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Links between lower urinary tract symptoms, intermittent hypoxia and diabetes: Causes or cures?

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Abstract

Bothersome lower urinary tract symptoms (LUTS) manifest as urinary frequency, urgency, incontinence and incomplete bladder emptying. Existing treatments ameliorate but do not eliminate most symptoms, leading to financial and personal burdens attributable to sustained medical therapies that may last a lifetime. The purpose of this review is to highlight evidence of causal associations between LUTS and several common comorbidities, including intermittent hypoxia (IH) concomitant with obstructive sleep apnea (OSA), obesity, metabolic syndrome and type 2 diabetes. Links between these conditions, including therapies targeted to co-occurring complications that have demonstrated benefits for LUTS, suggest compelling avenues of research and also underscore critical gaps in understanding the mechanisms underlying urinary dysfunction. These gaps are prominent in the IH field, where an acknowledged link between OSA and LUTS has gone largely uninvestigated. New tools, models, or reappropriation of existing ones, especially rodent models, is required to parse the associations between IH/OSA, LUTS and obesity/diabetes and to elucidate their underlying, and potentially shared, etiologies.

Keywords

intermittent hypoxia; obstructive sleep apnea; lower urinary tract symptoms; LUTS; type 2 diabetes; prostate

1. Overview of lower urinary tract symptoms

Lower urinary tracts symptoms (LUTS) encompass a broad group of symptoms affecting urination. Symptoms are categorized as storage, voiding or post-voiding. Storage symptoms include increased frequency or urgency of urination, urgency incontinence and repeated passage of urine at night (nocturia). Voiding symptoms consist of weak or intermittent stream, straining, hesitancy, terminal dribbling and incomplete voiding and urinary retention. Post-void dribbling is the predominant post-voiding symptom. The common occurrence of

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LUTS, especially among ageing men, combined with variability in the aspects of urination affected and presentation of symptoms, results in significant time and money spent on diagnosis and treatment.

The cumulative cost of managing LUTS is substantial, resulting in \$17.6 million in health care expenditures annually in the United States (Saigal and Joyce, 2005). In 2000, ~14.5 out of every 100 clinic and hospital outpatient visits in America were for LUTS (Wei et al., 2005). Age is a critical risk factor for LUTS: symptom incidence increases linearly with age at a rate of ~10% per decade between 40 – 79 years of age (Boyle et al., 2003; Parsons et al., 2008; Verhamme et al., 2002). Because the underlying mechanisms of LUTS are little understood, there is no existing treatment for the disease itself. Instead, the best available current medical option is to treat the symptoms of LUTS, but this approach is of limited effectiveness: few LUTS are eliminated by existing therapies, meaning most patients seeking treatment for their urinary symptoms will require lifetime therapy. Due to duration of treatment, along with symptom bother, LUTS exacts significant indirect costs. Approximately 10% of LUTS patients miss an average of 7.3 hours of work each year while pursuing diagnosis or seeking treatment (Saigal and Joyce, 2005). Further, quality of life is greatly impacted for LUTS patients, whose symptoms range from bothersome to potentially embarrassing and painful to lethal in infrequent cases of acute urinary retention (Agarwal et al., 2014; Kupelian et al., 2006; Robertson et al., 2007). LUTS have been shown to correlate significantly with erectile dysfunction, anxiety and depression (Coyne et al., 2009; Hansen, 2004; Kirby et al., 2013; Rom et al., 2012). In aggregate, the potential financial and personal burdens exacted by LUTS demand continued development of rapid and effective methods for diagnosis and treatment.

2. Causes of LUTS

Historically, the cause of male LUTS was believed to be due to a single factor: a large prostate. Over time, however, clinicians and researchers have come to understand that LUTS can derive from many origins. Today, known causes of LUTS are as diverse as the number of symptoms this syndrome comprises. These myriad causes may contribute to the variable efficacy of existing treatments and the heterogeneity of the patient population suffering from urinary dysfunction, which have long confounded clinicians. Probe research literature for LUTS or for similar terms and a litany of risk factors, related conditions and associated diseases is unveiled. This amalgamation of LUTS-related health concerns makes attempts to isolate and identify the underlying mechanism/s of LUTS appear intractable, and the task of defining new treatments and possible cures seem insurmountable. However, upon closer examination, overlap and similarities between these associations become apparent, providing insight into culpable pathways and revealing discernable avenues of research. One interesting pathology that associates with LUTS is systemic intermittent hypoxia (IH) as a consequence of obstructive sleep apnea (OSA). OSA is a sleep disorder with a long-acknowledged link to urinary problems, though the causes for development of LUTS in OSA patients have remained largely unexamined. In order to understand the factors that contribute to the urinary symptoms commonly associated with IH/OSA, we must also examine conditions that frequently accompany OSA: obesity, metabolic syndrome and type 2 diabetes. Thoughtful consideration of key LUTS comorbidities will allow us to gain an

appreciation for the complex phenotypic background on which LUTS typically present, complexity that must be taken into account to improve clinical outcomes and to ensure rigorous hypothesis testing. Also, to move beyond existing, marginally effective LUTS therapies, we must first assimilate the history of LUTS, which begins with the prostate. We can learn much about where we are going from realizing where we have been.

2.1. Enlarged prostate

Traditionally, the most common cause of LUTS is linked to the prostate, a male accessory sex gland that secretes components of semen and is found in most placental mammals. In humans, the prostate is located just below the bladder, completely surrounds the urethra and is encapsulated by a thick and inelastic fibromuscular band.

Prostate formation and growth throughout life are dependent on androgen receptor activation by the male hormone testosterone and its more potent metabolite, dihydrotestosterone (DHT). During puberty, prostate size doubles to approximately 20 g in response to increased male hormones and then remains relatively static in men throughout their 20s. A second phase of growth, also dependent on androgens, begins around age 30 and continues, yielding prostate weights of 33 g on average in men older than 70. Inappropriate age-related prostate growth is common and, in extreme cases, can result in a prostate that weighs in excess of 100 g (Berry et al., 1984). Inappropriate growth is known as benign prostatic enlargement (BPE), also commonly referred to as benign prostatic hyperplasia (BPH). Though the precise causes of BPE remain unclear, there is evidence that androgens are required in pathogenesis of the disease. Men whose testicles are removed before puberty and men who do not produce DHT do not develop BPE (Imperato-McGinley et al., 1992; Wu and Gu, 1991). However, the role hormones play in BPE is more complicated than mere presence or absence of androgens. The amount of testosterone in the blood decreases with age, leading to a relative increase in the proportion of estrogen, a shift that may promote prostate cell growth (Bjørnerem et al., 2004; Coffey and Walsh, 1990). Interestingly, levels of DHT do not change in older men despite falling testosterone levels, likely due to reduced metabolism (Horton, 1984). These data seem contradictory for, while levels of prostate growth-promoting hormones decrease (testosterone) or stay the same (DHT) with age, actual prostate growth continues in ageing men, sometimes unchecked. Perhaps relative levels of hormones are also important for regulation of growth, such as the ratio of testosterone to estrogen mentioned above. Thus, while it is clear that androgens are required for BPE onset, the importance of androgen dosage and potential roles for other hormones in BPE etiology remain to be elucidated.

Increased prostate size is believed to contribute to LUTS in part because outward growth of the prostate is hypothesized to be limited due to lack of compliance of the fibromuscular band that encapsulates the human prostate. As a result of this noncompliance, increasing prostate size due to BPE tends to press on the urethra, which the prostate surrounds, and the bladder, against which the prostate lies. These mechanical effects of the enlarged prostate can interfere with or inhibit urine flow, a condition known as bladder outlet obstruction, which manifests as one or more symptoms of LUTS (Furuya et al., 1982). Efficacy of a minimally invasive surgical treatment for BPE, transurethral incision of the prostate (TUIP),

provides support for the noncompliant fibromuscular band theory of LUTS pathophysiology. During TUIP, the prostatic capsule is incised but no tissue is removed; simply, the tissue is allowed to “open up,” releasing pressure on the urethra. Following TUIP, patients demonstrate improved International Prostate Symptom Scores (IPSS, a urinary symptom index used to quantify symptom severity), decreased incidence of nocturia and improved peak urine flow rate ($Q_{\max}$) (Tkocz and Prajsner, 2002; Yang et al., 2001). However, these improvements are typically only seen in men with small prostates (<30 mL) who are experiencing LUTS. If a large lobe is present, resulting in a prostate volume of 30–60 mL or more, TUIP is not recommended, as the presence of excessive hyperplastic tissue can continue to block urine flow. Instead, procedures that include removal or ablation of prostatic tissue are indicated (Christidis et al., 2017; Taylor and Jaffe, 2015). Thus, while the inelasticity of the prostatic capsule accounts for some aspects of bladder outlet obstruction, the sheer volume of hyperplastic prostate tissue also appears to contribute to blockage. Several population-based studies have shown an association between enlarged prostate and the need for surgery to relieve BPE symptoms (Roehrborn, 2008).

Medically, there are several approaches to ameliorate LUTS believed to be due to an enlarged prostate, including surgery, though that option is typically not a first-line treatment due to risk of serious and undesirable side effects, including incontinence and erectile dysfunction (Flynn and Webster, 2004; Sopko and Burnett, 2016). Instead, men experiencing mild symptoms may employ watchful waiting, which combines lifestyle modifications to manage symptoms with annual check-ups to monitor prostate size. If symptoms become more bothersome, pharmaceutical therapies may be pursued, such as 5-alpha reductase inhibitors that inhibit the enzyme that converts testosterone to the more potent agonist, DHT, thereby slowing prostate growth. When bothersome LUTS are refractory to drug therapies, if efficacy of these therapies wanes over time, or if LUTS are severe, patients may then choose to pursue surgical treatments. Several minimally invasive options to remove or ablate prostate tissue in an attempt to relieve bladder obstruction are routine, but in terms of LUTS treatment outcomes, the oldest and most invasive option available is also the most effective and durable one: complete removal of the prostate, or prostatectomy (Goldenberg et al., 2009; Gravas et al., 2015; National Cancer Institute, 2011; National Institute for Health and Care Excellence, 2015).

Despite a common perception of LUTS as deriving exclusively from prostate pathologies in the mind of the public and a preponderance of research and clinical efforts focused on causes and prevention or resolution of BPE to ameliorate LUTS, evidence is amassing that prostatic enlargement is far from the sole potential driver of LUTS. While severity of LUTS frequently correlates with increased prostate volume, there is a cohort of men with small prostates that report suffering from severe LUTS, as well as a cohort of men with large prostates that do not experience bothersome urinary symptoms (Turkbey et al., 2012). Further, and importantly, neither drug nor surgical interventions that target the prostate eliminate LUTS in all patients (Gravas et al., 2015). Of particular note, women suffer from and seek treatment for bothersome LUTS just as men do, in spite of the fact that women lack a prostate (Coyne et al., 2012; Milsom et al., 2012; Rosenblum et al., 2004; Scarpero et al., 2003).

Clearly, other factors can and must be involved in the etiology of LUTS, as evidenced by the fact that there are several notable therapies that have no known impact on prostate size or (presumed) compliance, yet improve urinary function. These include LUTS-targeted pharmaceutical therapies that act on smooth muscle or vasculature and treatments for LUTS comorbidities, such as continuous positive airway pressure therapy for IH associated with OSA, all of which also confer relief from urinary symptoms. The mechanisms of these unexpected therapeutic effects on LUTS are not known and reveal broad gaps in our understanding of the etiology of urinary dysfunction. Several of these examples are discussed in the following sections, beginning with obesity, metabolic syndrome and type 2 diabetes (section 2.2), then IH associated with OSA (section 2.3) and ending with a summary of other potential causes, including smooth muscle and vasculature (section 2.4).

2.2. Obesity, metabolic syndrome and type 2 diabetes mellitus

Incidences of obesity, metabolic syndrome and type 2 diabetes mellitus are on the rise, especially in the Western world. Each disease/syndrome constitutes a serious medical condition that requires appreciable health care expenditures and affects quality of life. Further, all three conditions are associated with a litany of comorbidities, many of which overlap (International Diabetes Federation, 2015; National Heart, Lung, and Blood Institute, 2016; World Health Organization, 2016). LUTS is among the complications common to all three conditions.

Obesity is defined as the accumulation of excess body fat to the extent that health may be impaired. The number of obese individuals has more than doubled worldwide since 1980. Increased body mass index (BMI), a value calculated based on an individual's weight and height and used to classify people on a scale from underweight to obese, is a risk factor for osteoarthritis, diabetes, cardiovascular disease and some cancers (World Health Organization, 2016). In addition to these conditions, several studies have demonstrated associations between obesity and LUTS. A survey of 27,858 Swedish men showed that participants exhibiting the highest abdominal obesity ratio were 22% more likely to suffer moderate to severe LUTS. Further, risk of severe LUTS increased by 13% for every BMI increase of 5 (Laven et al., 2008). Similarly, the Southern Community Cohort Study, a study of 7,318 men age 40 – 79 based in the southeastern United States, observed a 38% increased risk of moderate to severe LUTS with a BMI of at least 35 kg/m³. Additionally, severe obesity was significantly associated with development of LUTS in both white and African-American men (Penson et al., 2011). Kim et al. evaluated IPSS scores, a clinical measure of LUTS severity, for 73 male and 176 female patients seeking bariatric surgery. They reported that six out of seven IPSS scores were significantly higher for both the obese male and obese female groups (Kim et al., 2016).

Risk of LUTS also increases in patients with metabolic syndrome, defined as co-occurrence of at least three of five conditions comprising obesity, increased blood pressure (hypertension), high fasting glucose, high triglycerides and abnormal cholesterol levels (Rohrmann et al., 2005). Prevalence of metabolic syndrome is on the rise due to the escalating number of obese adults (National Heart, Lung, and Blood Institute, 2016). Increased risk of LUTS in patients with metabolic syndrome has been demonstrated in

several studies. In the Boston Area Community Health (BACH) Survey, results from 1899 men between the ages of 30 – 79 revealed that men experiencing LUTS had higher odds of metabolic syndrome comorbidity (Kupelian et al., 2013). A study of 490 male patients with metabolic syndrome from a community hospital urologic clinic in Brazil demonstrated a 2-fold increased risk in developing LUTS (Zamuner et al., 2014). Metabolic syndrome correlated with higher IPSS scores and treatment for LUTS, and LUTS severity increased when more components of the syndrome were present in a study of 4666 European men visiting a general practitioner (Pashootan et al., 2015).

Both obesity and metabolic syndrome carry with them the risk of developing type 2 diabetes mellitus, an obesity-induced resistance to insulin that results in high blood sugar levels over a prolonged period. 415 million people suffer from diabetes worldwide, with 29.3 million living in the United States. Up to 90% of this total represents type 2 diabetes. Due to the staggering number of people afflicted, the United States had \$320 billion in diabetes-related health care expenditures in 2015. In part, these costs are driven not only by the presence of diabetes in itself but also by a host of major complications that frequently accompany this condition (at least one in up to 50% of patients): diseases of the eye, mouth, heart, kidney, foot and nerves (International Diabetes Federation, 2015). Frequent urination is a remarkably common diabetic complication. For years, it was assumed this polyuria was the result of diabetic diuresis, or an increase in urine production resulting from decreased water reabsorption in the kidneys in response to high blood sugar levels. Eventually, studies using animal models showed diuresis in the absence of diabetes caused bladder remodeling, which can affect bladder function, but that those changes could not fully recapitulate the urinary profile of diabetic patients (Fathollahi et al., 2015). In other words, diuresis accounts for some, but not all, of the LUTS diabetics suffer, revealing another gap in knowledge as to what contributes to these additional diabetic urinary symptoms and highlighting, yet again, our incomplete understanding about the full complement of LUTS causal factors. Strikingly, up to 87% of insulin-dependent diabetic patients exhibit LUTS (Frimodt-Møller, 1980). Diabetics report urge incontinence, increased urine retention after voiding (post-void residual) and nocturia symptoms, among others (Kebapci et al., 2007; Lee et al., 2007). In fact, 25% of type 2 diabetic patients get up to go to the bathroom two or more times per night according the 2005–2008 National Health and Examination Survey study (NHANES) (Plantinga et al., 2012). Results from the Boston Area Community Health Survey (BACH, $n=1899$) reveal a significant association between high blood glucose or diabetes and moderate to severe LUTS (Kupelian et al., 2013). Researchers found a similar association between diabetes and severe LUTS using data from both the California Men's Health Study (CMHS), a survey of 84,170 men, and the Research Program and Genes, Environment and Health (RPGEH), a study of 140,139 men (Van Den Eeden et al., 2013). Additional evidence of the link between diabetes and LUTS originates from an Italian study of 544 LUTS patients, which demonstrated that insulin resistance was an independent predictor of severe LUTS (Russo et al., 2014).

Obesity and the diseases it contributes to, like metabolic syndrome and type 2 diabetes, are preventable and reversible conditions in many cases. Lifestyle changes that focus on healthy eating and increased physical activity combat obesity, though it is a complex problem that requires many supporting strategies to reverse. Interestingly, the potential to slow or reverse

obesity and, presumably, related conditions, through healthy living, raises the possibility that these same types of changes may be able to reduce severity or occurrence of LUTS as well. This possibility introduces additional areas of research, given that the collective associations of obesity, metabolic syndrome and type 2 diabetes with urinary symptoms render LUTS an alarmingly common problem. Note, however, that as with enlarged prostate, obesity, metabolic syndrome and type 2 diabetes comorbidities do not account for all LUTS patients. In the following section (2.3), we highlight evidence demonstrating that LUTS can occur in the absence of either obesity or diabetes.

2.3. Intermittent hypoxia as a consequence of obstructive sleep apnea

LUTS symptoms are frequently observed in obstructive sleep apnea (OSA) patients. OSA is a common sleep disorder characterized by repeated pauses in breathing due to upper airway obstruction. While OSA-induced interruptions in breathing can be brief, episodes may occur many times over the course of an hour, leading to one of the physiological hallmarks of OSA: intermittent hypoxia (IH), or periodic exposure to reduced blood oxygen. Together, hypoxia and sleep fractionation due to partial or full arousal when breathing arrests, cause daytime sleepiness, headaches, difficulty concentrating, forgetfulness, irritability and depression. Left untreated, IH resulting from OSA is linked to many serious conditions, encompassing hypertension, heart attack, stroke and diabetes (Dagur and Warren, 2015; International Diabetes Federation, 2008).

Many sleep apnea patients report problems with urinary frequency, incontinence and, in particular, nocturia. A study of 50 patients seeking evaluation for sleep apnea demonstrated that 44% of patients with OSA woke at least three times to urinate overnight, while only 5% of patients without sleep apnea woke that often (Coban et al., 2016). A multivariate analysis of sleep and urinary parameters in 32 Japanese men with OSA demonstrated a significant negative correlation between nocturia and sleep quality (Tsujimura et al., 2010). Remarkably, data collected from examination of 32 women who underwent a home sleep study revealed that nighttime urination was highly predictive of sleep apnea: 88% of patients experiencing nocturia also had OSA (Lowenstein et al., 2008). Further, OSA is observed in children and, among non-obese children, is believed to be due to craniofacial structure abnormalities (e.g., size or shape of chin, jaw or palate) or enlarged tonsils and adenoids, all of which can cause airway obstruction (Marcus, 2000; Umlauf and Chasens, 2003). OSA associates with nighttime enuresis (bedwetting) in normal weight children, and some studies indicate that adenotonsillectomy can decrease nighttime urine output (Barone et al., 2009; Heba et al., 2013; Marcus, 2000; Neshat et al., 2016). These results advance the idea that OSA can associate with urinary dysfunction independent of obesity and type 2 diabetes.

Several studies suggest that increasing severity of OSA associates with severity of LUTS, indicating that there may be a dose-response relationship between these two variables. The home sleep study of 32 women cited above demonstrated an inverse correlation between the amount of bother reported due to nighttime urination and percent of rapid eye movement (REM) sleep, an indicator of sleep quality (Lowenstein et al., 2008). A clinical study of 30 elderly adults with symptoms of sleep apnea and nocturia demonstrated an association between apnea-hypopnea index (AHI) scores, an index of sleep apnea severity, and volume

of nighttime urine output: a +10% increase in urine output doubled the odds of being in a more severe AHI category (Umlauf et al., 2004). A retrospective review of 196 sleep studies and a retrospective chart review of 1970 sleep-disordered breathing patients both found that AHI was an independent predictor of frequency of nighttime urination (Fitzgerald et al., 2006; Oztura et al., 2006). Data from the Complementary and Alternative Medicine for Urological Symptoms trial (CAMUS), a placebo-controlled, double-masked study of 369 men sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), revealed that men with severe sleep disturbance reported more bothersome LUTS and had a higher American Urological Association Symptom Index score (AUASI, a symptom severity score identical to the IPSS less one quality of life question) than men with mild sleep disturbance (Cakir and McVary, 2012). Interestingly, results from this same trial showed changes in sleep disturbance were more correlated with changes in AUASI scores for urinary symptoms that did not include nocturia than they were for nocturia alone, indicating that presence of LUTS other than nocturia may also contribute to poor sleep quality (Helfand et al., 2012).

In addition, OSA is associated with obesity and type 2 diabetes, both of which, as discussed in section 2.2 above, confer increased risk of LUTS. OSA occurs with increased frequency in obese patients: in obese adults, excess fat around the face and neck is thought to constrict the upper airway, contributing to OSA (Greenstone and Hack, 2014). Furthermore, a number of studies demonstrate an association between type 2 diabetes and OSA. Overall, an estimated 13% of men and 6% of women have moderate to severe sleep apnea but incidence is higher in diabetics (Peppard et al., 2013). Among 498 type 2 diabetic German patients who underwent a sleep study, 37% exhibited moderate to severe sleep apnea (Schober et al., 2011). Data from the Wisconsin Sleep Cohort population-based investigation ($n=1,387$) showed that incidence of diabetes increased with increasing severity of sleep disorder: 14.7% of people with moderate to severe sleep apnea were diagnosed with diabetes, while among subjects without sleep apnea, only 2.8% were diabetic (Reichmuth et al., 2005). Two separate studies of adults with no known diagnosis of diabetes, a Chinese survey of 270 subjects and a Swedish examination of 232 people, both showed that sleep apnea is a predictor of insulin resistance (Ip et al., 2002; Lindberg et al., 2012).

Fascinatingly, studies are beginning to demonstrate that treatments utilized routinely and successfully to remedy IH/OSA can simultaneously provide therapeutic benefits for LUTS and type 2 diabetes. The standard for OSA treatment is nasal continuous positive airway pressure (CPAP). A CPAP machine delivers a continuous stream of air through a mask worn over the nose; the positive pressure of the forced air keeps the airways open so breathing is not obstructed. In cases where tonsils or adenoids are enlarged, nasal polyps are present or facial deformities such as a deviated septum contribute to OSA, surgery may be a treatment option, though due to the invasiveness of surgery, CPAP has long been the first-line treatment recommendation. CPAP treatment was linked to improvements in glucose metabolism in a study of 25 type 2 diabetic patients. After 30 – 90 days of treatment, patients demonstrated significantly lower glucose values and hemoglobin A1c levels (an indicator of blood glucose levels over a 2 – 3 month duration), indicating improvements in glycemic control as a result of therapy (Babu et al., 2005). Meanwhile, both CPAP therapy and surgery have been shown to improve urinary symptoms. In an examination of CPAP

efficacy, 23 Chinese patients with nocturia were diagnosed with OSA following a sleep study. Urodynamic studies of these patients revealed dysfunction: patients had increased pressure build up and sensitivity to bladder filling, and weak bladder detrusor muscle contractions. Following three months of CPAP therapy, patients underwent follow up sleep and urodynamic studies. Frequency of nighttime urination decreased, while bladder muscle contraction improved (Hu et al., 2011). In a second study, 37 OSA patients with nocturia underwent surgery to remove or remodel throat tissue (e.g., tonsil removal). Three months postoperatively, successful surgeries (those with a >50% decrease in snoring) resulted in significantly fewer episodes of nocturia compared to failed surgeries (Park et al., 2016). While the last two studies were small and lacked controls, they offer intriguing results that support the idea that LUTS can be improved by therapies designed to treat OSA.

This article reviews overwhelming evidence of clinical associations between IH/OSA, LUTS and obesity/type 2 diabetes, both in terms of overlap between patient populations diagnosed with these conditions and in terms of possible dose-response relationships between co-occurring diseases. However, surprisingly little is known about whether or how one condition may contribute to etiology or pathophysiology of the others. Does the urge to go to the bathroom at night contribute to poor sleep quality observed in sleep disorders, or do OSA-related sleep disturbances render enough consciousness to drive a person to get up to urinate? Do the LUTS exhibited by type 2 diabetics simply result from diabetes-induced urinary dysfunction, or does sustained dysfunction contribute to pathology of the bladder or urethra, augmenting urinary symptoms? Recently emerging evidence that therapies targeted to one condition may improve symptoms of one of the others serves to further pique curiosity: if CPAP therapy for IH/OSA improves urinary symptoms, could CPAP therapy in diabetics improve urinary function in those patients as well? Indeed, understanding the underlying mechanisms for these diseases and how each may contribute to the others are tantalizing areas of future research that could drive both clinical diagnostics (e.g., should nocturia patients visiting a urology clinic be recommended for a sleep study to check for OSA?) and therapeutics (Fig. 1).

2.4. Other causes of LUTS and links to OSA

While this review has focused on associations between LUTS and obesity, metabolic syndrome and type 2 diabetes, especially in reference to their links with OSA and its physiological hallmark, intermittent hypoxia, there are myriad potential causes of LUTS. Cancer of the prostate or bladder associates with urinary symptoms, as do infection and inflammation of the prostate (e.g., prostatitis), bladder (e.g., cystitis) and urinary tract. Complications of the bladder and urethra, such as foreign bodies, ureteral stones, urethral stricture and bladder detrusor muscle underactivity or overactivity can lead to LUTS.

Changes in smooth muscle surrounding the bladder, urethra or prostate can affect tone, thereby altering compliance and contributing to LUTS. The role of smooth muscle in causing or exacerbating urinary symptoms is made clear by the demonstrated efficacy of several drug therapies routinely employed to treat prostate-related LUTS: alpha-adrenergic antagonists, muscarinic receptor blockers and phosphodiesterase 5 (PDE5) inhibitors all relax smooth muscle, which is believed to allow urine to pass more readily (Kaplan, 2006;

Lepor, 2016). Further, certain of these medications may be used in combination, e.g., alpha-adrenergic antagonists plus 5-alpha reductase inhibitors (discussed in section 2.1) to improve LUTS outcomes. (Roehrborn et al., 2010).

In addition to smooth muscle, structure or function of nerves and blood vessels may contribute to LUTS, though the mechanisms underlying their contributions are not well understood. Afferent nerve activity is responsible for transmitting sensory information from the bladder (e.g., increased pressure due to filling) to the central nervous system; perturbations of these signals can affect bladder sensitivity, leading to increased urinary frequency and urgency. Meanwhile, adequate blood flow to the bladder is also critical for normal voiding function: reduced blood flow due to vessel constriction or blockage can cause ischemia and lead to bladder underactivity, another aspect of LUTS (Andersson et al., 2017). Either nerves or blood vessels can be altered or damaged due to injury or disease. Diabetes exerts neuropathic effects, and neurogenic bladder, or lack of bladder control, can result from diabetes or from brain, spinal cord or nerve injury such as traumatic spinal cord injury, stroke, multiple sclerosis or Parkinson's disease. Microvasculature is also subject to diabetes-induced damage (Ismail-Beigi et al., 2010; Kebapci et al., 2007). Moreover, evidence from several studies demonstrates that PDE5 inhibitors may contribute to positive urinary outcomes by acting on nerves and vasculature of the prostate and bladder in addition to their effects on smooth muscle. Specifically, PDE5 inhibitors decrease bladder afferent activity, reducing bladder sensitivity and thus, frequency and urgency, and increase blood flow to the prostate, though how a change in prostatic blood flow might relieve LUTS is unclear (Yokoyama et al., 2015). Though not directly relevant to LUTS, it is interesting to note that PDE5 inhibitors are more commonly known for their widely successful role in treating erectile dysfunction, a common comorbidity of LUTS (Wang, 2010).

The number and variety of candidate LUTS mechanisms discussed in this section is not exhaustive; comprehensive reviews of the pathophysiology of LUTS are available elsewhere (Abdel-Aziz and Lemack, 2002; Brown et al., 2005; Lepor, 2005; Maharajh et al., 2015; McDonald et al., 2017; Rosen et al., 2005). However, this list of contributory mechanisms serves to underscore the fact that the underlying causes of urinary symptoms are poorly understood. Further, this section highlights fruitful avenues for future investigation, particularly in regard to the possibility that common comorbidities observed with LUTS may be the consequence of important shared pathogenic mechanisms.

Intriguingly, several of the LUTS complications discussed above are known outcomes of OSA. In light of these shared deleterious effects, a number of interesting hypotheses can be posed; we introduce several such hypotheses below. OSA has been linked to local and systemic inflammation, and treatment of sleep apnea with CPAP therapy improves levels of inflammatory markers, including C-reactive peptide (CRP), tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6) (Baessler et al., 2013; Nadeem et al., 2013; Zamarrn et al., 2012). Could inflammation associated with OSA establish a permissive environment for prostatitis or cystitis (inflammatory conditions) that give rise to LUTS? Sleep disorders often overlap with syndromes characterized by central sensitization (e.g., chronic pelvic pain, fibromyalgia), wherein the central nervous system increases sensory input across multiple organs, resulting in a host of symptoms (Fleming and Volcheck, 2015). Does nervous system

sensitization, either central as can be associated with OSA, or peripheral, as seen with diabetic neuropathy, alter signaling between the brain and the bladder or cause increased bladder sensitivity to filling, and therefore urgency or frequency? OSA associates with an increase in sympathetic activity to peripheral blood vessels, decreased blood flow due to vasoconstriction and may contribute to vascular endothelial dysfunction that can be ameliorated with CPAP therapy (Budhiraja et al., 2007; Somers et al., 2008). Sleep apnea is often accompanied by increased risk of stroke and heart disease, including hypertension, arrhythmia and heart failure (Lanfranchi and Somers, 2001). Moreover, hypoxia can trigger a series of changes that affect vascular smooth muscle cells, such as alterations in viability, proliferation, inflammation and tone (Chan and Vanhoutte, 2013). Will vascular changes that accompany OSA be evident in the bladder or prostate, potentially contributing to urinary dysfunction? These data and the questions they raise reveal further complexity regarding the emerging links between LUTS and OSA. Understanding of the associations between these diseases will require model systems that allow isolation of individual OSA variables to enable rigorous testing of its contribution to urinary dysfunction.

3. Using rodent models to interrogate comorbidities: IH/OSA, LUTS and obesity/diabetes

3.1. Existing models of diabetes, diabetic urinary dysfunction and IH

Animal models provide powerful tools for studying questions such as those posed in this review. Models allow investigation of disease-affected tissues and organs when such studies are not practical or possible in humans due to accessibility, timeline or ethical considerations. A number of rodent models have been developed that mimic aspects of diabetes (King and Bowe, 2016). Specifically, multiple models of type 2 diabetes have been used to study diabetic urinary dysfunction and have provided invaluable insights into the associations between these conditions (Daneshgari et al., 2009). Animal models also have been instructive in understanding the physiological effects of chronic (high-dose) and acute (low-dose) IH. Studies of rodents exposed to periodic episodes of low oxygen have helped elucidate mechanisms of morbidity that accompany chronic IH and reveal therapeutic effects of acute IH in respiratory motor plasticity (Dale et al., 2014; Gildeh et al., 2016; Kiernan et al., 2016).

Even though these rodent models have enabled advances in understanding the relationships between IH/OSA, LUTS and obesity/diabetes, knowledge gaps remain. While LUTS have been explored extensively in diabetic models, opportunities to interrogate urinary dysfunction in rodent IH models have been overlooked. Further, despite inescapable evidence that IH/OSA, LUTS and obesity/diabetes are closely associated, existing studies have failed to examine these conditions in concert, perhaps in part due to the challenge inherent in finding animal models that accurately recapitulate relevant aspects of all three conditions simultaneously. New tools, new models and/or reappropriation of existing ones will likely be required to parse the underlying etiologies of IH/OSA, LUTS and obesity/diabetes and the associations between them.

3.2. The trifecta: developing a model for studying urinary dysfunction in obese, diabetic mice exposed to chronic IH

Recently we teamed with collaborators to develop a unique model that allows us to examine IH, LUTS and obesity/type 2 diabetes in combination (Fig. 2A). The goals of our study are to determine, utilizing an animal model, whether IH/OSA contributes to urinary dysfunction in diabetic mice and to identify mechanisms of hypoxia-induced urinary complications as a first step in addressing whether such mechanisms are relevant in human disease. Our hypotheses are that IH causes urinary dysfunction in control mice and that IH exacerbates urinary dysfunction in a mouse model of diabetes.

To test our hypotheses, we selected the BTBR *Lep^{ob/ob}* mouse as a rodent model of type 2 diabetes. This mouse carries a spontaneous mutation in the leptin gene, which controls satiety, leading to overeating and obesity, on the BTBR background, which confers severe and rapidly progressive hyperglycemia. BTBR *Lep^{ob/ob}* males develop diabetes at six weeks of age (Hudkins et al., 2010; Stoeckl et al., 2000). We hypothesized the BTBR *Lep^{ob/ob}* mouse would recapitulate aspects of LUTS, as a different *Lep^{ob/ob}* model has previously been demonstrated to exhibit urinary dysfunction (Daneshgari et al., 2009). To introduce the variable of IH, 6- to 7-week old wild type and *Lep^{ob/ob}* mice were placed in a custom-designed chamber that was used to deliver a chronic IH protocol of 90 sec intervals of room air followed by 90 sec of 6% O₂ for 12 hr over 14 days; control animals were maintained in room air for the duration of the protocol. This model is designed to mimic the systemic reduction in blood oxygen levels observed with OSA. As discussed earlier in this review, the systemic hypoxia that characterizes OSA is associated with organism-wide changes in other systems, such as the immune system (e.g., systemic inflammation), vascular system and nervous system (e.g., central sensitization) (see section 2.4). Further, systemic inflammation, as well as changes in blood flow or nerve activity, are linked to LUTS (Hung et al., 2014) (also see section 2.4). Thus, we designed our model to be able to test whether systemic hypoxia can effect change in the urinary system, as measured by presence of or exacerbation of LUTS. Upon completion of the IH protocol, we evaluated aspects of mouse anatomy, physiology and urodynamics.

Preliminary data reveal changes in bladder morphology and voiding behavior with IH treatment. Pulse oximetry demonstrated that IH protocol-exposed experimental animals exhibited systemic hypoxia (data not shown). Hematoxylin and eosin staining of 7µm paraffin sections revealed microanatomical changes in the bladder urothelium following IH treatment, including edema and presence of enlarged urothelium cells (Fig. 2B). In both wild type and *Lep^{ob/ob}* BTBR mice, bladder weight relative to body weight increased under the IH protocol (Fig. 2C). We assessed potential changes in voiding function using void spot assays. Male wild type or *Lep^{ob/ob}* BTBR mice were individually placed in clean, empty cages lined with 3MM Whatman filter paper. Mice were housed for 4 hr with food but no water, after which the filter paper was removed and urine spots visualized under UV light and analyzed using Image J software. Total urine spot number was significantly decreased for wild type males experiencing IH treatment and spot number trended down for *Lep^{ob/ob}* mice exposed to IH (Fig. 2D). Interestingly, while spot number decreased, wild type spot area increased significantly with IH treatment, though no change was observed for *Lep^{ob/ob}*

males (Fig. 2E). At this early stage of analysis, it is difficult to determine what these results may indicate regarding the effects of hypoxia on urinary function, with or without the presence of diabetes. However, what these data do reveal is that, given a robust model system, the effects of diabetes (wild type vs. *Lep^{ob/ob}* BTBR mice) or hypoxia (room air vs. IH) on urinary function-related endpoints are different and can be separated. In other words, as discussed in section 2.4, we can isolate diabetic and OSA variables (i.e., IH) to rigorously test their potential individual contributions to urinary dysfunction.

4. Summary

While each condition of IH/OSA, LUTS and obesity/type 2 diabetes can manifest independently, the similar and overlapping associations between them demonstrates how these conditions can arise in any combination of two or all three. Remarkably, and of note for researchers, lifestyle changes and treatments for one condition can ameliorate symptoms of one or another of the other two comorbidities. This happenstance presents a perplexing but captivating chicken-or-egg problem: does one given condition tend to lead to another? Can research identify a root cause for an initiating event, helping to unravel the links between all of these conditions? Further, comorbidity and overlap in therapeutic benefits has clinical implications for the present day: perhaps sleep, urology and endocrinology clinics should be surveying their patients for symptoms that could indicate co-existence of other pathologies (e.g., do urology patients complaining of LUTS also report excessive snoring or pauses in breathing during sleep?) and targeting those patients for referrals.

In this review, we have summarized compelling evidence that highlights the overwhelming links between IH/OSA, LUTS and obesity/type 2 diabetes. We have discussed a host of possible causative factors and have highlighted persistent gaps in knowledge. While evidence shows damage or disease in compartments such as nerves, blood vessels and smooth muscle may underlie the prostatic, urethral or bladder anomalies that correlate with LUTS, it is staggeringly unclear how each compartment may contribute to symptoms individually, whether assaults across multiple compartments may change or worsen LUTS, or if damage to one compartment leads to damage in others to collectively confer urinary dysfunction. Basic scientific research using animal models to address these gaps and advance our understanding about the pathways, timing and tissue remodeling events involved in etiology of urinary dysfunction within these compartments is required before prevention, truly effective treatments or a cure for LUTS can be realized. The bonus, here, is that gains in understanding the mechanistic basis of LUTS as a standalone condition will almost certainly provide immediate benefits to those conditions with which LUTS frequently associates, like IH/OSA and obesity/type 2 diabetes.

While much research in obesity/diabetes, IH and urinary dysfunction focuses on these conditions in isolation, given their anastomotic relationships it is likely that interdisciplinary efforts to examine their shared features can and will yield promising insights into mechanism and potential therapies. Hopefully, inquiries such as those being posed by our lab, in conjunction with our collaborators, serve as an entry point to such interdisciplinary efforts. Further research and continued development of new questions and models to address

them is necessary, however, to uncover the mechanisms the underlie LUTS and to elucidate the ways in which pathologies like IH contribute to urinary dysfunction.

To conclude, much of the work cited in this review suggests that IH could be a common thread that is disrupted in LUTS, obesity and type 2 diabetes. These correlations casts IH as a “pathologic killer” when it comes to LUTS. In the presence of OSA, urinary symptoms are often more severe, and evidence indicates those changes occur in a dose-dependent manner. Further, treatment of OSA with CPAP therapy simultaneously confers improvements in LUTS (see section 2.3). Better understanding of the pathologic role of IH could be key in developing more effective therapies for OSA and its common comorbidity, urinary dysfunction. Intriguingly, precise timing and degree of IH can have a positive impact on its effect. Changes in IH periodicity confer demonstrated physiologic benefits. For example, athletes have used intermittent hypoxia training to boost performance, and therapeutic benefits of acute IH are well established for spinal cord injury patients (Astorino et al., 2015; Neubauer, 2001). Is it possible, then, that an acute IH schedule could confer benefits for LUTS, as it has for other endpoints? Can carefully managed IH be a “healing tonic” for severe urinary symptoms? Utilizing model systems such as those we have developed with our collaborators, along with new models or new applications of existing model systems, we will hopefully be able to provide answers to these timely and relevant questions.

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Highlights

- Lower urinary tract symptoms (LUTS) are a group of symptoms that affect urination.
- Few therapies eliminate LUTS, meaning a lifetime of treatments for most patients.
- Intermittent hypoxia, obesity and type 2 diabetes are common comorbidities of LUTS.
- Treatments for intermittent hypoxia, obesity and type 2 diabetes can improve LUTS.
- A new mouse model tests Intermittent hypoxia, obesity and type 2 diabetes in concert.

Hypotheses and Avenues of Research

- Can one condition contribute to etiology of another? If so, how?
- Can lifestyle modifications or therapies targeted to one condition simultaneously improve symptoms of a comorbid condition at the same time?
- Can systemic inflammation associated with IH/OSA create a permissive environment for prostatitis or cystitis that contributes to LUTS?
- Does nervous system sensitization alter signaling between brain and bladder or cause increased bladder sensitivity to filling, leading to LUTS?
- Will vascular changes that accompany IH/OSA be evident in the bladder or prostate and contribute to LUTS?
- Can the variables of IH, diabetes and LUTS be studied simultaneously in the same model system to provide insight into relative contributions of each to combined comorbidity?

Fig. 1. Clinical and pathological associations between intermittent hypoxia, obesity/type 2 diabetes and lower urinary tract symptoms highlight how considering these conditions in combination reveals new avenues of research and enables innovative hypothesis formation

Fig. 2. Chronic intermittent hypoxia treatment changes bladder anatomy and voiding behavior in wild type and diabetic *Lep^{ob/ob}* BTBR male mice

(A) With collaborators, we have developed a unique mouse model system that allows us to examine intermittent hypoxia (IH), LUTS and obesity/type 2 diabetes in combination. (B) 6- to 7-week old wild type (WT) and *Lep^{ob/ob}* BTBR male mice were housed in a custom-designed chamber and exposed to a chronic intermittent hypoxia (IH) protocol of 90 sec intervals of room air (Norm) followed by 90 sec of 6% O₂ for 12 hr over 14 days or maintained in room air for the duration of the protocol as a control. Upon completion of the IH protocol, aspects of mouse anatomy, physiology and urodynamics were evaluated. Following exposure to room air or IH, WT and *Lep^{ob/ob}* bladders were removed, fixed, embedded in paraffin and sectioned at 7 μ m. Hematoxylin and eosin staining of sections revealed changes in bladder urothelium with IH treatment; edema (arrow) and enlarged urothelium cells (arrowhead) are evident. Abbreviations used are d: detrusor muscle, u: urothelium. (C) IH treatment results in statistically significant increases in bladder weight relative to body weight for both WT and *Lep^{ob/ob}* mice. (D) Voiding behavior was evaluated using void spot assays. Mice were housed individually for 4 hr in cages lined with 3MM Whatman filter paper, after which the filter paper was removed and urine spots visualized under UV light and analyzed using Image J software. Total spot number is significantly decreased among WT mice exposed to IH. (E) WT mice exhibit a significant increase in mean spot area following IH treatment. Results are mean $\pm$ SE, n=5/group. Asterisk indicates significant difference from control p 0.05.