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REVIEW

Recent topics related to testosterone deficiency syndrome in Japan

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Androgens, the levels of which decrease with ageing, play many physiological roles in various organs. Testosterone deficiency syndrome (TDS) has received widespread attention in the last several years. First-line treatment for TDS should be testosterone replacement therapy (TRT), which is reported to improve several TDS symptoms. Recently, a clinical practice manual for TDS was written and published by a collaborative team from the Japanese Urological Association and the Japanese Society for the Study of the Aging Male to recommend standard procedures for the diagnosis, treatment, prevention and monitoring of adverse reactions to TRT and for post-treatment assessment. In this manual, intramuscular injection of testosterone enanthate or human chorionic gonadotropin and the testosterone gel 'Glowmin' were recommended as TRT. Currently, two topics related to TDS are being focused on in Japan: the relationship between TDS and metabolic syndrome and treatment options for eugonadal patients with TDS symptoms. In this review, the possibility of TRT for metabolic syndrome as well as the relationship between testosterone and adiponectin, which is a key molecule in metabolic syndrome, is discussed. Finally, the possibility of herbal medicines as a treatment option for patients with TDS is addressed, especially for eugonadal patients, because eugonadal men with TDS symptoms account for approximately 30% of the general population. The increase in the levels of several cytokines, such as IL-8, IL-13, interferon-γ and tumor necrosis factor-α, after herbal medicine treatment may be the reason for this efficacy.
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INTRODUCTION

Testosterone has a number of physiological roles in different organs and tissues with androgen receptors. The reported symptoms of testosterone deficiency syndrome (TDS)[1] are easily recognized and include diminished sexual desire and erectile quality, particularly that of nocturnal erections, changes in mood with concomitant decreases in intellectual activity and spatial orientation, fatigue, depression and anger, decreases in lean body mass with associated decreases in muscle volume and strength, decreases in body hair and skin alterations, and decreased bone mineral density resulting in osteoporosis.[2–6] Furthermore, low serum testosterone levels have been associated with increased mortality in male veterans.[7] Thus, TDS is not only a disease related to the quality of life but also a severe disease that may affect life expectancy. As in Western countries, the accepted first-line treatment for TDS in Japan is testosterone replacement therapy (TRT). Recently, a clinical practice manual for TDS was written and published by a collaborative team from the Japanese Urological Association (JUA) and the Japanese Society for the Study of the Aging Male (JSSAM) to recommend standard procedures for the diagnosis, treatment, prevention, and monitoring of adverse reactions to TRT as well as post-treatment assessment.[8] However, it is also apparent that not every symptom of TDS can be resolved through the endocrinological effects of TRT alone, and there are many eugonadal patients who complain of TDS-related symptoms.

In this review, the topics to be discussed include current treatment options for TDS in Japan, such as TRT for hypogonadal men and herbal medicine for eugonadal men, the relationship between TDS and another systematic disease, 'metabolic syndrome' (MS) and the treatment of eugonadal patients with TDS symptoms.

TESTOSTERONE TREATMENT FOR TDS

Concerning sexual function in men with TDS, there is a steady decline in orgasmic frequency, worsening erectile function,[9] and a decrease in sexual thoughts and enjoyment with ageing.[10] A statistically significant correlation exists between testosterone level and both erectile function and orgasmic function, as evaluated by the IIEF.[11] Furthermore, the frequency of early morning erections, the ability to maintain an erection, libido and ejaculation are improved by TRT.[12–16]

In relation to psychological function, mood, sense of well-being and anxiety are all improved by TRT in hypogonadal men.[17–19] TRT enhances spatial cognition in elderly men,[20] although a randomized controlled trial of TRT in healthy elderly men with normal to subnormal serum testosterone levels showed no improvement in cognitive function.[21] In patients with depression, the symptom score was inversely associated with serum testosterone level,[22] and several randomized controlled trails reported that TRT improved depression.[18,19]

Physiologically, bone mineral density is significantly correlated with serum testosterone level,[23–25] and hypogonadism is a well-known

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cause of male osteoporosis.[26–28] Testosterone deficiency was present in 71% of elderly men with hip fractures compared with only 32% of controls.[29] Many studies have reported an increase in bone mineral density as an effect of TRT.[30–35] The body composition measures of lean body mass, total adipose mass and muscle mass are correlated with the free testosterone level,[36,37] and several studies have shown that TRT decreased fat mass and increased lean body mass, muscle mass and strength.[38–43] Furthermore, several studies have shown that androgens may be beneficial in the treatment of bone marrow failure,[44–46] and TRT increases haematocrit values.[21,33,47,48]

Several types of testosterone preparations, such as buccal and oral tablets and capsules, both long- and short-acting intramuscular preparations, and implantable long-acting slow-release pellets and gels, are available worldwide, providing several treatment options for TDS. Recently, injectable testosterone undecanoate, which has long-term kinetics and offers a sustained close mimicking of eugonadal serum testosterone levels without supra- or subphysiological serum concentrations, has become a popular treatment tool for hypogonadism,[49] including that associated with TDS.[50] However, only injectable preparations of testosterone propionate and testosterone enanthate and oral preparations of methyltestosterone are available in Japan; oral, transdermal and long-acting injectable preparations are not available. Under the current situation, the JUA–JSSAM clinical practice manual recommends a treatment protocol employing testosterone enanthate, which is administered in an intramuscular dose of 125 mg once every 2 or 3 weeks or a dose of 250 mg once every 3–4 weeks:[8]

- Testosterone enanthate is administered intramuscularly at a dose of 125 mg every 2 or 3 weeks or 250 mg every 3–4 weeks.
- Human chorionic gonadotropin is administered intramuscularly at a dose of 3000–5000 units once or twice a week or every 2 weeks.
- Testosterone ointment is applied at a dose of 3 g once or twice a day on the skin of the scrotum (equivalent to 3 mg of testosterone each time it is administered).

However, because of the rapid peaks and troughs of testosterone levels and consequent fluctuations in symptom relief, short-acting testosterone enanthate injections have been discarded in most parts of the world as an unsatisfactory form of treatment.[51] Testosterone enanthate administration for 3 months was reported to be effective in 100 of 176 Japanese patients (56.8%) with TDS.[52] The JUA–JSSAM manual also recommends other treatment options for TRT, including human chorionic gonadotropin (hCG) and the testosterone gel 'Glowmin' (Daito Pharmaceutical Co. Ltd, Tokyo, Japan), which is a short-acting testosterone ointment produced by a domestic Japanese company. This preparation was approved by the Ministry of Public Health in 1965 and contains 100 mg of testosterone per 10 g of matrix (1%). The clinical effects of Glowmin in TDS patients were previously reported with respect to mental, physical and sexual functioning factors on the aging males' symptoms (AMS) scale; erectile dysfunction in IIEF-5; and the physical and social functioning roles as well as emotional and mental health from the MOS 36-item short form Healthy Survey (SF-36) questionnaire.[53] hCG is recommended to be administered intramuscularly at individual doses of 3000–5000 units once or twice a week or every 2 weeks. Injections of hCG do not increase the risk of testicular atrophy because hCG can induce testicular growth for patients with congenital hypogonadotropic hypogonadism.[54] We previously reported that serum concentrations of testosterone increased substantially, as expected, following TRT with hCG, and TDS symptoms improved substantially after this treatment.[55] Glowmin, applied at a dose of 3 mg twice daily on the scrotal skin for 12 weeks, resulted in substantial improvement of TDS symptoms due to the physiological elevation of serum testosterone.[53] Recently, substantial improvements in IIEF-5 and total International Prostate Symptoms Scale scores were reported after 3 months of TRT with 6 mg per day of Glowmin. Additionally, voiding disturbance appeared to improve more than storage disturbance. Thus, it has been speculated that TRT with Glowmin may be effective in the improvement of not only erectile dysfunction and TDS symptoms but also lower urinary tract symptoms (especially voiding disturbance) in Japanese patients with TDS.[56]

No recommendations as to the duration of TRT have been made in the guidelines of the International Society of Andrology, the International Society for the Study of the Aging Male or the European Association of Urology.[57] If a patient with TDS does not benefit from TRT, discontinuation of TRT is accepted without question. However, for patients with TDS who do benefit from TRT, there is no conclusive evidence as to whether discontinuation of TRT is possible or whether TRT must continue for the rest of their lives. We recently conducted a study of middle-aged men in whom TRT was effective and who were available for follow-up 3 months after the discontinuation of TRT. We ultimately reported that improvement in symptoms due to TRT may remain after the discontinuation of TRT, even though endocrinological status declines.[58] However, the number of patients in that study was small, and the duration of follow-up was only 3 months; a larger-scale study is necessary to clarify these findings.

TESTOSTERONE TREATMENT FOR METABOLIC SYNDROME

MS is characterized by central obesity, insulin resistance, dyslipidaemia and hypertension, and it is also a disease syndrome affecting the quality of life that has received increasing attention in the fields of medicine and public health.[59] Because one-third of men with type 2 diabetes mellitus are now recognized as being testosterone deficient,[60] low serum testosterone levels have been directly associated with MS in both cross-sectional[61] and longitudinal studies.[62] A low serum testosterone level has generally emerged as a reliable prognosticator of MS in men whose testosterone deficiency is genetic, iatrogenic following surgery,[62–64] or pharmacologically induced by gonadotropin-releasing hormone during prostate cancer treatment.[65] Serum testosterone levels are correlated with both lean body mass and total adipose mass.[36,37] Testosterone supplements decrease visceral fat and ameliorate insulin resistance.[66] Recently, it was reported from a Japanese laboratory that among 274 men who underwent general health checks, the frequency of MS was 22.5%, whereas that of TDS was 8.0%.[67] The most interesting findings in that study were that the serum testosterone level was significantly lower in the group with MS than that without MS and that when testosterone decreased significantly, it was associated with an increase in the number of MS conditions present. That study further showed that after adjustment for age, body mass index and waist circumference, testosterone was still significantly correlated with MS. Furthermore, another study in middle-aged Japanese men reported that age-adjusted regression analyses revealed that testosterone levels were significantly related to the MS conditions of obesity, hypertension, dyslipidaemia and insulin resistance.[68] These results in Japanese populations suggest that low testosterone is associated with MS and its conditions in middle-aged Japanese men. Recently, it has been reported that adipose tissue is an important endocrine organ that secretes hormones and cytokines and thus mediates metabolic and physiological effects in several organs. Among the hormones, adiponectin is the most abundant and exerts profound

anti-diabetic, anti-atherogenic and anti-inflammatory effects. It is believed to be a key molecule in the aetiology of MS.[69,70] Furthermore, adiponectin is inversely related to testosterone levels in both rodents[71] and humans.[72] Thus, although TRT is expected to be effective not only for treating TDS but also for MS on the basis of an established relationship between testosterone and MS, concern exists that TRT for TDS may cause MS as a result of decreased levels of adiponectin. Based on a multiple regression analysis, we recently reported that body mass index and sex hormone-binding globulin levels were the only factors influencing serum adiponectin levels, and no association between testosterone and adiponectin was found in 174 patients with TDS symptoms.[73] Furthermore, we also reported that there were no statistically significant differences in serum adiponectin levels before and after TRT in patients receiving TRT (**Figure 1**). Recently, it was found that there was no statistically significant difference in adiponectin levels between patients with and without TRT in a population with Klinefelter syndrome, which is the most representative disease of hypogonadism.[74] Although further studies with larger numbers of patients are necessary to confirm the safety and efficacy of TRT in the presence of MS, we do not believe at present that excessive attention needs to be paid to decreased adiponectin levels resulting from TRT in patients with TDS.

TREATING TDS WITH HERBAL MEDICINE

TDS symptoms are not substantially related to any endocrinological parameter.[75] We previously reported that TDS symptoms were not always related to serum testosterone levels based on a study of 90 self-referred TDS patients.[76] This discrepancy between testosterone level and TDS symptoms has also been reported in other studies; scores from the AMS scale[77] showed no statistically significant correlation with serum testosterone level in studies of 161 healthy, ambulatory, elderly men[78] and 81 self-referred TDS patients.[79] Many eugonadal patients complain of TDS symptoms, and eugonadal men with TDS symptoms account for approximately 30% of the general population in the United States.[80] It was also reported that eugonadal men (defined as having an analogue free testosterone level of >11.8 pg ml^{-1} according to the clinical practice manual of the JUA and JSSAM) accounted for 11.8% of 490 Japanese patients with TDS symptoms who visited a special TDS clinic.[52] Thus, the problem currently remains of how to treat such eugonadal patients with TDS symptoms by any means other than a testosterone preparation.

A number of herbal medicines are used to treat symptoms in menopausal women,[81,82] and thus, it has been suggested that herbal medicines might also be an option for the treatment of men with TDS symptoms. Additionally, several herbal medicines, such as *Piper methysticum* (*kava*)[83] and *St John's wort*, have been used to treat the TDS symptoms of anxiety and depression.[84,85] We recently reported that *saikokaryukotsuboreito* (SKRBT), which is widely used in Japan for a variety of clinical conditions, particularly neuropsychiatric disorders and erectile dysfunction, was effective in eugonadal patients with TDS symptoms; the AMS score was significantly decreased after treatment with SKRBT, without changes in testosterone level.[86] Because several studies have reported that antidepressants increase the production of several cytokines,[87,88] we also investigated the serum concentrations of cytokines before and after treatment with SKRBT and reported that the levels of four cytokines, IL-8, IL-13, interferon-γ and tumor necrosis factor-α (TNF-α), increased after treatment (**Figure 2**).[89] Recently, the results of an interesting study were reported showing that administration of *kamishoyosan*, an herbal medicine, increased plasma TNF-α levels in depressed menopausal patients and improved depressive status.[82] Thus, we speculate that administration of SKRBT increased the levels of plasma TNF-α and other cytokines and improved TDS symptoms, including depression, similar to the findings reported in the *kamishoyosan* study. The results of a recent study regarding the use of herbal medicines for TDS indicated that in 151 Japanese patients with TDS, the overall efficacy rate of several herbal medicines, including *keishibukuryogan*, *kamishoyosan*, *tokishakuyakusan*, *hachimijiogan*, *hochuekkito* and SKRBT, was 70.9%.[90] Furthermore, adverse reactions such as diarrhoea, nausea and eruption were observed in only four of 151 patients (2.6%), and none of the symptoms was severe. Thus, we

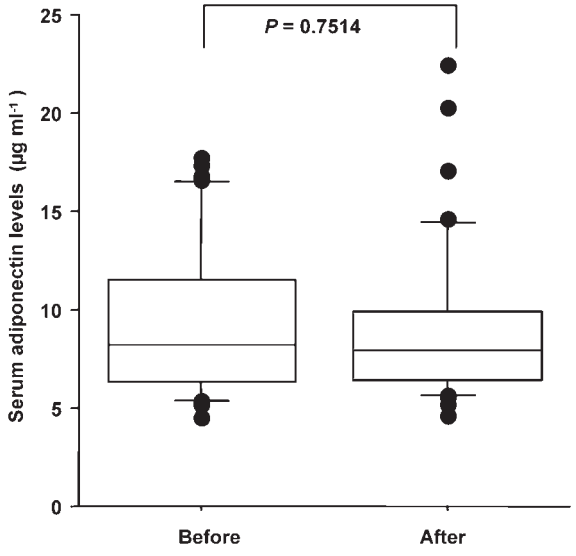

Figure 1 Serum adiponectin levels before and after testosterone replacement therapy (TRT) in patients with testosterone deficiency syndrome (TDS). The difference was not statistically significant.[73]

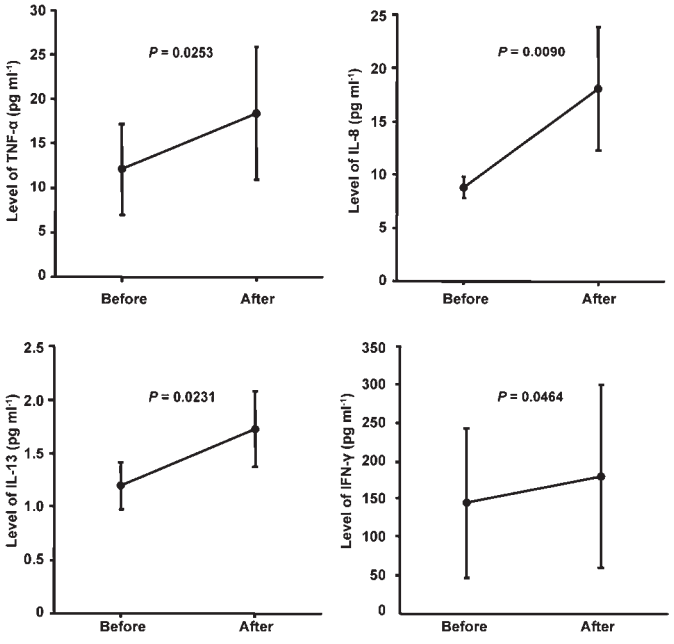

Figure 2 Cytokines with a statistically significant increase after treatment with *saikokaryukotsuboreito*.[89] Error bar, standard error. IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α.

conclude that certain herbal medicines should be considered treatment options for patients with TDS, especially for eugonadal patients.

CONCLUSIONS

Large-scale studies producing a high level of evidence regarding treatments for TDS have not been widely reported, especially from Japanese institutes. In this review, we first showed the efficacy of TRT for TDS based on previous reports. Although the available testosterone preparations are limited in Japan, we are in the process of obtaining evidence related to the efficacy of TRT according to the recommendations of the JUA–JSSAM manual. We also described how improvements in the symptoms of TDS may be maintained after the discontinuation of TRT, even when the serum concentration of testosterone returns to its low pre-treatment level. This is important information for physicians because it is not always necessary to continue TRT throughout an individual's life; rather, it may be possible to discontinue TRT after the effective period. Second, we focused on the possibility of TRT for treating MS. It is noteworthy that TRT does not affect adiponectin levels in older men, although it was speculated that the use of TRT to treat TDS may cause MS due to extremely decreased levels of adiponectin, which is currently thought to be a key molecule in the aetiology of MS. We finally focused on the efficacy of herbal medicine and the mechanisms by which herbal medicine can improve symptoms of TDS for eugonadal patients. Among patients with TDS symptoms in Japan, one-third are patients with hypogonadism, one-third are patients between a hypogonadal and eugonadal status, and one-third are eugonadal patients. It is necessary to choose treatment options based on patient status, and further experience will be required to draw conclusions concerning the best treatment for Japanese patients with TDS.

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