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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Testosterone and Cardiovascular Disease

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ABSTRACT

Testosterone (T) is the principal male sex hormone. As men age, T levels typically fall. Symptoms of low T include decreased libido, vasomotor instability, and decreased bone mineral density. Other symptoms may include depression, fatigue, erectile dysfunction, and reduced muscle strength/mass. Epidemiology studies show that low levels of T are associated with more atherosclerosis, coronary artery disease, and cardiovascular events. However, treating hypogonadism in the aging male has resulted in discrepant results in regard to its effect on cardiovascular events. Emerging studies suggest that T may have a future role in treating heart failure, angina, and myocardial ischemia. A large, prospective, long-term study of T replacement, with a primary endpoint of a composite of adverse cardiovascular events including myocardial infarction, stroke, and/or cardiovascular death, is needed. The Food and Drug Administration recently put additional restrictions on T replacement therapy labeling and called for additional studies to determine its cardiac safety. (J Am Coll Cardiol 2016;67:545–57) © 2016 by the American College of Cardiology Foundation.

Testosterone (T) is the principal male sex hormone, secreted primarily by the testes and, to a lesser extent, by adrenal glands. This hormone's androgenic effects are responsible for the maturation of male sexual organs, as well as for secondary sexual characteristics (growth of beard, axillary, and pubic hair, and deepening of voice). T is needed for the development of normal sperm production and contributes to sex drive. It also has anabolic effects, including promotion of muscle mass, strength, bone density, and maturation. T is also produced in small quantities in the ovaries; women have a much lower level of T than men. T levels decrease with age, and this decrease has been associated with an increase in atherosclerosis and cardiovascular risk. One might conclude that replacing T would reduce the risk; however, clinical studies on this concept have shown discrepant results. The purpose of this review is to discuss the basic endocrinology of T, hypogonadism in the young and the elderly, the association between low T and cardiovascular (CV) risk, and approaches to treating hypogonadism. This review will also discuss controversies regarding the administration of exogenous T to patients with hypogonadism, the use of T in heart failure, its effect on thromboembolism and ischemia/reperfusion injury, and recent changes in labeling for T replacement therapy (TRT).

THE HYPOTHALAMUS-PITUITARY-TESTES AXIS

The controller of the gonadal axis is gonadotropin-releasing hormone (GnRH), which is released from the hypothalamus (Figure 1). GnRH acts on the anterior pituitary to stimulate release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In men's testes, LH stimulates T synthesis by Leydig cells, and FSH stimulates spermatogenesis by

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ABBREVIATIONS AND ACRONYMS

6MWT = 6-min walk test

ADT = androgen deprivation therapy

CI = confidence interval

CV = cardiovascular

DHT = dihydrotestosterone

ECG = electrocardiogram

ED = erectile dysfunction

FDA = Food and Drug Administration

FSH = follicle-stimulating hormone

GnRH = gonadotropin-releasing hormone

HF = heart failure

LH = luteinizing hormone

MI = myocardial infarction

SHBG = sex hormone-binding globulin

T = testosterone

TRT = testosterone replacement therapy

Vo_2 = peak oxygen consumption

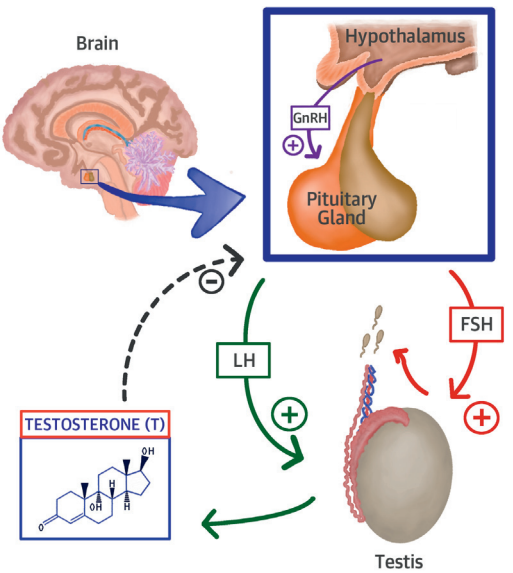
Sertoli cells. Only a small fraction of the total circulating T is in a free form, with the vast majority bound to sex hormone-binding globulin (SHBG) or albumin. Biologically active, free T binds to the androgen receptor present in the cytosol of most tissues (1). The T-androgen receptor complex then migrates to the nucleus, where it stimulates transcription of numerous genes. Interestingly, T serves as a prohormone for estradiol, via the action of the aromatase enzyme (present in many cardiovascular cell types), and dihydrotestosterone (DHT), via 5α-reductase activity. DHT is a more potent androgen than T, on the basis of its greater affinity for the androgen receptor and long residence time. However, circulating levels of DHT are generally one-tenth or less those of T. T, DHT, and estradiol then complete a negative feedback loop to the hypothalamus and pituitary. Several clinical conditions, including obesity, type 2 diabetes mellitus, hypothyroidism, polycystic ovarian syndrome, and nephrotic syndrome decrease SHBG levels (2), which can result in relatively more free T for any given total T. Older age, hyperthyroidism, and cirrhosis increase SHBG levels and can result in a free T concentration in the hypogonadal range, despite normal total T levels.

DEFINITION OF HYPOGONADISM

Male hypogonadism is the term used to describe a deficiency of T secretion from the Leydig cells of the testes (Figure 1). Depending on the pathophysiology, it may or may not be associated with infertility due to reduced spermatogenesis in the seminiferous tubules. Similarly, infertility may or may not be associated with hypogonadism. As an example, there are often microdeletions of the Y chromosome that are associated with male infertility, but with normal T synthesis.

Hypogonadism is classified as primary (testicular failure) or secondary, centrally mediated (hypothalamic or pituitary in etiology). Causes of primary failure include radiation therapy, trauma, infection (mumps), and ischemia (torsion). Common medications, including opioids, suppress release of GnRH from the hypothalamus, and glucocorticoids, which bind to the gonadotropic cell receptors, result in central suppression of the hypothalamus and pituitary. Milder forms of hypogonadism exist and are associated with aging and chronic disease.

FIGURE 1 GnRH Acts on the Anterior Pituitary to Stimulate Release of LH and FSH

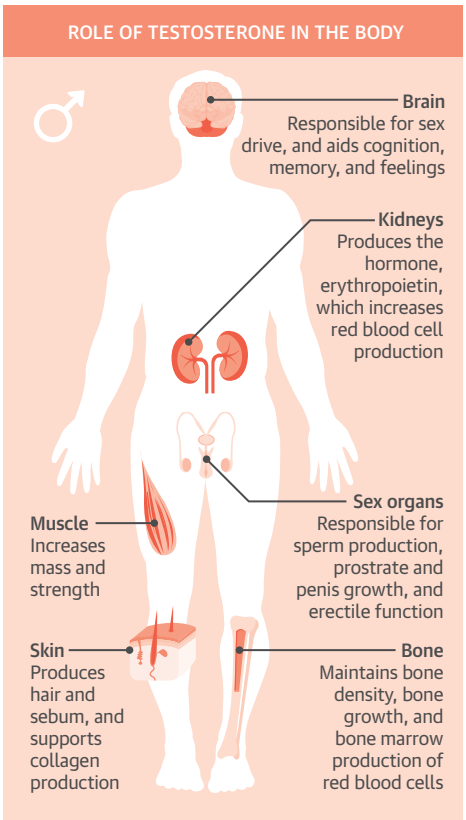


In men's testes, LH stimulates testosterone synthesis by Leydig cells, and FSH stimulates spermatogenesis by Sertoli cells. Testosterone then feeds back to the hypothalamus and pituitary, completing a negative feedback loop. FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; T = testosterone.

LABORATORY DIAGNOSIS. The laboratory diagnosis of hypogonadism requires documentation of low serum T levels on at least 2 morning samples drawn before 10 AM. Free T is considered the better test because total T can be elevated in situations of elevated SHBG (aging), or the total can be low when SHBG levels are reduced (diabetes, obesity). An analysis for FSH and LH should be done to distinguish between primary versus centrally mediated hypogonadism. If a pituitary tumor is of concern, then a prolactin level should be obtained. Although most agree that a total T of <300 ng/dl is considered low, it is best to use the normal ranges of the specific laboratory making the measurement.

SIGNS AND SYMPTOMS OF HYPOGONADISM. Signs and symptoms of hypogonadism (Central Illustration) are related to the patient's age. For example, delayed puberty is clearly a problem of congenital or childhood-associated hypogonadism. However, the changes in a post-pubertal male can be much more subtle. The Endocrine Society diagnostic guidelines for hypogonadism require both documentation of serum gonadal tests (at least 2 morning samples) and

CENTRAL ILLUSTRATION Testosterone Has Multiple Effects on the Body



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Testosterone affects the brain with stimulation of libido and aggression; muscle strength and mass; bone growth and density; sex organ growth, along with spermatogenesis and erectile function; kidney production of erythropoietin; and skin effects, including hair growth. T = testosterone.

the presence of symptoms (3). Specific signs and symptoms of male hypogonadism include vasomotor instability (hot flashes), decreased libido (4), and decreased bone mineral density (BMD) (5). There are clear data that T treatment will relieve hot flashes, improve libido, and increase bone mass (6). Similarly, there are consistent data from both the literature (7) and from studies of frail older men (8) that T therapy will increase lean body mass. In the recently published TOM (Testosterone in Older Men With Mobility Limitations) study, this increase in muscle mass translated to improved strength (8).

The data on erectile function generally show an improvement with T therapy, but the benefit is more pronounced in men with lower serum levels of T at baseline and in younger, healthier men, with little vascular disease.

Numerous studies have shown an age-related decline in both total and free T, even in the presence of an age-related increase in SHBG (9). The defect is thought to occur mainly at the level of the hypothalamus and pituitary gland, and is characterized as a blunted response to GnRH stimulation. Approximately 25% of men >65 years of age will have low total T levels, and at least 50% will have low levels when using free T as the diagnostic criterion.

Similarly, there are numerous chronic illnesses associated with reductions in serum T that can be attributed to inflammation with elevated cytokines. The frequency of male hypogonadism varies greatly on the basis of the population studied. It is no surprise that sicker men will have age-related declines. In population-based studies, the prevalence of hypogonadism is 54% in a hospitalized, ill population (10,11) and 50% among type 2 diabetes mellitus patients (12). As with age-related decline, it is unclear whether chronic illness-related decline should be treated with T therapy.

The less specific findings of reduced T levels include depression, fatigue, erectile dysfunction (ED), and reduced muscle mass. These nonspecific symptoms can be difficult to define in clinical trials. There is some improvement in the overall sense of well-being with T therapy (13), but the data are relatively few when it comes to randomized, placebo-controlled studies. One reason for this is the variability in age, symptoms, and serum T levels in the enrolled populations. It must be emphasized that the Food and Drug Administration (FDA) has never required that any new T product prove efficacy. The FDA only requires adequate pharmacokinetics.

LOW T LEVELS AND CARDIOVASCULAR RISK

As stated, serum T level declines gradually with age in most men (14). Epidemiological and observational studies have shown that low T is associated with increased CV disease risk (15–17). A meta-analysis of 70 studies indicated that patients with CV disease demonstrated significantly lower T and higher 17-β estradiol levels, which remained significant markers after adjusting for age and body mass index (16). In longitudinal studies, the baseline T level was lower in those with cardiovascular mortality.

Recent studies have described a relationship between low levels of endogenous T and atherosclerosis, coronary artery disease, or CV events. Men in the highest tertiles of T and bioavailable T had lower

relative risk of abdominal aortic atherosclerosis than men in the lowest tertile (18). Rosano et al. (19) found that patients with coronary artery disease had lower T levels than controls. Ohlsson et al. (20) observed that both serum T levels and SHBG levels were inversely related to the incidence of adverse major CV events. Hu et al. (21) described lower levels of T in men with coronary artery disease symptoms than in controls. Some studies have shown a negative correlation between the degree of angiographic coronary disease and T levels (19,21-23). In a recent paper, Alkamel et al. (23) described an association between low serum T levels and premature coronary artery disease in men 45 years of age and younger. Farias et al. (24) found a negative correlation between carotid intimal thickness and total T concentration in middle-aged men with type 2 diabetes. Patients who had low T levels were also more likely to demonstrate atherosclerotic plaques, endothelial dysfunction, and higher levels of high-sensitivity C-reactive protein. Lee et al. (25) observed a significant negative correlation between the level of total T and the Framingham Risk Score. Therefore, a host of observational studies suggest an association between low T levels and the presence of atherosclerosis, coronary artery disease, and coronary events. As recently stated by Shores and Matsumoto (26), "it is unclear if this is a causal association or due to low T being a biomarker of poor health."

THE USE OF TRT FOR YOUNG OR CONGENITAL HYPOGONADAL PATIENTS

Boys and men with a clear diagnosis of hypogonadism require life-long TRT. Examples include primary testicular failure from congenital causes, such as Klinefelter's syndrome (XXY), acquired testicular failure from mumps orchitis, or secondary testicular failure caused by alkylating agents.

For congenital causes, boys should start therapy about the time of normal puberty (i.e., <14 years of age) and continue for life. The type and route of administration for T is primarily of personal preference. Each differs by its pharmacokinetic profile or frequency of administration (27).

Caution should be used in the administration of T therapy to men who may be interested in fertility. One of the clear side effects of exogenous T is suppression of the endogenous gonadal axis, resulting in suppressed spermatogenesis.

THE USE OF TRT IN MATURE AND OLDER MEN WITH HYPOGONADISM

Age-related hypogonadism is common (28) and becoming more recognized, likely due, in part, to direct-to-consumer advertising. Various society guidelines emphasize the need to not only measure serum sex hormone levels (2 morning samples, a few days apart), but also to correlate them to symptoms and signs. Unfortunately, many of the symptoms are nonspecific, thus making it difficult to conclude whether the presenting clinical scenario is due to aging or hypogonadism.

The goal of TRT is to restore T levels to normal physiological ranges and to reverse the physiological effects of hypogonadism. Many placebo-controlled and noncontrolled trials have been carried out to investigate the effects of TRT in hypogonadal men and establish outcomes for the signs and symptoms that men experience from chronically low T (29). The most extreme example of acute hypogonadism is in men given androgen deprivation therapy (ADT) for prostate cancer (30,31). ADT has been shown to have severe adverse effects on metabolic markers, bone density, fatigue, sexual function, and even cognition. Reversing the effects with TRT and returning men to eugonadal levels of T has been clearly shown to reverse the effects of castrate levels of T achieved with ADT (32). In men with clinical hypogonadism without ADT, the studies of TRT have significant weaknesses, including a low number of subjects, variable selection criteria and definition of hypogonadism, dose of T, duration of administration, and outcomes measured (29).

TRT has been shown to improve symptoms of sexual dysfunction in men with significantly decreased T levels (33,34). Complaints of changes in sexual function, including ED, ejaculatory dysfunction, and reduced libido are among the most common presenting symptoms for hypogonadal men (34). The field of ED has reliable, validated instruments to assess symptoms of ED and its improvement with therapy, and several studies have demonstrated that T improves sexual dysfunction (35-38). Unfortunately, sexual dysfunction can also be caused by numerous other physiological abnormalities that result in either decreased vascular supply to the genitals or decreased libido (39). In addition, several studies have demonstrated the combination of TRT and a phosphodiesterase type 5 inhibitor to be beneficial for hypogonadal men with ED and have suggested an additive effect of these treatments (40,41).

Mood, depression, and cognition changes have been widely reported in association with hypogonadism (42,43). Studies have reported measurable depressive symptoms in men with significantly low T levels (43). The data on these changes and the benefits of TRT are less clear than with sexual dysfunction (44-48).

Fatigue is a common complaint of hypogonadal men seeking treatment (49,50). Fatigue and vigor improved in a placebo-controlled trial of TRT using a nonvalidated outcome instrument to assess fatigue (50).

TRT has been extensively studied for changes in muscle mass and body composition. The majority of these studies of body composition in hypogonadal men showed improvements by TRT in lean body mass with decreased fat mass (51–54).

In a recent study (55), those men treated with TRT and resistance training had a decrease in fat mass, and increases in lean mass and upper body strength compared with men taking placebo. In the TOM study of frail elderly men with mobility limitations, stair-climbing power, leg-press strength, and chest-press strength were significantly improved in men receiving TRT versus placebo (56). Spitzer et al. (57) reviewed TRT benefits on physical function, mobility, and frailty. Compared with men with normal T levels, hypogonadal men had poorer physical performance and mobility, and increased frailty.

In randomized, double-blind, placebo-controlled trials, TRT significantly increased BMD in hypogonadal men (58). Aversa et al. (59) evaluated effects of 36 months of TRT in a group of elderly men with mild osteopenia, metabolic syndrome, and T levels <320 ng/dl. BMD improved by 5% per year in the lumbar and femoral bone measurements. Because bone changes and osteopenia are often of long duration, TRT only results in a benefit for BMD when followed for more than 1 year. Although loss of height, fragility, fracture, and/or baseline abnormal dual-energy X-ray absorptiometry scan showing osteopenia are common indications for treatment (60,61), there are no data suggesting that TRT remedies bone fractures in fragile men (62). Thus, the use of bisphosphonates or other specific treatments has been advocated for true osteoporosis (63).

Hypogonadism is common in men with metabolic syndrome and type 2 diabetes mellitus, and is also associated with poor glycemic control, insulin resistance, visceral adiposity, and dyslipidemia (64,65). Diabetes mellitus is associated with hypogonadism in as many as 50% of patients with type 2 diabetes (50). In a recent review of 4 randomized clinical trials of TRT in hypogonadal men with type 2 diabetes mellitus, Corona et al. (66) reported that TRT contributed to reductions in fat mass, glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, and triglycerides, but produced no significant improvement in total and high-density lipoprotein, cholesterol, blood pressure, or body mass index. In a more recent meta-analysis of 5 studies of hypogonadal men with diabetes, Cai et al. (67) reported improvement in HbA_{1c}, fasting plasma glucose levels, fasting serum insulin, and triglyceride levels.

In summary, regardless of age, men with low serum T below the normal range and with convincing signs and symptoms of hypogonadism should be offered therapy. In all situations, there should be careful and thorough monitoring of complete blood count and prostate-specific antigen (PSA) for potential side effects. In addition, serum-free and/or total T levels should be monitored to ensure appropriate goal levels are met. Health care providers should discontinue T therapy, not only for adverse events, but also for lack of efficacy.

THE CONTROVERSY REGARDING THE EFFECT OF TRT ON THE CARDIOVASCULAR SYSTEM

Whereas most epidemiological studies have suggested that low T is associated with increased atherosclerotic disease (68), there is a raging controversy about the effects of TRT on CV events and mortality. Meta-analyses published between 2005 and 2010 (69–71) show that TRT, in general, had neutral effects on the occurrence of major, adverse CV events; T did increase hematocrit and hemoglobin, and had various small effects on lipid levels.

A paper by Basaria et al. (56), published in 2010 in the *New England Journal of Medicine*, entitled "Adverse Events Associated With Testosterone Administration," was the first of 3 original papers to warn physicians that there could be a potential issue regarding the administration of T and CV safety. The TOM trial was a placebo-controlled, randomized study designed to assess the effects of administering exogenous T gel or placebo on physical functioning and lower extremity strength in men 65 years and older who had baseline limited mobility and low total serum T levels. Adverse events were monitored by a data and safety monitoring board that stopped the study early because of a higher rate of CV events in the treated group. The men who received T did demonstrate greater increases in leg-press strength and other measures of muscle strength. However, 23 men in the T group versus 5 in the placebo group demonstrated CV-related adverse events of variable clinical importance. Some were major events, such as myocardial infarction (MI) (2 in the treated group), but others were softer endpoints and may not have been truly cardiac or may have been unrelated to the medicine (syncope, edema, ectopy on electrocardiogram [ECG], left ventricular strain pattern on an ECG, tachycardia with fatigue, carotid bruit, elevated blood

pressure). Limitations of this study have been pointed out, including that the participants had a high prevalence of chronic conditions, including pre-existing CV disease and risk factors for CV disease, and represented one population of older, immobile men, who received, in general, very high doses of T. It is not possible to extrapolate these findings to other formulations or doses of T, or to men with hypogonadism who do not have underlying CV disease, risk factors for CV disease, or mobility issues.

Vigen et al. (72) studied the relationship between T therapy and all-cause mortality, MI, and stroke in a population of male veterans. The study was a retrospective cohort analysis of men with low T levels (<300 ng/dl) who underwent coronary angiograms in the Veterans Affairs system. The primary outcome was the composite of all-cause mortality, MI, and stroke. At 3 years, Kaplan-Meier estimated cumulative percentages with the primary outcome were 19.9% in the no-T group and 25.7% in the T group. T was associated with an increase in events.

This paper has stirred much discussion. Some investigators pointed out that the raw data, before various statistical adjustments, actually showed an outcome that favored T (73-77). In their paper, the investigators state: "Of the 7486 patients *not* receiving T therapy, 681 died, 420 had MIs, and 486 had strokes" [italics added] (72). Therefore, 681 + 420 + 486 = 1,587/7,486 = 21% of patients not receiving T had an event. The investigators also state: "Of the 1223 patients receiving T therapy, 67 died, 23 had MIs, and 33 had strokes" (72). Therefore, 67 + 23 + 33 = 123/1,223 = 10% of patients receiving T had an event. Thus, if one looks at the raw numbers, T was associated with an event rate that was reduced by more than one-half, and it was not until statistical manipulations were performed that the opposite conclusion was reached. Other criticisms of this paper included the concern that men with MI or stroke who were given T after these events were excluded from analysis. However, had they been included, the rate of events in the no-treatment group would have been substantially increased. Starting on T did not ensure that it would be continued: 17.6% of patients in the T group had only 1 prescription filled, and only 60% of patients had follow-up T levels determined after therapy had started. In those patients that did have post-treatment levels determined, the average treatment level was only 332 ng/dl, which is lower than the usual therapeutic target level. Using patches in a large number of patients (63% of those on T) is problematic, as many patients suffer local reactions to the patches. The investigators have printed some corrections to the study, yet some investigators have called for retraction of this paper (78). The debate continues.

A third study that has contributed to the controversy regarding the safety of T was a paper published in 2014 by Finkle et al. (79). This was a cohort study that described the risk of developing a nonfatal MI after an initial prescription for TRT. The data were obtained from a large health care database and included 55,953 patients who received T. The investigators compared the rate of nonfatal MI in the 90 days after the initial prescription for T to the rate in the year before the prescription. The investigators found that for all T prescription subjects, the rate ratio (post/pre) was 1.36 (95% confidence interval [CI]: 1.03 to 1.81). The rate/ratio was even higher in men 65 years of age and older, at 2.19 (95% CI: 1.27 to 3.77); for men 75 years of age and older, it was 3.43 (95% CI: 1.54 to 7.56). For men younger than 65 years of age, the increased risk of developing a nonfatal MI was only observed in men with previous histories of heart disease. Whereas one of the strengths of this study was the large number of patients who were analyzed, its limitations included that the diagnostic indications for using T were not reported, and pre- and post-treatment drug levels of T were not available (78-80). In addition, T exposure was defined as a patient who had received a prescription for T. It is not known whether the patient, once receiving a prescription, actually had it filled, used it, or obtained and used refills. Data on nonfatal MI were captured, but data on other major adverse CV disorders (fatal MI, CV mortality, stroke) were not captured in this analysis. Three months is a relatively short time, and follow-up may not have been adequate.

A very recent study compared CV events in men receiving various forms of T therapy. Injection therapy was associated with higher event rates than topical gel or topical patches. However, this study did not have a control group for comparison, making interpretation incomplete (81).

Despite these recent studies showing an association of adverse CV outcomes to exogenous T use, there are an equal number of studies showing just the opposite. Shores et al. (82) reported an observational study of 1,031 male veterans, 40 years of age and older, who had low total T levels. Of the 1,031 men, 39% received T therapy as part of their routine medical care. Over an average follow-up time of 41 months, the death rate was 20.7% in men who did not receive T, and there were 5.7 deaths per 100 person-years; in men receiving T, the death rate was significantly lower, at 10.3%, and there were 3.4 deaths per 100 person-years. Even after the investigators adjusted for a number of confounding variables, the

risk of death was lower with T. The investigators pointed out many of the limitations of the study, including that it was observational, and bias may have been introduced. For example, physicians may have selected healthier men to receive T treatment. Other limitations were that study entry was based upon a single level, rather than at least 2 levels, as suggested by clinical guidelines; the investigators did not uniformly obtain T levels in the morning; levels of free T were not obtained; and symptoms of low T were not determined. The investigators do point out that in a prior study of the same patient group, the most common reasons for obtaining T levels were sexual dysfunction, osteoporosis, and urologic or endocrine disorders (83).

Baillargeon et al. (84) reported the risk of MI in a cohort of men 65 years of age and older receiving T, using a national sample from the Medicare beneficiary database. They identified 6,355 men who had received at least 1 intramuscular T treatment between January 1, 1997, and December 31, 2005, and then matched this cohort to 19,065 men who had not used T. The investigators reported that there was no increased risk of MI associated with T use. Of note, for men in the highest quartile of risk for MI, T therapy was associated with a lower incidence of MI. The investigators pointed out some of the limitations of their study. Their information on risk factors and outcomes were derived from diagnostic codes and charges for outpatient and hospital services; other formulations of T therapy were not assessed; and they did not determine use of other agents that may have reduced MI risk. Furthermore, their analysis did not capture medicines received outside the health plan. Baseline T levels were not available in the Medicare claims database. Because this was an observational study, selection bias might have been present.

There have been a few clinical trials that have focused on the use of T replacement therapy in hypogonadal men with diabetes or metabolic syndrome (85–87). These studies suggested that TRT reduced insulin resistance (85,87), improved survival, reduced major adverse CV events (85), and reduced ischemic burden (86) on ambulatory ECG monitoring (87).

Results of recent meta-analyses on the effects of TRT on CV risk have been contradictory, with one suggesting that TRT increases adverse CV events in studies not funded by pharmaceutical companies (88), and another showing that T was not associated with major adverse CV events and was actually protective in men with metabolic syndrome (89).

At the present time, the issue of the CV safety of T remains controversial (77,90–92). Some of the major reasons might include differences among the trials in inclusion and exclusion criteria; baseline T levels and degree of clinical hypogonadism; age; weight; underlying CV risk factors; patient mobility; duration of the study; variability in the definition of major adverse CV events; variability in the type of T preparation used (81); and lack of follow-up on T levels after starting TRT. However, 1 recent retrospective study examined the effect of TRT on normalization of total T levels and the effect of therapy on major CV outcomes. Sharma et al. (93) studied male veterans with low total T levels and described the association of TRT with all-cause mortality, MI, and stroke in 3 groups: those not receiving TRT; those receiving TRT and achieving a normal total T level; and those receiving T and failing to achieve a normal T level. Patients who received TRT and achieved normal levels had significantly lower all-cause mortality, lower risk of MI, and lower risk of stroke compared with patients who either were not on TRT or those on TRT who did not achieve a normal total T level.

Other reasons for discrepancies in published reports might relate to the type of T that is measured. Some investigators think that free T or bioavailable T levels should be measured, as well as total T. The types of statistical analyses in these studies were variable, and as pointed out, 1 study showed raw numbers that favored T therapy, whereas extensive statistical recalculation showed a detrimental effect of this therapy (72,73). The lack of prospective, double-blinded, placebo-controlled, randomized trials, in which major adverse CV events are a primary endpoint makes it difficult to determine the effect of T on the CV system. The National Institutes of Health-sponsored Testosterone Trials (T Trials), prospective, randomized studies of testosterone gel, were recently completed and included a trial evaluating the CV effects of T (94). The results will provide further assessment of CV risk after treatment with T.

PROPOSED PROSPECTIVE STUDY

A proposed study to definitively answer the question of whether TRT has adverse effects on CV safety is needed. It should be a large, prospective, randomized, placebo-controlled, double-blinded, long-term study (at least 1 year and preferably longer). Entrance criteria should require the men to have symptomatic hypogonadism, verified by low T (total, free, bioavailable) levels obtained on at least 2 separate morning blood draws. At least 2 T-type preparations should be studied (intramuscular injections and

gel formulation would be the 2 most likely candidates). Follow-up T levels should be monitored throughout the study. Major adverse CV/cerebrovascular events (MI, stroke, CV death) should be the primary endpoint and should be carefully defined. Secondary endpoints should include the individual components of the primary endpoints, hospitalization for acute coronary syndrome and/or heart failure, patient's vital signs (heart rate and blood pressure), ECG, as well as prostate abnormalities. Other secondary endpoints should include efficacy measures for T, such as questionnaires related to sexual health (libido and erectile function), tests of muscle strength, muscle mass, adiposity, effects of T on lipid and glucose levels, as well as insulin resistance, PSA, and other biomarkers. This proposed study should include thousands of patients studied over several years and, as it would be very expensive to carry out, include a consortium of pharmaceutical companies or government support, or perhaps a hybrid of support mechanisms.

POTENTIAL FUTURE CARDIOVASCULAR USES OF T

Besides safety issues of T, there has also been interest in its use as a potential therapy for certain CV disorders. These include using T for heart failure, angina, and ischemia/reperfusion injury.

T THERAPY IN HEART FAILURE WITH REDUCED EJECTION FRACTION

T deficiency (total and estimated free T) has been demonstrated in 26% to 37% of male patients with chronic heart failure (HF) with reduced ejection fraction (95-97). Reduced T levels are associated with increased systemic vascular resistance, lower heart rate variability, and depleted baroreflex sensitivity (98,99). In addition to the chronic anabolic state seen in HF, the reasons for reduced T levels are likely multifactorial, with hepatic congestion leading to an increase in SHBG levels, with a subsequent decrease in free T levels (100,101). Low T is frequently associated with impaired exercise tolerance and can exacerbate symptoms in patients with HF with reduced ejection fraction (101). The physiological pathways have not been fully delineated, but suggest a contributing role for reduced T in the symptomatic decline seen in HF. In men with HF, the rise in T levels seen with replacement therapy is a significant predictor for an increase in peak oxygen consumption (Vo_2) on exercise testing (102). T, administered intravenously, will acutely increase cardiac output and reduce peripheral vascular resistance (103). During chronic replacement, T therapy can reduce circulating levels of inflammatory mediators, including tumor necrosis factor alpha (TNF-alpha) and interleukin-1beta, thus potentially leading to a reduction of left ventricular muscle fibrosis (104).

EFFECT OF T SUPPLEMENTATION IN PATIENTS WITH SYSTOLIC HF

Toma et al. (105) conducted a meta-analysis of randomized controlled trials evaluating the effect of TRT on exercise capacity in HF patients. The 4 studies (N = 198; men, 84%; mean age 67 years) tested either transdermal or intramuscular T, given between 12 weeks to 12 months, and included an endpoint of a 6-min walk test (6MWT), incremental shuttle walk test, or peak Vo_2 by cardiopulmonary exercise test. They reported that 6MWT increased by 54.0 m, incremental shuttle walk test increased by 46.7 m, and peak Vo_2 increased by 2.7 ml/kg/min in the TRT patients versus placebo. The increase in peak Vo_2 and distance walked in the TRT group correlated with the increase in free or bioavailable T (105). This degree of improvement in the 6MWT is similar to that seen with other therapies in patients with HF. Interestingly, neither left ventricular ejection fraction (106-109) nor B-type natriuretic peptide (104,106) changed significantly in any of the studies in which they were reported. New York Heart Association functional class improved by ≥1 grade in 9.8% of patients in the placebo groups versus 35% of patients in the TRT group. There were no significant differences in major adverse cardiac events between the TRT and placebo groups (105). The results are likely relevant to women, on the basis of the suspected mechanisms of action and the corroborative results seen in 1 study that included only female patients with HF (107).

T IN MYOCARDIAL ISCHEMIA/REPERFUSION

Nicolli et al. (110) showed that patients who presented with ST-segment elevation MIs with angiographic or electrocardiographic evidence of microvascular obstruction were more likely to have low T levels than those without microvascular obstruction. This correlates with findings suggesting that T can induce relaxation of the coronary arteries (111). Malkin et al. (112) studied the effect of TRT in 10 men with ischemic heart disease and low T levels. Following 1 month of therapy, TRT had improved time to a 1-mm ST-segment depression on a Bruce protocol exercise treadmill test (increased by 74 s), improved mood assessed by questionnaire, reduced total cholesterol, and reduced serum TNF-alpha (one marker of inflammation). In a follow-up study, Mathur et al.

TABLE 1 Testosterone's Role in Therapy of True Symptomatic Hypogonadism in Young and Older Men

Organ	Young Men	Older Men	Ref. #
Libido	++	++	33–38
Erectile function	++	++	33–38
Cardiovascular	+	+	69–71
Mood	+	+	42,43
Cognition	+	+	47,48
Energy	+	+	49,50
Bone mineral density	++	++	58–63
Fat mass	++	++	54
Hematopoiesis	++	++	69,71
Muscle mass	++	++	53–55
Muscle strength	++	++	54–56
Insulin sensitivity	+	+	67
Sperm count	– –	– –	121

++ = strong evidence of positive effect; + = weak evidence of positive effect; – – = strong evidence of negative effect; – = weak evidence of negative effect.

(113) tested the effect on ischemia of TRT during 12 months of treatment. Long-term treatment with T again increased time to develop ischemia on a treadmill (129 s in T patients vs. 12 s in placebo patients, p = 0.02). Some, but not all, experimental animal studies have suggested that T administration might reduce myocardial infarct size. Herring et al. (114) and other scientists have recently reviewed these studies (115). In the Kloner laboratory, administration of T starting 1 week before experimental MI in the rabbit had a neutral effect on MI size, but did shorten the QT interval corrected for heart rate (116). Larger studies are needed to determine whether T has future potential as an anti-ischemic, antianginal therapy.

T AND DEEP VENOUS THROMBOSIS

The FDA label for T formulations includes venous thrombosis as a potential consequence of polycythemia that sometimes occurs in response to TRT. The FDA recently instructed manufacturers to broaden the T label warning of venous thrombosis to include risk, without necessarily having polycythemia. The broadened warning regarding venous thrombosis is on the basis of reports of venous thrombosis unrelated to polycythemia and from observational studies. One such study was a series of 9 patients reported to have a deep vein thrombosis or pulmonary embolism temporally related to T use (117). However, a case-controlled study of 30,572 men, 40 years of age or older, showed that T therapy in the 15 days before the event or index date was not associated with increased risk for venous thromboembolism and was not associated with administration route. When the exposure window was expanded to 30 or 60 days before the event, the study results did not significantly change (118). There are no prospective studies showing an association between T supplementation and venous thrombosis. Thus, the effect of T on the risk of venous thrombosis, beyond the impact of polycythemia, is unclear.

FDA-MANDATED CHANGE IN LABELING FOR TRT

On September 17, 2014, the U.S. FDA convened an advisory committee to review the use of TRT and its CV risks. The committee was asked to give an opinion on the current indications for TRT and whether manufacturers of T products should conduct studies to assess CV risks with the use of TRT. The committee

TABLE 2 Cardiovascular Effects of TRT

Cell/Tissue	Physiological Effect	Clinical Effect	Ref. #
Endothelial function	Enhanced vasodilatation	Increased peripheral and coronary blood flow	111,112
Hemodynamics	Decreased SVR Decreased LVEDP	Increased cardiac output	103,111,115
CV inflammation and atherosclerosis	No consistent data on CIMT, CRP, IL-1β, IL-6, IL-10, TNF-α	None	104
Conduction tissue	Decreased action potential duration and early afterdepolarizations	Shortens QTc interval, resulting in improved antiarrhythmic substrate	116
Lipid levels	No consistent effects demonstrated	None	69–71
Myocardial protection	Activation of STAT3	Decreased reperfusion injury	115
Atheroma	No consistent effect on VCAM1	No consistent effect on atherogenesis	113
Hemostasis	Increased TXA2 platelet aggregation	Thrombosis	117

CIMT = carotid artery intima-media thickness; CRP = high-sensitivity C-reactive protein; IL = interleukin; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; QTc = QT interval corrected for heart rate; STAT3 = cardioprotective signal transducer and activator of transcription; sVCAM-1 = soluble vascular cell adhesion molecule-1; SVR = systemic vascular resistance; TNF = tumor necrosis factor; TRT = testosterone replacement therapy; TXA2 = thromboxane A2 receptor expression; VCAM1 = vascular cell adhesion molecule 1.

panel concluded that there was not enough evidence that TRT was a significant CV risk for any given group of patients treated with TRT. The committee commented, however, that TRT safety in high CV-risk groups, such as older, diabetic, and obese men, needed further studies (119).

In March 2015, the FDA clarified recommendations for the use of TRT (120). They stated that TRT is approved only for men with documented low T caused by specific medical conditions. They also wrote that the benefits and safety of TRT are not clear for the aging male with low T, even if symptomatic.

In June 2015, the FDA further required manufacturers of TRT products to change their labeling to include additional warnings (119). These caveats included: TRT is indicated for replacement therapy only in males with conditions associated with a deficiency in endogenous T, specifically primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired). Before initiating TRT, providers must confirm the diagnosis of hypogonadism by measuring serum T in the morning on 2 separate days and confirm that these levels are below the normal range. Providers should make patients aware of the possible increased CV risk when initiating TRT (119). These recommendations on the product package inserts have stimulated insurance carriers to require similar measurements and documentation of cardiac health before paying for TRT.

CONCLUSIONS

Testosterone has a role in therapy of true symptomatic hypogonadism in both young and older men (**Table 1**). There appear to be no major concerns for using T in young, healthy men with specific indications for TRT. Testosterone has specific effects on the CV system (**Table 2**). The use of T in older men and those with known coronary artery disease is controversial. Asymptomatic, middle-aged and older men without a history of heart disease should be counseled about the uncertain CV risk. Randomized, controlled trials are needed. Finally, in our opinion, patients with recent MI, revascularization, poorly controlled HF, or stroke within the last 6 months are not good candidates for the initiation or maintenance of TRT, given the uncertainty of CV risk.

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