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Review

Clinical features of prefrail older individuals and emerging peripheral biomarkers: A systematic review

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ABSTRACT

Frailty is a geriatric syndrome characterized by the clinical presentation of identifiable physical alterations such as loss of muscle mass and strength, energy and exercise tolerance, and decreased physiological reserve. Individuals with one or two of these alterations are defined as prefrail. The clinical features of prefrail older individuals have been investigated to a lesser extent compared to the frail population, even though this intermediate stage may provide insights into the mechanisms involved in the physical decline associated with aging and it is considered to be potentially reversible. We performed searches in the Medline, Embase, Scopus, Cinahl, and Cochrane databases from January 1995 to July 2013 for papers about the identification of prefrail people aged 65 and older published either in English or Spanish, and the reference lists of from the articles retrieved were pearled in order to identify any which may have been missed in the initial search. Two independent reviewers extracted descriptive information on frailty criteria and outcomes from the selected papers: of the 277 articles retrieved from the searches and 25 articles retrieved from pearling, 84 met the study inclusion criteria. The prevalence of prefrailty ranges between 35% and 50% in individuals aged over 60, is more common in women, and the age and the number of comorbidities in these individuals is similar to their frail counterparts. Weakness is the most prevalent symptom in prefrail individuals although there are some sex differences. Some serum biomarkers seem to discriminate prefrail from non-frail individuals but further research would be required to confirm this.

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1. Introduction

Frailty is a state of increased vulnerability to stressors (Morley et al., 2013), characterized by decreased physical functioning and an increased risk for poor outcomes, such as a higher incidence of falls, fractures, disabilities, comorbidities, health care expenditure, and premature mortality (Fried et al., 2001; Fugate Woods et al., 2005; Woo et al., 2012). Recently, the influence of genetic background has been explored in order to explain the variability of frailty phenotypes (Dato et al., 2012). The concept of frailty has grown in importance because of the need to better understand the health trajectory of older people, and to prevent, or at least to delay, the onset of late-life disabilities (Fried et al., 2001; Henly et al., 2011). Several models have been developed to assess frailty including the frailty index and frailty clinical scale (Hyde et al., 2010; Mitnitski, Mogilner, & Rockwood, 2001; Rockwood, 2005; Rockwood & Mitnitski, 2007) but the most used is that of Fried et al. (2001). The fragility index takes all the deficits that are present in an individual into account, including active diseases, ability to perform daily living activities, and physical signs from clinical and neurological examinations (from 20 to 70 different deficits). A third model, the FRAIL scale, integrates features from each of these models, combining physical symptoms, the inability to walk or climb a flight of stairs, weight loss, and exhaustion, with the presence of multiple illnesses. A fourth model, developed from the Study of Osteoporotic Fractures (SOF), leads to results similar to those obtained by evaluating frailty with Fried's criteria (Kiely, Cupples, & Lipsitz, 2009). At present there is no consensus on which measure should be used in the assessment of frailty, although difficulties in assessing frailty according to Fried's criteria in very old subjects (more than 85 years old) due to the high number of comorbidities in this population suggests that the frailty index or cumulative deficits index might be better used in these cases (Collerton et al., 2012; Kulminski et al., 2008).

Frailty syndrome is usually defined according to a well-established, standardized phenotype, based on five physical criteria as described by Fried et al. (2001) in the Cardiovascular Health Study (CHS): a clinical definition which has also been validated by other groups (Ahmed, Mandel, & Fain, 2007; Fugate Woods et al., 2005; Graham et al., 2009; Wilhelm-Leen et al., 2009). People meeting three or more criteria are classified as frail, those with one or two as prefrail (or intermediate-frail), and people without any as non-frail (Fried et al., 2001). By revising the literature, we found that individuals who meet one or two Fried criteria (intermediate-frail or prefrail) are sometimes not included in clinical studies, or that no statistical comparisons are made between prefrail, non-frail, and frail groups in terms of evaluating them with clinical scales or biomarkers. Logistic regression model results from analyzing the associations between frailty and risk-factor biomarkers in non-frail and prefrail subjects are often combined to focus on frailty and to create conservative models (Michelon et al., 2006; Semba et al., 2006; Szanton, Allen, Seplaki, Bandeen-Roche, & Fried, 2008). We believe that early identification of the prefrail population and characterization of its features is crucial in order to set therapeutic guidelines and nursing interventions aiming to prevent or minimize the conditions inherent to prefrailty, its transition to frailty, and the risk of acute clinical complications or disability and dependence (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004; Walston et al., 2006). To our knowledge, to date no reviews have been published concerning the features of individuals in the prefrailty state, nor the presence of biomarkers related to prefrailty. In this work we specifically reviewed and discussed the following:

i. The features of prefrail individuals
ii. The progression of prefrailty
iii. The prevalence of Fried criterion in prefrail individuals
iv. Biomarkers for prefrailty

2. Materials and methods

The design of this study was developed according to PRISMA guidelines.

2.1. Literature search

A literature search using multiple electronic bibliographic databases was conducted. The Medline (OVID), Embase (OVID), Cinahl (OVID and EBSCO), Scopus, and Cochrane libraries were searched from January1995 to July 2013. Reference lists of all relevant articles were manually cross-referenced in order to identify additional articles. The primary search terms used were "*prefrail*" and "*prefrailty*". The search strategy used was *prefrail** with one of the following terms: *men, women, gender/sex differences, prevalence, physical activity, slowness, weakness, fatigue, weight loss, muscular strength, Fried criteria, age, aging, biomarker, white blood cells, leukocytes, inflammation, oxidative stress, testosterone, cortisol, vitamin, DHEAS (dehydroepiandrosterone)*, and *IL-6 (interleukin-6)*.

2.2. Inclusion/exclusion criteria

The following inclusion criteria were used: (1) acknowledged as an original article, (2) full-text published in either English or Spanish, (3) study participants were identified as "prefrail" or "pre-frail" in either the title, abstract, and/or text, (4) the frailty phenotype was assessed using the Fried criteria (Fried et al., 2001), (5) prefrail individuals were classified as those meeting one or two Fried criteria. Although most studies focused solely on analyzing and reporting on the frail group, the purpose of this systematic review was to focus exclusively on prefrailty.

2.3. Data collection and analysis

The database search results were uploaded into a web-based system which was used to manage the screening process, and duplicate citations were removed. To determine which studies would be included, four members of the review team independently screened the title and abstracts of the articles extracted from the literature search. The electronic full text was retrieved for studies on which the reviewers agreed, based on our inclusion/