Testosterone therapy in men with testosterone deficiency: Are we beyond the point of no return?

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Although testosterone therapy in men with testosterone deficiency was introduced in the early 1940s, utilization of this effective treatment approach in hypogonadal men is met with considerable skepticism and resistance. Indeed, for decades, the fear that testosterone may cause prostate cancer has hampered clinical progress in this field. Nevertheless, even after considerable knowledge was acquired that this fear is unsubstantiated, many in the medical community remain hesitant to utilize this therapeutic approach to treat men with hypogonadism. As the fears concerning prostate cancer have subsided, a new controversy regarding use of testosterone therapy and increase in cardiovascular disease was introduced. Although the new controversy was based on one ill-fated clinical trial, one meta-analysis with studies that utilized unapproved formulation in men with liver cirrhosis, and two retrospective studies with suspect or nonvalidated statistical methodologies and database contaminations, the flames of such controversy were fanned by the lay press and academics alike. In this review we discuss the adverse effect of testosterone deficiency and highlight the numerous proven benefits of testosterone therapy on men's health and debunk the myth that testosterone therapy increases cardiovascular risk. Ultimately, we believe that there is considerable scientific and clinical evidence to suggest that testosterone therapy is safe and effective with restoration of physiological levels in men with testosterone deficiency, irrespective of its etiology.

Keywords: Cardiovascular risk; Hypogonadism; Prostate cancer; Testosterone; Therapy

INTRODUCTION

The last 2 decades have witnessed a revolution in medical management of men with testosterone (T) deficiency (TD; also known as hypogonadism) [1-15]. TD has been recognized for more than 7 decades [16-18] and T therapy has been used clinically, as early as 1940, both in men and women [16-18]. However, a lack of understanding of the importance of this hormone in human physiology and in particular men's health became a hurdle in the path of clinical utilization of this therapeutic approach by the medical community to restore normal physiological levels of T in men with TD.

One of the major hurdles concerning T therapy in men with TD is the fear that T causes prostate cancer (PCa) [19]. This premise was based on the observation by Huggins and Hodges in 1941 [20] that T promotes progression of metastatic PCa. While the observation remains accurate, demonstrating that metastatic tumors retain expression and function of the androgen receptors (ARs) and therefore T will promote metastatic tumor growth, no evidence exists to suggest that T per se is a carcinogen that promotes development of PCa [19]. Nevertheless, this dogma was taught to medical
students, residents and fellows, for decades, and became a textbook message that T is a carcinogen and causes the development of PCa in men [19]. Although it has never been unequivocally demonstrated that T is an actual carcinogen and indeed promotes development of PCa in men, this myth took hold and attracted followers. However, if this were the case, then one would expect that PCa will be found in all young men over the age 18, since T levels are significantly higher in younger men than in older men [19]. This raises the fundamental question; why PCa is often detected in older men when T levels are significantly low, due to age? This question seems to be either difficult to answer by the myth followers or ignored by the proponents of the theory that “T causes PCa” [21].

A second hurdle hampering the clinical utilization of T therapy in men with TD is the notion that T increases risk of cardiovascular disease (CVD) [22-25]. Such claims were based on flawed studies with no designated primary outcome measures for CVD endpoints [22], retrospective observational studies with suspect methodology and unvalidated statistical methods [24,25] or meta-analysis which included data from studies with nonapproved formulations of T in men with severe liver disease [23]. These studies were vastly promoted in clinical circles [26] and the lay media [27-37], thus contributing to confusion, hype and hysteria. Furthermore, based on several case reports [38], the U.S. Food and Drug Administration (FDA) added a warning label with regard to the risk of T therapy and venous thromboembolism (VTE). This warning added another road block to advancing T therapy in men with TD. Finally, the FDA also suggested that age-related hypogonadism does not warrant treatment and only TD with recognized etiology merits treatment [39]. In this review, we wish to discuss the adverse impact of TD on men’s health and highlight the benefits and risks of T therapy in hypogonadal men. We wish to provoke the readership to critically think about the challenges and opportunities of T therapy and the future of this rapidly changing field in men’s health.

TESTOSTERONE DEFICIENCY

TD (hypogonadism) was recognized, as early as 1940s [16-18] as significant medical condition, which adversely impacts men’s health. TD is associated with increased incidence of metabolic syndrome, obesity, sexual dysfunction, impaired fertility, reduced motivation, increased fatigue, depressed mood, loss of bone and muscle mass, anemia, decreased energy and vigour, insulin resistance, diabetes, inflammation, dyslipidemia, sarcopenia and frailty, reduced quality of life (QoL) and increased mortality [1-15,40-44]. A substantial body of evidence indicates that coronary artery disease incidence and severity, carotid intima-media thickness, atherosclerosis is inversely correlated with serum T concentrations [45]. There is an urgent need among the medical community for greater awareness of the impact of TD on general health in men with TD.

BENEFITS OF T THERAPY IN MEN WITH TD

T elicits a range of physiological processes modulating the physiology and function of multiple organ systems, including muscle, fat, bone, brain, peripheral nerves, and the male genital and reproductive systems. T regulates the metabolism of carbohydrates, lipids and proteins, and influences muscle growth and adipogenesis [5-7,41]. Here in we provide a succinct summary of T therapy benefits on men’s health.

1. T therapy improves sexual function

Animal studies, with no exception, had demonstrated a critical role for androgens in regulating sexual function [46]. Recent clinical studies [3] have provided considerable evidence that T plays an important role in maintaining sexual function. The association of TD with erectile dysfunction and reduced libido in men is well-established. Observational studies, registries and clinical trials also demonstrated that T therapy produced significant improvements in sexual function in men with TD (Table 1) [3,47,48]. Thus the benefit of T therapy on improving sexual function can no longer be ignored or denied. Since sexual health is an integral element of overall health, and sexual dysfunction is associated with depression, reduced mood and loss of self-esteem, it is imperative to state that T therapy is an important therapeutic approach to improve men’s health and QoL.

2. T therapy increases lean body mass, reduces fat mass and improves body composition

It is universally accepted that T therapy in men with TD increases muscle mass and reduces fat mass (Table 2) [49]. T therapy improves bone mineral density [50,51], reduces adipogenesis [52,53] and improves anthropometric parameters (Tables 1 and 2) [8]. Most of studies reported to date show that T therapy increases lean body mass (LBM) [42,49]. Furthermore, long-term T therapy reduces weight (Fig. 1) [49], waist circumference (Fig. 2) [8,54] and body mass index (BMI) [8,45,54]. This is not surprising, since T regulates metabolism
of carbohydrates, lipids and proteins. Also T regulates muscle growth and function and inhibits adipogenesis. The fact that in some studies the aforementioned benefits were not observed is attributed in part to: (1) inclusion of relatively healthy, nonobese men with normal T levels, (2) short duration of T treatment, (3) varying T formulations used, and (4) poor adherence to T treatment. Nevertheless, the overwhelming consensus is that T therapy improves body composition in men with TD [1,2].

### Table 1. Established benefits of testosterone therapy

| Benefits of T therapy                                      | Reported studies                                                                 |
|-------------------------------------------------------------|----------------------------------------------------------------------------------|
| Improved sexual desire and erectile function                | · Corona G, et al. J Sex Med 2014;11:1577-92.                                    |
|                                                            | · Wang C, et al. J Clin Endocrinol Metab 2000;85:2839-53.                         |
|                                                            | · Hackett G, et al. J Sex Med 2013;10:1612-27.                                   |
|                                                            | · Boloña ER, et al. Mayo Clin Proc 2007;82:20-8.                                 |
|                                                            | · Snyder PJ, et al. N Engl J Med 2016;374:611-24.                                 |
|                                                            | · Cunningham et al. J Clin Endocrinol Metab. 2016 Jun 29                         |
| Improved energy, mood and vitality                         | · Hackett G, et al. J Sex Med 2013;10:1612-27.                                   |
|                                                            | · Tong SF, et al. Asian J Androl 2012;14:604-11.                                 |
|                                                            | · Pexman-Fieth C, et al. Aging Male 2014;17:1-11.                                |
|                                                            | · Yassin DJ, et al. J Sex Med 2014;11:1567-76.                                   |
| Increased lean body mass                                   | · Wang C, et al. J Clin Endocrinol Metab 2000;85:2839-53.                         |
|                                                            | · Finkelstein JS, et al. N Engl J Med 2013;369:1011-22.                          |
|                                                            | · Page ST, et al. J Clin Endocrinol Metab 2005;90:1502-10.                        |
|                                                            | · Bhasin S, et al. JAMA 2012;307:931-9.                                          |
|                                                            | · Svartberg J, et al. Int J Impot Res 2008;20:378-87.                            |
|                                                            | · O’Connell MD, et al. J Clin Endocrinol Metab 2011;96:454-8.                    |
| Reduced waist circumference                                | · Haider A, et al. Int J Endocrinol 2014;2014:683515.                            |
|                                                            | · Saad F, et al. Obesity (Silver Spring) 2013;21:1975-81.                         |
|                                                            | · Traish AM, et al. Int J Clin Pract 2014;68:314-29.                             |
|                                                            | · Yassin A, et al. Clin Obes 2013;3:73-83.                                       |
|                                                            | · Hackett G, et al. J Sex Med 2014;11:840-56.                                    |
| Reduced total body fat mass                                | · Srinivas-Shankar U, et al. J Clin Endocrinol Metab 2010;95:639-50.             |
|                                                            | · Finkelstein JS, et al. N Engl J Med 2013;369:1011-22.                          |
|                                                            | · Page ST, et al. J Clin Endocrinol Metab 2005;90:1502-10.                        |
|                                                            | · Bhasin S, et al. JAMA 2012;307:931-9.                                          |
|                                                            | · Svartberg J, et al. Int J Impot Res 2008;20:378-87.                            |
| Increased bone mineral density                             | · Sravberg J, et al. Int J Impot Res 2008;20:378-87.                             |
|                                                            | · Aversa A, et al. Aging Male 2012;15:96-102.                                   |
|                                                            | · Wang C, et al. J Clin Endocrinol Metab 2004;89:2085-98.                        |
|                                                            | · Wang C, et al. Clin Endocrinol (Oxf) 2001;54:739-50.                           |
|                                                            | · Snyder PJ, et al. J Clin Endocrinol Metab 1999;84:1966-72.                     |
| Increased insulin sensitivity                              | · Jones TH, et al. Diabetes Care 2011;34:828-37.                                 |
|                                                            | · Aversa A, et al. J Sex Med 2010;7:3495-503.                                   |
|                                                            | · Heufelder AE, et al. J Androl 2009;30:726-33.                                  |
| Reduced blood glucose & hemoglobin A1c                    | · Haider A, et al. Int J Endocrinol 2014;2014:683515.                            |
|                                                            | · Traish AM, et al. Int J Clin Pract 2014;68:314-29.                             |
|                                                            | · Hackett G, et al. J Sex Med. 2014;11:840-56.                                   |
|                                                            | · Haider A, et al. Obes Res Clin Pract 2014;8:e339-49.                           |

### 3. T therapy reduces cardio-vascular risk factors

It may be a surprise to many that T therapy in men with TD was used as early as 1940s to treat angina pectoris and peripheral vascular disease [16-18]. The elegant reporting by Lesser [18] in which significant improvement in physical function was demonstrated in subjects with angina pectoris subsequent to T therapy provided a glimpse of the potential role of this powerful hormone in vascular health. The role of androgens in vascular physiology is well-established and it is recognized that T plays an important role in cardiovascular...
function [5-7]. A host of cardiovascular risk factors such as obesity, metabolic syndrome, dyslipidemia, hypertension, insulin resistance and diabetes are increased with TD [5-7]. T therapy improves body composition, reduces body weight, waist circumference, and BMI (Tables 1 and 2) [4,8,41]. T therapy also ameliorates metabolic syndrome components [4,49], improves lipid profiles (Fig. 3), reduces blood glucose and hemoglobin A1c (Fig. 4), improves insulin sensitivity and reduces inflammation and attenuates systolic and diastolic blood pressure and improves cardio-metabolic functions [1,2,8]. These benefits are of significance to attenuation of atherosclerosis and improved cardiovascular health.

4. T therapy improves mood and depressive symptoms

The adverse impact of TD on mood and depressive symptoms has been reported in several studies [3,55-61]. Although the magnitude of improvements differed among the various studies, a link between TD, mood and depressive symptoms exists. As pointed out by Khera et al. [58], the association of increased depressive symptoms with TD is confounded by a host of comorbidities that contribute to depression as well as TD. In a multicenter, 12-month observational registry study (n=849) of men with TD treated with 1% T gel, Patient Health Questionnaire (PHQ-9) scores improved significantly (p<0.01) after 3 months of T therapy. By 12-month PHQ-9 scores demonstrated clinically meaningful improvement. In another study in which men (n=886) participating in the Diabetes Prevention Program were treated with metformin, T levels were associated with improvements in mood [59]. In another study Westley et al. [60] showed that depression and/or depressive symptoms were present in 56% of the subjects. In a meta-analysis of 16 randomized trials, Amanatkar et al. [55] found that T therapy had a significant effect on mood in men with TD. Wang et al. [56] demonstrated significant improvement

| Study | Testosterone formulation | Treatment period (mo) | Lean body mass | Fat mass |
|-------|--------------------------|-----------------------|----------------|---------|
| Mårin P, et al. Obes Res 1993;1:245-51. | Gel | 9 | ↑ | ↓ |
| Snyder PJ, et al. J Clin Endocrinol Metab 1999;84:2647-53. | Patch | 36 | ↑ | ↓ |
| Kenny AM, et al. J Gerontol A Biol Sci Med Sci 2001;56:M266-72. | Patch | 12 | ↑ | ↓ |
| Crawford BA, et al. J Clin Endocrinol Metab 2003;88:3167-76. | Mixed esters | 12 | ↑ | ↓ |
| Ferrando AA, et al. Am J Physiol Endocrinol Metab 2002;282:E601-7. | TE | 6 | ↑ | ↓ |
| Steidle C, et al. J Clin Endocrinol Metab 2003;88:2673-81. | Gel | 3 | ↑ | ↓ |
| Wittert GA, et al. J Gerontol A Biol Sci Med Sci 2003;58:618-25. | Oral TU | 12 | ↑ | ↓ |
| Casaburi R, et al. Am J Respir Crit Care Med 2004;170:870-8. | TE | 3 | ↑ | ↓ |
| Page ST, et al. J Androl 2005;26:85-92. | TE | 36 | ↑ | ↓ |
| Kapoor D, et al. Eur J Endocrinol 2006;154:899-906. | Mixed Esters | 3 | ↑ | ↓ |
| Bhasin S, et al. J Clin Endocrinol Metab 2005;90:678-88. | TE | 5 | ↑ | ↓ |
| Kapoor D, et al. Eur J Endocrinol 2007;156:595-602. | Mixed Esters | 3 | ↑ | ↓ |
| Bhasin S, et al. J Clin Endocrinol Metab 2007;92:1049-57. | Gel | 6 | ↑ | ↓ |
| Svartberg J, et al. Int J Impot Res 2008;20:378-87. | Injectable TU | 12 | ↑ | ↓ |
| Allan CA, et al. J Clin Endocrinol Metab 2008;93:139-46. | Patch | 12 | ↑ | ↓ |
| Srinivas-Shankar U, et al. J Clin Endocrinol Metab 2010;95:639-50. | Gel | 6 | ↑ | ↓ |
| Aversa A, et al. J Sex Med 2010;7:3495-503. | Injectable TU | 24 | ↑ | ↓ |
| Aversa A, et al. J Endocrinol Invest 2010;33:776-83. | Injectable TU | 12 | ↑ | ↓ |
| Behre HM, et al. Aging Male 2012;15:198-207. | Gel | 6 | ↑ | ↓ |
| Finkelstein JS, et al. N Engl J Med 2013;369:1011-22. | Gel | 4 | ↑ | ↓ |
| Francomano D, et al. Int J Endocrinol 2014;2014:527470. | Injectable TU | 60 | ↑ | ↓ |
| Bouloux PM, et al. Aging Male 2013;16:38-47. | Oral TU | 12 | ↑ | ↓ |
| Pexman-Fieth C, et al. Aging Male 2014;17:1-11. | Gel | 6 | ↑ | ↓ |
| Juang PS, et al. J Sex Med 2014;11:563-73. | Gel | 3 | ↑ | ↓ |
| Rodriguez-Tolrà J, et al. Aging Male 2013;16:184-90. | Gel/Injectable TU | 24 | ↑ | ↓ |
| Frederiksen L, et al. Age (Dordr) 2012;34:145-56. | Gel | 6 | ↑ | ↓ |
| Emmelot-Vonk MH, et al. J Am Med Assoc 2008;299:39-52. | Oral TU | 6 | ↑ | ↓ |
| Borst SE, et al. J Sex Med 2013;10:28-40. | TE | 12 | ↑ | ↓ |

TE, testosterone enanthate; TU, testosterone undecanoate.
in positive mood and reduction in negative mood with T therapy over a period of 36 months. Observational studies of 799 men on T therapy showed 22% reduction in fatigue scores over 6 months [57]. A modest improvement on global cognition with T therapy was also reported (Table 1) [61].
5. T therapy improves lower urinary tract symptoms

The fear that T may contribute to PCa and benign prostatic hyperplasia (BPH) had confounded the potential benefits of T therapy in ameliorating lower urinary tract symptoms (LUTS). T protects lower urinary tract (LUT) from metabolic syndrome-induced alterations and T treatment in animals with metabolic syndrome (MetS) counteracts the MetS-induced LUT alterations and attenuates the progression of LUTS [62]. Kathrins et al. [63] found no evidence to support that T therapy worsens LUTS symptoms or increase prostate volume in men with TD. Meuleman et al. [64] also reported that long-term T therapy had no deleterious effects on International Prostate Symptom Score (IPSS) total scores and did not change prostate volume or prostate-specific antigen (PSA) in men with TD. A registry study of 999 men with clinically diagnosed TD showed modest positive effects on LUTS [65]. In a systematic review and meta-analysis, Kohn et al. [66] concluded that T therapy did not worsen LUTS in men with TD. T therapy improved LUTSs in men with TD and mild BPH [67,68]. Okada et al. [69] demonstrated that T therapy has considerable therapeutic benefits on LUTS in Japanese men with TD.

6. T therapy reduces progression of sarcopenia and frailty

Age-related decline in muscle mass and function is known as sarcopenia and is often equated with muscle aging [42]. Clinically, sarcopenia is defined as loss of muscle mass with concomitant deterioration in physical function [43,51]. Sarcopenia is associated, in part, to loss of muscle fiber number and size concomitant with loss of limb motor neurons [70]. Sarcopenia is associated with slow gait speed and low grip strength and is central to development of frailty [42]. Sarcopenia is also associated with limited mobility, higher risk of falls and fractures, impaired physical function, disabilities, loss of independence, institutionalization, hospitalization and increased mortality. Reduced T levels are associated with observed loss of muscle mass and strength [71] and sarcopenia is commonly prevalent in older persons [72].

Considerable evidence exists suggesting that T therapy improves some of the components contributing to frailty and physical decline, such as sarcopenia, muscle strength and physical function [42,43,71]. A number of interventional and observational studies have demonstrated consistently that T therapy improves body composition and contributes to increased LBM and reduced FM [42-44,50,52,73-77]. Page et al. [50] demonstrated that T therapy in elderly men (n=70) with mean age of 71 years improved body composition. Srinivas-Shankar et al. [76] reported that in 274 community-dwelling intermediate-frail and frail elderly men at least 65 years of age that T therapy significantly increased LBM and reduced fat mass compared to placebo. These findings are congruent with data reported by Svartberg et al. [52] in which T therapy demonstrated significant improvement in LBM by approximately 42 kg and reduced fat mass with concomitant reduction in total body mass. In severely ill patients with liver cirrhosis and sarcopenia, T therapy resulted in an increase in LBM by 4.7 kg after one year of T therapy [78]. Additional evidence is surmised from studies in which T therapy in men with medically induced TD results in a dose-dependent increase in muscle mass and reduction in FM in young and elderly men [79]. Changes in FM correlated inversely with T dose and were significantly different in young vs. older men. Although T therapy consistently increased muscle mass in all reported studies, however, there are inconsistencies with regard to improvement in muscle.
Traish

Association between low testosterone and all-cause and cardiovascular mortality

| Study                                                                 | Study authors’ conclusions                                                                 |
|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| 1. Khaw KT, 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;116:2694-701. | “In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes. Low testosterone may be a predictive marker for those at high risk of cardiovascular disease.” |
| 2. Laughlin GA, et al. Low serum testosterone and mortality in older men. J Clin Endocrinol Metab 2008;93:68-75. | “Testosterone insufficiency in older men is associated with increased risk of death over the following 20 years, independent of multiple risk factors and several preexisting health conditions.” |
| 3. Menke A, et al. Sex steroid hormone concentrations and risk of death in US men. Am J Epidemiol 2010;171:583-92. | “Men with low free and bioavailable testosterone levels may have a higher risk of mortality within 9 years of hormone measurement.” |
| 4. Tivesten A, et al. Low serum testosterone and estradiol predict mortality in elderly men. J Clin Endocrinol Metab 2009;94:2482-8. | “Elderly men with low serum testosterone and estradiol have increased risk of mortality, and subjects with low values of both testosterone and estradiol have the highest risk of mortality.” |
| 5. Yeap BB, 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;99:9-18. | “Optimal androgen levels are a biomarker for survival because older men with midrange levels of T and DHT had the lowest death rates from any cause, whereas those with higher DHT had lower IHD mortality.” |
| 6. Muraleedharan V, et al. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol 2013;169:725-33. | “Low testosterone levels predict an increase in all-cause mortality during long-term follow-up. Testosterone replacement may improve survival in hypogonadal men with type 2 diabetes.” |
| 7. Pye SR, et al. Late-onset hypogonadism and mortality in aging men. J Clin Endocrinol Metab 2014;99:1357-66. | “Severe LOH is associated with substantially higher risks of all-cause and cardiovascular mortality, to which both the level of T and the presence of sexual symptoms contribute independently. Detecting low T in men presenting with sexual symptoms offers an opportunity to identify a small subgroup of aging men at particularly high risk of dying.” |
| 8. Hyde Z, et al. Low free testosterone predicts mortality from cardiovascular disease but not other causes: the Health in Men Study. J Clin Endocrinol Metab 2013;98:179-89. | “Low testosterone predicts mortality from CVD but is not associated with death from other causes.” |
| 9. Haring R, et al. Low serum testosterone is associated with increased mortality in men with stage 3 or greater nephropathy. Am J Nephrol 2013;33:209-17. | “In the case of early loss of kidney function, measured TT concentrations might help to detect high-risk individuals for potential therapeutic interventions and to improve mortality risk assessment and outcome.” |
| 10. Kyriazis J, et al. Low serum testosterone, arterial stiffness and mortality in male haemodialysis patients. Nephrol Dial Transplant 2011;26:2971-7. | “We showed that testosterone deficiency in male HD patients is associated with increased CVD and all-cause mortality and that increased arterial stiffness may be a possible mechanism explaining this association.” |
| 11. Carrero JJ, et al. Prevalence and clinical implications of testosterone deficiency in men with end-stage renal disease. Nephrol Dial Transplant 2011;26:184-90. | “Testosterone deficiency is a common finding among male ESRD patients, and it is independently associated with inflammation, cardiovascular co-morbidity and outcome.” |
| 12. Malkin CJ, et al. Low serum testosterone and increased mortality in men with coronary heart disease. Heart 2010;96:1821-5. | “In patients with coronary disease testosterone deficiency is common and impacts significantly negatively on survival.” |
| 13. Corona G, et al. Low testosterone is associated with an increased risk of MACE lethality in subjects with erectile dysfunction. J Sex Med 2010;7(4 Pt 1):1557-64. | “T levels are associated with a higher mortality of MACE. The identification of low T levels should alert the clinician thus identifying subjects with an increased cardiovascular risk.” |
| 14. Ponikowska B, et al. Gonadal and adrenal androgen deficiencies as independent predictors of increased cardiovascular mortality in men with type II diabetes mellitus and stable coronary artery disease. Int J Cardiol 2010;143:343-8. | “In diabetic men with stable CAD, testosterone and DHEAS deficiencies are common and related to high CV mortality.” |
| 15. Militaru C, et al. Serum testosterone and short-term mortality in men with acute myocardial infarction. Cardiol J 2010;17:249-53. | “A low level of T was independently related to total short-term mortality.” |
7. T therapy reduces all-cause and vascular mortality

The relationship between TD and increased all-cause mortality has been reported previously [1] (Table 3). A meta-analysis by Araujo et al. [84] in which 16,184 community dwelling men with mean follow-up of approximately 10 years showed that low T were associated with increased risk of cardiovascular (CV) related mortality. No studies have unequivocally established a direct relationship between low T and mortality, but it has been shown that higher T levels were correlated with reduced mortality and lowest T levels are associated with increased risk of CV-related and all-cause mortality.

8. T therapy improves QoL

TD significantly impairs QoL. T therapy improves depression, bone mineral density, energy, libido, erectile function, muscle mass, insulin resistance, and LUTS [86]. Nian et al. [87] reported on the effects of T therapy on QoL and showed that T therapy improves patients' health-related QoL in terms of the decrease in the Aging Male Symptom total score, the psychological, somatic and sexual subscale scores [87]. In a cohort of 223 patients, after adjustments for age and obesity men with normal T levels had significantly better physical and mental health as well as treatment satisfaction responses when compared to those patients with low T levels [88]. It was concluded that men with T levels ≥400 ng/dL reported some improved measures of health-related QoL including greater satisfaction with treatment outcome [88]. Lower T and greater severity of ED independently correlated with poorer physical function.

| Study                                                                 | Study authors' conclusions                                                                 |
|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| 16. Wikstrom et al. Endogenous sex hormones and the prospective association with cardiovascular disease and mortality in men: the Tromsø Study. Eur J Endocrinol 2009;161:435-42. | "Men with free testosterone levels in the lowest quartile had a 24% increased risk of all-cause mortality." |
| 17. Carrero JJ, et al. Low serum testosterone increases mortality risk among male dialysis patients. J Am Soc Nephrol 2009;20:613-20. | "Among men treated with HD, testosterone concentrations inversely correlate with all-cause and CV-related mortality, as well as with markers of inflammation. Hypogonadism may be an additional modifiable risk factor for incident mortality in dialysis patients." |
| 18. Shores MM, et al. Low serum testosterone and mortality in men. Arch Intern Med 2008;168:616-20. | "Low testosterone levels were associated with increased risk of all-cause and CV mortality." |
| 19. Nian et al. Low serum testosterone and mortality in male veterans. Arch Intern Med 2006;166:1660-5. | "Low testosterone levels were associated with increased mortality in male veterans. Further prospective studies are needed to examine the association between low testosterone levels and mortality." |
| 20. Araujo AB, et al. Clinical review: Endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2011;96:3007-19. | "Low endogenous testosterone levels are associated with increased risk of all-cause and CV death in community-based studies of men." |
| 21. Lerchbaum E, et al. Combination of low free testosterone and low vitamin D predicts mortality in elderly men referred for coronary angiography. Clin Endocrinol (Oxf) 2012;77:475-83. | "A combined deficiency of FT and 25(OH)D is significantly associated with fatal events in a large cohort of men referred for coronary angiography." |

DHT, dihydrotestosterone; IHD, ischemic heart disease; LOH, late onset hypogonadism; CV, cardiovascular disease; HD, hemodialysis; ESRD, end-stage renal disease; MACCE, major adverse cardiac events; DHEAS, dehydroepiandrosterone sulphate; FT, free testosterone.
social function, vitality and decline in general health domains of the 36-Item Short Form Survey. This is the first study to report that testosterone deficiency and severity of ED are both independently associated with reduced QoL in men with T2D [88,89]. Furthermore, ED and low testosterone are markers of poor health which impact on an individual's self-perception of their health status [89].

**RISKS OF TESTOSTERONE THERAPY**

1. **Prostate cancer**

   The relationship between T and PCa has been a subject of intensive debate [19,21]. The notion that T is critical for PCa growth made androgen deprivation therapy (ADT) the mainstay of treatment for advanced PCa. Epidemiological and clinical studies suggested that there is no association between T levels and risk of PCa [65,90-93]. There is no evidence to date to suggest that low T levels are protective against PCa and that physiological levels of T increase the risk of PCa. Interestingly, T levels decline with age and PCa incidence increases with age, suggesting that a low T level may contribute to the development of cancer and normal physiological T levels may be protective against PCa [94]. This concept is difficult to grasp in the light of myriad studies linking PCa growth to T on the basis of interpretation of data in which ADT results in regression of metastatic prostate disease. Recently, several studies have demonstrated that ARs in mature prostatic epithelium...
**Table 5. Testosterone therapy does not increase CV risk**

| Study | No. of men in study | Comments |
|-------|---------------------|----------|
| Sharma R, et al. Eur Heart J 2015;36:2706-15. | 83,010 Male veterans with documented low TT levels. | Normalization of TT levels was associated with a significant reduction in all-cause mortality, MI, and stroke. |
| Baillargeon J, et al. Mayo Clin Proc 2015;90:1038-45. | 30,572 Men 40 years and older who were enrolled in one of the nation’s largest commercial insurance programs between Jan 1, 2007, and Dec 31, 2012. | Testosterone therapy was not associated with an increased risk of VTE. |
| Eisenberg ML, et al. Int J Impot Res 2015;27:46-8. | 509 Men had charts available for review. | There appears to be no change in mortality risk overall for men utilizing long-term testosterone therapy. |
| Tan RS, et al. Int J Endocrinol 2015;2015:970750. | Electronic medical records were queried between the years 2009 and 2014 to identify patients diagnosed with hypogonadism, MI, and stroke, as indicated by ICD-9 codes. | Testosterone is generally safe for younger men who do not have significant risk factors. |
| Baillargeon J, et al. Ann Pharmacother 2014;48:1138-1144. | 6,355 Patients treated with at least 1 injection of testosterone matched to 19,065 testosterone nonusers | Older men who were treated with intramuscular testosterone did not appear to have an increased risk of MI. |
| Etminan M, et al. Pharmacotherapy 2015;35:72-8. | 934,283 Men aged 45–80 from the IMS LifeLink Health Plan Claims Database. | An association between MI and past or current TRT use was not found. |
| Anderson JL, et al. Am J Cardiol 2016;117:794-9. | A total of 4,736 men were studied. Subjects supplemented to normal testosterone had reduced 3-year MACE (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.56–0.98, p=0.04) compared to persistently low testosterone. | “We found no support for recent reports that there is an increased risk soon after initiation of TRT. A novel finding of this study is its ability to evaluate differing levels of testosterone achieved by treatment.” |
| Wallis CJ, et al. Lancet Diabetes Endocrinol 2016;4:498-506. | 10,311 Men treated with testosterone and 28,029 controls with a median follow-up of 5.3 years. Patients treated with testosterone had lower mortality than did controls (HR, 0.88; 95% CI, 0.84–0.93). Patients in the lowest tertile of testosterone exposure had increased risk of mortality (HR, 1.11; 95% CI, 1.03–1.20) and cardiovascular events (HR, 1.26; 95% CI, 1.09–1.46) compared with controls. By contrast, those in the highest tertile of testosterone exposure had decreased risk of mortality (HR, 0.67; 95% CI, 0.62–0.73) and cardiovascular events (HR, 0.84; 95% CI, 0.72–0.98), with a significant trend across tertiles (p<0.0001). | Long-term exposure to testosterone replacement therapy was associated with reduced risks of mortality, cardiovascular events, and prostate cancer. |
| Snyder PJ, et al. N Engl J Med 2016;374:611-24. | 790 Men 65 years of age or older with a serum testosterone concentration of less than 275 ng per deciliter and symptoms of hypoandrogenism received either testosterone gel or placebo gel for 1 year. | Seven men in each study group had major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) during the treatment period and two men in the testosterone group and nine men in the placebo group were adjudicated to have had major cardiovascular events during the subsequent year. |

CV, cardiovascular; TT, total testosterone; MI, myocardial infarction; VTE, venous thromboembolism; ICD-9, international classification of diseases, ninth revision; IMS, IMS health is a leading provider of information, services and technology for the healthcare industry around the world; TRT, testosterone replacement therapy; MACE, major adverse cardiovascular events.
are critical for maintaining the differentiated phenotype and overall homeostasis of the gland [90,95-98]. Haider et al. [93] examined data from 1,023 hypogonadal men receiving testosterone therapy. A total of 11 patients were diagnosed with PCa, with incidence of 54.4 per 10,000 patient-years. Baillargeon et al. [92] also concluded that exposure to T therapy was not associated with an increased risk of high grade PCa or receipt of primary ADT following diagnosis.

2. CVD risk

Proponents of the T controversy claiming that T therapy increased CVD risk in men with TD have attempted to make a case out of (1) one ill-fated clinical trial [22], which was terminated prematurely in part due to administration of supraphysiological doses of T in elderly frail men with limited mobility, (2) one meta-analysis [23], which included studies that should not have met the criteria for inclusion and (3) two flawed retrospective studies [24,25], with unvalidated scientific methods of analyses. These flawed studies were used by the lay media to promote scare tactics, hype and hysteria. A trail of events leading to this hype and hysteria is given in Table 4. It should be noted that some authors have attempted to link T therapy to disease mongering and to inventing a new disease [26,99]. These claims are baseless and unfounded in view of the scientific evidence that restoration of physiological levels of T are critical for maintaining men’s health. Interestingly, T therapy has been used as early as 1940s with no reported adverse effects on the CV system [1,2,16,18]. On the contrary, T therapy has been shown to improve the symptoms of angina pectoris and peripheral vascular disease [16,18]. A spectrum of recent studies (Table 5) have shown that T therapy does not increase the risk of CVD. In addition, several meta-analyses have shown that T therapy does not increase CV risk.

Table 6. Testosterone therapy does not increase CV risk

| Meta-analyses study | No. of studies included in the analyses | T therapy resulted in: |
|---------------------|----------------------------------------|-----------------------|
| Isidori AM, et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin Endocrinol (Oxf) 2005;63:280-93. | 29 | No Increase in CVD Risk |
| Haddad RM, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc 2007;82:29-39. | 30 | No Increase in CVD Risk |
| Fernández-Balsells MM, et al. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2010;95:2560-75. | 51 | No Increase in CVD Risk |
| Calof OM, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci 2005;60:1451-7. | 19 | No Increase in CVD Risk |
| Xu L, et al. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med 2013;11:108. | 27 | Increase in CVD Risk |
| Corona G, et al. Therapy of endocrine disease: testosterone supplementation and body composition: results from a meta-analysis study. Eur J Endocrinol 2016;174:R99-116. | 59 | No Increase in CVD Risk |
| Holmegard HN, et al. Sex hormones and ischemic stroke: a prospective cohort study and meta-analyses. J Clin Endocrinol Metab 2016;101:69-78. The Copenhagen City Heart Study, Denmark | 7 | No Increase in CVD Risk |
| Lv W, et al. Low Testosterone level and risk of Alzheimer’s disease in the elderly men: a systematic review and meta-analysis. Mol Neurobiol 2016;53:2679-84. | 11 | No Increase in CVD Risk |
| Neto WK, et al. Effects of testosterone on lean mass gain in elderly men: systematic review with meta-analysis of controlled and randomized studies. Age (Dordr) 2015;37:9742. | 74 | No Increase in CVD Risk |
| Corona G, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. Expert Opin Drug Saf 2014;13:1327-51. | 16 | No Increase of death or CVD risk |
| Guo C, et al. Efficacy and safety of testosterone replacement therapy in men with hypogonadism: A meta-analysis study of placebo-controlled trials. Exp Ther Med 2016;11:853-63. | | |

CV, cardiovascular; CVD, cardiovascular disease.
not increase the risk of CVD (Table 6). The analysis of the FDA [29] in response to a petition to place a black box on T products also concluded that there is no solid evidence that T therapy increases the risk of CVD. The reader is encouraged to read the elegant reviews by Morgentaler et al. [1,2] and Kloner [100] which addressed this topic in greater depth. Thus, there is no credible evidence to indicate that T therapy increases the risk of CVD. On the contrary, T therapy may be protective [9-15].

3. T therapy increased risk of VTE

Several case reports appeared in the literature suggesting that T therapy is associated with serious side effects and increased risk of VTE due to increased hematocrit seen in some men receiving T treatment attributed to testosterone’s ability to stimulate erythropoiesis [38]. As a result of these observations the FDA required pharmaceutical companies to add a warning label to their T products to indicate the risk of VTE due to T therapy. The FDA’s warning was based entirely on these observational case reports [38]. We should point out that new large observational studies [11,15] which investigated the potential adverse effect of T therapy in 30,572 middle-aged in older men and reported that filling a prescription for T therapy was not associated with an increased risk for VTE compared to men without a testosterone prescription [11,15]. These findings strongly suggest that T therapy does not increase the risk of VTE in men with TD.

WHY THERE IS SO MUCH UNEASE IN THE MEDICAL COMMUNITY REGARDING T THERAPY IN MEN WITH TD?

The distortion of the women health initiative (WHI) results both in academic discussions and in the lay media has set fear in the minds of the public, as well as in the medical community. It is disturbing to note that many clinicians will cite the WHI as a reason for not treating men with TD with T therapy. A set of events (Table 4) over the past decade has contributed to the current state of fear, hype and hysteria in the field of T therapy in men with TD. Many of these claims have risen through fear and lack of understanding the physiological role of androgens in human health. In addition, the publication of studies with little or no credible evidence regarding risk of CVD with T therapy [22-25] and the decades long fear of testosterone promoting PCa has compounded this fear [21]. The lay press has also created a negative atmosphere with hype and hysteria around the risks of T therapy that made many clinicians feel that they rather step aside the arena than clearly think about the medical benefits and risks of T therapy [26-37]. These factors together with the fear of litigation, at least in the United States, made many in the medical community prefer to shun T therapy than to understand it benefits, risks and health implications. It is not exaggerated to state that the unfamiliarity of many physicians with this complex subspecialty of andrology, which transcends endocrine hormones, cancer, vascular disease and sexual function has also contributed to this unease.

SUMMARY & CONCLUSIONS

The publication of “Testosterone therapy in older men” [3] should re-ignite the debate on the benefits and harm of T therapy in men. From the outset, we wish to point out that this large study confirms a longstanding and well-documented concept that T therapy has many benefits in men suffering from T deficiency. T therapy is associated with significant improvement in sexual activity, sexual desire and erectile function. Men receiving T therapy reported slightly better mood and lower severity of depressive symptoms. These findings, together with those discussed in this review, show that T therapy has many health related benefits. These include amelioration of the metabolic syndrome components, reduction in fat mass and increased LBM, reduced body weight and waist circumference, increased insulin sensitivity, improved lipid profile, improved blood pressure and reduced inflammatory markers, improved LUTS, reduced mortality and improvement in overall QoL. Thus, the argument that the benefits of T therapy remain unproven should be laid to rest once and for all and health benefits of T therapy can no longer be denied.

The purported adverse effects of T therapy on cardiovascular health is based on flawed studies and remains questionable, at best. As pointed out in several observational studies, meta-analyses, and clinical trials [1,2] T therapy did not cause CVD harm, contrary to previous claims (Tables 5, 6). The findings of a number of studies (Tables 5, 6) dispel claims that men treated with T are at higher risk of myocardial infarctions, stroke and death.

Of importance, the study by Snyder et al. [3] and the resolutions of the consensus panel on T [2] debunked the notion that age-related hypogonadism is not a clinical condition and should remain untreated. As reported in the study [3], T therapy in older men has several benefits and age-related hypogonadism is a clinical condition worthy of treatment. We hope that the findings of this large and well executed study [3] and the summary provided by the
consensus panel [2] will serve as a reminder to those who are beating the drums of fear and hysteria on the dangerous use of T in the treatment of men with TD and reassure men suffering from TD and their physicians that such fears and hysteria are unfounded. This study [3] among others should remind all of us to take a step back and bring common sense rather than emotional outbursts to the discussion. This study [3] gives testosterone the chance to be the “Comeback Kid”.

CONFLICTS OF INTEREST

The author has nothing to disclose.

REFERENCES

1. Morgentaler A, Miner MM, Caliber M, Guay AT, Khera M, Traish AM. Testosterone therapy and cardiovascular risk: advances and controversies. Mayo Clin Proc 2015;90:224-51.
2. Morgentaler A, Zitzmann M, Traish A, Fox, AW, Jones T. Hugh, et al. International expert consensus conference on testosterone deficiency and its treatment- resolutions and conclusions. Mayo Clin Proc 2016;91:881-96.
3. Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al. Effects of testosterone treatment in older men. N Engl J Med 2016;374:611-24.
4. Traish AM, Haider A, Doros G, Saad F. Long-term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: an observational, long-term registry study. Int J Clin Pract 2014;68:314-29.
5. Traish AM. Testosterone therapy in men with testosterone deficiency: are the benefits and cardiovascular risks real or imagined? Am J Physiol Regul Integr Comp Physiol 2016;311:R566-73.
6. Kelly DM, Jones TH. Testosterone: a vascular hormone in health and disease. J Endocrinol 2013;217:R47-71.
7. Kelly DM, Jones TH. Testosterone: a metabolic hormone in health and disease. J Endocrinol 2013;217:R25-45.
8. 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;40:162-70.
9. Anderson JL, May HT, Lapp in 411 hypogonadal men with obesity classes I-III: testosterone replacement therapy on myocardial infarction, stroke, and death in men with low testosterone concentrations in an integrated health care system. Am J Cardiol 2016;117:794-9.
10. Sharma R, Oni OA, Gupta K, Chen G, Sharma M, Dawn B, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J 2015;36:2706-15.
11. Sharma R, Oni OA, Chen G, Sharma M, Dawn B, Sharma R, et al. Association between testosterone replacement therapy and the incidence of DVT and Pulmonary embolism: a retrospective cohort study of the veterans administration database. Chest 2016;150:563-71.
12. Wallis CJ, Lo K, Lee Y, Krakowsky Y, Garbens A, Satkunasmhi R, et al. Survival and cardiovascular events in men treated with testosterone replacement therapy: an intention-to-treat observational cohort study. Lancet Diabetes Endocrinol 2016;4:498-506.
13. Etminan M, Skeldon SC, Goldenberg SL, Carleton B, Brophy JM. Testosterone therapy and risk of myocardial infarction: a pharmacoepidemiologic study. Pharmacotherapy 2015;35:72-8.
14. Baillargeon J, Urban RJ, Kuo YF, Ottenbacher KJ, Raji MA, Du F, et al. Risk of myocardial infarction in older men receiving testosterone therapy. Ann Pharmacother 2014;48:1138-44.
15. Baillargeon J, Urban RJ, Morgentaler A, Gluck CJ, Baillargeon G, Sharma G, et al. Risk of venous thromboembolism in men receiving testosterone therapy. Mayo Clin Proc 2015;90:1038-45.
16. Aub JC, Kety SS. Recent advances in testosterone therapy. N Engl J Med 1943;228:338-43.
17. Beaser SB, Massell TB. Therapeutic evaluation of testosterone in peripheral vascular disease. N Engl J Med 1942;227:43-4.
18. Lesser MA. Testosterone propionate therapy in one hundred cases of angina pectoris. J Clin Endocrinol Metab 1946;6:549-57.
19. Morgentaler A. Testosterone therapy can be given to men with no concern that it will promote prostate cancer development or progression: pro. J Urol 2016;196:985-8.
20. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin 1972;22:232-40.
21. Gleave ME, Klotz L. Testosterone therapy can be given to men with no concern that it will promote prostate cancer development or progression: con. J Urol 2016;196:985-8.
22. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, et al. Adverse events associated with testosterone administration. N Engl J Med 2010;363:109-22.
23. 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.
24. Vigen R, O'Donnell CI, Barón AE, Grunwald GK, Maddox TM, Bradley SM, et al. Association of testosterone therapy
with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013;310:1829-36.

25. Finkle WD, Greeneland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One 2014;9:e85805.

26. Perls T, Handelsman DJ. Disease mongering of age-associated declines in testosterone and growth hormone levels. J Am Geriatr Soc 2015;63:809-11.

27. The Editorial Board. Overselling testosterone, dangerously [internet]. The New York Times. 2014 Feb 4; Opinion page [cited 2014 Feb 5]. Available from: http://www.nytimes.com/2014/02/05/opinion/overselling-testosterone-dangerously.html.

28. Wolfe S, Carone M. Petition to the FDA on all testosterone products [Internet]. Public Citizen; 2014 [cited 2014 Feb 25]. Available from: http://www.citizen.org/documents/2184.pdf.

29. Woodcock. Citizen petition denial response from FDA CDER to public citizen [Internet]. Silber Spring (MD): U.S. Food and Drug Administration, 2014 [cited 2014 Aug 31]. Available from: http://www.citizen.org/documents/2020_FDA%20Final%20Response%20to%20Citizen%20Petition.pdf.

30. Quick study: testosterone supplement may have cardiovascular risks for older men [Internet]. The Washington Post. 2010 Jul 13 [cited 2016 Jul 15]. Available from: http://www.washingtonpost.com/wp-dyn/content/article/2010/07/12/AR2010071204179.html.

31. Testosterone treatments linked to heart risks [Internet]. USA TODAY. 2013 Nov 5 [cited 2014 Jan 29]. Available from: http://www.usatoday.com/story/news/nation/2013/11/05/testosterone-heart-attacks/3448543/.

32. Singer N. Selling that new-man feeling [Internet]. The New York Times. 2013 Nov 23. [cited 2016 Jul 15]. Available from: http://www.nytimes.com/2013/11/24/business/selling-that-new-man-feeling.html.

33. Silverman E. Doctors try to influence a medical journal poll on testosterone treatments [Internet]. The Wall Street Journal. 2014 Dec 2 [cited 2014 Dec 2]. Available from: http://blogs.wsj.com/pharmalot/2014/12/02/doctors-try-to-influence-a-medical-journal-poll-on-testosterone-treatments/.

34. Beck M. In men’s fight against aging, how much risk to take? The FDA is weighing whether testosterone-replacement therapy is safe. [Internet]. The Wall Street Journal. 2014 Oct 27 [cited 2014 Oct 27]. Available from: http://www.wsj.com/articles/in-mens-fight-against-aging-how-much-risk-to-take-1414443065.

35. Sifferlin A. Low-T drugs and heart risk: here’s the latest [Internet]. Time. 2015 Aug 11 [cited 2015 Aug 11]. Available from: http://time.com/3992444/testosterone-heart-disease/.

36. Lester M. Are you man enough? the truth about low testosterone. Time. 2014 Jul 31 [cited 2016 Jul 15]. Available from: http://time.com/3063213/low-testosterone/.

37. Endocrine Society. Too many men take testosterone when they don’t need it [Internet]. The Washington Post. 2014 Jan 13 [cited 2014 Jan 13]. Available from: https://www.washingtongpost.com/national/health-science/too-many-men-take-testosterone-when-they-dont-need-it/2014/01/13/d2ecc700-7956-11e3-af7f-13bf0e99656f_story.html.

38. Glueck CJ, Wang P. Testosterone therapy, thrombosis, thrombophilia, cardiovascular events. Metabolism 2014;63:989-94.

39. Nguyen CP, Hirsch MS, Moeny D, Kaul S, Mohamoud M, Joffe HV. Testosterone and “Age-Related Hypogonadism”--FDA Concerns. N Engl J Med 2015;373:689-91.

40. Antonio L, Wu FC, O’Neill TW, Pye SR, Carter EL, Finn JD, et al. Associations between sex steroids and the development of metabolic syndrome: a longitudinal study in European men. J Clin Endocrinol Metab 2015;100:1396-404.

41. Traish AM, Zitzmann M. The complex and multifactorial relationship between testosterone deficiency (TD), obesity and vascular disease. Rev Endocr Metab Disord 2015;16:249-68.

42. O’Connell MD, Tajjar A, Roberts SA, Wu FC. Do androgens play any role in the physical frailty of ageing men? Int J Androl 2011;34:195-211.

43. Albert SG, Morley JE. Testosterone therapy, association with age, initiation and mode of therapy with cardiovascular events: a systematic review. Clin Endocrinol (Oxf) 2016;85:436-43.

44. Corona G, Giagulli VA, Maseroli E, Vignozzi L, Aversa A, Zitzmann M, et al. Testosterone supplementation and body composition: results from a meta-analysis of observational studies. J Endocrinol Invest 2016;39:967-81.

45. Aversa A, Bruzziches R, Francomano D, Rosano G, Isidori AM, Lenzi A, et al. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. J Sex Med 2010;7:3495-503.

46. Traish AM, Park K, Dhir V, Kim NN, Moreland RB, Goldstein I. Effects of castration and androgen replacement on erectile function in a rabbit model. Endocrinology 1999;140:1861-8.

47. Brock G, Heiselman D, Maggi M, Kim SW, Rodr SW, Rodr SW, et al. Effect of testosterone solution 2% on testosterone concentration, sex drive and energy in hypogonadal men: results of a placebo controlled study. J Urol 2016;195:699-705.

48. Finkelstein JS, Lee H, Burnett-Bowie SA, Pallais JC, Yu EW, Borges LF, et al. Gonadal steroids and body composition, strength, and sexual function in men. N Engl J Med 2013;369:1011-22.

49. Traish AM. Testosterone and weight loss: the evidence. Curr...
50. Page ST, Amory JK, Bowman FD, Anawalt BD, Matsumoto AM, Bremner WJ, 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;90:1502-10.

51. Morley JE. Pharmacologic options for the treatment of sarcopenia. Calcif Tissue Int 2016;98:319-33.

52. Svarterg J, Agledahl I, Figenchau Y, Sildnes T, Waterloo K, Jorde R. Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. Int J Impot Res 2008;20:378-87.

53. Singh R, Artaza JN, Taylor WE, Braga M, Yuan X, Gonzalez-Cadavid NF, et al. Testosterone inhibits adipogenic differentiation in 3T3-L1 cells: nuclear translocation of androgen receptor complex with beta-catenin and T-cell factor 4 may bypass canonical Wnt signaling to down-regulate adipogenic transcription factors. Endocrinology 2006;147:141-54.

54. Francomano D, Buzziches R, Barbaro G, Lenzi A, Aversa A. Effects of testosterone undecanoate replacement and withdrawal on cardio-metabolic, hormonal and body composition outcomes in severely obese hypogonadal men: a pilot study. J Endocrinol Invest 2014;37:401-11.

55. Amanatkar HR, Chibnall JT, Seo BW, Manepalli JN, Grossberg GT. Impact of exogenous testosterone on mood: a systematic review and meta-analysis of randomized placebo-controlled trials. Ann Clin Psychiatry 2014;26:19-32.

56. Wang C, Cunningham G, Dobs A, Irwinmanesh A, Matsumoto AM, Snyder PJ, 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;89:2085-98.

57. Khera M, Bhattacharya RK, Blick G, Kusher H, Nguyen D, Miner M. The effect of testosterone supplementation on depression symptoms in hypogonadal men from the Testim Registry in the US (TRiUS). Aging Male 2012;15:14-21.

58. Khera M, Bhattacharya RK, Blick G, Kusher H, Nguyen D, Miner MM. The effect of testosterone supplementation on depression symptoms in hypogonadal men treated with a testosterone 1% gel. Aging Male 2014;17:1-11.

59. Khera M, Bhattacharya RK, Blick G, Kusher H, Nguyen D, Miner MM. The effect of testosterone supplementation on depression symptoms in hypogonadal men from the Testim Registry in the US (TRiUS). Aging Male 2012;15:14-21.

60. Westley CJ, Amdur RL, Irwig MS. High rates of depression and depressive symptoms among men referred for borderline testosterone levels. J Sex Med 2015;12:1753-60.

61. Wahejoeramono EJ, Ashi PR, Aniwiyanti V, Taddei K, Dhaliwal SS, Fuller SJ, et al. The effects of testosterone supplementation on cognitive functioning in older men. CNS Neurol Disord Drug Targets 2016;15:337-43.

62. Vignozzi L, Morelli A, Sarchielli E, Comeglio P, Filippi S, Cellai I, et al. Testosterone protects from metabolic syndrome-associated prostate inflammation: an experimental study in rabbit. J Endocrinol 2012;212:71-84.

63. Kathris M, Dosch K, Nimeh T, Canto A, Niederberger C, Seftel A. The relationship between testosterone-replacement therapy and lower urinary tract symptoms: a systematic review. Urology 2016;88:22-32.

64. Meuleman EJ, Legros JJ, Bouloux PM, Johnson-Levonas AO, Kaspers MJ, Elbers JM, et al. Effects of long-term oral testosterone undecanoate therapy on urinary symptoms: data from a 1-year, placebo-controlled, dose-ranging trial in aging men with symptomatic hypogonadism. Aging Male 2015;18:157-63.

65. Debruyne FM, Behre HM, Roehrborn CG, Maggi M, Wu FC, Schr Mag FH, et al. Testosterone treatment is not associated with increased risk of prostate cancer or worsening of lower urinary tract symptoms: prostate health outcomes in the Registry of Hypogonadism in Men. BJU Int 2016 Jul 13 [Epub]. http://doi.org/10.1111/bju.13578.

66. Kohn TP, Mata DA, Ramasamy R, Lipshtultz L. Effects of testosterone replacement therapy on lower urinary tract symptoms: a systematic review and meta-analysis. Eur Urol 2016;69:1083-90.

67. Shigehara K, Sugimoto K, Konaka H, Iljiima M, Fukushima M, Maeda Y, et al. Androgen replacement therapy contributes to improving lower urinary tract symptoms in patients with hypogonadism and benign prostate hypertrophy: a randomised controlled study. Aging Male 2011;14:53-8.

68. Ko YH, Moon du G, Moon KH. Testosterone replacement alone for testosterone deficiency syndrome improves moderate lower urinary tract symptoms: one year follow-up. World J Mens Health 2013;31:47-52.

69. Okada K, Miyake H, Ishida T, Sumii K, Enatsu N, Chiba K, et al. Improved lower urinary tract symptoms associated with testosterone replacement therapy in Japanese men with late-onset hypogonadism. Am J Mens Health 2016 Jun 2 [Epub]. http://doi.org/10.1177/1557988316628243.

70. Tomlinson BE, Irving D. The numbers of limb motor neurons in the human lumbosacral cord throughout life. J Neurol Sci 1977;34:213-9.

71. Bhasin S. Testosterone supplementation for aging-associated sarcopenia. J Gerontol A Biol Sci Med Sci 2003;58:1002-8.

72. von Haehling S, Morley JE, Anker SD. From muscle wasting to sarcopenia and myopenia: update 2012. J Cachexia Sarcopenia Muscle 2012;3:213-7.

73. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes
Testosterone therapy in men with testosterone deficiency

JH, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab 1999;84:1966-72.

74. Kenny AM, Kleppinger A, Annis K, Rathier M, Brower B, Judge JO, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. J Am Geriatr Soc 2010;58:1134-43.

75. Ferrando AA, Sheffield-Moore M, Yeckel CW, Gilkison C, Jiang J, Achacosa A, et al. Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. Am J Physiol Endocrinol Metab 2002;282:E601-7.

76. Srinivas-Shankar U, Roberts SA, Connolly MJ, O’Connell MD, Adams JE, Oldham JA, 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;95:639-50.

77. Caminiti G, Volterrani M, Iellamo F, Marazzi G, Massaro R, Miceli M, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. J Am Coll Cardiol 2016;67:775-83.

78. Sinclair M, Grossmann M, Hoermann R, Angus PW, Gow PJ. Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: a randomised controlled trial. J Hepatol 2016 Jun 14 [Epub]. http://doi.org/10.1016/j.jhep.2016.06.007.

79. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Mac RP, Lee M, et al. Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. J Clin Endocrinol Metab 2005;90:678-88.

80. Eichholzer M, Barbir A, Basaria S, Dobs AS, Feinleib M, Gualar E, et al. Serum sex steroid hormones and frailty in older American men of the Third National Health and Nutrition Examination Survey (NHANES III). Aging Male 2012;15:208-15.

81. Mohr BA, Bhasin S, Kupelian V, Araujo AB, O’Donnell AB, McKinlay JB. Testosterone, sex hormone-binding globulin, and frailty in older men. J Am Geriatr Soc 2007;55:548-55.

82. Hyde Z, Flicker L, Almeida OP, Hankey GJ, McCaul KA, Chubb SA, et al. Low free testosterone predicts frailty in older men: the health in men study. J Clin Endocrinol Metab 2010;95:3165-72.

83. Tajer A, O’Connell MD, Mitnitski AB, O’Neill TW, Searle SD, Huhtaniemi IT, et al. Frailty in relation to variations in hormone levels of the hypothalamic-pituitary-testicular axis in older men: results from the European male aging study. J Am Geriatr Soc 2011;59:814-21.

84. Araujo AB, Dixon JM, Suarez EA, Muray MH, Guey LT, Wittert GA. Clinical review: Endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2011;96:3007-19.

85. Yeap BB, Alfonso H, Chubb SA, Handelsman DJ, Hankey GJ, Almeida OP, 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:E9-18.

86. Khera M. Male hormones and men’s quality of life. Curr Opin Urol 2016;26:152-7.

87. Nian Y, Ding M, Hu S, He H, Cheng S, Yi L, et al. Testosterone replacement therapy improves health-related quality of life for patients with late-onset hypogonadism: a meta-analysis of randomized controlled trials. Andrologia 2016 Jul 8 [Epub]. http://onlinelibrary.wiley.com/doi/10.1111/and.12630/abstract;jsessionid=A784F440904F991C3EFA21E5E0DDD560.02t02.

88. Cohen A, Lapin B, Wang CH, Helfand B, Victorson D, Novakovic K. Variation in testosterone levels and health-related quality of life in men diagnosed with prostate cancer on active surveillance. Urology 2016;94:180-7.

89. Brooke JC, Walter DJ, Kapoor D, Marsh H, Muraleedharan V, Jones TH. Testosterone deficiency and severity of erectile dysfunction are independently associated with reduced quality of life in men with type 2 diabetes. Andrology 2014;2:205-11.

90. Simanainen U, Allan CM, Lim P, McPherson S, Jimenez M, Zajac JD, et al. Disruption of prostate epithelial androgen receptor impedes prostate lobe-specific growth and function. Endocrinology 2007;148:2264-72.

91. Endogenous Hormones and Prostate Cancer Collaborative Group, Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst 2008;100:170-83.

92. Baillargeon J, Kuo YF, Fang X, Shahinian VB. Long-term exposure to testosterone therapy and the risk of high grade prostate cancer. J Urol 2015;194:1612-6.

93. Haider A, Zitzmann M, Doros G, Isbarn H, Hammerer P, Yassin A. Incidence of prostate cancer in hypogonadal men receiving testosterone therapy: observations from 5-year median followup of 3 registries. J Urol 2015;193:80-6.

94. Prehn RT. On the prevention and therapy of prostate cancer by androgen administration. Cancer Res 1999;59:4161-4.

95. Wu CT, Altuwajiri S, Ricie WA, Huang SP, Yeh S, Zhang C, et al. Increased prostate cell proliferation and loss of cell differ-
entiation in mice lacking prostate epithelial androgen receptor. Proc Natl Acad Sci U S A 2007;104:12679-84.

96. Niu Y, Altuwaijri S, Lai KP, Wu CT, Ricke WA, Messing EM, et al. Androgen receptor is a tumor suppressor and proliferator in prostate cancer. Proc Natl Acad Sci U S A 2008;105:12182-7.

97. Bonaccorsi L, Muratori M, Carloni V, Marchiani S, Formigli L, Forti G, et al. The androgen receptor associates with the epidermal growth factor receptor in androgen-sensitive prostate cancer cells. Steroids 2004;69:549-52.

98. Leotoing L, Manin M, MontM D, Baron S, Communal Y, Lours C, et al. Crosstalk between androgen receptor and epidermal growth factor receptor-signalling pathways: a molecular switch for epithelial cell differentiation. J Mol Endocrinol 2007;39:151-62.

99. Fugh-Berman A. Should family physicians screen for testosterone deficiency in men? No: screening may be harmful, and benefits are unproven. Am Fam Physician 2015;91:226-8.

100. Kloner RA. Testosterone replacement therapy: new data on efficacy and cardiovascular safety. J Cardiovasc Pharmacol Ther 2016 Apr 28 [Epub]. http://doi.org/10.1177/1074248416646938.