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# Frailty, from Humans to Mouse Models

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## ABSTRACT

The frailty corresponds to a syndrome of well-defined biological and clinical characteristics within its physical phenotype, is multidimensional, dynamic and non-linear. It has a high prevalence in the elderly population and increases after 65 years of age. The syndrome of frailty can be considered as a state of predis-capacity or risk of developing a disability and dependence from a situation of incipient functional limitation. It is identified by a decrease in the resistance and the physiological reserves that lead to a deterioration of the physiological systems, causing adverse effects on health. This report aims to highlight the most useful mouse models used in the research based on the biological hypothesis of the human frailty syndrome. Animal studies provide opportunities that can help us understand the mechanisms that trigger frailty. In addition, they provide empirical evidence on their pathways and physio pathological mechanisms, as well as the identification of potential biomarkers to generate interventions and treatments that modulate or counteract the syndrome.

## INTRODUCTION: FRAILTY AS CLINICAL SYNDROME

Frailty is a concept that has increased substantially since the 1980s [1]. Different authors emphasize diverse aspects of frailty incorporating physical function, cognitive function and psychological and psychosocial factors, making it possible to differentiate characteristics of a phenotype which evolves towards a state of dependence, loss of the physiological reserves, uncoupling from the environment, chronic illnesses and their complications [2-4]. Most definitions include an excessive reduction of lean body mass (sarcopenia), a reduced ability to ambulate and move, and less physical activity with an added sense of weakness [5].

From the clinical point of view, frailty is considered a syndrome whose phenotypic expression is the result of a progressive decline of physiological functions in multiple body systems. In addition, it is accompanied by a state of greater vulnerability to stress that leads to an increased risk of dependence, functional deterioration, hospitalization and mortality in elderly people [1-3,6]. In 1988 Woodhouse defined frail elderly people as those more than 65 years of age who depended on others for the activities of daily living and were often under institutional care [7]. Later Gillick complements this concept emphasizing the social consequences of frailty [8].

Among geriatrics, the concept of frailty includes the presence of chronic diseases, alteration of gait, sensory deficits, poor self-perception of health, repeated falls, polypharmacy, frequent hospitalizations [1,9]. Also, it includes functional criteria

established in terms of dependence on the basic activities of daily life and dependence on instrumental activities. Among the cognitive and affective criteria, the concept of frailty includes depression and cognitive impairment. With respect to socioeconomic criteria it can be identified: living alone, recent widowhood, age over 80 and low income [3,6,7]. It is widely accepted that the prevalence of frailty increases dramatically with age, and appears to be a result of a vicious cycle influenced by endogenous and exogenous factors [4,9].

Now, the recognition of frailty supposes the recognition of frailty is an important challenge for clinicians and health agencies, since their presence suggests a greater risk of adverse effects on health, increased needs for long-term care, greater dependency and disability, as well as an increase in health spending, making necessary a timely intervention.

## FRAILTY CLINICAL PHENOTYPE

Strategies to differentiate frailty phenotypes benefit from multifactorial approaches that allow us to differentiate genetic, cellular, psychological, physiological and environmental risk factors [2,5]. From this point of view, Brocklehurst's Dynamic model of frailty model allows us to differentiate a balance between assets that help a person maintain their independence in the community, and deficits that threaten this independence. Among the factors of advantage are: health, functional capacity, a positive attitude towards health and other resources (social, spiritual, financial and environmental). While in the deficits are: chronic diseases, disability, dependence on others for activities of daily living and the burden of caregivers [6]. Rockwood and collaborators add an interaction of assets and deficits, "medical" and "social", that maintain independence, reinforcing the model dynamically, whose changes in the state can be recognized by adjusting the weights of the various assets and deficits [1,6].

At the same time, Campbell and Buchner [10], considered that frailty arises from a decline in the reserve of multiple systems, which places the frail older person 'at risk' for disability or death with minor stresses, a notion they call 'unstable disability'. In more advanced ages, frailty is equated with an increased risk of death associated with age, being a complex factor present during aging [1]. For its part Aubertin-Leheudre et al. organize the risk factors into four categories: physiological, such as immune system dysfunction; doctors, such as diabetes or cognitive impairment; sociodemographic and psychological, such as depression [4].

On the other hand, many hypotheses have been proposed about the causes or origin of frailty, being the most consensus: genetic disorders, diseases and injuries, lifestyle and aging [9]. Essentially is the result of multiple alterations among which endocrine, immunological and musculoskeletal dysregulations have been reported. Among them, sarcopenia (loss of strength and muscle mass) represents a fundamental element [11]. As a result, this scenario predisposes the elderly to have a greater number of diseases and adverse effects, derived from a lack of compensatory mechanisms and loss of homeostasis, due to a decline in multiple bodily systems (muscular, immune, neuroendocrine, vascular) with a decrease of their functional reservation [5,11,12].

## ASSESSMENT CLINICAL SIGNS OF DETERIORATION AND DISABILITY IN THE FRAILTY SYNDROME

In recent decades, numerous attempts have been made to find which criteria best identify frail patients. Fried, in 2001, elaborated a definition of "frailty phenotype" that consisted of the presence of 3 of 5 elements to be evaluated: 1) unintentional loss of ≥ 10 pounds in the previous year, 2) feeling of "being exhausted" reported by the patient, 3) weakness (measured by the strength of the fist closure, 4) slow gait and 5) little physical activity [5]. The predictive value of this scale was determined based on the data obtained in a prospective cohort study on cardiovascular health in people over 65 years of age. This model has been validated later through the data of the Cardiovascular Health Study. The Fried's study showed that patients who had three or more components of the phenotype had a higher risk of falls, loss of mobility, alteration in the ability to perform activities of daily living, hospitalization and death. The presence of up to two components would make up the risk group of preventive interventions. It was possible to demonstrate that the fragile group differed from the group with disability and from the group with comorbidity. In his work, Fried concludes that frailty is not synonymous with disability and that the terms are not exclusive [3,5]. Therefore, Fried's criteria have served as a model for the assessment of frailty in clinical scenarios where an accurate, easy and quick diagnosis is needed, including first

contact consultation for outpatients and frailty screening in different populations [4,11].

In the same way, Macknight and Rockwood have focused on investigating the presence of frailty as a predictor of morbidity and mortality in patients who live in nursing homes or patients in the perioperative period. They propose a multi-domain model that provides important ideas: (1) frailty represents a greater vulnerability; (2) is heterogeneous; and (3) it is associated with chronological aging. In effect, it becomes biological, as opposed to chronological age [1]. Therefore, any definition of frailty must include the following: multisystem impairment, instability, change over time, an allowance for heterogeneity within a population, an association with aging, an association with an increased risk of adverse outcomes [1,13].

Therefore, physical frailty and cognitive frailty have been differentiated. Being physical frailty, a clinical condition characterized by an abnormal decrease in physiological reserves that increases stress and reduces the ability of an individual to maintain homeostasis and, therefore, leads to vulnerability [4,5]. There are different evaluation guidelines to measure physical frailty being very important to describe between frailty and normal aging since they seem to be indistinct because some factors, such as sarcopenia and strength (dynapenia), occur throughout the aging process. In turn, the term cognitive frailty has been used as a general descriptor for the cognitive impairment that occurs when people reach an advanced age, or to refer to cognitive or pre-demential disorders that occur in association with other medical conditions. The term cognitive frailty implies a parallel with physical frailty. However, the definition of cognitive frailty depends on its diagnostic criteria [4].

To facilitate the ability to assess physical frailty, Studenski et al. [14] Report of the Global Clinic of Change in Physical Frailty of the Physical Environment of Frailty Includes: Medical understanding, Use of medical attention, Appearance, Perceived health, Activities of daily life, Emotional state and social status. His research looks at the geriatric clinical opinion about the change in physical frailty, agreeing on the evaluation and measurement criteria, so that his instrument discriminates the magnitude and direction of the change, capturing patterns of contributing impediments what makes it feasible to apply in clinical research [14,15].

There is also a consensus that frailty is a state of pre-disability, so that both its definition and measurement instruments should not appear determinants of disability. The overlap of frailty and disability is like the superposition of these with comorbidity. While many individuals who are fragile also have disabilities, frailty is not synonymous with disability, defined as the difficulty or dependency for some activities of daily life. In fact, frailty is a predictor of dependence as a physiological precursor of it [3-5].These hypotheses have been key the biological bases to develop the animal models.

## BASIC CLINICAL MEASUREMENTS OF FRAILTY IN HUMANS AND MOUSE MODELS

Clinical studies on frailty have limitations inherent to the population under study, heterogeneity of frail elderly. Many of the advances made by studies, observations and clinical trials have been able to provide intervention strategies for this age group, but they have not completely resolved the problem [16,17]. Although clinical studies are beginning to understand frailty, there is still a real lack of evidence to guide clinicians to identify, assess and treat frailty. Hence, animal models can help the study of frailty, reducing genetic and lifestyle factors that contribute or confuse the observed phenotypes [18].

Mice are the models of mammals widely used in research due to their relative ease of genetic manipulation, low cost and short lifespan [19]. Through mouse reproduction technology, researchers have been able to reduce biological variation as a source of experimental noise and have thus achieved successful advances in different fields. On the other hand, both the frailty phenotype of Fried and the frailty index of Rockwood have been translated into mice, so its applicability and translation to humans is directly benefited [11,20].

The molecular basis of frailty, a syndrome rather than a disease is little known, mouse models of frailty would be of great value to determine which are the pathways that trigger frailty. That is why different preclinical models of frailty in animals have been developed to explore or mimic the manifestations of frailty in humans, identifying keys that promote research in this field [16,21]. There are different models of study, from those that address biological protestors due to aging, others address the cumulative effects of deficits

and consequences of lifestyle, trying to quantify manifestations and deterioration. While others seek to recreate preclinical signs to improve rehabilitation strategies and timely treatments, recreating genetic models that recreate the etiology of frailty [16-19,21]. (Table 1) lists the most studied and applied models that simulate frailty in mouse models, in this table you can see the different measurements according to the clinical bases developed from the clinical studies conducted in different studies in humans.

Table 1: Mouse models for frailty: tools of comparative evaluation according to the parameters of the frailty index in humans.

| Clinical basis | Animal model concept | Experimental subject | Study | Parameters of frailty assessment and their applications |
|---|---|---|---|---|
| Biological Age and frailty in aging mice | *Biological age* | C57BL/6J (male mice) | Ingram and Reynolds [22] | Evaluate biological age through a battery of psychomotor tests: rotarod (balancing on rotating rod), grip strength, exploratory behavior and wheel running tasks. This study is not specifically for frailty but, it is useful for measuring general health or biological age in animal experiments on aging. |
| Frailty in Genetically manipulated mice | *IL-10 knock-out mice* | Female IL-$10^{tm/tm}$ mice on a C57BL/6J background | Walston et al. [24] | Based on the characterization of IL-$10^{tm/tm}$ genetically modified model. To explore the biological mechanisms of frailty. Model of inflammation and multisystemic decline. |
| Biological Age and frailty in aging mice | *Sarcopenia in frailty* | C57BL/6J (male breeder mice) and *Sprague Dawley male Rat* | Walter [9] | Characterization skeletal muscle aging in pre-clinical mammalian models. Measurement of muscular performance, size and architecture through micro X-ray computed tomography (micro-CT) imaging and muscle histology. |
| Based on Rockwood's Frailty Index | *Mouse frailty index* | C57BL/6J (male and female mice) | Parks et al. [19] | Evaluate different health parameters: activity levels, hemodynamics measures, body composition and basic metabolic status. The M*ouse frailty index* can be used to quantify frailty in aging mice. |
| Biological Age and frailty in aging mice | *C57BL/6J neuromuscular healthspan-scoring* | C57BL/6J (male mice) | Graber et al. [26] | The Neuromuscular healthspan scoring system provides a score each animal from three individual scores obtained from the functional assessment: rotarod, grip strength and the maximal isometric force. Also provide information the in vitro muscle contractility. |
| Based on Fried's Frailty Phenotype | *Frailty phenotype index* | C57BL/6J (male mice) | Liu and Graber (2014) | Assess levels of physical performance: grip strength, walking speed (rotarod), physical activity (voluntary wheel running), endurance (average of grip strength and walking speed test) |
| Based on Rockwood's Frailty Index | *Mouse clinical frailty index* | C57BL/6J (male and female mice) | Whitehead et al. [20] | Evaluate the parameters of possible deficits related to aging principally through visual inspection of the evaluator: Integument, physical/musculoskeletal, vestibulocochlear/auditory, ocular/nasal, digestive/urogenital, discomfort and body weight and temperature. This model is based on deficit accumulation throughout life and exhibits features observed in clinical studies in human. |
| Frailty in Genetically manipulated mice | *Cu/Zn superoxide dismutase knockout mouse* | Sod1KO mice | Deepa et al. [15] | The model shows alterations similar that characteristics to define human frailty: weight loss, weakness, low physical activity and exhaustion. Sod1KO mice show increased inflammation and sarcopenia. Useful to study the etiology of frailty. |
| Based on Fried's Frailty Phenotype | *Inactivity as a model of frailty (Valencia Score)* | C57BL/6J (male mice) | Gomez-Cabrera et al. [27] | The Score for frailty based on five Fried's criteria for frailty in human: they propose a Valencia score (frailty in rodents): weight loss unintentional, weakness, grip strength, poor endurance and energy, slow and low physical activity level (tight-rope test). The study speared in two groups the animals: sedentary mice and spontaneous wheel-runners. |

From the biological point of view, models such as the one developed by Ingram and Reynolds in male C57BL76J mice have been described. They observed at the same chronological age different biological ages as a manifestation of biological processes related to the passage of time, among the individual variables survival has a positive relationship, the lower the rate of decline in performance, the longer the life of the individuals [22]. The study by Ingram and Reynolds does not have a direct relationship with frailty, but it makes an approach to the individual differences between individuals from the biological point of view and the process linked to changes during aging [21,23].

On the other hand, Walston et al. [24] explores the biological mechanisms of frailty based on an inflammatory and immunological cellular model, which points towards the multisystemic decline that surrounds this syndrome [17,21]. The IL-10 model does not express the anti-inflammatory cytokine interleukin 10 (IL-10) and, like frail human beings, is more susceptible to the activation of the inflammatory pathway [24]. Walston suggests that increasing the age of IL-10 mice would develop physical and biological characteristics like those of humans, since it develops an inflammation and a decrease in strength that is compatible with human frailty at a younger age compared to the control type mice C57BL/6J [16,17,21].

In addition to the IL-10 model recognized as a genetic model, Deepa et al. [15], they developed a new genetic model Cu/Zn superoxide dismutase, which exhibits four characteristics that define frailty in humans: weight loss, weakness, low activity and exhaustion. The Sod1 KO animals of this model show increased inflammation and sarcopenia, playing a role in the etiology of frailty at the level of oxidative stress, mitochondrial dysfunction and cellular senescence. Although both genetic models are the

best available models of their type, there is no evidence of the role played by the expression of their genes in human frailty [15].

With a physiological approach based on the Rockwood Frailty Index, Whitehead et al., [20], proposes a series of parameters related to possible aging deficits [18]. Establishes a clinical index of frailty based on the concept of accumulated deficits in people providing information on activity monitoring, hemodynamic status, body composition, basic metabolism and organ function. In their study, 31 variables measured in male and female C57BL/6J mice were incorporated [15,25]. Their results demonstrated that a clinical index of non-invasive frailty can be used to quantify frailty in mice. In addition, their clinical frailty index showed a progressive increase with the age of the subjects [20].

In consideration to the impact that age has on the biological and physiological alterations of the frailty syndrome Parks et al., [19] developed a frailty detection and quantification tool in a mouse model associated with aging based on the frailty model of Rockwood [16]. Parks et al. [19] Developed an approach to quantify frailty with a Frailty Index (FI). To quantify frailty, they measured many health-related variables linked to the function of different systems that are known to change with age in both human and animal models. They selected 31 specific variables chosen to provide information about activity levels, hemodynamic status, body composition, basic metabolism and organ function. They measured all these variables in a small group of adult and aged mice to generate a unique FI score for each animal and we compared these scores between different groups (age, sex). Their results showed that the levels of frailty were similar in aged males and females. Furthermore, they found that there were no differences between the sexes in the parameters used to construct the FI in the aged group, although the middle-aged females had lower systolic blood pressure, lower lean tissue mass, and more body fatter than the males as reported previously in mouse models [19]. The frailty index developed by Parks et al. [19]. Is one of the most used indices in current investigations of frailty in mouse models. It has also allowed us to understand the relationship between frailty and cardiac changes that occur with aging.

Alternatively, Whitehead et al. [20] continued the research based on the Frailty index proposed by Parks et al. Whitehead et al, used a physiological approach that included the systems: musculoskeletal, ocular and digestive, by measuring 31 criteria that allowed quantification non-invasively in animals [16]. Frailty was studied in male and female C57BL/6J mice through a longitudinal study. As a result, they obtained that the frailty index score increases gradually in adult (5 months) to old (19 months) and very old (28 months) animals in males and females. In addition, the range of deficits accumulated in mice was like those observed in the clinic of human frailty. For the validation of the scale created by Whitehead et al., It was submitted to a correlation with scales applied in humans in its 31 criteria, as well as to the frailty index of Parks [20]. The limitation of the current indices applied in mouse models by both authors Parks and Whitehead, is that they do not include cognitive criteria or a social and hierarchical relationship between animals. Undoubtedly both indexes are very useful for the development of research in this field.

Also based on the frailty model of Rockwood, Graber et al. [26] developed a system of evaluation of frailty based on physiological and functional measurements to test the efficacy of possible interventions for sarcopenia and frailty in animal models of aging [16]. They developed a neuromuscular scoring system of the healthspan, evaluating male C57BL/6J mice of three ages: adults (6-7 months of age, 100% survival), old (24-26 months of age, 75% survival), and a group of elderly people (> 28 months of age, ≤50% survival). The functional performance was obtained from the rotarod tests and the inverted grip test. In addition, muscular contractility in vitro was determined. Among their results, they found that both functional capacity and strength deteriorate with age in the C57BL / 6J mouse as evidenced by decreases in the grip test, rotarod and muscle contractility [25]. This model can be used as a tool for researchers to evaluate interventions from the point of view of motor performance related to frailty syndrome.

Finally, among the most recent models of frailty study in mouse models is the one developed by Gomez-Cabrera et al. [27]. This model is based on the human frailty phenotype of Fried and aimed to create a score for frailty in experimental animals called "Criteria de Valencia". They also sought to determine

the effect of physical inactivity on the development of frailty. They included male C57Bl / 6J mice and compared the sedentary lifestyle versus the active lifestyle in terms of frailty by evaluating the clinical criteria used in humans: involuntary weight loss; bad resistance (execution time); slowness (running speed); weakness (grip strength) and low level of activity (motor coordination) in five different ages: 17, 20, 23, 26 and 28 months of age. Each criterion had a designated cut-off point to identify the mice with the lowest performance. Among its results it can be uncovered that spontaneous life-long exercise significantly delays frailty contrary to what happened in sedentary animals that become fragile as they get older. Gomez-Cabrera et. al, propose physical inactivity as an experimental model for the study of frailty [27].

## CONCLUSIONS

The concept of frailty is key in the context of geriatric care. It has evolved from Linda P. Fried's phenotypic frailty model and Kenneth Rockwood's cumulative deficit model, creating the theoretical construct that has allowed the understanding of the processes that frailty involves. Most authors agree that the most common clinical manifestations are an involuntary decrease in body weight, strength and muscle strength, balance and gait disturbances and a decline in physical mobility. The study of these clinical signs has allowed the understanding of the processes that condition the loss of the capacity of adaptation that elderly people present with frailty. The studies carried out in humans have limitations due to the heterogeneity of the syndrome, its manifestations involve affectation of several organs and bodily systems making it multidimensional. Faced with limitations in human studies, preclinical studies in animals provide opportunities to provide this evidence empirically, helping us to understand the mechanisms of frailty, identify potential biomarkers and explore interventions to modulate and generate treatments for frailty syndrome.

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