

Frailty, Physical Frailty, Sarcopenia: A New Conceptual Model

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Abstract. In the literature, different criteria have been validated to identify frail older subjects, which mainly refer to two conceptual models: the cumulative deficit approach proposed by Rockwood and the Physical Frailty (PF) phenotype proposed by Fried. Both models have received empirical validation. Nevertheless, the frailty phenotype is the most widely used and presents a characterized pathophysiologic background. The PF condition depicted by the frailty phenotype has shown to be predictive of major negative health-related outcomes, including mobility disability, disability for activities of daily living, institutionalization, and mortality. At the same time, it cannot be ignored that the PF phenotype presents substantial overlaps with sarcopenia, “a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death”. In fact, many of the adverse outcomes of frailty are probably mediated by sarcopenia. Therefore, sarcopenia may be considered both as the biological substrate for the development of PF and the pathway through which the negative health outcomes of frailty ensue. Although PF encompasses only a part of the frailty spectrum, the identification of a definite biological basis (i.e., skeletal muscle decline) opens new venues for the development of interventions to slow or reverse the progression of this condition. Here, we present a novel conceptualisation of PF which will possibly promote significant advancements over the traditional approaches to this syndrome by enabling the precise operationalisation of the condition, a clear identification of the affected population and the rapid translation of findings to the clinical arena.

Keywords. Ageing, Disability, Skeletal Muscle

Introduction

The demographic transition Europe has experienced over the last decades poses an unprecedented challenge from both a societal and healthcare perspective. The existing healthcare systems built around the traditional medical paradigm of patients suffering from a single acute illness are largely unprepared to face the increasing demands for health services that can specifically address the medical needs of older, multimorbid people [1]. It follows that, on the one hand, a large and growing segment of the older European population is currently suffering from medical conditions that cannot be efficiently managed by the available healthcare services. On the other hand, although

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prolongation of life remains an important public health goal, of even greater significance is that extended life would involve preservation of the capacity to live independently and function well. Indeed, disabling conditions have shown to be extremely burdening for the individual as well as for the sustainability of healthcare systems [2]. In this scenario, the geriatric syndrome of frailty gains special interest and importance.

1. Frailty as a Geriatric Syndrome

Based on a recent consensus definition, frailty consists in “a multidimensional syndrome characterized by decreased reserve and diminished resistance to stressors” [3]. Simplified, frailty is “an expression of the lack of adaptive capacity of the organism” [4]. From this perspective, frailty may be envisaged as a dynamic process of accelerated ageing [5], which, in its early phase, is characterised by the absence of disability [6,7].

According to the Survey of Health, Ageing and Retirement in Europe (SHARE) study, the prevalence of pre-frailty and frailty among 18,227 randomly selected community-dwellers aged 65+ years was 42.3% (40.5%-44.1%) and 17.0% (15.3%-18.7%), respectively [8]. In the absence of targeted interventions, the progression of frailty is marked by increased morbidity, disability, frequent and often inappropriate healthcare use, nursing home admission, and poor quality of life [9]. Detecting and contrasting frailty are therefore of outstanding importance for impeding the progression of the syndrome and preventing its detrimental consequences [10]. Indeed, once disability has emerged, the restoration of an adequate level of functioning is unlikely, especially when the age of the subject, the degree of disability or its duration increase [7].

Unfortunately, to date, no healthcare programs or pharmacological treatments are available for frail older people. This is largely due to the current lack of a precise, universal definition of frailty, which in turn is linked to the multidimensional nature of the condition [11]. It is therefore not by accident the syndrome is not yet nosographically considered (e.g., it is not listed in the International Classification of Diseases-10) [12]. Eventually, the existing gaps in knowledge are reflected by the absence of interventions (either pharmacological or behavioural) against frailty. Such a barrier may be overcome by developing and validating a robust conceptual framework of frailty to achieve a practical operationalisation of the syndrome [10]. This conceptualisation should also improve the definition of the pathophysiologic and clinical foundations of frailty to assist in the design and implementation of specific interventions aimed at restoring robustness or delaying the onset of adverse events (in particular, disability).

2. Frailty and Sarcopenia of Ageing: "Trapped into Causal Opacity"

In the literature, different criteria have been validated to identify frail older subjects, which mainly refer to two conceptual models: the cumulative deficit approach proposed by Rockwood et al. [13] and the physical frailty (PF) phenotype proposed by Fried et al. [14]. Both models have received empirical validation. Nevertheless, the frailty phenotype is surely the most widely used and possesses a better characterised pathophysiologic background [7,15]. The 5-item instrument proposed by Fried et al.

[14] is also particularly useful for the clinical screening of frailty and in the context of preventive strategies [16]. The PF condition depicted by the frailty phenotype has shown to be predictive of major negative health-related outcomes, including mobility disability, disability for activities of daily living, institutionalisation, and mortality [7].

At the same time, it cannot be ignored that the PF phenotype presents substantial overlaps with sarcopenia, “a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death” [17]. In fact, many of the adverse outcomes of frailty are probably mediated by sarcopenia [18].

Since the beginning (roughly about 15-20 years ago), sarcopenia and frailty have been studied in parallel. Being organ-specific, sarcopenia was more frequently object of research in basic science, whereas the concept of frailty tended to be more easily applied in the clinical setting. Nevertheless, it was quite inevitable that the two would have sooner or later started converging because both conditions are dealing with the common subclinical and clinical manifestations of ageing. Unfortunately, the definition of a clear framework in which sarcopenia and frailty can be accommodated and studied has yet to come. One of the major issues in this context is indeed the long-lasting, tiring, and potentially pointless controversy about the causal relationship existing between the two. Determining whether frailty is due to sarcopenia or sarcopenia is a clinical manifestation of frailty is consuming considerable efforts, but (from a very practical viewpoint) rather resembles the problem of “the egg and the chicken”.

Deconstructing the inner foundations of these “twin” conditions and trying to focus on shared and clinical relevant features might represent a pragmatic means to solve the dilemma.

3. Frailty, Physical Frailty, Sarcopenia: a New Conceptual Model

For the construction of a pragmatic conceptual model, sarcopenia may be considered both as the biological substrate for the development of PF and the pathway through which the negative health outcomes of frailty ensue (Figure 1).

Although PF encompasses only a part of the frailty spectrum, the identification of a definite biological basis (i.e., skeletal muscle decline) opens new venues for the development of interventions to slow or reverse the progression of this condition. In this regard, it is noteworthy that all of the components characterising PF and sarcopenia (PF&S) are measurable and quantifiable. Hence, the implementation of this conceptual model will possibly promote significant advancements over the traditional approaches to this syndrome by enabling the precise operationalisation of the condition, a clear identification of the affected population and the rapid translation of findings to the clinical arena. It is worth noting that such a conceptualisation renders PF&S similar to other common geriatric conditions, with the great advantage of making the syndrome more easily acceptable by healthcare professionals, public health authorities and regulatory bodies.

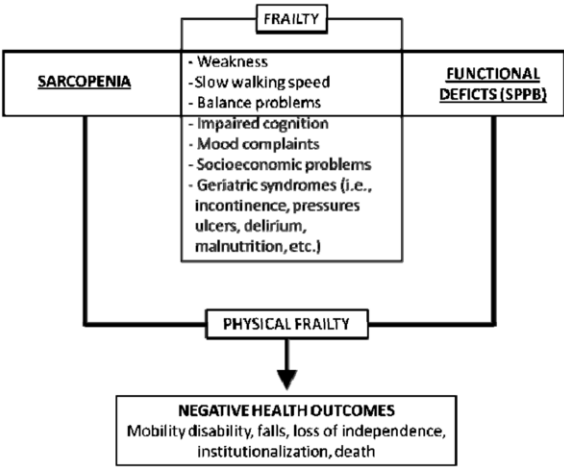


Figure 1. The grey areas highlight the operationalisation of the three components defining physical frailty and the adverse outcomes associated with this condition. SPPB, Short of Physical Performance Battery

4. Possible Strategies for Intervening Against PF&S

The recognition of sarcopenia as a major component of PF implies that interventions specifically targeting the skeletal muscle may provide therapeutic and preventive advantages against frailty and its clinical correlates. However, although observational studies and some randomized clinical trials (RCTs) have suggested a positive effect of regular physical activity (PA) and nutritional interventions on improving physical function and/or reducing symptoms of disability in healthy older individuals and those at risk for mobility disability, definite evidence from high-quality, large-scale clinical trials is still lacking.

The largest and longest study in this field is the Lifestyle Interventions and Independence for Elders (LIFE) study [19], a multicentre RCT conducted in the United States comparing a PA program with a successful ageing educational program in more than 1,600 sedentary older persons, over a follow-up of approximately 3 years. The primary outcome of the study is the incidence of mobility disability as expressed by incapacity to walk 400 metres.

Results from the LIFE pilot (LIFE-P) study showed that over 1 year of follow-up the Short Physical Performance Battery (SPPB) [20] score was significantly improved in the intervention group compared with controls [21]. Similarly, the 400-m walk speed was significantly increased by the intervention. The beneficial effects of the intervention on the SPPB score and the 400-m walk test were fairly uniform across subgroups defined by age, gender, race, baseline physical performance, and comorbidity.

Secondary analyses in the LIFE-P study database have shown that the PA intervention is able to significantly reduce the prevalence of PF and the number of frailty criteria over 1 year of follow-up compared with controls (unpublished results). Remarkably, the beneficial effects of PA on the frailty score were greater in participants who were frail at baseline. More in depth analyses show that the positive

effects of PA are exclusively due to the reduction of the sedentary behaviour criterion, while non-statistically significant variations were reported for the other frailty features. Although the LIFE study was not designed to operationalise a conceptual model of PF nor was the PA intervention specifically targeted against PF&S, these results suggest that behavioural interventions could positively impact PF&S.

Apart from small RCTs such as the FRAilty Screening and Intervention (FRASI) study [22], no large-scale intervention studies specifically targeting frail European older persons have yet been conducted. Given the complexity of the PF&S syndrome, it is likely that the implementation of multi-component intervention (MCIs), combining PA, nutrition and eventually drugs, might provide the greatest benefits in terms of prevention of incident disability and major negative health-related events.

The implementation of multi-component preventive interventions in older persons is particularly useful when dealing with age-related syndromic conditions requiring an immediate translation into clinical practice. Indeed, the simultaneous targeting of multiple and heterogeneous mechanisms underlying the disabling cascade may enhance the intervention effects.

Conversely, a monodimensional intervention may be insufficient at reversing the complex frailty status. At the same time, MCIs allow translating more easily the study results into clinical practice for the overall older population, thus reducing the well-known limited generalisation of “evidence-based studies”. It is noteworthy that such multi-component approaches resemble what is commonly done in usual clinical practice, in which the intervention is designed around the needs and resources of the individual.

5. Conclusions

The ongoing demographic transition is accompanied by substantial changes in medical needs and nosographic scenarios, which imposes major actions against common disabling conditions. Frailty and sarcopenia are highly prevalent, but not yet nosographically recognised geriatric syndromes that impact dramatically on the health status of older adults.

The lack of a widely accepted operationalisation of these conditions hampers the design of effective preventive and therapeutic strategies, which amplifies the socioeconomic burden associated with their detrimental consequences (e.g., disability). Not surprisingly, the need of refining the assessments of sarcopenia and frailty is perceived as a high priority by the scientific and medical community as well as by health authorities and regulators.

The core of the two conditions represented by the impairment in physical function in the absence of disability may optimally serve for (1) defining a novel target for interventions against disability, (2) facilitating the translation of the two conditions in the clinical arena, and (3) providing an objective, standardised, and clinically-relevant condition to be adopted by public health and regulatory agencies. Such conceptualisation might eventually encourage key stakeholders to join their efforts for approaching the sarcopenia and frailty conditions.

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