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The "BIOmarkers associated with Sarcopenia and PHysical frailty in EldeRly pErsons" (BIOSPHERE) study: Rationale, design and methods

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ABSTRACT

Sarcopenia, the progressive and generalised loss of muscle mass and strength/function, is a major health issue in older adults given its high prevalence and burdensome clinical implications. Over the years, this condition has been endorsed as a marker for discriminating biological from chronological age. However, the absence of a unified operational definition has hampered its full appreciation by healthcare providers, researchers and policy-makers. In addition to this unsolved debate, the complexity of musculoskeletal ageing represents a major challenge to the identification of clinically meaningful biomarkers. Here, we illustrate the advantages of biomarker discovery procedures in muscle ageing based on multivariate methodologies as an alternative approach to traditional single-marker strategies. The rationale, design and methods of the "BIOmarkers associated with Sarcopenia and PHysical frailty in EldeRly pErsons" (BIOSPHERE) study are described as an application of a multi-marker strategy for the development of biomarkers for the newly operationalised *Physical Frailty & Sarcopenia* condition.

1. Introduction

Over the last decades, Western countries have experienced a dramatic demographic transition. On a positive note, this is the successful result of advances in medicine and improved socioeconomic conditions. On the other hand, population ageing carries the downsides of challenging the societal structure, social security and healthcare systems [1].

As a matter of fact, existing healthcare systems conceived around the traditional paradigm of patients suffering from a single acute illness are unprepared to deal with the medical needs of older, multimorbid and functionally impaired people [2]. In this context, sarcopenia and physical frailty are increasingly recognised as prototype conditions around which current models of care may be re-shaped [3]. Indeed, the two conditions are based on a theoretical construct that surpasses the disease paradigm, thereby shifting the medical focus from the traditional concept of "healing through treating a single illness" toward a function-centred approach [4].

In the late '80s, Irwin Rosenberg [5], starting from the assumption that "there is probably no decline in structure and function more dramatic than the decline in lean body mass or muscle mass over the decades of life", coined the term "sarcopenia" to refer to the loss of muscle mass that accompanies the ageing process. From its original description as purely an age-dependent loss of muscle mass, the concept of sarcopenia has evolved into a more complex construct encompassing both quantitative (i.e., mass) and qualitative (i.e., strength and/or function) declines of skeletal muscle [6]. Though, depending on the cut-points used to distinguish "normal" from "abnormal" muscle-related parameters, the resulting phenotypes and risk profiles are only partly overlapping [7]. Despite this significant drawback, all of the existing

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definitions of sarcopenia predict negative health-related events in older people [8]. Indeed, sarcopenia has recently gained the dignity of a "disease entity" with the recognition of a dedicated ICD-10-CM code in September 2016 [9]. This landmark achievement, while adding further impetus to the study of muscle ageing, may leverage the agreement on a unique operational definition of sarcopenia. This, in turn, will facilitate the identification of sarcopenia determinants, promote the discovery of meaningful biological targets for treatment, and foster the incorporation of the condition in every-day practice [10].

Frailty is the term used to refer to a geriatric syndrome characterised by reduced homeostatic reserves, which exposes individuals at increased risk of negative health-related events [11,12]. A multitude of operational definitions of frailty have been proposed, each of them capturing specific aspects of the condition and identifying different risk profiles [13]. With the notable exception of the frailty index proposed by Rockwood and Mitnitski [14], the vast majority of available frailty scales point to physical function impairment as the central determinant of vulnerable health status [15]. When focused on the physical domain, the clinical picture of frailty shows remarkable overlap with sarcopenia [16]. This observation has led to envision muscle wasting as the biological substrate for the development of physical frailty (PF) and the pathway through which the negative health-related outcomes of PF ensue [17]. In other words, sarcopenia may be considered to be the "organ failure" underlying the clinical manifestations of PF (Fig. 1) [17].

The two conditions have therefore been merged into a new entity (i.e., PF & sarcopenia; PF&S) [18], defined by the following distinctive parameters:

(1) Low muscle mass, as determined by dual X-ray absorptiometry (DXA) using the cut-points recommended by the Foundation for the National Institutes of Health (FNIH) sarcopenia project [19];
(2) Low physical performance, defined as a summary score on the Short Physical Performance Battery (SPPB) [20] between 3 and 9; and
(3) Absence of major mobility disability, operationalised as inability to walk 400 m in 15 min without sitting, the use of a walker, help from another person or stopping to rest for more the 60 s at a time [21].

The PF&S operational definition, elaborated in the context of the "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) project (IMI–JU # 115621) [22], frames a pre-disability condition that can be diagnosed and monitored in an objective manner. At the same time, the recognition of a clear biological substrate (i.e., muscle atrophy) allows for the search of novel biomarkers which can be subsequently used for detecting and tracking the condition of interest, obtaining information about the underlying pathophysiology, and identifying meaningful targets for preventive or therapeutic interventions [23]. This has set the momentum for the conception of the "BIOmarkers associated with Sarcopenia and PHysical frailty in ElderRly pErsons" (BIOSPHERE) study.

2. Rationale of BIOSPHERE

With the intent of pushing forward the search for biological markers associated with PF&S, the BIOSPHERE study was designed to determine and validate a panel of biomarkers able to integrate specific biochemical measurements into the assessment of PF&S both in clinical and research settings.

The identification of PF&S relies on the assessment of parameters pertaining to different domains (i.e., clinical, functional and imaging). Although specific circulating markers have previously been associated with single domains of the PF&S condition, none of them has yet been incorporated into standard practice [24]. This is partly due to the existence of a heterogeneous (i.e., muscle-specific and non-muscle specific) set of candidate mediators and the lack of a "gold standard" biomarker for the prediction of clinically meaningful outcomes (Fig. 2) [25].

Given the complexity of PF&S, BIOSPHERE will apply multivariate modelling of an array of circulating mediators as a strategy to identify a set of biomarkers specific for the condition of interest. This task will be pursued through (a) the analysis of multiple circulating biomarkers that reflect specific pathophysiological processes directly and/or indirectly linked to muscle ageing and its clinical correlates, and (b) the development and validation of multivariate statistical models to identify specific biomarkers of PF&S.

3. Methods

3.1. Study design and population

BIOSPHERE has been conceived as a cross-sectional, case-control study, aimed at analysing a panel of candidate biomarkers for PF&S through multivariate statistical models. The study protocol was approved by the Ethics Committee of the Catholic University of the Sacred Heart (Rome, Italy). After obtaining written informed consent, 200 older persons, 100 cases (individuals with PF&S) and 100 controls (elderly non-sarcopenic persons with no functional impairment), aged 70+ have been enrolled. Recruitment strategies included the use of newspapers, radio and television advertisements. The study was also advertised via flyers and brochures available in patient waiting areas throughout the Teaching Hospital "Agostino Gemelli" of the Catholic University of the Sacred Heart. Finally, the study was presented in the

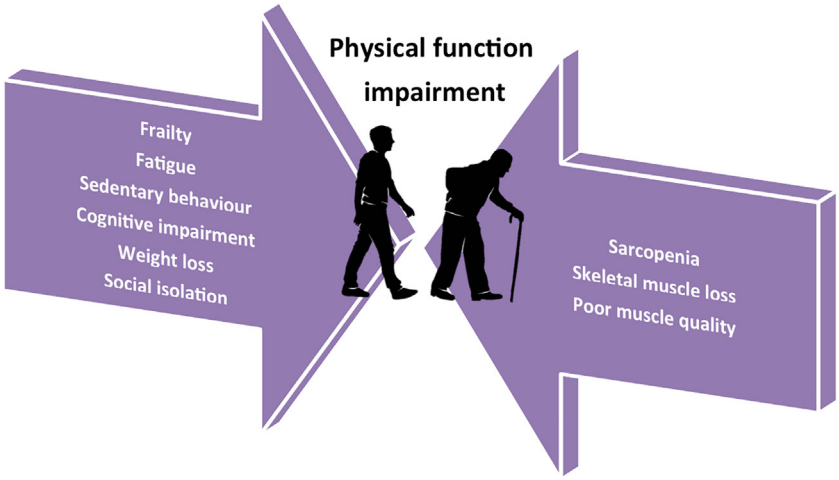

Fig. 1. Frailty, sarcopenia and physical function impairment: a tight relationship.