

Age-Related Testosterone Deficiency Merits Treatment

Abdulmaged M. Traish^{1,2,*}

Abstract

The negative effects of testosterone deficiency (TD) on human health and quality of life are well demonstrated, including signs, symptoms, metabolic syndrome, obesity, and increased mortality. Recently, substantial evidence emerged, demonstrating the benefits of testosterone therapy in men with classical and “age-related” hypogonadism. The US Food and Drug Administration (FDA) opposes testosterone therapy in men with age-related hypogonadism but not in men with classical hypogonadism. The FDA acknowledges that TD merits treatment, but the FDA made an artificial distinction between diagnoses where T treatment is warranted and others where the underlying diagnosis is unknown, and treatment is unwarranted. The FDA labeled the unknown category as “age-related.” Since the FDA is unable to demonstrate that one group differs in benefits or risks from the other, there are no bases for this distinction. This action by the FDA is not based on scientific or clinical evidence. There is no evidence that the response to testosterone therapy of “age-related” hypogonadism occurs via different physiological or biochemical mechanisms than those historically recognized conditions. Also, there is no evidence that “age-related” hypogonadism responds less well to testosterone therapy than “classical” hypogonadism. More importantly, there is no scientific or clinical evidence to suggest that the risks of testosterone therapy in men with “age-related” hypogonadism are worse or different for men with “classical” hypogonadism. For these reasons, we disagree with the FDA position on testosterone therapy in age-related hypogonadism.

Keywords: testosterone deficiency; classical hypogonadism; age-related hypogonadism, testosterone therapy

Introduction

Hypogonadism (henceforth referred to as “testosterone deficiency”) is a clinical syndrome characterized by low serum testosterone (T) and a host of clinical signs/symptoms.¹ T deficiency (TD) occurs as a result of testicular (primary) or pituitary/hypothalamic dysfunction (secondary) and is known historically as “classical” TD, or as a result of unknown underlying pathologies.

Although aging alone does not necessarily cause a significant decline in T levels,^{2–9} the predominant form of TD, in aging men, is mixed with primary and secondary

hypogonadism components, attributed to varying pathophysiology and comorbidities. Luteinizing hormone (LH) levels can vary in older men based on decreased numbers and function of Leydig cells, decreased sensitivity of the hypothalamus–pituitary gonadal axis to feedback inhibition, and/or decreased LH pulse amplitude despite normal pulse frequency. Decreased LH pulse amplitude may potentially be related to reductions in neuronal cell secretion of gonadotrophic-releasing hormone.^{10,11}

“Age-related” hypogonadism (TD) is defined as “a clinical and biochemical syndrome associated with advancing

Departments of ¹Urology and ²Biochemistry, Boston University School of Medicine, Boston, Massachusetts, USA.

*Address correspondence to: Abdulmaged M. Traish, MBA, PhD, Department of Urology, Boston University School of Medicine, 72 E. Concord Street, A502, Boston, MA 02118, USA, Email: atraish@bu.edu

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age, characterized by specific symptoms, and a deficiency in serum testosterone (T).¹² This syndrome, which often occurs in middle-age and older men, is often referred to as adult-onset hypogonadism.¹³ This syndrome does not meet the criteria for either *classical* primary (testicular failure) or secondary (pituitary or hypothalamic failure) hypogonadism. However, it exhibits elements of both presentations.¹³ It is noteworthy that the signs and symptoms of TD and the response to treatment are similar, irrespective of the underlying causes (Table 1).¹² It should be noted that “age-related hypogonadism” may be a misnomer since not all healthy men experience decline of T, as they age.²⁻⁹

“Age-related hypogonadism” was introduced by Nguyen and his colleagues in their perspective published in *New England Journal of Medicine (NEJM)*¹⁴ stating the position of the US Food and Drug Administration (FDA) on this important clinical issue. In this perspective, the authors strongly expressed concerns on “Testosterone and Age-Related Hypogonadism.” Henceforth, in this article, the use of “age-related hypogonadism” is to maintain consistent reference to the FDA original argument against the use of T in older men.

The FDA issued a statement in March 2015 opposing the use of T therapy (*TTh*) in the treatment of hypogonadism attributed to aging, without a defined cause. The FDA position on “age-related” TD is that this condition does not merit treatment.¹⁴ We disagree with the FDA position on this very point. Given next is a summary of the rationale as to why this condition should be treated as any other clinical condition.

On October 1, 2015, an international expert consensus panel convened to discuss the negative impact of TD on human health and quality of life and evaluated the merits of TTh in men with TD. The panel unanimously approved nine resolutions suggesting that: (1) symptoms and signs of TD occur as a result of low T and may benefit from T treatment regardless

of whether there is an identified underlying etiology; (2) there is no scientific basis for any age-specific recommendations against the use of T therapy in men.

Evidence for Benefits of T Treatment in Older Men with TD

TTh in men with TD has been clinically utilized since the 1940s with marked success¹⁵⁻¹⁷ and became FDA approved in the United States in the 1950s. *TTh* for TD has long been considered the standard of care. The main argument advanced by the FDA is that, although *TTh* is indicated for men with “classical” TD, there are insufficient data to support the use of *TTh* in men with “age-related” TD.¹⁴ Nevertheless, nearly all published data involve subjects with “age-related” TD.¹⁸⁻³⁶

There are almost no large studies on *TTh* in men with “classical” TD, because such cases are rare. It is unwarranted that the FDA recommendations remain standing despite the recent findings of the T-trials²⁶ and several meta-analyses of randomized clinical trials,³⁴⁻³⁶ which clearly demonstrated that TD has a negative impact on health and well-being and *TTh* of “age-related” TD improves body composition, glycemic control, and sexual function. Lower T levels are shown to be associated with increased mortality,³⁷ fracture risk,³⁸ and cardiovascular disease (CVD).^{39,40} The recent T trials have demonstrated that many of these changes attributed to T deficiency are reversible with *TTh* in older men.

The data from the largest National Institutes of Health (NIH)-funded, double blind, placebo-controlled T-trials in the United States, in 790 men with a mean age of 72 years, demonstrated that *TTh* significantly improved symptoms and abnormalities in men >65 years old without “classical” TD.¹⁹⁻²⁶ *TTh* improved all aspects of sexual function,^{19,20} improved walking distance by a small amount,²⁵ slightly improved mood and depression symptoms,¹⁹ improved hemoglobin and corrected mild and moderate anemia of both known and

Table 1. Signs and Symptoms of Testosterone Deficiency Irrespective of the Underlying Etiology

Signs and symptoms of “classical” hypogonadism	Signs and symptoms of “age-related” hypogonadism	Effects of TTh on the signs and symptoms of hypogonadism, irrespective of etiology
Decreased mobility	Decreased mobility	Improved
Increased sexual dysfunction	Increased sexual dysfunction	Improved
Reduced self-perceived vitality	Reduced self-perceived vitality	Improved
Diminished cognitive abilities	Diminished cognitive abilities,	Improved
Decreased bone mineral density	Decreased bone mineral density	Improved
Reduced glucose tolerance	Reduced glucose tolerance	Improved
Increased anemia	Increased anemia	Improved
Increased coronary artery disease	Increased coronary artery disease	Improved

Reference: Defeudis et al.¹³⁷
 TTh, T therapy.



unknown causes,²⁴ markedly increased volumetric bone mineral density and estimated bone strength,²³ and led to no notable increase in cardiovascular or prostate cancer risk and with fewer hospitalizations.²⁶

There is good evidence of benefit in men with metabolic diseases (diabetes, obesity), improving parameters of lean body mass, reduced body fat, waist circumference, and insulin resistance.^{14–23–36} The data from the T-trials and other clinical studies (Table 2) are in stark contrast to those reported in the aforementioned clinical studies^{41–44} which were significantly flawed and also could not serve as safety trials.⁴⁵

It is critical to highlight that the benefits of *TTh* in men with TD are similar, regardless of age or underlying condition.^{18–36} Thus, we conclude that, irrespective of age, the negative effects of TD on human health and quality of life are well demonstrated, including signs, symptoms, metabolic syndrome, obesity, and increased mortality.^{45–62} The benefits of *TTh* in men with TD were documented, regardless of age, in clinical trials, registry studies, observational studies, and systematic reviews and meta-analyses (Table 2), and were attributed to restoration of normal T levels.^{18–36}

Further, recent advances in endocrinology have uncovered several other etiologies that contribute to TD. These include obesity, diabetes, and opioid use. Interestingly, these etiologies are not encompassed in the indications listed by the FDA for T treatment, demonstrating that clinical science evolves, and the pathophysiological mechanisms of these newly identified idiopathic underpinnings of TD may be recognized and understood in the not-too-distant future.

Does It Really Matter What Causes Low T?

The FDA argues that “age-related” TD does not merit treatment.¹⁴ This argument was borne by the notion that “age-related” TD is a natural consequence of aging and should be left alone. It is illogical to conclude that because a condition is more common with age it does not merit treatment. Clinicians treat numerous “age-related” conditions, including hypertension, type 2 diabetes mellitus, arthritis, cataracts, atherosclerosis, and most cancers.

The FDA believes that if the underlying etiology of low T is classical hypogonadism (primary or secondary) then it merits treatment. However, the FDA believes that if low T is attributed to age-related hypogonadism, then it does not merit treatment, despite lack of any scientific evidence to support such contentions.^{19–26}

In addition, the FDA voiced a safety concern regarding *TTh* and risk of CVD based on the following: (1) one

clinical trial halted by the data safety monitoring board and again not designed as a safety trial,⁴¹ in which the authors concluded that the reported evidence may be due to “chance alone”; (2) two observational studies suggesting potential CVD risk associated with *TTh*. Both studies were fraught with methodological and statistical analyses that were not validated at the time^{42,43}; (3) one meta-analysis, which included studies that do not meet the criteria for inclusion.⁴⁴ These four studies have been rebutted in detail by many published studies and experts in the field.^{1,15,27–31,40,45,59,63–66}

Despite all the available evidence to the contrary, and the results of the recent T trials,^{19–26} the FDA concluded that, although the limitations and potential confounders or biases in these studies^{41–44} preclude a clear conclusion regarding the role of *TTh* in adverse cardiovascular outcomes, a possible association cannot be overlooked.¹⁴ The FDA recommended *TTh* only for “classical” TD but not for “age-related” TD.¹⁴ The FDA’s position insists that men afflicted with “age-related” TD should not be treated with T but should be offered behavioral and nutritional life approaches to attain healthier lifestyle. It is important to acknowledge that the FDA position about lifestyle treatment does not exclude the use of *TTh* in older men with TD. More often, such a combined approach may be synergistic and useful.

It is worth emphasizing that the FDA does acknowledge that TD is an indication for *TTh*, however limiting such treatments only to men who are diagnosed with “classical” TD. This action by the FDA is not based on scientific or clinical evidence and in my view is irrational. We should point out that the listed conditions of “classical” TD are largely of a historical nature, representing only those conditions of TD recognized by clinicians since the 1940s and 1950s (e.g., testicular failure due to varying pathologies, such as XXY karyotype (Klinefelter syndrome), toxicities (chemotherapy-induced), infectious destruction (mumps orchitis), or radiation-induced damage or physical trauma and injury or pituitary/hypothalamic dysfunction attributed to endocrine disruption or comorbidities).

Advances in science and clinical research have identified new risk factors for TD. These include obesity, diabetes, and metabolic syndrome and opioid use, among others.^{40,67–80} Therefore, it is irrational to dismiss these newly described conditions and advocate against *TTh* under the guise of “age-related” TD. Moreover, in the clinical setting, “age-related” or “idiopathic” TD is among the most common etiology noted. There is no evidence that the response to *TTh* of idiopathic



Table 2. Studies on Benefits of T Therapy in Older Men

Study	Type of study	n	Age (years)	Main outcome
Snyder et al. ¹⁹	RCT	790	65 years or older	TTh produced moderate benefit with respect to sexual function and some benefit with respect to mood and depressive symptoms.
Cunningham et al. ²⁰	RCT	470	65 years or older	TTh improved sexual desire and activity.
Snyder et al. ²³	RCT	211	65 years or older	TTh for 1 year of older men with low T significantly increased volumetric BMD and estimated bone strength, more in trabecular than peripheral bone and more in the spine than hip.
Snyder et al. ⁸¹	RCT	96	65 years or older	TTh of men older than 65 years of age decreased fat mass, principally in the arms and legs, and increased lean mass, principally in the trunk.
Snyder et al. ⁸²	RCT	96	65 years or older	TTh of men older than 65 years of age did not increase lumbar spine bone density overall, but increased it in those men with low T.
Srinivas-Shankar et al. ³⁰	RCT	274	65 years or older	TTh in intermediate-frail and frail elderly men with low to borderline-low T for 6 months may prevent age-associated loss of lower limb muscle strength and improve body composition, quality of life, and physical function.
Cunningham et al. ⁸³	RCT	790	65 years or older	TTh in older men with normal baseline PSA resulted in 5% increase in PSA of 1.7 ng/mL, and 2.5% increase of 3.4 ng/mL.
Stephens-Shields et al. ⁸⁴	RCT	235	65 years or older	TTh resulted in clinically meaningful improvement of sexual desire and is a change of score of ≥ 0.7 score of Question 1 of PDQ.
Bhasin et al. ²⁵	RCT	788	65 years or older	TTh consistently improved self-reported walking ability, modestly improved 6MWD in all men participating in the testosterone trials.
Mohler et al. ⁸⁵	RCT	788	65 years or older	TTh of 1 year in older men with low testosterone was associated with small reductions in cholesterol and insulin but not with other glucose markers, markers of inflammation or fibrinolysis, or troponin.
Resnick et al. ²¹	RCT	493	65 years or older	Among older men with low T and age-associated memory impairment, TTh for 1 year compared with placebo was not associated with improved memory or other cognitive functions.
Roy et al. ²⁴	RCT	126	65 years or older	TTh significantly increased the hemoglobin levels of those with unexplained anemia as well as those with anemia from known causes.
Benito et al. ⁸⁶	Prospective study	10	Median age 51 years (range, 31–78)	TTh in men with TD improved trabecular architecture.
Wang et al. ⁸⁷	Prospective study	163	Range 19–68	TTh improved sexual function and mood parameters rapidly and were maintained throughout T treatment. Significant increases in lean body mass and decreased fat mass were noted, and these changes were maintained with TTh.
Snyder et al. ⁸⁸	RCT	108	65 years or older	TTh of healthy elderly men for 3 years did not affect any of the lipid or apolipoprotein parameters that we measured.
Wang et al. ⁸⁹	RCT	227	Range 51 years	TTh decreased bone reapposition markers, an increased osteoblastic activity marker resulting in a significant increase in BMD.
Wang et al. ⁹⁰	RCT	227	Range 19–68	TTh improved sexual function and mood, increased lean mass and muscle strength (principally in the legs), and decreased fat mass.
Traustadottir et al. ⁹	RCT	129	65 years or older	The mean 3-year change in $\dot{V}O_2$ peak was significantly smaller in men treated with testosterone than in men receiving placebo and was associated with increases in hemoglobin.
Tappper et al. ⁹¹	RCT	76	Mean 37.3 \pm 8.2	Core muscles of the trunk and pelvis are responsive to testosterone administration.
Storer et al. ⁹²	RCT	156	65 years or older	TTh in older men for 3 years was associated with modest but significantly greater improvements in stair-climbing power, muscle mass, and power.
Storer et al. ⁹³	RCT	64	Mean 73.6 \pm 5.8	TTh in mobility-limited older men increased hemoglobin and attenuated the age-related declines in $\dot{V}O_2$ peak and $\dot{V}O_2/\theta$.
Basaria et al. ⁹⁴	RCT	308	60 years or older	TTh for 3 years vs. placebo did not result in a significant difference in the rates of change in either common carotid artery intima-media thickness or coronary artery calcium nor did it improve overall sexual function or health-related quality of life.

(continued)



Table 2. (Continued)

Study	Type of study	n	Age (years)	Main outcome
Al Mukaddam et al. ⁹⁵	RCT	32	Mean 47.2±4.7 (range 25–70)	TTh significantly increased the structural and mechanical properties of trabecular bone but decreased most of these properties of cortical bone.
Basaaria et al. ⁹⁶	RCT	84	Range 18–64	TTh produced greater improvements in pressure and mechanical hyperalgesia, sexual desire, and role limitation due to emotional problems. Testosterone administration was also associated with an improvement in body composition.
Gray et al. ⁹⁷	RCT	60	65 years or older	TTh in older men dose dependently improved some components of sexual function, namely, libido and erectile function, as well as one aspect of visuospatial cognition.
Storer et al. ⁹⁸	RCT	61		TTh produced specific effects on muscle performance; it increases maximal voluntary strength and leg power but does not affect fatigability or specific tension.
Saad et al. ⁹⁹	Registry observational study	411	Mean 59.46±7.05	TTh is an effective approach to achieve sustained WL in obese hypogonadal men irrespective of severity of obesity.
Saad et al. ¹⁰⁰	Registry observational study	255	Mean 58.02±6.30	TTh produced consistent reductions in body weight, waist circumference and body mass index.
Saad et al. ²⁷	Registry observational study	823	Mean 64.0±4.7	TTh produces reductions in weight, waist circumference, and body mass index.
Haider et al. ²⁸	Registry observational study	356	Mean 63.7±4.9	TTh in men with type 2 diabetes and TD improves glycemic control and insulin resistance. Remission of diabetes occurred in one-third of the patients.
Behre et al. ¹⁰¹	RCT	362	Range 50–80	TTh improved body composition and HRQoL in symptomatic men with low to low-normal T, with further improvements over the next 12 months.
Gianatti et al. ¹⁰²	RCT	80	Range 35–70	TTh did not substantially improve constitutional or sexual symptoms in obese, aging men with diabetes.
Ho et al. ¹⁰³	RCT	120	>40 years old	TTh is effective in improving health-related quality of life, as assessed by the AMS scale in men with TD.
Ng Tang Fui et al. ¹⁰⁴	RCT	100	Median age of 53	TTh improved TD symptoms over and above the improvement associated with weight loss alone, and more severely symptomatic men achieved a greater benefit.
Svartberg et al. ¹⁰⁵	RCT	69	Range 60–80	TTh improved body composition.
Kenny et al. ¹⁰⁶	RCT	67	Mean age 76±4	TTh in men with low T does not impair and may improve cognitive function.
Giltay et al. ¹⁰⁷	RCT	184	Mean 52.1±9.6	TTh may improve depressive symptoms, aging male symptoms, and sexual dysfunction in hypogonadal men with the MetS.
Amory et al. ¹⁰⁸	RCT	70	65 years or older	TTh in older men with low T increases vertebral and hip BMD over 36 months.
Aversa et al. ¹⁰⁹	RCT	52	Mean 57	TTh improved metabolic syndrome components.
Hildreth et al. ¹¹⁰	RCT	167	Mean 66±5	TTh improved body composition but had no effect on functional performance.
Traish et al. ¹¹¹	Registry observational study	255	Mean 58.02±6.30	TTh ameliorates metabolic syndrome components.
Traish et al. ¹¹²	Registry observational study	656	Mean 60.7±7.2	TTh reduced mortality related to CVD.
Rosen et al. ¹¹³	Registry observational study	999	Mean 59.1±10.5	TTh improved major QoL dimensions, including sexual, somatic, and psychological health, which were sustained over 36 months.
Tenover et al. ¹¹⁴	RCT	13	Range 57–76	TTh increased lean body mass and possibly a decline in bone resorption.
Marin et al. ¹¹⁵	Observational study	23	Mean 59.9	TTh decreased visceral fat mass without a change in body mass, subcutaneous fat mass, or lean body mass and reduced insulin resistance, improved blood glucose, diastolic blood pressure and reduced serum cholesterol.
Morley et al. ¹¹⁶	Alternate case control trial	14	Mean 76.5	TTh increased right hand muscle strength and osteocalcin concentration.
Sih et al. ¹¹⁷	RCT	32	Mean 65±7	TTh improved strength, increased hemoglobin, and it lowered leptin levels in older hypogonadal men.
Ferrando et al. ¹¹⁸	RCT	12	Mean 68±3	TTh increased net protein balance in the fasted state.
Steidle et al. ¹¹⁹	RCT	406	Mean 58±10.3	TTh significantly improved spontaneous erections, sexual motivation, sexual desire, and sexual performance.
Casaburi et al. ¹²⁰	RCT	53	Mean 67.1	TTh increased lean body mass and increased repetition maximum leg press strength.

(continued)



Table 2. (Continued)

Study	Type of study	n	Age (years)	Main outcome
Page et al. ¹²¹	RCT	70	Mean 71 ± 4	TTh improved physical performance, body composition, and fasting lipid profiles.
Giannoulis et al. ¹²²	RCT	43	Mean 69.9	TTh has beneficial effects on body composition and cardio-respiratory fitness.
Malkin et al. ¹²³	RCT	14	Mean 74.1 ± 2.3	TTh fasting insulin sensitivity in men with CHF may also increase lean body mass; these data suggest a favorable effect of testosterone on an important metabolic component of CHF
Allan et al. ¹²⁴	RCT	60	Mean 62.1 ± 1.0	TTh selectively lessened visceral fat accumulation without a change in total body FFM and increased total body FFM and total body and thigh skeletal muscle mass.
Sheffield-Moore et al. ¹²⁵	RCT	24	Mean 70 ± 2	TTh improved body composition and increased muscle strength.
Frederiksen et al. ¹²⁶	RCT	38	Range 68 (62–72)	TTh decreased subcutaneous fat on the abdomen and lower extremities, but visceral fat was unchanged.
Hoyos et al. ¹²⁷	RCT	67	Mean age 49 ± 12	TTh improved several important cardio-metabolic parameters.
Kenny et al. ¹²⁸	RCT	67	Mean 76 ± 4	TTh prevented bone loss at the femoral neck, decreased body fat, and increased lean body mass in a group of healthy men older than the age of 65 with low bioavailable testosterone levels.
McNicholas et al. ¹²⁹	RCT	208	Mean 57.9 ± 10.2	TTh increased lean body mass, produced a significant decrease in percentage body fat, and improved sexual performance, sexual motivation, sexual desire, and spontaneous erections.
Wittert et al. ¹³⁰	RCT	76	Mean 68.5 ± 6	TTh in older relatively hypogonadal men results in an increase in muscle mass and a decrease in body fat.
Kapoor et al. ¹³¹	RCT	24	>30 years	TTh reduces insulin resistance and improves glycemic control in hypogonadal men with type 2 diabetes.
Katznelson et al. ¹³²	RCT	70	Mean 73 ± 5.1	Improved quality of life.
Agledahl et al. ¹³³	RCT	26	Mean 68.9 ± 5.4	TTh exerted favorable effects on body composition; total fat mass was significantly reduced (pv0.001), whereas fat-free mass was significantly increased (pv0.001) in the testosterone-treated group.
Emmelot-Vonk et al. ¹³⁴	RCT	207	Mean 67.1 ± 5.0	TTh increased lean body mass and had mixed metabolic effects.
Mathur et al. ¹³⁵	RCT	13	Mean 64.8 ± 7.0	TTh has a protective effect on myocardial ischemia and is maintained throughout treatment without decrement.
O'Connell et al. ¹³⁶	RCT	274	Mean 73.9	The effects of TTh seen at 6 months on muscle strength, lean mass, and QoL in frail men are not maintained at 6 months post-treatment discontinuation.

AMS, aging male symptom scale; BMD, bone mineral density; CHF, congestive heart failure; CVD, cardiovascular disease; FFM, fat-free mass; HRQoL, health related quality of life; PDQ, Psychosexual Daily Questionnaire; PSA, prostate specific antigen; RCT, randomized clinical trial; TD, testosterone deficiency; 6MWD, 6-minute walk distance.

(or “age-related”) *TD* occurs via different physiological or biochemical mechanisms than those historically recognized conditions (i.e., *classical TD*). We should point out that clinical guidelines or recommendations from major medical societies failed to make any distinction regarding “age-related” *TD* and made no mention of differences in treatment approach because of this, including Endo Soc, American Urological Association (AUA), and the International Consultation for Sexual Medicine (ICSM).

We are not aware of any evidence provided by the FDA or to the FDA regarding *TTh* on CV safety in men with “classical” *TD*. Thus, to assume that *TTh* produces adverse effects in men with “age-related” *TD* but not in men with “classical” *TD* is simply an illusion. We conclude that the FDA recommendations regarding *TTh* in men with “age-related” *TD* are not evidence-based and unwarranted. It is unfortunate that this

particular distinction of *TD*, based on an historical recognition, was promoted almost entirely by the FDA, without scientific or clinical evidence.⁵ We are aware that the FDA, as a regulatory agency, has enormous responsibilities toward the safety of the U.S. public.

Indeed, this differs from the responsibilities of practicing physicians, which are to provide the utmost care for their patients and to relieve pain and suffering and improve quality of life. The FDA is not in the business of dictating the practice of medicine. The practice of medicine is often based on clinical guidelines that are evidence based. It should be emphasized that the T guidelines do not require that patients have classical hypogonadism to be treated. The T guidelines only require low serum T values and signs and symptoms of hypogonadism. The FDA is charged with regulating the pharmaceutical industry, but the FDA is not charged with regulating or providing guidance for the



practice of medicine. We, therefore, conclude that *TD* is a pathophysiological condition that merits *T* treatment, irrespective of the underlying causes or the historical terms used to describe it.

Conclusions

The negative effects of *TD* on human health and quality of life are well demonstrated, including signs, symptoms, metabolic syndrome, obesity, and increased mortality. Substantial evidence exists demonstrating benefits of *TTh* in men with “age-related” *TD* (Table 2).^{18–36,81–136}

More importantly, the *T* trials demonstrated that *TTh* confers significant and clinically meaningful health benefits in older men with low *T* and this treatment is safe and effective, irrespective of etiology.^{18–36}

In addition, the *T* trials provided compelling evidence that *T* therapy confers significant benefits in the growing population of men with obesity and/or type 2 diabetes.

We are aware that the FDA, as a regulatory agency, has enormous responsibilities toward the safety of the U.S. public. Indeed, this differs from the responsibilities of practicing physicians, which are to provide the utmost care for their patients and to relieve pain and suffering and improve quality of life. The FDA is charged with regulating the pharmaceutical industry, but the FDA is not charged with regulating the practice of medicine. We conclude that *TD* is a pathophysiological condition that merits *T* treatment, irrespective of the underlying causes, or the historical terms to define it.

Author Contribution

A.M.T. has conceptualized, drafted, written, and revised the article.

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References

1. Morgentaler A, Zitzmann M, Traish AM, et al. Fundamental concepts regarding testosterone deficiency and treatment: International expert consensus resolutions. *Mayo Clin Proc.* 2016;91(7):881–896.

2. Travison TG, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB. The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men. *J Clin Endocrinol Metab.* 2007;92(2):549–555.
3. Travison TG, Shackleton R, Araujo AB, et al. The natural history of symptomatic androgen deficiency in men: Onset, progression, and spontaneous remission. *J Am Geriatr Soc.* 2008;56(5):831–839.
4. Liu PY, Beilin J, Meier C, et al. Age-related changes in serum testosterone and sex hormone binding globulin in Australian men: Longitudinal analyses of two geographically separate regional cohorts. *J Clin Endocrinol Metab.* 2007;92(9):3599–3603.
5. Sartorius G, Spasevska S, Idan A, et al. Serum testosterone, dihydrotestosterone and estradiol concentrations in older men self-reporting very good health: The healthy man study. *Clin Endocrinol (Oxf).* 2012;77(5):755–763.
6. Handelsman DJ, Yeap B, Flicker L, Martin S, Wittert GA, Ly LP. Age-specific population centiles for androgen status in men. *Eur J Endocrinol.* 2015;173(6):809–817.
7. Khera M, Broderick GA, Carson CC, et al. Adult-onset hypogonadism. *Mayo Clin Proc.* 2016;91(7):908–926.
8. Swee DS, Gan EH. Late-onset hypogonadism as primary testicular failure. *Front Endocrinol (Lausanne).* 2019;10:372.
9. Traustadóttir T, Harman SM, Tsitouras P, et al. Long-term testosterone supplementation in older men attenuates age-related decline in aerobic capacity. *J Clin Endocrinol Metab.* 2018;103(8):2861–2869.
10. Vermeulen A, Kaufman JM. Ageing of the hypothalamo-pituitary-testicular axis in men. *Horm Res.* 1995;43(1–3):25–28.
11. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr Rev.* 2005;26(6):833–876.
12. Nieschlag E. Late-onset hypogonadism: A concept comes of age. *Andrology.* 2020;8(6):1506–1511.
13. Khera M, Broderick GA, Carson CC, et al. Adult-onset hypogonadism. *Mayo Clin Proc.* 2016;91(7):908–926.
14. Nguyen CP, Hirsch MS, Moeny D, Kaul S, Mohamoud M, Joffe HV. Testosterone and “age-related hypogonadism”—FDA concerns. *N Engl J Med.* 2015;373:689–691.
15. Aub JC. The use of testosterone. *N Engl J Med.* 1940;222:877–881.
16. Aub JC, Kety SS. Recent advances in testosterone therapy. *N Engl J Med.* 1943;228:338–343.
17. Lesser MA. Testosterone propionate therapy in one hundred cases of angina pectoris. *J Clin Endocrinol Metab.* 1946;6:549–557.
18. Wallis CJ, Lo K, Lee Y, et al. Survival and cardiovascular events in men treated with testosterone replacement therapy: An intention-to-treat observational cohort study. *Lancet Diabetes Endocrinol.* 2016;4(6):498–506.
19. Snyder PJ, Bhasin S, Cunningham GR, et al. Testosterone trials investigators effects of testosterone treatment in older men. *N Engl J Med.* 2016;374(7):611–624.
20. Cunningham GR, Stephens-Shields AJ, Rosen RC, et al. Testosterone treatment and sexual function in older men with low testosterone levels. *J Clin Endocrinol Metab.* 2016;101(8):3096–3104.
21. Resnick SM, Matsumoto AM, Stephens-Shields AJ, et al. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. *JAMA.* 2017;317(7):717–727.
22. Budoff MJ, Ellenberg SS, Lewis CE, et al. Testosterone treatment and coronary artery plaque volume in older men with low testosterone. *JAMA.* 2017;317(7):708–716.
23. Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, et al. Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: A controlled clinical trial. *JAMA Intern Med.* 2017;177(4):471–479.
24. Roy CN, Snyder PJ, Stephens-Shields AJ, et al. Association of testosterone levels with anemia in older men: A controlled clinical trial. *JAMA Intern Med.* 2017;177(4):480–490.
25. Bhasin S, Ellenberg SS, Storer TW, et al. Effect of testosterone replacement on measures of mobility in older men with mobility limitation and low testosterone concentrations: Secondary analyses of the Testosterone Trials. *Lancet Diabetes Endocrinol.* 2018;6(11):879–890.
26. Snyder PJ, Bhasin S, Cunningham GR, et al. Lessons from the testosterone trials. *Endocr Rev.* 2018;39(3):369–386.
27. Saad F, Doros G, Haider KS, Haider A. Differential effects of 11 years of long-term injectable testosterone undecanoate therapy on



- anthropometric and metabolic parameters in hypogonadal men with normal weight, overweight and obesity in comparison with untreated controls: Real-world data from a controlled registry study. *Int J Obes*. 2020;44:1264–1278.
28. Haider KS, Haider A, Saad, et al. Remission of type 2 diabetes following long-term treatment with injectable testosterone undecanoate in patients with hypogonadism and type 2 diabetes: 11-year data from a real-world registry study. *Diabetes Obes Metab*. 2020;22(11):2055–2068.
 29. Yassin A, Haider A, Haider KS, et al. Diabetes testosterone therapy in men with hypogonadism prevents progression from prediabetes to type 2 diabetes: Eight-year data from a registry study. *Diabetic Care*. 2019;42(6):1104–1111.
 30. Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: A randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab*. 2010;95:639–650.
 31. Navarro-Peñalver M, Perez-Martinez MT, Gómez-Bueno M, et al. Testosterone replacement therapy in deficient patients with chronic heart failure: A randomized double-blind controlled pilot study. *J Cardiovasc Pharmacol Ther*. 2018;23(6):543–550.
 32. Corona G, Giagulli VA, Maseroli E, et al. Testosterone supplementation and body composition: Results from a meta-analysis of observational studies. *J Endocrinol Invest*. 2016;39(9):967–981.
 33. Corona G, Rastrelli G, Morgentaler A, Sforza A, Mannucci E, Maggi M. Meta-analysis of results of testosterone therapy on sexual function based on international index of erectile function scores. *Eur Urol*. 2017;72(6):1000–1011.
 34. Cai X, Tian Y, Wu T, Cao CX, Li H, Wang KJ. Metabolic effects of testosterone replacement therapy on hypogonadal men with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. *Asian J Androl*. 2014;16(1):146–152.
 35. Algeffari M, Jayasena CN, MacKeith P, Thapar A, Dhillon WS, Oliver N. Testosterone therapy for sexual dysfunction in men with Type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. *Diabet Med*. 2018;35(2):195–202.
 36. Corona G, Isidori AM, Buvat J, et al. Testosterone supplementation and sexual function: A meta-analysis study. *J Sex Med*. 2014;11(6):1577–1592.
 37. Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Clinical review: Endogenous testosterone and mortality in men: A systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2011;96(10):3007–3019.
 38. Mellström D, Johnell O, Ljunggren O, et al. Free testosterone is an independent predictor of BMD and prevalent fractures in elderly men: MrOS Sweden. *J Bone Miner Res*. 2006;21(4):529–535.
 39. Ohlsson C, Barrett-Connor E, Bhasin S, et al. High serum testosterone is associated with reduced risk of cardiovascular events in elderly men. The MrOS (Osteoporotic Fractures in Men) study in Sweden. *J Am Coll Cardiol*. 2011;58(16):1674–1681.
 40. Boden WE, Miller MG, McBride R, et al. Testosterone concentrations and risk of cardiovascular events in androgen-deficient men with atherosclerotic cardiovascular disease. *Am Heart J*. 2020;224:65–76.
 41. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med*. 2010;363:109–122.
 42. Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*. 2013;310:1829–1836.
 43. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One*. 2014;9:e85805.
 44. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: A systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med*. 2013;11:108.
 45. Morgentaler A, Miner MM, Caliber M, Guay AT, Khera M, Traish AM. Testosterone therapy and cardiovascular risk: Advances and controversies. *Mayo Clin Proc*. 2015;90(2):224–251.
 46. Araujo AB, Kupelian V, Page ST, Handelsman DJ, Bremner WJ, McKinlay JB. Arch Sex steroids and all-cause and cause-specific mortality in men. *Intern Med*. 2007;167(12):1252–1260.
 47. Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. *Eur Heart J*. 2015;36(40):2706–2715.
 48. Page ST. Testosterone, cardiovascular disease, and mortality in men: Living in the dark. *Lancet Diabetes Endocrinol*. 2014;2(8):609–611.
 49. Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. *Arch Intern Med*. 2006;166(15):1660–1665.
 50. Khaw KT, Dowsett M, Folkard E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation*. 2007;116(23):2694–2701.
 51. Yeap BB, Alfonso H, Chubb SA, et al. In older men an optimal plasma testosterone is associated with reduced all-cause mortality and higher dihydrotestosterone with reduced ischemic heart disease mortality, while estradiol levels do not predict mortality. *J Clin Endocrinol Metab*. 2014;99(1):E9–E18.
 52. Shores MM, Mocerri VM, Gruenewald DA, Brodtkin KI, Matsumoto AM, Kivlahan DR. Low testosterone is associated with decreased function and increased mortality risk: A preliminary study of men in a geriatric rehabilitation unit. *J Am Geriatr Soc*. 2004;52(12):2077–2081.
 53. Tivesten A, Vandenput L, Labrie F, et al. Low serum testosterone and estradiol predict mortality in elderly men. *J Clin Endocrinol Metab*. 2009;94(7):2482–2488.
 54. Muralidharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur J Endocrinol*. 2013;169(6):725–733.
 55. Bentmar Holgersson M, Landgren F, Rylander L, Lundberg Giwercman Y. Mortality is linked to low serum testosterone levels in younger and middle-aged men. *Eur Urol*. 2017;71(6):991–992.
 56. Bianchi VE. Testosterone, myocardial function, and mortality. *Heart Fail Rev*. 2018;23(5):773–788.
 57. Muralidharan V, Jones TH. Testosterone and mortality. *Clin Endocrinol (Oxf)*. 2014;81(4):477–487.
 58. Adelborg K, Rasmussen TB, Nørrelund H, Layton JB, Sørensen HT, Christiansen CF. Cardiovascular outcomes and all-cause mortality following measurement of endogenous testosterone levels. *Am J Cardiol*. 2019;123(11):1757–1764.
 59. Morgentaler A. Testosterone deficiency and cardiovascular mortality. *Asian J Androl*. 2015;17(1):26–31.
 60. Shores MM, Biggs ML, Arnold AM, et al. Testosterone, dihydrotestosterone, and incident cardiovascular disease and mortality in the cardiovascular health study. *J Clin Endocrinol Metab*. 2014;99(6):2061–2068.
 61. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab*. 2012;97(6):2050–2058.
 62. Malkin CJ, Pugh PJ, Morris PD, Asif S, Jones TH, Channer KS. Low serum testosterone and increased mortality in men with coronary heart disease. *Heart*. 2010;96(22):1821–1825.
 63. Elliott J, Kelly SE, Millar AC, et al. Testosterone therapy in hypogonadal men: A systematic review and network meta-analysis. *BMJ Open*. 2017;7(11):e015284.
 64. Traish AM, Guay AT, Morgentaler A. Death by testosterone? We think not! *J Sex Med*. 2014;11(3):624–629.
 65. Oni OA, Dehkordi SHH, Jazayeri MA, et al. Relation of testosterone normalization to mortality and myocardial infarction in men with previous myocardial infarction. *Am J Cardiol*. 2019;124(8):1171–1178.
 66. Miner M, Morgentaler A, Khera M, Traish AM. The state of testosterone therapy since the FDA's 2015 labelling changes: Indications and cardiovascular risk. *Clin Endocrinol (Oxf)*. 2018;89(1):3–10.
 67. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab*. 2004;89:5462–5468.
 68. Braga PC, Pereira SC, Ribeiro JC, et al. Late-onset hypogonadism and lifestyle-related metabolic disorders. *Andrology*. 2020; 00: 1–9.
 69. Li FP, Wang CZ, Huang JM, et al. Obesity-associated secondary hypogonadism in young and middle-aged men in Guangzhou: A single-centre cross-sectional study. *Int J Clin Pract*. 2020;18:e13513.
 70. Dhindsa SS, Irwig MS, Wyne K. Gonadopenia and aging men. *Endocr Pract*. 2018;24(4):375–385.
 71. Laaksonen DE, Niskanen L, Punnonen K, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care*. 2004;27(5):1036–1041.



72. Laaksonen DE, Niskanen L, Punnonen K, et al. Sex hormones, inflammation and the metabolic syndrome: A population-based study. *Eur J Endocrinol*. 2003;149(6):601–608.
73. Giagulli VA, Castellana M, Murro I, et al. The role of diet and weight loss in improving secondary hypogonadism in men with obesity with or without type 2 diabetes mellitus. *Nutrients*. 2019;11(12):2975.
74. Sarkar M, Yates K, Suzuki A, et al. Low testosterone is associated with nonalcoholic steatohepatitis (NASH) and severity of NASH fibrosis in men with NAFLD. *Clin Gastroenterol Hepatol*. 2019 [Online ahead of print]; DOI: 10.1016/j.cgh.2019.11.053.
75. Dandona P, Dhindsa S. Update: Hypogonadotropic hypogonadism in type 2 diabetes and obesity. *J Clin Endocrinol Metab*. 2011;96(9):2643–2651.
76. Dhindsa S, Furlanetto R, Vora M, Ghanim H, Chaudhuri A, Dandona P. Low estradiol concentrations in men with subnormal testosterone concentrations and type 2 diabetes. *Diabetes Care*. 2011;34(8):1854–1859.
77. Dandona P, Dhindsa S, Chandel A, Chaudhuri A. Hypogonadotropic hypogonadism in men with type 2 diabetes. *Postgrad Med*. 2009;121(3):45–51.
78. Dandona P, Dhindsa S, Chaudhuri A, Bhatia V, Topiwala S, Mohanty P. Hypogonadotropic hypogonadism in type 2 diabetes, obesity and the metabolic syndrome. *Curr Mol Med*. 2008;8(8):816–828.
79. Chandel A, Dhindsa S, Topiwala S, Chaudhuri A, Dandona P. Testosterone concentration in young patients with diabetes. *Diabetes Care*. 2008;31(10):2013–2017.
80. Tripathy D, Dhindsa S, Garg R, Khaishagi A, Syed T, Dandona P. Hypogonadotropic hypogonadism in erectile dysfunction associated with type 2 diabetes mellitus: A common defect? *Metab Syndr Relat Disord*. 2003;1(1):75–80.
81. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab*. 1999;84:2647–2653.
82. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab*. 1999;84:1966–1972.
83. Cunningham GR, Ellenberg SS, Bhasin S, et al. Prostate-specific antigen levels during testosterone treatment of hypogonadal older men: Data from a controlled trial. *J Clin Endocrinol Metab*. 2019;104(12):6238–6246.
84. Stephens-Shields AJ, Wang C, Preston P, Snyder PJ, Swerdloff RS. Clinically meaningful change in sexual desire in the psychosexual daily questionnaire in older men from the T-trials. *J Sex Med*. 2019;16(7):951–953.
85. Mohler ER, Ellenberg SS, Lewis CE, et al. The effect of testosterone on cardiovascular biomarkers in the testosterone trials. *J Clin Endocrinol Metab*. 2018;103(2):681–688.
86. Benito M, Vasilic B, Wehrli FW, et al. Effect of testosterone replacement on trabecular architecture in hypogonadal men. *J Bone Miner Res*. 2005;20(10):1785–1791.
87. Wang C, Cunningham G, Dobs A, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *J Clin Endocrinol Metab*. 2004;89(5):2085–2098.
88. Snyder PJ, Peachey H, Berlin JA, et al. Effect of transdermal testosterone treatment on serum lipid and apolipoprotein levels in men more than 65 years of age. *Am J Med*. 2001;111(4):255–260.
89. Wang C, Swerdloff RS, Iranmanesh A, et al. Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men. *Clin Endocrinol (Oxf)*. 2001;54(6):739–750.
90. Wang C, Swerdloff RS, Iranmanesh A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab*. 2000;85(8):2839–2853.
91. Tapper J, Arver S, Pencina KM, et al. Muscles of the trunk and pelvis are responsive to testosterone administration: Data from testosterone dose-response study in young healthy men. *Andrology*. 2018;6(1):64–73.
92. Storer TW, Basaria S, Traustadottir T, et al. Effects of testosterone supplementation for 3 years on muscle performance and physical function in older men. *J Clin Endocrinol Metab*. 2017;102(2):583–593.
93. Storer TW, Bhasin S, Travison TG, et al. Testosterone attenuates age-related fall in aerobic function in mobility limited older men with low testosterone. *J Clin Endocrinol Metab*. 2016;101(6):2562–2569.
94. Basaria S, Harman SM, Travison TG, et al. Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels: A randomized clinical trial. *JAMA*. 2015;314(6):570–581.
95. Al Mukaddam M, Rajapakse CS, Bhagat YA, et al. Effects of testosterone and growth hormone on the structural and mechanical properties of bone by micro-MRI in the distal tibia of men with hypopituitarism. *J Clin Endocrinol Metab*. 2014;99(4):1236–1244.
96. Basaria S, Travison TG, Alford D, et al. Effects of testosterone replacement in men with opioid-induced androgen deficiency: A randomized controlled trial. *Pain*. 2015;156(2):280–288.
97. Gray PB, Singh AB, Woodhouse LJ, et al. Dose-dependent effects of testosterone on sexual function, mood, and visuospatial cognition in older men. *J Clin Endocrinol Metab*. 2005;90(7):3838–3846.
98. Storer TW, Magliano L, Woodhouse L, et al. Testosterone dose-dependently increases maximal voluntary strength and leg power but does not affect fatigability or specific tension. *J Clin Endocrinol Metab*. 2003;88(4):1478–1485.
99. Saad F, Yassin A, Doros G, Haider A. Effects of long-term treatment with testosterone on weight and waist size in 411 hypogonadal men with obesity classes I-III: Observational data from two registry studies. *Int J Obes (Lond)*. 2016;40(1):162–170.
100. Saad F, Haider A, Doros G, Traish A. Long-term treatment of hypogonadal men with testosterone produces substantial and sustained weight loss. *Obesity (Silver Spring)*. 2013;21(10):1975–1981.
101. Behre HM, Tammela TL, Arver S, et al.; European Testogel Study Team. A randomized, double-blind, placebo-controlled trial of testosterone gel on body composition and health-related quality-of-life in men with hypogonadal to low-normal levels of serum testosterone and symptoms of androgen deficiency over 6 months with 12 months open-label follow-up. *Aging Male*. 2012;15:198–207.
102. Gianatti EJ, Dupuis P, Hoermann R, et al. Effect of testosterone treatment on constitutional and sexual symptoms in men with type 2 diabetes in a randomized, placebo-controlled clinical trial. *J Clin Endocrinol Metab*. 2014;99:3821–3828.
103. Ho CC, Tong SF, Low WY, et al. A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptoms scale. *BJU Int*. 2012;110:260–265.
104. Ng Tang Fui M, Hoermann R, Prendergast LA, et al. Symptomatic response to testosterone treatment in dieting obese men with low testosterone levels in a randomized, placebo-controlled clinical trial. *Int J Obes (Lond)*. 2017;41:420–426.
105. Svartberg J, Agledahl I, Figenschau Y, et al. Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. *Int J Impot Res*. 2008;20:378–387.
106. Kenny AM, Bellantonio S, Gruman CA, et al. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. *J Gerontol A Biol Sci Med Sci*. 2002;57:M321–M325.
107. Giltay EJ, Tishova YA, Mskhalaya GJ, et al. Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome. *J Sex Med*. 2010;7:2572–2582.
108. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab*. 2004;89:503–510.
109. Aversa A, Bruzziches R, Francomano D, et al. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. *J Endocrinol Invest*. 2010;33:776–783.
110. Hildreth KL, Barry DW, Moreau KL, et al. Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. *J Clin Endocrinol Metab*. 2013;98:1891–1900.
111. Traish AM, Haider A, Doros G, et al. Long-term testosterone: Therapy in hypogonadal men ameliorates elements of the metabolic syndrome: An observational, long-term registry study. *Int J Clin Pract*. 2014;68:314–329.
112. Traish AM, Haider A, Haider KS, Doros G, Saad F. Long-term testosterone therapy improves cardiometabolic function and reduces risk of cardiovascular disease in men with hypogonadism: A real-life observational registry study setting comparing treated and untreated (control) groups. *J Cardiovasc Pharmacol Ther*. 2017;22(5):414–433.



113. Rosen RC, Wu F, Behre H, et al. Quality of life and sexual function benefits effects of long-term testosterone treatment: Longitudinal results from the registry of hypogonadism in men (RHYME). *J Sex Med*. 2017;14:1104e1115.
114. Tenover JS. Effects of testosterone supplementation in the aging male. *J Clin Endocrinol Metab*. 1992;75:1092–1098.
115. Mårin P, Holmång S, Jönsson L, et al. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. *Int J Obes Relat Metab Disord*. 1992;16:991–997.
116. Morley JE, Perry HM III, Kaiser FE, et al. Effects of testosterone replacement therapy in old hypogonadal males: A preliminary study. *J Am Geriatr Soc*. 1993;41:149–152.
117. Sih R, Morley JE, Kaiser FE, Perry HM III, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: A 12-month randomized controlled trial. *J Clin Endocrinol Metab*. 1997;82:1661–1667.
118. Ferrando AA, Sheffield-Moore M, Paddon-Jones D, Urban RJ, Wolfe RR. Differential anabolic effects of testosterone and amino acid feeding in older men. *J Clin Endocrinol Metab*. 2003;88:358–362.
119. Steidle C, Schwartz S, Jacoby K, et al. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J Clin Endocrinol Metab*. 2003;88:2673–2681.
120. Casaburi R, Bhasin S, Cosentino L, et al. Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2004;170:870–878.
121. Page ST, Amory JK, Bowman FD, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrinol Metab*. 2005;90:1502–1510.
122. Giannoulis MG, Sonksen PH, Umpleby M, et al. The effects of growth hormone and/or testosterone in healthy elderly men: A randomized controlled trial. *J Clin Endocrinol Metab*. 2006;91:477–484.
123. Malkin CJ, Jones TH, Channer KS. The effect of testosterone on insulin sensitivity in men with heart failure. *Eur J Heart Failure*. 2007;9:44–50.
124. Allan CA, Strauss BJ, Burger HG, Forbes EA, McLachlan RI. Testosterone therapy prevents gain in visceral adipose tissue and loss of skeletal muscle in non-obese aging men. *J Clin Endocrinol Metab*. 2008;93:139–146.
125. Sheffield-Moore M, Dillon EL, Casperson SL, et al. A randomized pilot study of monthly cycled testosterone replacement or continuous testosterone replacement versus placebo in older men. *J Clin Endocrinol Metab*. 2011;96:E1831–E1837.
126. Frederiksen L, Højlund K, Hougaard DM, et al. Testosterone therapy decreases subcutaneous fat and adiponectin in aging men. *Eur J Endocrinol*. 2012;166:469–476.
127. Hoyos CM, Yee BJ, Phillips CL, Machan EA, Grunstein RR, Liu PY. Body compositional and cardiometabolic effects of testosterone therapy in obese men with severe obstructive sleep apnoea: A randomised placebo-controlled trial. *Eur J Endocrinol*. 2012;167:531–541.
128. Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. *J Gerontol*. 2001; 56:M266–M272.
129. McNicholas TA, Dean JD, Mulder H, Carnegie C, Jones NA. novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. *BJU Int*. 2003;91:69–74.
130. Wittert GA, Chapman IM, Haren MT, Mackintosh S, Coates P, Morley JE. Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low-normal gonadal status. *J Gerontol*. 2003;58:618–625.
131. Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *Eur J Endocrinol*. 2006;154:899–906.
132. Katznelson L, Robinson MW, Coyle CL, Lee H, Farrell CE. Effects of modest testosterone supplementation and exercise for 12 weeks on body composition and quality of life in elderly men. *Eur J Endocrinol*. 2006;155:867–875.
133. Agledahl I, Hansen JB, Svartberg J. Impact of testosterone treatment on postprandial triglyceride metabolism in elderly men with subnormal testosterone levels. *Scand J Clin Lab Invest*. 2008;68:641–648.
134. Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: A randomized controlled trial. *JAMA*. 2008;299:39–52.
135. Mathur A, Malkin C, Saeed B, Muthusamy R, Jones TH, Channer K. Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men. *Eur J Endocrinol*. 2009;161:443–449.
136. O’Connell MD, Roberts SA, Srinivas-Shankar U, et al. Do the effects of testosterone on muscle strength, physical function, body composition, and quality of life persist six months after treatment in intermediate-frail and frail elderly men? *J Clin Endocrinol Metab*. 2011;9:454–458.
137. Defeudis G, Mazzilli R, Gianfrilli D, Lenzi A, and Isidori AM. The CATCH checklist to investigate adult-onset hypogonadism. *Andrology*. 2018;6:665–679.

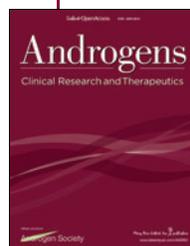
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Abbreviations Used

AUA = American Urological Association
BMD = bone mineral density
CHF = congestive heart failure
CVD = cardiovascular disease
FDA = US Food and Drug Administration
FFM = fat-free mass
LH = luteinizing hormone
HRQoL = health-related quality-of-life
ICSM = International Consultation for Sexual Medicine
NEJM = New England Journal of Medicine
NIH = National Institutes of Health
PDQ = Psychosexual Daily Questionnaire
PSA = prostate specific antigen
RCT = randomized clinical trial
T = testosterone
TD = T deficiency
TTh = T therapy
6MWD = 6-minute walk distance

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