Promise of Urinary Nerve Growth Factor for Assessment of Overactive Bladder Syndrome

Hann-Chorng KUO,1 Hsin-Tzu LIU,1 Zhonghong GUAN,2 Pradeep TYAGI,3 and Michael B. CHANCELLOR3*

1Department of Urology, Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan, 2Department of Urology, State University Of New York Downstate, New York, New York, USA, and 3Department of Urology, Oakland University, William Beaumont School of Medicine, Royal Oak, Michigan, USA

Overactive bladder syndrome (OAB) is highly prevalent bladder disorder in men and women. About 10–15% of the population suffers from urgency frequency with or without urgency urinary incontinence. It is estimated that 50–75% of patients with OAB may have urodynamic detrusor overactivity (DO). Urodynamic study invasive and most of the OAB patients might not accept it as a routine assessment. Therefore, a more objective and non-invasive test for diagnosis and assessing DO from OAB patients is needed. Recently, urinary nerve growth factor (NGF) has gained great interest in detecting DO in patients with OAB. Urinary NGF level was found to increase in OAB and urodynamic DO. Urinary NGF levels correlated with severity of OAB symptoms. Patients with either idiopathic or neurogenic DO may have increased urinary NGF levels. Urinary NGF levels have been shown to decrease in patients with patients with OAB and DO who have been well treated with antimuscarinics or botulinum toxin injection, but not in those with persistent OAB after treatment. Not all patients with OAB can have an elevated urinary NGF level; it may also be increased in patients with interstitial cystitis/painful bladder syndrome and other lower urinary tract diseases, suggesting urinary NGF expression could be a product of bladder inflammation and a limited specificity of urinary NGF for diagnosing DO. The source of urinary NGF has not yet been fully explored yet. Nevertheless, urinary NGF level is likely to be a promising biomarker for diagnosis of DO from OAB patients, to monitor therapeutic outcome and predict disease progression.

Key words biomarker, interstitial cystitis, nerve growth factor, overactive bladder, urinary incontinence

1. SEARCH FOR OAB SURROGATE BIOMARKERS

The overactive bladder (OAB) syndrome is a condition of urinary urgency, frequency with or without urgency incontinence, and is usually accompanied by frequency and nocturia. Urgency is the core symptom of OAB.1 OAB is highly prevalent in Western or Eastern countries.2,3 OAB is a subjective complaint reported by the patients based on their recognition of bladder condition, however, patients might not able to differentiate urgency from urge to void. Clinically, urgency perception or urgency severity scores (USS) and OAB symptom score are often used to grade the severity of OAB.4,5

Urodynamic study provides fundamental diagnosis of the presence of detrusor overactivity (DO), however, only 69% of men and 44% of women with urgency symptoms were found to have DO (OAB-dry), whereas 90% of men and 58% of women with urgency and urgency urinary incontinence (UUI) had DO (OAB-wet).6 In fact, many patients with increased bladder sensation (IBS, defined as having an early urge bladder sensation of less than 350 mL) without true urgency might be grouped into OAB-dry, and women with severe intrinsic sphincter deficiency are grouped into OAB-wet, which may cause a high non-response rate in clinical therapeutic trial.7 Voiding diary plus urgency severity score recording could be a better tool to assess the presence of DO in patients with OAB compared with diagnosis based on OAB symptom alone.8 However, this requires careful instructions to the patients and might not be valid in most of the busy clinics. There is an unmet need to discover and develop a better way to diagnose DO and to assess therapeutic outcome in patients with OAB.

2. NERVE GROWTH FACTOR IN THE LOWER URINARY TRACT

Nerve growth factor (NGF) is a small secreted protein that induces the differentiation and survival of particular target neurons. NGF is believed to be involved in the physiology of lower urinary tract and the pathophysiology
of DO of the urinary bladder, where it is synthesized by protein kinase C and PKA-dependent intracellular pathways. NGF is released from target cells under irritation due to inflammation, obstruction or denervation. NGF sensitizes afferent nerves and changes the phenotypes of C-fiber bladder afferent neurons which enhance synaptic transmission and produces pain sensation as well as increased urinary frequency (Fig. 1). NGF may sensitize afferent nerves linked to mechanical stretch and reflex bladder activity, which can result in DO. Chronic administration of NGF into the spinal cord or chronic administration of NGF into the bladder of rats has been demonstrated to induce bladder hyperactivity.

NGF has attracted considerable attention as a key player in the link between inflammation and altered pain signaling. NGF is expressed widely in various cells including urothelial cells, smooth muscle cells and mast cells and can activate mast cells to degranulate and proliferate. Increased expression of NGF is also present in bladder biopsies of women with interstitial cystitis/painful bladder syndrome (IC/PBS). NGF has been implicated as a chemical mediator of pathology-induced changes in C-fiber afferent nerve excitation and reflex bladder activity through activation of VR1 receptors. The repetitive stimulation of C-fibers from inflammation and upregulation of sensory nerves in the bladder lead to permanent alterations or central sensitization. Endogenous NGF seems to contribute to the lower urinary tract dysfunction (LUTD) after spinal cord injury (SCI) through regulation of neural function, as well as inflammation and pain. Blockade of NGF using antibody against NGF receptor prevents neural plasticity and bladder overactivity in experimental animals, suggesting sequestration of NGF can reduce inflammation and improve OAB or pain symptoms.

In humans, bladder tissue NGF is found to elevate with IBS and IC/PBS, in patients with idiopathic DO, and in men with bladder outlet obstruction (BOO). In patients with neurogenic DO (NDO), NGF levels increased in SCI as well as cerebrovascular accident (CVA). The urinary NGF levels are decreases after detrusor botulinum toxin A (BoNT-A) injection for NDO of SCI in association with the improvement of urinary incontinence. Together with several previous studies, urinary NGF may have a potential role as a urinary biomarker for IBS, IC/PBS, OAB and DO.

Previous investigations on the implication of NGF in OAB or DO usually measured the bladder tissue levels. Birder et al. measured NGF concentration using ELISA in the superficial bladder biopsies from 12 women with DO and 15 without urodynamic DO and did not find a significant correlation between the bladder NGF levels and DO. Compared with the results of urinary NGF in OAB and LUTD, measurement of NGF levels in urine sample is less invasive and may be more sensitive than those determined in the bladder tissue.

Visceral epithelia have been demonstrated to be a major site of NGF production and secreted NGF may regulate the function of adult visceral sensory and motor neurons. Exogenous overexpression of NGF in the urinary bladder produces bladder overactivity and a nociceptive Fos expression in the lumbosacral spinal cord. Kim and Park found that urinary NGF levels are increased in both men and women with OAB.

Fig. 1 Nerve growth factor (NGF) is released from target cells under irritation due to inflammation, obstruction or denervation. NGF sensitizes afferent nerves enhances synaptic transmission and produces pain sensation as well as increased urinary frequency. DRG, dorsal root ganglia.
evaluated urine NGF in OAB patients with DO, OAB without DO, BOO, and NDO. They concluded that urinary NGF levels are elevated in NDO and sensory urgency but not in idiopathic DO (IDO). The cause for this discrepancy is likely due to relatively small sample size in each group. Detrusor injection of BoNT-A in patients with IDO decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers, which results in decrease of urinary NGF levels as well as reduced urgency sensation. The reduced urinary NGF levels after BoNT-A injection in IDO or NDO is closely associated with these sensory receptors.

3. TECHNIQUE OF URINARY NGF MEASUREMENT

Measurement of urinary NGF levels is performed by the ELISA method using nondiluted urine samples. Voided urine is put on ice immediately and centrifuged at 3000 g for 10 min at 4°C. The supernatant is separated into aliquots in 1.5 mL tubes and preserved in a −80°C freezer. At the same time, 3 mL urine is taken to measure urinary creatinine level. urinary NGF concentration is determined using the Emax ImmunoAssay System (Promega, Madison, WI, USA) with a specific and highly sensitive ELISA kit. The samples were run in triplicates. When the urinary NGF concentration was higher than the upper detection limit (250 pg/mL) the urine samples were diluted to fit the detection limit. For urine samples with NGF concentrations lower than the detectable limit but above zero, a concentration method was performed using a column-protein concentration kit (Amicon Ultra-15, Millipore, USA) to measure the NGF value. The total urinary NGF levels are further normalized by the concentration of urinary creatinine (NGF/Cr level).

4. OAB AND URINARY NGF

Urinary NGF levels are found to increase in OAB patients in a recent study measuring urinary NGF levels in patients with IBS, OAB-dry and OAB-wet and in a group of control subjects without lower urinary tract symptoms. (Table 1) Urine samples were collected at a full bladder. Among the 40 subjects in the control group, urinary NGF was not measurable in 33 (83%) patients and the normalized NGF/Cr level was ≤0.05 in 37 (96.7%) patients. Urinary NGF/Cr levels were very low in the controls (mean ± SD, 0.041 ± 0.026) and patients with IBS (0.033 ± 0.02). In contrast, patients with OAB-dry (0.39 ± 0.08) and OAB-wet (1.7 ± 0.26) had significantly higher urinary NGF/Cr levels. Furthermore, patients with OAB-wet had significantly higher urinary NGF levels than OAB-dry patients (P < 0.0001). Patients with IBS without symptom of urgency had a urinary NGF level similar to that in the controls. These results suggest that elevated urinary NGF level plays an important role in mediating the urgency sensation in OAB patients. Therefore, urinary NGF level could be used as biomarker to differentiate OAB from IBS in patients with unclear clinical symptoms of frequency nocturia or urgency, in whom the increased awareness of bladder fullness or polyuria may be responsible for the symptoms.

One possible reason for the significantly higher urinary NGF levels in patients with OAB-wet than those in OAB-dry might be the higher percentage of DO in patients with OAB-wet. Digesu et al. investigated a group of 843 women classified as having an OAB and found that 54.2% of them had urodynamic proven DO.36 Hyman et al. also found a higher incidence of DO associated with UUI than those with symptoms of urgency and frequency or other lower urinary tract symptoms (75% vs 36%) in men.37 In a recent study using a voiding diary, USS and videourodynamic study as tools to assess OAB, we found urodynamic DO was present in most patients with OAB-wet (94.1%) or USS (495.5%); however, only 63.9% of patients with OAB-dry had DO.8 These clinical observations suggest that the incidence of DO is higher in OAB-wet than OAB-dry. Therefore, a higher urinary NGF level might reflect a higher possibility of the occurrence of DO.

TABLE 1. Urinary NGF/Cr levels in patients with OAB and IC/PBS in previous reports

<table>
<thead>
<tr>
<th>Control (n)</th>
<th>OAB-dry (n)</th>
<th>OAB-wet (n)</th>
<th>IC/PBS (n)</th>
<th>Statistics</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 0.041 ± 0.026 (40)</td>
<td>0.39 ± 0.08† (54)</td>
<td>1.70 ± 0.26† (80)</td>
<td>—</td>
<td>P = 0.000†</td>
<td>J Urol 2008; 179:2270-29</td>
</tr>
<tr>
<td>2 0.005 ± 0.003 (38)</td>
<td>BOO/non-DO/OAB 0.81 ± 0.062‡ (25)</td>
<td>BOO/DO/OAB 0.80 ± 0.021‡ (47)</td>
<td>—</td>
<td>P = 0.004†</td>
<td>Urology 2008 72:104-30</td>
</tr>
<tr>
<td>3 0.086 ± 0.022 (37)</td>
<td>OAB-dry + wet 1.00 ± 0.32 (33)</td>
<td>—</td>
<td>1.34 ± 0.347 (41)</td>
<td>P &lt; 0.001†</td>
<td>Urology 2008 72:104-30</td>
</tr>
<tr>
<td>4 0.09 ± 0.042 (28)</td>
<td>—</td>
<td>—</td>
<td>1.73 ± 0.44 (60)</td>
<td>P = 0.033†</td>
<td>BJU Int 2009 104:1476-32</td>
</tr>
<tr>
<td>5 0.05 ± 0.02 (49)</td>
<td>0.31 ± 0.11 (26)</td>
<td>1.83 ± 0.74 (22)</td>
<td>P = 0.902§</td>
<td>BJU Int 2009 104:1476-32</td>
<td></td>
</tr>
<tr>
<td>6 0.085 ± 0.041 (28)</td>
<td>0.296 ± 0.105 (28)</td>
<td>1.66 ± 0.623 (25)</td>
<td>P = 0.005†</td>
<td>BJU Int 2010 106:1661-26</td>
<td></td>
</tr>
<tr>
<td>7 0.09 ± 0.04 (27)</td>
<td>IBS 0.25 ± 0.10 (31)</td>
<td>DO 0.93 ± 0.77 (23)</td>
<td>1.35 ± 0.36 (40)</td>
<td>P = 0.44§</td>
<td>BJU Int 2010 106:1661-26</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard error. †Comparison of NGF/Cr with the controls. ‡Comparison of NGF/Cr between OAB-dry and OAB wet. §Comparison of NGF/Cr between IC/PBS and OAB wet or DO. BOO, bladder outlet obstruction; DO, detrusor overactivity; IC/PBS, interstitial cystitis/painful bladder syndrome; NGF/Cr, normalized by the concentration of urinary creatinine; OAB, overactive bladder.
5. IDO AND URINARY NGF

Rat experiments have shown that increased NGF expression leads to bladder overactivity with or without the association inflammation. After pudendal nerve ligation in rat models the bladder NGF protein and mRNA were significantly increased and the urinary frequency was increased. The bladder mRNA expressions of NGF and TRPV1 were found higher in the DO following urethral obstruction in rats. In a partial BOO rat model, increased urinary NGF levels were found in associated persistent DO after obstruction relief. The transgenic mouse model with urothelial NGF-overexpression were found to reduce bladder capacity, increased number and amplitude of nonvoiding bladder contractions and increased referred somatic pelvic hypersensitivity. These findings suggest NGF is involved in the neuromodulation of sensory pathways governing DO.

Clinically, we also found that urinary NGF levels increased in men with BOO and OAB and persistent OAB after medical treatment for BOO. In women with mixed stress and UI UI as well as those with de novo DO, urinary NGF levels were also increased. However, women with pure intrinsic sphincter deficiency did not have an elevated urinary NGF level. In a recent study comparing urodynamic DO and IBS, urinary NGF levels are significantly higher in DO than IBS bladders (Table 1).

Since urinary NGF is highly expressed in patients with OAB-wet, we hypothesize that determination of urinary NGF level could serve as a valuable biomarker for the diagnosis of DO and monitoring of disease progression of LUTD. Therefore, if we select OAB patients with elevated urinary NGF level for clinical trials of pharmaceutical treatment, the results of trial might reflect the real effects on DO. If urinary NGF levels can be reduced after successful therapy such as antimuscarinics or BoNT-A treatment for DO, measurement of urinary NGF could be a useful objective tool for assessing the therapeutic outcome of DO.

A cross-sectional study performed in 143 patients with IDO who had either no history of treatment, or were responders and non-responders to antimuscarinics treatment. The mean urinary NGF/Cr levels were significantly higher in 66 patients with untreated IDO compared to controls. Patients with well-treated IDO had reduced NGF/Cr levels whereas those with failed-treated IDO did not. Patients responding to 100 U BoNT-A treatment had significantly reduced urinary NGF/Cr levels in IDO patients compared to baseline levels. The NGF levels remained significantly higher at 3 months in seven IDO patients who also failed the BoNT-A treatment.

6. NDO AND URINARY NGF

A recent study also found that BoNT-A injections into detrusor decreased NGF bladder tissue levels in patients with NDO. Detrusor injection of BoNT-A reduced urgency sensation and decreased P2X3 and TRPV1 receptor expressions in suburothelium. We can hypothesize that urgency may be mediated by overproduction of sensory proteins such as NGF, prostaglandin E2 or calcitonin gene related peptide, or over-expression of receptors on suburothelial sensory fibers. NGF might play an important role in the connection between suburothelial sensory fibers and detrusor muscle excitability.

Increased expression of the neurotrophic factors NGF and brain derived nerve factor has been associated with animal models with SCI. Increased NGF levels in the rat bladders, dorsal root ganglia and spinal cord are believed to contribute to the emergence of detrusor-sphincter dyssynergia partially mediated by C-fiber bladder afferents after SCI. The SCI rats with higher severity of autonomic dysreflexia (AD) correlated with higher NGF expression in lumbosacral segments.

In a recent study, urinary NGF levels were measured in patients with NDO due to SCI at baseline and after antimuscarinic or BoNT-A injections. The urinary NGF/Cr levels were significantly elevated in NDO (0.62 ± 1.22) compared to that in the controls (0.005 ± 0.019). Patients with detrusor-sphincter dyssynergia and AD had a higher NGF/Cr level compared with those without AD, and the urinary NGF levels are higher in patients with high voiding pressure than low voiding pressure (Fig. 2). After BoNT-A injections, a successful result was achieved in 74% patients with NDO. At baseline, the urinary NGF/Cr levels were significantly higher in responders with NDO as well as in non-responders with NDO compared to controls. Analysis of the therapeutic outcome revealed a significant decrease in urinary NGF/Cr level in BoNT-A responders with NDO, but significant decrease in non-responders of NDO at 3 months was not observed. Persistent low urinary NGF/Cr levels compared to baseline were also detected at 6–12 months in 12 patients with NDO who had long lasting BoNT-A effect for more than 6 months.

In addition to NDO of SCI, elevated urinary NGF levels were found in patients with chronic CVA and OAB. The NGF levels were noted to associate with the severity of neurological impairment of CVA. The similar finding was also reported recently. However, another
study found urinary prostaglandin E2, but not NGF, was increased in patients with suprapontine brain diseases and associated OAB.  

7. LONGITUDINAL STUDIES OF URINARY NGF AFTER ANTIMUSCARINIC THERAPY IN OAB

Reduction of increased NGF levels in urine of OAB patients paralleled with the improvement of OAB symptoms after antimuscarinic therapy. This reduction of urinary NGF levels in OAB patients accompanying symptomatic improvement after the antimuscarinic treatment supports the existence of a link between NGF production and muscarinic receptor activation in OAB.  

Another recent longitudinal study measured urinary NGF levels in 38 normal controls and 70 OAB patients receiving tolterodine 4 mg QD. The urinary NGF/Cr levels and USS were compared at baseline, 1, 2 and 3 months after antimuscarinic treatment and 1 month after discontinuing treatment. After antimuscarinic treatment, urinary NGF/Cr levels were significantly reduced at 3 months in 50 responders who also had a reduction of USS by two or more scales but not in 20 non-responders who did not have a USS reduction by two scales. After discontinuing antimuscarinic treatment for 1 month, however, urinary NGF/Cr level was elevated again in 23 responders and in five non-responders. The USS significantly changed with the change of urinary NGF/Cr levels in responders at different time points. The change of urinary NGF levels is associated with the changes in USS after antimuscarinic treatment and discontinuance of medication (Fig. 3).

Studies on rodents have shown that NGF is taken up by sensory nerves and transported through the central nervous system in retrograde fashion. Urinary NGF levels are decreased in association with the reduction of urgency severity and increased when OAB symptoms recurred. A lag response time between changes in USS and NGF was noted in responders, which might be due to the time lag in the decrease of NGF production after antimuscarinic treatment. However, patients with improved USS may still have unresolved underlying pathophysiology of OAB. After antimuscarinic treatment for 3 months, the USS did not decrease to zero and urinary NGF levels also remained significantly higher than those of controls.

We recently assessed the changes of urinary NGF in OAB patients after antimuscarinic therapy for 12 months, which revealed that the decrease of urinary NGF levels failed to reach a nadir. Figure 4 shows the changes of urinary NGF/Cr levels with time after effective antimuscarinic treatment in 28 patients who had OAB symptomatic improvement up to 12 months. Although patients reported relief from OAB symptoms after long-term antimuscarinics treatment, urinary NGF/Cr levels decreased significantly from baseline (1.02 ± 1.02) to 1 month (0.45 ± 0.66), 3 months (0.52 ± 0.70), 6 months (0.18 ± 0.24), but remained stationary at 9 months (0.29 ± 0.43) and 12 months (0.28 ± 0.37). The urinary NGF levels at 12 months after antimuscarinic treatment were significantly lower than the baseline (P = 0.007), but were higher than the controls (0.05 ± 0.02) (Fig. 4).

8. BLADDER INFLAMMATION AND URINARY NGF IN OAB

Tyagi and Chancellor recently proposed the hypothesis that local inflammation is a cause and plays a central role in the etiology of the OAB. Multiplex analysis
revealed increased urinary cytokine levels in a rat model of cyclophosphamide-induced cystitis. Pre-clinical studies have shown that increased urine levels of monocyte chemoattractant protein 1 and CXC chemokines CXCL1 are evidence of bladder inflammation. Analysis of urine from a single void of OAB patients revealed significant elevation of chemokines and cytokines relative to asymptomatic controls. The higher urine cytokine levels in OAB-wet relative to OAB-dry suggest a relationship between OAB symptom severity and bladder inflammation. Inflammatory processes are likely to be involved in the etiology of the OAB. Thus, the elevated urinary NGF levels after long-term antimuscarinic treatment might imply the existence of a residual inflammation in the bladder or central nervous system.

One recent study found that serum C-reactive protein (CRP) and urinary NGF levels were elevated in patients with OAB and IC/BPS compared with the controls. Although the elevated serum CRP levels were not significantly correlated with urinary NGF levels in any subgroups, these two protein levels were highly correlated in OAB patients with a serum CRP > 3 mg/L. Furthermore, serum CRP levels were higher in OAB-wet than OAB-dry, which was similar to the presentation of urinary NGF levels, suggesting a locally inflammatory process might exist in the bladder in patients with OAB.

9. IC/PBS and Urinary NGF

In patients with IC/PBS, neurotrophins, including NGF, neurotrophin-3 and glial cell line-derived neurotrophic factor have been detected in the urine. Increased expression of NGF is also present in bladder biopsies from women with IC/PBS. Thus, target organ-neural interactions mediated through an increase of neurotrophins in the bladder and increase in transport of neurotrophins to the neuronal cell bodies inafferent pathways may contribute to the emergence of bladder pain in IC/PBS. Patients with IC/PBS who respond to intravesical BoNT-A injection have been shown to reduce bladder tissue NGF expression.

In a recent study of urinary NGF expression in women with IC/PBS, the urinary NGF/Cr levels were very low when the bladder was not distended and significantly elevated at fully distended bladder in IC/PBS patients. The study showed that patients with IC/PBS had increased urinary NGF/Cr levels compared to controls. However, urinary NGF/Cr levels were not correlated with visual analog score or cystometric bladder capacity at diagnosis, or maximal bladder capacity during hydrodistention.

10. Comparison of Urinary NGF Between OAB and IC/PBS

A recent study compared the urinary NGF levels among IC/PBS, OAB-dry and OAB-wet patients. The study found increased NGF levels in women with IC/PBS and OAB-wet or DO but not in controls and women with OAB-dry or hypersensitive bladder. Urinary NGF/Cr levels were not significantly different among patients with IC/PBS, OAB-wet or DO. However, urinary NGF levels were significantly higher in women with IC/PBS than in women with OAB-dry or IBS.

Previous studies have revealed that mast cells are multifunctional effectors of the immune system, and have been reported to play an important role in the pathophysiology of IC/PBS. Because there are similarities in the inflammatory protein expression between OAB and IC/PBS, we hypothesized that inflammatory reactions might also exist in the bladder tissue of OAB. A recent study revealed patients with OAB and IC/PBS all had a significantly greater number of mast cells in the bladder wall compared with controls. Bladder mast cell activation has been reported as a characteristic pathological finding in a subset of IC/PBS patients. Since patients with OAB and IC/PBS all had elevated mast cell activities compared with that of the controls in this study, it is possible that a common pathway of chronic inflammation exists in the pathogenesis between these two diseases. Therefore, it would be difficult to distinguish IC/PBS from patients with frequency urgency syndrome by the urinary NGF level.

Although urinary NGF/Cr levels were not significantly different between patients with IC/PBS and OAB-wet in this study, patients with IC/PBS had a significantly greater urinary NGF/Cr level than patients with OAB-dry (Table 1). The symptoms of IC/PBS and OAB-wet are reasonably distinct as patients with IC/PBS suffer from bladder pain and patients with OAB-wet suffer from urgency incontinence. By contrast, differential diagnosis between IC/PBS and OAB-dry based on symptoms is usually difficult. Therefore, urinary NGF/Cr level might be useful in differential diagnosis in patients with sensory bladder disorders.

11. Urothelial Dysfunction as a Cause of Urinary NGF Increases in OAB

Urothelial dysfunction is known to act as a key contributing factor of IC/PBS. Whether the urothelial dysfunction exists in OAB bladder has not been elucidated. Previous studies have shown that adherens junctions decreased in patients with DO and BOO. It is likely that urothelial dysfunction also play a role in the pathogenesis of DO or OAB. Whether the main elevated urinary NGF in DO bladders come from urothelium or detrusor remained undetermined. How the NGF protein excretes into the vesical lumen has also not been explored. The urothelial dysfunction could be a cause for the increased urinary NGF level in urine of DO bladders.

A previous study has shown that urinary NGF levels may increase in the unfilled bladder of patients with DO but not in the normal controls. At fully distended bladders, the urinary NGF levels were slightly increased in the normal controls. This observation implies that the urothelium may act as a barrier to prevent NGF leaking out of the bladder wall in resting state. At fully distended bladder, however, the highly secreted NGF might leak into the vesical lumen, higher in DO and lower in the control bladders. Recently, we investigated the bladder wall NGF
concentrations and found the urothelial NGF level was not different between DO and control bladders.\(^\text{39}\) It is possible that the elevated urinary NGF in DO bladder is caused by excretion of NGF through the dysfunctional urothelium. Further investigation targeting at urothelial dysfunction in OAB is needed and might have promising result.

12. CONCLUSION

Urinary NGF levels measurement in OAB can provide insight to the underlying pathophysiology. Significantly higher urinary NGF levels were measured in IDO and NDO patients compared to the controls and patients with IBS. Because urinary NGF level can be increased in a variety of LUTD, including IC/PBS, its sensitivity may be superior to its specificity. The specificity of diagnosing the presence of DO in patients with sensory bladder disorders solely by urinary NGF level is still limited. Measurement of urinary NGF levels may be more useful to evaluate IDO and NDO treatment outcome and predictor of disease progress rather than differential diagnosis of DO in OAB patients. The potential of urine biomarker of OAB is exciting and prospective randomized clinical studies in larger cohort of patients are currently underway to evaluate the clinically usefulness of urine NGF biomarker.

Disclosure

Dr. Chancellor is a consultant for Astellas and Pfizer. Dr. Guan is an employee of Pfizer.

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