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Lang, Pierre Olivier; Samaras, Dimitrios; Samaras, Nicolaos

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Testosterone Replacement Therapy in Reversing “Andropause”: What Is the Proof-of-Principle?

Pierre Olivier Lang,^{1,2} Dimitrios Samaras,³ and Nikolaos Samaras¹

Abstract

Testosterone replacement therapy is often equated with the macho male physique and virility and is viewed by some as an antiaging tonic. The growth in testosterone's reputation and its increased use by men of all ages has seemed to outpace the scientific evidences. This review will aim to examine the uncertainty regarding the nature and the clinical importance of the age-related reduction in the testosterone levels. Considerations will be given both to clinical symptoms, biochemical and clinical diagnostic criteria, and to the risk-to-benefit ratio of reversing late-onset hypogonadism in aging and older men.

Introduction

THE WORLD'S POPULATION IS AGING STEADILY.^{1,2} The optimism created by increased life expectancy is tempered by the reality of the increasing health care burden produced by global population aging.^{3,4} Chronic and degenerative disorders have become more and more prevalent, and multimorbidity is increasing with advancing age.^{3,5-7} In studying human longevity, one observation clearly stands out: The average life span of women is almost 10% higher than men.^{1,2} The fact that this gender-associated difference occurs in many mammalian species suggests that the hormonal environment may play a role in the aging process.^{6,8}

Not as readily evident nor as abrupt as the decline of estrogens in women, and associated with a greater interindividual variation compared to menopause,^{9,10} the syndrome of “andropause” is defined as the progressive decline (0.8%–2% each year) in testosterone (T) level, beginning at middle-age.¹¹⁻¹⁴ This decline is partly due to the age-related decline of the Leydig cell mass and/or to abnormalities in the hypothalamic–pituitary–testicular axis.^{15,16} Thus, some older men have primary hypogonadism with reduced testicular synthesis of T despite a secondary increase in level of luteinizing hormone (LH). However, LH concentrations often do not parallel the decline in T as a result of impaired gonadotrophin-releasing hormone (GnRH) secretion and alterations in gonadal steroid feedback mechanisms.¹⁵⁻¹⁷ In addition, alteration of peripheral components of the T axis has been found, such as an increase in sex hormone binding-globulin (SHBG) and aromatase (which causes the bioconversion of T to estrogens),^{18,19} and a decrease in 5 α -reductase

(which converts dihydrotestosterone to the active form of T).¹⁹ Although these age-related observations are important, it is also crucial to consider the effects of other factors, such as genetics, chronic diseases, medications, alcohol consumption, smoking, diet, and stress.¹⁹ Moreover, it has been shown that aging men with obesity and/or metabolic syndrome experience a significant decrease in T serum levels compared to aging, metabolically healthy men.²⁰⁻²² These data suggest that obesity could be more important than age *per se* in the pathophysiology of the aging-associated decline of T.^{23,24}

Clinical features of andropause include increased body fat, loss of muscle and bone mass, fatigue, depression, anemia, poor libido, erectile dysfunction, insulin resistance, and a higher risk of cardiovascular disease.²⁵⁻³⁰ However, the diagnosis of andropause is to a large extent dependent on biochemical assessment of T in blood.³¹ The serum T level is relatively simple to measure, and most practicing physicians determine total T (TT) levels as the initial laboratory assessment. However, it is important to note that T circulates in the blood in several forms. It is bound tightly to SHBG; only about 1%–2% of TT is unbound to proteins (free T [FT]), and a further 30%–50% is bound with low affinity to albumin. Therefore, only about 50% of TT is bioavailable.³² In most, but not all, clinical conditions, a measurement of TT is adequate for the evaluation of an individual. It is widely believed that the SHBG-bound T is not readily available to most tissues, whereas albumin-bound and FT are bioavailable. Because SHBG concentrations can be influenced by many factors (decreased by obesity, for example, and increased by aging), there are clinical situations in which

¹Medical School and University Hospitals of Geneva, Department of Internal Medicine, Rehabilitation and Geriatrics, Geneva, Switzerland.

²Translational Medicine Research Group, Cranfield Health, Cranfield University, Cranfield, United Kingdom.

³Medical School and University Hospitals of Geneva, Nutrition Unit, Geneva, Switzerland.

measured concentrations of TT may not reflect the bioavailable concentrations or the clinical status of the patient.^{33–36} In these circumstances, a supplemental test assessing bioavailable or FT is helpful in clinical decision making.^{36,37} However, different methods are available also for measuring TT and FT.^{32,36,37} All of these methods are generally adequate for the diagnosis of male hypogonadism, but marked variations can occur from one laboratory to another. Moreover, different studies have indicated large variations and/or lacks of specificity in measurements of serum TT and FT by different methods commonly used in clinical chemistry laboratories (see Fig. 1).^{12,37–39}

In recent years, there has been growing concern about the use of T replacement therapy (TRT) in middle-aged

and older men who have borderline TT or even normal TT levels according to their ages.⁴⁰ Indeed, despite the lack of precise criteria for andropause,²⁶ both cross-sectional and longitudinal studies have estimated that a substantial number of older men (*i.e.*, especially aged ≥ 70 years) may have low sex steroid hormone levels.^{8,10,41–49} This condition places them at higher risk for adverse health outcomes and premature death.^{8,28,50–55} This review will aim to examine the uncertainty regarding the nature and the clinical importance of the age-related reduction in the T levels. Considerations will be given both to clinical symptoms, biochemical and clinical diagnostic criteria, and to the risk-to-benefit ratio of treating low T levels in older men.

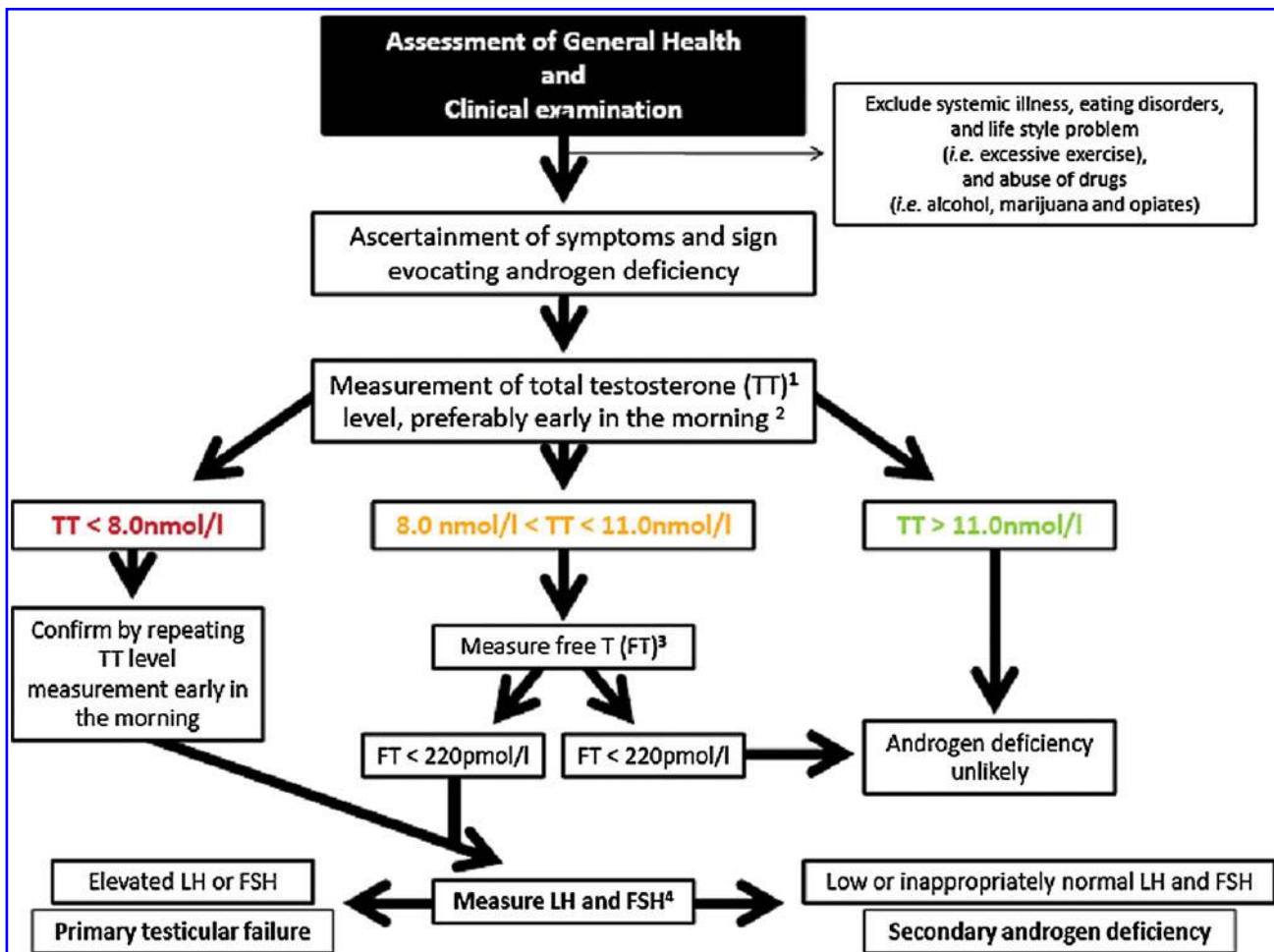


FIG. 1. Algorithmic approach to the diagnosis of androgen deficiency in aging and older men (Adapted from Bhasin et al.³¹ and Wu et al.²⁶). ¹Total testosterone (TT). There is a growing concern about the accuracy of the direct, automated immunoassays and immunometric assays for T, especially in low range of TT concentrations. Although liquid chromatography tandem mass spectrometry is now the reference method with the highest specificity for measuring sex steroids, the perfectly useful immunoassay for T and all mass spectrometry assays are not flawless either. Finally, the important point is the quality of the assay used, and not the technique. ²TT represents the sum of the bound and unbound testosterone and is affected by changes in sex hormone-binding globulin (SHBG). Its serum level is affected by the pulsatile, circadian, and circannual secretory rhythms. TT levels are highest in the morning hours after waking and are lower during the evening hours. Therefore, TT must be measured in the morning ³Free testosterone (FT). FT or unbound testosterone is the fraction that is neither bound to albumin nor to SHBG. ⁴The measurement of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels helps to determine whether the androgen defect resides at the testicular level or at the hypothalamic–pituitary site.

Clinical Meaningfulness of T Decline in Older Men

When menopause in women is an unquestionable condition, it has been widely debated whether otherwise healthy men, as a consequence of the physiological age-related decrease in androgenic production, develop a male climacteric syndrome.⁵⁶ In comparison with clinically well-defined menopause, andropause symptoms would be rather subtle and seem to affect sexual functions, bone and muscle mass, body composition, and cardiovascular health and results in mood and cognitive disorders.⁵⁵ However, it is important to state that some men have a lower than normal T level without signs or symptoms. Moreover, some of these signs and/or symptoms are a normal part of aging and others can be caused by various underlying factors, including medication side effects, thyroid problems, depression, and excessive alcohol use.⁵⁷ Finally, symptoms and low T do not often coincide, and there is a high background prevalence of symptoms in men with normal T levels. In addition, the clinical relevance of population-level associations between hormones and symptoms is still unclear given that the measurement of hormones in men is not a routine part of clinical practice in the absence of symptomatology.²⁸

Sexual function

Aging is usually associated with a decline in potency and sexual interest measured by frequency of orgasm or intercourse or by sexual satisfaction.^{57,58} This may suggest such changes in sexual behavior are androgen dependent, but this does not prove the cause. Although erectile dysfunction in older men is often of nonhormonal etiology, T deficiency accounts for 6%–45% of all cases.⁵⁹ In the large European Male Ageing Study conducted in 3,369 men aged 40–79 years, three sexual symptoms were associated with a serum T concentration <3.2 ng/mL.²⁶ Inversely, in the large Massachusetts Male Aging Study, a population-based cohort study of 1,709 men, Kupelian et al. found no association among TT, FT, SHBG, and erectile dysfunction.⁶⁰ T levels were associated with a decrease in risk of erectile dysfunction only in men with increased LH levels.

Bone mineral density

It has been shown that the bone mineral density (BMD) in healthy men declined from ages 20 to 90 years,⁶¹ and older men with androgen deficiency due to disease,⁶² or whose T has been lowered surgically or medically^{63,64} have a decline in BMD.²⁸ Data on the relationship between T levels and BMD are limited for adult men with normal TT.⁶⁵ Otherwise, in a population study (2,447 community-dwelling men aged ≥65 year), Fink et al. have demonstrated that prevalence of osteoporosis (at either the hip or the femoral neck) was inversely correlated with TT serum level, and was significantly higher in men with deficient TT (12.3%) compared to normal levels (6.0%).⁶⁶ Conversely, among osteoporotic men and those with normal BMD, the prevalence of TT deficiency was 6.9% and 3.2%, respectively ($p=0.01$).⁶⁶ Finally, the authors demonstrated that decreased TT levels were significantly associated with rapid hip bone loss.⁶⁶ Moreover, in 609 men aged ≥60 years, Meier et al. observed that the risk of fracture was significantly increased in men with reduced TT (hazard ratio [HR] 1.3%, 95% confidence interval [CI] 1.1–1.6).⁶⁷ At

baseline, in men with incident fractures, TT levels were significantly lower and SHBG significantly higher compared with those without fractures. After adjustment for SHBG levels, the serum TT (HR, 1.5%, 95% CI 1.2–1.8) was associated with overall fracture risk. After further adjustment for major risk factors of fractures, lower TT was still associated with the increased risk of fracture (hip, HR 1.9%, 95% CI 1.2–2.8; vertebral, HR 1.3, 95% CI 1.1–1.7). One study that included men of middle to older age reported, however, that levels of TT and FT were not correlated with BMD.⁶⁸ In addition, it is important to mention that many cross-sectional and prospective studies conducted in men have also demonstrated positive associations between estradiol (E₂) levels and BMD, bone morphology, or bone loss. The influence of E₂ generally appeared predominating compared to T.⁶⁸

Muscle mass and strength

Serum levels of TT and FT were found to be correlated to muscle mass, strength, and physical performance as well.^{55,69–71} In a cross-sectional population-based study (623 men, aged 65–88 years), Schaap et al. have shown that serum levels of TT and FT were positively associated with physical performance and muscle strength.⁶⁹ Similar results were found in the most recent wave of the Massachusetts Male Aging Study (684 men aged 55–85 years) in which O'Donnell et al. have measured muscle strength and physical performance.⁷⁰ More recently, to test the relationship between gonadal status and measures of physical performance, Maggio et al. have evaluated the effect of TT levels on hand grip strength and physical performance according to a short physical performance battery (SPPB) in 455 men (aged 65 years or older) from the InCHIANTI study (Invecchiare in Chianti, aging in the Chianti area).⁷¹ Three different groups of older men were created: Severely hypogonadal (TT levels ≤2.3 ng/mL); moderately hypogonadal (2.3 ng/mL < TT < 3.5 ng/mL); and eugonadal (TT ≥3.5 ng/mL). In the age- and body mass index (BMI)-adjusted analysis, there was a significant difference in hand grip strength and SPPB score according to the degree of hypogonadal severity, with severely hypogonadal men having lower values. In the multivariate analysis, grip strength, but not SPPB and other determinants of physical performance, was significantly different between the three groups.

Body composition and cardiovascular health

In epidemiologic studies, low T deficiency has been considered as a risk factor in itself for the subsequent development of central obesity, with insulin-resistance, type 2 diabetes mellitus (T2DM), metabolic syndrome, high-sensitivity C-reactive protein (hsCRP), and, finally, increased mortality.^{52,53,72–79} However, metabolic syndrome and T deficiency in men seem to be closely linked, and conversely there is strong evidence that a low T level and clinical hypogonadism have a high prevalence in men with metabolic syndrome and/or T2DM according to a recent review of existing observational and interventional data.^{20–22} Thus, many components of metabolic syndrome are adversely affected, especially in relation to cardiovascular risk in the presence of hypogonadism. Low T status and metabolic syndrome both appear to be independently associated with increased all-cause and cardiovascular mortality.^{28,80,81}

Hence, several studies have examined the impact of TT, FT, and SHBG levels on cardiovascular health or atherosclerosis^{54,72,82–87} Thus, from the analysis of the large Swedish arm of the cross-sectional Osteoporotic Fractures in Men study (3,014 men aged 69–80 years), Tivesten et al. observed that individuals with TT and FT levels within the lowest quartile have an increased odds of lower-extremity peripheral artery disease (*i.e.*, ankle and brachial index < 0.9).⁸⁴ Hak et al. in the Rotterdam Study have investigated the association of T and FT serum levels with aortic atherosclerosis (*i.e.*, radiographic detection of calcified deposits in the abdominal aorta) among 1,032 nonsmoking men aged 55 year and over.⁸³ Relative to men with hormone levels in the lowest tertile, men within the highest tertile had age-adjusted relative risks of 0.4 and 0.2, respectively, for the presence of severe aortic atherosclerosis. Additional adjustment for cardiovascular disease risk factors did not affect the results. Men with levels of TT and FT in subsequent tertiles were also protected against progression of atherosclerosis. Similar results were demonstrated in younger men with T levels < 9.8 nmol/mL.⁸⁵ In men aged 73–90 years, TT concentrations were inversely correlated with increased carotid intima media thickness (CIMT).⁸⁶ In a prospective analysis in 195 independently living older men, FT levels were inversely related to the mean progression of CIMT after adjustment on the usual cardiovascular risk factors; TT concentration were not.⁸² Interestingly, some investigators have demonstrated that low SHBG was more strongly associated with metabolic syndrome than low TT and was also a stronger predictor of incident metabolic syndrome in nonobese middle-aged and aging men.^{28,72,78,87} These findings are explained by the recognized association between low SHBG concentrations and insulin resistance, smaller and denser low-density lipoprotein cholesterol (LDL-C) molecules,²⁸ and increased mortality cardiovascular disease mortality in one study.⁵⁴ One prior study, however, did not confirm this⁸⁸ and was uncertain whether SHBG level in men is or is not associated with mortality from cardiovascular causes independently of TT or FT levels. In addition, male aging, by itself, is associated with an increase in central and upper body fat deposition.⁵⁷ This could be explained by the age-associated decline in growth hormone concentrations, which results in an increase in SHBG and therefore a reduction in FT concentration.⁸⁹

Mood and cognitive functions

The androgen deficiency of aging males is responsible for a variety of psychological and behavioral symptoms, mood, and cognitive disorders.^{57,90,91} However, all of those symptoms overlap with signs and symptoms of major depression and age-associated cognitive impairments.⁹⁰ Recently, in the Longitudinal Aging Study Amsterdam, Joshi et al. assessed yearly 608 men aged 65 years or older for the Center of Epidemiologic Studies-Depression (CES-D) scale.⁹² Serum FT concentrations below the threshold of 170 pmol/L were associated with depressive symptoms, even after correction for possible confounders, and men in the lowest quintile for FT were at greater risk for depressive syndromes compared to those in the upper four quintiles. In humans, the role of androgens has been described, albeit inconsistently, in the regulation of aggression, emotion, and personality. However, these direct effects appear to be greatly influenced by

social factors as well.⁹⁰ Sex hormones are also important for the development and maintenance of acquired cognitive capacities,⁹⁰ and changes in androgen levels modulate, at least in part, the cognitive changes with advancing age.⁵⁷ In a longitudinal study (407 men, aged 50–91 years), the FT index (*i.e.*, serum T/SHBG) was positively associated with scores on measures of verbal, visual memory, and visuospatial performances and inversely with rate of decline in visual memory.⁹³

Finally, clinical manifestations suspected to be caused by androgen deficiency are numerous; however, parallels between the clinical effects of aging and the age-related perturbations in TT, FT, and SHBG concentrations obscure its distinction from the normal aging process.²⁶ Moreover, the association of symptoms with a particular hormone concentration do not immediately indicate the causation.⁵⁷ Thus, one of the major limitations of longitudinal, cross-sectional, or population-based studies in indentifying T as predictors of hypogonadism-related health outcomes is the use of single baseline hormone measurement, which would not allow assessment of changes in levels over time.²⁸ Thus, additional population-based prospective studies are still needed to further evaluate the incidence of significant clinical outcomes, to solve the debate, and to determine the feasibility or desirability of interventional trials of T therapy in middle-aged and older men.

How Andropause May Contribute to Immunosenescence During Normal Aging

Changes in the immune system are also part of the normal aging process.³ Immunosenescence, the term commonly used to describe the age-acquired dysfunctional immunity, contributes to a less-than-optimal immune response to many antigenic stimuli (*i.e.*, from pathogens, vaccines, and diseases) compared to their younger counterparts.^{3,94} Although an individual's age is a major contributor, there is no single cause of immunosenescence.³ Thus, a compilation of immunological events are believed to result in this dysfunctional immunity, including thymic involution and the reduction in thymic output⁹⁵; the lifelong reshaping of the immune repertoire by persistent antigenic challenge⁹⁶; changes in antigen-presenting cells, including the function of their Toll-like receptor ligands⁹⁷; the reduced production of new B lymphocytes⁹⁸; and the impact of co-morbidities,⁶ the nutritional status of the individual,⁹⁹ the increase frequency of chronic low-grade inflammation,¹⁰⁰ and the age-related dysregulation of hormonal pathways.¹⁰¹

A reciprocal relationship between sex steroids and the immune system has been suggested for several years.¹⁰² Indeed, among the prominent effects of sex on aging is the response of the immune system. While not as dramatic as the role that estrogens and androgens play in sexual differentiation and reproduction,^{103,104} there is now evidence indicating that sex hormones influence the distribution and functions of virtually all immune cell types of both the innate and adaptive immune system.^{102–104} In fact, sex hormones modulate a large variety of phenomena involved in the immune response, including thymocyte maturation and selection, cellular transit, lymphocyte proliferation, expression of class II major histocompatibility complex molecules and receptors, and cytokine production as well.¹⁰² Furthermore, the

presence of specific receptors on immune cells indicates one mechanism by which these hormones exert their biological effects.¹⁰²

There is also a growing body of evidence demonstrating a gender difference in the immune response in human beings; in comparison to women, men mount less vigorous cell-mediated and humoral immune responses to antigenic stimulations via infection or vaccination.^{102,104,105} Furthermore, gender-associated differences in immune response are thought to be responsible for the greater susceptibility of women to autoimmune diseases such as rheumatoid arthritis (RA), multiple sclerosis, and systematic lupus erythematosus.¹⁰⁶ Sex-associated differences have also been shown in relation to infectious disease. These include dimorphism of the immune response as well as dimorphism associated to infection parameters; women experience significantly higher survival rates during infections and sepsis.^{103,107}

The well-described chronic low-grade inflammatory state in aged individuals without underlying disease^{6,100} is characterized in part by an increased circulating level of interleukin-6 (IL-6). This has been demonstrated in both mice and human models as being more prominent among old males,¹⁰¹ and similarly the upregulation of proinflammatory cytokine production as being associated with the age-related decline in androgens.¹⁰⁸ Furthermore, T deficiency induces IL-6 mRNA and protein synthesis in bone marrow cells obtained from young mice after orchidectomy.¹⁰⁹ *In vitro*, T reduced IL-6 production in macrophages,¹¹⁰ osteoblasts,¹¹¹ synovocytes,¹¹² and cell lines.¹¹³ One of the hallmarks of immunosenescence is the decreased proliferation of CD4⁺ lymphocytes and the decline in their production of the Th1-like cytokines (IL-2, interferon [IFN- γ]). In contrast, the production of the Th2-like cytokines (IL-4, IL-5, IL-6, tumor necrosis factor [TNF- α , IL-1 β , IL-18, IL-8, IL-12, and IL-10] is increased considerably.¹¹⁴ This shift from a Th1 to a predominantly Th2 phenotype results in an altered immune response and a higher susceptibility to bacterial and viral infections, as well as to an increased susceptibility to develop some of the main age-related diseases.⁷ The onset, magnitude, and kinetics of this shift from Th1- to Th2-like cytokine response has been well associated in animal models as being dependent on the sex hormone status.¹¹⁵

To the best of our knowledge and despite the growing interest in the understanding of the role of sex hormones and TRT in the homeostasis of immunity, actual data from studies conducted in healthy older men with late-onset hypogonadism are still lacking. However, by considering the well-demonstrated immune-suppressive activities exerted by androgens, male hormones, and their derivatives have been tested as therapeutic approaches in RA,¹¹⁶ in other autoimmune disorders,¹¹⁷ and in patients with Klinefelter syndrome (KS).¹¹⁸ Paradoxically, the lack of T in patients with KS-enhanced cellular and humoral immunity and TRT suppress this both in KS and in autoimmune diseases. Similarly, sex steroid ablation has been successfully tested in a clinical trial with chemical castration by administration of luteinizing hormone-releasing hormone (LHRH) antagonist after autologous and allogenic hematopoietic stem cell transplantation.^{119,120} This treatment was reported to induce strong CD4⁺ lymphocyte regeneration along with a more varied T cell antigenic repertoire and enhanced peripheral T cell activity.⁴ Elderly males undergoing orchidectomy for pros-

tatic carcinoma demonstrated an increase in circulating T cell numbers, particularly naïve T cells.¹¹⁹ Finally, currently available evidence suggests that the effects of T, whether it is T deprivation or TRT, on the immune system cannot be generalized because the effects may vary from immunosuppression to immunopotential. However, these conflicting results may be explained by handling of the cells for *in vitro* research, which results in changes in expression of various receptors or in priming of the cells. In addition, variability in results may be due by differences between systems, including *in vitro* and *in vivo* studies, and age and sex-hormonal status the levels of other sex and steroid hormones.¹⁰²

TRT: The Clinical Risk-to-Benefit Ratio

Whether, as in the female climacteric syndrome, changes in men as they pass from middle age to older age are attributed to the decline in sex hormone concentrations, the male climacteric symptoms should be readily reversible by TRT. Scientists have carefully explored the benefits of TRT, but most of its benefits have been postulated from studies involving younger hypogonadal patients or animal models.^{32,121} In younger men, the benefit-to-risk ratio is high. Instead, there have been fewer studies, particularly placebo-controlled randomized trials (RCT), in populations of middle-aged or older men who do not meet all the criteria for secondary hypogonadism.⁴⁰ Thus, the benefit-to-risk ratio of TRT in the aging male is still not known.²⁹

Evidence-based benefits

The best available data come from five RCT conducted in older men^{122–128} and two meta-analysis of RCTs.^{129,130} They have all investigated the effects of TRT either on body composition, bone metabolism, or serum profile in middle-aged or older men. All reported that the mean T concentration was increased with treatment excepting one.¹²⁶ Three studies reported several potential benefits.^{122,124,125,128} Among them, one only showed that TRT, with or without finasteride, significantly increased BMD at the lumbar spine and at the hip.¹²⁸ These positive effects on BMD have been more recently confirmed in 60 obese men (mean age 57±10 years) with metabolic syndrome and low serum T (T<3.2 ng/mL) regardless the presence of osteoporosis.¹³¹ Forty men received intramuscular T undecanoate four times/year for 36 months; 20 age-matched hypogonadal men in whom TRT was contraindicated were used as controls. With a study adherence of 50% without serious side effects, T undecanoate induced a significant improvement of bone mass after 36 months with a 5%/year increase, and this was without changes in BMI. A direct relationship between serum T and BMD increments at the lumbar and femoral sites was demonstrated. However, data measuring the impact of hormone replacement on fracture risk are still unavailable. In the meta-analysis of the 29 RCTs conducted by Isidori et al.,¹²⁹ the findings suggested that TRT resulted in a reduction of total body fat, increase in lean mass, and improved BMD at the lumbar spine. However, when physiologically appropriate doses are given to older men, the results are less impressive.^{57,122,123} No significant increase in muscle strength (*i.e.*, extension and flexion of the knee with a dynamometer) and various parameters of physical functions was detected.^{122,124} Reviews analyzing the

impact of TRT either on lipid profiles or on cardiovascular events in men with either low or low-to-normal T levels have not demonstrated any beneficial effects.^{129,130} Similarly, in a Cochrane database Systematic Reviews conducted with the aim to investigate whether TRT was an effective treatment for patients with lower limb atherosclerosis, the authors concluded there was no evidence to date that short-term TRT was beneficial.¹³² In addition, it was also not accompanied by any improvement in quality of life^{123,124} or sexual function,¹²³ according to specific questionnaires. However, TRT improved mood disorders³² and may improve cognitive function in frail elderly men.^{133,134}

Risks associated with TRT

Even if TRT may prevent or reverse the age-related declines in some functions, there is reason to wonder if it will also exacerbate major T-dependent conditions to which older men are particularly prone, including prostate cancer, benign prostatic hypertrophy, and cardiovascular diseases.^{135–137}

Despite prostate volume and serum prostate-specific antigen (PSA) increase in response to T,¹³⁸ recent reviews suggest that the longstanding fear of stimulating prostate cancer with TRT is without scientific basis.^{135,139} In a meta-analysis conducted by Calof et al.,¹⁴⁰ TRT was associated with a significantly higher risk of detection of prostate cancers, PSA > 4 ng/mL, and prostate biopsies in men with previous history of cancer (with disease-free ≥ 2 years and undetectable PSA levels); TRT improved T levels without increasing PSA values.^{33,141} Similarly, TRT seems to have no adverse effect on lower urinary tract symptoms or other prostate outcomes.¹³⁵ Despite these findings, the Endocrine Society's 2010 Clinical guidelines suggested digital rectal examination and measurement of serum PSA in men over 50 years before initiating TRT and, in men > 55 years to estimate prostate risk cancer using a prostate risk calculator (<http://deb.uthsca.edu/URORiskCalc/Pages/calcs.jsp/>).^{33,142}

A similar debate exists regarding the increased cardiovascular risk associated with TRT. While some reports suggest there is no association,¹³⁵ a recent RCT in 209 community-dwelling men (aged ≥ 65 years) assigned to receive placebo gel or T gel (daily for 6 months) was stopped before enrollment had been completed because much more adverse cardiovascular events were measured in the treatment group (*i.e.*, peripheral edema, elevated blood pressure, arrhythmias, electrocardiographic changes, stroke, syncope, and atherosclerosis-related events such as myocardial infarction, sudden death, angioplasty, and coronary artery bypass surgery).¹³⁶ Although the explanation formulated was the high prevalence of cardiovascular risk factors within the population study, this finding is of particular interest because this intervention study had also enrolled a population most likely to benefit from TRT. Other adverse effects have been also demonstrated; TRT is associated with an increase incidence of erythrocytosis^{135,140} and a dose-dependent decrease in HDL-C.¹⁴³ The last effect was observed with intramuscular administration only, but not with transdermal preparations.¹⁴⁴

TRT: Who and How?

The diagnosis of "andropause," according to current guidelines, is based on the presence of clinical symptoms together with a biochemical evidence of hypogonadism.^{25,33,145}

Who

As depicted in Fig. 1, the diagnostic work up should start with a general health and clinical examination to exclude acute and subacute illnesses. When symptoms suggestive of T deficiency are identified, a serum TT as the initial diagnostic test is then suggested. Serum should be drawn in the morning, because serum levels are usually lower in the afternoon.¹⁴⁶ A low value should be repeated at least once for confirmation.³³ TT levels < 8 nmol/L are generally accepted as being consistent with deficiency, but thresholds of < 14.0 nmol/L or 6.9 nmol/L for have also been recommended.^{28,31,33,147} Inversely, individuals with TT levels > 12.0 nmol/L are not likely to require TRT.^{31,32} TRT should only be offered to individuals with unequivocally and reproducibly low hormone levels in the absence of known pituitary or testicular diseases.^{25,32,33,147,148} However, TT or FT levels below which symptoms emerge and adverse health outcomes become obvious remain hotly debated.^{33,147} The prevalence of even the most specific sexual symptoms of androgen deficiency is relatively high among men with normal TT levels.⁴⁷ Interestingly, with the aim to better identify late-onset hypogonadism in middle-aged and older men, Wu et al. has surveyed a random population sample of 3,369 men aged 49–79 years and measured T and calculated FT levels to evaluate their association with clinical symptoms.²⁶

Using questionnaires, the authors have collected data regarding the individuals' general, sexual, physical, and psychological health. Finally, the presence of at least three sexual symptoms (*i.e.*, poor morning erection, low sexual desire, and erectile dysfunction), inability to perform vigorous activity (*i.e.*, running, lifting heavy objects, or participating strenuous sports), depression, and fatigue were significantly related to T levels, and thresholds for T were approximately 8 nmol/L for a decreased in frequency of sexual thoughts, 8.5 nmol/L for erectile dysfunction, 11 nmol/L for a decreased frequency of morning erections, and 13 nmol/L for diminished vigor. Concerning FT, thresholds for the three sexual symptoms were 160, 280, and 280 pmol/L, respectively, with a threshold of 160 pmol/L for both sadness and fatigue. No thresholds were identified for physical symptoms associated with FT or psychological symptoms with TT. These findings support the recommendation that TT be used as the primary biochemical diagnostic criterion.^{31,33,47,48} In addition, when TT levels were under 8 nmol/L, the addition measurement of FT did not make sense. However, applying a threshold for FT could be useful in individuals with multiple symptoms and a borderline TT concentration (8 to 11 nmol/L).²⁶

How

Aging and older men with unequivocally low serum T concentrations should undergo the same diagnostic evaluation for hypogonadism as young men (Fig. 1).^{27,31} According to the recently updated Endocrine Society guidelines, the goal of TRT is to restore the hormone concentration to the normal range; however, desirable concentrations should be lower than that for younger men (*i.e.*, 6.7–12.0 nmol rather than 13.4–17.3 nmol).^{31,33} TRT can be managed by administering one of the several available formulations (*i.e.*, by pills, injection, topical gel,

patch, tablets, or pellets) with appropriate attention to its pharmacokinetics.^{27,31} Intramuscular injections (200 mg T propionate, enanthate, or cypionate) last 10–14 days,³¹ requiring a bimonthly regimen and training in self-injection techniques. T undecanoate, a longer-acting T ester, is available in Europe but has not yet been approved by the U.S. Food and Drug Administration. It is both a desirable and safe option; patients benefit from the stable T levels and fewer required injections (1,000 ng every 12 weeks).¹⁴⁹ Oral T undecanoate has the convenience of oral administration without the same potential for liver toxicity as another oral T formulation, 17 α -testosterone.^{147,150} However, a short duration of action requires dosing two to three times a day, and clinical responses are less consistent than with the long-acting injectable formulation or the gel.^{147,150} Transdermal gel (AndroGel[®], Testogel[®], or Testim[®]) is easy to use with daily application (5 g/day) and excellent skin tolerability. Excepting costs, the major concern is the potential of transfer of T to a sexual partner or to individuals who may come in close contact.³¹ One 5-mg patch (Androderm[®] or Andropatch[®]) may not be sufficient enough to achieve target T levels; therefore, some patients may need daily administration of two 5-mg patches. The use of nongenital patches is associated with a high frequency of skin irritation.^{31,149} Bioadhesive buccal tablets (Striant[®]) and T pellets implanted (Testopel[®]) are new methods of delivery.^{27,31,149} Controlled-release, bioactive, 30-mg T tablets can be applied every 12 hr to the buccal mucosa. Gum problems and bad taste are associated with their use in 10%–20% of cases. Implants are subcutaneously inserted and three to six 200-mg implants could be necessary to maintain serum T to target level up to 6 months. The need for skin incision for insertion and removal and the risk for spontaneous extrusions and fibrosis at the site of insertion are some of potential drawbacks of this formulation.³¹

When all contraindications are ruled out, the efficacy is probably of lesser importance in the choice of the hormone formulation. The patient's own preference is often considered as the most important criterion. It seems, however, safer to initiate TRT with a short-acting formulation. Indeed, if a patient has side effects when using long-acting T, then the treatment could not be completely suspended. Following the initiation of TRT, changes in serum hormone levels are seen usually between 2 and 3 weeks. Whether this is a good sign that the therapy is working, any symptoms a man is experiencing are not actually reversed before 2–3 months. However, it is important to note that TRT typically induces a strong placebo effect in the initial stages of therapy.³⁰ This means that many men who are treated notice an improvement, not because the T-containing medication has improved their T but because of the psychological effect of taking it. In short, some men think T therapy is working and then feel better, even though the treatment is not working. This may lead to confusion and dissatisfaction as the placebo effect of treatment diminishes. Thus, the commonly held opinion about the duration of TRT is a 3- to 6-month trial in the absence of obvious adverse effects. It often takes that long for the placebo effect to dissipate. If TRT is felt to have had beneficial effects after 6–12 months and no adverse effects have arisen, then therapy should be continued; however, it should be reassessed at least on a yearly basis.

Is Age-Related Androgen Deficiency a Preventable Condition?

Some age-independent risk factors for low T levels that might operate independently have been proposed by several experts,^{28,49} and modification of those factors could potentially maintain T levels in desirable range values in aging men. While a medical history of orchitis, testicular trauma, or other pathology may be contributory,⁵⁷ interestingly, increased adiposity and obesity were strongly associated with lower TT, FT, and SHBG levels in middle-aged and older men.^{57,79,87,151–154} Similarly diabetes mellitus and insulin concentrations have been found to be indirectly correlated with SHBG and TT concentrations.^{155,156} With respect to lifestyle, excess intake of alcohol and physical and psychological stress were also associated with lower TT concentrations.^{157–159} Inversely, smoking seemed to be associated with increased levels of TT but not of FT.^{154,160} Therefore, the androgen bioactivity remains unchanged, which is caused by the increase of SHBG levels due to hepatotoxic effects of smoke.¹⁶¹ However, many studies have evaluated the effect of cigarette smoking on levels of male reproductive hormones, and findings still remain controversial.^{161–164}

Coffee consumption and physical exercise increased levels of TT and SHBG.^{154,160} Interestingly, with the aim to determine whether greater participation in healthier behaviors, (*i.e.*, refraining from smoking, maintaining physical activity, avoiding excessive alcohol consumption, eating more fish and less meat, avoiding adding salt to food, having a BMI < 25 kg/m², and consuming reduced-fat milk or skimmed milk) predicted reduced risk of subsequent lower circulating T in older men, Yeap et al. conducted a cross-sectional analysis of a population-based follow-up study concerning 3,453 men aged 65–83 years.¹⁶⁵ The results demonstrated that with a mean 5.7 years of follow-up, greater involvement in healthy lifestyle behaviors predicted higher T and SHBG levels. This relationship appears cumulative and may reflect an interaction between lifestyle and insulin sensitivity.¹⁵⁶ Successfully promoting healthy behaviors in older men could ameliorate the age-related decline in circulating T. Thus, even if smoking seemed to increase T levels, its deleterious effects on cardiovascular and respiratory health excludes it as an acceptable lifestyle intervention. However, it remains to be demonstrated whether prospective and RCTs investigating the effect of specific lifestyle interventions (*i.e.*, avoiding overweight) could prevent or ameliorate the decline in T levels during male aging.

Conclusion

T is often equated in the popular culture with the macho male physique and virility. Viewed by some as an antiaging tonic, the growth in T's reputation and its increased use by men of all ages has outpaced current scientific evidence. This review has demonstrated that further studies are needed to assess the efficacy and long-term effects of TRT in older men before the medical rationale of prescribing hormone replacement therapy for combating the adverse effects of aging can be established. Although promising, evidence for a definitive benefit or detriment is not conclusive, and treatment of late-onset hypogonadism is complicated. Finally, TRT should be only proposed and administered when the indication is clearly demonstrated and in the absence of

contraindications. In case of confirmed T deficit associated with some specific health outcomes, there is not any reason for throwing TRT back categorically. It is an effective medication responding to specific indications; however, these indications actually seem to concern only a very few men. Further research on physiologic regulation of endogenous levels, mechanism of action, and age-related changes in T levels also need to be addressed. There is still so much to learn about changes in endogenous T levels during aging and their impact on health outcomes.

Author Disclosure Statement

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Address correspondence to:
Pierre Olivier Lang
Hospital of Trois-Chêne
Chemin du Pont-Bochet
3 CH-1226 Thônex-Geneva
Switzerland

E-mail: pierre.o.lang@hcuge.ch

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