European Geriatric Medicine 6 (2015) 220–231

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Research paper

Counteracting inflammation and insulin resistance with diet and exercise: A strategy for frailty prevention?

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ARTICLE INFO

Article history:
Received 15 September 2014
Accepted 7 November 2014
Available online 16 April 2015

Keywords:
Frailty
Inflammation
Insulin resistance
Exercise
Diet
Nutritional supplementation
Physical activity

ABSTRACT

Frailty is a condition of increased vulnerability to cope with stressors, predisposing to the development of disability in basic and instrumental activities of daily living, falling, institutionalization and finally death. It is characterized by the loss of functional reserve in multiple domains resulting in a reduced tolerance to common external stresses. The pathogenetic steps conducting to frailty are not completely clear, but there is increasing evidence of a crucial role of insulin resistance and systemic inflammation in the development of frailty, disability, and related medical conditions. These two conditions may act directly, through a negative impact on homeostatic regulation and cross-systems compensation, or indirectly, by the effect of several diseases strongly related to frailty. Therefore, counteracting insulin resistance and systemic inflammation could be a powerful way to prevent the development of frailty and/or of its adverse outcomes. In this framework, diet and physical exercise may represent two important weapons in the prevention of frailty; indeed, current literature supports the effectiveness of a correct lifestyle based on a healthy diet (Mediterranean type diet) and regular physical exercise on frailty primary prevention. Studies on secondary prevention of frailty suggest that multi-component and resistance training, together with adequate energy and protein intake, might be helpful although data are still lacking. The efficacy of dietary supplementation in secondary prevention of frailty, albeit promising, remains to be confirmed in large clinical trials.

1. Introduction

Although the concept of becoming frail with ageing is not a recent acquisition, there is no universal agreement on its definition. According to the majority of authors, frailty is characterized by increased vulnerability to cope with stressors; thus, it is more likely to occur when an individual, after challenges, has a diminished ability to return to an homeostatic status [1]. Frail individuals have an higher risk of developing disabilities in basic (BADLs) and instrumental (IADLs) activities of daily living, falling, institutionalization, and death. Although different definitions have been proposed, two themes seem to better depict the frailty concept:

- loss of functional reserve in multiple areas/domains;
- existence at a level close to or past the threshold for failure, with reduced tolerance to common stresses.

Frailty has been defined as a "geriatric syndrome", indicating the accumulated effect of impairments in multiple domains that all together result in a particular adverse outcome. Different frail "phenotypes" have been proposed [2–4]. Fried et al. suggested a phenotype characterized by at least three out of five clinical criteria including unintentional weight loss ($\geq$ 4.5 kg in 1 year), self-reported exhaustion, reduced grip strength measure, slow walking speed, and low physical activity [2]. Most definitions of frailty involve decline in mobility, strength, endurance, nutrition, and physical activity as clinical components [2], while others include cognitive impairment and depression too [5]. Thus, there are several domains involved in frailty development including neurological control/cognition, mechanical performance/mobility (muscle/bone strength, joint function, balance, coordination, and motor processing), energy metabolism (nutrition and cardiopulmonary function), and physical activity [6,7]. Depression, pain, and

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http://dx.doi.org/10.1016/j.eurger.2014.11.010
1878-7649/

visual/auditory impairment might also be important determinants of frailty.

Although frailty has been often considered a synonymous of disability and multimorbidity, and might overlap with these conditions, it has specific and distinct characteristics [2]. As suggested by Clegg et al. [8] frailty might be viewed as the result of an acceleration in the progressive decline of multi-systemic homeostatic reserve related to aging, genetic, epigenetic, and environmental factors. As a matter of fact, in the Women's Health and Aging Study, Fried et al. found a significant non-linear positive relationship between the number of deregulated homeostatic systems and the prevalence of frailty [9]. A current pathogenetic hypothesis of frailty is based on interaction between aging and multiple chronic diseases. Aging itself is characterized by reduced reserve across different homeostatic systems; as a result, a multi-systemic impairment related to the accumulation of cellular/molecular damage, and loss of feed forward and feedback mechanisms among interacting systems is observed [8,10–12]. Multiple chronic diseases superimpose the weakened homeostatic systems by further reducing cross-system compensation, and favoring the onset of frailty. The importance of multimorbidity in the determinism of frailty has been underlined by Sanders et al. [13]. These authors used the "physiologic index of comorbidity" [14] to obtain a measure of "disease burden" (cardiovascular and kidney disease, diabetes, arthritis, depression and cognitive impairment). The finding of an association between frailty and disease burden, independent of diagnosed chronic conditions, emphasized the concept that unrecognized physiologic changes may contribute to frailty [13]. These and other data suggest that, although multimorbidity might not be a necessary condition for frailty, the presence of clinical/subclinical diseases might be really important for the development of frailty [2].

2. From pathogenesis to prevention of frailty

Starting from current pathogenetic hypothesis, the prevention of physical frailty in the population should be aimed to contrasting/eliminating the conditions consistently associated with frailty development, including:

- the multi-systemic impairment related to aging itself;
- the multi-systemic effects of multimorbidity and sub-clinical diseases.

The preventive approaches to frailty might be divided into primary and secondary prevention (Fig. 1). The first intervention should target robust or pre-frail adult-older individuals, with the aim to delay frailty onset by preventing chronic related diseases and by slowing down the decline in physiological reserve. Once the process of frailty has started, the targets of secondary prevention would focus on slowing down (reversing) its progression and delaying related adverse outcomes (i.e. falls, hospitalization, and disability) [15]. Interventions in secondary prevention of frailty may include correction of nutritional deficits, improvement of cognitive or depressive status, and promotion of physical activity. Actually, since we still do not have an accepted definition of the frail "phenotype", the distinction between primary and secondary prevention of frailty might be difficult in some cases. However, the key points of population-based primary prevention of frailty would be the identification of a pathogenetic background common to frailty phenotype and related chronic diseases. In this regard, Walston et al. [16] proposed a biological model in which different molecular mechanisms together with aging-related chronic diseases would lead to a condition of systemic inflammation (SI), insulin resistance (IR), and oxidative stress, which in turn would result in the development of frailty (Fig. 2). Genetics might influence this process; indeed, an association between frailty and several mitochondrial DNA variations has been reported [17]. Nevertheless, lifestyle seems to have a central role. Vita et al. found that smoking, elevated BMI, and poor physical exercise during adulthood predict disability and earlier mortality (two outcomes of frailty) in older age [18], while Bouillon et al. found that commonly used CVD risk scores in the adulthood similarly predict the risk of frailty [19].

Of interest, SI and IR (together with oxidative stress) have been consistently associated not only with frailty, but also with several frailty-related medical conditions including cardiovascular disease [20–24], heart failure [25–27], cognitive impairment/dementia [28–32], chronic kidney disease [33–36], sarcopenia [37–40], and

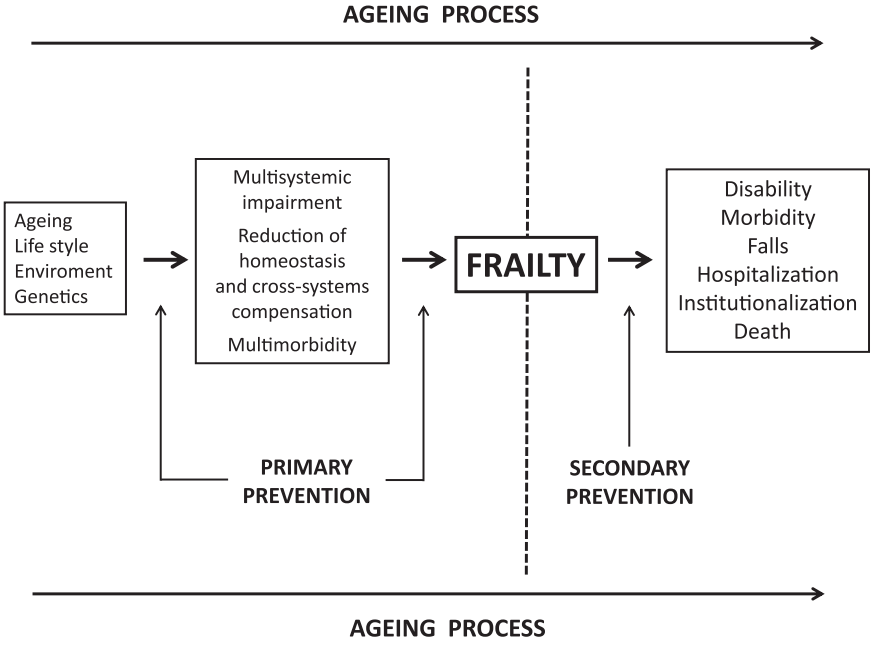

Fig. 1. Possible timing of primary and secondary prevention of frailty syndrome.