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Translational research and functional changes in voiding function in older adults

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Synopsis

This article describes a number of changes in lower urinary tract (LUT) function that occurs in the aging population as well as in animal models. Age-related LUT dysfunctions result from complex processes controlled by multiple genetic, epigenetic and environmental factors and accounts for high costs of healthcare. While the underlying factors that contribute to patient symptoms are not known, this article will discuss a number of risk factors that may play a role in age-related LUT dysfunction. In addition, while limited data is available using animal models of aging, there is evidence that many of the structural and functional changes observed in these studies appear to be similar to those observed in humans. A better understanding of factors and mechanisms underlying LUTS in the older population may lead to therapeutic interventions which may be used to reduce these dysfunctions.

Keywords

urinary bladder; voiding dysfunctions; ischemia; LUTS; overactive bladder; underactive detrusor; urinary incontinence; animal models

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Introduction

Aging-related bladder dysfunction and associated lower urinary tract symptoms (LUTS) represent an increasing problem in developed countries due to increased life time expectancy. LUTS are generally divided into storage (irritative), voiding (obstructive) and postmicturition components. Storage symptoms include urgency, frequency, nocturia, and urgency incontinence (= the overactive bladder (OAB) syndrome). Voiding symptoms comprise reduced force of stream, hesitancy, inability to empty the bladder, and straining. Postmicturition symptoms include feeling of incomplete emptying and postmicturition dribble^{1, 2}. Unfortunately, none of these symptoms is disease-specific or has a high correlation to a specific urodynamic pattern. Most of these symptoms have been suggested to be age-dependent, and attributed to various factors including reduced bladder capacity, changes in bladder sensation, and, on urodynamic investigation, detrusor overactivity (DO). However, the pathophysiology behind the dysfunctions is sometimes difficult to establish since what can be attributed to "normal aging" cannot be separated from what is caused by co-morbidities. LUTS is an increasing problem: an estimated 45 % of the 2008 worldwide population (4.3 billion) was affected by at least one LUTS, reducing the quality of life. By 2018, an estimated 2.3 billion individuals will be affected by at least one LUTS (18.4% increase)³.

Functional aging-related voiding changes

Functional changes in the urinary tract occur with both "normal" aging and in elderly individuals with different types of diseases. The pathophysiology of LUTS in older adults is multifactorial and includes comorbid medical illness, neurological and psychiatric conditions, medications, functional impairments and environmental factors^{4, 5}.

The overactive bladder

The OAB symptom complex comprises urinary urgency, with or without urgency incontinence, usually with frequency and nocturia *in the absence of other pathologies*⁶. Several reviews have discussed different aspects of OAB in older adults^{5, 7–10} and it has been well established that the syndrome increases with age, and that aging alone can be considered a major risk factor for developing these symptoms.

The OAB syndrome as defined by the ICS refers to idiopathic OAB⁶. Since the same symptoms can occur with known comorbidities probably involved in the pathophysiology of the symptoms, such as Parkinson's disease, multiple sclerosis, spinal injuries, Alzheimers disease, diabetes cystopathy etc, it is obvious that epidemiological studies focusing on idiopathic OAB underestimate the true prevalence of the symptom complex. The fact that aging alone, can be considered a major risk factor for developing the symptoms, means that current population forecasts, predicting a worldwide increase in the proportion of people aged over 65 years, with the greatest rise being in those aged over 80¹¹, also predicts an increase in patients with OAB symptoms. According to Irwin et al (2011) an estimated 455 million individuals worldwide experienced OAB in 2008, with numbers of affected individuals anticipated to increase to 500 million by 2013 (10.0% increase) and to 546 million by 2018 (20.1% increase)³. It can be expected that the healthcare burden associated

with OAB and other LUTS will increase and that the occurrence of OAB in the aging population will have important quality of life and economic consequences^{4, 12–15}.

Urinary incontinence (UI), in addition to urgency, may be one of the most relevant symptoms, given that other comorbidities may also limit the ability to remain dry¹⁶. The impact on the quality of life in this population is vast; incontinence remains a risk factor for nursing home placement^{17–19} and links with other conditions, including an increased risk of falls and fractures²⁰, sleep disorders and depression^{21–23}. The factor of age is in itself likely to exacerbate the problem as elderly men with LUTS report a poorer quality of life than younger men with the same condition²⁴.

Detrusor underactivity

Uroflow studies have demonstrated an age-dependent decrease in Q_{max} ^{25, 26}, which was confirmed and shown to be similar in both sexes^{27, 28}, however, not demonstrable in symptomatic elderly men with non-obstructive voiding dysfunction²⁹. Difficulties to empty the bladder ("detrusor underactivity": DU) may have many underlying causes and has been the subject of recent interest^{30–34}. Some of the most frequently discussed causes are impaired detrusor contractility and decreased bladder/urethral sensation^{35, 36}. Urodynamic assessment in older patients of both sexes without overt neurological disease showed higher residual volumes and lower detrusor shortening velocities, but no changes in isometric detrusor function³⁷. In a series of patients where the bladder capacity at first void was taken as measure of bladder sensation, this parameter showed a progressive increase with age, suggesting an age-dependent decrease in bladder sensation^{35, 36}, a finding confirmed by several other investigators^{28, 38}. In a clinical study of patients referred for LUTS or UI, Madersbacher et al. (1998) found an increase in postvoid residual, along with a decrease of flow rates, voided volumes and bladder capacity associated with increasing age²⁷. These findings were similar in both genders. Pfisterer et al. (2006) assessed a group of 85 female volunteers aged between 20 and 90 years using bladder diary, uroflowmetry and detailed videourodynamics²⁸. Bladder capacity did not change with age, but was smaller in women with DO on urodynamics. Urine production and urine frequency did not differ significantly with age. Bladder sensation, detrusor contraction strength, maximal flow rate and maximum urethral closure pressure were all negatively associated with age. It was concluded that there is a normal functional decline with aging in otherwise asymptomatic women. This study, thus suggested a progressive decrease in detrusor contraction strength, which was in line with the findings of van Mastrigt (1992), who demonstrated a statistically significant age-related decrease of the detrusor contractility parameter, W_{max} , in both sexes³⁹. Other investigators were unable to show any correlations between bladder contractility and age in symptomatic elderly men with nonobstructive bladder dysfunction²⁹, or between maximum detrusor pressure and detrusor pressure at peak flow rate and age in LUTS patients of both sexes²⁷. Direct study of detrusor contractility in vitro did not show any correlation between contractile force and age⁴⁰.

Normal age-related changes in the bladder and lower urinary tract should be clearly differentiated from pathological alterations seen with conditions such as OAB or LUTS. DO and the related condition, "detrusor hyperactivity with impaired contractile function"

(DHIC)⁴¹ can also present with advancing age and should be diagnosed adequately in elderly individuals. The currently available data from animal and human studies demonstrate that aging impacts the lower urinary tract function through ultrastructural and physiological alterations. The reported age-related changes in animals do not always correspond to what is found in humans, and should be interpreted with caution. Overall, in humans, bladder sensation and contractility seem to decrease with advancing age as a possible consequence of neuronal loss and remodeling of the bladder and urethra.

Animal models of aging-related bladder dysfunction

In vivo studies of bladder function

Animal models allow detailed investigation of structural and functional aspects of the micturition pathways and changes occurring with aging. Additionally, the genetically modified mouse models allow further understanding and targeting of specific genes. The influence of aging on bladder structure and/or function was studied in *in vivo* and/or *in vitro* studies performed mostly in rodents of different strains and/or gender. These include C57Bl6 mice (male, female 22–25 month old)^{42–44}, the senescent-accelerated prone mice (SAMP8; male, female, 36–38 week old)⁴⁵, Fisher 344 rats (male 22–24 month old)^{46, 47}, Fischer/Brown Norway rats (male 28–30 month old)⁴⁸, Wistar rats (male or female 22–37 month old)^{49–51}, Fisher 344 rats (female 24 month old)⁵², Sprague Dawley (SD) rats (male 18–24 month old)^{53,54}. Other species included dogs^{55, 56} and guinea pigs^{57–61}. As pointed out previously, the relation between aging per se and external influences on the detrusor from diseases in the nervous system, in the vascular supply, and in the lower urinary tract smooth muscles, is poorly understood in humans^{62–64}. In animals, kept under constant laboratory conditions, theoretically the influence of external influences can be reduced, which should enable the study the effect of age only on bladder function. However, this does not seem to provide consistent results in part due to differences in between species, gender or strain. A small number of studies have used *in vivo* methods such as the use of metabolic cages or cystometry for characterization of age related changes^{42, 45–49}. Metabolic cage data obtained from aged mice and senescent-accelerated prone mice (SAMP8)^{42, 45}, showed a significant increase in the number of urine spots, suggesting an increase in the frequency of voiding. Similarly, the frequency of voiding was increased in aging rats as well as in rats with chronic bladder ischemia (also a risk factor in aging)^{46, 47,65}. Cystometry studies yielded variable results. Smith et al., using a pressure/flow multichannel urethane-anesthetized mouse cystometry model, tested the hypothesis that *in vivo* detrusor performance does not degrade with aging⁴⁴. They found aging to be associated with an impaired ability to respond to the challenge of continuous bladder filling with cyclic voiding. However, among responsive animals, voiding detrusor contraction strength did not degrade with aging in this murine model and indirect measures suggested that bladder volume sensitivity was diminished. These findings seem to be in agreement with findings in humans showing that maximal detrusor pressure did not correlate with age⁶⁶, and that no age related changes in maximum detrusor pressure or $P_{det.Qmax}$ could be demonstrated in men and women with LUTS²⁷. On the other hand, Pfisterer et al. (2006) found that maximum urethral closure pressure, detrusor contraction strength, and urine flow rate declined significantly with age, and so did bladder sensation²⁸. Other reports indicate increase in voiding pressure threshold in aged

rodents^{52, 53}, suggesting possible disturbances in the afferent system that can include decreased afferent excitability, impaired communication between urothelium and afferent nerves and/or other mechanisms. Baseline intravesical pressure was also increased^{48, 53}, suggesting changes in the smooth muscle/bladder wall that may impact storage function. Micturition pressure (reflects contractility of the smooth muscle as well as function of the efferent system) was found to be variable^{44, 48, 53}, suggesting changes in more than one component of the system.

In vitro studies of bladder function

To further understand the *in vivo* data, a number of studies have performed various types of *in vitro* experiments. The overriding goals were to investigate individual components of the micturition pathway including bladder nerves (afferent, efferent), the urothelium and lamina propria as well as the smooth muscle.

Afferent nerves—Although scarce, studies using aged mice revealed augmented afferent nerve firing during bladder filling and increased afferent discharge in response to low threshold volumes only (male mice⁴²). These results suggest that afferent activity during filling phase may be enhanced and this may be an underlying mechanism for symptoms of urgency and frequency reported in older adults. Studies in rats indicated that the conduction velocity of myelinated and unmyelinated fibers did not appear to change with age, however, there was a reduction in the number of small diameter (predominantly unmyelinated) fibers⁵⁰. These changes, if occurring in humans, may account for alterations in bladder sensations in older adults.

Urothelium/Lamina propria—Histological evaluation indicated a number of structural changes in the urothelium and lamina propria. These include urothelial thinning (male Fischer/Brown Norway rats)⁴⁸, granular appearance of umbrella cell layer, discoidal vesicles, electron dense bodies and vacuoles in umbrella layer, often containing what appears to be cellular debris in all layers and increased cellularity (number of different cell types many around blood vessels) in lamina propria in female mice⁶⁷. Other studies have shown increased ROS in cultured urothelial cells from mice male⁶⁸, decreased total antioxidant capacity and significantly increased levels of lipid peroxides (MDA) and iNOS (markers of oxidative stress) and ultrastructural alterations in mitochondria with accumulation of lipofuscin⁶⁹. Furthermore, alterations in the collagen content have been reported, though results are not consistent. For example, changes include a generalized increase in collagen content in male Fischer/Brown Norway rats⁴⁸ versus an increase only in the bladder neck in male SD rats⁵³ as compared to decreases in the smooth muscle and lamina propria areas in female Wistar/Rij rats⁴⁹. In contrast, few functional studies of aging urothelium have been performed. For example, aging mice have been associated with increased ATP release and a corresponding decrease in acetylcholine. Urothelial cells were also more sensitive to purinergic agonists and P2X₃R expression was increased⁴². These changes may contribute to bladder overactivity and hypersensitivity.

Efferent transmission and smooth muscle—The efferent transmission is mostly cholinergic in nature in humans and cholinergic and purinergic in rodents. In aged bladder

tissue from humans and rats, a decrease in the atropine sensitive component of the efferent transmission has been reported^{48, 53, 70}. This correlates with structural changes reporting a reduction (~40%) in the number of AChE-positive neurons in the intramural plexus in guinea pigs⁶⁰. These alterations may impact the strength of the contraction and may contribute to changes in voiding function (underactive bladder).

A number of structural and functional changes have been reported in the smooth muscle. Several studies investigated the ability of smooth muscle to handle changes in intracellular calcium. While responses to strong depolarization using KCl were shown to be variable^{42, 43, 48, 49, 51, 53}, muscle strips from aged rodents were more susceptible to calcium channel antagonists and to reduced extracellular calcium⁵⁴. Also aged dissociated smooth muscle cells show differences in mobilization of intracellular calcium⁴³. Altogether, impaired ability of the smooth muscle to handle changes in levels of intracellular calcium coupled with decreased muscle mass and increased collagen content⁴⁸ may represent underlying mechanisms for changes in bladder contraction strength with age.

Bladder storage and voiding phases involve several main transmitters (norepinephrine, ACh and ATP) and their associated smooth muscle receptors (beta-adrenergic, muscarinic and purinergic receptors). During storage, norepinephrine released from the sympathetic nerves relaxes the smooth muscle via beta-adrenergic receptors (β -ARs), particularly β_3 -ARs in human^{71, 72}. Studies on the effect of aging on bladder β -ARs have yielded inconsistent results⁵. In the bladder of male Sprague Dawley rats and female Wistar/Rij, the receptor density did not seem to significantly change^{53, 49}. Latifpour et al (1990) reported that the number of β -ARs increased with age in rabbit bladder dome and base⁷³. In contrast, a study using male Fischer 344 rats reported a decrease in β -ARs in aged rats⁷⁴. A similar decrease was also reported for human bladder⁷⁵. Functionally, weaker smooth muscle response (relaxation) to noradrenaline, isoproterenol or the beta-3 adrenoreceptor agonist BRL37344, have been reported in bladder from male Wistar rats⁵¹. Even if changes in β -AR function in older adults cannot be excluded, there is no evidence that the clinical response to β_3 -AR agonist treatment (mirabegron) is reduced in the geriatric population⁷⁶.

Voiding is achieved via release of ACh in human (and ACh and ATP in rodents) from the parasympathetic nerves to contract the bladder, concomitant with NO release in the urethra to relax the urethra smooth muscle. In the detrusor, muscarinic receptors (particularly M3) mediate the bladder contraction. Aging dependent changes in muscarinic receptors have yielded contradictory results, in part due to species and strain differences. In male Fischer 344 rats⁷⁷ and male mice⁴² muscarinic receptor mediated detrusor contraction was found to be increased. In contrast, in male Sprague-Dawley rats^{53, 78, 79}, male Fisher/Brown Norway⁴⁸ and male mice⁴³ muscarinic receptor mediated detrusor contraction was decreased, while in male Wistar⁸⁰ and female Wistar/Rij rats⁴⁹ there was no change. Even if there may be aging-dependent changes in muscarinic receptor function in humans, this does not seem to affect the clinical response to antimuscarinic drugs^{81–83}.

In summary, while a number of reports indicated structural and functional changes in the aged bladder, *in vitro* data do not always match the *in vivo* observations. The potential

translational value may be increased if both *in vivo* and *in vitro* parameters could be studied in the same animal.

Risk factors

Gender differences

Irwin et al. (2011) estimated the prevalence of OAB worldwide as being greater in women versus men in 2008 (11.6% vs 9.7%, respectively)³. The difference was expected to be maintained also in 2013 (11.7% vs 9.8%) and 2018 (11.9% vs 10.0%). Some of the gender differences in bladder function and control can obviously be attributed to gross anatomical differences, but there is evidence that other factors can contribute^{18, 84, 85}. For example, there are significant gender differences in coping strategies with better coping mechanisms demonstrated among elderly women⁸⁶. This may be related to differences healthcare-seeking behavior and receiving treatment. Older men seek more often professional help for their incontinence compared to women. However, women are more often treated^{87, 88}. The risk of incontinence in older individuals with restricted mobility may be greater in women than in men depending on the greater physical effort required by women in preparing for micturition. Urinary incontinence has been shown to be associated with a higher mortality, however only among elderly men⁸⁹. Urinary incontinence has a greater negative impact on sexuality in elderly men compared to elderly women^{90, 91}. However, in older females with incontinence a main reason for not being sexually active was lack of a partner. Although for only 5% was urinary incontinence the main reason for not having sex, about 25% of the sexually active women reported a negative influence of urine loss on their sex life⁹¹.

Atherosclerosis and Oxidative stress

Aging is associated with an impairment of blood vessel function and changes may occur in the vasculature on the molecular, cellular, structural and functional levels^{92–94}. Vascular aging is characterized by endothelial dysfunction^{95, 96} and starts already in young adults by slow and progressive vascular remodeling, and early signs of declining endothelial function may manifest before the fourth decade of life⁹⁷. Endothelial dysfunction leads to oxidative stress, and increased levels of pro-inflammatory cytokines^{94, 98}, which represents an independent risk factor for development of atherosclerosis and hypertension. Recent evidence from epidemiologic, clinical and animal basic research suggests that aging-associated changes in the pelvic vasculature, resulting in atherosclerosis and vascular dysfunction, may be important factors in the generation of LUTS.

BPH/BOO is a common condition in elderly men and BOO can be associated with reduced bladder blood flow. Berger et al. (2006) found that in BPH/BOO patients with severe vascular damage (diabetes mellitus type 2), LUT perfusion and International Prostate Symptom Score (IPSS) were significantly worse compared to BPH/BOO patients without diabetes and healthy controls.

Chronic bladder ischemia can occur independently of BOO in older adults. The vascular supply to the human genitourinary tract, including the bladder, prostate, uterus, urethra, and penis, is primarily derived from the iliac arteries. The abdominal aorta and its branches,

especially the bifurcation of the iliac arteries, are particularly vulnerable to atherosclerotic lesions⁹⁹. Atherosclerotic obstructive changes distal to the aortic bifurcation will have consequences for the distal vasculature and LUT blood flow. Epidemiological studies have investigated the association between LUTS and vascular risk factors for atherosclerosis such as hypertension, hyperlipidemia, diabetes mellitus and nicotine use^{100, 101}, and Pohnholz et al. (2006) suggested the potential role of atherosclerosis in the development of LUTS in both sexes¹⁰⁰. Takahashi et al. (2012) also indicated the association between severity of atherosclerosis and male LUTS¹⁰². Pinggera et al. (2006), using transrectal color Doppler ultrasonography, showed that elderly patients with LUTS had a significant decrease in bladder blood flow compared with asymptomatic young individuals¹⁰³. They also found a negative correlation between decreased LUT perfusion and IPSS in these elderly patients. This implies that coexisting vascular disease-related chronic ischemia may be more detrimental to bladder dysfunction than BPH/BOO alone. Histological studies have shown fibrosis formation or denervation in the bladder samples from elderly male and female patients without BOO^{104–106}. These observations were supported by the study of Kershen et al. (2002) which showed that decreased bladder blood flow and decreased bladder wall compliance correlated strongly, suggesting structural changes in the bladder wall induced by ischemia¹⁰⁷. Moreover, pelvic arterial insufficiency such as caused by atherosclerosis, is also strongly associated with erectile dysfunction (ED)^{108, 109}. The close association between LUTS and ED has been documented in elderly men^{110–112}. Thus, these clinical studies may suggest aging-associated alteration of pelvic vasculature as a common etiology in the development of both conditions^{113, 114}.

Evidence from clinical and basic research suggests that atherosclerosis in both genders can induce a reduction of bladder blood flow, leading to chronic ischemia. Chronic bladder ischemia and repeated ischemia / reperfusion during a micturition cycle may produce oxidative stress, leading to denervation of the bladder and the expression of tissue damaging molecules in the bladder wall^{65, 115, 116}. Masuda et al. (2008) suggested that oxidative stress mediates bladder hyperactivity through sensitization of afferent pathway in the bladder of rats¹¹⁷. Studies in animal models suggest that the extent of bladder dysfunction in chronic ischemia depends on the degree and duration of ischemia^{118–120}. This appears to be responsible for the development of DO progressing to DU and inability to empty the bladder¹²⁰. When bladder ischemia becomes severe and prolonged, progression of denervation and damage to detrusor muscle with fibrosis formation may cause DU and voiding symptoms.

Summary

In view of the complex control of the lower urinary tract, underlying symptoms of the aging bladder include incontinence, overactivity and/or the inability to empty. The underlying mechanisms that may contribute to these symptoms are not known but are likely to be controlled by multiple genetic, epigenetic and environmental factors. Future translational studies should be aimed at unraveling the pathology of the aging bladder and to develop new modalities targeting pathological processes for the treatment of age-related bladder control problems.

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Key points

1. Lower urinary tract symptoms (LUTS) significantly increase with age and include a prevalence of overactive bladder symptoms and even impaired bladder contractility.
2. The pathophysiology of LUTS in older adults is multifactorial and includes comorbid medical illness, neurological and psychiatric conditions, medications, functional impairments and environmental factors.
3. Many age-related changes in bladder function may have an origin that is myogenic, neurogenic and/or ischemic in nature.
4. Many of the structural and functional changes observed in (some) animal models of aging appear to be similar to those described in humans.
5. Though several factors have been identified as playing a potential role in these age-related symptoms, the influence in any patient group is unknown.