Urinary biomarkers of overactive bladder

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To the Editor: Overactive bladder (OAB) is a common clinical manifestation of voiding dysfunction. The incidence of OAB among people over 18 years old is 5.9%, and is known to increase with age up to an incidence of 11.3% in people over 40 years old in China. OAB seriously affects the quality of life, causing great inconvenience to patients' work and home life that can result in a variety of physiologic, psychologic, and social problems. The diagnosis of OAB depends mainly on the patient's subjective clinical symptoms, as well as auxiliary examination including invasive urodynamic examination, a urination diary, and a symptom questionnaire, which can lack objectivity and accuracy. Thus, in recent years, there has been interest in identifying biomarkers of OAB. Potential biomarkers of OAB identified to date include the nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF).

Previous studies have shown higher urinary NGF[1] and BDNF[2,3] levels in patients with OAB than in females without lower urinary tract symptoms. NGF level is positively correlated with the severity of OAB.[1] Antimuscarinic drug treatment can relieve symptoms and reduce urinary NGF levels.[4,5] Therefore, urinary NGF and BDNF levels are potential biomarkers of OAB. The present study investigated the levels of these biomarkers in females with OAB, aiming to identify the possible use of these substances for OAB diagnosis and severity assessment. We also explored the clinical diagnostic threshold and accuracy of each biomarker, providing reference values for these potential urinary biomarkers in OAB diagnosis in future studies.

We recruited 30 cases of untreated OAB in female patients with a mean age of 62.0 ± 15.5 years as the OAB group, and 25 female patients with a mean age of 66.6 ± 11.8 years as the control group from August 2014 to February 2015. We then compared variables between the two groups. The urinary creatinine (Cr) values were 0.64 ± 0.47 and 0.75 ± 0.51 mg/mL for the OAB and control groups, respectively, which did not have a significant difference. The mean total overactive bladder symptom score (OABSS) in the OAB group was 8.9 ± 3.5 points, which was significantly higher than that in the control group (1.7 ± 1.6 points, $P < 0.01$) [Supplementary Table 1, http://links.lww.com/CM9/A28]. The mean urinary NGF/Cr and BDNF/Cr levels in the OAB and control group are shown in Supplementary Table 2, http://links.lww.com/CM9/A28. Urinary NGF/Cr and BDNF/Cr were significantly higher in the OAB group than in the control group ($P = 0.04$ and $P < 0.01$, respectively). In the OAB group, the numbers of patients in the mild, moderate, and severe subgroups were 7, 13, and 10. The numbers of patients in the dry and wet OAB subgroups were 9 and 21, respectively. Correlation analysis showed that urinary NGF/Cr and BDNF/Cr levels were positively correlated with total OABSS scores [Supplementary Figure 1, http://links.lww.com/CM9/A28]. In words, the heavier the severity of OAB symptoms, the higher the levels of these four biomarkers.

Based on *post hoc* multiple comparison tests of urinary NGF/Cr and BDNF/Cr levels in the different subgroups, it was found that urinary NGF/Cr levels in the severe OAB subgroup were significantly higher than those in the control group and mild OAB subgroup ($P < 0.01$). In addition, urinary BDNF/Cr levels in controls were significantly lower than those in patients with moderate to severe OAB ($P = 0.03$ and $P < 0.01$, respectively), as well as patients with mild and severe OAB ($P = 0.01$) [Supplementary Table 3, http://links.lww.com/CM9/A28]. Furthermore, urinary NGF/Cr and BDNF/Cr levels were both significantly elevated in patients with wet OAB compared with controls and the dry OAB subgroup ($P < 0.05$) [Supplementary Table 4, http://links.lww.com/CM9/A28]. *Post hoc* multiple comparisons of urinary NGF/Cr and BDNF/Cr levels of different OAB symptoms according to OABSS showed that the levels of urinary NGF/Cr and BDNF/Cr were significantly correlated with the degree of urinary urgency ($r = 0.55$, $P < 0.01$ and $r = 0.43$, $P = 0.02$, respectively). The results were similar for patients with urge urinary incontinence (UUI) ($r = 0.59$, $P < 0.01$ and

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Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000214

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Chinese Medical Journal 2019;132(9)

Received: 05-11-2018 **Edited by:** Yuan-Yuan Ji

$r=0.52$, $P<0.01$, respectively) [Supplementary Table 5, http://links.lww.com/CM9/A28].

The levels of these two biomarkers were analyzed by the receiver operating characteristic (ROC) curve to evaluate the diagnostic value of OAB. The area under the curve (AUC) was 0.793 and 0.739, respectively, for the two biomarkers ($P<0.01$ and $P=0.01$, respectively). The sensitivity and specificity of these biomarkers according to the cutoff values are shown in Supplementary Table 6, http://links.lww.com/CM9/A28. These findings suggest that urinary NGF/Cr has the highest predictive value for diagnosis of OAB, while BDNF/Cr has the second highest predictive value.

Exploration of the pathogenesis, diagnosis, and treatment of OAB is a hot topic in the field of urinary continence. Many animal and clinical trials have been carried out to identify biomarkers that reflect the state of OAB and to evaluate treatment effect accurately and objectively. Liu and Kuo[1] and Antunes-Lopes *et al*[2] both found that urinary NGF/Cr was elevated in patients with OAB. Similarly, Kim *et al*[6] revealed that the levels of urinary NGF in patients with OAB were significantly higher than those in controls, although Cr value was not adjusted to urine concentration in their study. Moreover, significant increases in urinary NGF/Cr levels were observed between patients with wet and dry OAB by Liu *et al*,[4,7] suggesting that urinary NGF/Cr levels are positively related to OAB severity. In the present study, we reached the same conclusion regardless whether the total score of OABSS or combined with UUI or it was not defined as a severity classification. Therefore, urinary NGF/Cr levels could potentially be used for diagnosis and evaluating the severity OAB. According to our results, the sensitivity and specificity can reach 93.3% and 64.0%, respectively, with a cutoff value of 26.32 pg/mg.

Wang *et al*[3] reviewed 90 female patients with OAB and 45 women without lower urinary tract symptoms and found that urinary BDNF/Cr levels were significantly elevated in patients with OAB. In their study, all patients were divided into subgroups with OABSS scores of 0-2, 3-5, 6-8, 9-11, and 12-14. Urinary BDNF/Cr levels were significantly correlated with this stratification, supporting that BDNF/Cr is positively correlated with the severity of OAB symptoms. Antunes-Lopes *et al*[2] reached the same conclusions in their study. The results of the present study are consistent with those of previous research. It should be pointed out that Wang *et al*[3] suggested that the BDNF/Cr content in urine was 80 times that of NGF/Cr, and that the AUC was higher in the ROC curve for BDNF/Cr content. Urinary BDNF/Cr levels thus seem to have more diagnostic and predictive value than NGF/Cr. In the present study, the content of urinary BDNF/Cr was about 21.2 times that of NGF/Cr (range: 2.6–63.0) while the AUC of BDNF/Cr was lower than that of NGF/Cr (0.739 *vs.* 0.793), which differs slightly from the previous study. The reasons for this difference might relate to differences in the urinary BDNF/Cr and NGF/Cr contents due to use of different reagent kits. Large-scale trials are thus needed to precisely evaluate BDNF/Cr and NGF/Cr values in OAB diagnosis in the future.

After analysis of urinary BDNF/Cr and NGF/Cr levels in 37 patients with OAB, Antunes-Lopes *et al*[2] found that, compared to controls, 12 patients had increased BDNF/Cr and NGF/Cr levels, 14 patients had only increased BDNF/Cr levels, 2 patients had only increased NGF/Cr levels, and nine patients showed no increased biomarkers. Thus, they suggested that different phenotypic patients with OAB might have different pathophysiologic mechanisms. In our study, there were also four different BDNF and NGF phenotypes in the OAB group. Compared to the control group, 20 patients were observed to have increased BDNF/Cr and NGF/Cr levels, 4 patients had only increased BDNF/Cr levels, 1 patient had only increased NGF/Cr levels, and five patients showed no increased biomarkers. However, the hypothesis of different phenotypes representing different pathophysiologic mechanisms and the correlated mechanisms of these phenotypes requires further validation and discussion.

This study analyzed the relationship between these urinary biomarkers and the symptoms of OAB, including urinary frequency, nocturia, urinary urgency, and UUI. It was found that the severity of urinary urgency and UUI were positively related to NGF/Cr and BDNF/Cr levels in urine. However, there were no significant differences for other variables. The results are in accordance with the clinical manifestations of OAB, supposing that urinary urgency is the core symptom of OAB and might be accompanied by UUI, and that urinary frequency and nocturia are not the core symptoms. Our study also demonstrated the value of urinary NGF/Cr and BDNF/Cr levels for OAB diagnosis.

Our study is subject to several limitations. First, it was a small-scale study and only two biomarkers were assessed. Additionally, only untreated female patients with OAB were included. As we did not consider patients with secondary OAB, treatment history, or male patients, our results may not generalize to other patient groups with OAB. Finally, we did not assess the value of these biomarkers after standard treatment for therapeutic assessment. Further efforts could focus on these aspects and large multi-center trials are needed to validate our conclusions.

Overall, this study demonstrated that urinary NGF/Cr and BDNF/Cr levels in untreated female patients with OAB are significantly higher than those in females without lower urinary tract symptoms. These levels correlated positively with the severity of symptoms, suggesting that they may be useful biomarkers for diagnosis of OAB.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgements

The authors thank the entire staff of the Department of Urology, Peking University Third Hospital.

Conflicts of interest

None.

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How to cite this article: Tian XJ, Liu C, Liu K, Tang SY. Urinary biomarkers of overactive bladder. Chin Med J 2019;132:1104–1106. doi: 10.1097/CM9.0000000000000214