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EDITORIAL

Finding good biomarkers for sarcopenia

Gesine Scharf · Joerg Heineke

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Abstract The term sarcopenia describes the age-related loss of skeletal muscle mass and function. While this process, in principal, occurs in every adult person and already starts around the age of 40, it is associated with disability, morbidity, and increased mortality in some individuals. In the absence of clear clinical manifestation, we today lack the ability to differentiate between physiological and pathological sarcopenia. In this regard, we need good biomarkers that can be quantified in a reliable, cost-effective manner and that guide diagnosis and therapy of pathological sarcopenia in routine clinical practice and clinical trials. We suggest that a combination of serum markers, diagnostic imaging, and functional tests of muscle function would constitute an ideal biomarker panel. Importantly, sarcopenia biomarkers will have to be tested and validated in clinical trials.

1 Sarcopenia: definitions, epidemiological and pathophysiological considerations

Sarcopenia describes the loss of skeletal muscle mass and function during aging. The process starts around the age of 40 and progresses at a rate of 8 % loss of muscle tissue per decade until the age of 70, when muscle loss accelerates to 15 % per decade [1]. In parallel, leg strength is reduced by 10–15 % per decade until 70 years of age, and then by 25–40 % per decade [2, 3]. Sarcopenia is therefore a physiological process ("physiological sarcopenia"). However, in some individuals (estimated 14 % in the group aged 65–75 and 45 % of people older than 85 years), sarcopenia leads to a severe functional impairment and the need for assistance in basic daily activities [4]. Under these circumstances, sarcopenia is associated with a marked increase in morbidity (falls, frailty, prolonged hospitalization and recovery from disease, and long-term disability) and even mortality [5]. For this state, we suggest the term "pathological sarcopenia." As of today, we are still lacking the diagnostic tools to accurately differentiate between physiological and pathological sarcopenia, unless a clinical event (e.g., a fall or disability) has emerged. It would be of great value for these patients to learn about their disease at an early stage in order to take precautions in daily living and to initiate therapy. The socioeconomic relevance is demonstrated by direct healthcare costs caused by sarcopenia, which are estimated at $18.5 billion for the USA in 2000. Strikingly, a decrease in the prevalence of sarcopenia by only 10 % would save $1.1 billion per year in the US healthcare expenditures [6].

Different pathologic mechanisms are identified that contribute to the syndrome of sarcopenia. Loss of α-motoneurons, high levels of inflammatory cytokines, and immobility are major problems that occur in aging organisms and lead to skeletal muscle fiber atrophy as well as decreased motor precision, coordination, and reduced strength [7]. Sarcopenia is not necessarily associated with weight loss because the reduction of muscle is often associated with an expansion of fat mass. As a matter of fact, in addition to its crucial function for body movement, skeletal muscle also fundamentally impacts systemic metabolism and whole-body energy expenditure. Ken Walsh and colleagues [8], for instance, have generated a mouse model with increased skeletal muscle mass due to skeletal muscle specific overexpression of the proteinkinase B/Akt. Muscle growth in these transgenic mice exclusively depends on hypertrophy of fast glycolytic type IIb fibers. This mouse, which is called "the MyoMouse," is protected from diet-induced obesity and hepatic steatosis and exerts improved metabolic parameters. It is hypothesized that skeletal muscle releases endocrine factors ("myokines") with metabolic

G. Scharf · J. Heineke (✉)
Medizinische Hochschule Hannover, Klinik für Kardiologie und Angiologie, Rebirth–Cluster of Excellence,
Carl-Neuberg Str.1,
30625 Hannover, Germany
e-mail: Heineke.Joerg@mh-hannover.de

activity [9]. As an example, the myokine irisin has recently been identified and demonstrated to be induced upon exercise and to improve obesity and glucose homeostasis [10]. We speculate that the preferential atrophy of type II muscle fibers in sarcopenia also impairs myokine release and therefore metabolic function of muscle. Indeed, epidemiological data indicate that sarcopenic patients are at higher risk to develop insulin resistance and metabolic syndrome [11–13].

Therapeutic options for sarcopenia are still scarce (for review, see [7]), but muscle resistance training, for example, has been shown to improve muscle mass and strength in sarcopenic patients [14]. New drugs such as myostatin inhibitors or activin receptor antagonists are currently being tested for their effects on muscle mass and strength and might enable new therapeutic options for patients with pathological sarcopenia in the future [15].

2 Biomarkers of sarcopenia: state of the art and future perspectives

In order to be able to correctly diagnose, monitor, and treat sarcopenia, good biomarkers are needed for routine clinical practice as well as for the conductance of clinical trials, in which various novel treatment regimens are tested for their impact on the disease. In this regard, biomarkers could provide a standardized and international comparable readout for therapeutic success.

What are the features of the *ideal* biomarker for sarcopenia? Benchmarks for biomarkers have been previously suggested by D.A. Morrow and J.A. de Lemos [16]: first, the biomarker needs to be quantified in an accurate and reproducible manner and the assay must be accessible, conductable at reasonable cost, and suitable for high-throughput analysis. For example, an enzyme-linked immunosorbent assay (ELISA) to measure a (still elusive) specific serum protein as biomarker for sarcopenia, which has been carefully validated to indeed accurately determine the concentration of this protein, would fit these criteria. ELISAs can easily be high throughput and can principally be conducted by every lab at low cost. Second, the biomarkers must add new information that cannot be obtained by a careful clinical assessment alone or preexisting tests. Importantly, the biomarker needs to show a strong correlation with the disease and its outcome in clinical studies. For example, a specific serum marker that detects emerging sarcopenia (*before* gross loss of muscle function or mass occurs) and that also strongly correlates with mortality or hospital admissions, falls, or fractures due to sarcopenia would be desirable. Since some loss of muscle function and muscle mass occurs in every adult during aging, it is extremely important that the biomarker can reliably discern between physiological and pathological sarcopenia. Third, and perhaps most importantly, the ideal biomarker needs to help the clinician to manage patients with sarcopenia: it must help to decide whether therapy is needed, select therapy, and also to monitor disease progression and treatment response. The biomarker could also show a specific etiology of sarcopenia and therefore entail specific treatment as a step toward personalized medicine. As an example, in some patients, vitamin D deficiency might contribute to the progression of pathological sarcopenia, and only in these patients vitamin D supplementation might prevent sarcopenia from becoming symptomatic [17]. There will not be only *one* biomarker that perfectly matches the above-mentioned criteria, but it should be our goal to have a panel of complementary biomarkers (likely within multiple classes: imaging, serum biomarkers, and functional tests), which together constitute the ideal panel of markers.

Where are we now? It is quite clear that we are at the very beginning of our quest for good biomarkers in sarcopenia. But since we have to start somewhere, the recommendations from the *International Working Group on Sarcopenia* for the use of biomarkers in clinical trials are a very important first step [18]. It lists what we currently have, which basically amounts to imaging-related quantification of muscle mass by either magnetic resonance imaging (MRI), computed tomography (CT), or dual energy x-ray absorptiometry scan and functional tests to quantify muscle function (like the test of gait speed or the hand-grip strength test). In terms of imaging, all three modalities (with a little advantage of MRI and CT) are well suited to accurately detect muscle mass (and at the same time also the amount of fat). Unfortunately, all are mainly available at big medical centers and not at the general practitioners office. In addition, CT and MRI are rather expensive tests. These drawbacks are not that troublesome for clinical trials but more so in routine clinical application (for example for the general practitioner, who certainly is the first contact for the majority of sarcopenic patients). Furthermore, imaging only detects sarcopenia after loss of muscle mass already occurred and not in the early stage of disease or in people at high risk for pathological sarcopenia. As pointed out by Cesari et al. [18], muscle function is an important second dimension of sarcopenia. Muscle performance can be measured in a low-cost and standardized manner and, importantly, measures of lower-extremity function are highly predictive of subsequent disability in people at risk [19]. Unfortunately, these tests can be markedly influenced by comorbidities that are often found in older patients, like degenerative or inflammatory diseases of the musculoskeletal system. While it makes sense to combine the assessment of muscle mass and function, the biggest uncertainty today relates to the thresholds that need to be applied in imaging and muscle performance tests in order to distinguish between health and disease, physiological, or pathological sarcopenia, or put in other words, to distinguish between conditions that are associated with adverse clinical outcome and require therapeutic intervention and those that do not.

In the future, our first task will be to evaluate current biomarkers and the thresholds, as suggested by Cesari et al. [18], for correlation with clinical outcome and perhaps with therapeutic intervention in clinical trials. The results of these trials will tell us whether biomarkers and thresholds can be upheld in accordance to the above-mentioned criteria for good biomarkers. It is likely that some of the suggested thresholds will have to be adjusted.

Our second, equally important task will be to identify *novel* biomarkers of sarcopenia. Biomarkers derived from blood or urine can easily be measured in a standardized, high-throughput, and low-cost way (for example by ELISA) and are therefore very desirable. The serum makers that we currently have mostly all relate to inflammation (like tumor necrosis factor-α or interleukin-6) and are not at all muscle-specific. One prominent muscle-specific hormone strongly inhibiting muscle mass is the transforming growth factor-β-related protein myostatin [20]. Myostatin is mainly expressed in skeletal muscle and in minor quantities also in fat and heart [20]. Importantly, myostatin is present in serum, and local overexpression of myostatin as well as peripheral myostatin overexpression (for example, in the heart) in mice leads to a dramatic reduction in skeletal muscle mass [21, 22]. Unfortunately, a reliable assay to quantify myostatin in human serum or plasma is still lacking, but once this hurdle is taken, myostatin is clearly high on the list of candidate biomarkers of sarcopenia. In addition to biomarkers that relate to pathogenesis, others could indicate the impairment in muscle function. As already alluded to above, we speculate that the endocrine release of myokines from skeletal muscle might be impaired in pathological sarcopenia, and therefore myokines could serve as good biomarkers to monitor endocrine muscle function. One myokine high on the list of potential candidates in this regard is irisin, which was just recently identified [10].

Once the first clinical trials in sarcopenic patients have been conducted and therefore serum samples of well-characterized patients (according to the suggestions by Cesari et al. [18] in this issue of the *Journal of Cachexia, Sarcopenia and Muscle* [18]) are available, these (and more) potential serum biomarkers need to be tested at first in these cohorts. It is very likely that novel biomarkers will not only provide information about the diagnosis and prognosis of sarcopenic patients but also reveal crucial pathomechanisms and, most importantly, might lead the way to successful therapies.

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Conflict of interest None.

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