Can we define and characterise the ageing lower urinary tract? – ICI-RS 2015

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Abstract

The prevalence of lower urinary tract (LUT) symptoms increases with age but the aetiology is unknown. This article aims to identify research directions that clarify the basis of this association. The initial question is whether biological age is the variable of interest or a time-dependent accumulation of factors that impact on LUT function at rates that differ between individuals. In particular, the accumulation of conditions or agents due to inflammatory states or tissue ischaemia are important. Much of the above has been concerned with changes to bladder function and morphology. However, the outflow tract function is also affected, in particular changes to the function of external sphincter skeletal muscle and associated sacral motor nerve control. Nocturia is a cardinal symptom of LUT dysfunction and is more prevalent with ageing. Urine production is determined by diurnal changes to the production of certain hormones as well as arterial blood pressure and such diurnal rhythms are blunted in subjects with nocturia, but the causal links remain to be elucidated. Changes to the central nervous control of LUT function with age are also increasingly recognized, whether in mid-brain/brainstem regions that directly affect LUT function or in higher centres that determine psycho-social and emotional factors impinging on the LUT. In particular, the linkage between increasing white matter hyperintensities and LUT dysfunction during ageing is recognized but not understood. Overall, a more rational approach is being developed to link LUT dysfunction with factors that accumulate with age, however, the precise causal pathways remain to be characterized.

An increased prevalence of LUT disorders is associated with age, but questions remain unresolved that surround this simple statement. For example, does LUT dysfunction develop as a natural ageing process or is it dependent on other factors that have a cumulative effect on the LUT until a threshold breakdown occurs? Furthermore, what regions of the LUT are most affected that eventually lead to dysfunction: the contracting detrusor, the outflow tract, sensations during bladder filling, or central and peripheral control of LUT function? Nearly all these questions remain unanswered and it is the purpose of this article to introduce specific areas of interest and highlight research questions that may shed light on why LUT dysfunction occurs more as the arrow of time progresses.

Ageing as an entity. Although the passage of time is associated with increased LUT dysfunction, no causal relationship has been demonstrated and is equally possible to assert that as a person lives longer there is a greater likelihood they will acquire conditions that may impact on LUT function. Thus, the process of age-related changes based on chronological age alone is unlikely to develop our understanding of age-associated LUT dysfunction.

Longitudinal studies of sufficient magnitude and length are very difficult to carry out; therefore to truly ascribe physiological changes to the passage of time we need to agree upon a description of physiological or perhaps pathophysiological age to conduct robust cross-sectional studies. It is likely that a mere absence of symptoms or overt major systems disease will be insufficient.

Biological systems have a significant reserve to ensure adequate function over a lifespan despite external stresses – a property called compensation. Failure (decompensation) occurs if the biological reserve collapses due to excessive stresses or if the compensatory alterations induce their own dysfunction. This is captured in a redundancy model of ageing whereby systems are described as "blocks" which do not age *per se,* but fail for various reasons and an ageing effect occurs as redundancy is exhausted [1]. The rate of failure of "blocks" within a system varies and also depends on the number of remaining "blocks", some of which may be critical for survival. This latter dependency may indicate an intrinsic phenomenon affecting the whole organism leading to failure of the weakest link or critical system [2].

Two examples of cumulative changes that can exert long-term impact on the urinary tract are inflammaging and gradual accumulating ischaemia in the LUT itself or its nervous control. Inflammaging is characterised by upregulation of the inflammatory response that occurs with advancing age [3] due to cumulative lifetime exposures to antigenic loads from clinical and subclinical infections as well as non-infective antigens. The consequent inflammatory response elicits the release of additional cytokines resulting in a pro-inflammatory state. Irreversible cellular and molecular damage, that is not clinically evident, therefore slowly accumulates over decades. Equally, perfusion impairment as a result of conditions such as atherosclerosis affects both voiding and storage LUT function independent of age [4], but the critical sites of ischaemic damage to the LUT and its regulators have not yet been identified.

In addition to the accumulation of pathological impacts, the elderly also tend to be exposed to more general pressures that can impact on LUT function. Two examples again illustrate the range of these confounding factors. The elderly tend to take an increasing number of different medications for other conditions. However, it is difficult to assess how this spectrum of polypharmacy affects LUT function but must always be considered as a complicating factor. Secondly, fluid intake in the elderly can be very different from the general population, especially those in care homes where intake can be very low. Prolonged dehydration leading to renal failure can diminish the ability of the kidneys to appropriately concentrate urine and in some generate polyuria, whilst in others oliguria will impact on normal bladder wall filling sensations.

Changes to structure and function of the bladder with ageing: human and animal studies. Several variables have been formulated for use in human studies that measure detrusor contractile strength, when voiding, including the bladder contractility index (BCI) and the Watts Factor [5]. Cohort studies show a small decline of BCI with age (6) and calculation of the maximum detrusor-Watts Factor during voiding shows age-dependent reductions of about 15% and 35%, in men and women respectively, between 50 to 80 years of age (P Rosier, ICS-2015, abstract 267). It remains to be ascertained how

these clinical indices are interpreted in terms of physiological function associated with LUT contractile function.

To gain insight into particular pathological changes associated with LUT dysfunction, 'aged' animals are used in comparison to younger ones. However, most laboratory animals have much shorter life-spans than humans and changes occurring in animal models, throughout their lifespan, may not mirror those in humans. One determination of an ageing animal is the appearance of biomarkers associated with senescence, as may occur in humans over 65 years, and using this criterion, rats and mice older than 18-24 months and guinea-pigs older than 30 months would be appropriate [7]. However, many reports from 'aged' models use younger animals and so some of the resulting data must be interpreted with caution.

With respect to human tissue, increasing age and bladder outflow obstruction (BOO) is associated with an increase of the collagen:muscle ratio in tissue biopsies from men [8] and mirrored in a decline of *in vitro* contractility [9]. However, the greater fibrosis with BOO is associated with greater detrusor voiding pressure indicating bladder wall hypertrophy [10]. These changes are reflected in some, but not all, animal equivalents [7,11]. In addition, the bladder wall contains various cell types such as epithelial cells, nervous and vascular supplies, connective tissue, interstitial cells and immune system cells. Interaction between these different cell types is complex and regulation of bladder function depends upon integration of their individual activities. Investigation of the interactions between these cells types, as a function of age, should provide important insights into LUT dysfunction. The passage of time has other, profound effects, such as denervation of afferent and efferent nerves to bladder tissues [7,11]. This may be countermanded by increased release of neuroactivators from the mucosa during external stresses [12,13]. Thus far, it has not been possible to use animal models to determine if changes occurring to LUT function in ageing humans are part of a senescence process or the accumulation of pathological burdens that gradually degrade function.

Impact of ischemia on the aging process of the bladder. Ageing is associated with impaired blood vessel function, characterised by endothelial dysfunction mediated largely by NO insufficiency through

oxidative stress and chronic low-grade inflammation [14]. Arterial endothelial dysfunction is the primary antecedent for atherosclerotic diseases, which can result in bladder ischaemia and the development of LUTS [15]. Elderly patients with LUTS do have a significantly greater bladder blood flow resistance index, measured with transrectal ultrasound colour Doppler, in comparison to younger (40 yrs) people with low symptom scores [16]. Pelvic arterial insufficiency can result in the development of detrusor overactivity and eventually detrusor underactivity [17]. One mechanism is potentially through bladder ischaemia and bladder wall hypoxia [18], with resultant oxidative stress, increased muscarinic receptor activity, ultrastructural damage and neurodegeneration [19].

It would be desirable to treat not only LUT symptoms (LUTS) induced by chronic ischemia, but also the progression of morphological changes that occur in detrusor muscle and other structures within the bladder wall. Several drug types have been proposed as having potential to influence some of these changes. The α_1-adrenoceptor blocker silodosin, the β_3-AR agonist mirabegron, and the free radical scavenger melatonin all had a protective effect on both urodynamic parameters and *in vitro* functional and morphological bladder changes even though they do not prevent development of neointimal hyperplasia and bladder ischaemia in animal models: the PDE5 inhibitor tadalafil did not demonstrate any positive effect on urodynamic parameters [20]. This variety of effective agents suggests a multifactorial pathogenesis of bladder dysfunction induced by chronic ischaemia. As several of the agents are used clinically to relieve LUTS these results have translational value, and should be used to design clinical studies to demonstrate whether progression of ischemia-related functional and morphological bladder changes can be limited.

The bladder outflow tract with ageing. The external urethral sphincter (EUS) contains a crucial ring of striated muscle, the rhabdosphincter. With increasing bladder filling, tonic EUS contractions progressively increase, but at the initiation of voluntary voiding both the bladder neck circumferential muscle fibers and the EUS relax as the bladder dome contracts. Somatic motor neurons from Onuf's nucleus in the sacral spinal cord innervate, via the pudendal nerve, and excite muscle fibres of the EUS via acetylcholine acting on nicotinic receptors. Glutamate is the main excitatory neurotransmitter on

these motor neurons, which in turn is augmented by serotonin and noradrenaline, demonstrating a complex control of rhabdosphincter function by Onuf's nucleus [21,22]. Stress urinary incontinence (SUI) is prevalent in the older population and importantly is due to failure of the EUS mechanism. There remains little information about the pathological changes that accompany development of SUI but may include: a loss of muscle fibre numbers; reduced contractile performance; denervation of motor nerves; failure of neurotransmission at the motor end plate; or changes to the spinal control system. Pelvic nerve neuropathy might play a role in women with SUI [23] and animal models of pudendal nerve transection showed atrophy of the EUS striated muscle [24]. Intraurethral sonography also shows a decrease of sphincter muscle thickness as a function of patient age in women with SUI [25]. However, a great deal remains to be determined about the muscle mechanics of EUS striated muscle, how contractile function is regulated via Onuf's nucleus, and what changes of function occur that are associated with SUI and its relation to increasing age of the patient.

Nocturia, an age-determined phenomenon? The prevalence of nocturia, awakening at least once a night to void and followed by sleep, increases with age and two or more episodes is associated with increased risk of falls and fractures, cardiovascular events and poor sleep quality [26]. A frequency-volume chart is useful to determine whether nocturia is due to a reduced bladder capacity, nocturnal polyuria, 24-hour polyuria or a combination [27]. In addition, patients with nocturnal polyuria can be classified as those with a raised free water or sodium clearance at night. Sleep, bladder capacity and urine production are subject to circadian rhythms that diminish with increasing age [28, 29] and are driven by cyclical release of hormones such as vasopressin (ADH), angiotensin, aldosterone and melatonin [29,30]. These hormones not only regulate renal sodium and water handling but can also directly or indirectly influence arterial blood pressure (ABP). The association between ABP and renal function, especially in relation to nocturnal urine volumes [31], has several consequences. During sleep ABP falls by 10-20%, in part due to physical inactivity (of interest the extent of this diurnal variation may be an independent predictor of cardiovascular dysfunction). The diurnal variation is also less in subjects who exhibit nocturia [32]. Indeed, the association between arterial blood pressure and nocturnal urine volumes may explain why subjects with essential hypertension

experience a greater incidence of nocturia and increased night-time sodium excretion, compared to the normal population [29]. However, the precise causal linkages between cardiovascular function and nocturia remain to be evaluated.

Contribution from the brain and other external factors to dysfunction of bladder structure, function and voiding. Increasing evidence suggests that, with ageing, central nervous control of the LUT is affected. Normal voiding engages a spino-midbrain-spinal neural loop. Afferent information on bladder status is relayed to the midbrain periaqueductal grey matter (PAG) and thereafter to the pontine micturition centre (PMC), the source of spinally-projecting neurons that control motor outflows to the detrusor and sphincter muscles. During bladder filling, tonic inhibition of the voiding circuit by GABA is imposed at a midbrain level and results in a low level of PAG activation [33]. However, once the voiding threshold is reached, the GABA tone is lifted with a stepped increase of PAG activation and recruitment of the PMC as the circuitry switches to voiding mode [34]. In humans and other socialised species voiding occurs only when the individual judges it to be appropriate, even when the bladder is full. Forebrain structures, probably the prefrontal cortex, must exert control over the basic pontine and sacral voiding circuits [35]. fMRI imaging during bladder filling shows that at low volumes, when there is little conscious bladder sensation, midbrain and parahippocampal regions are activated, but not cortical areas. However, with a full bladder strong sensations ensue and the insula (thought to encode visceral sensation) and dorsal anterior cingulate/supplementary motor complex are activated, with some studies also showing de-activation in the prefrontal cortex [36,37]. In ageing individuals, even those with normal LUT control, decreased responses to bladder filling are observed in the right insula, consistent with its role in perception of visceral sensation. Failure to detect sensation until the bladder is extremely full may contribute to the development of urgency. In elderly urgency incontinent individuals, activation in the anterior cingulate gyrus is stronger than normal which may represent a sign of urgency [34,38].

The presence in these brain regions of white-matter hyperintensities (WMH), which are structural abnormalities which appear with ageing and may be linked to small vessel disease, are associated with

LUT disorders. WMH in the right inferior frontal region and cingulate gyrus are associated with urinary incontinence [39] and with detrusor overactivity when present in the right anterior thalamic radiation, which connects prefrontal regions with the thalamus and pontine voiding circuit.

Bladder compliance increases with age in animal models [40], an effect which may contribute to the increased volume at which a first desire to void occurs in humans as they age [41]. The effect on compliance is more evident *in vivo* than with *ex vivo* bladders and suggests that the central nervous system mechanism regulating compliance [42], requires further evaluation.

Psychosocial factors may also influence LUT function. Young adult mice when socially deprived developed non-voiding bladder contractions, similar to detrusor overactivity, and a decreased micturition interval in the short term (two weeks), but longer exposures increased both bladder capacity and micturition interval with resultant remodeling of the bladder wall [43]. One potential contributing factor may be altered release of corticotropin releasing factor (CRF), with more CRF immune-reactive neurons in the PMC after social stress. Ageing is associated with behavioural changes, including elevated anxiety or depression, narrowed social engagement, and cognitive impairment. The extent to which these factors contribute to age related LUT dysfunction is worthy of further investigation.

The use of mathematical models to address interpretation of changes to LUT function with ageing. The Valentini–Besson–Nelson (VBN) model [44] is a quantitative description of mechanistic phenomena that govern micturition including: detrusor contractility and viscoelasticity, urethral elasticity and sphincteric compression, hydrodynamics of turbulent incompressible fluids and abdominal straining. Each phenomenon can be separately studied: however when combined, as during voiding, they constitute an intricate set of variables that is best analysed with computer models such as VBN® software. Inputs include filling volume and catheter size (and gender); outputs are computed voiding curves, flow rate and detrusor pressure *vs* time. The status of the urethral sphincter is described by an

"equivalent compression" VBN parameter U (units of pressure) and interpreted as a real compression or change to its effective cross-section. Detrusor force is characterized by the dimensionless VBN parameter k.

An example of the use of the VBN model with urodynamic data is how detrusor contraction and sphincter function change with age in two populations of non-neurogenic women (20-90 years), with or without obstruction, and referred for evaluation of LUT disorders. Modelling showed that in both groups k was constant with respect to age until an average menopausal time (50 years), and then decreased abruptly with further ageing (by 23% from 50 - 90 years). With obstructed patients, k was greater and there was a significant correlation between the values of k and U in both groups at all ages. These observations are consistent with a deterioration of detrusor force and loss of striated sphincter function especially once the menopause has been achieved and is consistent with other studies [45,46].

Research questions

A large number of factors currently associated with ageing may also be linked to disordered LUT function. However, in most cases a causal relationship has not been established and a number of key topics require investigation:

1   Can we define better our concept of 'ageing', is it related merely to the passage of time or the expression of particular biomarkers? Included in this is a need to collect better epidemiological data with regard to LUT dysfunction over a wide age range.

2   Define the role of chronic bladder ischemia in the pathophysiology of human ageing-related LUT dysfunction.

3   Develop better animal models of LUT functional changes related to ageing, rather than the middle-aged normal animals used by many groups today? How do we extrapolate findings from these models to the human condition with respect to LUT dysfunction?

4   Characterise the physiological properties of rhabdosphincter skeletal muscle (human and animal tissues) and how these alter in well-defined pathological conditions, e.g. sarcopenia.

5   Understand better the sacral control of pudendal nerve outputs related to effects of ageing and/or 'chronic load' to the external urethral sphincter and or the pelvic muscles.

6   Describe the age-dependence of circadian rhythms in hormones regulating renal sodium/water balance and blood pressure in the evaluation of patients with LUT dysfunction.

7   Describe the effects of changes in bladder sensation, detrusor overactivity and nocturnal polyuria on LUT disorders. Determine the effect of nocturia and nocturnal polyuria in patients treated for sleep disorders.

8   Increase our understanding of how ageing affects specific areas of the brain that control the storage/voiding cycle.

9   Explain the association of white matter hyperintensities, associated with older age and cognitive decline, with LUT dysfunction.

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