LUTS IN PELVIC ISCHEMIA: A NEW CONCEPT IN VOIDING DYSFUNCTION

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Running head: LUTS in pelvic ischemia

Key Words: LUTS, bladder, prostate, ischemia, oxidative stress

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ABSTRACT

Lower urinary tract symptoms (LUTS) are a group of voiding symptoms affecting both genders as they age. Traditionally, LUTS in men were commonly attributed to bladder outlet obstruction (BOO) due to benign prostatic enlargement (BPE). It was later shown that, in approximately one third to more than one half cases, LUTS in men are not associated with BOO. Urodynamic changes in the male bladder and symptom scores in the aging men were found to be identical to their age-matched female counterparts. These observations suggested that LUTS in the elderly do not necessarily relate to BOO and may result from local changes in bladder muscle, nerves and blood vessels. However, aging factors predisposing to bladder dysfunction and LUTS remain unknown. Growing evidence suggests that aging-associated pelvic ischemia may be a primary factor in the development of non-obstructed non-neurogenic overactive bladder and LUTS. First identified in experimental models and later in clinical studies, pelvic ischemia has been shown to compromise the lower urinary tract structure and lead to dysfunction. Structural and functional consequences of bladder and prostate ischemia have been documented in animal models. Clinical studies have shown that bladder and prostate blood flow decreases with aging. The severity of LUTS in the elderly patients correlates with the degrees of bladder ischemia. LUTS improvement with alpha blockers has been associated with increased bladder blood flow. Pelvic ischemia may be an independent factor in non-obstructed non-neurogenic bladder instability and LUTS. Further research into the pathophysiology of LUTS in pelvic ischemia may lead to better management of this problem in the elderly population.
INTRODUCTION

Lower urinary tract symptoms (LUTS) are bothersome constellation of voiding symptoms affecting both men and women as they age. They include urgency, frequency, incontinence, nocturia, intermittency, slow stream, hesitancy, post micturition dribble and the sensation of incomplete bladder emptying. While the incidence of LUTS increases with aging, our understanding of the mechanisms for LUTS in the elderly is evolving.

A recently described etiology of LUTS in the elderly is pelvic vascular disorders and interruption of blood flow to the pelvic organs. First identified in experimental models and later in clinical studies, pelvic ischemia has been shown to compromise the bladder structural integrity, increase prostate tone and lead to detrusor overactivity. The histopathological changes secondary to pelvic ischemia can lead to LUTS of varying severity. In male patients with pelvic blood flow disturbances, medications intended to either decrease the size of the prostate (5-alpha reductase inhibitors) or relax the bladder neck and external sphincter (alpha blockers) may fail to completely relieve symptoms of bladder outlet obstruction.

This article summarizes the relevant data regarding the epidemiology of vascular disorders and LUTS, clinical evidence of LUTS in the setting of pelvic ischemia, its pathophysiology, and potential therapeutic strategies that have been shown to ameliorate ischemia-associated voiding dysfunction.

VASCULAR RISK FACTORS AND LUTS: EPIDEMIOLOGY

Risk factors for vascular disease include smoking, alcohol use, diabetes mellitus, hypertension, high cholesterol, low physical activity, and elevated body mass index (BMI). The association between varying risk factors for vascular disease and LUTS in men has been well described.(11, 20, 45, 60, 63) In 1990, Diokno et al. studied the link between medical co-morbidities and urinary incontinence in non-institutionalized elderly patients and found that cardiovascular disease was associated with urinary incontinence.(20) Two years later they reported that transient ischemic attacks were associated with what were described as moderate to severe “bladder emptying” symptoms.(21) A study from the Netherlands in 2009 also reported men being treated for cardiovascular (CV) diseases were more likely to report LUTS.(33)
There have also been several community- and clinical-based studies documenting the relationship between the presence of vascular risk factors and LUTS in men. The odds of reporting LUTS was shown to increase by 39% in current smokers and 34% in former smokers. (34) A retrospective cohort study of 617 men with LUTS revealed that 43% reported a history of hypertension, more than half had a history of smoking, were overweight, or had hyperlipidemia, and 29% had elevated blood glucose. In this study, smoking history was an independent predictor of moderate to severe LUTS and patients with moderate to severe LUTS were more likely to have at least one CV risk factor. (41) Studies of risk factors among African American men found similar prevalence rates and noted that alcohol consumption, smoking, history of hypertension, diabetes, heart disease and age were independent predictors of LUTS. (27) Myocardial infarction was also found to be more prevalent in men undergoing prostatectomy for benign prostatic hyperplasia (BPH) than in the general population. (51) Wehrberger et al. reported that the 10-year risk for CV disease or stroke among men without LUTS and patients with moderate and severe LUTS were 6.9%, 10.5% and 15.9%, respectively. (59, 60) Studies comparing the presence of CV risk factors to validated LUT symptom scores have shown that LUTS severity closely correlates with the number of CV risk factors. (23, 31, 48)

Pelvic atherosclerosis may also be a unifying mechanism of LUTS-associated erectile dysfunction (ED) in the elderly population. As most cases of ED relate to vascular insufficiency, its close association with LUTS may suggest vascular regulation of both conditions. (12) In a survey of over 4000 men, the prevalence of LUTS among men with and without ED was 72.2% and 37.7%, respectively. (13) Another study documented that the severity of both LUTS and ED increases with the severity of vascular disorders in the elderly patients. (6) Epidemiologic correlation of CV disease and LUTS were supported by documentation of thicker carotid artery walls and severe arterial stiffness in the carotid and femoral arteries of male and female patients reporting LUTS. (55)

**LUTS IN PELVIC ISCHEMIA: CLINICAL EVIDENCE**

The concept of pelvic ischemia and the epidemiologic association of LUTS with vascular disease are supported by clinical measurement of lower urinary tract perfusion and documentation of bladder and prostate ischemia in elderly patients with LUTS. Clinical studies revealed that pelvic ischemia is measurable and decreased blood flow
significantly correlates with bladder dysfunction and LUTS in the elderly population. Kershen et al. showed that human bladder blood flow decreases with filling at cystometric capacity as intra detrusor vessels are compressed, followed by a rebound period of increased blood flow after emptying (Figure 1). It was shown that decreased blood flow to human bladder significantly correlates with reduced compliance. In pelvic ischemia, filling appeared to reduce bladder blood flow to extremely low levels and leads to reperfusion injury due to sharp rebounds of blood flow after emptying. Pinggera et al. measured lower urinary tract perfusion in men with LUTS and documented significant decrease in bladder and prostate blood flow with increase in age. This study established a direct link between impaired perfusion and bladder dysfunction showing that the degrees of lower urinary tract ischemia significantly correlates with the severity of LUTS. They also showed that women with LUTS have decreased bladder perfusion compared to controls. In men, LUTS improvement with alpha adrenoceptor blockers was associated with significant increase in bladder blood flow. Berger et al. found that increased vascular resistance in the transitional zone of the prostate is associated with clinical BPH. Atherosclerotic vascular disease defined by ultrasound of the carotids was found to be associated with reduced flow rate, smaller storage capacity, and more episodes of frequency. Measurement of prostatic perfusion using MRI and comparing this to validated surveys of erectile function and LUTS showed similar results.

Impairment of pelvic blood vessels during surgery may also contribute to bladder dysfunction and LUTS. Genitourinary morbidities have been documented in most patients with known pelvic ischemia after aortic surgery. Several studies have shown that bladder blood flow markedly decreases after pelvic surgery to correct prostatic obstruction and remains impaired. Surgical disruption of bladder blood flow has been shown to result in symptoms of detrusor overactivity. While some of the symptoms resolve within a year, perhaps due to collateral development, there is a subset of patients who will continue to have persistent bladder overactivity and in some cases urge incontinence. Buttock claudication, a marker of pelvic ischemia, develops in most patients undergoing surgery to repair abdominal aortic aneurysms.
**PATHOPHYSIOLOGY**

Structural and functional consequences of lower urinary tract ischemia depend on the severity and duration of arterial insufficiency. Ischemia activates a cascade of molecular reactions and downstream pathways in both bladder and prostate involving cell survival signaling, upregulation of cytokines and accumulation of inflammatory eicosanoids and leukotrienes.\(^{(1-5,54)}\) In the bladder, short-term ischemia initiates receptor modifications and leads to smooth muscle instability and overactivity, while prolonged ischemia exhausts the smooth muscle energy resources, induces extensive inflammation and leads to fibrosis, degeneration and ultimately underactivity.\(^{(1-5)}\)

Azadzoi et al. were the first to document bladder dysfunction and increased prostate contractility in an animal model of pelvic atherosclerosis.\(^{(1,4)}\) They also showed that human bladder smooth muscle cells are highly reactive to hypoxia and oxidative stress conditions.\(^{(5)}\) Exposure of cultured human bladder smooth muscle cells to hypoxia and oxidative stress impaired cellular antioxidant capacity and led to protein oxidation, lipid peroxidation and profound ultrastructural damage (Figure 2).\(^{(5)}\) The underlying mechanisms of ischemic injury appear to involve oxidative stress, free radical injury to smooth muscle cells, epithelium, mitochondria, ER and nerve fibers, impairment of NO/cGMP pathway, activation of degenerative processes, and deposition of collagen\(^{(3, 5, 44)}\). Interestingly, investigations into the common pathways of LUTS-associated ED also suggest pelvic atherosclerosis, impaired NO/cGMP pathway, autonomic hyperactivity, metabolic syndrome, and the Rho kinase/endothelin pathway as unifying mechanisms.\(^{(32, 38)}\)

Chronic pelvic ischemia was also shown to induce prostatic stromal fibrosis, decrease cGMP, and increase prostate tissue sensitivity to contractile stimuli.\(^{(1, 54)}\) The PDE-5 inhibitors were shown to reduce prostate tissue contractility and increase cGMP levels.\(^{(1)}\) Lukas et al. reported that arterial occlusion results in apoptosis of the prostate tissue in adult rats, but did not affect cell proliferation.\(^{(35)}\) Cellular and molecular changes in chronic prostate ischemia appear to be similar to those reported in chronic bladder ischemia.\(^{(58, 52, 14)}\)
Effective treatment of LUTS in pelvic ischemia may rely on vasodilation to improve blood perfusion, relaxation of the detrusor and bladder neck smooth muscle, and antioxidant and scavengers of free radicals to protect against oxidative damage. (39, 42)

Alpha-blockers, specifically alpha-1 receptor antagonists, are the first line treatment for LUTS. It has been shown that alpha-blockers primarily improve lower urinary tract blood flow. (46) Pinggera et al. conducted a sonographic-urodynamic study in 19 men and found that treatment with alpha blockers reduces irritative symptoms and improves bladder capacity. (46) LUTS improvement in these patients was associated with increased bladder blood flow. (46) Similar results were reported in a rat model of pelvic atherosclerosis. (50)

PDE-5 inhibitors have been shown to improve bladder blood flow and prevent bladder dysfunction in the rat model of pelvic ischemia. (16) In clinical studies, once daily low dose tadalafil (5mg) has also been shown to significantly improve LUTS and ED symptoms in men. (49)

Free radical scavengers, such as melatonin and Co-enzyme Q-10, have been shown to prevent free radical damage associated with hypoxia-reperfusion injury and chronic ischemia in the rat bladder. (27–30, 43, 62, 64) Eviprostat, an antioxidant phototherapeutic agent used in Japan and Europe for treatment of LUTS has also been shown effective in suppressing overactivity and protecting against oxidative damage in a rat model of pelvic ischemia. (37)

In addition to the above-mentioned pharmacotherapies, injection of adipose derived stem cells into the ischemic bladder wall has been shown to preserve bladder function, blood vessel density, and nerve fiber content. (25) The mechanism is poorly understood, although the effects are not restricted to stem cells found in adipose tissue. Chen et al. demonstrated that bone marrow stem cells are also effective in protecting the bladder from hypoxia-reperfusion damage, although they appear to preserve smooth muscle content as well. (15)
CONCLUSION

Epidemiologic data and clinical studies suggest a close correlation between vascular risk factors, pelvic ischemia, lower urinary tract dysfunction, and the development of LUTS in elderly patients. The same risk factors that predispose patients for atherosclerosis, coronary artery disease and peripheral vascular problems may also predispose elderly to LUTS in these populations. The severity of LUTS has been shown to correlate with the number of vascular risk factors, and patients with LUTS have higher mortality from cardiovascular disease or stroke. Simultaneous development of LUTS and ED in patients with vascular risk factors suggest that pelvic atherosclerosis may also be a unifying mechanism of LUTS-associated ED. (17, 24)

The etiology of LUTS is multifactorial, and despite the numerous treatment strategies available, very few have been examined in clinical studies in diverse populations of men and women. In addition, the exact mechanism of LUTS in human bladder and prostate tissues has yet to be identified. Animal models have implicated oxidative stress, free radical injury, impairment of the NO/cGMP, and Rho kinase/endothelin pathways, activation of degenerative processes, and deposition of collagen as pathways for the development of LUTS secondary to pelvic ischemia. While oxidative damage in cultured human bladder and prostate cells has been documented, in vitro studies of human tissue samples from patients with known pelvic ischemia are limited.

From a clinical standpoint, it is critical to obtain a careful history to identify medical co-morbidities and treat them in conjunction with LUTS. Patients may require medications to treat their symptoms as well as protect them from further tissue damage, and one size does not fit all in this constellation of symptoms. Further research into the pathophysiology of lower urinary tract ischemia may lead to prophylactic strategies and more effective management of LUTS in elderly patients.

ACKNOWLEDGMENT: Supported by Grant BLR&D MERIT 1I01BX001428 from the U.S. Department of Veterans Affairs.
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cytokines in a rat model of atherosclerosis-induced chronic bladder ischemia.


FIGURE LEGENDS:

**Figure 1:** Bladder blood flow constantly changes with filling, contraction and emptying. This figure shows human bladder blood flow and intravesical pressure during step-wise filling. Bladder blood flow initially increases with filling. However, at 100% cystometric capacity, bladder blood flow significantly decreases then rebounds following drainage, suggesting bladder vulnerability to ischemia/reperfusion and oxidative injury (*From Kershen et al., J Urol, 168:121-125, 2002*). This study showed a significant correlation between decreased human bladder blood flow and diminished bladder wall compliance.

**Figure 2:** Transmission electron microscopy showing ultrastructural features of human bladder smooth muscle cells exposed to hypoxia and oxidative stress conditions versus cells cultured in normoxia. Normal cytoplasmic structures, mitochondria with distinctive membrane and cristae, and a normal lining of ER are shown in cell sample from normoxia condition. Swollen and elongated mitochondria with deformed membrane, swollen deformed ER, and lysosomal activity are shown in cells exposed to hypoxia. Swollen mitochondria with shattered or totally lost cristae, swollen and partially degraded ER and accumulation of lysosomes are shown in cells exposed to oxidative stress. White arrows point to mitochondria, black arrows point to ER and double arrows point to lysosomes. All images were recorded at 30,000x (*From Azadzoi et al., Urology 78: 967e9 - 967e15, 2011*).
CHANGES IN HUMAN BLADDER BLOOD FLOW WITH FILLING