

OPERATIONALIZATION OF THE PHYSICAL FRAILTY & SARCOPENIA SYNDROME: RATIONALE AND CLINICAL IMPLEMENTATION

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Abstract - Over the years, different operational definitions have been elaborated to identify frail older persons, but none of them has received unanimous consensus. This, in turn, has hampered the clinical implementation of frailty as well as the design of targeted interventions. To overcome the current limitations in the field, a novel operationalization of physical frailty (PF) is proposed which grounds its roots in the recognition of sarcopenia as its central biological substrate. This conceptualization is based on the fact that the clinical picture of PF overlaps substantially with that of sarcopenia. The two conditions may therefore be merged into a new clinical entity, the PF & sarcopenia (PF&S) syndrome, in which muscle loss represents both the biological substrate for the development of PF and a major pathway whereby the negative health outcomes of PF occur. All of the components defining the PF&S syndrome are measurable in an objective manner, which will facilitate its incorporation into standard practice. The recognition of a precise biological substratum for PF&S (i.e., skeletal muscle decline) also opens new venues for the development of preventive and therapeutic interventions.

Key words: aging; physical performance; functional impairment; skeletal muscle; disability; organ failure

I. INTRODUCTION

Healthcare systems are increasingly faced with a growing population of older adults characterized by the co-existence of multiple, chronic disabling conditions [1]. The gap between the demand of effective intervention strategies and the availability of medical programs specifically dedicated to older adults results in inappropriate use of resources and escalating healthcare expenditures [1,2]. Functional dependence, in particular, poses a serious threat on the sustainability of healthcare systems [3]. Hence, although prolongation of life remains a major public health goal, specific strategies should be developed to preserve physical function into late life and maximize disability-free life expectancy.

In this scenario, the geriatric syndromes of frailty and sarcopenia have gained special interest due to their association with a number of potentially preventable adverse health outcomes. These syndromes may therefore well serve as paradigmatic conditions around which healthcare systems can be re-shaped and optimized to address the specific medical needs of older persons [4,5].

Despite the efforts of many researchers, frailty and sarcopenia are still "orphan" of firmly established operational definitions and evaluation methodologies, and this has so far impeded their translation into every-day

clinical practice [6]. The ultimate consequence of these persisting uncertainties and debate is the lack of effective interventions to prevent the development and impede the progression of the two conditions. Such an *impasse* might be overcome through the development and validation of a conceptual framework specifically elaborated to facilitate the translation of frailty and sarcopenia in clinical practice. To this aim, the pathophysiological and clinical foundations of the two conditions should be precisely defined, in order to assist in the design and implementation of *ad hoc* preventive and therapeutic interventions. Such an ambitious task represents a major objective of the «Sarcopenia and Physical Frailty IN older people: multi-component Treatment strategies» (SPRINTT) study, a research project recently funded by the Innovative Medicine Initiatives (IMI) [7].

II. PHYSICAL FRAILITY AND SARCOPENIA: AN INNOVATIVE THEORETICAL APPROACH

In the literature, different criteria have been proposed to identify frail older persons, which mainly refer to two conceptual models: the cumulative deficit approach, proposed by Rockwood et al. [8], and the frailty phenotype, proposed by Fried et al. [9]. Both models have received empirical validation; yet, the frailty phenotype has some recognizable advantages, which are probably responsible for its more frequent use in the geriatric literature. First, it has a solid, well-characterized pathophysiological background [9,10]; second, its definition, based on only five items, makes it more easily applicable than the complex and cumbersome cumulative deficit approach; third, and most importantly, it identifies frailty at an early stage, before overt disability has developed, therefore opening venues to preventing interventions. The condition depicted by the frailty phenotype is, indeed, predictive of major negative health-related outcomes, including disability in the domains of mobility and self-care (basic activities of daily living), institutionalization, and mortality [10].

Although the pathways leading to the development of frailty and its progression towards disability are complex, and encompass a variety of mechanisms besides those centered on muscle structure and function, the frailty phenotype shows substantial overlaps with the clinical picture of sarcopenia [11]. Indeed, physical function impairment represents the inner core shared by the two conditions. Based on this observation, a novel operationalization of physical frailty (PF) is proposed, which recognizes sarcopenia as its central biological substrate [8]. According to this proposition, the decline in muscle mass and function during aging would represent the pathway through which the negative health outcomes of PF ensue [12]. To put it differently, sarcopenia may be envisioned as the "organ failure" underlying the clinical manifestations of PF [11]. It follows that the two conditions may be merged into a

new clinical entity, the PF & sarcopenia (PF&S) syndrome, with important implications for its clinical implementation and the development of dedicated healthcare initiatives.

Notably, all of the components describing the PF&S model are measurable and quantifiable. The implementation of such a paradigm would therefore allow the accurate operationalization of PF&S, a clear identification of the affected population, and the rapid translation of research findings to the clinical arena. Such a conceptualization would also make PF&S comparable to other chronic degenerative conditions of old age (e.g., chronic obstructive pulmonary disease and congestive heart failure) because mirroring the paradigm of a biological substratum for a specific set of symptoms/signs determining a measurable decreased function [11]. The PF&S syndrome may thus gain its spotlight among the geriatric "giants" [13], besides becoming easily acceptable by healthcare professionals, public health authorities, and regulatory bodies.

III. THE PF&S SYNDROME: FROM "BRAINSIDE" TO BEDSIDE

As previously elaborated, the proposed conceptualization of PF&S involves a set of objectively measurable domains that encompass the full spectrum of the condition, from biological substrate to clinical framing (Figure 1). The muscle atrophy component can easily be quantified with available techniques (e.g., dual energy X-ray absorptiometry [DXA]). Through the adoption of Classification and Regression Tree (CaRT) models, the Foundation for the National Institute of Health (FNIH) initiative has recently identified cut-points of low lean mass that are associated with increased risk of mobility disability [14,15]. It appears then reasonable that FNIH criteria, rather than consensus definitions of sarcopenia, be used to identify the muscle atrophy component of PF&S.

At the clinical level, the manifestations of PF&S (e.g., impaired balance, slow gait, muscle weakness) can be measured in an objective manner using specific tools, such as the Short Physical Performance Battery (SPPB) [16-18]. This tool has shown to predict major negative health-related events (including disability, institutionalization, and mortality), and also provides an accurate picture of the "biological age" of an older person [16-19]. At the same time, the SPPB is strongly related with the quantity and quality of skeletal muscle, and is therefore able to capture the core of PF&S [4]. In particular, a cutoff of 9 (included) at the SPPB allows the identification of older adults at increased risk of adverse health events, including reduced quality of life, disability and mortality [16,17,20].

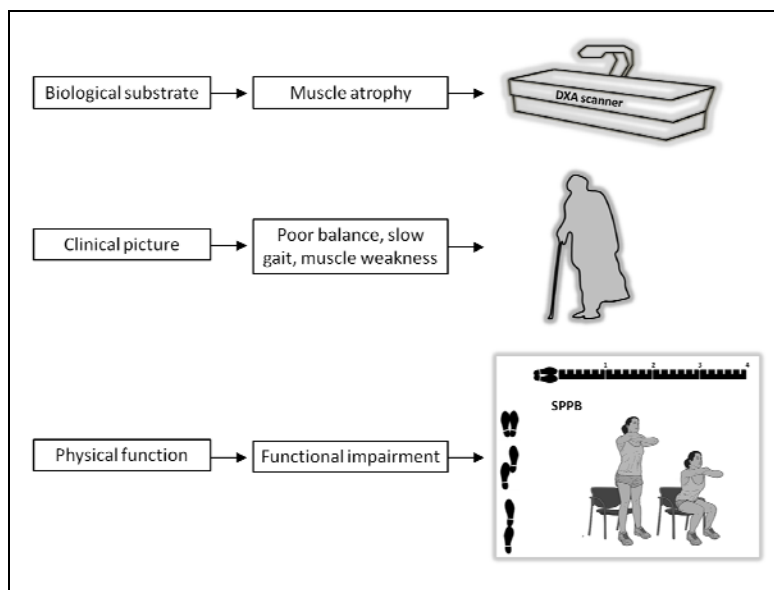


Fig. 1. Physical frailty and sarcopenia (PF&S): from concept to practice. The PF&S condition can be objectively measured in all its domains, spanning from biologic substrate (reduction in muscle mass) up to its clinical manifestations. The muscle domain can be measured using standard techniques, such as dual energy X-ray absorptiometry (DXA). The clinical "identikit" of an older person with PF&S can be sketched as the "perfect storm" of poor balance, slow gait and muscle weakness. This picture can easily be quantified using specific tools, such as the Short Physical Performance Battery (SPPB).

IV. CONCLUSION

The ongoing demographic transition is accompanied by substantial changes in medical needs and nosographic scenarios, which imposes the development of counteractions against highly prevalent disabling conditions. The traditional paradigm of a "standalone-disease medicine" has clearly become outdated in a clinical world dominated by older persons suffering from multiple chronic conditions and mutually interacting syndromes [21]. On the other hand, although the transition from the disease-centered model of care to a "holistic" approach is crucial in geriatric care, the identification of pathophysiological mechanisms altering key functions for the older person (e.g., physical function) and potentially usable as targets for interventions are still necessary. The operationalization of PF&S herewith proposed surpasses the traditional paradigm of healing through treating a single disease, and may support the design of future non-pharmacological and pharmacological strategies aimed at improving the older person's health status by focusing on the functional domain [11,22,23].

REFERENCES

- [1] Mander T. Longevity and healthy ageing - Will healthcare be drowned by the grey Tsunami or sunk by the demographic iceberg? *Post Reprod Health* 2014;20(1):8-10.
- [2] Bien B, McKee KJ, Döhner H, Triantafillou J, Lamura G, Doroszkiewicz H, Krevers B, Kofahl C.
- [3] Fried TR, Bradley EH, Williams CS, Tinetti ME. Functional disability and health care expenditures for older persons. *Arch Intern Med.* 2001;161(21):2602-2607.
- [4] Cesari M, Landi F, Vellas B, Bernabei R, Marzetti E. Sarcopenia and physical frailty: two sides of the same coin. *Front Aging Neurosci* 2014;6:192.
- [5] Beaudart C, Rizzoli R, Bruyère O, Reginster JY, Biver E. Sarcopenia: burden and challenges for public health. *Arch Public Health* 2014;72(1):45.
- [6] Buckinx F, Rolland Y, Reginster JY, Ricour C, Petermans J, Bruyère O. Burden of frailty in the elderly population: perspectives for a public health challenge. *Arch Public Health* 2015;73(1):19.
- [7] Marzetti E, Calvani R, Landi F, Hoogendijk E, Fougère B, Vellas B, Pahor M, Bernabei R, Cesari M, on Behalf of the SPRINTT Consortium. Innovative Medicines Initiative: the SPRINTT project. *J Frailty Aging* 4(4):207-208.
- [8] Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173(5):489-495.
- [9] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56(3):M146-M156.

Disabled older people's use of health and social care services and their unmet care needs in six European countries. *Eur J Public Health* 2013;23(6):1032-1038.

- [10] Lang PO, Michel JP, Zekry D. Frailty syndrome: a transitional state in a dynamic process. *Gerontology* 2009;55(5):539-549.
- [11] Landi F, Calvani R, Cesari M, Tosato M, Martone AM, Bernabei R, Onder G, Marzetti E. Sarcopenia as the biological substrate of physical frailty. *Clin Geriatr Med* 2015;31(3):367-374.
- [12] Marzetti E, Calvani R, Bernabei R, Leeuwenburgh C. Apoptosis in skeletal myocytes: a potential target for interventions against sarcopenia and physical frailty. *Gerontology* 2012;58(2):99-106.
- [13] Sayer AA. Sarcopenia the new geriatric giant: time to translate research findings into clinical practice. *Age Ageing* 2014;43(6):736-737.
- [14] Cawthon PM, Peters KW, Shardell MD, McLean RR, Dam TT, Kenny AM, Fragala MS, Harris TB, Kiel DP, Guralnik JM, Ferrucci L, Kritchevsky SB, Vassileva MT, Studenski SA, Alley DE. Cutpoints for low appendicular lean mass that identify older adults with clinically significant weakness. *J Gerontol A Biol Sci Med Sci* 2014;69(5):567-575.
- [15] McLean RR, Shardell MD, Alley DE, Cawthon PM, Fragala MS, Harris TB, Kenny AM, Peters KW, Ferrucci L, Guralnik JM, Kritchevsky SB, Kiel DP, Vassileva MT, Xue QL, Perera S, Studenski SA, Dam TT. Criteria for clinically relevant weakness and low lean mass and their longitudinal association with incident mobility impairment and mortality: the foundation for the National Institutes of Health (FNIH) sarcopenia project. *J Gerontol A Biol Sci Med Sci* 2014;69(5):576-583.
- [16] Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994;49(2):M85-M94.
- [17] Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med* 1995;332(9):556-561.
- [18] Guralnik JM, Ferrucci L, Pieper CF, Leveille SG, Markides KS, Ostir GV, Studenski S, Berkman LF, Wallace RB. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci* 2000;55(4):M221-M231.
- [19] Studenski S, Perera S, Wallace D, Chandler JM, Duncan PW, Rooney E, Fox M, Guralnik JM. Physical performance measures in the clinical setting. *J Am Geriatr Soc* 2003;51(3):314-322.
- [20] Bandinelli S, Lauretani F, Boscherini V, Gandi F, Pozzi M, Corsi AM, Bartali B, Lova RM, Guralnik JM, Ferrucci L. A randomized, controlled trial of disability prevention in frail older patients screened in primary care: the FRASI study. Design and baseline evaluation. *Aging Clin Exp Res* 2006;18(5):359-366.
- [21] Tinetti ME, Fried T. The end of the disease era. *Am J Med* 2004;116(3):179-185.
- [22] Landi F, Martone AM, Calvani R, Marzetti E. Sarcopenia risk screening tool: a new strategy for clinical practice. *J Am Med Dir Assoc* 2014;15(9):613-614.
- [22] Cesari M, Fielding R, Bénichou O, Bernabei R, Bhasin S, Guralnik JM, Jette A, Landi F, Pahor M, Rodriguez-Manas L, Rolland Y, Roubenoff R, Sinclair AJ, Studenski S, Trivison T, Vellas B. Pharmacological interventions in frailty and sarcopenia: report by the international conference on frailty and sarcopenia research task force. *J Frailty Aging* 2015;4(3):114-120.