

REVIEW

Testosterone replacement therapy for late-onset hypogonadism: current trends in Korea

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Testosterone levels in men older than 40 years can decrease at a rate of 1%–2% per year, and reports show that more than 50% of 80-year-old men have testosterone levels consistent with hypogonadism. Late-onset hypogonadism (LOH) is a clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms of serum testosterone deficiency. In recent decades, the concept of LOH in ageing men has become familiar in European countries and the United States. It is also a topic of interest and debate throughout Korea. However, most of the data regarding advantages or disadvantages of testosterone replacement therapy (TRT) as treatment for LOH have been primarily obtained from studies on Western populations; therefore, studies of the effects of TRT in Asian men, who may have different serum testosterone compared to Western men, are needed. TRT is commonly prescribed in Korea, despite the paucity of studies on the effects of TRT in Asian populations. Data from various TRT studies based on Korean have shown its efficacy in increasing serum testosterone levels and improving subjective symptoms as assessed by questionnaires. Currently, patches and short-acting intramuscular injections are displaced by gels and long-acting formulations. However, to prevent overdiagnosis and overtreatment, indication for TRT should include both low testosterone levels and symptoms and signs of hypogonadism.

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INTRODUCTION

Late-onset hypogonadism (LOH) is a clinical and biochemical syndrome associated with advancing age resulting from age-related changes in the interactions between hypothalamus/pituitary factors and testicular factors. This syndrome is characterized by typical symptoms of serum testosterone deficiency. Increased longevity and population ageing are expected to result in an increase in the number of men with LOH. Therefore, social interest in testosterone replacement therapy (TRT) has increased over the past few decades.

In recent decades, LOH in ageing men has become common in European countries and the United States,^{1,2} and it has also attracted interest in Korea. An epidemiological research study conducted via email of 5795 Korean men of at least 40 years of age, using the Androgen Deficiency in Aging Men (ADAM) questionnaire, revealed that 64.6% of respondents had symptoms of LOH, and more than 50% of respondents complained of a decline in erection, endurance and/or sexual desire. When asked whether they intended to undergo TRT, 96% of respondents who complained of erectile dysfunction and decreased endurance and/or sexual desire said that they would accept treatment.³

To provide appropriate guidelines for investigation, treatment and monitoring of LOH in ageing Korean men, the academic committee of the Korean Society for Aging Male Research released guidelines on LOH in men in 2006.⁴ Currently, TRT in Korea is a commonly used LOH treatment modality and is prescribed not only by urologists, but also by primary physicians. Because most studies investigating the

effects of TRT on LOH have been released by Western centres and because ethnicity may affect serum testosterone levels,^{5–9} data on the effects of TRT in Asian populations are needed. In this review, we summarize the results of studies on TRT in the Korean population and discuss the implications of these findings for TRT in general.

LITERATURE SELECTION

To obtain TRT literature pertaining to the Korean LOH population, MEDLINE searches were performed until December 2010 using the keywords ‘testosterone’ and ‘testosterone replacement therapy’. Furthermore, the *Korean Journal of Urology* and the *Korean Journal of Andrology*, both open-access journals, were searched using the same keywords, as were the official journals of the Korean Urological Association and The Korean Society for Sexual Medicine and Andrology.

Of the 29 studies detected using the search strategy outlined above, only 10 studies were selected. These papers were written in either Korean or English, and contained clinical data on TRT, serum testosterone measurements and accurate definitions of LOH based on administration of a symptom-based questionnaire. Studies without clear guidelines on inclusion criteria for TRT and studies with animal-based experiments were excluded from this review. To identify the incidence of LOH in the Korean population, two epidemiological studies without definite serum testosterone cutoffs were also included. The detailed characteristics of the studies selected were summarized in **Table 1**.

Table 1 Summary of contemporary Korean data on LOH and ART

Study	Patient No.	Study design	Testosterone preparation	Indication and normal cutoff of patient	Questionnaire used	Methodology of testosterone measurement	Time of testosterone measurement	Complication of testosterone replacement
Hong and Ahn (2002) ¹²	28	Non-control prospective trial	Oral TU 160 mg for 3 weeks, then 80 mg up to 3 months	LOH symptom 2.8 ng ml ⁻¹ (T) 13 pg ml ⁻¹ (FT)	ADAM	RIA	9–11 a.m.	No significant adverse event
Park <i>et al.</i> (2003) ¹³	39	Placebo-controlled prospective trial	Oral TU 160 mg for 3 months	LOH symptom 400 ng ml ⁻¹ (T)	ADAM PNUHQoL	RIA	—	No dropout
Seo <i>et al.</i> (1998) ¹⁴	21	Non-control prospective trial	Non-scrotal transdermal patch (5 mg) for 16 weeks	ED 3.0 ng ml ⁻¹ (T) Age over 40 years	—	RIA	—	Dropout 22% Skin irritation 4
Bae <i>et al.</i> (2005) ¹⁶	135	Retrospective observational trial	Oral TU 160 mg, then increase dosage	LOH symptom 2.55 ng ml ⁻¹ (T) Age over 50 years	—	—	9–10 a.m.	—
Park <i>et al.</i> (1999) ¹⁸	56	Placebo-controlled prospective trial	Non-scrotal transdermal patch (12.2 mg) for 3 weeks	ED 500 mg dl ⁻¹ (T) Age over 55 years	PNUHQoL	—	—	Dropout 25% due to skin reaction Skin rash in 64.2%
Park <i>et al.</i> (2007) ³⁴	87	Non-control prospective open label multicentre study	Testosterone gel (50 mg) for 12 weeks	LOH symptom 350 ng dl ⁻¹ (T) 73.5 pg ml ⁻¹ (FT)	AMS	—	8–11 a.m.	Nine complications Acne: 3 Itching sense: 2 PSA rising :1 Voiding dysfunction :1 Nocturia : 1 -Hot flushing : 1
Bae <i>et al.</i> (2006) ³⁵	73	Retrospective trial	Testosterone gel (50 mg) over 3 months	LOH symptom 3.5 ng ml ⁻¹ (T)	AMS	—	9–10 a.m.	No severe systemic adverse event
Bae <i>et al.</i> (2008) ³⁸	33	Non-control prospective trial	TU 1000 mg IM	LOH symptom 3.5 ng ml ⁻¹ (T) Age over 40 years	AMS IPSS	—	9–11 a.m.	No adverse event No dropout
Moon <i>et al.</i> (2010) ³⁹	133	Non-control prospective multicentre study	TU 1000 mg IM	LOH symptom 3.5 ng ml ⁻¹	AMS IIEF GEQ	—	7–11 a.m.	Eight adverse events: dyspnea, hot flushing, acne, gynecomastia Dropout 15%
Park <i>et al.</i> (2009) ⁴⁵	38	Retrospective trial	TU 1000 mg IM or testosterone gel for 18 weeks	ED, non-responder to PDE5 inhibitor 350 ng dl ⁻¹	IIEF	—	—	No adverse event No dropout

Abbreviations: ADAM: Androgen Deficiency in Aging Men; AMS: Aging Male Symptoms Scale; ED: erectile dysfunction; FT: free testosterone; GEQ: global efficacy question; IIEF: International Index of Erectile Function; IPSS: International Prostate Symptom Score; LOH: late-onset hypogonadism; PDE5, phosphodiesterase type 5; PNUHQoL: Pusan National University Quality of Life Scoring System; RIA: radioimmunoassay; T: serum testosterone; TU: testosterone undecanoate.

DEFINITION AND DIAGNOSIS OF LOH

Precise criteria for accurate diagnosis of LOH have not yet been established, making recognition of many afflicted individuals difficult. This leads to delays in early diagnosis and efficient treatment. At the same time, many individuals with symptoms related to natural ageing are incorrectly diagnosed as having testosterone deficiencies. Therefore, it is important for urologists to recognize manifestations of LOH in ageing men and to perform evaluations necessary for documentation, treatment and monitoring of LOH.

Given the present imprecision of diagnoses, current guidelines recommend using a combination of clinical and laboratory factors for diagnosing LOH.¹⁰ The ISA, ISSAM, EAU and Korean Society for Aging Male Research define LOH as ‘a clinical and biochemical syndrome associated with advancing age and characterized by the typical symptoms of serum testosterone deficiency’. This definition of LOH requires the presence of both clinical symptoms and hypogonadism. However, clinical translation of these two conditions is complex.

Current LOH guidelines on serum testosterone levels suggest a normal lower cutoff limit of 346 ng dl⁻¹ (12 nmol l⁻¹) total testosterone (TT) or 72 pg ml⁻¹ (250 pmol l⁻¹) free testosterone (FT).⁴ However,

clinical implications of testosterone levels outside of these reference ranges are not clear because of variable measurements among assays and variable assay sensitivities. Additionally, numerous testing kits are available and the strength of the correlation between results from different kits is unknown.¹¹ Furthermore, in most Korean studies, the methods used to measure serum testosterone levels were not clearly defined. Only three studies clearly stated that TT levels were measured by radioimmunoassay.^{12–14} Additionally, variable cutoffs ranging from 255 to 500 ng dl⁻¹ were used from the late 1990s to the early 2000s^{12–18} to define the lower normal limit of serum testosterone levels. This variability increased the complexity of using testosterone levels to diagnose LOH. Fortunately, most studies after the publication of clinical recommendations by Korean Society for Aging Male Research in 2006 used the same TT cutoff level of 350 ng dl⁻¹. However, no clear data supporting the validation efficacy of this cutoff were provided; therefore, this cutoff value requires further validation in Asian populations.

In unclear cases, it is important to evaluate the levels of FT and bioavailable testosterone to obtain estimates of free testosterone and testosterone bound to albumin, respectively. Despite recommendations to use equilibrium dialysis to measure FT, most Korean studies

measured FT using a direct radioimmunoassay or by calculating FT with the Vermeulen equation because of the long time required for equilibrium dialysis measurements.^{12,14} Variations in FT levels in the Korean studies may therefore be an artefact of the assay method, which limits clinical interpretations of the Korean data. This is not only an issue with Korean studies; standardisation of testosterone measurements is still a controversial issue in the field of LOH.¹⁹ Additionally, declines in TT and FT values are accelerated by chronic disease and obesity.¹¹

Adding to the complexity, many LOH symptoms are shared by other conditions^{20,21} or are physiologically associated with ageing,²² including decreases in muscle mass, bone mass, energy and libido, and increases in fatigue, among others. Currently, the ADAM²³ and the Aging Male Symptoms Scale (AMS)²⁴ questionnaires are the most commonly used methods to assess LOH symptoms in Korea. However, the results of these questionnaires are not tightly correlated with low testosterone levels, particularly in men with borderline-low serum testosterone levels. As part of a LOH screening program, Park *et al.*²⁵ examined the relationships among ADAM questionnaires, International Index of Erectile Function (IIEF)-5 scores and total serum testosterone levels among 409 healthy volunteers over the age of 40 years. While 92.5% of the men provided answers to the ADAM questionnaire that were indicative of LOH, only 23.7% of the subjects met the biochemical diagnostic criteria for LOH with TT levels less than 350 ng dl⁻¹. There was no relationship between serum testosterone levels and symptoms of LOH. There was also no significant correlation between IIEF-5 scores and serum testosterone levels.²⁵ These observations have been reinforced by other researchers who analysed the correlations between responses to the ADAM questionnaire and the AMS scale in 265 patients who were older than 40 years.²⁶ In this report, Park *et al.*²⁶ showed that TT was not correlated with responses to the ADAM, AMS or IIEF questionnaires. In contrast, TT demonstrated significant negative correlations with weight, abdominal circumference, body mass index and triglyceride levels ($P < 0.05$). Thus, physicians should keep in mind that while the sensitivity of these questionnaires is high,^{24,27} the questionnaire scores do not closely correlate with low testosterone levels, restricting their use in clinical diagnosis of LOH when used as a single indicator. Therefore, questionnaires are not recommended for screening for LOH in men receiving health care for unrelated reasons.²⁸ Additionally, there is marked inter-individual variation in testosterone levels at which symptoms occur.^{29,30} However, these questionnaires may be useful during treatment follow-up after TRT to evaluate changes from baseline status.

TRT AND THE EFFICACY OF TRT IN SYMPTOMATIC KOREAN LOH PATIENTS

The aim of TRT is to establish a physiologically normal concentration of serum testosterone to correct androgen deficiency, relieve its symptoms and prevent long-term sequelae. Replacement therapy is usually life-long, and the choice of preparation depends on age, convenience, cost, side effects, availability, and the patient and/or physician preference. Several testosterone preparations with varying pharmacokinetic profiles are currently available. Various delivery methods are available for testosterone therapy, including oral preparations, transdermal gels, buccal formulations, subcutaneous implants and intramuscular injections.^{31–33}

Oral preparations

Oral testosterone undecanoate (TU) has been available since the early 1970s. Oral TU is co-absorbed with a lipophilic solvent from the

intestine into the lymphatic system, thereby circumventing first-pass inactivation in the liver. Since its introduction, TU has been widely used in Korea and has an excellent safety record. Two early Korean studies demonstrated the effectiveness an initial dose of 160 mg oral TU (Andriol, NV Organon, The Netherlands) in increasing testosterone levels and improving LOH symptoms.^{12,13} However, the numbers of patients evaluated in these two studies were small (28 and 39, respectively), and these studies focused only on the short-term efficacy of the oral preparation. Additionally, there were differences in inclusion cutoffs for normal serum testosterone levels between these two studies and neither study was randomized.

A well-known limitation of oral TU treatment is its low efficacy; TU rarely raises testosterone levels above the mid-range. This limitation is mainly due to an approximately 7% bioavailability and a short half-life that requires patients to have multiple daily doses.¹⁵ To increase TU efficacy in increasing testosterone concentrations, Bae *et al.*¹⁶ analysed variables that determined the effect of oral TU on TRT. They reviewed 135 medical records from patients with testosterone deficiency syndrome who were followed for a mean duration of 311 ± 283 days. These patients took a mean daily dose of 3.5 ± 1.3 tablets. Bae *et al.*¹⁶ found that patients who took the tablets during meals showed a significantly higher peak testosterone level than those who ingested the tablets after meals ($P = 0.04$). Additionally, serum testosterone levels were positively correlated with dosage only up to four tablets per day. However, their criterion for abnormal TT levels (< 2.55 ng ml⁻¹) was lower than currently recommended.

Transdermal patches and gels

Transdermal testosterone is available as either scrotal or non-scrotal skin patches, and these patches raise circulating testosterone levels in elderly men to approximately the same levels as in healthy men. Patches are applied to the skin of the upper arm, back, abdomen or thighs, and are changed every 24 h. They deliver 5–6 mg per day of testosterone at a low- to mid-normal range. This preparation is therefore ideal for elderly men for whom treatment may need to be stopped suddenly if prostate-related side effects develop.¹⁷ Two Korean studies conducted in the late 1990s investigated the efficacy of these patches, focusing on improvement of erectile dysfunction,^{14,18} however, neither study was randomized. While a significant increase in serum testosterone levels was observed when compared with baseline¹⁴ and placebo levels,¹⁸ there were no significant changes in scores in Watts (sexual arousal, desire, orgasm and satisfaction) and Davidson (number and quality of penile erections) questionnaires.¹⁴ Additionally, 22% and 25% of the patients dropped out of the respective studies because of skin irritation symptoms, with dropout rate that was similar to that of studies performed on Western populations.

To avoid the high incidence of skin reactions, transdermal testosterone gels are increasingly being used instead of these patches. The efficacy and safety of 1% transdermal testosterone gel patches in Korean LOH patients were evaluated in two studies using the same inclusion criteria and focusing on improvements in AMS questionnaire scores.^{34,35} Using a cutoff of 350 ng dl⁻¹ for TT, both TT levels and AMS scores increased significantly in both studies 12 weeks after administration. An improvement in all subscales of the AMS system was also noted in both studies, and the sexual subscale showed the greatest improvement. In a multicentre study of five urological centres, all IIEF domains showed significant improvement.³⁴ The incidence of skin-related adverse events was quite low (7.4%, 5/68⁴¹) compared with testosterone patches, which was consistent with studies in Western populations (4%–5.5%). Furthermore, no severe

adverse events induced patients to drop out in either of the two Korean studies.

Intramuscular injection

Parenteral preparations are inexpensive and have long been the mainstay of TRT. These preparations include testosterone enanthate, testosterone cypionate and mixed testosterone esters. They are given every 2–3 weeks by deep intramuscular injection, usually producing supraphysiological peaks and hypogonadal depressions in testosterone levels. Fluctuation in testosterone levels can induce so-called ‘roller-coaster’ effects, which are characterized by alternating periods of symptomatic benefits and returning to baseline symptoms.³⁶ To overcome these limitations, a new depot intramuscular injection containing 1000 mg of TU has been recently introduced to maintain stable physiological levels of testosterone for 12 weeks.³⁷ While this long duration of action can create problems if there are complications associated with testosterone therapy, it is an excellent alternative for treating male hypogonadism.

An initial Korean study by Bae *et al.*³⁸ illustrated that intramuscular injection was highly efficacious. It increased serum TT levels and improved total AMS scores, especially the sexual subscale score. In a recent prospective study from nine andrological centres involving 133 Korean patients, injectable TU significantly decreased cholesterol, improved total IIEF scores and all five IIEF domain scores, and improved total AMS scores and all three AMS subscales.³⁹ While TU caused significantly elevated levels of haemoglobin, haematocrit and prostate-specific antigen (PSA) at 24 weeks, serum TT levels were maintained within normal ranges, and no serious adverse reactions were observed.

Based on these efficacy data for TRT, use of TRT combined with a phosphodiesterase type 5 (PDE5) inhibitor has been attempted by several groups. Because the most common symptom of hypogonadism is low libido,^{40–42} these combinations may plausibly have a synergistic effect. In humans, patients with organic erectile dysfunction (ED) had 40% lower serum-free testosterone level than those with psychogenic ED, and free testosterone levels were positively associated with peak systolic velocity and resistive indexes of cavernosal arteries.⁴³ For patients with arteriogenic ED and low-to-normal androgen levels, short-term testosterone administration improved cavernosal blood flow and responses to sildenafil.⁴⁴ Park *et al.*⁴⁵ reported that combination therapy with a PDE5 inhibitor and TRT in ED patients with LOH after failure of PDE5 inhibitor monotherapy had synergistic effects.⁴⁵ IIEF was evaluated as a primary end point in 38 men who showed no response to PDE5 inhibitor therapy at the maximal recommended dose and who had less than 350 ng dl⁻¹ TT. After 14 weeks of TRT alone, PDE5 inhibitor was added to the TRT regimen for an additional 4 weeks. At week 18, 84.2% of patients (32/38) showed a response. No patients dropped out of the study, and no major adverse events occurred. These outcomes suggest potentially using TRT for treating ED patients who are unresponsive to PDE5 inhibitor alone.

Reviewing Korean data on TRT, we found two common limitations. First, the number of patients evaluated in most studies was relatively small; only one study had a population of 100 patients. This limitation makes it difficult to detect ethnic discrepancies in the published data. The second limitation common to Korean studies were caused by the study design. Most data were from single-centre trials, with only two exceptions. There were no randomized clinical trials, but two studies were conducted as placebo-controlled trials. Moreover, most studies focused only on short-term efficacy, with little information available

regarding long-term safety or complications. Despite these limitations, in general, the outcomes of Korean studies did not differ significantly from studies in Western populations that reported that TRT therapy is both safe and efficacious.

CURRENT DATA ON CONTRAINDICATIONS FOR TRT

Current substitution treatment with testosterone is characterized by safety and a paucity of side effects.⁴⁶ However, there are risks for developing prostate cancer or worsening symptoms such as benign prostatic hypertrophy, liver toxicity, liver tumours, sleep apnoea, congestive heart failure, gynecomastia, infertility and skin disease. These TRT-associated risks are dependent on age, life circumstances and comorbid conditions.⁴⁷

Among these, the greatest concerns for androgen replacement are potential side effects on the prostate. Suspicions of prostate or breast cancer are currently the only absolute contraindications for TRT.¹⁰ However, not many studies have addressed these issues.^{48,49} Some studies have suggested that if PSA increases above 4.0 ng ml⁻¹ or if there is an increase in baseline PSA higher than 1.4 ng ml⁻¹ during the 12 months after starting TRT, a more detailed urological evaluation and a withdrawal from hormone treatment should be considered.⁵⁰ Another study of 81 hypogonadal men undergoing TRT demonstrated that prostate cancer incidence did not differ in individuals undergoing TRT when compared with the general population.⁵¹

In all published Korean studies that we surveyed, patients with prostate cancer or PSA levels greater than 4.0 ng ml⁻¹ were excluded. Therefore, we were not able to determine whether TRT has tumourigenic effects in this patient population. In four Korean prospective trials containing data on serial changes in serum PSA levels, two studies found no alterations^{34,38} in serum PSA levels, and two studies found significant increases in serum PSA levels after intramuscular TU injection.^{39,52} Lee *et al.*⁵² followed 47 Korean TRT patients for a mean period of 7.9 months. The patients were classified into two groups based on their initial PSA levels of either above (Group 1) or below 2.5 ng ml⁻¹ (Group 2) PSA. When serum PSA levels were compared between these two groups, increases in PSA levels were greater in Group 1 (0.61±2.25 ng ml⁻¹) than in Group 2 (0.28±0.65 ng dl⁻¹). However, the ratio of the PSA increase was 18.2% in Group 1 and 38.3% in Group 2. A total of four patients (16.7% of Group 1 and 3.4% of Group 2) with a serum PSA level greater than 4 ng ml⁻¹ after TRT underwent a prostate biopsy; however, no patients were found to have prostate carcinoma.

Potential aggravation of benign prostatic hyperplasia is another concern associated with TRT. By increasing serum androgen levels, TRT may potentially initiate or worsen lower urinary tract symptom (LUTS) in older men. However, studies on the relationship between serum testosterone and LUTS have given mixed results, with some studies reporting inverse associations and others showing no association.^{53,54} To date, no Korean studies have reported that higher testosterone increases the risk for LUTS.^{55–57} Sohn *et al.*⁵⁸ evaluated 90 men with LUTS and reported that serum testosterone had no significant correlation with International Prostate Symptom Score (IPSS), prostate volume, PSA or maximal flow rate.⁵⁸ Lee *et al.*⁵⁹ found that prostate volume showed a negative correlation with serum-free testosterone levels. Similarly, based on an analysis of 287 patients with a mean age of 62 years, Kim *et al.*⁶⁰ reported that calculated free testosterone and bioavailable testosterone were negatively associated with IPSS total scores and subscores (voiding symptoms) after adjusting for age, prostate volume, high sensitivity C-reactive protein, and the homeostasis model assessment of insulin resistance ($P<0.05$).

These data indicate that endogenous testosterone improves lower urinary tract function and that LOH may be a pathophysiological mechanism connecting LUTS and metabolic syndrome in men. In this era of androgen replacement therapy, an increasing body of studies based on small patient populations has demonstrated that TRT has positive effects on LUTS symptom scores and uroflow parameters. According to our data on 17 TRT patients followed for an average of 15.7 months, TRT improved total IPSS score, irritative symptoms (IPSS questionnaire items 2, 4 and 7), and obstructive symptoms (IPSS questionnaire items 1, 3, 5 and 6) without the use of an alpha-blocker. However, to accurately determine the effect of ART on LUTS, randomized and controlled studies of large populations are required.

In the last few years, associations between testosterone levels and metabolic and cardiovascular functions have become a prominent research focus. Longitudinal epidemiological studies have found low testosterone levels to be associated with increased risks for cardiovascular mortality,⁶¹ and recent clinical trials have demonstrated that TRT also improves ischaemic thresholds.^{62,63} However, there is still controversy regarding potential cardiovascular risks from TRT, particularly after the release of randomized placebo-controlled clinical trial data by Basaria *et al.*⁶⁴ These authors reported that five serious cardiac events occurred in their TRT group, with no such events occurring in their placebo group. Although a recent meta-analysis did not find that TRT was a risk factor for adverse cardiovascular events, the results of the Basaria *et al.*⁶⁴ study emphasize the need for future randomized clinical trials.

CONCLUSIONS

LOH is a common condition in ageing Korean men. However, when LOH is diagnosed based on a single indicator, it may be overdiagnosed and overtreated. Indications for TRT should include both low testosterone levels and symptoms and signs of hypogonadism. It is imperative to use a recommended laboratory methodology to exactly estimate serum TT and/or bioavailable testosterone levels from an early morning sample. Although contra-indications for testosterone supplementation in ageing men are controversial due to the lack of large-scale studies, long-term studies of the benefits and risks of TRT in Korean men suggest that TRT can yield a wide range of benefits in men with hypogonadism, particularly with respect to sexual function. Data from various TRT studies have also shown its efficacy in increasing serum testosterone levels and improving subjective symptoms as assessed by questionnaires. Patches and short-acting intramuscular injections are currently being displaced by gels and long-acting formulations.

To overcome the common limitations of existing studies on the effects of TRT, such as the small number of patients evaluated and the absence of a randomized comparative study design, future randomized studies based on larger patients' samples are required. Successful management of TRT requires appropriate evaluation and an understanding of the benefits and risks of treatment.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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