

Testosterone Deficiency and Testosterone Treatment in Older Men

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Keywords

Frailty · Sarcopenia · Testosterone · Testosterone deficiency · Hypogonadism · Functional independence

Abstract

Frailty is a clinical condition related to changes in metabolism, to sarcopenia, and to decline in muscle mass and strength, bone mineral density, and physical function with aging. The pathophysiology of frailty is multifactorial and associated with comorbidities. Testosterone is implicated in regulating metabolic functions, maintenance of muscle and bone, and inhibition of adipogenesis. In older individuals, reduced testosterone is thought to contribute to an altered state of metabolism, loss of muscle and bone, and increased fat, leading to sarcopenia, sarcopenic obesity, and frailty. While no direct relationship between testosterone deficiency (commonly known as hypogonadism) and frailty has been established (due to the multifactorial nature of frailty), clinical evidence suggests that testosterone deficiency is associated with increased sarcopenia and obesity. Testosterone treatment in frail older men with limited mobility and with testosterone deficiency improved insulin resistance, glucose metabolism, and body composition. These changes contribute to better physical function and improved quality of life.

Because frailty increases disability, comorbidities, and the risk of hospitalization, institutionalization, and mortality in older men, it is warranted to explore the potential usefulness of testosterone treatment in frail men with hypogonadism in order to attenuate the progression of sarcopenia and frailty. In this paper, we will discuss the impact of testosterone deficiency on frailty and the potential role of testosterone treatment in ameliorating and reducing the progression of frailty. Such an approach may reduce disability and the risk of hospitalization and increase functional independence and quality of life.

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Introduction

Frailty is an age-related state of vulnerable health with a serious impact on functional dependence and quality of life (QoL) [1, 2]. Frailty encompasses neurological deficits, metabolic dysfunction, bone and skeletal muscle loss, and a decline in cognitive function [1, 2]. A number of potential pathophysiological mechanisms are believed to contribute to the onset and progression of frailty. Among these are: (1) reduced circulating levels of sex steroid hormones, (2) growth hormone deficiency, (3)

vitamin D deficiency, (4) insulin resistance-related comorbidities, (5) chronic inflammation, (6) endocrine disruptions, (7) oxidative stress, (8) cardiovascular (CV) and metabolic dysfunction, (9) nutritional deficiencies, (10) mitochondrial dysfunction, and (11) subclinical multisystemic impairments. Thus, it is difficult to assign a single set of specific mechanisms to the onset and progression of frailty, due to the multifactorial pathophysiology of frailty [3].

Frailty is a common finding in geriatric patients and associated with a burden of comorbidities including myocardial infarction, chronic heart failure, angina, claudication, arthritis, cancer, diabetes, hypertension, and chronic obstructive pulmonary disease contributing to the increased prevalence of disabilities and increased mortality rates among patients with frailty. Because of their increased disability and dependence on others, frail older individuals experience reduced QoL and increased morbidity, resulting in institutionalization and increased mortality [4–7]. For these reasons, frailty is a public health threat with a serious economic impact – in light of an increasing life expectancy and the financial challenges facing health care systems worldwide.

Testosterone is a metabolic and vascular hormone with multiple physiological effects in various target tissues and organs. Testosterone is critical for maintaining muscle mass and function, bone mass, and body composition. Testosterone levels decrease with age, and reference ranges generated from community-based samples of men provide a rational basis for categorizing testosterone levels as low (<350 ng/dL; 12 nmol/L) or normal. Therefore, testosterone deficiency contributes to the onset and progression of sarcopenia, to obesity, and, ultimately, to frailty.

Testosterone deficiency is associated with reduced lean body mass (LBM; primarily muscle mass), bone mineral density (BMD), increased fat mass (FM) with concomitant changes in body composition, reduced physical function and performance, reduced cognitive function, increased depressive symptoms, and increased risk of falls and bone fractures [1–3, 5, 8–12]. Testosterone deficiency is also associated with fatigue, the metabolic syndrome, and anemia [13]. For these reasons, it is believed that testosterone deficiency is related not only to sarcopenia and frailty, but also to an increased risk of institutionalization, hospitalization, and mortality [7, 10–12]. Because of the multifactorial nature and the complex pathophysiology of frailty, there is no single accepted clinical treatment approach for the management of this serious condition in the elderly [3].

The goal of this paper is to summarize and appraise the available evidence pertaining to utilization of testosterone treatment in older men with testosterone deficiency and how this treatment may contribute to improved LBM and BMD, lower FM, enhanced physical and cognitive function, QoL, and reduced hospitalization, institutionalization, and mortality. The potential risks of testosterone treatment in older men will also be addressed.

Effects of Testosterone Deficiency and Testosterone Treatment on Body Composition, Sarcopenia, and Sarcopenic Obesity

Age-related decline in muscle mass and function is known as sarcopenia and is often equated with muscle aging [1, 5, 14]. Clinically, sarcopenia is defined as loss of muscle mass with concomitant deterioration in strength and physical function [1, 5, 14]. Sarcopenia is attributed, in part, to loss of muscle fiber number and size concomitant with loss of limb motor neurons. It is associated with slow gait speed and low grip strength and is central to development of frailty [1, 2, 5, 14]. Sarcopenia is also associated with limited mobility, a higher risk of falls and fractures, impaired physical function, disabilities, loss of independence, institutionalization, hospitalization, and increased mortality. A host of factors contribute to the onset and progression of sarcopenia, which include malnutrition, a sedentary lifestyle, chronic diseases, endocrine disruption, and other comorbidities [1, 3, 5, 14]. Sarcopenia is commonly prevalent in older persons [15], suggesting a link between testosterone deficiency and sarcopenia. Testosterone deficiency is related to reduction in muscle mass and in BMD, and adversely impacts the physiology of the CV system as well as cognitive function.

Considerable evidence exists suggesting that testosterone treatment improves some of the components contributing to frailty and physical decline, such as sarcopenia, muscle weakness, and reduced physical function [1, 2]. A number of interventional and observational studies have demonstrated consistently that testosterone treatment improves body composition and contributes to increased LBM and reduced FM [1, 8, 9, 16–18]. Page et al. [9] demonstrated that testosterone treatment alone or with finasteride, a 5 α -reductase inhibitor blocking conversion from testosterone into dihydrotestosterone, improves body composition. These authors studied older men ($n = 70$) with a mean age of 71 years and total testosterone levels <350 ng/dL for up to 36 months. A signifi-

Table 1. Interventional studies assessing the effects of testosterone therapy on LBM and strength

Study	N	Method	LBM	Strength
Blackman et al. [55], 2002	21	DXA	↑	↔ total body strength
Brill et al. [56], 2002	10	hydrostatic weighing	↔	↔ knee extension and flexion
Clague et al. [57], 1999	7	DXA	↔	↔ grip strength, knee extension and flexion
Emmelot-Vonk et al. [58], 2008	113	DXA	↑	↔ grip, leg strength
Ferrando et al. [21], 2002	7	DXA	↑	↑ leg extension, leg flexion, triceps extension, biceps curl
Giannoulis et al. [59], 2006	23	DXA	↔	↔ grip strength, knee extension and flexion
Kenny et al. [16], 2001	24	DXA	↑	↑ knee extension
Liu et al. [60], 2002	20	BIA/anthropometry	↑	↔ knee extension and flexion, shoulder extension and flexion
Ly et al. [61], 2001	17	DXA	↑	↑ knee flexion ↔ knee extension, shoulder flexion and extension
Morley et al. [62], 1993	8		N/A	↑ grip strength
Nair et al. [63], 2006	27	DXA	↑	↔ chest press, double leg press, knee extension
Page et al. [9], 2005	24	DXA	↑	↑ grip strength ↔ knee extension and flexion
Sattler et al. [64], 2009	40	DXA	↑	↑ composite strength at high dose
Sheffield-Moore et al. [23], 2011	24	DXA	↑	↑ triceps extension, biceps curl, knee extension and flexion
Sih et al. [65], 1997	17		N/A	↑ grip strength
Snyder et al. [20], 1999	96	DXA	↑	↔ grip strength, knee extension and flexion
Srinivas-Shankar et al. [18], 2010	130	DXA	↑	↑ knee extension ↔ knee flexion, grip strength
Tenover [66], 1992	13	hydrostatic weighing	↑	↔ grip strength
Urban et al [67], 1995	6		N/A	↑ knee extension and flexion
Wittert et al. [68], 2003	39	DXA	↑	↔ grip strength, knee extension, plantar flexion

BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry; LBM, lean body mass; N/A, not assessed.

cant improvement in LBM with testosterone or testosterone + finasteride was noted compared to placebo at 6, 12, and 36 months, while FM decreased. These findings suggest that testosterone treatment improves metabolic function and contributes to increased muscle mass and reduced adipogenesis.

Srinivas-Shankar et al. [18] reported that in 274 community-dwelling intermediate-frail and frail older men ≥ 65 years of age with a total testosterone level ≤ 12 nmol/L or a free testosterone level ≤ 250 pmol/L who were randomized to transdermal testosterone (50 mg/day) or placebo gel for 6 months, testosterone treatment significantly increased LBM and reduced FM compared to placebo.

These findings are concordant with those reported previously [8] in which testosterone treatment for 1 year in older men demonstrated a significant increase in LBM by approximately 4.2 kg and reduced FM with a concomitant reduction in total body mass. O'Connell et al. [1] summarized the observational and interventional studies and showed that a large number of studies demonstrated significantly increased LBM with testosterone treatment. These findings clearly demonstrate that testosterone treatment improves LBM and reduces FM in men with low circulating testosterone levels (Table 1).

Additional evidence is obtained from studies in which testosterone treatment in men with medically induced

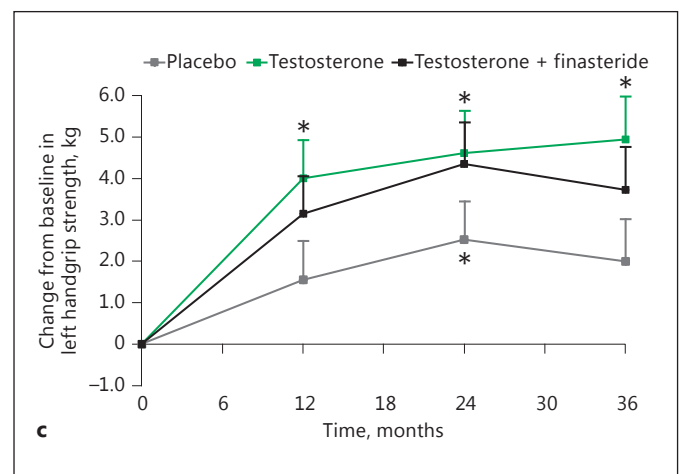
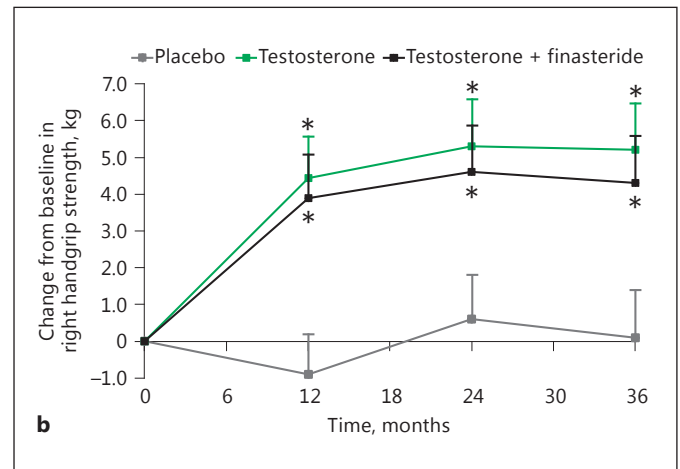
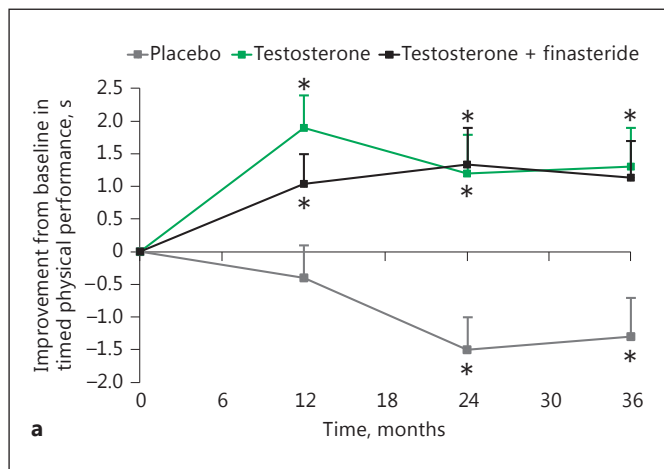


Fig. 1. Change in physical function and strength in older hypogonadal men treated with testosterone, testosterone + finasteride, or placebo for 36 months. Change (mean \pm SEM) in a composite timed physical performance test (PPT; **a**), in right handgrip strength (**b**), and in left handgrip strength (**c**) is displayed. Overall, the testosterone groups were significantly different from the placebo group for the PPT and for right handgrip strength ($p < 0.0002$ for both the testosterone and the testosterone + finasteride groups vs. the placebo group for both measures). In this study, 70 men aged ≥ 65 years with low serum testosterone levels were assigned to receive testosterone alone, testosterone + finasteride (to exclude effects mediated by the conversion of testosterone into dihydrotestosterone), or placebo. Functional parameters and body composition were assessed over time [9].

testosterone deficiency resulted in a dose-dependent increase in muscle mass and a reduction in FM in young and older men [19]. In a randomized, double-blind trial of 60 ambulatory, healthy older men 60–75 years of age who had normal serum testosterone levels, the subjects were treated with a long-acting gonadotropin-releasing hormone agonist to induce medical castration. The subjects were then treated with placebo or with escalating doses of testosterone enanthate weekly for 20 weeks. The changes in LBM and muscle strength in the older men correlated with the testosterone doses and were not significantly different from those reported for younger men [19]. The changes in FM correlated inversely with the testosterone dose and were significantly different between young and older men. High normal testosterone levels produced the most significant gains in LBM and muscle strength [19]. Although testosterone treatment consistently increased muscle mass in all the studies re-

ported, there were inconsistencies with regard to improvement in muscle strength and physical function [10–12].

Effects of Testosterone Deficiency and Testosterone Treatment on Muscle Strength and Physical Function

Although a large number of observational and interventional studies have demonstrated that testosterone treatment in men with testosterone deficiency improves LBM and reduces FM, the effects of testosterone treatment on muscle strength and physical function remain hotly debated. Snyder et al. [20] reported that increasing testosterone levels in healthy men >65 years of age decreased FM and increased LBM, but did not increase the strength of knee extension and flexion, as measured by dynamometer. In contrast, others [21] showed that tes-

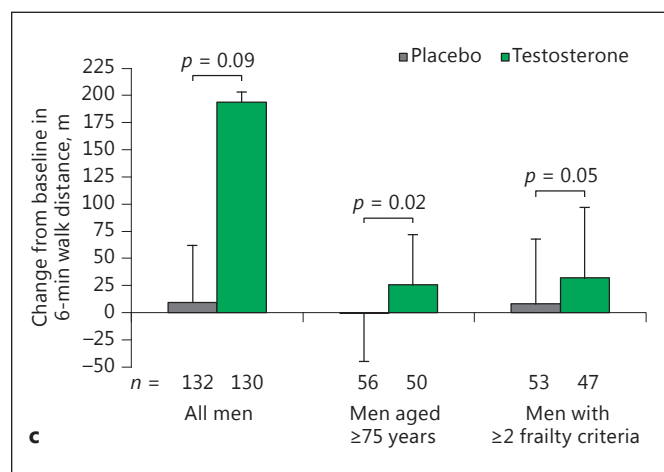
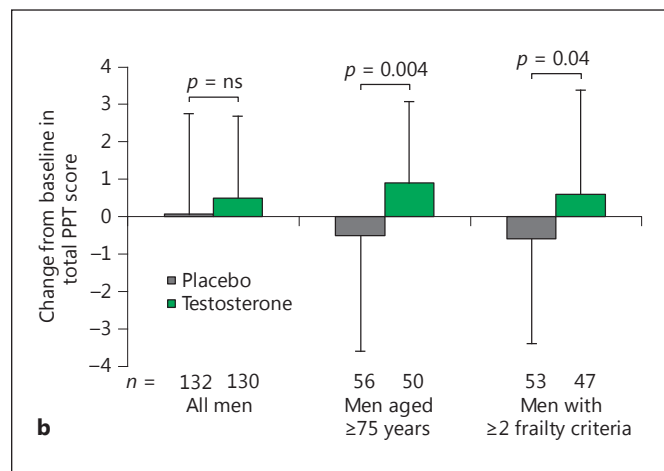
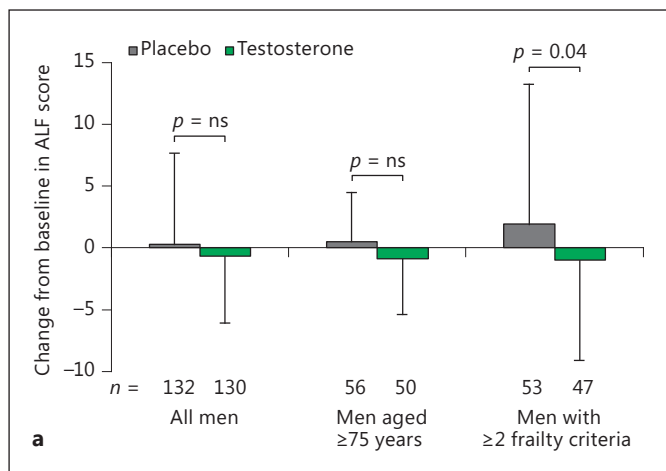


Fig. 2. Change (mean \pm SD) from baseline in ALF score (a), in total physical performance test (PPT) score (b), and in 6-min walk distance (c) in all men, in men aged ≥ 75 years, and in men with ≥ 2 frailty criteria after 6 months of treatment with testosterone. In this double-blind, placebo-controlled study, 274 pre-frail and frail men aged ≥ 65 years with low serum testosterone levels were randomized to testosterone or placebo for 6 months. Outcome measures included muscle strength, body composition, physical function, and self-reported quality of life [18].

tosterone treatment for up to 6 months improved muscle function in men >60 years old. Improvements in muscle function in a testosterone-treated group compared to a placebo group were noted in biceps curl, triceps extension, leg curl, and leg extension. Similarly, Page et al. [9] showed that at each time point, timed physical performance and changes in grip strength from baseline were improved in older men treated with testosterone, but not in men treated with placebo (Fig. 1).

In a randomized controlled trial, 209 community-dwelling men (mean age 74 years) with limitations in mobility and a total serum testosterone level of 100–350 ng/dL or a free serum testosterone level of <50 pg/mL were randomly assigned to receive placebo or testosterone gel (to be applied daily for 6 months) [22]. A significantly greater proportion of men treated with testosterone demonstrated improved leg press and chest press strengths (43 vs. 18%, $p = 0.01$) and stair-climbing power (28 vs.

10%, $p = 0.03$). The increases in leg press strength and stair-climbing power were attributed to the changes in testosterone levels increasing muscle mass. However, measures of physical activity, walking speed, self-reported function, and fatigue did not change significantly between groups. Srinivas-Shankar et al. [18] reported in a similar trial that the aggregated locomotor function test (ALF) score and the physical performance test (PPT) score were both improved by testosterone treatment for 6 months in older frail men with limited mobility when compared with a placebo group [18]. Most importantly, when the ALF score, the PPT scores, and the 6-min walk test values were evaluated for men with ≥ 2 frailty criteria, considerable improvements in all 3 functional parameters were noted with testosterone treatment but not with placebo (Fig. 2). Lower-limb muscle strength parameters as assessed by isometric and isokinetic extension and flexion were all improved by testosterone treatment; how-

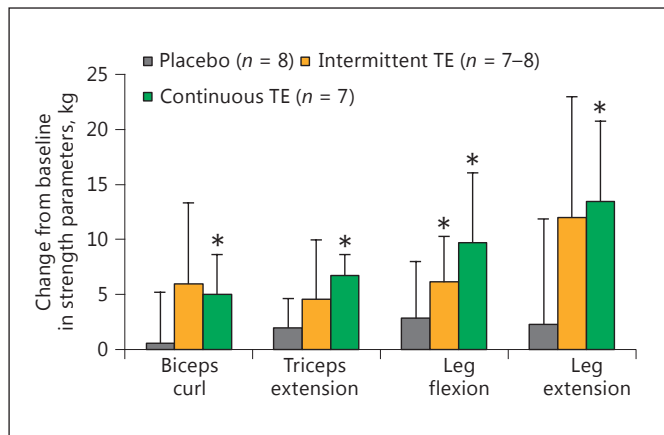


Fig. 3. Change (mean \pm SD) in strength in men aged 70 ± 2 years before and after 5 months of continuous treatment with testosterone enanthate (TE), monthly intermittent TE, or placebo. In this study, 24 older men underwent different regimens of testosterone administration or placebo. The main outcomes included body composition and upper and lower body strength [23].

ever, only isometric extension peak torque results reached significance.

Sheffield-Moore et al. [23] demonstrated changes in muscle strength in 24 community-dwelling older men 70 years of age with testosterone levels <500 ng/dL after 5 months of testosterone treatment compared with placebo. Changes in arm curl, leg curl, arm extension, and leg extension were all significant when compared with a placebo group (Fig. 3). The authors concluded that testosterone treatment improved body composition and increased muscle strength compared with placebo.

Effects of Testosterone Deficiency and Testosterone Treatment on BMD, Falls, and Fractures

A number of studies have demonstrated that testosterone deficiency contributes to reduced BMD and that testosterone treatment improves BMD in older men. In men >65 years of age with low pretreatment testosterone concentrations, increasing testosterone levels increased BMD. No changes in BMD were found in men with normal testosterone levels [20]. Svartberg et al. [8] demonstrated an improvement in BMD in the lumbar spine and total hip in older men treated with testosterone. A significant increase in risk of falls was observed with reduced bioavailable testosterone levels in a cohort of 2,578 relatively healthy men (aged 65–99 years) followed

up for 4 years in the MrOS Study [24]. Approximately 56% of the men in this study reported at least 1 fall, and many fell frequently. Low testosterone levels were associated with increased fall risk. Men (65–69 years old) were at higher risk of fall with low testosterone than were older men (80 years old), and the association between low testosterone and fall risk persisted after adjustment for performance. It was also noted that low testosterone levels were related to reduced physical performance.

Serum testosterone levels are reduced in older men with osteoporotic hip fracture. This may be attributed in part to bone loss as a result of testosterone deficiency contributing to fragility fractures in men. In view of the underdiagnosis and undertreatment of osteoporosis in men, this represents a health care burden if it remains undiagnosed and untreated. Bischoff-Ferrari et al. [25] examined the relationship between testosterone levels and risk of falls in older men ($n = 199$) aged ≥ 65 years living at home over a follow-up period of 3 years with assessment of baseline testosterone levels. The men in the highest quartile of total testosterone had a 78% decreased fall risk. The odds ratio decreased with increasing levels of testosterone based on the quartile assessment, even after adjustments for age, BMI, 25-hydroxyvitamin D, sex hormone-binding globulin, physical activity, smoking, alcohol use, and the number of comorbidities.

Effects of Testosterone Deficiency and Testosterone Treatment on Mood and Cognition

The association between low testosterone levels and depressed mood in older men is well documented, with an inverse relationship between testosterone levels and severity of depression in healthy older men. Ucak et al. [26] assessed elements of the comprehensive geriatric assessment like activities of daily living (ADL), instrumental ADL (IADL), the Mini-Mental State Examination (MMSE), the Mini Nutritional Assessment (MNA), and the Geriatric Depression Scale (GDS) in 250 older men with compensated hypogonadism and in 250 older men with normal hormone levels. Measures of ADL, IADL, MMSE, and MNA scores were significantly lower in the compensated hypogonadism group when compared with the normal testosterone group, independent of age and BMI, suggesting that testosterone-deficient older men exhibited significantly worsening cognitive function, nutritional status, and mood compared with healthy controls.

Impact of Testosterone Deficiency and Testosterone Treatment on Anemia

The prevalence of anemia increases from approximately 5% at the age of 65 years to >20% among independently living individuals at the age of 85 years [27]. Among geriatric inpatients, the prevalence of anemia is even higher (>40%) [28]. The recently published, first German multicenter study on anemia prevalence revealed a prevalence of >50% [29]. Approximately 30% of all anemia cases in the elderly are of unknown etiology. A reduction in testosterone levels has been suggested as contributing to the development of anemia [13]. According to WHO criteria, the prevalence of anemia among men (hemoglobin [Hb] <130 g/L) increased with age from 0.6 to 29.6%, compared with an increase from 0.5 to 27.8% according to the overall 2.5th percentile for men (Hb <129 g/L). For men, Hb declined from the age group of 55–64 years [30]. Anemia is a frequent symptom of testosterone deficiency and may be a factor contributing to the loss of energy and vitality observed in hypogonadal patients. Stimulation of erythropoiesis depends on androgen levels even in older men. Although men with testosterone deficiency are not always diagnosed with anemia, the relationship between testosterone deficiency and low hemoglobin is significant, suggesting that low testosterone is one of the causal factors of anemia. Zhang et al. [31] investigated the effects of testosterone treatment in 58 patients with testosterone levels <235 ng/dL and mild symptoms of testosterone deficiency. Hb, hematocrit, anemia risk factors, whole blood viscosity, and anthropometrics were measured. Hb and hematocrit significantly increased after testosterone treatment, by an average of 2.46 g/dL ($p < 0.001$) and 3.03% ($p < 0.001$), respectively. The prevalence of anemia significantly decreased from 29.6 to 10.0% ($p < 0.001$), and patients with anemia showed a significant increase in erythropoietin after testosterone treatment. An increase in whole blood viscosity and increased hematocrit levels were observed until 54 weeks, even if whole blood viscosity and hematocrit levels stabilized after 18 weeks. Despite these findings, the underlying erythropoietic mechanisms of testosterone are still unclear [32]. Given the fact that anemia impairs functional outcome in geriatric patients [33, 34], an additional negative impact on physical ability caused by dysregulation of testosterone [35] could be detrimental for functional recovery in these patients.

Effects of Testosterone Deficiency and Testosterone Treatment on Frailty

Frailty encompasses a host of changes in body composition, muscle strength, and physical function. A role for testosterone deficiency in the development of frailty has been proposed on the basis of the pleiotropic effects of testosterone on many physiological functions. It is well known that testosterone regulates protein synthesis, nitrogen retention, and carbohydrate and lipid metabolism, and that it inhibits adipogenesis. Testosterone also stimulates erythropoiesis, improves BMD, and is thought to improve appetite and food intake in frail subjects. Testosterone deficiency is implicated in decline in muscle mass, in the onset and progression of sarcopenia, and in reduced muscle strength and physical function.

It is well established that testosterone levels decline with age and a large fraction of men older than 70 years are androgen deficient. Reduced testosterone levels are associated with frailty [5, 14]. Low testosterone levels in frail older men with limited mobility are related to dependency in ADL and to increased hip fractures. In the Massachusetts Male Aging Study, the probability of frailty increased with reduced total testosterone. Also, it is believed that men with low free testosterone levels had 57% higher odds of reporting incident mobility limitation and 68% higher odds of worsening of mobility limitation [11]. In 3,616 community-dwelling men aged 70–88 years, fatigue, difficulty climbing a flight of stairs, difficulty walking >100 m, the presence of >5 illnesses, or weight loss >5% were associated with low testosterone levels [10].

Testosterone treatment contributes to significant increases in muscle mass and strength in older men, especially in those with heart failure [36]. The frailty index (a composite of a large number of components representing signs, symptoms, and functional impairments that accumulate with age) is significantly associated with lower total testosterone, free testosterone, and DHEAS levels even after adjustment for confounders such as BMI and age. This has led to the suggestion that a high frailty index is related to testicular dysfunction and that testosterone levels may represent a marker of frailty. This point is important, because recent data have shown not only beneficial effects of testosterone administration in patients with heart failure, but also that sarcopenia is highly prevalent among these patients [37, 38]. Krasnoff et al. [11] reported in a longitudinal analysis of incident mobility limitation that after adjusting for age, BMI, smoking, and comorbidities (CV disease [CVD] and cancer), each 1-SD increase in free testosterone level was associated with a

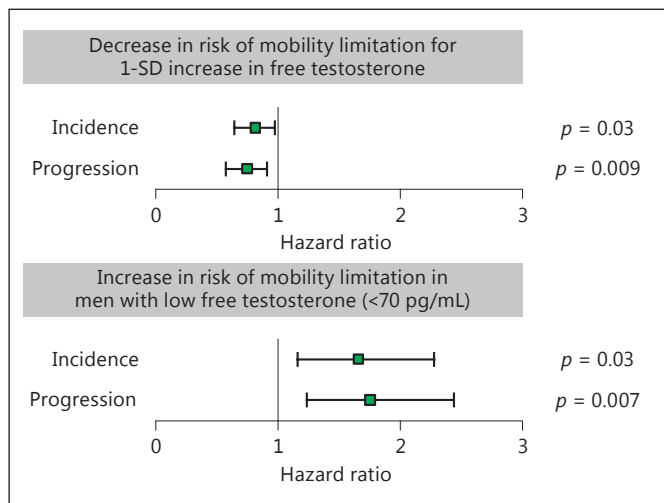


Fig. 4. Longitudinal analyses of incident mobility limitations among 1,445 men (mean age 61.0 ± 9.5 years) who attended Framingham Offspring Study examinations 7 and 8 (a mean of 6.6 years apart). Continuous free testosterone (FT) hazard ratios for a 1-SD increase in hormone levels, adjusting for age, BMI, smoking, and comorbidities (cardiovascular disease and cancer). The upper panel shows that each 1-SD increase in FT level was associated with a 22% (OR = 0.78; 95% CI 0.62–0.97) decrease in the risk of developing mobility limitation and a 25% decrease in progression of mobility limitation. The lower panel shows the association of low FT (<2.5th percentile [<70.0 pg/ml]) at baseline examination 7 with the risk of developing (incident) mobility limitation or of reporting worsening mobility limitation at examination 8. The FT hazard ratios were adjusted for age, BMI, smoking, and comorbidities. The squares indicate point estimates for hormones, and the lines indicate 95% CI. Self-reported mobility limitation, subjective health, usual walking speed, and grip strength were assessed [11].

22% (OR = 0.78; 95% CI 0.62–0.97) decrease in the risk of developing mobility limitation and a 25% decrease in the risk of worsening mobility limitation (progression) (Fig. 4). Srinivas-Shankar et al. [18] demonstrated that testosterone treatment in frail older men resulted in improvements in QoL using a validated health-related instrument (the AMS Questionnaire). The improvement in muscular strength, tiredness, and general well-being was also associated with improvements in the psychological, sexual, and somatic subscales. Improvement in perception of physical functioning among older men was also reported by Snyder et al. [39].

It is important to note that in some studies, testosterone treatment did not lead to functional improvement, irrespective of increased muscle mass [16]. Therefore, while an association between testosterone deficiency and frailty exists, the complex and multifactorial nature of

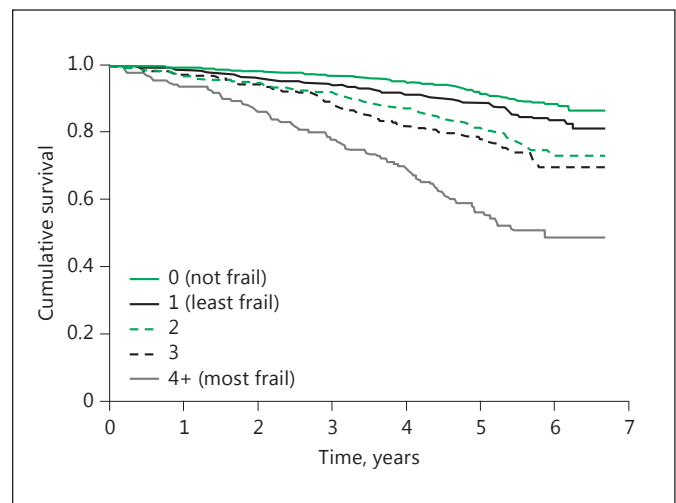


Fig. 5. Kaplan-Meier survival curves for the association between FRAIL scale scores at wave 2 and subsequent all-cause mortality in the HIM Study in Western Australia. In this prospective cohort study, frailty was assessed in 3,616 community-dwelling men aged 70–88 years between 2001 and 2004, and reassessed in 1,586 men aged 76–93 years in 2008–2009. Testosterone and SHBG levels were measured at baseline [10].

frailty does not permit correction of these complex pathophysiological processes with a single agent such as testosterone; thus, combined approaches that utilize exercise, nutrition, and other modalities should be considered. However, testosterone does confer some measure of improvement in frail older men. Low serum testosterone has been reported to be associated with increased mortality, even after adjusting for medical morbidity and other clinical covariables such as waist circumference, smoking habits, alcohol consumption, physical activity, renal insufficiency, and levels of DHEAS. Low testosterone concentrations may be related to increased CV risk factors including reduced levels of high-density lipoprotein cholesterol, increased triglycerides, BMI, and diabetes prevalence. Hyde et al. [10] showed that the association between frailty and all-cause mortality became stronger with the increased components of frailty (Fig. 5). Lower free testosterone was independently associated with frailty at baseline and follow-up.

Discussion

Frailty is a clinical syndrome related to changes in metabolism concomitant with sarcopenia, a decline in muscle mass and strength, bone loss, and reduced physical

function with aging. Testosterone is a metabolic and vascular hormone implicated in a host of metabolic functions, and reduced testosterone levels with age may contribute drastically to the changes noted in body composition and sarcopenic obesity. Although a direct relationship between testosterone deficiency and frailty is not established (due to the multiple factors that contribute to the pathophysiology of this syndrome), a number of studies have suggested that testosterone treatment in frail older men with low testosterone levels improved body composition, QoL, and physical function [7, 10, 11].

Testosterone is a critical modulator of overall health, and testosterone deficiency may contribute directly to increased frailty [10]. Data from patients treated with androgen deprivation therapy for prostate cancer suggest that testosterone is a risk factor rather than a marker for frailty. This is further supported by the observation that post-testosterone treatment benefits in frail older men are lost if testosterone treatment is discontinued, suggesting that reduced testosterone levels represent a risk factor not a marker for frailty.

Substantial evidence exists suggesting that testosterone treatment improves muscle mass, reduces FM, and may improve strength and physical function. Testosterone treatment brings about a significant increase in muscle strength in older men. More importantly, it is compelling that men with heart failure had significant improvements with testosterone treatment in a multitude of physical functions [36]. As shown by Hyde et al. [10] and Krasnoff et al. [11], low free testosterone was independently associated with frailty and worsening of mobility limitations in older men. Furthermore, Eichholzer et al. [12] reported that low free testosterone levels and higher SHBG levels are associated with a significant increase in frailty, even after adjustments for age, race, and ethnicity.

Testosterone treatment improved insulin resistance and glucose metabolism, increased total body mass, and decreased FM [36]. The reported increase in disability, comorbidities, and death rates among frail older individuals with testosterone deficiency warrants providing testosterone treatment to attenuate the impact of sarcopenia, to reduce disability, and to increase functional independence. Testosterone treatment coupled with exercise in patients with and those without heart failure showed improvements in LBM and functional capacity [17, 36]. This suggests that testosterone treatment with exercise attenuates muscle sympathetic hyperactivity and muscle wasting, thus improving functional capacity in hypogonadal patients with heart failure. The increased muscle wasting in patients with heart failure leads to sarcopenia

[37], a fact that has been acknowledged in the guidelines for the diagnosis and treatment of heart failure only recently [40]. It is not surprising that abdominal obesity together with loss of skeletal muscle mass (sarcopenic obesity) contributes to higher all-cause and CV mortality.

The relationship between testosterone deficiency, frailty, hospitalization, and mortality remains to be investigated. Baillargeon et al. [6] reported that older men with testosterone deficiency who were treated with testosterone therapy had a reduced risk of rehospitalization. Furthermore, patients with sarcopenic obesity appear to have a significantly increased risk of all-cause mortality [4]. While the relationship between testosterone deficiency and sarcopenic obesity remains unclear, low endogenous testosterone levels are associated with a greater risk of all-cause mortality [7].

According to most studies, testosterone treatment increases muscle mass, reduces FM, and improves BMD. However, the effects of testosterone treatment on muscle strength, physical function, and cognition remain inconsistent and, at best, controversial. It is important to note that effects of low testosterone levels on fall risk and bone fracture have been widely reported, and testosterone treatment reduces the risk of falls and hip fracture. The relationship between low testosterone and the prevalence of anemia appears to be well understood, albeit complex, and testosterone treatment reduces the risk of anemia.

We wish to point out that the decline in muscle strength with aging often surpasses the decline in muscle mass. Therefore, it is imperative to examine the relationship of decreased muscle fiber number and muscle fiber size to muscle strength. Testosterone treatment in men with testosterone deficiency may result in muscle fiber hypertrophy but may not increase muscle fiber number or size. One potential possibility is that the growth in muscle mass may not translate into strength due to the fact that there are only small gains in muscle mass with no increase in fiber number or size and no changes in neural connections. This would explain the lack of improved muscle strength and function noted in some studies. Also, one must consider that a threshold level of strength is required for maintaining physical function and independence. Thus, in men with testosterone deficiency and low strength, testosterone treatment may normalize small gains in muscle mass and strength which may be considered a substantial functional benefit, but are considered too small when compared to those in young men. Nevertheless, however small, any incremental improvement in muscle mass and strength in older frail men in response to testosterone treatment is beneficial, since this small

change in muscle strength will attenuate the progressive decline in physical function and improve physical and functional independence. There is an urgent need to identify those older men with testosterone deficiency who may benefit from testosterone treatment by improving muscle mass and physical function and by retaining independence and QoL [1, 2, 5, 14].

The purported increased risk of CVD in response to testosterone therapy remains largely unsubstantiated [41–47]. Careful evaluation of the data from the TOM trial – which was designed to investigate the effects of testosterone therapy on physical function in elderly frail men with limited mobility [22] but was not designed to investigate the effects of testosterone treatment on CVD risk – suggests that the data presented do not support the claim that testosterone has adverse effects on CV function. As stated by the authors themselves, “the cardiovascular adverse events reported in the TOM trial were diverse and may have variable clinical importance. The lack of a consistent pattern in these events and the small number of overall events suggest the possibility that the differences detected between the two trial groups may have been due to chance alone.” [22] Most of the CV events reported in this trial were not prespecified or defined in the clinical trial protocol and were not major CV events. For example, pedal edema was the most frequent adverse event noted in the testosterone treatment arm (5 of 25 events). Other events consisted of syncope, nonspecific ECG changes, palpitations, and premature ventricular contractions. Many of these CV events are of questionable clinical significance. These findings are incongruent with data reported previously from a similar trial [18], in which no CVD adverse side effects were reported for the testosterone treatment arm. The study by Vigen et al. [48, 49] grossly misreported primary data, as the absolute risk was actually far lower in men receiving testosterone therapy than in untreated men. The original publication included data on 100 women, from the supposedly all-male study population [48, 49], suggesting data contamination, as was pointed out in multiple reports [41–47]. The overwhelming data mismanagement and contamination makes the evidence derived from this study not very credible. The meta-analysis by Xu et al. [50] did not define the nature of the CV events. This meta-analysis included data from the Copenhagen Study [51], in which men with liver cirrhosis were treated with an unapproved, compounded testosterone formulation, raising circulating testosterone levels 10- to 20-fold above the normal physiological levels. The study also included data from the report on the TOM study [22], which was not designed to investigate

CV risk, and the events reported are, at best, questionable. The latter 2 studies [22, 51] contributed >35% of all events included in this meta-analysis [50]. If these 2 aforementioned studies were omitted, the results of this meta-analysis would be similar to those reported in other studies [41, 42].

The study by Finkle et al. [52] had incomplete or unavailable laboratory data to confirm hypogonadism or to assess whether patients treated with testosterone achieved normal testosterone levels. The reported increase in rates of nonfatal myocardial infarction in the period up to 90 days following a testosterone prescription compared with the prior 12 months was much smaller than that estimated using the NIH calculator. It was not possible to compare the results from a parallel group that did not receive testosterone. The report by Finkle et al. [52] precludes interpretation of the data with any level of accuracy or confidence, since it is not possible to compare results across studies due to differing outcomes and populations. Therefore, the claim that testosterone causes harm by increasing CVD risk [22, 48–50, 52] is, at best, unsubstantiated, thus limiting the credibility and validity of such studies and diminishing the weight of their evidence. The FDA [53] made its own analysis of the aforementioned studies and determined that the evidence presented lacks credibility. Furthermore, several large observational studies and meta-analyses, as well as a large placebo-controlled clinical trial of >790 men [20], have shown that testosterone therapy does not pose an increased CV risk as purported in the aforementioned studies [22, 48–50, 52]. In fact, some suggested that testosterone therapy is cardioprotective [54]. The growing evidence in the literature indicates that testosterone therapy lowers CV risk rather than increasing harm [41–47].

It should be noted that in many studies, the findings may be confounded by the short duration of treatment, as well as by inaccuracies in the methods of assessment of body composition or physical function. It should also be pointed out that long-term testosterone treatment provides the most impressive gains in LBM and reductions in FM, and therefore may contribute to improved muscle strength and physical performance. Furthermore, there is a large number of assessment outcome measures and selection biases such as inclusion of healthy functioning individuals with normal or low-normal testosterone levels and exclusion of those with poor health. In addition, the number of patients in most of the available studies was small, i.e., <100. These confounders contribute to the observation that improvements in muscle strength and physical function are often modest or absent. Long-acting

testosterone formulations and longer treatment durations were shown to yield substantial gains in LBM, suggesting that pharmacokinetics and adherence to treatment may be important factors that need to be evaluated more carefully when assessing changes in both body composition and muscle strength in older men with testosterone deficiency. The issue of patient adherence to testosterone treatment is of critical importance. It is a factor that must be considered with regard to the impact of testosterone treatment and reported improvements in body composition, muscle mass and strength, and physical function. We have to note that transdermal formulations need self-administration and may not be well absorbed by obese men. Similarly, short-acting injections need frequent administration every 10–14 days and may result in mood swings. Long-acting injections (4–5 injections/year) are under full control of the physician, therewith ensuring compliance.

Another confounding factor is the combination of testosterone treatment with exercise. A growth in muscle mass may be a prerequisite for enabling older men to increase physical activity and engage in exercise [19]. Thus,

future studies should consider the impact of dosage, testosterone formulation, duration of treatment, and the sensitivity of measures for assessing physical performance and function – as well as of excluding men with normal testosterone levels – in order to resolve the existing inconsistencies between the various findings reported.

Even modest improvements in muscle mass and strength and gains in physical function in response to testosterone treatment may be of great importance for attenuating the progression of muscle and physical decline in older men. The challenge remains how to differentiate frail older men who may benefit from testosterone treatment from those who may not.

In summary, the data available today suggest a strong relationship between testosterone deficiency and frailty, and such findings warrant further investigation into the effects of testosterone treatment in attenuating and preventing the incidence or progression of sarcopenia and frailty, in reducing hospitalization, institutionalization, and disability, and in improving physical functional independence and QoL in older men.

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