Hypogonadism and voiding dysfunction in men

Many problems may arise as men age: hypogonadism, metabolic syndrome, hypertension, hyperlipidemia, low sexual drive, poor erection, ejaculation disturbance, and finally lower urinary tract symptom ([LUTS] including voiding difficulty and poor ability to hold urine). All of these symptoms significantly lower the quality of life.

In recent decades, there have been many population-based cohort aging studies in North America and Europe. These studies have discussed all symptoms and comorbidities of aging. The results of these studies showed that there is a close relationship between erectile dysfunction and LUTS. In the Massachusetts Male Aging Study, erectile dysfunction (ED) was noted at 39% in 40-year-old men, and it increased to 67% in 70-year-old men. In the Baltimore Longitudinal Study 1057 patients were observed for 30 years. The results showed the prevalence of LUTS or benign prostatic hyperplasia was 26% in men in their 40s, and it increased to 79% in men in their 70s. The Olmsted County Study followed patients for up to 12 years, and demonstrated that the prevalence of LUTS was 26% in men in their 40s, and 46% in men in their 70s. The Spanish EDEM study, included 2476 men ranging in age from 25 years to 70 years. The results revealed the overall prevalence of ED (by International Index of Erectile Function questionnaire) was 18.9%, with a level of 8.5% in men in their 20s and 30s, increasing to 48% in men in their 60s. Interestingly, LUTS is the strongest risk factor of ED, the odds ratio (OR) was 2.67. The German Cologne Male Survey included 5000 men, aged from 30 years to 80 years. The results showed that ED occurred in 19.2% of the population, at 2% in men in their 40s and 53% in men in their 80s. While LUTS occurred in 72.2% in men with ED, it was seen in 37.7% of men without ED. The UrEpik study included 4800 men from four countries aged from 40 years to 79 years, showing that ED prevalence was 21.1%, and the OR of diabetes mellitus (DM) patients was 1.57, and in LUTS patients was 1.39. We can draw some common facts from the epidemiological evidence. The facts are: (1) aging is closely related to LUTS; (2) aging is also associated with metabolic syndrome and overactivity of the autonomic nervous system; and (3) erectile dysfunction and LUTS are tightly bound with hypogonadism and metabolic syndrome.

In this issue, Shen and Chuang evaluated the prevalence and associated factors of androgen deficiency (AD) in men with LUTS in a cohort of Taiwanese men. They concluded that a considerable portion of men comorbid with LUTS had AD. The major associated factor of AD was a waist circumference (WC) > 90 cm, therefore WC measurement should be done routinely in men with LUTS. Physicians should pay more attention to those with WC > 90 cm in order to identify and treat these patients earlier to improve symptoms of LUTS and life quality.

What is the relationship between hypogonadism and LUTS? Regarding the relationship of testosterone levels and LUTS symptoms, we can find different conclusions from studies in the literature. Studies from Austria, USA, and Taiwan showed that there are no effects present between testosterone and LUTS. However, two recent articles from Korea reported a significant negative correlation of testosterone levels and the severity of LUTS. One study from Japan showed dehydroepiandrosterone sulfate, not testosterone, is associated with LUTS.

Some studies showed that testosterone replacement therapy (TRT) is an effective treatment for hypogonadal men with LUTS. The most recent randomized controlled trial (RCT) was from the Kanazawa group, showing significant treatment response in relieving LUTS symptoms, maximal flow rate, and voided volume. However, other RCTs performed in earlier years did not show positive responses.

Let us examine the questions again: “Is hypogonadism a cause for LUTS?”, and “Will TRT improve LUTS in hypogonadal men?”. To answer these questions, we need to go back to the basics. The embryological development of the lower urinary tract and reproductive tract is highly controlled by sex hormones. It also contributes to the proportion of collagen and smooth muscle in the pelvic organs throughout the later life. The androgen and estrogen receptors are widely distributed in urothelium, detrusor muscle, and neurons in autonomic ganglia of the prostate plexus. The target organs or tissues are very broad, covering the urothelial sensation, detrusor contractility and bladder outlet status. According to the international prostate symptom score (IPSS), LUTS includes both voiding function and storage function. Some earlier articles discussed only the global change in IPSS, without separating these two functions. There are seven questions present in the IPSS, Questions 1, 2, 3, 4, and 7 standing for storage symptoms. I have suggested the acronyms “WISE” and “FUN” to facilitate the grouping of these questions in 2001, where “WISE” means the voiding score, and “FUN” is the storage score. Using subscore analysis, we noticed some more interesting findings. Kim et al. studied over 900 Korean men and showed the storage subscore is related to total testosterone levels. More interestingly, those who had fewer nocturia (≤ 3) had much higher testosterone levels than those who had nocturia four times and above. The study by Amano et al. observed
41 Japanese hypogonadal men, in which the IPSS global score, and both storage and voiding subscore, improved significantly following testosterone replacement. Recently, another observational study by Ko et al. also showed global improvement, and both voiding and storage subscore improvement in the Korean cohort.

We can modify the well-accepted theory suggested by McVary to illustrate some pathophysiological maps, in order to examine the underlying mechanism for the improvement in LUTS after testosterone replacement in hypogonadal men. He proposed four theories to explain the mechanism. The first is the nitric oxide/nitric oxide synthase (NO/NOS) theory; the second is autonomic hyperactivity and metabolic syndrome hypothesis; the third is Rho-kinase activation/endothelin pathway; and the fourth is the pelvic atherosclerosis theory.

For the NO/NOS theory, hypogonadism predisposes to a metabolic derangement, including hyper-insulinemia, dyslipidemia, and diabetes, which promote the reduction of NOS expression and NO production in the prostate and bladder. Subsequently, it will promote smooth muscle cell proliferation, and results in structure changes in the prostate. It also enhances smooth muscle contraction in both the bladder and prostate, resulting in functional changes. The common effects contribute to LUTS. For the autonomic hyperactivity and metabolic syndrome hypothesis, hypogonadism causes sarcopenia in skeletal muscle, and results in physical inactivity. This can occur in combination with metabolic derangements, such as insulin resistance, glucose intolerance, central obesity and dyslipidemia, as well as aging. All increase the sympathetic tone. The effects increase smooth muscle tone to cause detrusor overactivity, and promote prostate growth to make LUTS more severe. The Rho-kinase activation/endothelin pathway indicated that the activation of Rho kinase via metabolic and autonomic stimulation, such as noradrenaline and ET-1, results in the deactivation of the myosin-regulated light chain phosphorylase, which enhances the contraction of the smooth muscle in the prostate. Finally, the atherosclerosis theory is related to poor blood perfusion to the pelvic organs, and long-term ischemia which induces the expression of TGF-β. This promotes collagen formation and fibrosis in the bladder wall, and impairs the bladder compliance. A recent rat model carried out in China showed the role of TGF-β in castration-induced bladder wall fibrosis. Control rats were compared with castrated rats, rats which were given testosterone replacement, and rats with anti-TGF-β antibody but without testosterone replacement. The results showed the recovery effects of procollagen mRNA and compliance in both the testosterone replacement group and the TGF-β antibody treated group. They concluded that TGF-β plays an essential role in androgen deprivation-induced bladder fibrosis and dysfunction, and it might offer a potential target for the prevention and treatment of bladder dysfunction associated with androgen deficiency. A recent study in Taiwan showed the influence of androgen receptor CAG repeat polymorphism in men with normal testosterone levels. They found men with longer CAG repeat lengths have a higher risk of developing andropausal symptoms. This may also explain in part why the testosterone levels are not related to LUTS symptoms in some studies. A recent experiment using a rat model with hyperPRL demonstrated the mechanism of hyperPRL-induced hypogonadism (unpublished data). This is considered to be related to the fact that testicular interstitial TNF-α suppresses the Leydig cells under PRL stimulation. The hyperPRL rats showed increased fibrosis and decreased smooth muscle in the cavernosal tissue. Interestingly, the authors found the structural change in the penis can be recovered by giving testosterone replacement alone. The rats were given testosterone enanthate, and were sacrificed for tissue examination 1 week after treatment. Following testosterone treatment, smooth muscle areas increased significantly on the penis section. The collagen analysis showed significant reduction in collagen III density in the treated groups. The ratio of collagen III to collagen I reduced significantly as well. These experiments imply that testosterone may act upon the regulation of mesenchymal stem cell to differentiate into smooth muscle cells or fibroblasts in other pelvic organs or tissue.

In addition to the theories and hypotheses proposed, there are a few new directions deserving our attention. These include the studies on estradiol, 5-α reductase and aromatase function in the effects of testosterone replacement, and other aspects such as the involvement of inflammatory factors, enzyme activities, and androgen receptor CAG repeat polymorphism.

We can use Hill’s causality criteria to examine the causal effects between two entities. They include strength of association, consistency between studies, dose—response effect, temporal relationship, and biological plausibility. On examining all of the evidence, we know that LUTS and hypogonadism are highly prevalent in aging men, and there are strong and consistent relationships between them. But there are some other important points waiting to be proven, for example, is the severity of hypogonadism an important risk factor for LUTS? Is the relationship still significant after controlling for other comorbidities, such as metabolic syndrome or erectile dysfunction? Therefore, based on Hill’s causality criteria, only when the above two questions are answered can we conclude that hypogonadism is an independent risk factor for LUTS.

In conclusion, the relationship of testosterone and voiding function might be indirect and complicated, involving multiple mechanism pathways and many different organs. Hypogonadism can be connected to many pathological conditions, therefore restoration of testosterone levels in symptomatic patients seems a cost-effective measure. More RCTs with larger patient numbers, more ethnicity involvement and longer follow-up are mandatory to understand the relationship between hypogonadism and LUTS.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

Sources of funding

No Funding was received for the work described in this article.

References


William J. Huang*

Department of Urology, School of Medicine, Shu-Tien Urological Research Center, National Yang-Ming University, Taipei Veterans General Hospital, Taipei, Taiwan

* Corresponding author. Department of Urology, School of Medicine, Shu-Tien Urological Research Center, National Yang-Ming University, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei, 11217, Taiwan.

E-mail address: jshuang@vghtpe.gov.tw.

16 May 2016

Available online 16 June 2016