Diagnosis and Treatment of Testosterone Deficiency: Updated Recommendations From the Lisbon 2018 International Consultation for Sexual Medicine

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ABSTRACT

Introduction: The International Consultation for Sexual Medicine met in Lisbon in 2018 to review updated recommendations regarding testosterone deficiency (TD) and its treatment.

Aim: To provide updated clinical recommendations regarding TD and its treatment.

Methods: A Medline search was performed for testosterone (T) articles published since the 2015 International Consultation for Sexual Medicine report. Recommendations were presented at the Lisbon meeting, and feedback was incorporated into final recommendations.

Main Outcome Measures: Selected topics for these updates included terminology, clinical diagnosis, sexual function, prostate, cardiovascular, metabolic conditions, anemia, bone health, and therapeutic options.

Results: The terms "testosterone deficiency" (TD) and "testosterone therapy" (TTh) were endorsed over numerous competing terms. The wide interindividual variability of sex hormone binding globulin concentrations influences the interpretation of total T concentrations. Symptoms of T deficiency more closely follow free T than total T concentrations. Symptomatic men with total T <350 ng/dL or free T <65−100 pg/mL may reasonably undergo a trial of T therapy. An empirical 6-month trial of TTh may be considered in men with strongly suggestive symptoms and values above these thresholds. Morning blood testing is indicated in men <40 years of age. Men >40 years may undergo initial afternoon testing, as long as confirmatory morning blood tests are later obtained. High-level evidence demonstrates TTh in men with TD improves sexual desire and erectile function. The weight of evidence indicates that TTh is not associated with increased risk of prostate cancer, cardiovascular events, or worsening lower urinary tract symptoms. Bone density and anemia are improved with TTh. Obesity and type 2 diabetes are associated with TD, and TTh provides consistent improvement in metabolic parameters. Multiple safe and effective therapeutic options are available to treat men with TD.

Conclusions: Treatment of TD offers multiple benefits for sexual symptoms as well as for general health, without compelling evidence for increased risk of prostate cancer or cardiovascular events. **Morgentaler A, Traish A, Hackett G, et al. Diagnosis and Treatment of Testosterone Deficiency: Updated Recommendations From the Lisbon 2018 International Consultation for Sexual Medicine. Sex Med Rev 2019;7:636−649.**

Key Words: Testosterone; Hypogonadism; Testosterone Deficiency; Testosterone Therapy; Libido; Recommendations

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INTRODUCTION

Diagnosis and treatment of testosterone (T) deficiency (TD; also known as *hypogonadism*) has been evolving rapidly, especially in the past 4 years since the topic was addressed by the 2015 International Consultation on Sexual Medicine (ICSM) report, published in 2016.[1] Because of that report's comprehensive nature and the relatively short intervening time interval, we here provide an update on a selected set of topics, focusing primarily on areas where there have been significant new investigative results or important changes that impact clinical decision-making.

Recommendations have been a key feature of these ICSM reports and are again provided here (Table 1). However, because this report represents an update rather than a comprehensive review of the field, we offer recommendations only for the topics covered. Absence of comment on prior recommendations does not indicate agreement or disagreement.

METHODS

Authors were selected on the basis of their clinical knowledge, research expertise, or both. One author was assigned to write a draft for each section. The entire manuscript was then circulated to the entire writing group for comments and discussion. This material was then presented orally at the meeting of the ICSM in Lisbon, Portugal, in February 2018, and feedback from members was incorporated into the final version of the report. Recommendations were reached by consensus and were assigned a level of evidence (LOE). We recognize that controversy remains for some recommendations.

We have attempted to maximize readability of this document by sacrificing some degree of study details for the sake of brevity. Readers are encouraged to consult the primary literature sources for the full scope of a given study and to be able to draw their own conclusions.

The tremendous interest in the scientific community regarding T deficiency and T therapy is evidenced by a MEDLINE search using the terms testosterone (T), human, male, and clinical trials that revealed 309 published articles from January 1, 2015—April 30, 2019. Despite this wealth of new research, clinical practice in many instances remains based on old practices and attitudes and weak evidence. The goal of this report is to advance the field by drawing conclusions based on the best and most current available evidence in the contemporary medical literature.

Terminology

Many terms have been coined for the clinical syndrome associated with reduced serum T concentrations, leading to unnecessary confusion. We endorse the 2015 ICSM terminology of *testosterone deficiency* (TD) for the clinical condition, and T therapy (TTh) for treatment.[1] The term *testosterone deficiency* (TD) is preferred over terms such as hypogonadism, late-onset hypogonadism, adult-onset hypogonadism, and others, because of its clarity and simplicity.[2]

Other terms introduced or reintroduced over the last several years include "classical hypogonadism," which refers to a limited set of medical conditions long-known to cause reductions in serum T levels, and "functional hypogonadism," which refers to reductions in serum T levels noted in association with metabolic dysregulation or other conditions with the potential for improvement, in which case there may be amelioration of serum T concentrations.[3–9] Both of these terms make unnecessary value judgments about whether the observed TD merits treatment. By analogy, the term *hypertension* is well understood, regardless of whether there is an identified underlying cause and whether the hypertension may potentially be ameliorated by weight loss or stress reduction. For these same reasons of clarity and simplicity, TTh is preferred over T replacement therapy or T supplementation.[1,2] We believe the field will be enhanced by uniform adoption of this terminology.

In addition, we encourage simplifying the classification of TD into primary and secondary types and eliminating the term "mixed." Primary TD occurs when serum T is low and luteinizing hormone (LH) is elevated, indicating testicular insufficiency or failure. Secondary TD occurs when serum T is low and LH is normal or decreased, indicating an abnormality at the level of the hypothalamus, pituitary, or both.

Recommendation

1. Consistent use of the term "testosterone deficiency (TD)" is encouraged over the numerous other terms used for this condition (Expert Opinion).

2. Similarly, consistent use of the term "testosterone therapy (TTh)" is encouraged over other multiple terms (Expert Opinion).

3. Testosterone deficiency may be categorized as primary (low testosterone concentrations accompanied by elevated concentration of LH) or secondary (low testosterone concentrations accompanied by low or normal concentrations of LH) (Disease Classification).

Clinical Diagnosis

TD is a clinical condition characterized by low serum T concentrations and clinical manifestations consisting of symptoms, signs, or both. The most common and reliable symptoms are sexual.[10] These include reduced or absent libido, erectile dysfunction, difficulty achieving orgasm, reduced intensity of orgasm, and reduced sexual sensation in the genital region. Nonsexual symptoms include fatigue, lack of energy, decreased vitality, depressed mood, irritability, clouded cognition ("brain fog"), and decreased motivation. Signs of TD include anemia and decreased bone mass.

These symptoms may occur singly or in any combination. Decreased libido is one of the primary symptoms of TD.[10] It may occur, with or without any of these other symptoms or signs, and is strongly suggestive of TD in men >50 years without

Table 1. Recommendations

Terminology
1. Consistent use of the term, "testosterone deficiency (TD)", is encouraged over the numerous other terms used for this condition (Expert Opinion).
2. Similarly, consistent use of the term, "testosterone therapy (TTh)," is encouraged over other multiple terms (Expert Opinion).
3. Testosterone deficiency may be categorized as primary (low testosterone concentrations accompanied by elevated concentration of LH) or secondary (low testosterone concentrations accompanied by low or normal concentrations of LH) (Disease Classification).
Clinical Diagnosis
1. Testosterone deficiency is associated with a characteristic set of symptoms, of which sexual symptoms often predominate, including decreased libido (LOE 2, Grade B).
2. A total T threshold of 350 ng/dL (12.1 nmol/L) may be used as a practical guide, (LOE 3, Grade C).
3. Clinical presentation may aid diagnosis. Rigid application of diagnostic thresholds based on total T values is discouraged (LOE 2, Grade B).
4. The symptoms of TD correspond more closely to free T concentrations than total T concentrations (LOE 2, Grade B)
5. The clinical interpretation of total T is confounded by wide interindividual variability of SHBG concentrations (LOE 2, Grade B).
6. The diagnosis of TD may be made on the basis of free or bioavailable T concentrations, even if total T concentrations appear normal (LOE 2, Grade B).
7. Proposed diagnostic thresholds for free T by calculation or equilibrium dialysis range from below 65 pg/mL to below 100 pg/mL (225–347pmol/L) (LOE 3, Grade C).
8. An empirical trial of TTh may be offered for 6 months in a man with symptoms suggestive of TD but whose total or free T concentrations appear normal. Treatment should be discontinued after 6 months if no symptomatic benefit has been achieved (LOE 4, Grade C).
9. We recommend morning blood testing in men <40 years. For men >40 years, afternoon testing is permissible as long as a confirmatory morning blood test is subsequently obtained (LOE2, Grade B).
10. There is insufficient evidence as yet to recommend fasting state for testosterone blood testing (Expert Opinion).
Sexual Health
1. Sexual symptoms are a prominent presenting feature for men with TD (LOE 1, Grade A).
2. Testing for TD should be performed in men with decreased libido, erectile dysfunction, and difficulty achieving orgasm (LOE 2, Grade B).
3. Testosterone therapy may improve libido, erection quality, and other sexual symptoms (LOE 1, Grade A).
4. Testosterone therapy may salvage erectile function in men who have failed PDE5 inhibitors (LOE 2, Grade B).
Anemia and Bone Health
1. Testosterone levels should be determined in men presenting with unexplained anemia (LOE 2, Grade B).
2. Testosterone therapy should be considered as a possible treatment for anemia (LOE 2, Grade B).
3. Bone density testing with DXA should be considered in men diagnosed with TD. (LOE 2, Grade C).
4. T levels should be determined in men presenting with low-trauma fractures (LOE 2, Grade C).
5. Testosterone therapy increases BMD and bone strength (LOE 2, Grade A).
6. Reduced bone mass may be a reasonable indication for TTh even in a symptom-free man with TD (LOE 2, Grade C).
Prostate
1. Testosterone therapy does not appear to increase the risk of bothersome voiding symptoms (LOE 2, Grade B).
2. Testosterone therapy does not appear to increase the risk of developing a diagnosis of PCa (LOE 2, Grade B).
3. Current evidence suggests it may be reasonable to offer TTh to selected men with a history of PCa, particularly those who appear to be disease-free after definitive treatment of low-risk, localized disease. However, safety data are limited (LOE 3, Grade C).
4. Men with baseline serum T less than 250 ng/dL (8.7 nmol/L) are likely to exhibit a rise in PSA with TTh (LOE 2, Grade B).
Cardiovascular
1. The weight of evidence indicates TTh is not associated with increased CV risk (LOE 1, Grade A).
2. A number of studies indicate TTh may provide cardiovascular benefits (LOE 1, Grade A).
3. TTh improves a number of metabolic parameters associated with increased CV risk, such as fat mass, dyslipidemia, and insulin resistance (LOE 1, Grade A).
Metabolic conditions
1. Metabolic conditions, such as T2DM, obesity, and the metabolic syndrome, are associated with testosterone deficiency (LOE 2, Grade B).
2. Testing for TD should be considered in men with metabolic conditions (LOE 3, Grade C).
3. TTh causes reductions in fat mass, and increased lean mass (LOE 1, Grade A).
4. There may be a role for TTh in the management of metabolic conditions, including obesity (LOE 3, Grade C).

(continued)

Table 1. Continued

Treatment options
1. There are numerous testosterone formulations available in many countries, all of which may be used effectively to treat TD (LOE 2, Grade B).
2. Individual considerations should guide choice of treatment option (Expert Opinion).

CV = cardiovascular; DXA = dual x-ray absorptiometry; PDE5 = phosphodiesterase type 5; LH = luteinizing hormone; LOE = level of evidence; SHBG = sex hormone binding globulin; T = testosterone; TD = testosterone deficiency; TTh = testosterone therapy; T2DM = type 2 diabetes mellitus.

obvious other causes, such as major depression, relationship issues, stress, or use of medications known to influence libido, most notably selective serotonin reuptake inhibitors.[11,12]

An intense area of debate has been how to define who is a candidate for T therapy. It has been well acknowledged that the available data do not provide a clear threshold for total T that separates men who may benefit from TTh from those who may not.[2] This explains the lack of consensus regarding diagnostic criteria for total T among various guidelines and recommendations, because these thresholds are not evidence -based and thus are arbitrary.

There is growing awareness that total T concentrations are, at best, a rough guide to a man's androgen status, and, therefore, the traditional emphasis on total T contributes to the challenges of clinical diagnosis.

Data by Antonio et al[13] from the European Male Aging Studies showed that calculated free T corresponded with symptoms, whereas total T did not. This is consistent with the physicochemical properties of T, because unbound T is a lipophilic molecule which freely passes through cell membrane phospholipid bilayers into the cytoplasm of target cells, whereas T bound to sex hormone-binding globulin (SHBG) is unable to do so to any appreciable degree.[14,15]

An additional confounder with use of total T is the wide variability of SHBG concentrations. In a series of 1,000 consecutive men (mean age 53 years) presenting to a men's health center, the mean SHBG concentration was 31.8 nmol/L, yet the range varied nearly 20-fold, from 6−109 nmol/L. Concentrations were elevated in 9% of men 55 years and older, and 2% in men <55 years. A remarkably wide variation was noted in both younger and older men, which in turn has a strong influence on total T concentrations. A generous or elevated SHBG concentration will cause the total T concentration to appear normal even if free or bioavailable T concentrations are profoundly depressed.[16]

Although total T has long been the standard means to determine TD, current evidence argues for greater recognition of the role of free T for diagnostic purposes. Historical claims that free T assays are unreliable if not performed by the labor-intensive equilibrium dialysis method are contradicted by modern evidence that shows strong correlations ($r > 0.9$) between the direct analog test and calculated free T when compared with equilibrium dialysis.[17] Another factor that confounds the interpretation of testosterone levels is variability in androgen receptor sensitivity, based on CAG repeat polymorphisms.[18]

There are sufficient data to recommend 350 ng/dL (12.1 nmol/L) as a reasonable threshold to determine TD in the symptomatic man. However, rigid application of this threshold is problematic, because of a number of factors that confound the interpretation of total T, including variability of SHBG concentrations and variation in sensitivity of the androgen receptor on a genetic basis, as noted above.

Free T appears to be a useful indicator of androgen status, and there should be no hesitation on the part of clinicians to offer TTh to symptomatic men if free T is low and total T appears normal. Diagnostic thresholds for free T have not been rigorously determined; however, threshold values with a range of 65−100 pg/mL have been recommended[19] and appear reasonable. The three most commonly used methods to determine free T—direct, by calculation (calculated free T cFT), and by equilibrium dialysis—have been shown to provide highly correlated results,[20,21] and any of these may be used. Note that direct measurement provides numerical values that are approximately one-eighth of those observed with cFT and equilibrium dialysis.[21] A value <1.5 ng/dL by direct assay is approximately equal to cFT of 100 pg/mL and is suggestive of TD.[22] An empirical trial of TTh of 6 months may be offered to men with strongly suggestive symptoms and serum free or total T concentrations above recommended thresholds. If no symptomatic benefits are observed by 6 months, TTh should then be discontinued. Reference values for total and free T provided by individual laboratories vary widely and are not clinically derived; these should not be used to determine whether a man is a candidate for TTh.[23]

A new area of uncertainty is the traditional recommendation to obtain blood tests in the morning, based on diurnal variation in healthy young men in which the highest serum T concentrations are observed in the early morning.[24,25] This diurnal variation is markedly blunted in men >40 years.[26,27] In 1 U.S. study of 3,001 men ≥40 years, there was no change in mean serum T from 6:00 AM through 2:00 PM and only a 13% decline from 2:00 PM to 6:00 PM.[27] While some on our panel continue to recommend morning blood testing, it must also be acknowledged that the literature fails to demonstrate that doing so improves identification of men with TD, regardless of age, who might benefit from treatment.

There are also recent data indicating that a glucose load can reduce serum T compared with fasting.[28,29] It remains to be determined how this observation should impact clinical

recommendations as to whether serum T testing requires obtaining a fasting sample. Fasting samples may be useful for determination of blood sugar and lipids, which are key cardiovascular risk factors associated with TD.

Recommendations

1. Testosterone deficiency is associated with a characteristic set of symptoms, of which sexual symptoms often predominate, including decreased libido (LOE 2, Grade B).
2. A total T threshold of 350 ng/dL (12.1 nmol/L) may be used as a practical guide. (LOE 3, Grade C).
3. Clinical presentation may aid diagnosis. Rigid application of diagnostic thresholds based on total T values is discouraged (LOE 2, Grade B).
4. The symptoms of TD correspond more closely to free T concentrations than total T concentrations (LOE 2, Grade B)
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6. The diagnosis of TD may be made on the basis of free or bioavailable T concentrations, even if total T concentrations appear normal (LOE 2, Grade B).
7. Proposed diagnostic thresholds for free T by calculation or equilibrium dialysis range from below 65 pg/mL to below 100 pg/mL (225-347pmol/L) (LOE 3, Grade C).
8. An empirical trial of TTh may be offered for 6 months in a man with symptoms suggestive of TD but whose total or free T concentrations appear normal. Treatment should be discontinued after 6 months if no symptomatic benefit has been achieved (LOE 4, Grade C).
9. We recommend morning blood testing in men <40 years. For men >40 years, afternoon testing is permissible as long as a confirmatory morning blood test is subsequently obtained (LOE2, Grade B).
10. There is insufficient evidence as yet to recommend fasting state for testosterone blood testing (Expert Opinion).

TESTOSTERONE AND SEXUAL FUNCTION

Testosterone influences sexual function at multiple levels. In conjunction with sexual stimulation it facilitates increased release of neurotransmitters such as dopamine, nitric oxide, oxytocin, noradrenaline and serotonin, α-melanocyte−stimulating hormone, vasopressin, and ACTH.[30,31] The combined effects influence desire, erection, and ejaculation. Erection is enhanced by a positive effect of endothelial and neuronal nitric oxide synthases within the corpus cavernosum upregulating the cyclic GMP pathway, resulting in vascular smooth muscle relaxation and increased blood flow. Phosphodiesterase type 5 (PDE5) inhibitors function through enhancing cGMP persistence within the corpus cavernosum by reducing its degradation.[30,31]

Testosterone Deficiency and Sexual Symptoms

Sexual symptoms are a prominent feature of TD and are often the impetus for men in seeking medical attention.[32] The European Male Ageing Study studied >3,400 men across 8 European centers, concluding that the sexual triad of low desire, loss of nocturnal erections, and erectile dysfunction (ED) were the strongest predictors of TD.[10] Other sexual symptoms of TD include difficulty achieving orgasm, reduced intensity of orgasm, and reduced sexual sensation in the genital region. Zitzmann et al[33] studied 434 men with TD, reporting thresholds for symptoms, with sexual desire declining to <15 nmol/L but ED not appearing until levels fell below 8 nmol/L. Hackett et al[34] confirmed these findings in a study of 550 men with type 2 diabetes and TD, finding ED in 77%, with the influence of low T being seen below 8 nmol/L suggesting that vascular and neuropathic factors were major contributors to ED in men with type 2 diabetes (T2DM).

Sexual Benefits of Testosterone Therapy

Several recent clinical trials and meta-analyses have demonstrated important sexual benefits of TTh in men with TD[35−38]. A meta-analysis of placebo-controlled trials by Corona et al[35] revealed that men treated with TTh demonstrated greater improvement in sexual desire, erectile function, and greater sexual activity compared with men treated with placebo. Whereas mild ED may respond fully to TTh, additional therapies, such as phosphodiesterase type 5 (PDE5) inhibitors, may be required to treat more-severe cases of ED.[35] Other studies in men with T2DM suggest that the best sexual responses to TTh are seen with baseline levels <8 nmol/L. Sexual desire may improve rapidly, by 6 weeks, but ED improvement may take ≥6 months.[36]

The Testosterone Trials[37,38] involved 790 men ≥65 years assigned to either 1% T gel or placebo for 12 months. TTh was associated with increased sexual activity, libido, and erection quality. Greater improvements vs placebo were also noted for physical function, vitality, and mood, all of which may indirectly benefit a man's sexual function. Although clinicians have been aware of these changes for decades, this large, multicenter, prospective trial provides high-level confirmation of those observations.

Hackett et al[39] studied 200 men with TD and T2DM in a double-blind, placebo controlled study. Significantly greater improvement in erectile function was noted with TTh compared with placebo and was stronger for men with baseline T <8 nmol/L. Additional results included improvements in sexual desire, ejaculatory function, and intercourse satisfaction at 6 months.[36] Early improvement in sexual desire strongly predicted later improvement in ED.[39] A 12-month extension study revealed even greater improvement in erection quality with the addition of a PDE5 inhibitor to TTh. Long-term registry studies suggest that erectile function may continue to improve over several years with TTh.[39]

It has been recognized clinically that men with ED who have failed treatment with a PDE5 inhibitor can frequently be salvaged by correcting a TT of <12 nmol/L, although 1 trial showed significance only <10.4 nmol/L.[40] Failure of PDE5 inhibitors in these men may also be related to previously undetected low desire, ejaculatory or orgasmic function, or dislike of on-demand therapy. T therapy may potentially address these issues.[35]

Recommendations

1. Sexual symptoms are a prominent presenting feature for men with TD (LOE 1, Grade A).
2. Testing for TD should be performed in men with decreased libido, ED, and/or difficulty achieving orgasm (LOE 2, Grade B).
3. Testosterone therapy may improve libido, erection quality, and other sexual symptoms (LOE 1, Grade A)
4. Testosterone therapy may salvage erectile function in men who have failed PDE5 inhibitors (LOE 2, Grade B).

ANEMIA AND BONE HEALTH

Anemia

It has long been recognized that TD may be associated with anemia, and one of the oldest indications for the therapeutic use of androgens has been the treatment of anemia. This indication has largely been abandoned. Testosterone therapy is known to produce an increase in hematocrit and hemoglobin and may even cause erythrocytosis, particularly with parenteral TTh.[41] Anemia is common in the elderly and may be associated with weakness and frailty.[42] Its prevalence in men >50 years has been estimated at 11%[1] to 28%.[43] Anemia has been reported to be an independent risk factor for death.[44] The high prevalence of anemia should not be considered "normal aging"; rather, it is a sign of health deterioration and disease.[43]

The physiological mechanisms by which T influences erythropoiesis have not been fully established. Suggested mechanisms include myelostimulating effects by hematopoietic growth factors in bone marrow stromal cells[45] or influence on iron bioavailability.[46]

In the Testosterone Trials,[47] there were 126 men with anemia, with a mean age of 74.8 years. Treatment with T gel vs placebo resulted in a greater percentage of men demonstrating increased hemoglobin concentration >1 g/dL, in 54% vs 15%, respectively, and resolution of anemia in 58% for the TTh group compared with 22% for those who received placebo.

Bone Health

Sex steroids, including testosterone, are major determinants of bone turnover and remodeling. Multiple studies have shown an association between reduced bone mass and low T levels, and men with low bioavailable T have been shown to be at increased risk for non-vertebral fracture in the Osteoporotic Fractures in Men Study, involving 1,436 community-dwelling men ≥65 years.[48–50] In a clinical series of 339 young men <50 years with TD, dual x-ray absorptiometry revealed bone mass consistent with a diagnosis of osteopenia at the hip, lumbar spine, or both in 35.3% and osteoporosis in 2.8%.[51]

A number of studies have demonstrated a beneficial effect of TTh on bone density in men with TD.[52,53] Behre et al[53] showed that testosterone therapy significantly increased bone mineral density (BMD) in 72 hypogonadal men regardless of age. Aversa et al[54] reported that testosterone replacement in middle-aged men with TD significantly increased spine and femoral BMD after 3 years. Results from the Testosterone Trials showed that TTh was associated with greater increases than placebo for spine and hip BMD, as well as increased bone strength. The improvement in bone strength was more pronounced for the spine over hip.[55,56]

Recommendations

1. Testosterone levels should be determined in men presenting with unexplained anemia (LOE 2, Grade B).
2. Testosterone therapy should be considered as a possible treatment for anemia (LOE 2, Grade B).
3. Bone density testing with dual x-ray absorptiometry should be considered in men ≥50 years diagnosed with TD (LOE 2, Grade C).
4. Testosterone levels should be determined in men presenting with low-trauma fractures (LOE 2, Grade C).
5. Testosterone therapy increases BMD and bone strength (LOE 2, Grade A).
6. Reduced bone mass may be a reasonable indication for TTh even in an asymptomatic man with TD (LOE 2, Grade C).

PROSTATE

Ever since the work of Huggins and Hodges[57] in 1941, there has been concern that administration of T would increase the risk of prostate cancer (PCa), as well as benign enlargement of the prostate. This concept was widely taught for decades, yet was without evidentiary support.[58] Current research indicates that physiological levels of serum testosterone have already saturated prostatic androgen receptors, and even supraphysiological doses of TTh have a negligible stimulatory effect on the prostate.[59,60] The saturation point, namely the T concentration at which androgen binding to the androgen receptor is maximal, appears to be approximately 250 ng/dL (8.7 nmol/L). In a 6-month placebo-controlled T gel study, men with baseline T <250 ng/dL demonstrated significant increase in serum prostate-specific antigen (PSA) with TTh, but men with baseline T >250 ng/dL showed no increase.[61] A similar result was observed in a registry trial.[62] A saturation curve for PSA and T with a similar saturation point was observed in a series of 2,997 men presenting to an andrology center.[63] Marks et al[64] showed in a double-blind, placebo-controlled trial of 44 men with TD that T

injections for 6 months did not alter intraprostatic androgen levels, tissue biomarkers, or gene expression.

Benign Prostatic Hyperplasia

Several studies have shown no worsening of lower urinary tract symptoms (LUTS) for men who receive TTh, and several have reported improvement in LUTS.[64–70] In the Testosterone Trials, the number of men who developed a score >19 on the International Prostate Symptom Score questionnaire was nearly identical for those treated with TTh or placebo.[71] In a meta-analysis of 14 randomized controlled trials involving 2,029 men, there was no significant change in the international prostate symptom score among men who received TTh compared with men who received placebo.[72] The long-held belief that TTh will exacerbate LUTS because of enlargement of benign prostatic hyperplasia is not supported by current evidence.

Prostate Cancer

The evidence suggests that TTh is not associated with increased risk of developing PCa. In a population-based matched cohort study of men ≥66 years involving 38,340 men, the risk of developing a diagnosis of PCa was less for men treated with TTh than untreated control subjects, and greater duration of TTh was associated with greater reduction in risk.[73]

There is currently considerable interest in whether men with PCa may be candidates for TTh if they have TD. Testosterone therapy does not appear to increase cancer recurrence in hypogonadal men after radical prostatectomy[74] or treatment with radiation by external beam, brachytherapy, or both.[75] In one study, progression rates over 3 years were no different for 28 men on active surveillance who received TTh compared with 96 men who did not receive TTh.[76] Although there are no large prospective controlled trials regarding the risks of PCa recurrence or progression with TTh, the available evidence fails to support the long-standing prohibition against the use of TTh in men with PCa.

Recommendations

1. Testosterone therapy does not appear to increase the risk of bothersome voiding symptoms (LOE 2, Grade B).
2. Testosterone therapy does not appear to increase the risk of developing a diagnosis of PCa (LOE 2, Grade B).
3. Current evidence suggests it may be reasonable to offer TTh to selected men with a history of PCa, particularly those who appear to be disease-free after definitive treatment of low-risk, localized disease. However, data are limited (LOE 3, Grade C).
4. Men with baseline serum T <250 ng/dL (8.7nmol/L) are likely to exhibit a rise in PSA with TTh (LOE 2, Grade B).

CARDIOVASCULAR HEALTH

Substantial evidence has shown that testosterone deficiency is associated with increased risk of all-cause mortality, which can be accounted for mainly by cardiovascular deaths.[77–79] Populations of men with proven cardiovascular disease and who are at high risk of this condition, including those with T2DM and metabolic syndrome, have an increased prevalence of low testosterone levels.[80,81] Longitudinal epidemiologic studies have reported an increased number of major cardiovascular events in men with low testosterone levels.[82,83]

Chronic stable angina and chronic heart failure are 2 major serious clinical consequences of coronary heart disease. Both conditions significantly affect quality of life and cause recurrent hospital admissions. Testosterone therapy has been shown to have specific actions on improving exercise-induced cardiac ischemia (time to 1-mm ST depression) in men with chronic stable angina.[84,85] Testosterone appears to act as a coronary vasodilator, mediated by L-calcium blockade and potassium channel opening in vascular smooth muscle cells.[85] Chronic heart failure has a poorer prognosis than many cancers. Testosterone therapy promotes better functional exercise capacity, VO_{2max}, and cardiac output and reduced peripheral vascular resistance and can result in improved New York Heart Association Class of heart failure.[86]

Testosterone deficiency is associated with an adverse effect on key cardiovascular risk factors, which include dyslipidemia, hyperglycemia and insulin resistance, hypertension, and central obesity.[87] In men with type 2 diabetes or metabolic syndrome, TTh has, in the majority of studies, been reported to reduce waist circumference and percentage body fat and increase lean mass.[88] T replacement therapy also has beneficial effects on ameliorating insulin resistance, lowering total and low-density lipoprotein—cholesterol and atherogenic lipoproteins. Some studies, however, have reported a small reduction in high-density lipoprotein—cholesterol, whereas other trials show no change or an increase.[88] Testosterone also suppresses the production of proatherogenic cytokines and raises interleukin-10, an anti-atherogenic cytokine. Taken together, TTh has favorable actions on major elements that contribute to cardiovascular risk.[85]

Testosterone deficiency has an adverse effect on cardiac electrophysiology, causing prolongation of the QTc interval. A prolonged QTc increases the risk of ventricular tachycardia and fibrillation and Torsades de pointe. Atrial fibrillation is more common in men with low testosterone than in men who are on TTh.[89]

The risk of TTh on major adverse cardiovascular events (MACE), including death, has been a topic of considerable interest and investigation. Although most studies have reported reduced mortality rates and MACE with TTh,[90–92] a small number of studies have suggested increased cardiovascular (CV) risk with TTh.[93,94] Randomized controlled trials of ≤3 years' duration have not reported an increase in MACE either with or without pre-existing cardiovascular disease.[95,96] However, none were adequately powered to assess for cardiovascular safety. 1 randomized controlled trial in elderly men with frailty initiated therapy with high unlicensed testosterone doses and reported an increase with TTh in a wide variety of cardiovascular-related

adverse events, including a majority of questionable significance, such as non-specific changes on electrocardiography. However, there were few MACE, and this trial cannot be considered normal clinical practice.[97] A few observational studies have suggested the possibility of increased CV risk during the initial phase of TTh[98,99]; however, we note this was not observed in the Testosterone Trials. An intriguing study by Sharma et al[100] reported that normalization of serum T with TTh was associated with reduced mortality and MACE, whereas untreated men with TD and those who were treated but never achieved normalization of serum T were at increased risk.

A substudy of the Testosterone Trials reported greater increase in coronary artery non-calcified plaque volume in the T arm compared with in the placebo group. However, coronary calcium scores were unchanged and not different between groups. No MACE occurred in either group.[101] In the full study population for the Testosterone Trials, involving 790 men, the number of MACE were identical (n = 7) for the T- and placebo arms in the first year. During a second observation year without treatment, there were 9 MACE in the placebo arm and only 2 in the T arm.[37] A large observational study involving >38,000 men revealed that greater duration of TTh was associated with reduced cardiovascular events.[73] This study supports a potential role of TTh in the amelioration of atherosclerosis. Review of the cardiovascular literature since 2015 revealed that MACE were decreased with TTh in 5 studies, unchanged in 14, and increased in 0.[102]

Recommendations

1. The weight of evidence indicates TTh is not associated with increased CV risk (LOE 1, Grade A).
2. A number of studies indicate TTh may provide cardiovascular benefits (LOE 1, Grade A).
3. TTh improves a number of metabolic parameters associated with increased CV risk, such as fat mass, dyslipidemia, and insulin resistance (LOE 1, Grade A). .

TESTOSTERONE AND METABOLIC CONDITIONS

T is a metabolic hormone regulating carbohydrate, protein, and lipid metabolism. It is a key modulator of muscle growth and differentiation, and it inhibits adipogenesis.[85,102–112] The role of androgens in fuel metabolism is of paramount importance, with clinical implications regarding the metabolic syndrome (Met S), obesity, insulin resistance (IR), T2DM, and changes in body composition and anthropometric parameters.

TD is associated with reduced lean body mass, increased fat mass, hyperglycemia, hyperlipidemia, and IR, contributing to a host of metabolic dysfunction, including Met S. A large number of studies, including randomized clinical trials, observational and registry studies, as well as meta-analyses, have documented that TD is an independent risk factor for Met S.[113–116] Furthermore, a complex and multifactorial relationship between TD and obesity exist, suggesting that the relationship between TD and obesity/DM is bidirectional.[103,117] Considerable evidence exists suggesting that TTh ameliorates Met S components, improves lipid profiles, reduces blood glucose and glycated hemoglobin (HbA1c), improves insulin sensitivity, reduces inflammation, attenuates systolic and diastolic blood pressure and improves cardiometabolic functions.[109,112,118–121]

New provocative research indicates that TTh may offer benefits for men with obesity. A clinical cohort with follow-up of 8 years demonstrated large reductions in mean waist circumference and body fat,[122] with sustained, progressive weight loss of 19.3 kg over the 8-year span. This was associated with reductions in total cholesterol, low-density lipoprotein, triglycerides, and HbA1c.

Reduced T levels are associated with increased risk of T2DM,[123–131] and higher endogenous T levels were associated with a 42% lower risk of T2DM.[127] Men with type 1 diabetes mellitus do not appear to have a high prevalence of androgen deficiency.[128] Analysis[127] of several prospective studies[114,132–136] revealed that men with higher endogenous T levels had a 42% lower risk of type 2 diabetes compared with those with lower concentrations.

In a meta-analysis of controlled TTh trials, Corona et al[130] showed that TTh significantly reduced hyperglycemia and HbA1c and improved the HOMA-IR index. In obese men with TD, TTh produced significant reductions in weight and waist circumference and improved blood glucose and HbA_{1c} levels. In addition, TTh was associated with reduced serum concentrations of transaminases, suggesting a reduction in liver fat content, reduced inflammatory response, and improvement in liver function.

These results indicate that TTh has considerable metabolic activity that may offer important health benefits, especially for those with obesity and metabolic conditions, such as T2DM. At present, the data do not support the use of TTh in the treatment of T2DM. However, we note recent recognition of this interesting relationship between T and metabolic conditions noted by major medical groups[137,138] and the investigation of T therapy in a large diabetes trial.[139]

Recommendations

1. Metabolic conditions, such as T2DM, obesity, and the metabolic syndrome, are associated with TD (LOE 2, Grade B).
2. Testing for TD should be considered in men with metabolic conditions (LOE 3, Grade C).
3. Testosterone therapy causes reductions in fat mass, and increased lean mass (LOE 1, Grade A).
4. There may be a role for TTh in the management of metabolic conditions, including obesity (LOE 3, Grade C).

TESTOSTERONE THERAPY

Testosterone therapy is available in several forms, including a number of formulations introduced over the last several years. All

can increase testosterone levels and thereby address signs and symptoms of TD.

Parenteral injections

Injections of the testosterone esters—cypionate and enanthate—have been available for several decades and are generally administered intramuscularly at intervals of 1−2 weeks. Intramuscular injections of testosterone undecanoate are widely available as a depot formulation given every 12 weeks. A lower-dosage formulation available in the United States is administered every 10 weeks. A newly approved autoinjector device for T enanthate in the United States delivers weekly doses of 50−100 mg testosterone enanthate subcutaneously, enhancing ease of use for patients.[140] Injections are usually inexpensive and provide reliable absorption. Limitations include fluctuations in T levels among the short-acting formulations, but not the longer-acting T undecanoate, and greater risk of erythrocytosis than topical formulations.

Pellets

Testosterone pellets are not as widely available around the world as other forms of TTh. These are placed subcutaneously, usually in the buttock, and offer a long-acting form of TTh of 3−4 months. Advantages include relatively stable T concentrations and compliance. Disadvantages include the requirement for a small office procedure with local anesthesia and risks of hematoma, pellet extrusion, and infection.

Transdermal

There are multiple transdermal formulations, including patches, gels, creams, and liquids. These require daily application. Advantages include non-invasiveness and availability of dose adjustment. Disadvantages include less reliable absorption and the potential for transference to sexual partners and children via skin contact.

Nasal Gel

A recently introduced nasal gel provides good serum T concentrations without concerns of transference. It has a short half-life, requiring application 2−3 times daily. Preliminary studies indicate only minor suppression of gonadotropins, suggesting that this formulation may not suppress spermatogenesis as much as other forms of TTh.[141]

Oral

Oral alkylated T preparations have been available for many decades, but their use is now discouraged because of the risk of liver toxicity. Oral testosterone undecanoate is available in many countries and is not associated with liver toxicity, presumably because of its absorption via intestinal lymphatics, thereby avoiding first-pass liver exposure. Limitations include the need to take the medication together with a fatty meal to achieve adequate absorption.

Recommendations

1. There are numerous testosterone formulations available in many countries, all of which may be used effectively to treat TD (LOE 2, Grade B).

2. Individual considerations should guide choice of treatment option (Expert Opinion).

THE FUTURE OF TESTOSTERONE

Testosterone deficiency and its treatment has been a controversial topic for many years, yet there is now high-level evidence that TD is associated with major health risks, including death, and that TTh offers important sexual and general health benefits. As evidence mounts that TTh does not appear to be associated with PCa and CV risks, healthcare providers may feel more comfortable prescribing TTh to men with sexual symptoms.

New and provocative data suggest there may be a role for TTh in men with metabolic conditions, such as obesity and T2DM, and it may even provide cardioprotective benefits. New formulations are likely to provide ever-greater convenience and acceptability. Testosterone therapy is a valuable tool in the therapeutic armamentarium of healthcare providers, and its use alleviates symptoms in a large percentage of symptomatic individuals.

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