The Clinical Care of Frail, Older Adults

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KEYWORDS

• Frailty • Intervention • Exercise • GEM • GCA
• Interdisciplinary care

Frailty and its management represent an emerging area of clinical care in older adults. Geriatricians have long recognized a syndrome of multiple comorbid conditions, immobility, weakness, and poor tolerance of physiologic stressors in older adults.[1] Patients with these characteristics are described as frail and suffer increased adverse clinical outcomes, such as acute illness, falls, disability, institutionalization, and death.[2] Recent advances in research have better characterized frailty syndrome and its pathophysiology, including the dysregulation of homeostasis in musculoskeletal, neuroendocrine, and immune systems. Although curative treatments for frailty are currently unavailable, exercise intervention and geriatric interdisciplinary assessment and treatment models can improve clinical outcomes in this patient population. Given the high morbidity and mortality secondary to frailty, increased awareness of this syndrome, its early diagnosis, and therefore, timely implementation of beneficial interventions are essential in improving health outcomes in affected older adults.

The purpose of this article is to review the clinical spectrum of frailty in older adults, its biologic etiology, and potential clinical interventions. The first section briefly outlines several operational definitions of frailty and the associated clinical signs, symptoms, and outcomes. The second focuses on the biologic mechanisms hypothesized to underlie frailty, particularly in the musculoskeletal, endocrine, and immune systems. The final section discusses treatment options for frail, older adults, including physiologic system-targeted interventions and geriatric models of care. Similar reviews have been published previously.[3–5]

FRAILTY SYNDROME: DEFINITIONS AND CLINICAL OUTCOMES

To provide optimal clinical care for frail older adults, it is pertinent that clinicians recognize the range of signs, symptoms, and adverse outcomes associated with frailty syndrome. Frailty at the end stage is clinically apparent and is often identified through evidence of recurrent falls and injuries, disability, susceptibility to acute illness, and poor ability to recover from acute stress.[6] Although frailty is more common in older

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adults and in those with multiple comorbidities, it certainly can occur independent of advanced age, disability, or specific diseases.[2] Various definitions of frailty have been proposed; however, the operational definition of frailty varies widely according to the conceptual framework; none are considered the gold standard, and few, if any, are used in clinical practice.[6] Most definitions of frailty describe a syndrome characterized by progressive multisystem decline, loss of physiologic reserve, and increase vulnerability to disease and death. Although some researchers define frailty by physical parameters, such as decline in muscular strength, mobility, endurance, physical activity, balance, and weight loss,[2,7,8] others view frailty in a broader sense and incorporate cognitive impairment and psychosocial dimensions in its assessment.[3,8,9]

Definitions that use physical decline as a proxy of frailty frequently use instruments that measure performance and functional changes in mobility and strength. For example, Studenski and colleagues[10] demonstrated that lower extremity performance battery of gait speed and chair stand and tandem balance tests were independent quantitative predictors of 12-month hospitalization rate as well as health and functional decline in 487 older adults seen in primary care settings. In the Zutphen Elderly Study, Chin and colleagues[7] compared 3 working definitions of frailty in 450 older men living independently: (1) inactivity plus low energy intake, (2) inactivity plus weight loss, and (3) inactivity plus low body mass index. The combination of inactivity plus weight loss was the most predictive of mortality and functional decline over 3 years of follow-up. Furthermore, men with the combination of inactivity plus weight loss also had overall poorer grip strength and walking speed and increased disability compared with more active men whose weight was stable.

Fried and colleagues[2] conceptualized frailty as a geriatric syndrome resulting from cumulative decline in multiple physiologic systems. Frailty is present when three of 5 criteria (unintentional weight loss, self-reported exhaustion, poor grip strength, slow walking speed, and low physical activity) are present, reflecting the notion that frailty is a syndrome with a critical mass of signs and symptoms and has a stepwise impact on clinical outcomes. The Cardiovascular Health Study (CHS) tested and validated this definition of frailty in 5317 community-dwelling men and women aged 65 years and older. This frailty phenotype was independently predictive of incident falls, worsening mobility or activity of daily living (ADL) disability, hospitalization, and death over 3 years, even after adjusting for health status, socioeconomic status, and disability. The frailty definition developed in the CHS was subsequently validated in a population of community-dwelling older women in the Women's Health and Aging Studies (WHAS).[11]

Other definitions of frailty use clinical information to identify older adults at risk of adverse outcomes.[3] For examples, Rockwood and colleagues[9] included impairment of cognition, mood, mobility, balance, ADLs, instrumental ADLs, nutrition, and other comorbidities in the assessment of frailty. This frailty index has been demonstrated to be highly predictive of mortality and hospitalization in older adults.

BIOLOGIC BASES OF FRAILTY

Although the biologic mechanisms of frailty are not completely understood, its underlying cause is thought to be multisystemic and probably involves the dysregulation of neuromuscular, endocrine, and immune systems.

Skeletal Muscle

Given that weakness and poor physical performance are principal to most definitions of frailty,[12,13] sarcopenia, defined as the loss of muscle mass and strength, is probably

a key physiologic contributor to frailty. This process begins after peak muscle mass and strength are attained at ages 20 to 30 years and has an accelerated rate of decline after age 50 years.[14,15] Sarcopenia can be further accelerated by chronic illness and is a major cause of disability and frailty in the elderly.[13] Causes of this physiologic decline include age-related changes in alpha-motor neurons, type I muscle fibers, muscular atrophy, growth hormone (GH) production, sex steroid levels, and physical activity. Also, increased production of catabolic cytokines and poor nutrition are potentially important causes of sarcopenia.[13,16]

Endocrine Systems

Sex steroids and insulinlike growth factor 1 (IGF-1) are central to skeletal muscle metabolism. Changes in regulation of these hormones secondary to aging or disease states are likely to accelerate the decline in muscle strength and mass in older adults with physical frailty.[17] The age-related rapid decrease of estrogen in postmenopausal women and gradual decrease of testosterone in older men lead to decline in muscle mass and muscle strength.[18–20] Serum levels of the sex hormone dehydroepiandrosterone sulfate (DHEA-S) and IGF-1, a signaling target of GH, are significantly lower in frail than nonfrail older women.[21] Furthermore, lower serum IGF-1 level is associated with progressive disability, poor muscle strength, slow walking speed, and increased mortality in the WHAS, suggesting a potential role for GH-IGF-1 somatotropic axis dysregulation in the development of frailty.[22,23]

Several other hormones, including cortisol and vitamin D, have been associated with frailty in older adults. The loss of stringent regulation of the hypothalamic-pituitary-adrenal axis is hypothesized to cause an age-related increase in cortisol production, which leads to decreased skeletal muscle mass and strength.[5] This hypothesis is supported by recent epidemiologic evidence that demonstrates a positive association between higher levels of evening cortisol, 24-hour mean cortisol, and blunted diurnal variation of cortisol, with the frailty burden and clinical presentation observed in frail older women in the WHAS.[24] Finally, low 25-hydroxyvitamin D level, commonly seen in older adults, is a risk factor of falls, fractures, sarcopenia, poor physical function, and disability.[25–27] Recent findings from the prospective cohort Invecchiare (Aging) in Chianti (*InCHIANTI*) study and the Longitudinal Aging Study Amsterdam (LASA) suggest that vitamin D insufficiency is also associated with prevalent and incident frailty, particularly in older men.[25,26]

Inflammation

Chronic inflammation characterized by chronic elevation of serum levels of proinflammatory cytokine interleukin 6 (IL-6) is strongly associated with frail older adults in the WHAS.[28] Furthermore, C-reactive protein (CRP), an acute-phase reactant directly upregulated by IL-6, is positively associated with baseline and incident frailty in the LASA[25] and CHS.[29] Finally, elevated neutrophils and macrophages are independently associated with prevalent frailty in the WHAS.[30]

Of the known inflammatory changes that occur in frail older adults, high IL-6 is most predictive of poor functional and clinical outcomes in chronic diseases and in frailty. IL-6 is a biologically important cytokine that is tightly regulated by the immune system. Its age-related increase is partially due to the loss of suppression from the decrease in estrogen and testosterone levels that occurs with aging.[31] High and chronically elevated levels of serum IL-6 are strongly associated with multiple disease states (diabetes, anemia, arthrosclerosis, heart failure, and dementia) and predict poor clinical outcomes (increased disability and mortality as well as sarcopenia) in older adults.[31–35] Furthermore, IL-6 may have hematologic effects in frail older adults by

activating the clotting cascade (factor VIII, fibrinogen, and D-dimer) and inhibiting erythropoiesis via interference with normal iron metabolism.[29,36] Although the exact mechanism of chronic inflammation in the pathogenesis of frailty remains unknown, the persistent elevation and dysregulation of IL-6 may be a key step in this disease process and a potential target for future interventions.

Multisystemic Contributions to Frailty

The cause of frailty in older adults is likely to be multisystemic rather than due to dysregulation in a single physiologic system. Although age-related or disease-associated changes in the neuromuscular, endocrine, and inflammatory systems can independently lead to increased vulnerability to poor outcomes in older adults, aggregate alterations in these systems may have synergistic adverse effects. For example, the combination of high IL-6 and low IGF-1 serum levels confers a higher risk of progressive disability and mortality in the cohort of community-dwelling women in the WHAS than either factor alone, suggesting a possible synergistic effect.[21,23] Similarly, greater levels of production of tumor necrosis factor alpha (TNF-α) and IL-6 and decreased IGF-1 are associated with increased mortality in community-dwelling older adults in the Framingham Heart Study.[37] Ultimately, multiple dysregulated systems interacting in nonlinear ways have been shown to be associated with frailty, leading to speculation that interventions in one system may improve other systems.

TREATMENT OPTIONS FOR FRAIL, OLDER ADULTS

To date, exercise and geriatric interdisciplinary assessment and treatment models are the only options that have been demonstrated to improve clinical outcomes in frail, older adults. As understanding of the biologic basis of frailty improves, more effective therapeutic regimens that target specific physiologic systems and alternative models of geriatric care are likely to be developed.

Physiologic-System-Targeted Interventions

Exercise intervention

Aging-related loss of muscle mass and strength due to sarcopenia is a significant cause of disability in frail older adults.[13] Numerous studies have shown that regular exercise training improves muscle strength, aerobic capacity, balance, and mobility and reduces falls in older adults.[38,39] Other benefits of regular exercises include improvement in performance of ADLs, postponement of disability, and continuance of independent living in oldest subjects.[40,41] Also, exercise can reduce chronic elevations in inflammatory mediators.[42]

In a study of frail, female, nursing home residents whose average age was 87 years, Fiatarone and colleagues[43] demonstrated that progressive resistance exercise training resulted in significant increases in muscle strength (113%), gait velocity (12%), and cross-sectional thigh-muscle area (3%), compared with the control group. Stair-climbing power and spontaneous physical activity also increased in the group that participated in exercise intervention, further supporting the idea that high-intensity resistance training could counteract sarcopenia and physical frailty in the very old. Tai Chi, a dynamic balance exercise, was shown to significantly decrease falls in frail, older adults during and after the intervention period in the Frailty and Injuries: Cooperative Studies of Intervention Techniques (FICSIT) trials.[39] Also, meta-analyses of the FICSIT trials showed that exercise significantly improved quality of life and emotional health and that exercise-related joint and muscle stresses did not increase bodily pain in older adults.[44]

In a recent systematic review, Chin and colleagues[38] examined 20 randomized controlled trials published from 1995 to 2007 that evaluated the effects of 23 different exercise training programs on physical performance in older people with varying degrees of frailty. Most of these interventions were facility-based, group-exercise programs composed of resistance training (n = 9); Tai Chi training (n = 2); or multicomponent training, including resistance, endurance, balance, and flexibility exercises (n = 12); performed thrice a week for 45 to 60 minutes. Fourteen of these trials demonstrated a beneficial effect of exercise on functional performance, suggesting that older adults with different levels of baseline functions could benefit from exercise training. Five of the studies that did not show significant benefit of exercise were performed in a highly frail population, suggesting that the degree of frailty may play a role in dictating effectiveness of exercise programs.

In summary, exercise training improves functional performance, fall prevention, quality of life, and emotional health in older, frail patients. Although evidence suggests that a structured exercise program enhances functional performance across the frailty spectrum, its benefits in the most severely frail patients may be limited. Despite these positive outcomes, specific guidelines of exercise programs (type, intensity, frequency, and duration) for frail, older adults have not been established. Because resistance exercise has been shown to be well-tolerated by older adults,[45] resistance training with exercise machines and body weight or elastic bands, with sessions lasting 30 minutes twice a week, should be implemented in frail, older adults who can safely participate. In more frail patients, structured resistance training can be modified and administered with assistance by caretakers for community-dwelling patients or can be incorporated into restorative therapy programs for long-term-care residents.

Hormonal intervention

Because decline in circulating levels of sex steroids, DHEA-S, vitamin D, and IGF-1 are associated with frailty in older adults, hormone replacement may be a potential therapeutic intervention to improve muscle mass and strength and, ultimately, to improve clinical outcomes. However, to date, the efficacy of hormonal replacement therapy in treating frailty has not been established. Hormone therapy is not currently recommended for the clinical management of frail older adults in the absence of clear clinical deficiencies.

Although multiple clinical studies have shown that testosterone replacement in older men can increase lean muscle mass, muscle strength, and aerobic endurance and reduces whole-body and trunk fat, its effect on functional performance has yielded mixed results.[46–49] Because of the absence of consistent beneficial effects of testosterone replacement and its associated adverse effects on prostate enlargement and hyperlipidemia, testosterone replacement as an intervention for frailty is not recommended. Similarly, although vitamin D replacement in older adults with vitamin D deficiency increases muscle strength and function and decreases falls and hip fractures, its efficacy in frailty intervention has not been reported.[19,50,51] Finally, GH administration to older adults with low IGF-1 levels increases lean body mass and bone mineral density and reduces body fat mass, but its effect on frailty remains unknown.[52]

Anti-inflammatory intervention

Although substantial evidence supports the relationship between chronic IL-6 elevation and frailty-related outcomes, including muscle mass decline, disability, and mortality, pharmacologic treatments aimed at reducing inflammation in frail, older adults have not been developed. The use of TNF-α antagonist as an antirheumatic

agent has effectively reduced systemic symptoms of rheumatoid arthritis similar to those observed in frailty, including weakness and fatigue.[53] Because inflammation has a significant etiologic role in rheumatoid arthritis and frailty, using specific anti-inflammatory modulators may potentially delay the onset or progression of frailty while reducing symptoms and improving quality of life.

Models of Care for Frail and Vulnerable Older Adults

Comprehensive geriatric interdisciplinary assessment and treatment

Comprehensive geriatric assessment with implementation of an interdisciplinary treatment plan improves the clinical outcome and quality of life of the frail, older adult.[3,5] The overall objectives of this intervention are to improve physical and psychological function, reduce hospitalization and long-term care placement, improve quality of life, and decrease early mortality in older adults.[54] The interdisciplinary assessment and care team usually consists of a geriatrician, a nurse, a social worker, and an occupational or physical therapist. Patient assessment includes data collection via detailed medical history and physical examination and a thorough discussion and synthesis of relevant psychosocial and medical data and environmental resources, followed by the formulation of treatment goals and management plans developed with the direct participation of the patient and caregivers.

Geriatrics-focused interdisciplinary management of older adults can be grouped into 2 models of care: (1) geriatric evaluation and management (GEM), in which the interdisciplinary team actively follows up on the patient and directs medical care, and (2) comprehensive geriatric assessment (CGA), in which the consultative interdisciplinary team makes specific recommendations to the patient's primary care provider rather than directly implementing care.[3,5] In both the GEM and CGA models, interdisciplinary geriatric assessments associated with ongoing follow-up care targeted at vulnerable older adults have demonstrated improved clinical outcomes. For example, a single outpatient CGA coupled with an adherence intervention prevented functional and quality-of-life decline among community-dwelling older persons who had at least one of the 4 following geriatric conditions: falls, urinary incontinence, depressive symptoms, and functional impairment.[55] Similarly, a meta-analysis on 28 controlled trials of 4959 subjects allocated to CGA linked with long-term management showed improved survival and function in older persons.[56] Boult and colleagues,[57] conducted a randomized controlled trial of GEM intervention targeted at older patients at risk of repeated hospitalization and found that participants of GEM were less likely to lose functional ability, experience increased health-related restrictions in their daily activities, or use home health care services during the 12 to 18 months after randomization. Because CGA and GEM are most effective when treatment plans are implemented, monitored, and revised through close follow-up, the active participation of the patient and caregivers in these interventions is essential to its success.[57] Lastly, the importance of a collaborative relationship between the patient and the primary care physician in CGA should not be understated. It has been shown that patient adherence to CGA treatment plans is significantly increased when the patient and the primary care physician concur on recommended geriatric health care.[58,59]

All-inclusive care for the elderly

Because frail, older adults experience more adverse effects of hospitalization, alternative programs that provide modest medical intervention and palliative care in the patients' home or in the outpatient clinic have been developed. The most widely used model of this type is the Program for All-Inclusive Care of the Elderly (PACE). The core features of PACE include targeting nursing home-eligible participants who

choose to receive long-term care services in the community, integrating funding and provider financial risk through capitated Medicare and Medicaid reimbursement, delivering integrated service through adult day care centers, and using interdisciplinary teams for case management.[60] The interdisciplinary team consists of trained geriatrics providers, nurses, physical and occupational therapists, and social workers. Additional patient-centered services include home nursing and home health aide services, transportation, and adult day care. The goals of PACE are to improve patients' functional status and to maintain quality of life by allowing frail older adults to remain in their communities and by preventing institutionalization. Patients enrolled in this program receive complete long-term care and are transitioned to appropriate settings of care, including hospitals, assisted living, nursing homes, and palliative care, as clinically indicated. Although initially conceived as a community-based program, variations of the PACE model have recently been successfully demonstrated in 3 Veterans Affairs (VA) medical centers.[61] The successful partnership of PACE with the VA to provide care for veterans suggests that PACE should not be viewed as a niche program and that other VA-community partnerships for care provision of frail older adults should be identified and implemented.

The acute care for elders model

Similar to outpatient management of older adults, the geriatrician-led interdisciplinary team approach has been shown to improve functional status, reduce acute care hospital days and readmission, and lower mortality rate in hospitalized acutely ill frail older patients.[62,63] The most frequently used model to deliver interdisciplinary inpatient care for frail older patients is the Acute Care for Elderly (ACE) unit. Key features of the ACE unit include a more homelike environment, patient-centered care that includes plans for preventing disability and iatrogenic illness, and comprehensive discharge planning and management.[64] In a randomized control trial of older community-dwelling patients admitted to a hospital for acute medical illnesses, ACE intervention decreased ADL decline or nursing home placement and improved provider and patient satisfaction without increasing hospital length of stay or costs.[64]

Screening and Treatment Algorithm

Physicians who are not familiar with the clinical care of frail, older adults may not easily recognize frailty in its early stage. Also, the lack of a uniform definition and diagnostic criteria make early diagnosis of frailty syndrome difficult. Therefore, assessment tools that can predict the risk of functional decline, disability, and frailty and instruments that can be easily administered during routine physician visits by nongeriatricians should be used as screening tools for frailty.[65] Examples of these assessment tools include the physical performance battery of gait speed, standing balance, and time to rise from chair[66]; the Edmonton frail scale[67]; and the validated CHS frailty phenotype.[2]

In managing older adults, diseases such as major depression, heart failure, and occult malignancy with symptoms overlapping those of frailty need to be ruled out and treated first. Once a frail, older adult is identified, the patient should be initiated on exercise intervention and referred for geriatrics-focused interdisciplinary management (GEM, CGA; **Fig. 1**). A patient who is nursing home-eligible should be referred to PACE for all-inclusive care. In an increasingly frail patient, caretakers should implement structured resistance training programs at home or through community resources (adult day care and senior centers with exercise therapy) and long-term care facilities (restorative therapy). In an acutely ill frail older adult, inpatient management should be delivered in an ACE unit. In the frailest patient, palliative care should be considered and implemented if appropriate. Finally, it is crucial that patient-centered

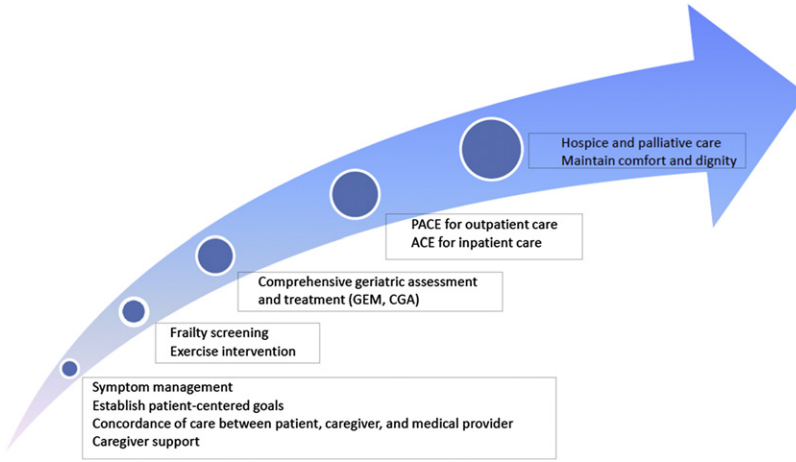

Fig. 1. Clinical management along the spectrum of frailty in older adults. The direction of arrow reflects increasing frailty. Each circle indicates potentially beneficial interventions at different stages of frailty syndrome.

goals remain the focus of the management plan and that the patient, the caregivers, and the interdisciplinary team concur on recommended care throughout the spectrum of frailty in older adults.

SUMMARY

Frailty in older adults is associated with high morbidity and mortality. Clinicians should have heightened awareness of the signs and symptoms of frailty syndrome, make timely diagnosis, and implement exercise therapy and geriatrics-focused interdisciplinary management to improve health outcome in this most vulnerable subset of older adults. Although curative therapy for frailty is not available, advances in frailty research is likely to lead to improved pharmacologic or nonpharmacologic interventions in the near future.

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