Biomarkers in overactive bladder: Where do we stand today?

Without curative treatment, biomarkers' role remains limited

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Biomarkers are measurable characteristics that reflect physiological and pathogenic processes, or pharmacological responses to therapeutic interventions.[1] In overactive bladder (OAB), biomarkers can be urine, blood or genetic assays, urodynamic and imaging tests, able to determine the occurrence of detrusor overactivity (DO) during bladder filling, and questionnaires.[2,3]

Whatever the concept one has of a biological marker, the ideal test to be used as a biomarker in OAB is yet to be identified. Nevertheless, it is easy to agree upon several features, which lacking, will downbeat the enthusiasm for the test. Required characteristics include: to be non-invasive, to be measured by a simple and reproducible method in easily collectable biological samples, to really help in establishing the diagnosis, prognosis and recurrence of OAB symptoms.[2,4] Not irrelevant, the routine use of the biomarker should influence the outcome of OAB treatment and be cost effective.

Cost-effectiveness is a serious issue in OAB management and in biomarkers research. In the current paradigm, treatment is initiated following the presumption of bothersome OAB symptoms, urgency upfront as the leading complain, and the exclusion of obvious local diseases, as urinary tract infections (UTI), bladder tumours or voiding dysfunctions with significant post-void residual volume. Is it cost-effective to defer treatment until a biomarker establishes unequivocally the diagnosis of OAB? Will OAB management be improved with this new paradigm? That, of course, will depend upon the sensitivity, specificity and the cost of the biomarker.

Additionally, OAB is defined as a symptom complex that may be associated with other conditions. According to the International Continence Society (ICS) OAB is defined as urinary urgency, with or without urgency urinary incontinence, usually accompanied by frequency and nocturia.[5] As an obvious corollary, it is difficult to support the prescription of current or very soon available medications, like antimuscarinics, β3-adrenergic receptor agonists, or onabotulinumtoxinA in individuals without symptoms, despite a positive biomarker. In fact, all these therapeutic options are symptomatically oriented and not intended to cure OAB.

There are, however, some patients who might immediately benefit from the existence of an OAB biomarker. These are patients with stress urinary incontinence (SUI), who also complain of urgency when a few drops of urine leaking into the posterior urethra trigger a sensation of impending micturition. Another group of patients that might benefit from biomarkers are those with mixed urinary incontinence (MUI).

As a matter of fact, MUI is still treated empirically, after presuming from the medical history and bladder diary which symptoms are more relevant. In addition, one cannot ignore that urgency is difficult to explain by caregivers and difficult to understand by individuals who never felt the sensation of impending micturition difficult or impossible to differ. Confusion with urge, a bladder sensation that refers to a strong desire to void, but still with full control of bladder function, is a classical example of a sensation that may be hard to discriminate from urgency.[6] Finally, phenotyping or genotyping patients may become relevant once difficult treatment options become available.

Urodynamics

Urodynamics was the first test investigated as a potential OAB biomarker. Unfortunately, it is invasive and DO can only be identified in roughly half of the patients with OAB.[7] Moreover, DO can be present in healthy individuals without OAB symptoms, and does not predict the response of OAB patients to antimuscarinics.[8] Near-infrared spectroscopy (NIRS), an optical technology, is being investigated as a non-invasive method to identify DO. This technique detects changes of oxyhemoglobin (O2Hb) and deoxyhemoglobin (HHb) in the bladder wall during involuntary bladder contractions. Initial reports indicated a high sensitivity and specificity,[9] but a recent study involving a hundred women with OAB symptoms concluded that NIRS is an unreliable method for detecting DO in OAB.[10] Therefore, this technique is far from being reproducible and is not easily available.

Bladder wall thickness

Bladder wall thickness (BWT) is another potential biomarker. As OAB has been linked to DO, it has been hypothesized that frequent detrusor contractions would cause increased BWT. In women with OAB symptoms, BWT is about 3mm higher than that of healthy individuals.[11,12] In addition, BWT can differentiate women with SUI or DO, the later having a higher BWT.[13]

Moreover, it was noted a decrease in BWT after antimuscarinic treatment,[14] suggesting that this marker can also be used to assess the efficacy of this therapy. However, other reports are contradictory. Chung et al. found that the thickness of the bladder muscle layer in women with and without OAB symptoms was not significantly different, and did not vary with the urodynamic status.[15] Other drawbacks that limit the use of this technique as a biomarker is the lack of standardisation. Should BWT be measured with the bladder empty, or distended to a certain volume? Should one rely on BWT or simply on the thickness of the detrusor layer? Which probe and route should be used to measure BWT? The use of a transvaginal route limits the application of this biomarker in males.

Neurotrophic factors

Neurotrophic factors are essential proteins for the differentiation, survival and maintenance of sensory neurons, which are emerging key players in OAB.[16] Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) are present in the urine of healthy individuals at low concentrations. The release of these factors seems to be constant along the day, without evidence of a circadian rhythm.[17]

NGF and BDNF are released from the urothelium and bind specific tyrosine kinase (Trk) receptors, TrkA and TrkB receptors, respectively, both abundantly expressed in the urothelium and bladder sensory afferents.[16,18] GDNF binds to GDNF family receptor α1 (GFRα1).[19] NGF and BDNF, which are committed with the peptidergic subpopulation of primary afferents, where shown to be substantially increased in the urine of OAB patients.[2,17,20] In contrast, the concentration of GDNF, which regulates the nonpeptidergic subpopulation of sensory afferents, was not altered in the urine of those patients.[17] This finding, not only discards GDNF as a candidate for OAB biomarker, but also eliminates nonpeptidergic sensory afferents as pivotal players in OAB pathophysiological mechanisms.[17]

Several studies have reported increased levels of NGF in the urine of OAB patients.[17,20,21,22] Patients with urgency urinary incontinence tend to have higher urinary concentrations of NGF than OAB dry patients.[23] However, other studies reported contradictory findings between urinary and urothelial concentrations of this neurotrophin.[24] Urinary levels of NGF decrease upon OAB management, including lifestyle intervention,17

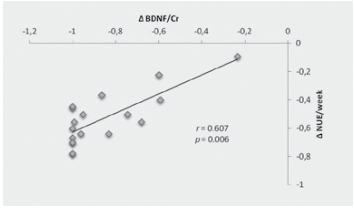

Fig. 1: Correlation between variations of urinary brain-derived neurotrophic factor/creatinine (BDNF/Cr) ratio and the number of urgency episodes per week (NUE/week), after lifestyle intervention plus antimuscarinic treatment, in overactive bladder (OAB) patients. A significant correlation was found (r = 0.607, p = 0.006). r = Pearson product-moment correlation coefficient.

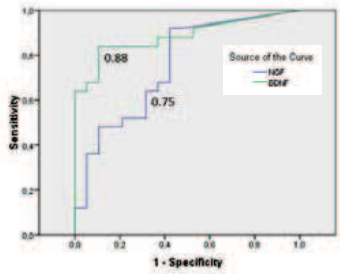

Fig. 2: Receiver operating characteristic (ROC) analysis for NGF and BDNF. The area under the curve (AUC) for NGF was 0.75 and for BDNF was 0.88. A threshold urinary BDNF/Cr of 300 pg/mg provided a sensitivity of 84% and a specificity of 90%, while a urinary NGF/Cr value of 275 pg/mg, granted a sensitivity of 52% and a specificity of 79%.

antimuscarinic treatment[17,25] and detrusor injection of onabotulinumtoxinA.[26]

In a recent study, Antunes-Lopes et al. showed that BDNF was also markedly increased in OAB patients, particularly those with the wet form of the condition.[17] Remarkably, BDNF levels were highly sensitive to OAB treatment. Both lifestyle intervention and antimuscarinic treatment caused a marked significant decrease in urinary BDNF concentration. In addition, a strong correlation was found between the decrease of urinary BDNF concentration and the reduction of the number urgency episodes per week (Figure 1).[17] In receiver-operator characteristic (ROC) analysis, the area under the curve (AUC) for BDNF was higher compared to NGF (Figure 2).[2] Interestingly, BDNF regulation was shown to be altered in patients suffering from depression and irritable bowel syndrome, two conditions frequently associated with OAB.[27,28]

Other potential biomarkers

It is known for many years that prostaglandins are involved in the control of bladder function.[29] Several studies using cyclooxygenase (COX) inhibitors have tried to decrease prostaglandin synthesis using flurbiprofen or indomethacin, although with limited success.[21,22] In a more recent study by Liu et al., the urinary levels of PGE2 in controls, OAB wet and OAB dry patients were similar. Therefore, there is no evidence to support prostaglandins as biomarkers for OAB.

Other putative biomarkers can be OAB susceptibility genes.[4] Microarray analysis revealed that 16 genes were differently regulated (8 up-regulated and 8 down-regulated) in all patients with OAB in comparison to healthy individuals. A sex-based analysis demonstrated 74 genes that were differentially regulated in males (25 up-regulated and 49 down-regulated), and 30 in females (13 up-regulated and 17 down-regulated).[30] Although the immediate consequences of this finding are still difficult to foresee, it is important to retain that most of these genes encode structural proteins relevant for the regulation of bladder wall tissue.

A limited role

OAB is a prevalent cause of lower urinary tract dysfunction, found to affect approximately 11.8% of the population living in the western world. Incidence increases with age indicating that the number of cases will rise in the next years.[31] Currently, diagnosis of OAB is based on patient self-reporting symptoms. Without a curative treatment, the role of a biomarker will be limited. Nevertheless, the introduction of an objective, reliable biomarker could facilitate the differential diagnosis of OAB with other conditions. This can be relevant in cases in which patients' complaints are not clear or can be confused with other causes of incontinence, eventually requiring a different treatment, as it is the case with SUI and MUI.

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