Frailty Syndrome in Geriatric Medicine

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Abstract: Frailty syndrome is frequently encountered in elderly populations. Frailty has been defined as a geriatric syndrome of increased vulnerability to environmental factors. Although knowledge of this syndrome continues to develop, there are still many areas of uncertainty. The pathophysiological pathways, role of biomarkers in the early identification of this syndrome and best management strategies are still under investigation. This study is a literature review of articles published on frailty syndrome in English, French and Spanish. Frailty and aging are similar processes with some differences. Multiple pathophysiological models of frailty have been studied. Factors associated with frailty include hormonal adjustments, sarcopenia and vitamin deficiencies among others. Biomarkers have been studied, but they are not specific. Phenotypes have been developed, but early recognition and prevention of this syndrome are still difficult. In conclusion, early recognition of this syndrome is of paramount importance. Preventative strategies need to be studied. The role of specific biomarkers in early detection of frailty needs to be defined. Clinical trials are needed to find better interventions for this syndrome.

Key Indexing Terms: Frailty syndrome; Prevention strategies; Elderly populations. **[Am J Med Sci 2012;344(5):395–398.]**

Frailty syndrome is frequently encountered in elderly populations. Frailty has been defined as a geriatric syndrome of increased vulnerability to environmental factors.[1–5] This syndrome is characterized by reduced physiological reserves, affecting multiple organ systems, and has been related to increased morbidity and mortality.[2] Considered synonymous with disability and comorbidity, frailty is highly prevalent in old age and puts the elderly population at high risk for falls, hospitalization and mortality.[3] In this syndrome, multiple deficits, such as sarcopenia, functional decline, neuroendocrine dysregulation and immune impairments, can occur in combination.[6]

Numerous authors have studied the factors associated with frailty syndrome. In the Women's Health Study of 543 participants aged 70 to 79 years, Blaum et al[7] found that hyperglycemia is associated with a greater prevalence of prefrail and frail statuses. Factors such as comorbidities, body mass index and inflammation could not explain the aforementioned association.

Many molecular, physiological and clinical pathways have been hypothesized.[5,7,8] Vanitallie[9] has described the contribution of sarcopenia to frailty syndrome in elderly patients, noting that sarcopenia (measured through total body protein) and visceral protein depletion (measured through transthyretin and retinol-binding protein, which in turn indicate protein-calorie malnutrition) are closely related to the development of frailty in elderly patients. An Italian study reviewed 923 participants aged >65 years enrolled in the Invecchiare in Chianti Study. The main objective of this study was to validate the measurement of muscle density and ratios of muscle and fat areas through the use of peripheral quantitative computed tomography measures, and then to validate these results with Fried's scale of frailty. The authors have found that frail individuals have lower muscle density and muscle mass and higher fat mass than nonfrail persons.[10]

Although knowledge of this syndrome continues to develop, there are still many areas of uncertainty. The pathophysiological pathways, role of biomarkers in the early identification of this syndrome and best management strategies are still under investigation. In this study, we examine the epidemiology, pathophysiology, role of biomarkers, role of frailty indices, classification of frailty, and management and prevention of this deadly syndrome.

EPIDEMIOLOGY OF FRAILTY: AN INTERNATIONAL PERSPECTIVE

Weiss[11] has estimated the prevalence of frailty to be around 7% to 10% in community dwellers. Other studies have shown that geriatric frailty is found in 20% to 30% of the elderly population >75 years and increases with advancing age.[5] Frailty corresponds with an extreme phenotype of aging.[9] As the world's population ages, more patients will exhibit frailty, which will increase the pressure on health services worldwide.

Many studies have reviewed the "gray epidemics" and their implications on the frequency of frailty in the setting of aging. One major concern in this area is the lack of an integrated approach to deal with the potential spike in frailty that many countries will likely experience in the coming years. A cross-sectional study by Gurina et al[12] of 611 community-dwelling elderly patients (>65 years) showed that the prevalence of frailty in a Russian sample was approximately 21%. There was a correlation between older age and higher prevalence of frailty status. The frequency of frailty in this study was higher for women than for men; however, it increased rapidly in women >75 years. These results have been corroborated by other studies that have reflected similar patterns of frailty in community-dwelling populations.[13,14]

Any discussion of frailty's prevalence must take ethnic differences into consideration. Some studies have indicated that ethnic-based scores seem to be accurate in determining frailty prevalence. Espinoza et al[15] found differences in frailty prevalence in Mexican-Americans compared with European Americans when a conventional score versus an ethnic-based score was used. The authors found a higher prevalence of frailness in Mexican-Americans when a conventional score was used and no difference between these 2 groups when an ethnic-based score was used. The authors recommended carefully selecting the frailty score to be used when dealing with different ethnic groups. The same authors in another longitudinal study showed that frailness may be related to ethnic background; over 10 years, 606 patients from European and Mexican backgrounds showed no difference in frailty prevalence at any given time, but Mexican-Americans tended to become less frail compared with European Americans of the same age group.[15] Ethnic differences have also been found in other studies. African

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Americans were more than twice as likely to be frail as Caucasians in the Cardiovascular Health Study (13% versus 6%) and the Women's Health Study (16% versus 10%).[16]

An international perspective of frailty shows marked differences between North America and Europe and other continents. According to a survey of 7334 adults aged ≥60 years living in 5 large Latin American or Caribbean cities, the prevalence of frailty varied from 30% to 48% in women and from 21% to 35% in men, which was much higher than that of their American and European counterparts. These differences have yet to be studied.[17]

Multiple factors are epidemiologically identified with frailty. They include old age (>75 years), female gender, low socioeconomic status, multiple comorbidities, disability (inability to perform activities of daily living), cognitive dysfunction, depression and poor nutritional status.[13,14]

The prevalence of frailty in long-term care settings and nursing homes has not been explored in depth. It appears to be much higher than that of community dwellers, but more studies are needed to determine the exact prevalence of frailty in these settings.[13,14,18] In one of the few studies in this area, Matusik et al[18] evaluated the impact of frailty and cognitive disorders on mortality outcomes in a cohort of 66 nursing home residents >65 years. The prevalence of frailness in this population was 34.9%, and that of cognitive dysfunction was 55.8%. The authors found that the combination of these 2 variables negatively affects survival at 12 months.[18] In a review, Rockwood et al[19] evaluated 3 measures of frailty in a nursing home population. The authors found that no matter which scale is used, the prevalence of frailty in nursing home populations is higher than that of community dwellers and that mortality rates are also much higher in nursing home residents.

Thus, not only is the prevalence of frailty dependent on multiple factors such as geographical location, acute care versus long-term care and ethnicity, but also is dependent on the frailty indices used. Factors associated with frailty (old age, female gender, socioeconomic status, multiple comorbidities and disability) have been identified in multiple studies. The long-term care setting seems to harbor the frailest patients, although more research studies to determine the accurate prevalence of this syndrome in long-term care settings are needed. The aging of the global population further complicates this picture. The overall increase in frailty will definitively have an impact on health services in developed and developing nations; health services need to redirect their efforts toward frailty prevention strategies as opposed to dealing with frailty complications. More strategies are needed to deal with this upcoming epidemic.

PATHOPHYSIOLOGY OF FRAILTY: THE CASCADE OF FRAILTY AND THE ROLE OF BIOMARKERS IN FRAILTY

Fedarko[20] has reviewed the difficulties in differentiating frailty from normal aging. The 2 processes share common characteristics, including a diminished response to environmental agents. An interesting difference pointed out by Fedarko is the loss of the continuity of the homeostasis cycle (global) in normal aging as compared with frailty, a condition in which there is more of a partial loss in the metabolic and muscular domains.

Many models for frailty have been suggested. Two of the most common are the accumulation of deficits suggested by Rockwood et al[19] and the more phenotypic-related approach suggested by Fried et al.[16] The pathophysiology of frailty seems to be complex, and different mechanisms have been established. A key factor in the development of frailty is sarcopenia. The factors associated with sarcopenia include age-related changes in alpha motor neurons, type I muscle fibers, muscular atrophy, growth hormone production, sex steroid levels and physical activity. At the same time, catabolic cytokines and poor nutrition are potentially important causes of sarcopenia.[17] Sex steroids and insulin-like growth factor-1 deregulation have also been connected to sarcopenia. In addition, vitamin D deficiency has been studied as a risk factor for sarcopenia and subsequent frailty.[21]

A study reviewed a subcohort of participants from the Cardiovascular Health Study observed from 1989/1990 through 1998/1999. The participants included 3141 community-dwelling adults aged 69 to 74 years without frailty or any other illness. The researchers looked for factors associated with frailty status in these patients and found, interestingly, that insulin resistance and inflammation were associated with frailty.[8]

Frailty is a dynamic process. Multiple definitions and scores have been used to classify patients. Interestingly, these classifications of frailty may not be of practical use in clinical practice.[19] Different models of frailness exist and have been reviewed. Cigolle et al[22] operationalized frailty in 3 different models based on functionality, health burden and comorbidities.

Besides clinical classification of frailty, other factors have been related to the onset and continuum of frailty. Factors such as hyperglycemia, insulin resistance and inflammation, sarcopenia, and high levels of interleukin (IL)-6, IL-1, IL-2, neopterin, and interferon-gamma and/or tumor necrosis factor-alpha (TNF-α) have been related to frailty in elderly patients.[23]

When frailty is assessed in relation to comorbidities, it is highly related to cardiovascular disease. In a review of cardiovascular disease and frailty, Afilalo[1] found a prevalence of 25% to 50% in patients with cardiovascular conditions, depending on the frailty score used. Among this population, patients suffering from heart failure and those undergoing invasive procedures have higher rates of frailty and worse outcomes compared with their nonfrail counterparts. Another interesting correlation exists between frailty and patients suffering from chronic obstructive pulmonary disease (COPD). Galizia et al,[24] in a 12-year follow-up study of 498 elderly patients with COPD and 799 without COPD, found a direct correlation with mortality outcomes in those suffering from COPD. Because the authors used a frailty score that significantly predicted mortality in patients with and without COPD, the presence of frailty in patients with COPD may be used as a prognostic tool for increased mortality. Therefore, as suggested by Galizia et al[24] and other authors,[25] frailty and chronic diseases may share common pathways in their pathogenesis.

The search for serological markers that could define frailty is under way. High levels of IL-6 predict future disability in elderly people.[23] Somatic and mitochondrial DNA mutations have also been proposed to play a role in the development of frailty. The mutations accumulated in postmitotic cells could lead to senescence, low testosterone levels or low cholesterol levels.[23,24,26] At the same time, C-reactive protein and TNF-α have been studied as biomarkers for frailty. Along the same lines, certain hormones (growth hormone, insulin-like growth factor-1, testosterone and estrogens) have been linked to frailness. A recent study of 1705 elderly men showed that age-related changes in blood androgens and estrogens may contribute to the development or progression of frailty in men.[27] Interestingly, neither of these biomarkers alone has helped to define frailty in clinical settings; therefore, the quest for a combination of clinical findings, biomarkers and predictive scores is still ongoing. More research in this field is definitely needed. The inclusion of frail elderly patients in randomized controlled trials has not been the norm in research studies.