Frailty: An Emerging Geriatric Syndrome
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ABSTRACT

Frailty is a new and emerging syndrome in the field of geriatrics. The study of frailty may provide an explanation for the downward spiral of many elderly patients after an acute illness and hospitalization. The fact that frailty is not present in all elderly persons suggests that it is associated with aging but not an inevitable process of aging and may be prevented or treated. The purpose of this article is to review what is known about frailty, including the definition, epidemiology, and pathophysiology, and to examine potential areas of future research. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Aging; Frailty; Geriatrics

The relentless path to old age, frailty, and death has been a hopeless enigma of medicine. In Ptolemy’s treatise, the last age of life from 68 years to death was described as “dispirited, weak, easily offended, and hard to please.” Aristotle further explained this stage as a period when the body’s heat dissipates and is no longer able to provide energy and balance; the loss of inward heat depressed the spirit, caused illness, and decreased strength, and eventually human beings lost their passion for life and succumbed to death.1 In 1908, Eli Metchnikoff asked, “How can we transform to a normal and physiological condition, old age, at present utterly pathological, unless we first understand the most intimate details of its mechanism?”2 This question is just beginning to be answered almost a century later as geriatricians struggle to define frailty. This article will review the definition, epidemiology, pathophysiology, and treatment of frailty, and examine potential areas of future research.

FRAILTY DEFINED

Frailty, a fairly common biological syndrome in the elderly, is identified by decreased reserves in multiple organ systems. It may be initiated by disease, lack of activity, inadequate nutritional intake, stress, and/or the physiologic changes of aging. Frailty develops slowly in a stepwise process, with increments of decline precipitated by acute events. It is manifested as loss of skeletal muscle mass (sarcopenia), abnormal function in inflammatory and neuroendocrine systems, and poor energy regulation. In the frail elderly, there is homeostenosis, or a decreased ability in the body’s physiologic response to maintain homeostasis in times of acute stress. In essence, frailty is a product of “excess demand imposed upon reduced capacity.”3 Once the elderly become frail, there is often a rapid, progressive, and self-perpetuating downward spiral toward failure to thrive and death.4

BACKGROUND

Contrary to popular belief, not all elderly are frail.5 Only 3% to 7% of elderly persons between the ages of 65 to 75 years are frail.6 The incidence of frailty increases with age, reaching more than 32% in those aged more than 90 years.7 Furthermore, once a person is pre-frail, he or she is more likely to progress to frailty, thus emphasizing the downward spiral affect of this syndrome.8

Frailty can be a primary or secondary diagnosis. Notably, 7% of the frail elderly have no illness, and 25% have only 1 comorbid diagnosis.6 Researchers have demonstrated that even when individuals with acute and chronic medical conditions were excluded, 7% of the population aged more than 65 years and 20% of the population aged more than 80 years were frail.5 On the other hand, frailty may occur as a result of an acute event or the end stage of many chronic conditions, including atherosclerosis, infection, malignancy, and...
For example, severe congestive heart failure can lead to decreased activity, decreased nutritional intake, and increased inflammation and circulating cytokines. The combination of these factors eventually leads to cardiac cachexia and frailty.

The phenotypic picture of frailty can be confused easily with disability; however, investigators have sought to differentiate them. Disability, defined as the inability to perform activities of daily living (ADL), instrumental activities of daily living (IADL), or difficulty with mobility, does not affect the body across multiple organ systems.9 Among frail elderly persons, only 60% have difficulty completing IADL, and 27% cannot complete ADL; furthermore, only 28% of disabled elderly persons are frail.10 Even when adjustments are made for disability and comorbidity, elderly persons with a diagnosis of frailty continue to have a higher mortality rate.11 Although disability may contribute to frailty and vice versa, the 2 diagnoses are distinct from each other.

Frailty has been described as having a continuum. The initial stage of frailty, in which patients demonstrate fewer than 3 of the characteristics diagnostic of frailty, is referred to as the pre-frail stage. Studies show that pre-frail elderly persons are more likely than non-frail elderly persons to develop the full syndrome.10 Pre-frail elderly persons also have an increased risk of falls, institutionalization, and mortality but not as high as the frail elderly.

During the pre-frail stage, the frailty syndrome may be reversed.

Multiple studies have shown the benefit of exercise, stretching, resistance training, and tai chi on frailty. Frailty markers have been shown to improve after 30 to 60 minutes of exercise, done 3 times a week.

By recognizing the frailty syndrome and suggesting lifestyle changes, physicians may help patients prevent comorbidities later in life.

### CLINICAL SIGNIFICANCE

- When compared with non-frail elderly, pre-frail elderly have an increased risk of falls, institutionalization, and mortality but not as high as the frail elderly.
- During the pre-frail stage, the frailty syndrome may be reversed.
- Multiple studies have shown the benefit of exercise, stretching, resistance training, and tai chi on frailty. Frailty markers have been shown to improve after 30 to 60 minutes of exercise, done 3 times a week.
- By recognizing the frailty syndrome and suggesting lifestyle changes, physicians may help patients prevent comorbidities later in life.

### SIGNIFICANCE

Why is frailty important? Currently 20% of the population of the United States are aged more than 65 years, and the most rapidly growing segment of our population are those aged more than 85 years. The incidence of frailty increases with age and will become more prevalent as our population continues to grow old.13 Studies show that 3% to 7% of people aged more than 65 years are frail; this percentage increases to 20% to 26% for elderly persons in their 80s and to 32% for those in their 90s.7 The 4-year incidence of frailty in the elderly is 7%;10 a similar study in the Hispanic population showed the 7-year incidence to be 7.9%.8 In general, the elderly population has a greater percentage of females and frailty is considerably higher in women.14 After adjustment for age, race, sex, smoking, and comorbid illness, frail patients have 1.2- to 2.5-fold increase in their risk for falls, decreased mobility, worsening ADL, institutionalization, and death.10 A separate, cross-sectional observational study reported that frail patients had a significantly increased risk of cardiovascular disease, hypertension, cancer, and death, even after adjusting for chronic conditions.15 As the elderly population continues to grow, the impact of frailty will be felt throughout families and pervade our economic, health care, and social systems.

### A WORKING DIAGNOSIS OF FRAILTY

The diagnosis of frailty has taken time to evolve. Initial studies showed a decrease in strength and balance to be predictors of frailty.16,17 However, in the elderly, multiple causes can lead to such a state, including immobility, decreased appetite, poor nutrition, and chronic illness. On this basis, a “cycle of frailty” was hypothesized. The Figure helps conceptualize this cycle and highlights the interdependence of various factors that may cause patients to enter this cycle. For example, poor dentition itself cannot cause frailty; however, it can lead to chronic undernutrition and eventually sarcopenia, thus placing the patient in the cycle of frailty. Poor dentition can also lead to infection and periodontal disease, which may cause an increase in inflammatory markers and cytokines, once again placing the patient in this cycle.

More recently, Fried10 conducted a detailed study analyzing multiple demographic, medical, and laboratory markers to statistically determine a definition of frailty. A diagnosis of frailty requires 3 of the following 5 characteristics (Table):

- Decreased walk time, as defined by a 15-foot walk test.
- Decreased grip strength, measured by a dynamometer.
- Decreased physical activity, measured by the Minnesota Leisure Time Activity Questionnaire.18
Exhaustion, measured by the Center for Epidemiologic Studies Depression Scale.

More than 10 pounds or 5% of weight loss in the last 1 year.

This set of criteria indirectly measures the manifestations of frailty, most important, sarcopenia as measured by grip strength, malnutrition as measured by weight loss, and fatigue as measured by the Center for Epidemiologic Studies Depression Scale. Recently, these criteria were applied to data from the Women’s Health and Aging Studies. By using this definition, a similar incidence and prevalence of frailty were observed; in addition, statistical correlations between the incidence of frailty and the development of disability, falls, institutionalizations, and mortality mirrored the results found in Fried’s study. Although Fried’s definition of frailty is most widely accepted and will be the definition referenced in this article, other indices of frailty have also been published.

Not all that appears to be frailty is frailty. The differential diagnosis of frailty includes congestive heart failure, polymyalgia rheumatica, Parkinson disease, rheumatoid arthritis, occult malignancy, and infection. A new onset or an

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**Table** Criteria Used to Define Frailty

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Loss</td>
<td>Greater than 10 lbs or 5% of weight loss in the last year</td>
<td></td>
</tr>
<tr>
<td>15-Foot Walk Time</td>
<td>Height ≤173 cm</td>
<td>Height ≤159 cm</td>
</tr>
<tr>
<td></td>
<td>≥7 seconds</td>
<td>≥6 seconds</td>
</tr>
<tr>
<td>Grip Strength</td>
<td>BMI ≤24</td>
<td>BMI ≤23</td>
</tr>
<tr>
<td></td>
<td>≤29</td>
<td>≤17</td>
</tr>
<tr>
<td></td>
<td>BMI 24.1-26</td>
<td>BMI 23.1-26</td>
</tr>
<tr>
<td></td>
<td>≤30</td>
<td>≤17.3</td>
</tr>
<tr>
<td></td>
<td>≤32</td>
<td>≤18</td>
</tr>
<tr>
<td></td>
<td>BMI &gt;28</td>
<td>BMI &gt;29</td>
</tr>
<tr>
<td></td>
<td>≤21</td>
<td>≤21</td>
</tr>
<tr>
<td>Physical Activity (MLTA)</td>
<td>&lt;383 kcal/wk</td>
<td>&lt;270 kcal/wk</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>A score of 2 or 3 on either question on the CES-D*</td>
<td></td>
</tr>
</tbody>
</table>

*How often in the last week did you feel this way?*

(a) I felt that everything I did was an effort.

(b) I could not get going.

0 = 1 day; 1 = 1-2 days; 2 = 3-4 days; 3 = more than 4 days.

BMI = body mass index; MLTA = Minnesota Leisure Time Activity Questionnaire; CES-D = Center for Epidemiologic Studies Depression Scale.
exacerbation of any of these diseases could present as frailty; however, all of these illnesses are treatable and should be excluded before attributing a decline to frailty.6

Other Markers of Frailty
Although not part of the definition, other demographic and neuroendocrine markers also have been associated with frailty. Demographic markers include female sex, African-American race, lower education level, lower income, chronic illness, and disability.10,23 In the previous study, chronic illnesses associated with frailty included cardiovascular disease, pulmonary disease, arthritis, and diabetes; cancer was an exclusion criteria. Cognitive limitations and depression were also more prevalent, despite the exclusion of patients taking antidepressants or having a mini-mental status examination score of less than 18.

Researchers also have evaluated the inflammatory and neuroendocrine changes in frailty. Walston and others28,29 looked extensively at frailty markers in the Cardiovascular Health Study Cohort. When excluding patients with diabetes or cardiovascular disease, frail patients had an increased C-reactive protein (CRP) and fibrinogen (odds ratio 2.0-3.0). CRP has been shown to activate the inflammation and clotting cascade, including d-dimer and factor VIII, both of which are elevated in frail patients. CRP also causes an increase in circulating interleukin-6; Leng and others24 confirmed that frail patients have higher levels of interleukin-6.

Glucose intolerance also was noted; both fasting/prandial glucose and insulin levels were elevated in frail patients (odds ratio 1.5-2.6).25 Glucose intolerance is often associated with sarcopenia. In addition, recent research shows that hyperinsulinemia and hypertriglyceridemia may be associated with cognitive decline and leptin resistance, resulting in appetite suppression and decreased nutritional intake.

Serum levels of insulin-like growth factor-1 and dehydroepiandrosterone were significantly lower in frail patients as well.26 Dehydroepiandrosterone, a weak androgenic steroid that is a precursor of testosterone, plays a role in maintaining muscle mass and suppressing inflammation. Insulin-like growth factor-1 stimulates growth hormone release that regulates cell growth and development, and is often decreased in patients with diabetes or malnutrition.

No relationship between frailty and lipid profiles or albumin has been seen.21 It is important to note that it remains unknown whether the above neuroendocrine changes cause frailty or whether the reverse is true.

Markers of Aging
Before the formulation of Fried’s definition, researchers using various criteria for frailty noted other demographic trends in patients who appeared to be frail. Not all of these markers have been validated using Fried’s definition. One study linked frailty in men to depression, inactivity, weight loss, decreased peak flow, and decreased cognition. Furthermore, a decline in peak flow, cognition, vision, and physical activity over a 3-year period was linked to frailty in women.11 Other studies have found incontinence, poor hearing, and a feeling of loss of control over one’s life to be associated with frailty.11 A study based in China found that social factors, such as limited contact with relatives, blue-collar occupations, and absence of religious or community activities, were more likely to be seen in the frail elderly.27

Many gerontologic studies have shown inflammatory and neuroendocrine markers linked to aging, but these experiments have not been reproduced in the frail population.28,29 In times of stress, cortisol secretion and pituitary reactivity are increased in older adults.30 Although increased levels of cortisol have not been directly linked to frailty, this can lead to the frailty phenotype, including increased risk of infection, sarcopenia, and insulin resistance. Tumor necrosis factor-α has also been linked to aging and sarcopenia; studies attempting to link this cytokine to frailty are currently under way.31 More recently, leptin, a hormone that controls appetite and body fat stores, and ghrelin, a hormone that inhibits leptin, have been shown to be links in the endotoxin-induced cachexia suspected in frailty.32 A recent study, using an alternative definition of frailty, showed that elderly persons had lower 25(OH)D levels (odds ratio 2.6).33

Frailty and Its Causes
What causes frailty? Although many studies have shown associations between the incidence of frailty and factors that may lead to the condition, a definitive correlation has not been established. It also remains unclear why factors trigger frailty in some individuals but not in others. Experts speculate that certain environments, medications, age-related changes, and diseases make a particular genotype of people vulnerable to frailty.5,34

Data from the Women’s Health Initiative study showed that obesity, anorexia, smoking, and depression may lead to the development of frailty.35 Multiple aging studies showed that cumulative predictors over 3 decades, including heavy drinking, cigarette smoking, physical inactivity, depression, social isolation, poor perceived health, and chronic illnesses, led to increased morbidity in the elderly but not necessarily frailty.36

At the cellular level, Bortz37 proposed a theory referred to as “the physics of frailty,” which postulates that a loss of functional competence at a cellular level, along with thermodynamic decline and a loss of energy stores, leads to physiologic decline. Walston38 further adds that the cause of frailty might be at the molecular level; mechanisms related to aging, such as oxidative damage, telomere shortening, gene expression changes, and cellular senescence, may contribute to the dysregulated inflammatory and neuroendocrine signaling that leads to frailty. Genetic research also has been done linking Apo E to frailty as well.39
CLINICAL RESEARCH

Research also has begun in the clinical realm. Although a detailed discussion of clinical research is beyond the scope of this article, a general overview is provided.

Atherosclerosis contributes to frailty by decreasing blood flow and oxygenation to muscles, leading to sarcopenia. It indirectly contributes to cognitive impairment, through strokes, and to decreased physical activity in congestive heart failure and myocardial infarction. The Cardiovascular Health Study showed that cardiovascular disease, most notably heart failure (odds ratio 7.5), was associated with an increased likelihood of frailty. In elderly patients with no history of cardiovascular disease, subclinical cardiovascular disease, measured by carotid ultrasound, ankle-brachial index, and left ventricular hypertrophy, was also linked to frailty. Obesity also carries a high risk of frailty.

Anemia is increased in frail patients; researchers have noted a direct correlation between decreased hemoglobin and increased frailty. Furthermore, anemia in the frail population has been linked to elevation of interleukin-6. Patients with chronic renal insufficiency, after adjustment for other comorbidities, also have a higher risk of frailty.

Research also has shown that frailty and concurrent inflammation affect the treatment of infectious diseases. Chronic cytomegalovirus infection has been associated with frailty, but further studies are needed to establish a causal relationship. Frailty is more often seen in both depressed and cognitively impaired patients. Increased inflammation, but not necessarily frailty, has been shown to prevent wound healing as well.

Treatment

There is limited treatment available for frailty. The goal of initial treatment is the optimal management of all medical illnesses that may cause frailty. The second step is to prevent sarcopenia through muscle-strengthening exercises. Multiple studies have shown the benefit of exercise, stretching, resistance training, and tai chi on frailty. Frailty markers have been shown to improve after 30 to 60 minutes of exercise, done 3 times per week, for 3 to 6 months. Exercise also has been shown to decrease the level of inflammatory markers. However, studies have not been done to show improvement in mortality with exercise; it is known, however, that exercise does not improve morbidity or mortality in the general elderly population.

Nutritional research conducted on the elderly population may shed some light on possible treatments for frailty. It has been found that increased caloric intake has little benefit in improving health status in the elderly; however, there does seem to be some benefits gained from a nutritional program when combined with an exercise program to increase expenditures by 1000 kcal/week. The appetite stimulants megestrol acetate and dronabinol have been of minimal benefit in improving appetite in geriatric nursing home patients; moreover, these drugs are associated with significant adverse effects.

It has been noted that as people age, levels of testosterone and DHEA, 2 hormones that have been shown to maintain muscle strength, decrease. However, investigators have been unable to demonstrate any benefit from hormone replacement.

CONCLUSION

An understanding of what Eli Metchnikoff once referred to as the “intimate details” of the mechanisms behind an “utterly pathological” old age has just begun. It is now known that old age is not synonymous with the frailty syndrome. Still, frailty has only recently been defined, and frailty research is in its early stages. Acceptance of a formalized set of criteria for the diagnosis of frailty will facilitate studies. Potential areas of investigation include the underlying pathophysiology of primary frailty and the contributions of other comorbid diagnoses to the clinical picture. Further investigation may illuminate its symptoms and impact on the body’s various organ systems, and how best to treat those who are frail. By identifying the risk factors for frailty, a window of prevention before the development of frailty may be found. Last, the effect of frailty on other organ systems may be elucidated. Successful investigations may lead to pharmacologic or other treatment modalities to address the needs of frail and pre-frail patients, and prevent both the development and the effects of this geriatric syndrome.

References