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Biomarkers in the Overactive Bladder Syndrome

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1. Introduction

Overactive bladder (OAB) is a symptomatic complex affecting both men and women. The overall incidence is above 10% but may exceed 40% in the elderly population (Irwin et al., 2006; Irwin et al., 2009; Sexton et al., 2009a). OAB is defined by the International Continence Society (ICS) as a clinical syndrome characterized by urinary urgency, with or without incontinence, usually with frequency and nocturia (Abrams et al., 2002, 2003; Hashim & Abrams, 2007). Urgency, which is a storage symptom defined as a sudden compelling desire to pass urine difficult to defer, is the hallmark symptom as it is the only one that must be present in order to establish the diagnosis of OAB (Abrams et al., 2002, 2003). Several comorbidities are very common among OAB patients, including depression, insomnia and fractures (Coyne et al., 2008; Sexton et al., 2009a; Sexton et al., 2009b). The economic costs of OAB, associated with medical consultations, therapy and diminished productivity at work, may reach billions of dollars (Irwin et al., 2009) and will certainly increase with the demographic shift of an ageing population.

The true causes of urgency/OAB remain poorly understood. The difficulty in establishing animal models that accurately represent urgency/OAB still holds. It was originally thought that the origin of OAB could be ascribed to anomalies in the neuromuscular junction and myocytes. More recent data indicate a strong involvement of bladder sensory mechanisms involving the urothelium and suburothelial afferent nerves. In addition, dysfunction of central nervous system centres that control the micturition reflex, including the Periaqueductal Gray (PAG) and pontine micturition centre, has been implicated in the genesis of OAB (Fowler et al., 2008; Drake et al., 2010; Fowler & Griffiths, 2010).

No cure exists for OAB. Management is initiated by exclusion of confounding diseases and by the introduction of conservative measures, including limiting fluid intake, avoiding caffeinated, acidic and carbonated drinks, weight reduction, smoke avoidance and bladder training. If bothersome OAB symptoms persist, patients are initiated on antimuscarinic

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therapy, the current mainstay for pharmacological management of OAB (Henderson & Drake, 2010; Athanasopoulos & Cruz, 2011). Nevertheless, despite significant improvement, antimuscarinics still produce important side-effects that may lead patients to discontinue treatment (Andersson, 2004; Andersson et al., 2009; Gulur & Drake, 2010). Moreover, antimuscarinics are contra-indicated for patients with narrow angle, may interfere with cognitive function and aggravate constipation (Gulur & Drake, 2010), all of which commonly occur in the typical OAB age group. More recently, the administration of vanilloids and botulinum toxin have been proposed as a possible treatment for OAB but these approaches should be taken with care as they are off-label procedures (Cruz & Dinis, 2007; da Silva & Cruz, 2009).

The key symptom in OAB, urgency, may often be confounded with urge to void. Urge is a normal bladder sensation, the intensity of which is proportional to the degree of bladder filling and allows the subject to fully control bladder function. Differentiation between urge and urgency may not always be an easy task for the caregiver or patients, particularly those who are cognitively impaired by age or disease (Michel & Chapple, 2009a, b). In addition, grading urgency is a difficult task to be accomplished by the clinician, even with the use of standardized questionnaires (Nixon et al., 2005; Starkman & Dmochowski, 2008). Currently, there is no objective test to diagnose OAB although several attempts have been made in order to overcome this. Here, we will review recent data proposing new biomarkers for a better characterization of OAB patients. The value of a biomarker in medicine is considerable and lies in its ability to identify the disease, back diagnostic and therapeutic decisions and establish a valuable prognosis to the condition. In addition, it will positively influence the outcome of the condition. In OAB, investigators have focused on bladder parameters (the presence of detrusor overactivity and the thickness of the bladder wall), serum proteins (the C reactive protein) and urinary elements (prostaglandins, cytokines and neurotrophins).

2. Bladder criteria

2.1 Detrusor overactivity

Detrusor overactivity (DO) is the urodynamic observation of involuntary detrusor contractions during the filling phase of cystometry (Abrams et al., 2002). Thus, DO can only be detected by urodynamic assessment, an invasive and expensive test. It has been demonstrated that DO was present in approximately 45% of OAB-dry and 60% of OAB-wet patients (Hashim & Abrams, 2006). As the main symptoms of OAB may suggest the presence of DO, several attempts have been made in order to correlate urgency with DO. However, in a recent study it was shown that reports of urgency sensations during filling cystometry were as likely to occur before or after an episode of DO and approximately one third of the DO events recorded were not associated with urgency (Lowenstein et al., 2009). In addition, DO, may be found in healthy individuals (Heslington & Hilton, 1996; van Waalwijk van Doorn et al., 1997; Hashim & Abrams, 2006). In fact, in the study by Hashim and Abrams 36% of the OAB patients studied (1076) did not present DO and more than 30% of individuals without OAB had DO (Hashim & Abrams, 2006). In addition, DO does not predict the response of patients to antimuscarinic treatment (Malone-Lee & Al-Buheissi, 2009). Hence, the combination of the discomfort felt by patients during an urodynamic evaluation with a low predictive value both for the diagnosis

and successful outcome of OAB treatment impedes the routine use of urodynamic assessment for the majority of OAB patients. In a recent study, investigators tried to identify the presence of involuntary detrusor contractions through near-infrared spectroscopy (NIRS), a non-invasive method (Farag et al., 2011a; Farag et al., 2011b). NIRS is an imaging technique that can be used to monitor haemodynamic events. As the name indicates, it uses light in the near-infrared area, which is able to penetrate the skin. It is absorbed by oxyhaemoglobin and deoxyhaemoglobin, the levels of which can reflect oxygen consumption. In those studies, investigators were able to demonstrate that detrusor contractions were accompanied by changes in those chromophores (Farag et al., 2011a; Farag et al., 2011b). The overall specificity of NIRS to detect DO was 86% when measuring oxyhaemoglobin, 80% for deoxyhaemoglobin and 72% for the sum of both chromophores. Despite obvious limitations, such as the inclusion of more men than women, results are interesting and deserve further investigation.

2.2 Bladder wall thickness/Detrusor thickness (BWT/DT)

In patients with bladder outlet obstruction, the thickness of the total bladder wall or simply the thickness of the detrusor layer was shown in several studies to be significantly increased in OAB patients when compared with healthy volunteers (Hakenberg et al., 2000; Oelke et al., 2006; Oelke et al., 2007). Hence, it was forwarded that BWT/DT could be influenced by the work overload of the bladder wall introduced by DO. Indeed, some authors have reported a trend of increasing DT associated with the severity of urgency as reported by Panayi and coworkers (Panayi et al., 2010). Khullar and co-workers analysed the total BWT via transvaginal ultrasound in a group of female patients with idiopathic DO (Khullar et al., 1996). They found that 58.7% of all analysed subjects had a mean BWT greater than 5 mm, 94% of which had DO. Only 1.6% of subjects had DO with a BWT of 3.5 mm or less. The authors proposed that the measurement of mean BWT by transvaginal ultrasound, with a cut-off of 5mm, is a suitable screening method (Khullar et al., 1996). In addition, by determining BWT also with transvaginal ultrasound, Kuhn and co-workers were able to differentiate between women suffering from stress urinary incontinence or bladder outlet obstruction (Kuhn et al., 2011). In OAB patients, DWT was reduced after anti-muscarinic treatment (Liu et al., 2009b; Kuo et al., 2010b). In addition, a positive correlation has been found between the presence of OAB and high BWT/DT (Robinson et al., 2002; Kuo, 2009).

However, the reliability of DT as a marker for DO or OAB is still debatable. BWT/DT are typically measured by ultrasound. One particular problematic issue is the well-known bias associated to the different operators of ultrasound. Another unsolved issue regards the best way to measure BWT/DT. Should the bladder be empty or filled? If filled, at which volume? Should one use an abdominal or transvaginal approach? Which are the costs? In addition, several studies failed to demonstrate significant differences between healthy controls, patients with DO, bladder outlet obstruction or with increased bladder sensation (Blatt et al., 2008). More recently, Liu et al measured the DT in normal controls and patients suffering from OAB or interstitial cystitis (Liu et al., 2009b). They found a wide variation amongst all groups of individuals with a trend of higher BWT/DT in OAB-wet patients that did not reach statistical significance. In another study, no differences in the BWT/DT were found between OAB patients and individuals with no OAB symptoms (Chung et al., 2010).

Clearly, the measurement of BWT or DT by ultrasound faces some drawbacks that are not yet overcome. Intra- and inter-operator variability in ultrasound measurements is probably the most important one. The use of different ultrasound probes, as well as in the resolutions of ultrasound-generated images (Kuo, 2009), is another limiting factor to the use of BWT/DT as a biomarker. Although clinically appealing, more studies are necessary before it becomes a tool for daily practice.

3. Urinary biomarkers

3.1 Prostaglandins

Prostanoids (prostaglandins and thromboxanes) are synthesized by cyclo-oxygenase (COX), present in several tissues including the bladder wall (Khan et al., 1998; Lecci et al., 2000; Azadzo et al., 2003; Andersson & Wein, 2004). Two COX isoforms exist. COX-1 is expressed constitutively and participates in normal bladder function whereas COX-2 is activated during cystitis (Lecci et al., 2000; Tramontana et al., 2000). Prostanoid synthesis can be induced by physiological stimuli (for example, detrusor muscle stretching), injuries of the mucosa, nerve stimulation, ATP and inflammatory mediators such as bradykinin and the chemotactic peptide N-formyl-L-methionyl-L-leucyl-L-phenylalanine (Khan et al., 1998; Andersson & Wein, 2004).

Prostaglandin (PG) E₂ is one of the most abundant prostanoid in the bladder (Jeremy et al., 1987; Khan et al., 1998). In rats, intravesical administration of PGE₂ facilitates micturition, increases basal intravesical pressure and induces bladder hyperactivity (Ishizuka et al., 1995). In the urethra, topical application of PGE₂ causes relaxation of the sphincter (Yokoyama et al., 2007). Likewise, intravesical instillation of an inhibitor of the COX-2 enzyme improved bladder function in an animal model of OAB (Jang et al., 2006). This supports a role for this prostanoid during bladder dysfunction and has justified a few inconclusive clinical trials regarding the use of non-steroidal anti-inflammatory drugs in the treatment of OAB. So, expectations were raised when Kim and co-workers found that levels of PGE₂ and PGF_{2α} were significantly higher in male and female OAB patients than in healthy controls (Kim et al., 2005; Kim et al., 2006). However, PG concentrations were not corrected for urine concentration. After correction for creatinine values, Liu and co-workers found no significant differences in PGE₂ content in patients with OAB wet, OAB dry and controls (Liu et al., 2010).

Thus, at this moment the role of urinary PGs, most notably PGE₂, as a putative tool for OAB diagnosis and follow-up is highly debatable. Moreover, the measuring methods rely on labour-intensive and expensive laboratory procedures. In addition, although it is relatively consensual that prostanoids participate in the mechanisms of OAB, it is not known if the recommended OAB therapies effectively reduce the PGs levels.

3.2 Urinary cytokines

The presence of cytokines in the urine has been addressed in various bladder and kidney disorders, including chronic renal disease, interstitial cystitis and vesicoureteral reflux (Ninan et al., 1999; Abdel-Mageed et al., 2003). It has been suggested that OAB may result from an underlying inflammation of the bladder, a hypothesis supported by recent studies

reporting the presence of histological signs of inflammation in biopsies from OAB patients (Comperat et al., 2006; Apostolidis et al., 2008). However, confirming the presence of inflammation through biopsies is certainly an invasive procedure not exempt of morbidities. The detection of signs of inflammation in the urine of OAB patients is a more attractive alternative. Tyagi and co-workers have recently collected urine samples from patients and determined the levels of various cytokines, chemokines, growth factors and soluble receptors (Tyagi et al., 2010). Using a luminometry-based assay, they found a significant increase, when compared with controls, in the concentration of various elements, including the monocyte chemotactic protein-1 (MCP-1), the soluble fraction of the CD40 ligand, the macrophage inflammatory protein (MIP-1 β) and interleukins 10, 5 and 12. Another group of researchers also analysed of urine samples from healthy individuals and OAB patients using a proteomic approach (Ghoniem et al., 2011). Interestingly, their results indicate that while the concentration of certain elements increases (such as interleukin 16), the concentration of others decreases (such as interleukin 7). Thus, the actual role of all of these cytokines in OAB is far from being well understood, undermining its utility as biomarkers.

3.3 Neurotrophins

Neurotrophins are tissue-derived trophic factors necessary for the embryonic differentiation, survival and maintenance of neuronal cells both in the peripheral and central nervous system (Pezet & McMahon, 2006). The most well studied neurotrophins are Nerve Growth Factor (NGF) and Brain Derived Neurotrophic Factor (BDNF). They exert their effects via their specific tyrosine kinase (Trk) receptors. NGF binds to TrkA while TrkB is the receptor of BDNF. Both TrkA and TrkB are present in the bladder urothelium and sensory afferents innervating the organ (Qiao & M.A. Vizzard, 2002; Murray et al., 2004).

3.3.1 Nerve Growth Factor (NGF)

NGF has attracted considerable attention in the Urology field. It is accepted that NGF is produced by detrusor muscle cells and by the urothelium (Steers et al., 1991; Steers et al., 1996; Clemow et al., 1997; Clemow et al., 2000; Steers & Tuttle, 2006). In humans and in rodents, the production of NGF in the lower urinary tract and in the neuronal circuits regulating bladder function is increased in pathological conditions, including cystitis and spinal cord injury (Lowe et al., 1997; Vizzard, 2000; Murray et al., 2004). In addition, exogenous NGF is known to induce bladder overactivity, irrespective of the route of delivery (Lamb et al., 2004; Yoshimura et al., 2006; Zvara & Vizzard, 2007). Likewise, manipulation of NGF levels improves bladder function and referred pain in rats with cystitis (Hu et al., 2005; Frias et al., 2009).

Recent studies have demonstrated the presence of NGF in the urine of OAB patients (Kim et al., 2005; Kim et al., 2006; Liu & Kuo, 2008; Liu et al., 2009a, b; Liu et al., 2009c; Jacobs et al., 2010; Liu et al., 2011a). Levels were significantly higher than in healthy individuals and subsided after successful treatment with antimuscarinics (Liu et al., 2009b) or botulinum toxin-A (Liu et al., 2009a), in parallel with a decrease in the USS score. Based on these results, some authors have forwarded the use of NGF as presumed biomarker for OAB (Kuo et al., 2010a). Nevertheless, caution should be advised as most studies have not been placebo controlled which may hamper the interpretation of results.

3.3.2 Brain Derived Neurotrophic Factor (BDNF)

The presence and role of BDNF in the bladder has been scarcely analysed and available results mostly refer to rodent models of bladder dysfunction. Like NGF, BDNF can be synthesized by bladder cells, most notably the urothelium during cystitis (Pinto et al., 2010a) or spinal cord injury (Vizzard, 2000). The expression of TrkB is also abundant in sensory neurons innervating the bladder wall (Qiao & Vizzard, 2002; Murray et al., 2004). Like in somatic tissue (Kerr et al., 1999; Thompson et al., 1999), BDNF expression in the bladder seems to be under the control of NGF (Schnegelsberg et al., 2010; Girard et al., 2011). BDNF appears to be a key participant in bladder dysfunction in an animal model of cystitis as its sequestration improved both bladder reflex activity and peripheral hypersensitivity (Frias et al., 2009; Pinto et al., 2010a).

In humans, it has been reported that urinary BDNF is elevated in patients suffering from bladder pain syndrome/interstitial cystitis (Pinto et al., 2010b). In OAB, a recent study demonstrated that urinary BDNF was also elevated and significantly decreased after therapeutic intervention (Antunes-Lopes et al., 2011). In addition, the concentration of urinary BDNF was shown to be decreased to normal values after successful OAB treatment (Antunes-Lopes et al., unpublished observations). This may indicate that, like NGF (Kuo et al., 2010a), urinary BDNF may serve as an OAB biomarker. However, further studies are necessary to fully understand the importance of BDNF in OAB, particularly how it can influence the OAB outcome.

4. Urinary proteomics

There is a considerable interest in urine as a source of biomarkers for bladder pathologies, OAB assuming one of the foremost active areas of research. Indeed, urine is one of the most versatile biofluids as it can be easily obtained in large quantities with non-invasive methods and is stable in comparison with other fluids. Several peptides and low molecular weight proteins can be found in urine. When urine is collected for analysis, most of them should have undergone physiological proteolysis as urine may stagnate for hours in the bladder before micturition occurs. This might constitute an advantage as, in contrast with blood, serum or plasma, urinary proteins and peptides will not undergo further degradation upon collection (Kolch et al., 2005; Omenn et al., 2005).

With the advent and improvement of proteomic analysis, increasing attention has been given to the description of the urinary proteome. The number of proteins identified in the human urine is still increasing and is well above 1500 (Adachi et al., 2006; Good et al., 2010). The combination of different analysis methods and sample treatment recently allowed the identification of more than 100 000 peptides, 5000 of which were present in more than 40% of the individuals analysed (Coon et al., 2008). Several methods are currently being used to analyse the urinary proteome, including two dimensional gel electrophoresis mass spectrometry (2DE-MS), liquid chromatography MS (LC-MS), surface-enhanced laser desorption/ionization (SELDI-TOF) and capillary electrophoresis MS (CE-MS). If interested in more details and the specific advantages and disadvantages of each method, the readers are advised to seek that information elsewhere (Decramer et al., 2008).

With the recent advances in urinary proteomics, researchers are becoming more aware of problems arising during storage and preparation of samples. One important issue is the

stability of urine samples. Studies show that sequential freeze/thaw cycles may affect the concentration of certain proteins. Schaub and co-workers showed that there were no significant differences in the protein profile between samples analysed before freezing and after 1 to 4 freeze-thaw cycles (Schaub et al., 2004). These results have been confirmed in subsequent studies by non-related groups (Fiedler et al., 2007; Thongboonkerd, 2007). No data is available regarding the proteomic analysis of the urine of OAB patients.

5. Serum biomarkers

5.1 C- reactive protein (CRP)

CRP is a highly conserved plasma protein. It was identified in the 1930's in the sera of patients in the acute phase of pneumonia by Tillet and co-workers (Tillett & Francis, 1930; Black et al., 2004). Further studies demonstrated that the concentration of CRP in plasma is significantly increased during inflammatory states, a characteristic that has often been used for diagnostic purposes. In what concerns the urinary tract, plasma CRP has been used to monitor the progression of bladder cancer (Hilmy et al., 2006; Gakis et al., 2011a; Gakis et al., 2011b). As far as we are aware, CRP has been addressed in OAB only in a recent pilot study. Chung and co-workers observed higher levels of serum CRP in OAB patients than in controls, particularly in the group of OAB wet patients (Chung et al., 2011). Both urinary CRP and the amount of CRP mRNA present in the bladder wall were very low, indicating that the serum is the body fluid of choice to measure this protein. However, one should be aware that serum CRP would most likely reflect the presence of any inflammatory condition (Black et al., 2004), making its use as a putative biomarker in OAB is very modest.

5.2 Serum NGF

Like in urine, the presence of NGF in the serum of OAB patients has also been investigated (Liu et al., 2011b). The authors found a positive correlation between urinary and serum NGF contents. Interestingly, serum NGF remained elevated in OAB patients not responding to antimuscarinic treatment, suggesting that increased circulating NGF may be a factor in refractory OAB. This is, however, the only available study regarding serum NGF levels in OAB. It is presently not clear if the high content of NGF in the serum was strictly associated with OAB or dependent on associated comorbidities (hypertension, diabetes, coronary arterial disease, etc.) (Brown et al., 2000). More studies are needed in order to fully understand the relevance of serum NGF in OAB.

6. Conclusion

Clinicians and researchers are still far from having a tool to efficiently detect and monitor OAB. Several attempts have been made to identify specific bladder parameters, serum and urinary proteins that could fulfil such purpose. In all cases, researchers have come across issues. Due to several problems, the real clinical relevance of each proposed biomarker is still very much unclear, most of the publications reflecting more the willingness of the investigators rather than the true scientific value of findings. More studies are clearly necessary. In the near future, it is likely that some of these issues are overcome, as researchers are increasingly aware of the need to standardize methodologies and are already proposing basic protocols that could be easily adopted by most laboratories. Multicentre

collaborative studies are also necessary to increase the size of the cohorts analysed and decrease the obvious bias of single centre findings. Hopefully, this area of research will arrive to a positive destiny with a beneficial impact on the diagnosis and outcome of OAB patients.

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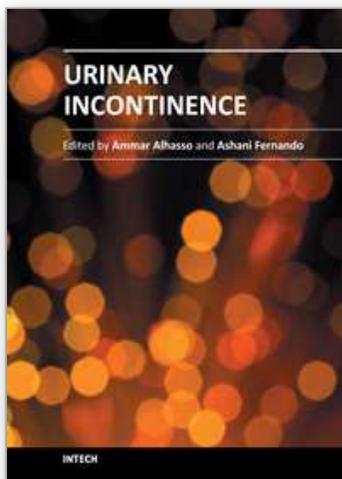
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Management strategies are framed within a multidisciplinary team structure and as such a range of specialists ranging from psychologists, specialist nurses, gynaecologists and urologists author the chapters. There are some novel methods outlined by the authors with their clinical application and utility described in detail, along with exhaustive research on epidemiology, which is particularly relevant in planning for the future.

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