
Aging, Disability and Frailty

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Key Words

Aging · Disability · Frailty

Abstract

Despite multiple and often overlapping definitions of disability and frailty, both are common clinical characteristics of aged individuals though not identical. The geriatric syndrome of frailty is described as status of global impairment of physiological reserves involving multiple organ systems. The clinical correlate of frailty manifests as increased vulnerability, impaired capability to withstand intrinsic and environmental stressors, and limited capacity to maintain physiological and psychosocial homeostasis. Geriatric frailty is found in 20–30% of the elderly population over 75 years and increases with advancing age. It was reported to be associated with long-term adverse health-related outcomes – increased risk of geriatric syndromes, dependency, disability, hospitalization, institutional placement, and mortality. The clinical phenotype of frailty manifests as multi-system pathologies characterized by low physical activity, global weakness with low muscle strength, fatigability/exhaustion, overall slowness particularly of gait, loss of weight among others. These above-mentioned clinical symptoms could be explained by (or related to) some ‘preclinical’ diagnoses such as sarcopenia, osteopenia, nonspecific balance disorders, nutritional problems, and overall deconditioning. More recent studies found the frailty clinical phenotype to be associated with pathologic laboratory markers (IL-6, CRP, 25-hy-

droxyvitamin D, IGF-1, D-dimers), which suggest possible pathogenesis involving hormonal dysregulation, immunaging, pro-coagulation and pro-inflammatory status. In the article, current recommendations for future research strategies of frailty syndrome will be discussed.

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Introduction

Functional decline, disability, and frailty are common geriatric conditions which belong to the larger family of ‘geriatric syndromes’. These common conditions hold substantial implication for functioning of older people and for their quality of life. Disability and frailty have common characteristics: both are rather prevalent in older population, of multifactorial nature and share some risk factors and pathophysiological mechanisms [1]. Though in recent years some pathophysiological pathways involved were elucidated, we are still lacking suitable complex models for these conditions. Simple linear models of one causal condition do not address the complexity of multiple potential pathways, their interactions and possible preventive strategies. The goal of the article is to describe geriatric syndromes of disability and frailty, to discuss the possible relation to nutritional status, and to propose potential approaches for conducting translational basic, clinical and policy research.

Disability in Old Age

As the population ages, disability is becoming an increasingly important concept both for its public health consequences as adverse health outcomes and increasing costs as well as for impaired quality of life of the older population [2]. With advancing age, functional capacity in performing advanced (e.g. instrumental) and even basic (e.g. self-care) activities of daily living (ADL) is becoming increasingly limited. Among the population 70 years and older 20–30% report disability in mobility, instrumental and/or basic ADL [3]. According to the WHO model, functional capacity over the course of life reaches its peak at early adulthood and decreases steadily with advancing age. At a certain point of decline, it reaches the disability threshold. However, the rate of decline is highly individual. It could be substantially modified both by intrinsic factors (e.g. physiologic changes with aging and comorbid diseases and impairments) and environmental situation (e.g. social, behavioral and economic factors) [4]. Targeted interventions may slow down the age-associated decline of functional capacity and performance and prolong the disability-free life span.

The disablement process has been extensively studied since the early 1970s. The concept of disablement pathways from pathology → impairment → disability → handicap has been established and became the basis for the disability classification proposed by the WHO in the early 1980s. Later on, this classification was updated in 2001 and became known as the ICF, International Classification of Functioning, Disability and Health [4].

Currently, disability is defined as difficulty or dependency in carrying out activities necessary for independent living, including roles, tasks needed for self-care and household chores, and other activities important for a person's quality of life [5]. For diagnosis of disability as a medical condition, self-reported questionnaires or performance-based tests are used. In the field of geriatric medicine, disability screening is recommended in persons aged 70 years and older as well as screening for disability risk factors (impaired mobility, muscle strength, balance, sensory functions) [6, 7]. Although self-perceived difficulty in performing ADL is the most commonly used definition, some studies define disability as dependency on help from another person. In another context disability may also be understood as a social phenomenon (e.g. one's ability to carry out distinct social role) or as a social construct (e.g. level of dependency as

entitlement for societal help as 'disability allowances' or eligibility for formal services).

Despite the year-long concept of disability, the direct cross-country comparisons of disability prevalence have been difficult due to methodological issues. However, longitudinal trends of disability showed decreasing prevalence by 1.2% a year during the 1980s and 1990s in some countries (US, France, Germany, and Japan), while others (Netherlands, UK, and Australia) showed no change [2, 3].

Recent evidence has shown that about half of the disability cases develop slowly, usually in association with chronic disease, comorbidities, and frailty; in the other half of cases, the disablement process is abrupt, following severe health events. It matches the progressive versus catastrophic disability described by Ferrucci et al. [8]. In a recent US study, Hardy et al. [9] demonstrated the dynamic nature of disability. They followed 754 community-living elderly aged 70 years and older for 5 years and found several episodes of disability in 56% of the study participants; however, most episodes were brief and overall 81% of the participants recovered. The individual patterns of disability were highly variable from a single, short discrete episode to recurrent episodes and prolonged or permanent disability. Higher rates and increased severity of disability episodes were found in frail individuals. The spectrum of disability patterns reflects the complexity of the disablement process: the interplay between precipitating event (fall, hospitalization) and predisposing risk factors [6, 7].

In clinical practice, disabled elderly people are often described interchangeably as dependent, with multiple chronic conditions, comorbid, or frail. All these terms are describing the most physically vulnerable subset of the elderly population in need of enhanced care. To find a clinical consensus, Fried et al. [5] conducted a survey among 62 geriatricians asking about terms of frailty and disability. 98% of the respondents felt that frailty and disability are 'not the same'. However, the causal relationships were not as clear: disability was understood by responding geriatricians to be the cause of frailty (88%) as well as its consequences (90%). The clinical inconsistency reflects frequent overlapping of comorbidity, disability, and frailty, which was confirmed by the results of the Cardiovascular Health Study [10]. These three conditions were found to be interrelated in terms that frailty and comorbidity predicted subsequent disability; disability may lead to frailty and worsen comorbidity, and frailty could contribute to the progression of chronic diseases. Therefore, Fried et al. [5] argue that, though interrelated and

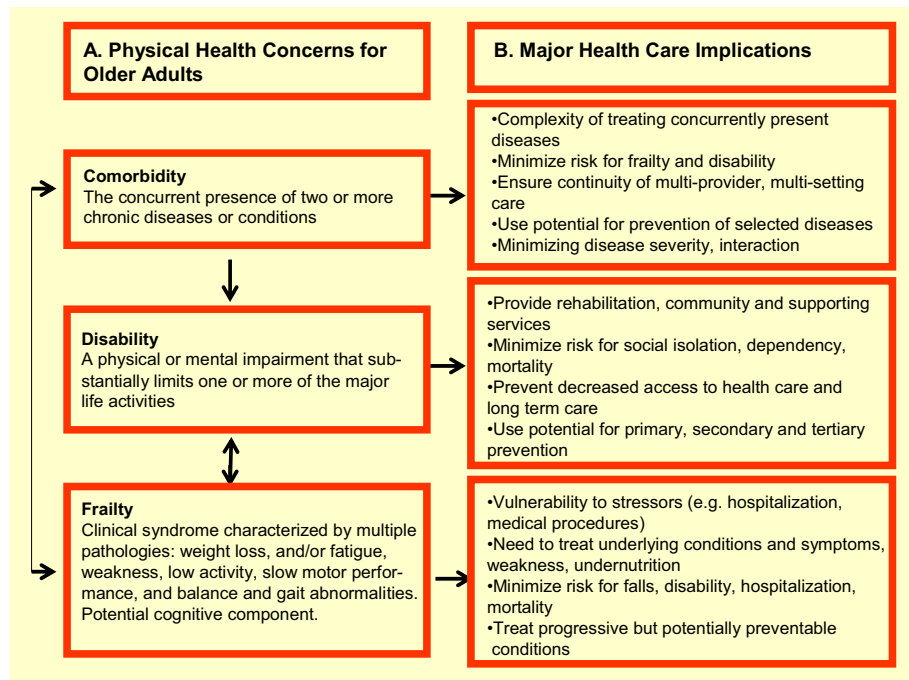


Fig. 1. Comorbidity, disability, and frailty: definitions and major health care implication. Modified from Fried et al. [5].

sharing some risk factors, disability, frailty, and comorbidity are clinically distinct entities with different prognosis and health care implications (fig. 1).

Frailty: A Clinical Phenotype

Though frailty is a commonly used term in clinical practice and this condition has been known for more than 30 years, it remains an evolving concept lacking consensus definition and unique diagnostic criteria [11]. Recently, the IANA Task force on Frailty Assessment of Older people in Clinical Practice conducted a literature search followed by a European, Canadian, and American Geriatric Advisory Panel expert meeting to find consensus in frailty definition and diagnosis as a starting point for intervention trials [11].

Frailty is described as:

‘A state of increased vulnerability to stressors that results from decreased physiological reserves and multi-system dysregulation, limited capacity to maintain homeostasis and to respond to internal and external stresses. Frailty is an aggregate expression of risk resulting from age- or disease-associated physiologic accumulation of subthreshold decrements affecting multiple physiologic systems resulting in adverse health outcomes’ [5].

Frailty as a clinical entity belongs to the family of geriatric syndromes and should be distinguished from the

aging process. As a syndrome, frailty is defined by symptoms and signs clusters which form its clinically complex profile known as ‘frailty clinical phenotype’. The most researched cluster is the physical frailty phenotype, but currently a much broader definition of frailty is accepted involving cognitive, functional, and social domains. For physical frailty, the widely used domains are ‘shrinking’ with weight loss and sarcopenia, weakness with low grip strength, exhaustion or poor endurance, slow motor performance (e.g. slow walking speed, decreased balance) and low physical activity as a marker of low energy expenditure [5].

Another working group led by Rockwood et al. [12] defined frailty as an accumulation of deficits (impaired continence, walking, cognition and ADL disability). Later, they broadened the definition to more than 70 items in several other domains (cognition, mood, motivation, communication, mobility, balance, ADL, bowel and bladder functions, nutrition, comorbidities, and social resources) aggregated in the ‘Frailty Index’ first used in the Canadian Study of Health and Aging [13]. Based on Frailty Index scores, a 7-point frailty scale was created which scored well in predicting mortality and institutionalization. An individual’s frailty index score reflects the proportion of potential deficits and indicates the likelihood that frailty is present. It enables vulnerability to be summarized quantitatively [14]. A similar concept

as the deficit-related Frailty Index was proposed by Mitnitski et al. [15] based on structured (geriatric) clinical examination. The deficits included were vision and hearing loss, impaired mobility, gait abnormality, impaired vibration sense, tremor, limb tonus abnormality, vascular problems, diabetes, hypertension, gastrointestinal and urinary problems, skin problems, change in sleep and ADL difficulties in bathing, toileting, grooming, dressing, cooking and going out, and was predictive of mortality.

The prevalence of frailty in the Cardiovascular Health Study reached 7% in 65+ community-dwelling participants and 30% in the subgroup of 80 years and older, and the Women's Health and Aging Study of moderately to severely disabled women population aged 65 gave a prevalence of frailty of 28% [5, 10]. The prevalence of frailty ranges substantially depending on criteria used, but was shown to increase with advancing age. Further studies confirmed that frailty has been associated with several adverse health outcomes: incident falls, hospitalization, institutionalization, worsening of mobility, overall disability, and death [5, 11, 15–17].

As with disability, the process of becoming frail is a dynamic one. Many authors consider frailty as a continuum from robustness to pre-frail to fully expressed syndrome of frailty. However, pre-frail individuals (not fully complying with frailty criteria or with the frailty threshold as expressed by the Frailty Index) may either enter the frailty state or reverse/recover to the non-frail one. With this dynamic concept of frailty, there is an 'intervention window' to prevent frailty or reverse it particularly in the group of pre-frail individuals.

The pathophysiologic mechanisms of the frailty process are not yet fully understood.

Central to the frailty definition has been the concept that multiple systems must be involved. The most commonly suggested multisystem impairments involve dysregulation of neuromuscular, endocrine, and immune systems with aging. Low-level inflammation, sarcopenia, osteopenia, and nutritional changes are diagnosed and often presence of other contributing factors of chronic and acute illness, and environmental stresses could be found. Aging is associated with increased serum levels of inflammatory markers [C-reactive protein and inflammatory cytokines (interleukin-6)] suggesting a low level of inflammation (inflammaging), and with pro-coagulation markers (D-dimers). These biological markers were correlated with increasing disability, mortality, and/or frailty. Puts et al. [18] studied selected endocrine and inflammatory markers in relation to frailty and found in-

creased C-reactive protein, low serum 25-hydroxyvitamin D and low IGF-1 associated with prevalent and/or incident frailty. Other studies confirmed low levels of growth hormone and IGF-1 with aging and their association with low muscle mass, declined functioning and disability which are closely related to frailty [17, 19]. Though no single biological marker of frailty has been recommended for clinical diagnosis, Balducci [20] proposes to assess the presence of frailty in geriatric patients with cancer to help in predicting the tolerability of chemotherapy. In addition to clinical assessment of frailty symptoms and signs, he suggests to assess potential biological markers of frailty: serum levels of interleukin-6 and D-dimers, other inflammatory cytokines, and the circulating level of C-reactive protein.

The role of hormonal dysregulation both hypothalamo-pituitary-gonadal/adrenal and growth hormone-IGF-1 axes for the development of sarcopenia and osteopenia is not yet fully elucidated but seems to be a complex, mutually interrelated process. The presence of endocrine-immune dysregulation with declining estrogen and androgen levels contributes to an increase in local bone cytotoxic cytokines followed by increased osteoclastogenesis and bone loss. Low gonadal hormones and low IGF-1, combined with high peripheral levels of inflammatory mediators, cytokines, low vitamin D and pro-coagulation state enhance the risk of sarcopenia and frailty [21]. Sarcopenia, an age-related decline in muscle mass and muscle quality, enhances the risk of frailty, contributing to several frailty symptoms such as weakness, low walking speed, low physical activity and energy expenditure, and possibly to impaired balance, impaired mobility, and falls. The downspiral of frailty is significantly influenced by impaired nutrition which contributes further to weight loss, low BMI, protein catabolism, worsening of sarcopenia and of immune functions.

Nutrition: An Important Frailty Domain

Nutrition has been recognized as an important component of healthy aging. One of the main phenotypic characteristics of frailty is 'shrinking', defined by muscle and total body mass wasting [10]. In the majority of frailty definitions some information about nutrition are part of the frailty criteria (table 1): some studies use weight loss of different severity and duration, some use low BMI, and others use ADL as cooking and meal preparation. In few studies, frailty was defined exclusively by physical

Table 1. Nutritional and nutrition-related components of frailty criteria in selected studies

Study/cohort	Nutrition criteria	Additional nutrition-related criteria
Women's Health and Aging Study [Bandein-Roche et al: J Gerontol Biol Sci Med Sci 2006;61A:262–266]	weight loss: BMI <18.5 10% weight loss since age of 60 at base-line	exhaustion, low physical activity, slow walking speed
Cardiovascular Health Study [Fried et al: J Gerontol Biol Sci Med Sci 2001;56A: M146–M156]	weight loss >10 pounds unintentionally in past year	exhaustion, weakness (grip strength), slow walking speed, low physical activity
Women's Health Initiative Observational Study [Woods et al: J Am Geriatr Soc 2005;53:1321–1330]	unintentional weight loss >5% or self-reported loss of >5 pounds	exhaustion
inChIANTI Study [Ble et al: J Gerontol Biol Sci Med Sci 2006;61A:278–283]	weight loss: self-reported 4.5 kg in past year	exhaustion, slow walking speed, weakness (grip strength)
Canadian Study of Health and Aging [Rockwood et al: CMAI 2005;173:489–495]	cooking, gastrointestinal problems	ADL, hearing and vision, gait, comorbidities
Zutphen and SENECA Studies [Chin et al: J Nutr Health Aging 2003;7:55–60]	weight loss 6% or more in 4–5 years low BMI	physical inactivity
EPIDOS [Nourshahemi et al: J Gerontol Biol Sci Med Sci 2001;56A:448–453]	instrumental ADL (shopping, cooking)	SPPB (Short Physical Performance Battery), grip strength, gait speed
Population Toulouse 1991,1993 and Albuquerque 1993 [Vellas et al: J Nutr Health Aging 2006;10: 456–463]	MNA (Mini-Nutritional Assessment)	none

performance tasks without a nutritional component [11].

In a study comparing 3 different criteria of frailty in two populations (Zutphen and SENECA Study), Chin et al. [22] used combinations of (a) inactivity + low energy intake, (b) inactivity + weight loss, and (c) inactivity + low BMI to define frailty. Inactivity defined as the lowest tertile of the activity questionnaire on housework, leisure time activity and sport + weight loss of 6% or more in 4–5 years were found to be the best predictors of death and functional decline over a 3-year period. Chin proposed this tool as a practical and inexpensive screening for identifying elderly people with less favorable health and nutrition characteristics and poorer physical functioning. Vellas et al. [23] evaluated the Mini-Nutritional Assessment (MNA), an instrument used for nutritional status assessment, as a screening tool for frailty in the elderly population of Toulouse and Albuquerque. MNA scores between 17.5 and 23.5, which identify persons at risk of malnutrition, appeared to be a good single marker

of frailty and correlated with weight loss, poor appetite, and functional and cognitive decline.

Considering frailty as a wasting (shrinking) syndrome, its relation to obesity remained unclear for a long time. Recently, Blaum et al. [24] analyzed data from the Women's Health and Aging Study subpopulation of participants with baseline BMI over 18.5 and found overweight associated with pre-frailty and obesity associated with both pre-frailty and frailty. Therefore, both under-nutrition and obesity should be viewed as potential markers or signs of frailty.

Conclusions

Frailty and disability are distinct clinical entities, partially overlapping but clearly distinguishable. As no single definition of frailty exists, the recent consensus of the 'Geriatric Advisory Panel of the IANA Task Force on Frailty' recommends avoiding disability markers as part

of the frailty definition [11]. Complex, mutually interrelated pathophysiological mechanisms are involved in the manifestation of frailty. However, the causal pathways to frailty may be common to other geriatric syndromes [1]. In this complex model, it is difficult to distinguish the cause of frailty from the outcomes of frailty. This distinction of causes versus outcomes and recognition of the role of risk and contributing factors will be important in future frailty research to avoid confusing results. Several working groups are addressing future frailty research which must combine a basic system biology perspective with multidisciplinary aging research and translate results into clinical practice and policy [11, 16, 19, 25]. As

recent data support the idea of preventability and/or reversibility of the frailty phenotype, it is important to design larger intervention trials to prove the efficacy of physical activity and exercise, hormonal replacement therapies, nutritional interventions, and comorbid diseases management.

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