REVIEWS

SARCOPENIA IN PRIMARY CARE: SCREENING, DIAGNOSIS, MANAGEMENT

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Abstract: Detection of sarcopenia in primary care is a first and essential step in community-dwelling older adults before implementing preventive interventions against the onset of disabling conditions. In fact, leaving this condition undiagnosed and untreated can impact on the individual's quality of life and function, as well as on healthcare costs. This article summarizes the many instruments today available for promoting an earlier and prompter detection of sarcopenia in primary care, combining insights about its clinical management. Primary care physicians may indeed play a crucial role in the identification of individuals exposed to the risk of sarcopenia or already presenting this condition. To confirm the suspected diagnosis, several possible techniques may be advocated, but it is important that strategies are specifically calibrated to the needs, priorities and resources of the setting where the evaluation is conducted. To tackle sarcopenia, nutritional counselling and physical activity programs are today the two main interventions to be proposed. Multicomponent and personalized exercise programs can (and should) be prescribed by primary care physicians, taking advantage of validated programs ad hoc designed for this purpose (e.g., the Vivifrail protocol). It is possible that, in the next future, new pharmacological treatments may become available for tackling the skeletal muscle decline. These will probably find application in those individuals non-responding to lifestyle interventions.

Key words: Skeletal muscle, aging, geriatrics, physical function, muscle strength.

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Introduction

"Sarcopenia" is a term referred to the progressive loss of skeletal muscle mass typically occurring with advancing age, as defined by Irwin Rosenberg in 1989 (1). Since then, the term has been used to more broadly embrace the age-related skeletal muscle decline, including both decrease in mass as well as reduction in strength and performance. To date, several definitions of sarcopenia have been proposed in the literature, and different consensus articles have tried to operationally frame this condition. Unfortunately, despite the fact that sarcopenia has even received a specific ICD-10 code in October 2016 (2), there is still no agreement in the scientific community about the gold standard definition to adopt for capturing this condition (3). Table 1 presents the most widely used definitions of sarcopenia currently available in the literature.

Sarcopenia still represents an underdiagnosed condition in daily practice, leaving untreated many cases amenable of interventions. Given the aging of the population, it is important that primary care physicians become familiar with the management of this condition for multiple reasons:

1) Detecting sarcopenia should be part of the routine visit due to the simplicity of the necessary tools and for the limited time required;
2) Sarcopenia is considered a reversible condition and can be contrasted by correct nutrition advices and personalized physical activity programs (4, 5);
3) Interventions directed against geriatric conditions, such as sarcopenia, are usually developed with long-term objectives (6), thus likely to involve the co-management by the primary care physician;
4) The management of a clinical condition, especially at advanced age, is strongly facilitated when the primary care physician (the one who best knows the clinical characteristics and behaviours of the patient) plays an active role;
5) Tackling sarcopenia is of primary importance in the community, where the vicious cycle of disability may still be amenable of reversion;
6) Recognizing sarcopenia in primary care may improve the design of the optimal care plan for the older person.

The present article is aimed at summarizing available evidence about the diagnosis and therapeutic process that can be activated for sarcopenia in primary care. The available diagnostic tools to recognize and quantify sarcopenia will be critically discussed. In particular, it will be considered that the operational definition of sarcopenia in primary care should be balanced to the limited availability of resources and time in this specific setting.

Prevalence, clinical relevance and costs

According to the World Health Organization (WHO), in 2050 there will be at least 2 billion persons aged 65 years or older, compared to the current 600 million. The increasing life expectancy is a worldwide demographic phenomenon, parallel to the growing number of persons affected by age-related

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Table 1
Main definitions of sarcopenia

Year	Society	Definition	Parameters
2010	European Working Group on Sarcopenia in Older Persons (EWGSOP)(47)	Syndrome characterized by progressive and generalized loss of mass and skeletal muscle strength associated with an increased risk of adverse events such as disability, poor quality of life and death	Muscle mass, muscle strength, physical performance Cut-points not provided
2011	International Working Group on Sarcopenia(48)	Age-related loss of muscle mass and function. It is a complex syndrome that is associated with muscle mass loss isolated or in conjunction with increased fat mass	Muscle mass, physical performance Cut-points are provided
2011	Society for Sarcopenia Cachexia and Wasting Disorders (49)	Syndrome characterized by reduction of muscle mass associated with limited mobility, not as a result of specific pathological conditions or cachexia	Muscle mass, physical performance Cut-points are provided
2014	FNIH Sarcopenia Project (50)	Functional limitation in presence of weakness (reduced strength) as a result of reduced muscle mass	Muscle mass, muscle strength Physical performance used as an outcome Cut-points are provided
2019	European Working Group on Sarcopenia in Older Persons (EWGSOP2) (17)	A progressive and generalised skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality	Muscle mass, muscle strength, physical performance Physical performance used to measure severity Cut-points are provided

chronic conditions (including sarcopenia).

In the absence of a gold standard for capturing sarcopenia, the estimate of its prevalence remains quite variable. Furthermore, the prevalence of sarcopenia is also highly influenced by the studied population and the setting where the condition is looked for, thus limiting the availability of single and reliable estimates. Nevertheless, a relatively robust evaluation of the phenomenon sets the prevalence of sarcopenia to be between 8.4% and 27.6% in community-dwelling older persons (7, 8), 14-33% in long-term care residents and 10% in acute hospital care population (9).

Sarcopenia is more likely to be present in men than in women and tends to increase with advancing age. Asians, persons with low body mass index, and those with low education represent other groups of people at higher risk of sarcopenia (7).

Sarcopenia has been associated with many negative health-related outcomes, including disability, poor physical function, falls, fractures, loss of independence, hospitalizations, institutionalization, and mortality. In patients with several comorbidities and clinical conditions (e.g., patients with cancer or undergoing surgery), sarcopenia has shown to represent a negative prognostic factor (10, 11).

Analyses conducted on Third National Health and Nutrition Examination Survey (NHANES III) database have calculated the direct costs of sarcopenia. Sarcopenia was found to cost about$18,5 billion ($10.8 billion in men, $7.7 billion in women) per year in the United States, and it represented about 1.5% of total direct health care costs calculated in the year 2000 (12). Reducing the prevalence of sarcopenia by 10% would result in about $1.1 billion savings per year. And this without considering the indirect costs of sarcopenia, such as the loss of productivity for the individual as well as for the eventual caregivers(12).Another example of how burdensome is sarcopenia for public health is brought by a Portuguese study showing that sarcopenia is independently related to hospitalization costs, independently of age. Sarcopenia was responsible for adding €884 per patient (95% confidence interval [95%CI] €295-€1,476) to hospital care costs, that represents a 58.5% increase. Again, these figures are likely underestimating the economic burden of sarcopenia because not taking into account the indirect costs (13).

In order to adequately tackle sarcopenia and prevent its detrimental consequences (for both the individual and the healthcare system), it is mandatory to design and implement an effective plan of action. In fact, it is important to preventively track sarcopenia when it is still reversible, and before its vicious cycle might cause the onset of frailty and disability.In this context, it is noteworthy that not everyone with sarcopenia is disable, but the condition substantially increases the risk of disability (14). Not surprisingly, sarcopenia is frequently considered as a condition to target for avoiding the most negative consequences of the disabling process. At the same time, the positioning of sarcopenia at the initial phases of

Table 2
The"red flag" method, SARC-F, and other instruments for the assessment of sarcopenia in the primary care setting

SCREENING	Find Cases	The Red Flag Method	Clinician's observation: weakness, visual identification of low muscle mass, slow gait speed
			Subject's complaints: weight loss, muscle weakness, fatigue, falls, mobility impairment, loss of energy, sedentary behaviour
			Clinician's assessment: malnutrition, chronic diseases, inflammatory disorders
		SARC-F	Strength; Assistance in walking; Rise from a chair; Climbing stairs; Falls
		Yubi Wakka Test	Measuring the calfcircumference with the sum of person's both hands, checking whether or not the non-dominant calf circumference is "bigger", "just fits" or is "smaller" compared with the finger ring circumference
		Anthropometry	Body mass index, calf circumference, mid-arm muscle circumference, skinfold thickness, waist circumference
DIAGNOSIS	Assess	Muscle Strength	Handgrip strength, chair stand test
	Confirm	Muscle Quality/Quantity	BIA, DXA, CT, MRI
	Severity	Physical Performance	Usual gait speed test, SPPB (gait speed, balance test, chair stand test), TUG

BIA: Body Impedance Analysis; DXA: Dual-energy X-ray Absorptiometry; CT: computed tomography; MRI: magnetic resonance imaging; SPPB test: Short Physical Performance Battery test; TUG: Time Up and Go.

physical dysfunction automatically indicates this as a condition of special interest for primary care professionals. In other words, the detection of sarcopenia (or, at least, the suspicion of it) in primary care might promote the implementation of successful interventions when the person is still independently living in the community.

Screening

It is recommended that adults aged 65 years and older should be screened annually for sarcopenia, or after the occurrence of major health events (falls, hospitalization).

It is also advisable screening older adults on the occasion of the first consultation or, for instance, at annual health check-up or flu vaccination appointments (15).

For the screening of sarcopenia in primary care, several instruments and methodologies have been developed over the years. It is generally recommended that the presence of sarcopenia should be suspected in every individual aged 65 years or older, presenting signs or symptoms suggestive of skeletal muscle impairment (3). A recent consensus paper promoting the identification and management of sarcopenia in primary care has proposed the so-called "Red Flag Method"(3) (Table 2). The purpose of this method is to generate alerts about those physical manifestations typically caused by sarcopenia that can be 1) reported by the subject, or 2) evaluated by the physician during the clinical assessment. In other words, the Red Flag Method may represent a sort of checklist for supporting the physician at the identification of several neglected signs, symptoms and conditions behind which sarcopenia might be hidden(3). The pedagogical value of the method should also be acknowledged. In fact, healthcare professionals may find in it a way for being trained at the clinical manifestation of sarcopenia, becoming more familiar with it, and introducing the process in the daily routine.

Alternatives to formal/structured assessments might also be found in actions made by the individual during the clinical contact. For example, hints about the possible presence of sarcopenia might be provided by the strength of the individual's handshake, his/her walking speed from the waiting room to the office, or observing how the person sits down and stands up from the chair.

If the Red Flag Method is based on a relatively long list of items to consider in the identification of possible sarcopenia, John Morley recently developed an ad hoc instrument (i.e., the SARC-F questionnaire) for a more rapid screening of the condition(16). SARC-F is the acronym of Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls. Each of these items receives a score ranging between 0 (absence of the sign) and 2 (inability or severe issue). A total score equal to or higher than 4 points is predictive of sarcopenia and poor health-related outcomes. The SARC-F can be used to identify individuals in the need of a more detailed and careful assessment of sarcopenia, and potentially lead to a more in-depth analysis of the case through the comprehensive geriatric assessment. Interestingly, in the revised version of the European recommendations for the definition and diagnosis of sarcopenia, designed by the European Working Group on Sarcopenia in Older People (EWGSOP), the use of SARC-F is suggested for the early identification of individuals amenable of further evaluation (17). This choice is motivated by the low sensitivity and high specificity of the instrument (17, 18).

Another opportunity for promoting the inclusion of the sarcopenia assessment in primary care can be found in a wider

use of anthropometry. Although they would be useful to assess the body composition, the most commonly considered imaging methods might be unfeasible in primary care. Anthropometry (i.e., the measurement of body mass index, waist circumference, calf circumference, mid-upper arm circumference, and/or skinfold thickness) may provide easily applicable, inexpensive, and non-invasive techniques for identifying individuals at risk of presenting low muscle mass (19, 20). Recently, the Yubi-Wakka (finger-ring)test has also been proposed in this context. This is a simple self-screening method to quickly assess sarcopenia, comparing the calf circumference with the ring generated by the individual's fingers (21).Table 2 lists several methods to be considered for the screening of sarcopenia in primary care.

Diagnosis

As mentioned, a gold standard definition to diagnose sarcopenia is today not yet available. In general, the available recommendations coming from different panels of experts and task forces tend to indicate the need of combining a quantitative dimension (capturing the skeletal muscle mass) and a qualitative one (assessing the skeletal muscle function). Whereas the assessments of skeletal muscle strength and/or physical performance are relatively easy to be conducted, the body composition evaluation might be challenging in the primary care setting. In fact, general practitioners may not have easy/immediate access to the suggested methodologies for measuring the skeletal muscle mass, or (at best) may have to rely on suboptimal techniques. For this reason, the accurate diagnosis of sarcopenia is likely to require the referral to specialized centres, where the dual energy X-ray absorptiometry (DXA) or other (more sophisticated) techniques (e.g., magnetic resonance imaging or computerized tomography) are available. At best, the quantification of the skeletal muscle mass in primary care might be estimated using the bioelectrical impedance analysis (BIA). This technique is inexpensive, easy to use, and readily reproducible, although its results might be inaccurate, especially in the presence of certain clinical conditions (e.g., in the presence of fluid retention).

Nevertheless, a lot can still be done in primary care to detect the sarcopenia condition. The identification of individuals with sarcopenia might also start by measuring some neglected signs or symptoms of muscular poor health, for example by formally and routinely testing muscle strength/performance. In this context, the routine adoption of the handgrip strength is widely recommended and relatively easy to implement in primary care and represents a cornerstone parameter for the diagnosis of sarcopenia (22–24). In case a dynamometer is not available, the Chair Stand Test can be a valid and reliable alternative for measuring the muscle strength (17).

It is likely that, in the next future, novel methodologies will be developed for supporting Physician to diagnose sarcopenia. One of themost promising ones is represented by the deuterated creatine (D3-creatine) dilution method, which is able to provide a direct quantification of the individual's muscle mass via the ingestion of deuterium-marked creatine and is the only technique providing a direct and unbiased estimate of muscle mass.

Although its use is currently limited to the research setting(19), this method has relevant potential for diffusion in primary care because 1) based on the simple administration of a pill and a urine analysis (to be performed after 24-48 hours), and 2) overcoming the need of the above-mentioned diagnostic tools for body composition assessment.

Management

Primary care physicians may play a crucial role in the identification of individuals exposed to the risk of sarcopenia or already presenting this condition. They may preventively act providing recommendations for managing reversible risk factors (e.g., sedentary behavior, unhealthy diet) and eventually referring them to specialists for further evaluation.

To date, no pharmacological agent is available for the treatment of sarcopenia, but several molecules (at different stages of development) are in the pipelines of pharmaceutical industries. Thus, physical activity and nutritional interventions currently represent the basis of the clinical management of sarcopenia(25,26). Unfortunately, there is still a general lack of knowledge among healthcare professionals for correctly prescribing personalized interventions of physical activity and/or healthy diet.

Physical activity

The design ofa person-tailored physical activity program for tackling sarcopenia is not easy, especially if considering 1) the clinical complexity of older persons presenting this condition, and 2) the lack of adequate training that healthcare professionals may receive for this task during the curriculum of traditional study. Nevertheless, the beneficial effects that a physical exercise program may exert in frail and/or sarcopenic individuals is very well documented (27).

In general, multicomponent/combined exercise programs including aerobic activities, resistance training, and flexibility exercises are recommended. These should be proposed by primary care physicians to frail and/or sedentary community-dwelling persons as part of clinical routine (15). In this context, the material produced by VIVIFRAIL project is important to be mentioned (28). VIVIFRAIL was designed to provide support to primary care physicians in the prescription of personalized programs of physical activity. The program is based on a preliminary assessment of the individual's physical performance, muscle strength, balance, and risk of falls. The results of such evaluation are then used to design an intervention that is tailored to the individual's capacities and deficits. Importantly, VIVIFRAIL is designed for empowering the individual at monitoring his/her progresses (29). The

VIVIFRAIL material is available at the project website (www.vivifrail.eu), and an app has also been developed for supporting the individual and the healthcare professionals.

Another project to be mentioned for its potential of reshaping the management of sarcopenia is "The Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) study(30). This project, funded by the Innovative Medicines Initiative (IMI), is aimed to developing an operational definition of sarcopenia that might be acceptable by regulatory agencies. The project includes a randomized control trial designed to test the effects of a multidomain lifestyle intervention (mainly based on physical activity and nutritional counselling) on a condition combining physical frailty and sarcopenia. Interestingly, the target condition was theoretically framed in order to mirror the nosological conditions that are traditionally object of observation by regulatory agencies. The developed operational definition has been preliminarily endorsed by the European Medicines Agency before the beginning of the SPRINTT randomized controlled trial. At the end of the trial, investigators will be in the position of 1) estimating the prevalence of the novel condition in the general population, 2) ascertain the reversibility of the condition after implementation of lifestyle changes promoting healthy ageing, and 3) identify a subgroup of individuals resistant to the beneficial effects of physical activity and healthy diet. In particular, this latter point is of special interest because paving the way towards the profiling of future candidates to pharmacological interventions against sarcopenia (31).

Nutrition

Malnutrition is a condition due to a protein or other nutrient imbalance, responsible for negative effects on body composition, physical function, and clinical outcome. It plays a key role in the pathogenesis of sarcopenia and fragility. It is necessary to recognize malnutrition early in older adults to plan nutritional programs aimed at improving the outcome (32).

In hospital settings Nutrition Risk Screening-2002 (NRS-2002) or Malnutrition Universal Screening Tool (MUST) are used for the screening of malnutrition whereas Mini Nutritional Assessment (MNA) is considered the gold standard for the older adults hospitalized or in an outpatient setting. In the subject at risk of malnutrition, the evaluation of the nutritional status must be carried out.

These screening tools help to have a patient-centered approach, provide adequate nutritional advice, and monitoring nutritional status over time (33, 34).

An example of malnutrition prevention is the "Health Enhancement Program (HEP)", a randomized trial with robust results. After an initial assessment conducted by a trained staff of each participant's health and functional status, a personalized plan was carried out to counteract disability risk factors. The program consists in motivational strategies to promote behavioral changes in depression, poor nutrition, and a sedentary lifestyle. At one year follow up, compared with enrollment, a reduction of risk factors was registered (35).

An attempt of intervention in frail older adults in a clinical setting is the program of the Geriatric Frailty Clinic (G. F. C.) at the Gerontopole of Toulouse. Older adults, considered as frail by their General Practitioner, underwent a multidisciplinary evaluation at the G.F.C where the team members proposed a Personalized Prevention Plan (PPP); in case of malnutrition, detected by the MNA, a nutritionist was asked for improve dietary intake with specific recommendations. A follow-up, consisted of a nurse call after one month and three months, was organized to determine the intervention's efficacy. After one year the Geriatrician reassessed the patient's improvements with a multidisciplinary evaluation (36).

Recently, two consensus papers (promoted by the European Society for Clinical Nutrition and Metabolism and the PROT-AGE study group) agreed that people aged 65 years or older require a higher intake of proteins compared to what usually recommended for activating muscle protein synthesis and maintaining muscle health. Therefore, both groups recommended the assumption of at least 1–1.2 g of proteins/kg/day in older persons, pushing even higher this minimum threshold in the presence of catabolic or muscle wasting conditions (37, 38).

About the quality of proteins, essential amino acids (EAAs; in particular leucine) are recognized as providing an important anabolic stimulus. In fact, leucine is able to increase muscle protein synthesis in older people, as also confirmed in a recent meta-analysis. In fact, its consumption has been found to be directly correlated with muscle mass in healthy older people (39).

β-hydroxy β-methylbutyrate (HMB) is one of the metabolites of leucine that is able to exert anabolic effects. HMB is frequently used by athletes to improve their physical performance and has also showed promising results in improving muscle mass and strength in older adults. When applied to bed resting older people, HMB stimulated muscle mass preservation. HBM supplementation combined with exercise seems to promote the regenerative capacity of skeletal muscles (25).

For what concerns vitamin D, its supplementation is surely useful for correcting states of insufficiency or deficiency (40, 41). Nevertheless, no evidence supports its use in individuals with normal vitamin D concentrations for improving muscle health.

Drugs

No drugs are currently registered for use in the treatment of sarcopenia, and no pharmacological intervention can be accepted as first-line therapy of sarcopenia (15). However, several new molecules are currently under study at various stages of development. It is noteworthy the special interest devoted by regulatory agencies in this field. Both the Food and Drugs Administration and the European Medicines Agency are

paving the way for structuring pharmacological research on this topic.

Despite the urgency of the problem, the development of pharmaceutical therapies for sarcopenia and frailty has lagged, in part because of the lack of consensus definitions for the two conditions. In 2015,an experts' group gathered during the International Conference on Frailty and Sarcopenia Research (ICSFR) to discuss challenges related to drugs designed to the target the biology of frailty and sarcopenia (8).

Based on the available evidence, myostatin antagonists, like Bimagrumab, may be promising candidates to treat people with low lean muscle mass, in particular people older than 70 years. Bimagrumab is a monoclonal antibody that blocks the binding of myostatin to activin, thus blocking its negative regulation of muscle growth (42). Young men treated with a single dose of Bimagrumab may experience an increase in muscle mass similar to that induced by 12 week of high-intensity resistance training(43,44), while sedentary adults may receive a benefit equivalent to 9 months of jogging 12-20 miles per week (45).

Researchers are also focused on selective androgen receptor modulators (SARMs). These are a class of androgen receptor ligands that increase low lean muscle mass by binding to the androgen receptor in muscles. Different molecules have already undergone phase I, II and III trials, but at the moment longer studies are required to demonstrate the long-term safety and the efficacy of these drugs (8).

Inflammatory modulators, such as those acting on the tumour necrosis factor-α (TNFα) and interleukin-1 (IL1), are also under study. Systemic inflammation and the increasing of TNFα and IL1 in blood lead to muscle atrophy (46). Inflammatory modulators could limit the reduction of skeletal muscle by reducing pro-inflammatory cytokines.

Conclusions

Sarcopenia is the age-related progressive decline of skeletal muscle. It is a common age-related condition, and has a relevant impact on the person's quality of life and functioning, as well as on healthcare costs.

Primary care physicians may play a pivotal role in the identification of the risk of sarcopenia in the aged population. Indeed, the primary care physician may detect the early manifestations of this condition and lead to its fast diagnosis and care. In this framework, multiple instruments have been developed for promoting the detection of sarcopenia in primary care. Once sarcopenia is identified, a comprehensive assessment of the individual may lead to person-tailored interventions based on nutritional counselling and physical activity programs. In the next future, the availability of pharmacological therapies could be able to prevent the skeletal muscle decline in those individuals resistant to the benefits of healthy lifestyle prescriptions.

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