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# Determinants of Frailty and Longevity: Are They the Same Ones?

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## Abstract

Older people are at risk of developing frailty with advancing age. The prevalence of frailty increases from 2.5–3% in adults aged 65 years to 30–35% in those older than 85 years. These results suggest that an association exists between longevity and frailty. However, at the same time, even at advanced age, the majority of older adults are free of frailty, suggesting that factors different from those contributing to or produced by the life length are involved in producing frailty. Genetic and epigenetic factors, nutrient-sensing systems, mainly the so-called insulin/insulin-like growth factor-1 signaling pathway, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, inflammation, and some hormonal systems are involved in longevity. However, factors involved in frailty are mainly inflammation and hormones, with an anecdotal role for genetic and other potential factors, but even these two common factors seem to regulate longevity and frailty in different ways. Moreover, their effect on frailty seems to change when they are acting in combination.

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## Introduction

During the last century, life expectancy and prevalence of disability have increased in parallel. Life expectancy has increased from 30–35 years at the beginning of the last century to figures approaching 85 years in many of the more industrialized countries [1]. At the same time, and especially during the second half of the 20th century, there has been an increase in the prevalence of disability in those same

countries [2]. Although in the last decades the rate of increase in life expectancy has apparently started to decline and the prevalence of disability has begun to stabilize or smoothly decrease [2–4], there is still a tendency to believe that the changes that promote and accompany the extension of longevity are the same as those underlying disabling processes in general, and frailty in particular. If this holds true, frailty and disability should be an inevitable consequence of the aging process, an inexorable result of prolonging the duration of our life. If this is not true, i.e. longevity and frailty only share some common mechanisms but they are regulated in different ways to increase longevity or, on the opposite, to produce frailty, increasing longevity without experiencing relevant frailty will be feasible. However, disentangling longevity and frailty can be a tricky task because one of the characteristics of frailty, no matter the chosen conceptual model, is to predict death.

Both longevity and frailty share some common facts, with the loss of functional reserve being the most relevant [5, 6]. Although frailty is more prevalent with increasing age, the majority of the people never reach a state of frailty even when they reach advanced age. Thus, at a first glance, it looks like longevity and frailty share some causes that act by similar mechanisms (i.e. involved both in longevity and frailty); other causes (e.g. sexual hormones) produce beneficial effects prolonging longevity but increasing the risk of frailty, and, finally, some exclusive causes that operate independently are based on different mechanisms.

Furthermore, while the mechanisms involved in longevity seem to exert their effects in the majority of cells, organs, and systems (although at a different rate and intensity), the mechanisms involved in frailty seem to be of importance in the organs and systems related to energy consumption and mobility, mainly the osteo-muscle-skeletal system and the peripheral nervous system.

Finally, some chronic diseases and conditions have been especially related to frailty: ischemic heart disease, heart failure, chronic obstructive pulmonary disease, type 2 diabetes mellitus, cognitive dysfunction/dementia, and arthritis. The majority of them show some common pathophysiological characteristics that involve inflammation, insulin resistance, nutritional deficits, and musculoskeletal deficits affecting mobility and function.

## **Longevity and Functional Reserve**

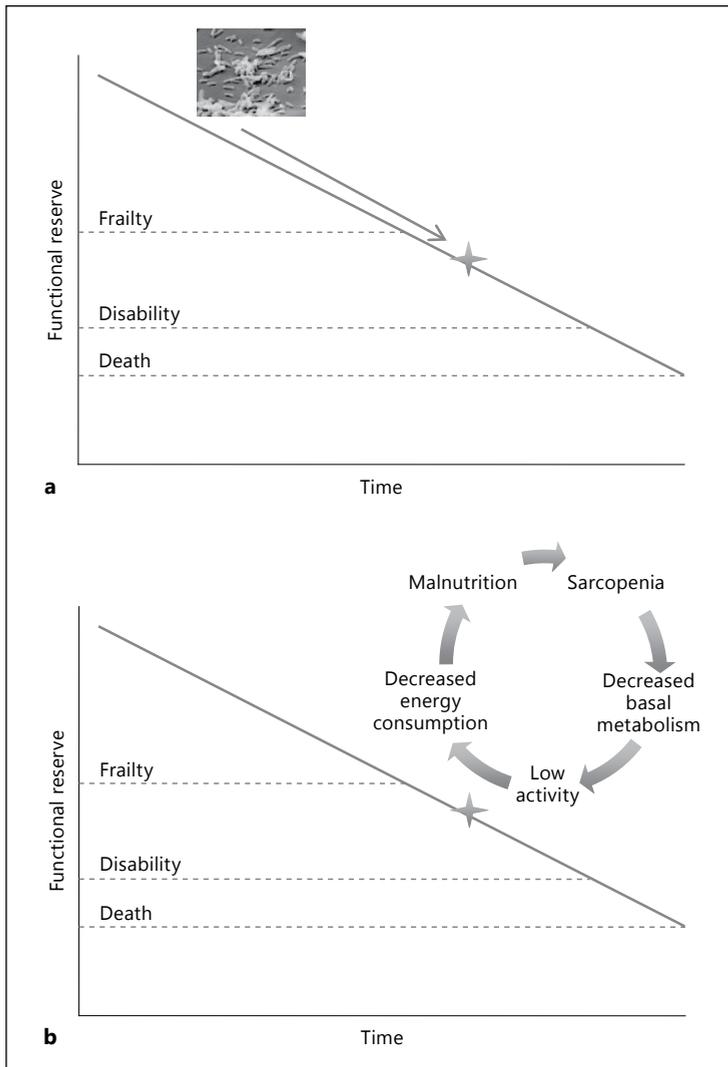
As previously stated, one of the most important changes accompanying the aging process is a progressive loss of functional reserve. This process starts at the end of the maturational phase and lasts until death. Only after losing around 70% of our functional capacity, we are at risk of experiencing frailty or disability [7]. When the loss exceeds 80%, the risk of death occurs. During lifetime, function declines at a

rate of 0.5% per year in all systems, with most data being available for those aged 30–70 years [8], although data from the Baltimore Longitudinal Study, measuring peak treadmill oxygen consumption, suggest that this rate can be accelerated with advancing age, reaching rates of 2% per year in the 70s and beyond [9]. This general, basal rate, which is based on intrinsic aging and insusceptible to changes (including leisure time physical activity), makes it unlikely to cross the line of 30% of remaining function that determines the presence of frailty or disability. But this basal rate can be accelerated under different extrinsic circumstances, with a rate ranging from a mean of 1% per week to 2% per year, leading to catastrophic or slowly accumulating decrements that will lead to different rates of aging. These different rates have a high interindividual variability, which is one of the main factors contributing to the high phenotypic heterogeneity that is typical in older people. Moreover, the differences in the rate of aging may also explain the differences in the trajectories of people during their last year of life. In this regard, it is noteworthy that frail decedents are more than 8 times more likely than sudden-death decedents to be dependent on help in activities of daily living [10], which illustrates the proximity of frailty to disability, with low functional reserve (a characteristic of frailty) being one of the most important risk factors for disability.

### **Disease, Functional Reserve, and Frailty**

Having in mind this general scheme, which is the role for disease and other conditions, and which are the mechanisms increasing the rate of functional loss? Although there are several models to explain this relationship, probably a more comprehensive one was released in the Report of the National Institute on Aging on Comorbidity [11]. According to this report, aging produces few generalized changes (inflammation, oxidative stress, apoptosis, hypoxia, and hormonal changes). When diseases or conditions that exhibit all or some of these changes among their pathophysiological mechanisms coexist with aging, they aggravate these physiological impairments to finally produce clinical consequences that ultimately affect the functional status of older people (fig. 1a).

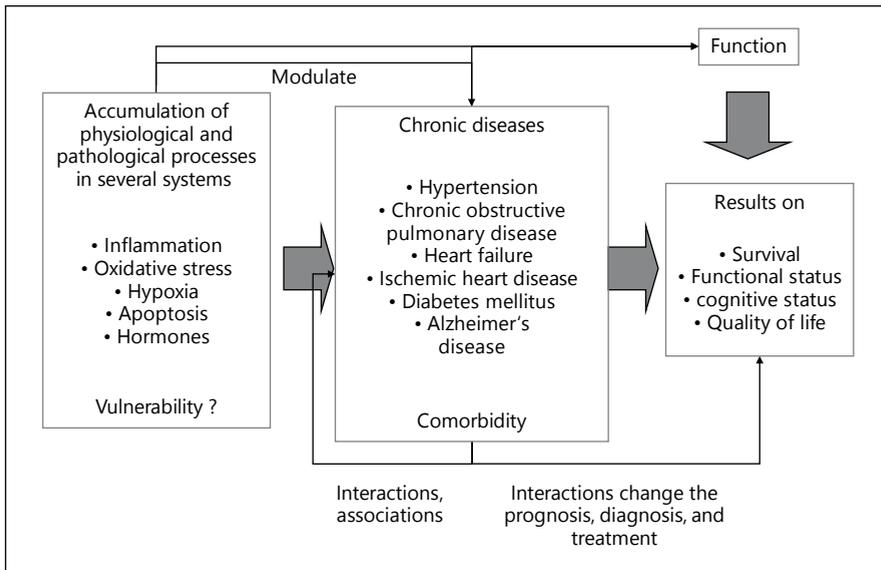
In other words, and according to our scheme, chronic disease accelerates the rate of functional loss, acting as the precipitating factor of frailty and disability (fig. 2). At the same time, once the disease(s) has produced its effect, its consequences (frailty or disability) evolve independently (fig. 1b). In fact, in very old people, the accuracy of comorbidity for predicting death and disability is lower than that of frailty. As a consequence, if you only treat the diseases/conditions but not the functional deterioration produced by them, the clinical symptoms of the diseases will improve but functional impairment will remain unchanged.



**Fig. 1. a** Disease accelerates the rate of decline of functional reserve, facilitating the occurrence of frailty. **b** Once frailty has been established, it progresses autonomously.

### Longevity and Frailty: Biological Background

Frailty is in essence the final product of the interrelation between the aging process and different chronic diseases and conditions. Thus, several of the changes accompanying the aging process and some of the causes and mechanisms underlying them should be also present in frailty (table 1). In some way, these are the longevity-associated mechanisms predisposing to the development of frailty.



**Fig. 2.** Model for the relationship between aging and disease to produce frailty and functional decline.

**Table 1.** Relationships between different factors and longevity/frailty

	Longevity	Frailty
Genetic factors	Associated	Associated ( $\pm$ )
Epigenetic factors	Associated	NR
Cellular senescence	Associated	NR
Mitoch. dysfunction	Associated (-)	Associated (-)
Inflammation	Associated (-)	Associated (-)
IIS pathway	Associated (-)	Associated (+)
Testosterone	Associated ( $\pm$ )	Associated (+)
Estradiol	Associated (+)	Associated (-)
Protein glycosylation	Not relevant	Associated

IIS = Insulin/IGF-1 signaling; regarding longevity: + = higher levels increase the life span; - = higher levels decrease the life span; regarding frailty: + = higher levels protect against frailty; - = higher levels favor frailty.

### Longevity

In a recent review paper on the causes and mechanisms of aging [12], four main causes have been identified as the ‘primary hallmarks’ of aging by determining the original damage: genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis. All of them produce damage in nuclear and mitochondrial DNA or changes in the proteasome resulting in proteotoxic effects

due to the accumulation and aggregation of unfolded proteins. Consequently, and in response to this damage, the other three sets of mechanisms try to mitigate this damage, but in case of persistent damage, these initially protective mechanisms become deleterious. These so-called ‘antagonistic hallmarks’ are deregulated nutrient-sensing, mitochondrial dysfunction, and cellular senescence. The main component of the first of them is the insulin/insulin-like growth factor (IGF)-1 signaling pathway, including all its downstream components. This pathway is associated with higher longevity when its performance is reduced at any level [13], and it is probably responsible for the life-prolonging effect of dietary restriction that has been shown in many species, including (although with controversial findings) nonhuman primates [14].

Mitochondrial dysfunction, whatever the responsible mechanism (e.g. mitochondrial DNA mutation or mitophagy), increases the generation and release of reactive oxygen species (ROS). At low concentrations, ROS play a significant role in cellular and intercellular signaling that facilitates cell survival and the occurrence of many significant cellular processes, whereas irreversible damage to different cell structures is caused above a certain threshold [15]. Finally, cellular senescence has been regarded as a defensive mechanism against malignant cell transformation. However, with aging, the clearance of these senescent cells is decreased; decreased clearance that in addition to a decreased capacity of progenitor cells to reestablish well-functioning cell numbers results in the accumulation of senescent cells with the ensuing consequences. One of these consequences is an increase in the production of cytokines [16]. In this regard, the role of p53 and p16<sup>INK4a</sup> seems to be of importance, and their levels are associated with chronological age [17]. Interestingly, however, the suppression of p16<sup>ink4a</sup> in transgenic mice has shown to have an effect which does not prolong longevity but rather delay the onset of some phenotypes associated with disorders that typically appear in older animals [18].

The interaction between the four mechanisms causing the original damage and the three ones trying to tackle it, is going to produce consequences on two main systems that will be finally responsible for the aging phenotype: stem cell exhaustion and altered intercellular communication, which are controlled by changes in immune and inflammatory responses (inflammaging) [19] and the endocrine system.

### *Frailty*

Several systems and factors have been involved in the generation of frailty. The loss of functional capacity and functional reserve that is characteristic of frailty is mainly due to changes in two systems: hormonal dysregulation and inflammation, which, in turn, can be modulated by both genetic and environmental

influences. The changes in these physiological systems, in addition to the compromise in several regulatory functions, finally impact on different target organs (bone, brain, vessels, and muscle). Among these organs, the effect on skeletal muscles and its energetic mechanisms (both energy production and energy expenditure, with a predominance of catabolism over anabolism) has a pivotal role in producing the clinical phenotype.

Before looking at some of these changes, it should be underscored that one of the main characteristics of frailty is its multidimensional nature, with an increasing risk of frailty when several systems are involved in a dose-dependent relationship [20]. Thus, when facing the biological basis of frailty, we should consider the effect of the combination of several factors instead of the individual effect of each one alone.

*Inflammation.* Frailty has been associated with several traditional markers of inflammation [21] (e.g. IL-6, TNF- $\alpha$ , C-reactive protein, fibrinogen, D-dimer, and leukocytes). The origin of this low-grade inflammatory status that accompanies frailty is an issue of controversy, and among the different candidates are the increase in senescent cells, decreased response to Toll-like receptor ligation [22], decreased muscular activity, and upregulated expression of some stress-responsive inflammatory pathway genes [23]. However, the role of the adipose tissue seems to be predominant. Several sources of evidence have found a possible connection between the adipose tissue and muscular fibers, with a fluent dialogue between both tissues by means of adipokines and myokines [24]. Two short comments to this issue: although the relationship between adipose tissue has been mainly established with visceral adipose tissue, one of the changes in the body composition during the aging process is a progressive infiltration of skeletal muscles by adipose tissue, with the metabolic characteristics of this adipose tissue being similar to those of the visceral adipose tissue. In this regard, it should be highlighted that the amount of intermuscular fat is not affected by physical activity [25]. The second comment concerns the relationship of obesity with both longevity and frailty. The relationship between body mass index (BMI) and mortality changes with age. Although a high BMI in young adults increases the risk of death, this relationship is U-shaped in older people, with the optimal BMI being in the range of overweight and stage-1 obesity, probably reflecting the changing proportion between muscle mass and fat mass with age.

However, the effect of BMI on frailty seems to be more linear, with a direct relationship between frailty and BMI, with the paradigm of this relationship being the one observed in sarcopenic obesity. Furthermore, both overweight and obesity during adulthood have been associated with the development of pre-frailty and frailty in the elderly [26].

*Hormonal Changes:* Frailty is associated with an impairment in different anabolic hormones. Although some disparate effects of inflammation on longevity and frailty have been cited previously, it is in the field of hormones where these disparate effects are probably more relevant. Three main groups of hormones are involved in frailty: growth hormone (GH)/IGF-1 and insulin, sexual hormones (testosterone and estradiol), and cortisol/dehydroepiandrosterone (DHEA) [27].

DHEA is a steroid precursor of testosterone. DHEA and its sulfated form DHEA-S are produced by the adrenal cortex, and the biological role of these hormones is not yet well defined. Observational cohort studies have demonstrated that plasma levels of DHEA and its sulfated form decline by 80% between the ages of 25 and 75 years, and this decrease is greater after 80 years. In parallel, muscle mass and strength also decline with age, and both low DHEA plasma levels and a high cortisol/DHEA ratio predict the risk of developing frailty [28]. Published data about DHEA replacement in older people are confusing and conflicting. In fact, there are few studies on DHEA supplements and evaluation of muscle function. Moreover, most of them are performed in small cohorts aged between 50 and 70 years, making extrapolation of the results to the general population of older people a major issue [29]. In addition to its association with frailty, serum DHEA-S is also a predictive factor for long-term longevity, as higher plasma concentrations have been associated with greater longevity [30].

It has been well established that in subjects over 65 years of age serum testosterone levels tend to be considerably reduced, a state that has become known as andropause. Free testosterone levels begin to decline at a rate of 1% per year after age 40 years. It is estimated that 20% of men aged 60–80 years have levels below the lower limit of normality of adult men. This decrease has been directly associated with low longevity [31] in men and frailty in older men and women [32]. In women, although low testosterone levels seem to be also related to frailty [32], the most important issue from a hormonal point of view is menopause, which causes a sudden drop in sex steroid hormones resulting in loss of bone density but also in muscle weakness. Moreover, a recent study [33] suggested that the relationship between frailty and estrogens could be opposite to the one expected: frailty seems to be associated with high estrogen levels in older (i.e. postmenopausal) women. In addition, and in contrast to what occurs with testosterone, high levels of estrogen are associated with increased longevity, but also with frailty, especially if they are associated to inflammation. So the beneficial effect of estradiol on survival [34] is opposed to the effect on frailty.

GH levels also decrease with age. Compared with nonfrail older adults, frail older adults have lower levels of IGF-1, a GH-stimulated messenger molecule. In this same regard, insulin resistance is also associated with frailty, supporting the

contribution of low-functioning insulin/IGF-1 signaling to a prolonged survival but, at the same time, to the presence of frailty. In addition, mitochondrial dysfunction in skeletal muscles seems to be one of the factors involved in the generation of insulin resistance in older people due to a poor utilization of glucose secondary to impaired oxidative phosphorylation, which results in increased ROS levels. Furthermore, sirtuins also have disparate relationships with longevity and frailty. In mice, while sirtuin 1 does not produce any effect on longevity but improves the health status, sirtuin 6 prolongs longevity by an effect mediated by IGF-1 without having any effect on the health status. Finally, sirtuin 3 seems to be involved in the beneficial effects of caloric restriction on longevity in mammals.

Interestingly, the role of the combination of these factors in the association with frailty has been extensively studied, and some relationships with frailty are stronger (which is the case for estradiol and inflammation, previously commented) or subject to changes. In this later case, among the different combinations of factors, it is worthy to mention the association between inflammation (assessed by white blood cell counts) and IGF-1. The highest odds ratio for the association with frailty was observed when both inflammation and IGF-1 were in the high tertile, changing the relationship of isolated IGF-1 with frailty [35].

Finally, genetic factors have also been involved in the development of frailty. With longevity being a familial trait, some authors have tried to associate longevity of the parents with frailty (or less frailty) in the offspring, and found a relationship between the age of the parents and the performance in some functional tasks (but not in all of them) [36]. Although there are few studies on the genetic background of frailty, polymorphisms in some groups of human genes related with apoptosis and transcription regulation could be involved [37].

Telomere length has also been studied with disparities in the results. While some authors have found a marginal association between telomere length and longevity in older people, the majority of works have reported an absence of associations between mean telomere length and percentage of short telomeres with longevity. However, one group has found a relationship between telomere length in leukocytes and disability (i.e. in activities of daily living) in nondiabetic subjects [38].

Finally, some factors with no potential direct relationship with longevity, e.g. glycoproteins (including HbA1c) [39] and vitamin D, have also been related with a higher risk of developing frailty in humans.

In summary, longevity and frailty share some of their underlying mechanisms. This fact may explain why they are closely related and the association between advanced age and a higher prevalence of frailty, but at the same time longevity and frailty differ in some characteristics. First, while aging/longevity is a universal and intrinsic phenomenon, frailty is modified by external factors

and has its main impact on four organs. Second, some factors that prolong longevity (favorable effect on the duration of life) increase the risk of frailty (unfavorable effect on the quality of life), while others protecting from frailty shorten the life expectancy. These different characteristics may explain the different courses of longevity and the functional status in many older people, opening opportunities for intervention.

## Disclosure Statement

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