

---

## Frailty and Muscle Function: Role for Testosterone?

U. Srinivas-Shankar · Frederick C.W. Wu

Department of Endocrinology, University of Manchester, Manchester Royal Infirmary,  
Manchester, UK

---

### Abstract

Frailty is a clinical syndrome characterised by reduced physiologic reserve affecting multiple organ systems and is associated with increased risk of falls, fractures, hospitalisation and death. The impact of age-related physical frailty on well-being and health in older men and the potential for prevention and treatment are beginning to be explored. Frailty is multifactorial with aging, comorbidity, sarcopenia, and endocrine immune dysfunction contributing to the condition. Falling testosterone levels with advancing age are associated with muscle loss (sarcopenia) and strength. Among the various therapeutic options being considered, testosterone supplementation offers promise due to its anabolic effects on muscle. In this review, we discuss the syndrome of frailty, its relationship with low testosterone and the effects of testosterone supplementation in healthy and unhealthy/frail older men on muscle mass, strength and physical performance.

Copyright © 2009 S. Karger AG, Basel

Faced with an ageing population, physical frailty is increasingly being recognised as an important health issue worldwide. The burden that this condition is likely to place on health care systems is set to increase in the coming decades. Though there is no universally accepted definition, most researchers agree that it is a distinct clinical syndrome with reduced physiologic reserve affecting multiple organ systems and associated with increased susceptibility to adverse outcomes [1, 2]. It is an aggregation of risk resulting from age or pathology-related summation of decrements affecting various organ systems that renders the individual vulnerable to functional decline.

Based on clinical consensus and research evidence, a phenotype of the clinically frail older adult was operationalized by Freid et al. [2]. The criteria include low-grip strength, self-reported exhaustion, weight loss, low physical activity, and slow walking speed. Those who satisfy three or more criteria are categorised as frail, while those who fulfil one or two criteria are categorised as intermediate or pre-frail. The above definition was tested in the Cardiovascular Health Study in a sample of 4,317 community-dwelling adults aged 65 years and older.

## Consequences of Frailty

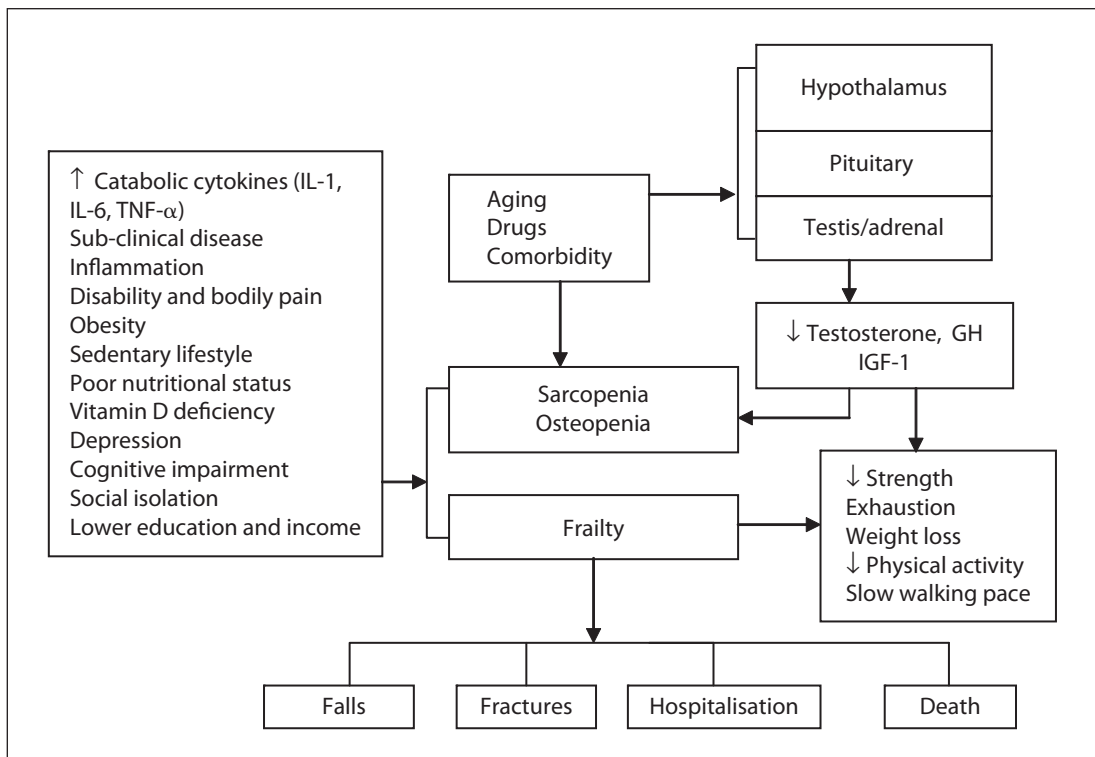
The prevalence of frailty in a cardiovascular health study was 6.9% [2]. The ultimate physical and clinical manifestations of being frail are its association with adverse health outcomes including, increased risk of falls, fractures, diminished ability to perform activities of daily living (ADL), institutionalisation, hospitalisation and death. In the cardiovascular health study [2], frail people had a sixfold higher mortality than people who are not frail for a 3-year cumulative survival. They also had a higher risk of first hospitalisation (59%), first fall (28%), worsening activities of daily living (39%) and mobility disability (51%), compared to men who are not frail over a 3-year period. People who were pre-frail had an intermediate risk of the above-mentioned adverse outcomes, as well as twice the risk of becoming frail over 3–4 years of follow-up compared to people who are not frail.

## Aetiopathogenesis of Frailty

Frailty is multi-factorial in aetiology (fig. 1) with age-associated skeletal muscle loss (sarcopenia), comorbidity, hormonal dysregulation, and immune dysfunction contributing. The summative effect of the hormonal dysregulation, increased levels of catabolic cytokines and immune system dysfunction results in an accelerated loss of muscle mass [3]. This loss of muscle mass (sarcopenia) is central to the concept of physical frailty and explains its manifold manifestations. Decrease in muscle mass and muscle strength, in combination with reduced endurance contributes to reduced physical activity. Maximal oxygen uptake declines and this contributes to muscles fatigue that occurs more easily with advancing age [4].

Comorbidity is an important cause of frailty. Certain comorbid conditions such as lung disease, cancer, cerebrovascular disease and diabetes are more likely to be associated with muscle loss. Comorbid illness act in multiple ways including via their effect on GH pulsatility, leading to a decrease in IGF-1 and the hypothalamopituitary gonadal axis leading to low testosterone (T) levels.

There is a complex physiological interaction between various anabolic hormones (GH, IGF-1 and T), inflammatory cytokines (IL-2, IL-6, TNF- $\alpha$ ), biochemical and molecular pathways mediating catabolism of muscle protein, contributing to age related muscle loss and consequently to physical frailty. Dysregulation of the inflammatory response plays a major role in the age-related muscle loss and decline of physical performance [5]. An increase in the release of catabolic agents including, interleukin-6 (IL-6), TNF- $\alpha$ , and C-reactive protein are associated with reduced muscle mass, physical performance and strength. These agents promote a negative protein balance, and together with elevated markers of blood clotting (factor VIII, D-dimer) contribute to ageing-associated sarcopenia and physical frailty. This is supported by the association between high levels of inflammatory markers (IL-6 and



**Fig. 1.** Schematic diagram representing the aetiopathogenesis, consequences and interaction between low testosterone and frailty.

CRP) and low-grip strength [6]. Further, inflammatory cytokines (IL-6) might inhibit the secretion of IGF-1 and adversely affect its biological activity.

Hypothalamopituitary gonadal and adrenal axis and the somatotrophic axis have been implicated in the aetiopathogenesis of frailty. A decrease in the production of anabolic hormones (testosterone, GH and IGF-1) impairs the capacity of skeletal muscle to incorporate amino acids and synthesise proteins.

It is known that DHEA and DHEAS levels decline with age. Data from the InCHIANTI study [7] suggest that DHEAS levels are related to lower extremity muscle strength and calf muscle area among men aged between 60 and 79 years. Leng et al. [8] have reported that frail people have lower levels of serum IGF-1 and DHEAS and higher levels of IL-6 than non-frail, age-matched individuals. There is loss of pulsatile GH secretion and a decline in IGF-1 levels (including muscle IGF-1) with aging. More than a quarter of circulating IGF-1 is produced by the skeletal muscle and reduced muscle IGF-1 signalling leads to muscle atrophy. Furthermore, there is also an association between IGF-1 levels and measures of physical performance. It has been shown that frail older men have lower levels of IGF-1 levels compared to

non-frail men. The association between testosterone and frailty is discussed in more detail later in the chapter.

### **Testosterone and Aging**

It is well known that total testosterone (TT) levels decrease with age in men from 40 years onwards. The age related decline in free testosterone (FT) and bioavailable testosterone (BT) is greater than TT due to an increase in SHBG with age. Although testosterone levels decrease with age, this decrease in TT is not invariable as a proportion of elderly men have levels in the range of normal young men. The fall in TT with age is exacerbated by comorbidity and chronic use of medication (steroids, opioid analgesia).

### **Association of Low Testosterone with Frailty**

Hypogonadism and physical frailty are multifactorial syndromes and share common aetiologies (fig. 1). Many chronic conditions including, obesity, type 2 diabetes, chronic obstructive pulmonary disease (COPD), liver disease and rheumatoid arthritis are associated with low levels of testosterone and frailty. Some symptoms and signs associated with low testosterone levels are similar to the manifestations of frailty. Loss of muscle mass and strength, lethargy or exhaustion is common to both the conditions.

Persistently low testosterone levels are associated with chronic diseases (rheumatoid arthritis, diabetes, cancer, chronic obstructive pulmonary disease, acquired immunodeficiency syndrome (AIDS)). There is a decrease in endogenous secretion of TT by as much as 30–50% in men with AIDS [9] and a high prevalence of hypogonadism has been shown with COPD [10]. Furthermore, the treatment of several chronic conditions with drugs including steroid, chemotherapeutic agents and opioids might be associated with low testosterone levels. Low testosterone levels have been shown to be associated with decreased physical function and increased risk of 6-month mortality [11].

### **Relationship between Testosterone and Muscle Mass and Strength**

It is well known that muscle mass and strength are related to circulating testosterone levels. Men with primary or secondary hypogonadism or those on androgen deprivation therapy show a decrease in muscle mass and strength and increase in body fat. In a cross-sectional study of 121 men aged 65–97 years, Baumgartner et al. [12] showed that grip strength and appendicular muscle mass were significantly correlated with TT and FT. Further, Perry et al. [13] among men aged 70–102 years,