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Lower Urinary Tract Symptoms and Aging: The Impact of Chronic Bladder Ischemia on Overactive Bladder Syndrome

Key Words

Overactive bladder · Aging · Vascular disease · Ischemia · Lower urinary tract symptoms

Abstract

Introduction: The overactive bladder syndrome (OAB) is one of the most common and bothersome subsets of lower urinary tract symptoms (LUTS), affecting predominantly the aged population, with a worldwide distribution. This syndrome has not been completely understood, yet the aging process and the decreased blood flow to the bladder have been highlighted as closely related to this phenomenon. **Materials and Methods:** We performed a search on the online database PubMed/MEDLINE with the following MESH terms: 'Overactive Bladder AND (Ischemia OR Aging OR Vascular Disease)'. We considered manuscripts written in English and published in the last 10 years (2004–2014, October). Additional manuscripts, such as referenced by reviews, were further included. **Results:** The aging process and the structural and functional changes resulting from an ischemic process emerge as important features that contribute to OAB. The ischemic-induced molecular and structural modifications that occur in the bladder have only recently been the objective of thorough studies, which link cardiovascular risk factors, vascular lesions and OAB. New animal models are being created to test new areas of treatment or prevention

of ischemic-induced bladder dysfunction. **Conclusion:** Recent data point out that several physiological and pathological modifications that occur in the bladder associated with OAB and aging are closely related to ischemia.

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Introduction

The International Continence Society defines overactive bladder syndrome (OAB) as urinary urgency, with or without urgency incontinence, usually with frequency and nocturia, in the absence of infection or other pathology [1]. In a cross-sectional, population-based study conducted in 5 Western countries, the prevalence of lower urinary tract symptoms (LUTS) was 62.5% in men and 66.6% in women above 40 years. In this same study, OAB was present in 10.8% of men and 12.8% of women [2]. Ikeda et al. [3] found a prevalence rate of 18.4% in a population above 70 years, whereas in individuals above 85 years, Wehrberger et al. [4] reported a prevalence of 55% in women and 50% in men.

In the year 2000, the economic burden associated with OAB in Italy, Germany, Sweden, Spain and United Kingdom was estimated to be a total of €4.2 billion. This number is anticipated to increase to €5.2 billion in 2020 (26% rises) [5]. This increasing cost was also reported outside

predominantly Caucasian European countries. In Korea, the economic cost to treat OAB between 2006 and 2007 grew from 117 billion to 145 billion Korean Won [6].

OAB is associated with multiple comorbidities such as bowel urgency, osteoporosis, cystitis, imbalance and ankle swelling [7]. It is also associated with other negative outcomes such as depression, social isolation [8], impaired work productivity, higher rates of unemployment and lower sexual satisfaction [9]. Aging of western population is expected to increase the number of OAB patients as well as their median age. Elderly OAB patients have more difficulties in understanding their condition and get less satisfaction from treatment [10].

Functional and Structural Changes during Bladder Aging

Normal bladders show adaptive mechanisms that are able to adjust the functional bladder capacity to urine production, in order to minimise the changes in voiding frequency. As a matter of fact, on a healthy female cohort, Amundsen et al. [11] reported a compensatory mechanism in which an increase in the 24 h voiding volume is accompanied by a greater increase in the functional bladder capacity than in the voiding frequency. However, with aging, this adaptive characteristic feature of the bladder becomes less evident. An increase in the urine output resulted in a significant rise of the 24 h voiding frequency along with a reduction, rather than an increment, of the functional bladder capacity [11]. These age-related changes have also been detected at urodynamic testing. Actually, in women suffering from LUTS, there is a persistent correlation between age and terminal detrusor overactivity, which is defined as a single involuntary detrusor contraction occurring at maximal cystometric capacity. Such involuntary contractions are expected to increase the need of sudden voiding or even precipitate urinary incontinence [1].

In what concerns bladder structure, it seems undoubtedly that aging severely alter its properties. Elbadawi et al. [12] extensively studied the aged human bladder under the electron microscope. In bladders from OAB patients, an atypical pattern consisting of widened spaces between cells, reduction of intermediate cell junctions, increase of protrusion junctions and ultra-close cell abutments was observed. In another study performed in bladders from patients with bladder outlet obstruction, variations in muscle cell size and shape, abnormal fascicle arrangement and collagenosis were described [13], loosely cor-

responding to the myohypertrophy pattern originally described by Elbadawi et al. [14]. Interestingly, aging without micturition dysfunction seems to only marginally affect the detrusor ultrastructure. The membrane of detrusor muscle cells from healthy aged individuals becomes dominated by dense bands with depleted caveolae, slightly widening the spaces between muscle cells with and low-collagen content increase [15]. The caveolin-1 knockout mouse model may support the importance of this structure in bladder aging. When comparing 3-month-old and 1-year-old caveolin-1 knockout mice vs. age-equivalent healthy mice, the knockout group showed a diminished contractile response to electric stimulation and carbachol [16].

Daly et al. [17] found significant changes when comparing 24-month-old mice with 3-month-old controls. They reported an elevated voiding frequency accompanied by an increased release of ATP and a decreased release of Ach, a rise in the number of spontaneous detrusor contractions, an increment in the contractile detrusor response to muscarinic and purinergic agonists and an increase in the frequency of afferent nerve impulses. Using a spontaneously hypertensive rat model, Jin et al. [18] performed several cystometric evaluations at different timepoints (12, 17 and 20 weeks of age). The appearance of detrusor overactivity occurred between the 12th and the 17th weeks, suggesting a relationship between aging and bladder overactivity.

Aging, Oxidative Stress and Inflammation

The relationship between the aging process and the oxidative stress has been widely studied in the past years. Although the precise mechanisms underlying their contributions for bladder aging are unclear for the majority of the cases, their association is object of extensive and multidisciplinary research. In fact, the pro-inflammatory state that occurs alongside the aging process is believed to cause molecular and structural damage, with the reactive oxygen species (ROS) appearing to play a key role [19, 20].

In agreement with this hypothesis, Nocchi et al. [21] observed a statistically higher concentration of intracellular ROS, O_2^- and 8-OHdG (8-hydroxydeoxyguanosine) in urothelial cells of 24-month-old mice when comparing with 5-month-old mice. Extra-vesical application of hydrogen peroxide (H_2O_2) as pro-oxidative stimuli resulted, at last, in the contraction of the detrusor muscle. Similar results were obtained by Masuda et al. [22], who ob-

served that intravesical administration of H_2O_2 in normal rats induced bladder overactivity, as shown by a reduction in the intercontraction interval between detrusor contractions. Also in rats, Homan et al. [23] observed that a single intravesical injection of H_2O_2 significantly increased the number of voids, which lasted up to 7 days. The effects of H_2O_2 are significantly diminished by antioxidants such as dimethylthiourea or deferoxamine, indicating that those effects are ROS-mediated [22]. The role of prostaglandin-like compounds synthesised during oxidative stress reactions seems also to implicate the role of ROS as inducing factors of bladder overactivity in mice and rabbits. Isoprostane 8-epi $PGF2\alpha$, one of these products, is produced and secreted during bladder contraction and induces a dose-dependent contraction on bladder smooth muscle strips [24].

In OAB patients, the association between aging and inflammation was explored by measuring the levels of several cytokines, chemokines and growth factors in urine samples. It was reported an age-related elevation of NGF (nerve growth factor), MCP-1 (monocyte chemoattractant protein-1) and chemokine receptor CXCL-1 values [25]. Another study found a significant 10-fold increase in urinary levels of MCP-1 and sCD40L (soluble fraction of the CD40 ligand) between OAB patients and healthy controls [26]. When studying the variations in cytokine levels between OAB patients, urinary tract infection patients and a control group, Ghoniem and his research team found that MCP-1, chemokine ligand 17 (CCL17)/18 (CCL18) and tumor necrosis factor receptor superfamily member 6 (Fas/TNFRSF6) were exclusively expressed in OAB. On the other hand, they could not show any variation of NGF expression, significantly demonstrated in other studies [27]. This may be due to different patients' inclusion criteria or different assay methods used in the studies [25, 27, 28].

Liu et al. [28] measured NGF levels in OAB females. When these levels were compared to those of the control group, they reported a significant increase in the NGF levels. However, an association between age and NGF levels was not found. Antunes-Lopes and his team confirmed the association between OAB and urinary NGF. In addition, this group further investigated the association between brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor levels and OAB. As observed for NGF, higher urinary levels of BDNF were reported in the OAB group. Interestingly, a significant decrease of NGF and BDNF levels were observed in the urine of OAB patients after successful antimuscarinic treatment [29].

Ischemia and OAB in Humans

The association between cardiovascular risk factors and OAB has been studied only recently. In a large cohort of patients (1,724 men and 812 women), a potential relationship between vascular risk factors (such as diabetes mellitus, hypertension, nicotine use and hyperlipidemia) and the International Prostate Symptom Score was detected. The presence of 2 or more vascular risk factors was associated with a risk-gain of having moderate to severe LUTS of 39% in men and 56% in women [30].

Uzun et al. [31] used the thickness of the carotid intima-media and the carotid-femoral pulse-wave velocity as surrogate makers of vascular impairment in OAB patients. A prospective cross-sectional study was performed, which enrolled 38 males and 28 females with OAB and 62 individuals without LUTS, used as controls. The OAB group had a significant increase in carotid intima-media and carotid-femoral pulse-wave velocity, thus illustrating an association between vascular impairment and bladder dysfunction.

The role of bladder ischemia for the development of LUTS was further investigated by Pinggera et al. [32] who using transrectal colour Doppler ultrasonography evaluated the bladder neck perfusion of 32 elderly patients with LUTS (12 women and 20 men with a mean age of 82.3 and 79.4 years, respectively). Two control groups of 10 young healthy women (mean age 42.3 years) and 10 young healthy men (mean age 41.5 years) were used. It was found that, irrespective of gender, there was markedly lower bladder neck perfusion in the elderly group with LUTS than in the younger group. The frequency of day and night micturition showed a strong negative correlation with bladder neck perfusion. Therefore, this study suggests that a decreased perfusion of the urinary bladder might be involved in the pathophysiology of LUTS in aging individuals.

Wada et al. [33] investigated bladder vascular resistance as a surrogate marker of bladder perfusion in 33 men with LUTS before and after prostate removal. Healthy young male ($n = 10$) and age-matched individuals ($n = 10$) were used as controls. Authors concluded that bladder vascular resistance decreased significantly after prostatectomy, although the decrease was less in patients with persistent symptoms of urgency, suggesting a role of bladder ischemia in the origin of persistent OAB symptoms.

Bunn et al. [34] systematically reviewed 27 studies to determine if there was a link between metabolic syndrome (METS) and OAB in women. Only 3 out of 27 studies used the full definition of METS. The others con-

centrated their analysis on the relation between OAB and obesity. As a majority of these studies found a nexus between METS and OAB, the authors pointed out obesity and METS to be predictive factors of LUTS in women. Interestingly, METS was not associated with a rise in the OAB score in a Japanese cohort, eventually indicating that in Asia and Europe/America populations, METS may negatively influence bladder function in a different way [35].

Animal Models of Ischemia-Induced Bladder Dysfunction

Numerous animal models have been developed in order to investigate the association between ischemia and bladder dysfunction using mice, rats and rabbits [36–48].

In order to determine the correlation between atherosclerosis and OAB, a German group described the morphological and functional changes of the bladder in double apoE/LDL E knockout mice. These mice develop systemic and peripheral atherosclerosis, as well as vasa vasorum neovascularisation, due to characteristic lipoprotein metabolism changes induced by a deficiency of the apolipoprotein E-receptor and low-density lipoprotein receptor. To avoid neurogenic-dependent bladder dysfunction, all mice with neurological impairment were discarded. Compared with age-matched wild type mice, the 60-week-old double apoE/LDL E knockout mice showed decreased micturition intervals, impaired bladder functional capacity, decreased bladder wall vascularisation and infiltration of all bladder layers by inflammatory cells [36]. As attractive as this model might be, one must be cautious in its interpretation. In fact, in an apolipoprotein E (apoE) knockout mice model known for aortic and iliac atherosclerosis induction, no alterations in the contractile responses of the detrusor muscle were found. This might be due to the more gradual atherosclerosis onset or to a different degree of arterial obstruction [41].

Nomiya and his team induced bladder ischemia by subjecting Sprague-Dawley rats [39, 40] to iliac artery injury, followed by a 2% cholesterol-enriched diet during 8 weeks. These rats developed atherosclerotic iliac occlusion and had a significant increase in voiding frequency and a decrease in the voiding volume [39]. In this model, a reduced response to electric and carbachol stimulation was also observed. Ischemic bladders also had extensive collagen deposits at histological examination [40].

Yoshida et al. [37], using a Watanabe heritable hyperlipidemic rabbit model, observed significant atheroscle-

rosis of the internal iliac arteries, a thickening of their media and several cystometric changes towards detrusor overactivity, indicating a correlation between bladder dysfunction and hyperlipidemia.

To detect the influence of ischemia/reperfusion cycles on rabbit bladder, Juan et al. [38] and his team exposed the bladder of New Zealand White rabbits to a 2 h ischemia period and reported a diminished contractile response to electric and ATP stimulation. After immunoblotting analysis, they have found significant increases in several calcium-sensitive and smooth muscle tension regulatory proteins.

Purinergic receptors also suffer morphologic and biochemical changes induced by bladder ischemia. Zhang et al. [42], in an ischemic rabbit model induced by bilateral atherosclerosis of the internal iliac arteries, found a significant upregulation of several bladder P2X receptors within 8 weeks-period of ischemia. In a similar bilateral iliac injury model, Azadzi et al. [43] reported an ischemic-induced overactivity on rabbit bladders that gave rise to a significant elevation of ROS and nitrosative stress products that could account for the decreased nerve density and the transient elevation of NGF levels. Using the latter model, another group found swollen mitochondria characteristic of oxidative damage [44]. This rabbit model of bladder ischemia has also shown to increase the expression of hypoxia-inducible factor, transforming growth factor β , NGF and vascular endothelial growth factor [45].

Moderate ischemia generated a statistically significant rise on the spontaneous release of prostaglandins (thromboxane A₂ and PGF₂ α) and leukotrienes (LT B₄/C₄/E₄) in rabbits [46]. Ischemia may also increase the release of leukotrienes from the urothelium [47]. Prostaglandins in women [49] and leukotrienes in guinea-pigs [48] were also implicated in bladder contractility changes.

These data strongly suggest that ischemia causes profound changes in the bladder functional metabolism, which may eventually appear only if a certain level of ischemia is overcome. The issue of reversibility is not yet clear, however. This point will be analyzed in the next section.

Treatment of Ischemic OAB

As recent data point towards a causal relationship between ischemia and OAB, many studies have been performed to determine the capacity of several pharmacological agents in reverting ischemia-induced bladder dysfunction. Nevertheless, one should keep in mind that

even in the presence of an ischemic-induced OAB, simple therapeutic measures may be extremely effective. For example, it was found that alkalinisation of urine improved LUTS [50].

Das et al. [51] using a model of chronic bladder outlet obstruction, showed that doxazosin, a nonspecific α -adrenoreceptor antagonist currently used to treat LUTS associated with benign prostatic hyperplasia, reduced bladder hypertrophy and partially prevented contractile dysfunction. The increase in bladder blood flow in obstructed bladders caused by doxazosin was forwarded as an explanation for the protective effect of the α -adrenoreceptor blocker agent. Similar results were found in the spontaneously hypertensive rat model by Inoue et al. [52]. Silodosin, another α -adrenoreceptor antagonist, successfully ameliorated micturition frequency, urinary NGF levels and voided volume. However, silodosin failed to reverse decreased bladder compliance, which may be attributed to the weak effect of this drug on bladder blood flow. In fact, silodosin in contrast with doxazosin, is a highly selective α -1A antagonist and therefore has little effect on blood vessels.

Further exploring the bladder ischemia-induced OAB hypothesis, Pinggera et al. [53] investigated the effects of α -adrenoreceptor blocker tamsulosin in urodynamic testing and vascular doppler-measurements of bladder and prostate arteries during a 5-week treatment period. The initial measurements showed a decreased maximum cystometric capacity and a low urinary tract perfusion in the OAB symptomatic individuals. After 5-week treatment, tamsulosin improved LUTS. Concomitantly, the drug approached doppler-parameters and bladder cystometric capacity to those of young-healthy-controls [53]. These data should, however, be seen with caution since in men with benign prostatic hyperplasia, chronic α -blocker treatment does not decrease the rate of urinary retention that this study could suggest [54, 55].

The effect of tadalafil, a phosphodiesterase-5 inhibitor with strong vasodilation effect, was recently investigated in a rat model of bladder ischemia [56]. Male rats with arterial injury and cholesterol-rich diet maintained artery occlusion even though receiving tadalafil. Nevertheless, several functional and morphologic parameters were successfully improved by this agent, resulting in diminishing bladder overactivity. Improved parameters included micturition intervals, bladder capacity and voided volume. Contractile responses of bladder strips to KCl, electrical field stimulation and carbachol were significantly improved after tadalafil, while the collagen deposits were decreased. However, due to the high doses of tadalafil used,

these findings cannot be immediately seen as therapeutic opportunities.

Sawada et al. [57] accessed the protective effect of a β -3 agonist on an ischemic rat model. The β -3 receptors are largely found in human bladder [58] and mirabegron, a β -3 agonist, has been recently introduced in OAB armamentarium [59]. In a model of bladder ischemia induced by arterial injury, mirabegron was able to reduce bladder hyperactivity [57]. Anti-muscarinic drugs may also be used to treat predominantly storage LUTS [60]. At this moment, it is unclear if these drugs act exclusively in bladder contractility or if they also have some effect on blood flow.

Several studies suggested the effective role of anti-oxidant agents in the protectiveness and reversal of bladder ischemia lesions [61–64]. Eviprost [61], Coenzyme Q10 [62, 63] and melatonin [64] were found to reverse several bladder functional injuries caused by bladder ischemia, contributing to strengthen the oxidative/pro-inflammatory theory behind a decreased bladder blood flow. Finally, stem cell therapy is also making its entry in the field of the ischemia-induced bladder dysfunction. Recent studies showed an interesting capacity to improve bladder dysfunction in rat models of bladder ischemia [65, 66].

Conclusion

Recent data point that several physiological and pathological modifications that frequently occur with aging are closely related to OAB. Additionally, it is highlighted that ischemia may be an important contributor to the development of molecular and structural changes associated with bladder overactivity and aging.

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