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Review

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.

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 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 h 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

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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 20 s. 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