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Frailty Syndrome: A Transitional State in a Dynamic Process

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Frailty · Physiopathology · Prevention

Abstract
Frailty has long been considered synonymous with disability and comorbidity, to be highly prevalent in old age and to confer a high risk for falls, hospitalization and mortality. However, it is becoming recognized that frailty may be a distinct clinical syndrome with a biological basis. The frailty process appears to be a transitional state in the dynamic progression from robustness to functional decline. During this process, total physiological reserves decrease and become less likely to be sufficient for the maintenance and repair of the ageing body. Central to the clinical concept of frailty is that no single altered system alone defines it, but that multiple systems are involved. Clinical consensus regarding the phenotype which constitutes frailty, drawing upon the opinions of numerous authors, shows the characteristics to include wasting (loss of both muscle mass and strength and weight loss), loss of endurance, decreased balance and mobility, slowed performance, relative inactivity and, potentially, decreased cognitive function. Frailty is a distinct entity easily recognized by clinicians, with multiple manifestations and with no single symptom being sufficient or essential in its presentation. Manifestations include appearance (consistent or not with age), nutritional status (thin, weight loss), subjective health rating (health perception), performance (cognition, fatigue), sensory/physical impairments (vision, hearing, strength) and current care (medication, hospital). Although the early stages of the frailty process may be clinically silent, when depleted reserves reach an aggregate threshold leading to serious vulnerability, the syndrome may become detectable by looking at clinical, functional, behavioral and biological markers. Thus, a better understanding of these clinical changes and their underlying mechanisms, beginning in the pre-frail state, may confirm the impression held by many geriatricians that increasing frailty is distinguishable from ageing and in consequence is potentially reversible. We therefore provide an update of the physiopathology and clinical and biological characteristics of the frailty process and speculate on possible preventative approaches.

Introduction

The borders between age and frailty appear to be so indistinct that it is widely supposed that at a specific age, all people become frail [1]. Medical practitioners have often used the term frailty to characterize the weakest and

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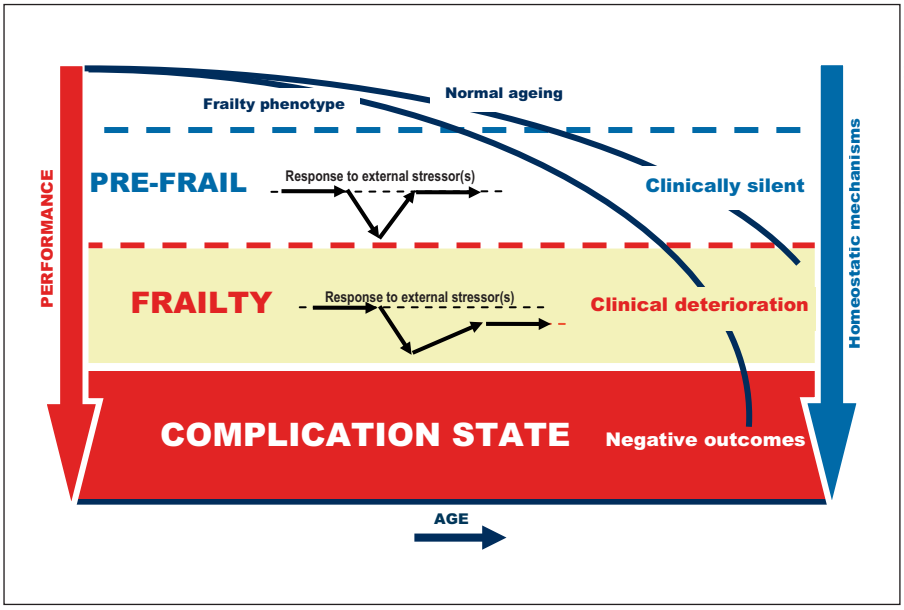

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Fig. 1. Development of frailty with advancing age.

most vulnerable subset of older adults. However, 'frail' is not a synonym for comorbidity or disability, nor is it an adequate term to describe the oldest old adults [2]. Recent research efforts have helped to better define the clinical and physiological characteristics of frailty and to highlight the vulnerability of frail, older adults to poor health outcomes [3]. The definition of frailty has evolved over the years from a description of dependence on others to a more dynamic model that encompasses biomedical and psychosocial aspects. Frailty is an extended process of increasing vulnerability, predisposing to functional decline and ultimately leading to death [4, 5]. Different presentations of frailty are encountered by the clinician, so that it can be viewed as a multidimensional construct that involves more than just simple dependence for activities of daily living (ADL). It is a complex interplay of a person's assets and deficits as a result of the combination of factors such as age, gender, lifestyle, socioeconomic background, comorbidities and affective, cognitive or sensory impairments [1]. Frailty is seen as the loss of functional homeostasis, which is the ability of an individual to withstand illness without loss of function [6]. During the frailty process, physiological reserves decrease, while increasing physiological resources are required to repair and maintain the functioning of the ageing body, inexorably decreasing the remaining available reserves. Nevertheless, it has been postulated that 30% of normal physiological reserves allow adequate maintenance and functioning of essential organs [7]. Thus, frailty appears to be a transitional state in the dynamic process from robustness to functional decline (fig. 1). Since frail older adults often have multiple age- and disease-related impairments that limit their ability to perform ADL, frailty can be seen as a manifestation of the degradation of multiple physiologic systems that are responsible for healthy adaptation to stresses [4].

This article focuses primarily on the definition, physiological aspects and detection of the frailty process and possible preventative approaches. It describes clinical and biological phenotypes of frailty that may help to facilitate future research. The potential involvement of inflammatory, endocrine, skeletal muscle and neurologic systems are considered.

Description of the Frailty Process

In relation to the decline in homeostatic reserves, 3 stages in the frailty process can be described: a pre-frail process, the frailty state and frailty complications [8]. The dynamics of the frailty process are presented in figure 1. The pre-frail process, which is clinically silent, corresponds to the state where physiological reserves are sufficient to allow the organism to respond adequately to any insult such as acute disease, injury or stress, with a chance of complete recovery. Perceptions of the 'frailty state' as a distinct entity with multiple manifestations were explored by a survey of geriatricians' opinions on the rela-

tionship between frailty and disability, conducted in 6 medical schools by means of a standardized self-administered questionnaire [9]. Of the 62 geriatricians who responded, 98% stated that frailty and disability are separate clinical entities, although they thought them causally related; 97% supported a statement that frailty involves the concurrent presence of more than one characteristic. At least 50% cited one or more of the following characteristics as likely to be observed in association with frailty (descending order of citation): undernutrition, functional dependence, prolonged bed rest, pressure sores, gait disorders, generalized weakness, age >90 years, weight loss, anorexia, fear of falling, dementia, hip fracture, delirium, confusion, going outdoors infrequently and polypharmacy [9]. The frailty state is characterized by slow, incomplete recovery after any new acute disease, injury or stress, confirming that the available functional reserves are insufficient to allow a complete recovery. These multisystem deregulations became clinically apparent either when unmasked by stressors or as part of the clinical phenotype of a final common pathway [10]. Complications of the frailty process are directly related to physiologic vulnerability resulting from impaired homeostatic reserve and a reduced capacity of the organism to withstand stress. They lead to a high risk of falls, functional decline leading to disability, polymedication, an increased risk of hospitalization, cross-infection, institutionalization and death [5, 6, 11]. In the study Survey in Europe on Nutrition and the Elderly, a Concerted Action, Chin et al. [12] examined a cohort of elderly people living independently (450 individuals aged 69–89 years), where inactivity and weight loss were used as criteria to identify the frailty subgroup. The authors found that the most significant symptom associated with inactivity was unintentional weight loss. Low energy intake and lean body mass were not statistically significant [12]. Physical inactivity combined with unintentional weight loss significantly predicted the 3-year disability risk [odds ratio (OR) 5.2, 95% confidence interval (CI) 1.04–25.8] and mortality risk (OR 4.1, 95% CI 1.8–9.4) in the studied population. Fried et al. [11] have developed and operationalized a phenotype of frailty based on a secondary analysis of the Cardiovascular Health Study. In this study, 5,317 men and women aged 65 years and older were followed for 3 years [11]. The results showed that nearly 60% of the frail elderly had been hospitalized, while 39% had worsening of their ability to carry out ADL. In the Swiss Interdisciplinary Longitudinal Study on the Oldest Old, a 5-year prospective, population-based study of 295 Swiss octogenarians, the authors proposed a definition of frailty syndrome based on 19 variables aggregated in 5 dimensions: mobility, sensory abilities, physical disorders, energy and memory [13]. Frail octogenarians were defined as meeting at least 2 of these 5 criteria. At the end of the study period, outcomes in the group defined as frail were significantly different from the non-frail group, with an increased risk of falls [relative risk (RR) 1.82, 95% CI 1.01–3.27], disease (RR 2.73, 95% CI 1.58–4.71), dependence (RR 4.42, 95% CI 1.44–13.62) and death (RR 2.02, 95% CI 1.25–3.27) [13, 14]. In addition, frailty also contributes to an increased burden on caregivers.

Physiopathology of the Frailty Process

Frailty is increasingly recognized as a collective entity and as being both a clinical syndrome and a progressive process with a latent phase [2]. The beginning of the 'frailty cycle' consists of the accumulation, with ageing, of the effects of lack of physical exercise, inadequate nutrition, unhealthy environment, injuries, disease and drugs (recreational, social and medication). These interconnected factors lead to chronic undernutrition, consolidated by age-related changes, causing loss of bone and skeletal muscle mass. Sarcopenia is a process whereby a loss of reserve capacity results in an increased sense of effort for a given exercise intensity. The lactate threshold of an individual increases with age, forcing older individuals to exercise at a greater percentage of their maximal capacity. As the perception of exercise effort increases, older individuals become more likely to avoid exercise. A vicious cycle then begins; as regular physical activity decreases with age, there is a downregulation of physiological systems as they adapt to reduced exercise and stress levels. With age, the decline in general function of cardiovascular and skeletal muscle reserves, as well as a reduction in maximum oxygen volume, contribute to an increased perception of effort required for a particular task compared to that required when younger [15]. If tasks are perceived as more difficult, the likelihood of avoidance of physical effort is increased, and as more occasions of physical effort are avoided, exercise performance continues to decline, contributing to additional physiological decrements in functional reserve capacity, leading to more sarcopenia, which increases restriction of physical activity [16, 17]. These physiological changes result in a significant decrease in resting metabolism and an important reduction of total energy expenditure. Reduced energy output might be thought to reduce the consequences of undernourishment. Thus, the frailty cycle,

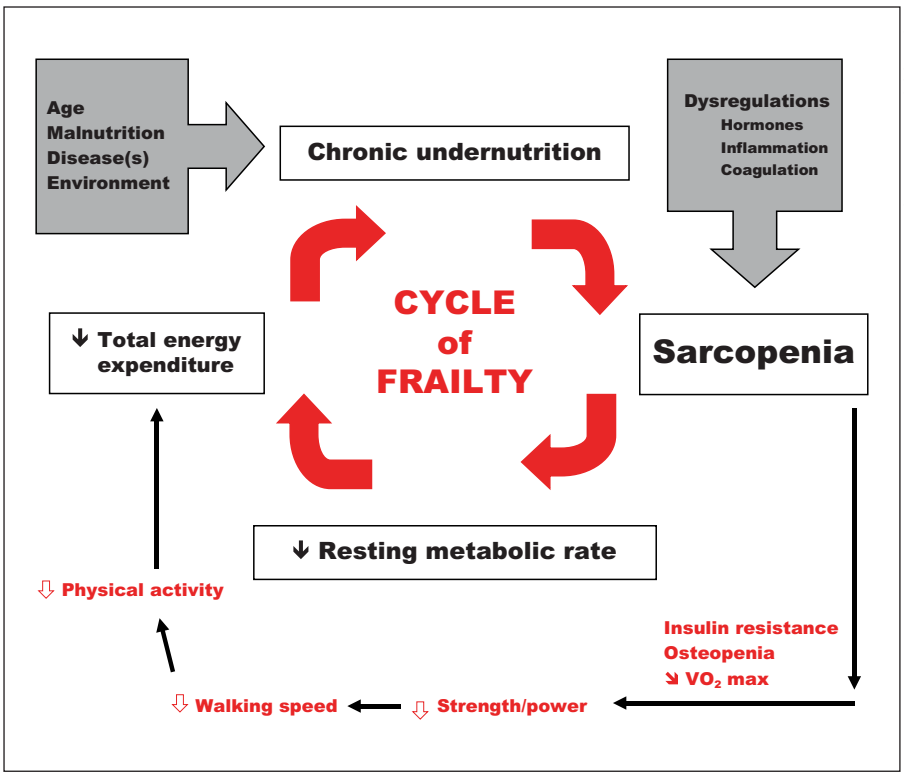

Fig. 2. The cycle of frailty (adapted from Fried et al. [11]).

presented in figure 2, is completed and self-maintained [2].

In the literature, there is some evidence that sarcopenia and undernutrition lead to these deleterious effects [18]. The biology of sarcopenia remains elusive. Various mechanisms have been proposed to explain the change in total muscle mass, including the following: (1) a lack of regular physical activity ('use it or lose it'); (2) a change in protein metabolism (a deficit between protein synthesis versus degradation); (3) alterations in the endocrine milieu [increase in insulin resistance contributing to diabetes and, by inhibition of the nitric oxide cascade, to sarcopenia, decreases in growth hormone, insulin-like growth factor (IGF)-1 and testosterone, and an increase in cortisol and cytokines]; (4) oxidative stress; (5) inflammation, as confirmed by biological markers such as increased white blood cells counts, interleukin (IL)-6 and C-reactive protein (CRP); (6) muscle protein turnover including neuronal activity mediated through motor neurons (denervation versus reinnervation); (8) altered gene expression, and (9) apoptosis [2, 19–22]. Skeletal muscle protein turnover is a complexly regulated process that affects protein synthesis and/or protein degradation. Both extracellular and intracellular markers suggest that no single mechanism may account solely for sarcopenia. To prevent sarcopenia, nutrition and especially amino acid intake seem to be important in maintaining protein turnover; however, optimal intake and which specific amino acids are unknown. Nutritional aspects which remain to be determined include whether vitamin and mineral supplements are useful or even necessary and whether hormone supplements are beneficial. Regular physical exercise seems to be beneficial, but how much is required? Physiological factors that contribute to the process of sarcopenia and frailty are multifactorial, occurring over a prolonged time period with possibly no identifiable single cause or mechanism. Clinical interventions may also need to be multifaceted [22].

As shown in figure 1, the transition from the pre-frail process (latent phase) to the frail state (clinically apparent) is generally marked or provoked by a trigger event such as injury, acute disease and/or psychological stress. Thus, the frailty process is linked to inadequate adaptability in all these interconnected systems. It is essential to fully appreciate that frailty is an adverse health condition which should be regarded as having severe clinical consequences. In the Women's Health and Aging Study, Bandeen-Roche et al. [23] followed a cohort of frail adults

(aged 70–79 years) for 3 years and reported the significant outcomes. These outcomes included incident falls (OR 1.18, 95% CI 0.63–2.19), a higher risk of developing disabilities in basic ADL (OR 10.44, 95% CI 3.51–31.00) and/or instrumental ADL (OR 15.79, 95% CI 5.83–42.78) and a higher risk of death (OR 6.03, 95% CI 3.00–12.08) [23]. Complications of frailty are well described; however, the mechanisms underlying the crucial latent 'pre-frail' step are not yet understood. Our goal as researchers should be to gain an improved understanding of the complex biological factors leading to age-related muscle loss beyond those attributable to a simple decrease in physical activity and to deleterious chronic undernutrition. Recent physiopathological data on the frailty process suggest that it may be possible to avoid, prevent or postpone frailty [17].

The Clinical and Biological Phenotypes of Frailty

The development of an operational definition of frailty, agreed on by all researchers in the field, is essential if progress is to be made in its management and treatment. Frailty has often been considered as synonymous with disability or comorbidity, but it is now becoming recognized as a distinct clinical syndrome with a biological basis [11]. There is no universally used screening tool for identifying the frailty phenotype or predicting adverse outcomes related to frailty, although a number of models exist. These models contain various combinations of the following parameters: weakness, fatigue, weight loss, decreased balance, low levels of physical activity, slowed motor processing and performance, social withdrawal, mild cognitive changes and increased vulnerability to stressors [3]. By definition, manifestations associated within a syndrome occur in combination, and no single manifestation is sufficient to identify subjects with the syndrome. Based on these impairments, a working group has established that a combination of inactivity and weight loss is a significant predictor of disability and mortality [12]. A consensus report from a group of Italian and American researchers has been published advocating that criteria to define physical frailty be based on impairments in physiological domains that include mobility, balance, muscle strength, motor processing, cognition, nutrition, endurance and physical activity [24]. The 'Frailty Task Force' of the American Geriatric Society adopted the suggestion of Fried et al. [11] as the best current working definition. They proposed that frailty be considered a clinical syndrome, defined by the presence of 3 or more of the following symptoms: (1) unintentional weight loss (4–5 kg in 1 year); (2) self-reported exhaustion; (3) weakness (grip strength <20% in the dominant hand); (4) slow walking speed (<20% for time to walk 15 feet), and (5) low physical activity (<20% for caloric expenditure). Clinical signs of these symptoms are represented by undernutrition, sarcopenia, osteopenia and balance and gait disorders. This frailty phenotype was independently predictive, over 3 years, of incident falls, worsening mobility or reduced ADL, hospitalization and death, with unadjusted hazard ratios ranging from 1.82 to 4.46 and hazard ratios of 1.29–2.24 adjusted for the presence of a number of health, disease and social characteristics predictive of 5-year mortality. The presence of 2 of the above-mentioned symptoms defines the 'pre-frail' state of the frailty process, and the presence of 3 corresponds to the 'frailty' state. Applying these criteria, the prevalence of frailty was 6.9% in the population studied by Fried et al. [11], and the 4-year incidence was 7.2%.

Other Important Clinical Domains of Frailty

This working definition of frailty, based on Fried's criteria, is very useful; however, it is only based on physical symptoms and signs. It neglects other potentially important components of the syndrome such as mood, cognition, sensory impairments and socioeconomic aspects of older adults' lives. Moreover, no biological markers are included in the frailty syndrome defined by Fried et al. [11]. It is not satisfactory to define frailty in the physical domain alone, since there are several other domains (noted above) which have not yet been examined but are widely recognized as part of the frailty state [25].

In the Beaver Dam Eye Study, with a 4.5-year follow-up, some potential frailty markers were examined in a cohort population of 2,962 subjects recruited between 1998 and 2000 [26]. The results showed that the robust elderly have better visual acuity and contrast sensitivity than the frailest elderly, who were defined in this study as those unable to stand from sitting in a single attempt and having the slowest quartile gait time, the lowest quartile peak expiratory flow and lowest hand grip strength [26]. This study revealed gait time abnormality to be an early sign of frailty, while the inability to stand from sitting at one attempt, reduced peak expiratory flow and low grip strength characterized severe frailty. The most severely frail had the poorest survival, independent of age, gender and disease (diabetes, cardiovascular disease and arterial hypertension). However, these two last conditions (cardiovascular disease and arterial hypertension)

also impact directly on the severity of frailty and survival [27]. In the current working definition of frailty [5], sensory impairment is not included.

The longitudinal Cardiovascular Health Study (4-year follow-up) assessed daily functioning using the ratio of ADL to instrumental ADL and depression (10-item Center for Epidemiologic Studies Depression Scale) in 5,888 old individuals and showed that persistently depressed individuals (n = 119) had a 5-fold increased risk (OR 5.27, 95% CI 3.03–9.16) and temporarily depressed individuals (n = 259) a 2-fold increased risk of functional decline (OR 2.39, 95% CI 1.55–3.69) compared to nondepressed or low dysthymic subjects (n = 378) after adjustment on baseline ADL/instrumental ADL scores, gender and age [28]. These results reveal mood disturbance to be a crucial factor in the risk of frailty and as such it should be included in the working definition of frailty.

Similarly, cognitive performance should be included in the working definition of frailty. There is some evidence that cognition can have an impact on functional decline [12]. The Nun Study prospectively investigated the role of low normal cognitive function in the subsequent loss of independence in ADL. Of 678 elderly nuns who completed cognitive and physical function assessments in 1992/1993, 575 were reassessed in 1993/1994. Participants with low normal cognitive function at first assessment had twice the risk of losing independence in 3 ADL domains by the second assessment relative to those with high normal cognitive function. This relationship was largely due to a progression from low normal cognitive function at first assessment to impaired cognitive function at second assessment and was associated with an elevated risk of losing independence in 6 ADL domains [29]. In the Hispanic Established Population Epidemiological Study of the Elderly, Ottenbacher et al. [30] found a prevalence of frailty of 20% after evaluating 621 noninstitutionalized Mexican American older people (aged 70 years or over). In this study, cognition was found to be related to frailty in men but not in women [30]. These results show that the currently recognized working definition of frailty is inadequate, as cognitive performance should be included in the assessment of frailty [31].

In addition to Fried's criteria, numerous other cohort-based definitions of frailty have been elaborated and published. Some of these include functional and cognitive impairment (e.g. Canadian Study of Health and Ageing Clinical Frailty Scale) [32]. Others are based on a comprehensive geriatric assessment (Frailty Index) [33] or are similar to the definition proposed in the Epidemiology of Osteoporosis Study, with a combination of biological, physiological, social and environmental changes [34]. The criteria used predicted several adverse outcomes like hip fracture, disability, hospitalization and death [31]. Various frailty models are available, and assessment of frailty remains very heterogeneous.

This issue of a lack of consensus on the definition of frailty and its components arose in a recent review by Abellan van Kan et al. [31]. However, these authors recommended the consideration of frailty as a predisability stage, making disability a consequence of frailty rather than its cause. Whether disability should be considered in frailty definitions and assessment tools may be debatable; its exclusion renders many assessment tools and definitions inadequate. Rockwood et al. [35] have demonstrated the varying ability to express different grades of frailty between several different models of frailty.

Biological Markers of Frailty

The Cardiovascular Health Study, using the currently recognized working definition of frailty, compared biological inflammatory markers between 299 frail and 2,298 non-frail individuals. It was observed that CRP, fibrinogen, factor VIII and D-dimers were significantly higher in the frail elderly than in the non-frail ($p < 0.001$) [36]. Similarly, the Duke Established Populations for Epidemiologic Studies of the Elderly, a 5-year follow-up of 1,723 subjects of 71 years and over, demonstrated that the combination of the highest quartiles of IL-6 and high D-dimer blood levels doubled the relative risk of death over 5 years [37].

In addition to these inflammatory markers, there is growing evidence that a rise in insulin resistance occurs as individuals grow older. This is more than a simple metabolic finding; it has been identified as a major risk factor for many age-related diseases linked to altered lipid metabolism, increased inflammatory state, impaired endothelial functioning, prothrombotic status and atherosclerosis. Considering that insulin resistance is related to many of the clinical features of frailty such as skeletal muscle weakness, lower-extremity mobility problems, cognitive decline and body composition changes, it may also be considered a key biological component of some clinical aspects of the frailty syndrome in ageing individuals [19]. It has recently been suggested that insulin, long considered anabolic by reducing protein degradation, can also stimulate protein synthesis [38]. Age-related insulin resistance contributes to sarcopenia via inhibition of the nitric oxide cascade, resulting in lower absorption of available amino acids for protein

synthesis, thus contributing to the initiation of the frailty process [22]. Moreover, comparative specific dosages of IGF-1 and dehydroepiandrosterones (DHEAs) in frail (n = 18) and non-frail individuals (n = 33) have demonstrated that these hormonal secretions are significantly lower in the frail than in the non-frail [39]. In addition to growth hormone, IGF-1 and DHEAs appear to be implicated in muscle growth and repair [22]. Conceiving frailty as a multisystem decline and a consequence of changes in neuromuscular, endocrine and immune systems, Puts et al. [40], in a prospective cohort study with 3-yearly measurements, examined the association of serum concentrations of 25-hydroxy-vitamin D (25 OH-D), IL-6, CRP and IGF-1 with prevalent and incident frailty. Frailty was defined as the presence of 3 or more of the following 9 frailty indicators: low body mass index (<23), low peak expiratory flow (≤ 270 liters/min), poor distance vision and hearing problems, incontinence, low sense of mastery, depressive symptoms and reduced physical activity. Low 25 OH-D levels were strongly associated with the prevalence and incidence of frailty; moderately elevated levels of CRP were associated with incident frailty [40].

Frailty Prevention

As frailty is a progressive condition that begins with a preclinical stage, there are opportunities for early detection and prevention [10]. With the clinical recognition of the frailty state, validated rehabilitative programs able to postpone or reduce such severe consequences as functional decline and death may be proposed.

Since the preclinical stage of the frailty process is latent and clinically silent and not apparently linked with any disease condition, it remains difficult to detect. On the other hand, the clinical frailty stage could be detected by a suitable assessment tool. To be relevant in clinical practice, this tool should be easy to use in clinical settings, quick and reliable. Many specific assessment tools have been developed in recent years. Some of these are described below, prior to a discussion of the development of prevention strategies.

Screening Tools for Frailty

Consistent with Fried's approach to frailty, a Clinical Global Impression Measure for Frailty has been developed and validated [41]. It includes 6 intrinsic domains (mobility, balance, strength, endurance, nutrition and neuromotor performance) and 7 consequent domains (medical complexity, healthcare utilization, appearance, self-perceived health, ADL and emotional and social status). The Clinical Global Impression Measure for Frailty has validity, reliability and feasibility for use in clinical research; however, it is rather impractical in a clinical setting, as it requires ascertainment of grip strength, walking speed and physical activity, as well as knowledge of the underlying population distributions of these measures, which also vary with sex and body size. The Short Physical Performance Battery (gait speed, repeated chair stands and tandem balance test) was validated in the Established Population Epidemiological Study of the Elderly cohort study investigating aged community-dwelling persons and showed a high predictive value for subsequent disability [42]. The Frailty Index, as proposed by Mitnitski et al. [43], is a multidomain evaluation of frailty in older people based upon 20 deficits observed throughout a wide and structured clinical examination. The list of deficits includes sensorial losses, impaired functionality, impairment in ADL, skin, gastrointestinal and urinary problems, diabetes and hypertension. A Frailty Index based upon the Comprehensive Geriatric Assessment, proposed by Jones et al. [33], is a stratified evaluation tool that describes 3 levels of frailty. Despite the number of published assessment tools, the lack of a universally used screening tool for identifying the frailty phenotype has been highlighted in the review by Abellan van Kan et al. [31]. Gait speed could represent the most suitable measure in both research and clinical evaluation, as assessment of gait speed is a quick, inexpensive and highly reliable measure of frailty [33].

Preventive Strategies

Prevention of frailty is the ultimate aim. It is possible to differentiate frailty, which seems to be reversible, from ageing, which is not. Interventions have been made in older adults that target correlates or specific components of frailty. Lebel et al. [44] proposed an approach to combat frailty in 6 different modes: (1) adequate diet with sufficient protein, vitamin and mineral intake; (2) regular physical exercise, practiced alone or in groups, such as stretching, walking, dancing, dynamic balance exercise and lifting weights; (3) regular monitoring of individual basic abilities, such as walking, equilibrium and cognition; (4) prevention of infections by flu, pneumococcal and herpes zoster vaccines; (5) anticipation of stressful events such as elective surgery, and (6) rapid reconditioning after stressful events via renutrition and individually tailored physiotherapy.

Table 1. Studies of strategies to prevent frailty

Study	Definition of frailty	Study design	Study population	Prevention strategy	Outcomes
Binder et al. [45]	2 of the following 3 criteria: – modified Physical Performance Test score – peak oxygen uptake – self-reported difficulty with 1 or 2 basic Katz's ADL or 2 Lawton's IADL	RCT 9 months follow-up	150 men and women 78 years of age or older sedentary mild to moderate physical frailty	physical therapy program: – flexibility exercises – light weight resistance exercises – balance exercises – endurance training	improvement of physical function in subjects with mild to moderate frailty
Gill et al. [46]	disability scale = 8 ADL: walking, bathing, upper- and lower-body dressing, transferring from a chair, using toilet, eating and grooming scores ranged from 0 to 16 (higher scores indicating more severe disability)	RCT 12 months follow-up	188 men and women 75 years of age or older physically frail	physical therapy program: – balance exercises – muscle strength – ability to transfer – mobility	improvement of physical function in subjects with moderate frailty but not those with severe frailty; no beneficial effect on the frequency of admission to a nursing home
Arora et al. [49]	VES-13 score = self-report: age, ability to perform 6 physical and 5 functional activities, self-rated health scores ranged from 0 to 10 (higher scores indicating highest risk) deemed vulnerable if score ≥3	no RCT hospital stay	328 men and women 65 years of age or older deemed vulnerable	inpatient interview and chart review using ACOVE-QIs in general hospital care and geriatric conditions	poorer quality-of-care process for geriatric conditions

RCT = Randomized controlled trial; IADL = instrumental ADL; VES-13 = Vulnerable Elders Survey-13.

Amongst these modes, based on intervention studies detailed below and presented in table 1, only physical activity (particularly strength and balance, but also endurance training) has the most apparent potential for improving physical function. In a randomized controlled trial of 150 sedentary community-dwelling men and women aged 78 years or older with mild to moderate physical frailty, Binder et al. [45] assessed the effect of exercise training on frailty. Frailty was defined by the presence of 2 of the following 3 criteria: modified Physical Performance Test score between 18 and 32; peak oxygen uptake between 10 and 18 ml/kg/min, and self-reported difficulty with 1 basic ADL or 2 instrumental ADL (assessed by the Functional Status Questionnaire). The control group benefited from a 9-month program of flexibility exercises, while the exercising group benefited from a 9-month program of flexibility exercises, light weight resistance and balance exercises, plus endurance training. The results were very impressive by the end of the study, confirming the possible reversibility of the functional decline in the exercising group; the modified Physical Performance Test score was 1 and 5.2, the peak oxygen uptake was 0.9 and 3.6 ml/kg/min and the Functional Status Questionnaire score was 1.6 and 4.9 in the control and exercising groups, respectively. In a second controlled study, Gill et al. [46] randomly assigned 188 older adults of 75 years or more who were physically frail and living at home to undergo a 6-month, home-based intervention program. This included physical exercise therapy and focused primarily on improving underlying impairments in physical abilities, including balance and muscle strength, the ability to transfer from one position to another and mobility. The control group underwent an educational program. The primary outcome was the change in score on a disability scale based on 8 ADL, i.e. walking, bathing, upper- and lower-body dressing, transferring from a chair, using the toilet, eating and grooming, assessed at baseline and after 3, 7 and 12 months. Scores on the scale ranged from 0 (slight disability) to 16 (severe disability). Participants in the intervention group had lower functional decline over time, as assessed by disability scores, than participants in the control group. The disability scores in the intervention and control groups were 2.3 and 2.8, respectively, at baseline; 2.0 and 3.6, respectively, at 7 months ($p < 0.01$), and 2.7 and 4.2, respectively, at 12 months ($p < 0.05$). However, the benefit of intervention was only observed among participants with moderate frailty and not those with severe frailty. The frequency of admission to a nursing home did not differ signifi-

cantly between the two groups. This home-based program was shown to be able to reduce the progression of functional decline among physically frail elderly people [46]. These two studies demonstrate that frailty may be preventable and that progression of frailty can be slowed and delayed. Vanitallie [47] noted the following: 'One characteristic of the frailty syndrome, that distinguishes it from the effects of ageing *per se* is the potential reversibility of many of its features'. Nutritional interventions based on caloric intake alone have not been demonstrated to be effective. Infectious disease prevention by vaccination (combating the increased susceptibility of older adults to infection and attenuating the effects of immune system ageing) is a very interesting potential mechanism for the reversal of frailty which has yet to be clinically explored [48].

Potential drug interventions include anabolic hormones (e.g. megestrol, growth hormone secretagogues, testosterone and DHEA). Clinical trials suggest that, in the absence of exercise, these tend to increase muscle mass with no effect on strength or function; furthermore, their side effects limit feasibility. Similarly, clinical trials with erythropoietin, β2-adrenergic receptor agonists, angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have not demonstrated clear benefits [3].

In a clinical setting, an interesting preventive study has been conducted by Arora et al. [49]. The specific aims of this study were to adapt the Assessing Care of Vulnerable Elders (ACOVE) quality indicators (QIs) [50] to evaluate hospital care in a sample of vulnerable elderly patients. The ACOVE-QIs were designed to evaluate processes of care for a broad set of medical conditions, including general medical conditions (e.g. diabetes mellitus and heart failure) and conditions prevalent in geriatric medicine (e.g. dementia and delirium, pressure ulcers and urinary incontinence). This study focused on 'vulnerable elders' as defined by the Vulnerable Elder Survey-13 , a validated tool based on age, self-reported health and functional status [51]. Amongst 600 participants, 58% were deemed vulnerable. The results showed substantial variation in quality-of-care processes across several domains of care for hospitalized vulnerable elders, with poorer care for conditions found in geriatric patients than for general medicine [49]. This suggests that more in-depth training for medical professionals is needed in the hospital care of older patients, and that there is a need to focus on frailty prevention. At the University of Chicago, a teaching program to improve the hospital care of older patients was delivered to non-geriatrician doctors who serve the inpatient hospital service and teach medical students and residents. An assessment of whether this type of education improves quality of care for frail elders, as measured by the ACOVE-QIs, is currently under way.

Conclusion

We have the capacity to differentiate the frailty process from normal ageing, and while the definition of this entity is not perfect, much progress is being achieved. The frailty state is characterized by physical symptoms such as weakness, slowed performance, unintentional weight loss, fatigue and low activity, and by many biological changes such as altered nutritional markers (low albumin), increased inflammatory responses (IL-6 and CRP), modification of the clotting process (factor VIII, D-dimers), dysfunction of endocrine regulation (glucose intolerance, increase in IGF-1, androgen, DHEA and cortisol) and low 25 OH-D. Most often, frailty is distinguished from the preclinical stage by the addition of a stressor, which is not necessarily associated with overt disease or dysfunction. The working definition of frailty, based on Fried's criteria, is useful but unsatisfactory and needs to be enlarged by the inclusion of other domains such as mood and cognitive disorders. Detection of the frailty process and recognition of the frailty state are necessary in order to postpone or prevent their multiple severe consequences, such as repeated falls, fractures, increased medication, hospitalization, infection, institutionalization and death. However, a specific assessment tool to identify the population at risk, which is easy to use, quick and reliable, is not currently available.

In conclusion, frailty can be differentiated from ageing, but unlike ageing, it can be prevented and possibly reversed. A deeper understanding of the physiopathological mechanisms of the frailty process will be instrumental in changing the perception of this concept.

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