Lower urinary tract symptoms in older men: does it predict the future?
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**Lower Urinary Tract Symptoms**

The term *lower urinary tract symptoms (LUTS)*, encompasses three groups of symptoms: voiding symptoms (slow stream, splitting or spraying, intermittency, hesitancy, straining, and terminal dribble), postmicturition symptoms (sensation of incomplete emptying, postmicturition dribble), and storage symptoms (urinary frequency, nocturia, urgency, and urgency urinary incontinence). Historically, we have used the terms *prostatism* and *symptoms of benign prostatic hyperplasia* to describe lower urinary tract symptoms in men. The umbrella term LUTS was originally introduced in 1994 to dissociate urinary symptoms in the male patients from any implied specific site of origin of symptoms, such as the prostate. This is important as the symptoms are neither sex, age, nor disease specific.

LUTS may be related to bladder outlet obstruction (BOO) as a result of benign prostatic obstruction (BPO). BOO is often associated with benign prostatic enlargement resulting from the histologic condition of benign prostatic hyperplasia (BPH). However, this is not invariably the case. Failure to empty the bladder can be related either to an outlet obstruction or to underactivity of the detrusor muscle, or to a combination of both. Figure 1 outlines the various causes related to LUTS.

A global view of LUTS, namely one that focuses on the lower urinary tract as an integrated functional unit, but at the same time reflects pathophysiologic conditions in the body as a whole, is more likely to improve a clinician’s ability to manage LUTS and patient outcomes.

**Lower urinary tract symptoms in primary care**

Many adults experience LUTS. In the Dutch population, the prevalence of mild to severe LUTS varies from 20-25% in men aged 40 years or older, increasing with age. Over one third of men aged 50 or more are living with moderate to severe symptoms, equating to 24 million in countries of the European Union.

The incidence of LUTS in the general practice population increases up to 18.7 /1000 patients/year for men aged 85 years and older.

The International Prostate Symptom Score (IPSS) is the questionnaire usually used to quantify the severity of LUTS. The IPSS was created in 1992 by the American Urological Association (AUA) and is also referred to as the AUA-symptom score. The questions include feeling of incomplete bladder emptying, frequency, intermittency, urgency, weak
stream, straining and nocturia, each referring to symptoms during the last month. The scores are divided into three categories: No-Mild LUTS (IPSS 0-7), Moderate LUTS (IPSS 8-19), and Severe LUTS (IPSS>20). The international prostate symptom score (IPSS) increases by 0.3 points per year in male patients from the general population.

Of all men with LUTS, 60-70% visit their general practitioner for this reason. The decision to visit the GP for LUTS is influenced by previous disease, comorbidities, personal characteristics, personal interpretation of symptoms, fear of cancer and social factors. When voiding symptoms are accompanied by pain, haematuria, acute urinary/urine retention or signs of infection, patients are more prone to visit the GP. A Dutch primary care study, a questionnaire among men aged 50 years and older, revealed that fear of cancer is an independent predictor of GP visit, as is information from diverse media.

**Figure 1. Conditions related to LUTS**

*drugs related to LUTS: diuretics, calcium channel blockers, caffeine, alcohol, decongestants, or antihistamines*
LUTS and comorbidities

Age is one of the most important risk factors for LUTS. Other common age-related conditions are cardiovascular diseases, diabetes, chronic kidney disease, depression, and cognitive impairment. Although symptoms such as urinary incontinence and nocturia are often dismissed as normal ageing conditions, evidence from epidemiological studies suggests that LUTS is related to several pathophysiological conditions independent of age.

Benign prostatic hyperplasia and overactive bladder, both possible causes of LUTS, are linked to type 2 diabetes, obesity, and hypertension. Also LUTS is related to an increased risk of recurrent falls in older men, particularly those with urgency, nocturia, or hesitancy. Furthermore, a strong relation between LUTS and erectile dysfunction (ED), which is independent of age and comorbidities, has been demonstrated.

The precise mechanisms for the associations between LUTS and comorbidities are not fully understood. In a nutshell: there are links between autonomic nervous system overactivity, the vascular system of the bladder, and the increasing severity of LUTS. Glucose intolerance is also related to the enlargement of the prostate and neurological regulatory mechanisms of the bladder can be affected by stroke, MS, and other neurological diseases.

More recently, it has been suggested that a number of cardiovascular, metabolic, and endocrine risk factors are related to LUTS. Specifically, recent attention has focused on pelvic arterial atherosclerosis as one of the important risk factors for LUTS and ED.

LUTS and ED are related. The association between ED and CVD has also been studied, and this relation seems to be significant (see below). It is therefore interesting to consider whether LUTS and CVD are related, because the relation between LUTS and CVD would be clinical relevant. If there is a causal relation between LUTS and CVD, diagnosis of LUTS could help identify men at risk for cardiovascular diseases. This could possibly further prevent cardiovascular diseases, and reduce mortality from CVD in the future.

Some comments can already be made about the association between ED and CVD. This relation has been studied mostly in cross-sectional and second line clinical settings. The suggested causal relation between ED and CVD is not proven in the primary care population of men with ED. A possible explanation for this is the different age.
distribution of men with ED in the primary care population (more younger men) and the greater number of psychological causes of ED in primary care. These differences explain why the urologist screens patients with ED for CVD (risk factors) and the GP does not.36

Aims of this thesis
The main objective of this thesis is to improve our knowledge of the epidemiology of comorbidities in men with lower urinary tract symptoms. We want to gain more knowledge about the multifactorial aetiology and the multidisciplinary approach of LUTS. Since the 1990s, following the introduction of the drugs registered for the treatment of LUTS, men with LUTS can also be treated in primary care. The ‘shared care’ of LUTS has developed since then. There are, however, differences in morbidity between primary care and clinical care. The general practitioner sees a lot of healthy people, and a few unhealthy people. Instead, the clinical specialist sees a lot unhealthy people. These important epidemiological differences are interesting, and have to be incorporated in the patient approach of the diverse disciplines. As a general practitioner I am particularly interested in the epidemiology of LUTS in a primary care setting. In the Netherlands the general practitioner has a central role and he/she acts as a gatekeeper to all further secondary care. Improved knowledge of the pathophysiological mechanisms and epidemiology of comorbidities in men with LUTS will contribute to an appropriate use of health care focussed on the needs of elderly men.

For this study, we have focussed in particular on the triangular relation between LUTS, ED, and CVD (Figure 2). Although many studies have demonstrated relations between LUTS and comorbidities, the setting and design of the studies differ substantially. Therefore we address the following aspects on which the literature is scarce.

First we address the relationship between LUTS, ED, and CVD described in the following settings: the community based setting, the clinical setting, and the primary care setting. In Chapter 2, the associations between lower urinary tract symptoms, erectile dysfunction, and cardiovascular diseases in different male populations are described in a review. This review prompted us to design the studies described in Chapters 3, 4 and 5. In Chapter 3 we describe the association between LUTS and ED in a longitudinal, primary care setting. The relation between LUTS and CVD in the primary care setting is described in Chapter 4. We use longitudinal data from the Registration Network Groningen, a primary care registration network. We also focus on the relation between LUTS and CVD in open population. Therefore we use longitudinal data from the Krimpen study, a community based study. The results of this longitudinal cohort study are
described in Chapter 5. In a systematic review and meta-analysis, Chapter 6 summarises all results so far from longitudinal data concerning the relation between LUTS and CVD. In Chapter 7 we reflect on our main findings, and speculate on the implication of our results. We address the role of the general practitioner in the multifactorial approach of LUTS, prevention, and early diagnostics. We also address the focus on the role of longitudinal (registration) studies in primary care.

**Fig. 2. Aims of this thesis: the relation between Lower Urinary Tract Symptoms (LUTS), Erectile Dysfunction (ED), and Cardiovascular Disease (CVD).** PC: primary care, QOL: quality of life

**References**


