Neurourology and Urodynamics 35:278–282 (2016)

# Lower Urinary Tract Symptoms and Metabolic Disorders: ICI-RS 2014

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**Aims:** To investigate the link between lower urinary tract symptoms (LUTS) and metabolic disorders. **Materials and Methods:** This report results from presentations and subsequent discussions about LUTS and metabolic disorders at the International Consultation on Incontinence Research Society (ICI-RS) in Bristol, 2014. **Results:** There are common pathophysiological determinants for the onset of LUTS and the metabolic syndrome (MetS). Both conditions are multifactorial, related to disorders in circadian rhythms and share common risk factors. As in men with erectile dysfunction, these potentially modifiable lifestyle factors may be novel targets to prevent and treat LUTS. The link between LUTS and metabolic disorders is discussed by using sleep, urine production and bladder function as underlying mechanisms that need to be further explored during future research. **Conclusion:** Recent findings indicate a bidirectional relationship between LUTS and the MetS. Future research has to explore underlying mechanisms to explain this relationship, in order to develop new preventive and therapeutic recommendations, such as weight loss and increasing physical activity. The second stage is to determine the effect of these new treatment approaches on the severity of LUTS and each of the components of the MetS. *Neurourol. Urodynam. 35:278–282, 2016.*


**Key words:** lower urinary tract symptoms; metabolic syndrome; circadian rhythms

## INTRODUCTION

Worldwide prevalence of the metabolic syndrome (MetS) ranges from <10% to as much as 84%, depending on the composition of the studied population (age, sex, race, and ethnicity), region, environment and the definition of the syndrome used.[1] There are common pathophysiological determinants for the onset of lower urinary tract symptoms (LUTS) and the metabolic syndrome, which comprises impaired glucose handling, central obesity, arterial hypertension, microalbuminuria, and dyslipidemia. Both conditions are multifactorial and share common risk factors such as obesity and glucose intolerance.[1–3] An American study in patients over 60 years showed a strong positive association between markers of the MetS (history of diabetes mellitus (DM), arterial hypertension, and increasing glycosylated hemoglobin) and LUTS.[4] Prospective evaluation of American men showed an increasing risk for the onset and progression of LUTS with increasing body mass index (BMI), waist circumference and weight gain.[5] As in men with erectile dysfunction (ED), these potentially modifiable lifestyle factors may be novel targets to prevent and treat LUTS.[6]

## METABOLIC SYNDROME AND ERECTILE DYSFUNCTION

Epidemiological surveys have emphasized the link between sexual dysfunction and metabolic or cardiovascular risk factors in both men and women. Men complaining of ED show a higher risk for stroke, cardiovascular disorders, coronary heart disease and overall mortality; and this increase is independent of conventional cardiovascular risk factors. Men with ED should be evaluated adequately to identify these reversible risk factors, because potential benefits of lifestyle changes may be particularly important in patients with ED and cardiovascular or metabolic comorbidities, such as DM or hypertension. Therefore, lifestyle changes and risk factor modification must accompany or precede any pharmacological treatment. Experimental and epidemiological studies have linked regular physical activity and improvement of BMI to a reduced risk for ED. However, it should be emphasized that more controlled prospective studies are necessary to determine the effects of lifestyle changes in prevention and treatment of ED and the benefit of these lifestyle modifications on overall cardiovascular and metabolic health.[6]

## ROLE OF CIRCADIAN RHYTHMS

Emerging evidence from animal and clinical research reveals that conditions where the behavioral sleep-wake cycle is not in synchrony with the biological circadian system, so-called "circadian misalignment," may be putative risk factors for both metabolic disorders and LUTS. These circadian rhythms are controlled by a master circadian clock in the hypothalamus and play a major role in regulating day-to-night rhythms of

Eric Rovner led the peer-review process as the Associate Editor responsible for the paper.
Potential conflicts of interest: Dr. Denys reports grants from Astellas, AMS, Allergan, Bard, Pfizer, Ferring and Medtronic during the conduct of the study and outside the submitted work. Dr. Tubaro reports grants and other support from Allergan, Astellas, AMS, GSK, Pfizer, Pierre Fabre, Takeda Millennium and Shyonogi outside the submitted work. Dr. Abrams reports grants and personal fees from Astellas,and personal fees from Pfizer, Ferring, Proctor and Gamble, ONO and Ipsen during the conduct of the study. Dr. Everaert reports grants from Allergan, AMS, Astellas, Bard, Pfizer, Ferring, Medtronic, Hollister, Wellspect and Coloplast during the conduct of the study and outside the submitted work.
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Received 30 December 2014; Accepted 23 February 2015
Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/nau.22765

feeding behavior, sleep-wake cycles, tissue metabolism, and hormonal secretions, . This central clock is synchronized to our own 24 hr-rhythm by light signals conducted via the retino-hypothalamic tract. It then relays information via neuronal and hormonal pathways to higher brain regions and tunes the peripheral clocks of various organs such as heart, muscles, kidney, bladder, . Although these interactions are yet not fully understood, the chronobiology of micturition has already been described in detail on a molecular level in rodent models.[7]

The finding that humans void less frequently during sleep compared to the awake period is because of a decreased arousal in the brain, a decreased urine production rate in the kidneys and an increased functional bladder capacity during sleep.[7] Consequently, deficiencies in this triad of circadian variations are associated with nocturnal LUTS (Table I). First, impaired arousal during sleep is observed in children with enuresis, which emphasizes the important influence of sleep on LUTS. On the other hand, there is also a link between sleep disorders such as obstructive sleep apnea syndrome (OSAS) and the MetS,[7] with obesity as a well-studied risk factor for the development of both conditions.[1] Second, the observation of a nocturnal decrease in diuresis is not only caused by changes in food and fluid intake, but also by day to night variations in urine production. This is the result of circadian oscillating genes involved in the regulation of water and electrolyte excretion, which is typically disturbed in patients with nocturnal polyuria.[7,8] Glycosuria is the main cause of nocturnal polyuria by increasing solute diuresis in diabetic patients.[9] Third, healthy adults show higher voided volumes during nighttime compared to daytime. These variations are related to oscillations in connexin-43, a protein associated with changes in functional bladder capacity.[7] Diabetic cystopathy is an example of a link between changes in functional bladder capacity and metabolic disorders.[10] It manifests as an impaired bladder sensation, which leads to an increased bladder capacity and urinary retention that usually occurs asymptomatically until they have a secondary urinary tract infection.[11]

Circadian disorders may result in impaired glucose tolerance with higher diabetes risk in non-diabetic individuals and poor glycemic controls in patients with DM. Recent development of ambulatory blood pressure monitoring changed the focus towards the evaluation of circadian rhythm and day to night differences in blood pressure. Healthy adults show a circadian rhythm with a 10–20% fall in blood pressure during sleep, which is driven by physical inactivity and largely independent of any endogenous rhythm.[12] Ambulatory blood pressure monitoring in adults showed a significantly higher average drop in sleep systolic blood pressure in those without nocturia compared to those with any severity of nocturia.[12,13] This phenomenon of non-dipping is an independent predictor of overall mortality, cardiovascular mortality and cardiovascular events and may, therefore, be a more sensitive risk marker than average daytime or 24-hr blood pressure.[14,15]

**TABLE I. Role of Circadian Rhythms[7,33]**

| Circadian rhythm in: | ☼ | ☾ |
|---|---|---|
| Brain (sleep) | ↑ | ↓ |
| Kidney (urine production) | ↑ | ↓ |
| Bladder (functional capacity) | ↓ | ↑ |

[7,35] The finding that humans void less frequently during sleep ( ☾ ) compared to the awake period ( ☼ ) is because of a decreased arousal in the brain, a decreased urine production rate in the kidneys and an increased functional bladder capacity during sleep compared to the awake period.[7,35]

## SLEEP

Sleep deficiencies are the result of multiple underlying conditions, including insufficient sleep, periodic limb movement disorders during sleep (PLMS), narcolepsy, insomnia, OSAS, shift work, and nocturia, and are related to metabolic diseases such as obesity, DM and hypertension, through multiple pathophysiological mechanisms, such as changes in food intake and physical activity, levels of leptin and gherlin, inflammation, oxidative stress, and increased sympathetic activity. On the other hand, sleep deficiencies can also result in LUTS. Despite the discovery of these associations, the causal relationship between sleep disorders, LUTS and the MetS requires further exploration.[16,17]

### Sleep and Metabolic Syndrome

Patients with short sleep durations (<5–6 h) have an increased risk to develop metabolic disorders.[18] This central role for sleep is reinforced by the observation that treatment of patients with OSAS with continuous positive airway pressure (CPAP), compared to sham CPAP, reversed different components of the MetS.[19]

### Sleep and Lower Urinary Tract Symptoms

Nocturia is one of the most prevalent and bothersome LUTS and a leading cause of sleep disturbance in adults.[20,21] Behavioral treatment strategies for insomnia significantly reduces the number of nocturnal voids.[22] which suggests that nocturia, in some individuals, may be considered as a result rather than a cause of sleep disorders. There is also an increased risk of developing LUTS including urinary incontinence and nocturia, in patients with a poor baseline sleep quality and sleep restriction, with BMI as a potential mediator of this relationship.[3] This reinforces the hypothesis that some LUTS may be a result rather than a cause of sleep disorders.

OSAS occurs when a person's airway is blocked despite efforts to breathe. This results in a negative intrathoracic pressure, an increased secretion of the atrial natriuretic peptide and stimulation of natriuresis. This nocturnal polyuria is a potent cause of nocturia, and can lead to nocturnal enuresis and nocturnal incontinence, which improves when the underlying OSAS is treated with CPAP.[23] There is also some evidence that there is a relationship between OSAS, overactive bladder and urgency incontinence.[24]

Children with nocturnal enuresis have a significant higher periodic limb movement index, arousal index and awakening index compared to control subjects, which emphasise the central involvement of sleep in the pathophysiology of nocturnal enuresis.[25] Preliminary results reveal that treating enuretic children with desmopressin lowers the periodic limb movements index and improves sleep.[26] In adults, idiopathic restless legs syndrome is associated with significantly higher nighttime diuresis, increased sodium and chloride excretion and lower osmolality excretion.[27]

## KIDNEY: URINE PRODUCTION

The rate of urine production affects filling and emptying symptoms of the lower urinary tract, both during daytime and nighttime. Only limited research is available on the impact of the MetS on diuresis rate, and even less to what extent this might influence the presence and severity of LUTS. Summarizing the physiology of urine production is useful to understand the potential influence of metabolic disorders on LUTS.[8]

### Physiology of Renal Function

The kidneys receive about 20–25% of cardiac output, or over 1,700 L plasma per day, of which only 180 L is filtered. Since the majority of this filtrate is reabsorbed, daily urine production is only 1.5–2 L. This is regulated by complex interactions between urine concentrating and diluting mechanisms, which operate by controlling glomerular filtration, solute diuresis and water diuresis (Fig. 1).[9]

The glomerulus receives its blood supply from an afferent arteriole of the renal circulation and drains into an efferent arteriole. The resistance of these arterioles is auto-regulated and determines the fraction of plasma that is filtered through the glomerular capillaries into the Bowman's capsule, which empties the filtrate into the proximal tubule. Therefore, an increase in intravascular volume or blood pressure stimulates glomerular filtration. Future research needs to explore the underlying mechanisms that explain this increased glomerular filtration (glomerular hyperfiltration, activation of silent nephrons, ).

The majority (95–99%) of the filtered osmoles are reabsorbed together with water in the proximal tubule, and for a minor part in the loop of Henle and the distal tubule of the kidney. Natriuresis is the most important type of solute diuresis and regulated by salt dietary intake and hormonal mechanisms, including the atrial natriuretic peptide (ANP) and the renin–angiotensin–aldosterone system (RAAS), which are controlled by intravascular volume and blood pressure. Other types of solute diuresis are glycosuria in patients with DM and excretion of urea due to a high protein diet or hepatic diseases.[9,28] The association between food and fluid intake and urine production illustrates the link with obesity.

Free water (without osmoles) is mainly reabsorbed in response to the antidiuretic hormone vasopressin (ADH). Its secretion is mainly stimulated by hyperosmolality and volume depletion and results in a reduced urine production by increasing reabsorption of free water via aquaporins in the collecting tubules.[9]

### Evaluation of Diuresis in Patients With (Nocturnal) Polyuria by Using a Renal Function Profile

Renal function profiles have recently been used in research settings to distinguish between pathophysiological causes of nocturnal polyuria in adults with nocturia[8,29] and in children with nocturnal enuresis.[30] It is a 24-hr urinalysis, recorded separately from the bladder diary, in which patients are asked to collect urine in separate 3 hr volumes, for analysis of diuresis rate, osmolality, and sodium, urea, and creatinine concentrations. Also a blood sample is taken to determine serum osmolality, creatinine, sodium, and urea in order to calculate the renal clearance of each of these substances.[8,29] Discrimination between disturbances in glomerular filtration, water diuresis and solute diuresis as pathophysiologic mechanisms of (nocturnal) polyuria may complement bladder diaries as a key tool in categorizing the basis of LUTS.

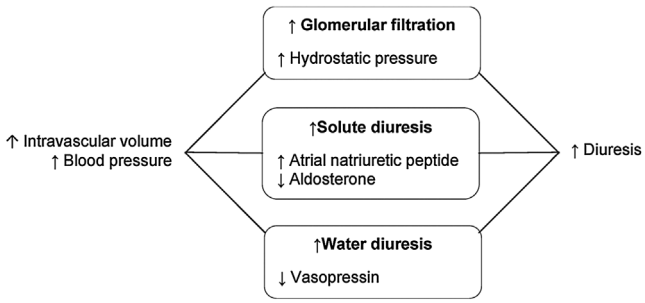


**Fig. 1.** Renal function and urine production.[9]

### Diuresis and Metabolic Disorders

Obesity is an important driving force behind the MetS and an independent risk factor for the development and progression of chronic kidney disease. One of the explanations for this observation is the presence of an overactive RAAS in obese persons, despite sodium retention and increased intravascular volume. Together with a stimulated sympathetic nervous system as well as physical compressing of the kidneys by visceral adiposity, it impairs pressure natriuresis and increases renal tubular sodium reabsorption, which leads to intravascular expansion and hypertension. This stimulated RAAS in the presence of a high salt and calorie diet plays a key role in the development of hypertension and cardiovascular complications.[31,32]

By increasing renal plasma flow and glomerular pressure, obese adults show a rise in glomerular filtration and filtration fraction. This may result initially in proteinuria, which precedes the decline in glomerular filtration by years, and the later occurrence of glomerulosclerotic damage, which is observed before the development of DM and renal failure.[31,32]

The definition of 24-hr polyuria states that a urine output higher than 40 ml per kilogram bodyweight per hour is abnormal.[29] Thus, with higher body weight, a higher 24-hr urine output is permitted, regardless of body height. We suggest that the relation between BMI, diuresis, and glomerular filtration is evaluated, in order to determine if there is a compensatory increase in glomerular filtration to prevent sodium and fluid retention in patients with metabolic disorders during early stages of their disease.

## BLADDER FUNCTION

### Circadian Rhythm of Bladder Function

To guarantee normal micturition, the central and peripheral nervous systems control the contraction of the smooth muscles of the bladder once a sensation of fullness is perceived. Connexin-43 is a gap junction protein in the bladder that enhances intercellular transmission and sensitizes the response of bladder muscles to cholinergic stimulation. As a result, an increase in connexin-43 level results in a decreased functional bladder capacity and an increased micturition frequency in rats. The existence of this peripheral clock in the bladder was recently proven and found to contribute to diurnal changes in bladder capacity in order to avoid disturbance of sleep by micturition. Wild-type mice show an internal clock with a circadian rhythm in bladder connexin-43 levels and functional bladder capacity, while such rhythms are completely lost in mice with a dysfunctional biological clock.[7,33]

### Bladder Function and Metabolic Disorders

Although it is not possible to outline one obvious relation between bladder dysfunction and the MetS, there are a number of potential mechanisms suggesting a link that may provide specific approaches in the management of LUTS in the future, for example the components of the MetS, hypogonadism, inflammation.[34]

Abdominal obesity, for example, is associated with decreased physical activity and may be associated with increased sympathetic activity, which is associated with both the development and progression of benign prostate hyperplasia (BPH) to benign prostatic obstruction (BPO) and the severity of LUTS. This reduced physical activity also leads to abnormal blood glucose levels and hyperinsulinemia; and, in addition, prolonged periods of increased serum glucose have a selective neurotoxic effect on parasympathetic neurons, affecting bladder smooth muscle tone.[35]

Because testosterone is converted to estradiol in adipose tissue, obese men have lower testosterone and higher estrogen levels compared to normal-weight men. This can potentially result in symptoms of an overactive bladder (OAB) due to detrusor overactivity, since estrogens play a major role in activating M3-muscarinic receptors. The presence of DM, hypertension and hyperlipidemia is also a risk factor for developing low testosterone levels or late onset hypogonadism, which is also associated with LUTS and may be treated with hormone replacement therapy.[36] Long-term testosterone therapy for obese hypogonadal men with DM reduced waist circumference and body weight and also improved DM and other cardiometabolic risk factors.[37] On the other hand, physical activity maintains normal steroid hormone and insulin levels that are essential in maintaining a healthy BMI.[35]

Histopathological examination of BPH specimens demonstrates a link between the presence of components of the MetS and a higher degree of intraprostatic inflammation, which is a crucial component of BPH pathogenesis. Corona et al. made a graphical representation of a proposed a multifactorial pathogenesis of both BPH and LUTS with an important role for prostate inflammation, MetS, sex steroid environment and bladder function (Fig. 2).[34]

## RESEARCH QUESTIONS

Future research has to determine the role of sleep, kidney function and bladder function in the onset and progression of LUTS in patients with metabolic disorders. By using validated questionnaires on sleep and LUTS, polysomnography, bladder diaries, pad tests and renal function profiles, each of the following research questions has to be explored in specific patient populations with impaired glucose handling, central obesity, arterial hypertension, microalbuminuria and dyslipidemia:

### Role of Sleep

- What is the effect of sleep disorders (OSAS, PLMS, ) and sleep deprivation on daytime and nighttime LUTS?
- Can we identify sleep-related risk factors for progression of LUTS?
- What is the effect of treating sleep disorders in patients with LUTS?
- Do we need to screen for sleep disorders in patients with LUTS?

### Role of Kidney and Bladder Function

- What is the association between diuresis, daytime LUTS and nighttime LUTS?
- What are the genetic and molecular mechanisms leading to local circadian rhythms in the bladder and the kidney?
- What is the value of renal function profiles for the differentiation of the pathophysiological causes of (nocturnal) polyuria?
- Do renal function profiles play a role in a more causal treatment of patients with (nocturnal) polyuria (e.g., antidiuretic treatment in patients with increased water diuresis, diuretic treatment in patients with increased solute clearance, )?
- What are the underlying mechanisms (glomerular filtration, solute diuresis, water diuresis, ) to explain associations between different components of the MetS, diuresis rate and LUTS?
- Do lifestyle modifications such as weight loss, increased physical activity, decrease in arterial hypertension, affect diuresis rate and LUTS? Can it prevent or delay LUTS onset in asymptomatic patients, attenuate LUTS severity in symptomatic patients and obviate the need for medical or surgical treatment?

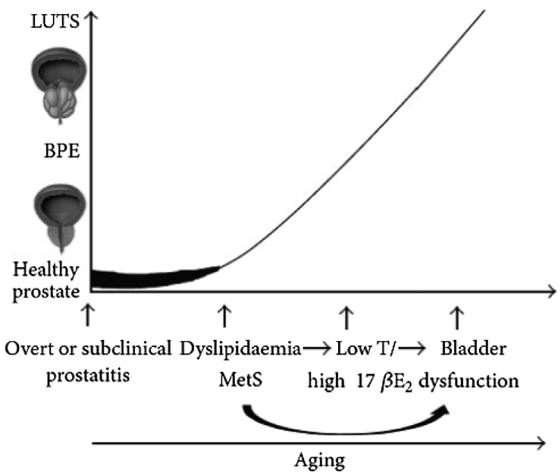


**Fig. 2.** Graphical representation of a proposed multifactorial pathogenesis of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS).[34] BPE, benign prostate enlargement; $E_2$, estradiol; LUTS, lower urinary tract symptoms; MetS, metabolic syndrome; T, testosterone.

## CONCLUSION

Recent findings indicate a bidirectional relationship between LUTS and the MetS, both multifactorial conditions with an increasing worldwide prevalence. Future research has to explore underlying mechanisms to explain the various relationships between LUTS and different aspects of the MetS. This can be a first step towards the development of new preventive and therapeutic recommendations, such as weight loss and increasing physical activity. The second stage is to determine the effect of these new treatment approaches on the severity of LUTS and each of the components of the MetS.

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