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INVITED COMMENTARY

Male Endocrinology

Testosterone replacement therapy: dilemmas and challenges in China and Asia

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Late-onset hypogonadism (LOH) has been described as a clinical syndrome comprising symptoms consistent with androgen deficiency and a circulating concentration of testosterone in the low-to-normal range in some middle-aged and elderly men. The presence of symptoms may affect the health and quality of life in aging men and it has become a hot spot in global medical research, diagnosis, and treatment in the recent years. With the acceleration of the aging process of populations in China and Asia, the health and quality of life of the aging men have attracted a wide attention. China has the largest population in the world, and a recent epidemiological study suggested that the prevalence of LOH in China is 10%–20%.¹ In another two Chinese studies^{2,3} using 0.3 nmol l⁻¹ and 0.169 nmol l⁻¹ as distinct cutoff points for calculated free testosterone (cFT), the prevalence of androgen deficiency defined by a cFT value below the cutoff was 13.0% and 30.3% in men aged 40–49 years, 31.8% and 43.13% in men aged 50–59 years, 30.1% and 57.35% in men aged 60–69 years, and 46.7% in men >70 years.²

EXISTING QUESTIONNAIRES NEED TO BE VALIDATED FOR CHINESE AND OTHER ASIAN POPULATIONS

In November 2001, ISSAM chairman B Lunenfeld recommended the use of the Turkey Istanbul Bosphorus questionnaire due to its simplicity and convenience in the academic report on LOH at the Third International Conference on Reproductive Endocrinology in Beijing.⁴ The questionnaire includes physical symptoms, vascular symptoms, mental and psychological symptoms, and sexual dysfunction, a total of 17 items, which are simple and easy to operate. However, the origin of the questionnaire is still unknown, and it has not been widely assessed and validated in Chinese aging populations so far.⁵

More recently, the Aging Males' Symptoms (AMS) scale has been used more widely than the Androgen Deficiency in the Aging Males' (ADAM) questionnaire in case finding within an Asian population.⁶ One study of Chinese community-dwelling older men comparing questionnaires for screening for LOH was carried out in 2011.⁷ The use of enzyme-linked immunosorbent assay (ELISA) to measure serum total testosterone (TT), sex hormone-binding globulin (SHBG), and serum albumin concentrations to calculate cFT is the most popular method (the formula can be obtained from the website: <http://www.issam.ch/freetesto.htm>). The sensitivity and specificity of the ADAM questionnaire were 86.6% and 24.5% for low free testosterone (FT) defined as <5 ng dl⁻¹ (173 pmol l⁻¹), while the sensitivity and specificity of AMS scale were 35.29% and 63.49% for the same cFT cutoff, respectively. In that case, the investigators advocated that the combination of ADAM and AMS questionnaires may possess better utility for screening of androgen deficiency and monitoring testosterone replacement therapy (TRT).⁷ Due to its higher sensitivity, ADAM questionnaire was advocated as a screening or case finding

instrument for older Chinese men in population. It was also suggested that AMS might be useful for therapeutic monitoring of TRT in older Chinese men due to its moderate specificity.

However, another study of questionnaires for population surveys and screening of clinical signs and symptoms of androgen deficiency and low serum T in Shanghai, China, showed that the sensitivity and specificity of ADAM questionnaire were only 78.7% and 14.8%, and those of AMS questionnaires were also low at 54.0% and 41.2%, respectively.⁸ Furthermore, a study performed in Taiwan, China, also reported that both questionnaires had low sensitivity and specificity to detect androgen deficiency and low serum T.⁹ In addition, this study recommended that a complete physical and biochemical checkup should also be conducted in patients at risk or suspected of androgen deficiency. Thus, both ADAM and AMS questionnaires have limited value in Chinese populations.

Recently, two TRT studies of aging men in Taiwan, China and Shanghai, China, evaluated the correlation between sexual function as assessed by the International Index of Erectile Function (IIEF-15) scores and symptoms of LOH.^{10,11} The findings from these studies suggested a significant improvement in IIEF-15 scores after TRT, which was in agreement with the evaluation of ADAM and AMS questionnaires. However, investigators from the United Arab Emirates (UAE) recommend the AMS scale for assessing clinical symptoms of hypogonadism, while doctors in Korea studied various types of questionnaires to evaluate LOH.^{12,13} Therefore, these questionnaires may have limited value in screening for the presence of androgen deficiency, while they may capture an improvement in symptoms in the setting of TRT.

In the recent years, Chinese andrologists have proposed a simplified version of the AMS (concise scale of AMS [cAMS]) using correlation analysis between serum androgen (TT, cFT, or free testosterone index [FTI]) concentrations and symptoms of androgen deficiency in a large clinical multicenter study with 5980 participants (age ≥40 years old). In this study, 10 of 17 symptoms of AMS were significantly correlated with cFT and FTI. When comparing the scores from androgen deficiency symptom scales and serum cFT or FTI level, the total scores including the sexual function, autonomic nervous disorder symptom, or psychological and physical symptom ≥17 points were considered to be positive for cAMS (unpublished article).

Therefore, the AMS and ADAM questionnaires that were designed and tested first in older, non-Asian men need to be modified for the older Asian men. However, the use of such questionnaires should not replace a careful clinical assessment for relevant symptoms and signs before making a diagnosis of androgen deficiency.

ARE THERE ANY DIFFERENCES IN THE CUTOFF VALUE OF SERUM T FOR DIAGNOSIS OF TESTOSTERONE DEFICIENCY IN AGING ASIAN MEN?

Due to differences in the ethnicities, living environment, dietary habits, and metabolism, Asian men and Caucasian men appear to have different thresholds of serum T for the symptoms of hypogonadism and the cutoff value of serum T for the diagnosis of LOH.

One review article from Korea published in 2011 suggested that LOH should be defined by the presence of at least one clinical symptom associated with serum TT concentration of <346 ng dl⁻¹ (12 nmol l⁻¹)

or cFT concentration of $<72 \text{ pg ml}^{-1}$ (250 pmol l^{-1}).¹³ In addition, the Korean Society for Aging Male Research has recommended the serum TT cutoff concentration of 350 ng dl^{-1} (12 nmol l^{-1}) for the diagnosis of LOH in 2006, and experts from Taiwan, China, have recommended a similar threshold of TT for the diagnosis of LOH.¹⁴ A recent study from Israel¹⁵ used serum TT concentration of $<12.1 \text{ nmol l}^{-1}$ and FT concentration of $<225 \text{ pmol l}^{-1}$ (65 pg ml^{-1}) as the cutoff value of LOH, a threshold that is very close to that recommended by the European Association of Urology (EAU) guidelines. However, the cutoff values of serum TT $<8.9 \text{ nmol l}^{-1}$ and cFT $<210 \text{ pmol l}^{-1}$ with at least three sex symptoms such as decreased libido, irritability, and decreased energy are recommended now in Chinese aging population (unpublished data). Since there is a large individual difference in serum TT concentrations, the Japanese Urological Association not only recommends EAU guideline with the serum cFT value lower than 225 pmol l^{-1} (65 pg ml^{-1}) as the diagnostic criteria for LOH regardless of symptoms, but also refer to bioavailable T as being associated with androgen deficiency.¹⁶ Therefore, the criteria for defining LOH in Asian men remain unclear.

IS TRT THE ONLY OPTION FOR LOH IN CHINA AND ASIA?

There is a consensus regarding the effectiveness of TRT for men with proven androgen deficiency (e.g., due to diseases of the hypothalamus, pituitary gland, or testes) in China and Asia; however, the role of TRT and its safety in men with LOH is still controversial. It is not unique in China, but many countries in Asia may face the same problem. Although the accelerated growth of prescriptions has resulted in a nearly fourfold increase in the number of TRT prescriptions in the last 5 years, the average consumption of all the available androgen products for their medical indications in China is only about \$64 million or so. Owing to price and Asian traditional culture, older men do not visit doctors for the symptoms of androgen deficiency. Even if some men seek diagnosis and treatment, they are often willing to take traditional Chinese medicine (TCM) as the first choice. Androgen preparations prescribed for therapy of LOH cannot be reimbursed by Medicare in mainland China. Only androgen therapy for hypogonadism due to pathology of the hypothalamus, pituitary gland, or testes is reimbursable in China. Many aging men and also some specialists do not pay much attention to the symptoms of androgen deficiency.¹⁷ In China and surrounding countries, many men choose urologists rather than endocrinologists to prescribe T for androgen deficiency.

In addition to Western medicine, there are many alternative medicines, particularly TCM in Asia. Doctors are also exploring the application of traditional treatment solely or combination with androgen preparations for the diagnosis and treatment of androgen deficiency. One study from Shanghai community including 461 aging men investigated the distribution of TCM syndromes and clinical characteristics which are similar with Western medicine in LOH patients.¹⁸ "Liver and kidney yin deficiency" (sexual dysfunction + physiologic symptoms) was the most common TCM syndrome followed by "kidney yang deficiency" (sexual dysfunction), "kidney deficiency and liver stagnation" (sexual dysfunction + emotional and cognitive disorder), and "heart and spleen deficiency" (vascular symptoms and metabolic syndrome). Meanwhile, there have been many TCMs, such as Jin Gui Shen Qi pills, Qi-Lin pills, and Compound Xuan-Ju capsule, which could play a role in "warming the kidney" (regulating the pituitary-gonadal axis) to strengthen "yang" (vascular function and androgen level) and nourishing essence (trace elements and vitamin supplement) so as to treat the androgen deficiency. The combination of TCM and Western medicine might improve the symptoms of LOH with lower dosages of androgens and fewer adverse effects, but more research is needed in this area.¹⁸⁻²¹

TRT AND RISK OF CARDIOVASCULAR DISEASES (CVDS) IN CHINA AND ASIA

Recently, findings from a few studies of non-Asian men asserted that there is a higher risk of CVD-related adverse events in aging men who received TRT.²²⁻²⁴ Among them, one systematic review and meta-analysis was heavily criticized for methodological reasons because it included studies using oral formulations for TRT in aging men and reported several cases of advanced liver cirrhosis after TRT, which suggested selection bias on recruitment of patients.²⁰ In addition, several studies categorized any bleeding events, such as esophageal varices, as a CVD-related adverse event.²²⁻²⁴ In a randomized clinical trial in which older men with mobility limitations were given a relatively high starting dose of testosterone, an excess of cardiovascular-related adverse events was reported in the testosterone arm.²⁵

There is no firm evidence or definitive study to define the likelihood of cardiovascular adverse events from TRT in Chinese or Asian men owing to lack of well-designed clinical trials in these populations. Notwithstanding, some of the studies containing TRT in the treatment of comorbid disease, such as diabetes, obesity, metabolic syndrome, and congestive heart failure, have been published in the recent years.^{10,12,13,26-31} Several studies examining the correlation of androgens and cardiovascular risk in Asia including Korea and the UAE over the past decades have reported a significant inverse correlation of serum T with cardiovascular risk markers and demonstrated higher T in physiological range with lower markers of atherosclerosis and inflammation.^{10,12,28-30} Moreover, a prospective study in Taiwan, China, demonstrated that TRT could protect the endothelial cells through nitric oxide (NO) release and reduce the risk factors of CVDs around 12-month therapeutic session.⁹ However, it remains unclear as to whether TRT will have beneficial, adverse, or neutral effects on the cardiovascular system in men.³²⁻³⁵ There are recognized contraindications to TRT, for example, those men who have been diagnosed with prostatic cancer.³⁶

PROSPECTS FOR FUTURE STUDIES

Questionnaires or scales used for screening for LOH need to be further simplified, modified, and validated to make them applicable to the Chinese and Asian, non-Chinese aging male population. Furthermore, correlations between symptoms and signs of testosterone deficiency and cutoff values of serum T must be defined in these populations. Men with androgen deficiency due to disease of the hypothalamus, pituitary gland, or testes should be considered for TRT. However, the role of TRT in men with LOH in the absence of hypothalamic, pituitary, or testicular axis has not yet been established and needs to be clarified. Finally, it is necessary to launch popular science educational programs for Asian men, conduct and publish more research specific to Asian men, and formulate evidence-based guidelines for the diagnosis and treatment of hypogonadism in Asian men.

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