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| **LOWER URINARY TRACT SYMPTOMS(LUTS) IN MALES: A REVIEW OF PATHOPHYSIOLOGY**  |
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**LOWER URINARY TRACT SYMPTOMS (LUTS) IN MALES: A REVIEW OF PATHOPHYSIOLOGY**

**Abstract**

Lower urinary tract symptoms (LUTS) refer to the symptom complex that is the common pathway for diseases affecting the lower urinary tract. It manifests as either irritative or obstructive symptoms. LUTS have long been recognised as a significant cause of morbidity in both sexes. The long term sequelae of the underlying cause are also a significant cause of mortality.

LUTS have been noted to have a recognisable progression pattern that worsens with age. This is of particular concern in African countries that continue to evolve in terms of the population dynamics. This evolution has resulted in an increase in the geriatric population in both developed and developing countries. There has been a concordant increase in the recognition of the symptom complex with age. This results in a significant percentage of males presenting with LUTS and secondary complications.

Several factors interact to produce LUTS. Complex pathophysiological pathways have been investigated to define the roles of individual and cumulative risk factors in an attempt to provide better therapeutic options. It is imperative for scientists to identify reversible factors that influence LUTS. Treatment of the complex of symptoms has the potential to utilise a significant proportion of the healthcare budget. Identification of modifiable risk factors in the pathogenesis of LUTS allows for more cost effective prevention and management of the disease.

This article will discuss the definition and pathogenesis of LUTS with particular emphasis on the role of metabolic factors. An algorithm for assessment, initial management, and referral criteria is also included.

**Introduction**

Lower urinary tract symptoms (LUTS) are defined as a complex of symptoms that may affect storage or voiding.[1](#_ENREF_1) They are broadly divided into irritative and obstructive LUTS[1](#_ENREF_1) and maybe secondary to changes in the bladder or in the bladder outlet.[2](#_ENREF_2) Irritative LUTS includes frequency, urgency, nocturia and urge incontinence.[1](#_ENREF_1) Obstructive LUTS includes hesitancy, poor stream as well as incomplete voiding.[1](#_ENREF_1)

LUTS are a significant cause of morbidity [3](#_ENREF_3)in both sexes. [4](#_ENREF_4) In men, it describes symptoms encountered commonly, but not exclusively in the prostate,[5](#_ENREF_5), [6](#_ENREF_6) generally secondary to benign prostate hypertrophy(BPH). [3](#_ENREF_3) LUTS and BPH have been noted to increase with age. [4](#_ENREF_4) Reported prevalence suggests the rates may be as high as 79% in males over the age of 70 years.[7](#_ENREF_7) This is of particular concern in African countries[8](#_ENREF_8) that continue to evolve in terms of population dynamics. The total proportion of South Africans aged 65 years of age and older is projected to increase from 3.4% in 1995 to 7.5% in 2025.[9](#_ENREF_9) Since LUTS increases with age, this will translate to a concordant increase in prevalence of LUTS.

In addition to the recognised impairment of physical wellbeing, the EpiLUTS study also illustrated an increase in the incidence of depression and anxiety in this population.[4](#_ENREF_4) The overall mental, physical and social wellbeing of these patients is ultimately affected.[10](#_ENREF_10), [11](#_ENREF_11) Treatment of the complex of symptoms therefore utilises a significant proportion of the healthcare budget. [12](#_ENREF_12) Since LUTS are significant causes of morbidity and mortality, they extend the demands on an already overburdened South African health infrastructure.

**Pathophysiology of LUTS**

LUTS are due to a complex interaction between the bladder and the outflow tract in male patients. Therefore, factors that affect the function of the bladder, prostate and urethra may contribute to LUTS.[13](#_ENREF_13) Age, hormones, inflammatory processes, lifestyle, metabolic diseases, congenital factors, socioeconomic factors [14](#_ENREF_14)and nocturnal enuresis have been investigated as the cause of LUTS with varying results. This supports the ideology that extraneous factors and local factors need to be considered in planning treatment.

Racial preponderance differs[15](#_ENREF_15), [16](#_ENREF_16) with African Americans clearly showing increased rates of BPH and LUTS. A West African based study showed a much lower prevalence than African Americans.[17](#_ENREF_17) This may suggest that environment may still have a greater role to play than ethnicity.[17](#_ENREF_17) Nocturnal enuresis [18](#_ENREF_18) and low birth weight have also been linked to LUTS later on in life. [19](#_ENREF_19) This may justify aggressive screening efforts in these higher risk groups.

The bladder and prostatic urethra are lined by urothelium.[20](#_ENREF_20) Urothelium has a recognised barrier function but also acts as afferent receptors,[21](#_ENREF_21) producing stimuli in response to local changes. The urothelium also has paracrine, and autocrine secretory functions that affects the adjacent urothelium, nerves and blood vessels.[21](#_ENREF_21) Disruption of these pathways due to epithelial dysfunction may disrupt normal signalling pathways, producing LUTS.

**Table 1: CAUSES OF LUTS**

**Prostate:**

Benign Prostatic Hypertrophy

Prostatitis

**Bladder:**

Overactive Bladder

Urinary Tract Infection

Neurogenic Bladder

Bladder Calculus

Bladder Tumour

Foreign Body

Detrusor Underactivity

**Miscellaneous**

Distal ureteric calculus

Urethral stricture

*Age*

Age has been affirmatively linked with LUTS, [4](#_ENREF_4), [22](#_ENREF_22) producing hormonal changes,[23](#_ENREF_23) and altered mitogenesis [24](#_ENREF_24)which has a definitive link to BPH and LUTS. Aging is associated with inflammation[23](#_ENREF_23) and this also occurs in the prostate. The normal aging process produces a profibrotic milieu in the prostate through the action of cytokines[23](#_ENREF_23) produced by stromal fibroblasts. Confounding variables that are associated with age and LUTS, such as metabolic diseases including diabetes and hypertension may be related to the aetiology, or may be coincidentally found with increasing age. Diabetes has been linked directly to inflammation[23](#_ENREF_23), [24](#_ENREF_24). Whilst the mechanism may be a combination of these factors, there is a definite increase in LUTS associated with age.

*Hormones and Growth Factors*

Androgens are postulated to impact on prostate growth as well as lower urinary tract function by multiple mechanisms. In addition to the direct trophic effect on prostate growth, testosterone may also act on detrusor receptors thereby affecting bladder function.[2](#_ENREF_2) With age there is a decrease in circulating androgens as well as a decrease in Sex hormone binding Globulin( SHBG) noted.[23](#_ENREF_23) Testosterone still has a permissive role in the local growth of the prostate..[23](#_ENREF_23) The growth of the prostate is dependent on the interaction of growth factors and hormones on the epithelium and stromal architecture in the prostate.[23](#_ENREF_23) Oestrogen plays an important role in mitogenesis and stromal growth seen in BPH [25](#_ENREF_25) Peripheral aromatisation converts testosterone to oestrogen.[23](#_ENREF_23) Androgens are confirmed to increase the volume of the prostate[25](#_ENREF_25) and oestrogen produces a mitogenic effect on the prostatic stroma.[23](#_ENREF_23) Interaction between these hormones therefore contributes to changes in the architecture of the bladder outlet.

Several growth factors and their receptors are identified within the epithelium and the stroma of the prostate. These include Vascular Endothelial Growth Factor(VEGF), Fibroblast Growth Factor( FGF) and Epithelial Growth Factor( E- GF).[26](#_ENREF_26) Chronic states of hypoxia within the prostate upregulates these factors producing angiogenesis and stimulating prostate growth.[26](#_ENREF_26) Insulin Growth Factor( IGF – 1) is an important additional growth factor in the prostate.[27](#_ENREF_27)

*Inflammation*

Inflammation of the prostate has also been affirmatively linked to LUTS and BPH [16](#_ENREF_16), [24](#_ENREF_24), [28-31](#_ENREF_28) and this has been histologically confirmed.[24](#_ENREF_24) Aging is associated with inflammation[24](#_ENREF_24) and maybe one of the pathways by which increased incidence of LUTS is associated with aging. This is substantiated by the increased levels of C- Reactive Protein (CRP)[29](#_ENREF_29) noted in patients with BPH, and LUTS.

*Lifestyle Factors*

Smoking increases the risk of LUTS.[32](#_ENREF_32), [33](#_ENREF_33) An increase in severity of LUTS is noted with higher smoking burden.[34](#_ENREF_34) Nicotine enhances sympathetic activity and increases testosterone.[35](#_ENREF_35)

 Heavy alcohol consumption is associated with an increased risk of LUTS.[34](#_ENREF_34), [35](#_ENREF_35) Alcohol produces chronic effects by causing changes in the oestrogen: testosterone ratio. [34](#_ENREF_34) These pathways may provide potential factors that can be modifiable risk factors for LUTS.

*Metabolic Factors, Metabolic Syndrome and Obesity*

Several overlapping mechanisms may explain the demonstrated link between obesity, the Metabolic Syndrome and LUTS. There is an established risk between obesity, BPH[27](#_ENREF_27), [28](#_ENREF_28), [36-38](#_ENREF_36) and LUTS, with both an increase in prevalence and severity of LUTS.[19](#_ENREF_19) Metabolic Syndrome is associated with irritative LUTS.[39](#_ENREF_39) Recent literature suggests that abdominal circumference may be a more specific marker[16](#_ENREF_16), [19](#_ENREF_19), [38](#_ENREF_38) of the severity of obesity and specific studies have shown that this may be more significant in LUTS.[40](#_ENREF_40)

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| **Table2 . Current deﬁnition of Metabolic Syndrome**[**31**](#_ENREF_31) |
| **Adult Treatment Panel III criteria**1. Abdominal obesity (for men, waist circumference > 102 cm)2. Hypertriglyceridemia (> 1.69 mmol / L; > 150 mg /dL)3. Low high-density lipoprotein cholesterol (for men, < 1.04 mmol / L; < 40 mg /dL)4. High blood pressure (> 130 / 85 mmHg)5. High fasting glucose (> 6.1 mmol / L; > 110 mg /dL) |
| **Additional criteria**1. Increased C-reactive protein2. Autonomic-sympathetic overactivity |

Adipocytes in peripheral fat aromatise testosterone [41](#_ENREF_41) into oestrogen.[16](#_ENREF_16) Oestrogens exert a stimulatory effect on stromal growth,[23](#_ENREF_23) causing an increase in static outflow obstruction to the urinary tract producing significant LUTS. These adipocytes also produce proinflammatory cytokines[16](#_ENREF_16) and this supports the inflammation that occurs in the prostate.[7](#_ENREF_7) This hypothesis is supported by the noted increase in CRP in patients [29](#_ENREF_29), [31](#_ENREF_31) with BPH, LUTS and obesity. CRP is an inflammatory mediator and is a non- specific marker for inflammation.[11](#_ENREF_11) It is noted to be increased in both metabolic syndrome as well as in LUTS associated with BPH.[31](#_ENREF_31) Thus inflammation may be a common pathway for the features encountered in both pathologies.

Men with increased body mass index also have insulin resistance and resultant hyperinsulinaemia.[2](#_ENREF_2), [42](#_ENREF_42) Insulin has similar structure to IGF -1 and thus binds to the IGF receptor[2](#_ENREF_2), [26](#_ENREF_26) in the prostate resulting in stimulatory effect on prostate growth,[43](#_ENREF_43) increased risk of symptomatic BPH[44](#_ENREF_44) and LUTS. Men with hyperinsulinaemia have increased free SHBG as well as androgen entering the prostate,[26](#_ENREF_26) with resultant prostatic enlargement

Obese patients develop autonomic hyperactivity[26](#_ENREF_26), [42](#_ENREF_42), [43](#_ENREF_43), [45](#_ENREF_45) which has been independently implicated in the in pathophysiology of LUTS. Joseph et al showed that there was no correlation noted between prostate volume and LUTS.[34](#_ENREF_34) This would suggest either dynamic factors in the prostate or extrinsic factors play a significant role in LUTS. The prostatic capsule smooth muscle contains sympathetic receptors that increase capsular tension.[46](#_ENREF_46) Hence autonomic hyperactivity exacerbates dynamic outflow resistance in the lower urinary tract resulting in LUTS. Increased sympathetic activity of the smooth muscle may affect the bladder also contributing to LUTS.[47](#_ENREF_47) Alpha receptors are found in both blood vessels and the bladder neck.[22](#_ENREF_22) These common receptors in both may account for the findings of hypertension in patients with LUTS and explain why alpha blockers produce a therapeutic effect in both conditions.

The Metabolic Syndrome was described to link a number of medical conditions that are proposed to be related to changes in cellular metabolism that may share common aetiological pathways. Several studies have shown an increase in the prevalence of LUTS and BPH in patients with Metabolic Syndrome.[7](#_ENREF_7), [40](#_ENREF_40), [42](#_ENREF_42), [43](#_ENREF_43), [48](#_ENREF_48) They present more frequently with irritative LUTS [39](#_ENREF_39), [40](#_ENREF_40), [49](#_ENREF_49) with a notable increase in the volume of the prostate in these patients.[7](#_ENREF_7), [43](#_ENREF_43) Several defining criteria overlap with the pathophysiologic mechanisms already discussed. Whether these individual pathologies have a cumulative effect and produce these symptoms or whether Metabolic Syndrome and LUTS are linked via a common pathway such as a vascular or inflammatory pathway remains to be elucidated.

Hypertension, one of the criteria for Metabolic Syndrome has been independently linked to LUTS.[50-53](#_ENREF_50) Patients experience an increased likelihood of irritative LUTS.[34](#_ENREF_34), [54](#_ENREF_54) In addition patients with hypertension are more likely to undergo urologic surgery.[26](#_ENREF_26) Alpha blockers which are commonly used to treat LUTS are also used to treat hypertension, suggesting a common receptor pathway.[46](#_ENREF_46) In addition the sympathetic over activity noted in hypertension[3](#_ENREF_3) may produce the voiding related symptoms. Hypertension is also associated with atherosclerosis. It has been postulated that pelvic ischemia may also provide a stimulus for BPH.[47](#_ENREF_47) Due to the resultant ischemia, growth factors within the pelvis are upregulated resulting in prostatic growth. All these factors may produce variable contributions to this association.

Diabetes Mellitus has been directly linked to LUTS[34](#_ENREF_34), [49](#_ENREF_49), [52](#_ENREF_52), [55](#_ENREF_55), [56](#_ENREF_56) due to both prostate and bladder related effects. Increased fasting plasma glucose levels [44](#_ENREF_44) are associated with BPH.[32](#_ENREF_32), [57](#_ENREF_57) Hyperinsulinaemia causes insulin binding to IGF- 1 Receptor in the prostate resulting in direct trophic effect.[43](#_ENREF_43) The secondary increase in free IGF-1 also augments this growth.[44](#_ENREF_44) Hyperinsulinaemia increases sympathetic activity and calcium[44](#_ENREF_44) within the detrusor. In addition the microvascular changes encountered in diabetes affect the detrusor muscle.. The net result is a peripheral neuropathy, sensory deficit, decreased contractility and emptying disorders in these patients.[58](#_ENREF_58)

Hyperlipidaemia has been positively associated with LUTS. These patients have hypertriglyceridemia[49](#_ENREF_49) and a decrease in High Density Lipoproteins (HDL)- cholesterol levels.[26](#_ENREF_26), [49](#_ENREF_49), [52](#_ENREF_52), [59](#_ENREF_59) There is a postulated increase in the catabolism of HDL cholesterol and upregulation of Low Density Lipoproteins(LDL) in metabolic syndrome that may stimulate the growth of the prostate and increase the risk of LUTS.[26](#_ENREF_26)

**Table 3 : EVALUATION OF MALE PATIENT WITH LUTS**

**History:**

LUTS ( Irritative or Obstructive)

Associated haematuria

**Past Medical and Surgical History:**

Concomitant medical conditions, Diabetes Mellitus, Hypertension, Hypercholesterolaemia)

Medication History (including testosterone supplementation)

Previous urological surgery

Risk factors for stricture including catheterisations, perineal trauma, previous urethritis

Risk factors for haematuria including smoking, radiation, occupational exposure, bilharzia, bladder calculi

Family History of BPH

**Physical examination**

Including: Body mass Index

Abdominal Circumference

Full Abdominal and Genital Examination

Focused Neurological Examination

Digital rectal Examination

**Investigations**

Urine dipstick- proceed to microscopy and culture if abnormal result

Urea and Electrolytes

 Prostate Specific Antigen (PSA)

Ultrasound Kidney for renal impairment or chronic retention

**INITIAL MANAGEMENT OF LUTS BY FAMILY PHYSICIAN**

**SIGNIFICANT LUTS**

**MILD LUTS/ MINIMAL BOTHER:**

WATCHFUL WAITING

**Haematuria**

**Urinary Tract Infection**

**Abnormal PSA**

**Abnormal Digital Rectal Exam**

**Palpable bladder**

**Neurogenic Bladder**

**Renal Impairment**

**Hydronephrosis**

**LIFESTYLE MODIFICATION**

WEIGHT LOSS

DRUG MODIFICATION/ SUBSTITUTION

FLUID AND ALCOHOL MODERATION

BLADDER TRAINING (Timed voiding and

Double voiding

+/- TRIAL OF ALPHA BLOCKER

 (Tamsoulosin or Doxazosin

**REFER TO UROLOGIST**

No response to lifestyle modification and alpha blocker

**Conclusion**

LUTS in males is due largely to BPH. Genetic factors, hormones, inflammation and aging have a vital role to play in the aetio-pathogenesis of BPH and LUTS. However reversible factors are also being increasingly recognised in this disease complex. The manipulation of these factors will provide invaluable adjuncts to future treatment strategies developed for LUTS.

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