results in higher diagnostic accuracy. Measurement of Pves.iso requires special equipment, and the reported results are predominantly from one specific study group.

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