Sarcopenia

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ABSTRACT

Sarcopenia, the loss of muscle mass and function with age, is highly relevant to clinical practice as it has been associated with a wide range of ageing outcomes including disability and shorter survival times. As such it is now a major focus for research and drug discovery. There has been recent progress in the development of consensus definitions for the diagnosis of sarcopenia, taking the form of measurements of muscle mass and strength or physical performance. These definitions form potential inclusion criteria for use in trials, although the optimum choice of outcome measures is less clear. Prevalence estimates using these new definitions vary, although they suggest that sarcopenia is a common (approximately 13% from one study) clinical problem in older people. A range of lifestyle factors have been investigated in regard to the development of this condition, and progressive resistance training is the most well-established intervention so far. There is also marked research interest in the role of diet, although so far the value of supplementation is less clear. Other potential treatments for sarcopenia include the angiotensin-converting enzyme inhibitors, with some evidence that they can improve physical performance in older people. Future research directions include an increased understanding of the molecular and cellular mechanisms of sarcopenia and the use of a life course approach to explore the possibility of earlier intervention and prevention. Arq Bras Endocrinol Metab. 2014;58(5):464-9

Keywords

Sarcopenia; muscle mass; physical performance; aging

RESUMO

A sarcopenia, definida como a perda de função e massa muscular que ocorrem com a idade, é altamente relevante para a prática clínica, pois está associada a vários desfechos negativos, incluindo diminuição da funcionalidade e da sobrevida. Houve recente progresso no desenvolvimento de definições para o diagnóstico da sarcopenia, e estas atualmente se compõem tanto de medidas de massa e força muscular quanto do desempenho físico. Essas definições são potencialmente úteis como critérios de inclusão em pesquisas científicas, todavia a escolha de desfechos é menos clara. As estimativas de prevalência utilizando essas novas definições variam, mas elas sugerem que a sarcopenia é um problema clínico comum (cerca de 13% a partir de um estudo) em pessoas idosas. Uma série de fatores de estilo de vida foi investigada em relação ao desenvolvimento dessa condição, e o treinamento de resistência progressiva é a intervenção mais bem estabelecida até o momento. A intervenção dietética também foi aventada como um fator modificável, embora menos clara que a anterior. Outros tratamentos potenciais para sarcopenia incluem os inibidores da enzima conversora de angiotensina, com alguma evidência de que eles podem melhorar o desempenho físico em idosos. Pesquisas futuras que abordem uma maior compreensão dos mecanismos moleculares e celulares da sarcopenia, além de abordagens precoces que possam vir a modificar o surgimento da sarcopenia, são necessárias. Arq Bras Endocrinol Metab. 2014;58(5):464-9

Descritores

Sarcopenia; massa muscular; desempenho físico; envelhecimento

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Received on Mar/10/2014
Accepted on Apr/22/2014

DOI: 10.1590/0004-2730000003345

INTRODUCTION

The term sarcopenia, from the Greek meaning loss of flesh, was first suggested by Rosenberg in 1989 (1), with more recent definitions incorporating the loss of muscle function as well as the loss of muscle mass that occurs with ageing (2). It is a common and increasingly important condition as populations grow older, associated with subsequent disability, morbidity and frailty; indeed muscle tissue is recognised to have a wide range of functions in both health and disease (3). Sarcopenia is also associated with substantial financial cost: the healthcare costs of sarcopenia in the USA in 2000 were estimated to be $18.5 billion (4). However perhaps the most striking indication of the importance of sarcopenia comes from the evidence linking poor muscle function, in particular weak grip strength, to increased all-cause mortality rates in middle-aged and older people (5). The aim of this review is to summarise current approaches to the diagnosis and treatment of sarcopenia, as well as future directions for research in this important area.

DIAGNOSIS

Diagnostic criteria are clearly essential for the recognition of sarcopenia in clinical practice and for use in clinical trials. There has been considerable recent progress in this area, with the publication of several similar (although not identical) consensus statements on the measures to use for diagnosis. The algorithm published by the European Working Group on Sarcopenia in Older People (EWGSOP) in 2010, requires the presence of either low gait speed or low muscle strength to then test for low muscle mass as shown in figure 1 (2). The approach recommended by the International Working Group on Sarcopenia in 2011 is similar, with low gait speed or evidence of impaired physical function (those who are bedridden or unable to independently rise from a chair) being an indication to measure muscle mass (6). The components of these algorithms fall into three broad groups: physical performance (such as gait speed), muscle strength and muscle mass. This section now briefly reviews the measurement techniques for each of these three categories, along with their associations with major ageing outcomes.

Components of recent definitions of sarcopenia

Physical performance

Older people with slow gait speed have been found to be at an increased risk of subsequent disability, falls, cognitive decline, institutionalisation and mortality (7-9). Gait speed is readily assessed in the clinical setting by measuring the time taken to walk a set distance, such as 4 m, at usual pace. Although there appears to be a continuous relationship between gait speed and outcomes such as mortality (9), for clinical purposes a range of cut-points have been proposed such as 0.8 m/s, as used in the EWGSOP definition for sarcopenia (2). Other measures of which have been studied in older people including standing balance and chair rise times, and in both poorer performance has been linked to increased mortality rates (5). The combination of these measures and gait speed has been used in epidemiological studies in the form of the Short Physical Performance Battery, the results of which are graded on a 12-point scale which is predictive of ageing outcomes (10,11). There is evidence that gait speed alone may have similar predictive power to the complete battery of tests (12).

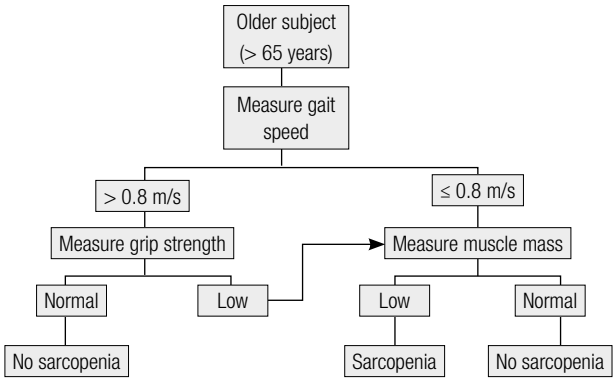

Figure 1. The algorithm suggested by EWGSOP for diagnosing sarcopenia (2).

Muscle strength

Several measures exist for the measurement of muscle strength. Grip strength has been recommended as the most practical method of measuring muscle strength in the clinical setting (2) and has been found to correlate physical performance measures in the lower limbs (13). The Jamar dynamometer being the most commonly described device (14). In a systematic review, seven out of 10 studies of older people found that weak grip predicted either incident disability or worsening of existing disability (8). There is strong evidence linking grip strength with mortality rates, with a meta-analysis of 14 studies showing a graded relationship between weaker grip and increased risk of death (5); the hazard ratio comparing the lowest to the highest quarters of

grip strength was 1.67 (95% CI: 1.45, 1.93). Whereas associations between measures of physical performance and mortality have been assessed mainly in older populations, four of the studies included in the grip strength meta-analysis had an average age at baseline of below 60 years, and the findings here were similar. Normative data are available for grip (15,16) and cut-points have been proposed, such as 30 kg in men and 19 kg in women (17).

Muscle mass

Possible techniques for measuring muscle mass in the clinical setting include anthropometry, bioelectrical impedance (BIA) and dual energy x-ray absorptiometry (DXA). Anthropometric measures are prone to error and are not considered to be suitable for assessing muscle mass in older people (2). Bioelectrical impedance (BIA), which produces estimates of total fat mass and lean mass, has the advantage over DXA that the equipment used is portable. However a recent review questioned to what extent BIA provides additional information beyond that from anthropometric measurements (weight and height) alone (18). The third technique, DXA, can accurately estimate the proportion of lean tissue, fat tissue and bone, although access to scanning equipment may be a limiting factor. Baumgartner and cols. (19) proposed an index of relative skeletal muscle mass, in the form of appendicular skeletal muscle mass (kg) from DXA divided by height (m) squared. They also suggested cut-offs for sarcopenia in the form of two standard deviations below the gender-specific young adult mean: 7.26 kg/m^2 for men and 5.45 kg/m^2 for women.

As described above, more recent definitions of sarcopenia have used measures of physical performance and muscle strength to screen for the need to perform tests of muscle mass. Interestingly there is evidence that strength may be more predictive of the risk of subsequent disability (20) and mortality (21) than muscle mass. There is also debate around the feasibility of measuring muscle mass in the potentially large numbers of older people who may fall below thresholds proposed for physical performance and strength (22).

Recent applications of a sarcopenia algorithm

Several studies have applied the framework for the diagnosis of sarcopenia proposed by the EWGSOP. Patel and cols. (23) examined the prevalence of sarcopenia in a cohort based in the United Kingdom at mean age 67 years, with 4.6 and 7.9% of men and women, respectively, meeting criteria based on gait speed, grip strength and lean mass. Akune and cols. (24) used an older Japanese cohort (mean age 75 years) and found an overall prevalence of sarcopenia of 13.8% in men and 12.4% in women, as well as a clear tendency for the prevalence to increase with age. As we move on to considering treatments for sarcopenia, it is worth noting that a further application of the EWGSOP algorithm is as the inclusion criteria for intervention studies. The question of what outcome measures should be used in such studies is less clear, however (25).

TREATMENT

There are a range of potential treatments for sarcopenia, such as the established role of exercise programmes, along with the potential to modify diet and also drug treatments. There exists marked variation between older individuals in terms of strength and performance, suggesting that factors such as lifestyle may contribute to the development of sarcopenia (26). As described in the following sections, observational studies are helpful in this regard by identifying possible areas for intervention.

Exercise

Progressive resistance training (PRT), where participants exercise against an increasing load, is the most studied form of exercise intervention. The 2009 Cochrane review (27) included studies with an average age of at least 60, the majority of which were high-intensity programmes performed twice or three times per week in gym or clinic-based settings. The outcomes used in different studies varied but there was evidence of a moderate-to-large beneficial effect of PRT on strength in the lower limb, as well as a moderate effect on gait speed. Other types of exercise intervention include aerobic exercise, balance and flexibility training and functional training. These have been less studied in regard to outcomes related to sarcopenia; perhaps unsurprisingly, interventions such as aerobic exercise do not show the consistent effects seen from PRT (28).

Observational studies have the potential to address questions around the types of physical activity that people generally undertake (as opposed to the specific interventions, such as PRT programmes). They are also of use for investigating longer term relationships; for

example, there is evidence that being more physically active in middle age is beneficial for strength in early old age (29,30). This may be through attenuating the typical age-related decline in strength. This life course approach to sarcopenia (31) is considered further in the section on future research.

Diet

Less is known about dietary interventions than the established role of resistance training. There is considerable recent literature which suggests that several aspects of diet may be important in the development of sarcopenia (32). Food intake falls by approximately 25% from 40 to 70 years of age, and particularly if combined with a tendency towards a monotonic diet, may lead to inadequate nutrient intake. Three key areas have been considered with respect to diet in sarcopenia: protein, vitamin D and antioxidants.

Protein provides the amino acids required for muscle synthesis. There is also evidence that the amino acid leucine may activate the signalling pathways leading to protein synthesis (33). A trial in relatively young (mean age 71) and healthy men failed to show on effect on muscle mass or strength, however, perhaps because the group studied tended to have diets already replete in leucine (34). There is also a general concern that the muscle synthesis in older people following a protein load may be blunted (35), leading to the suggestion that recommended overall protein intakes for older people should be increased. Observational evidence shows a clear association between protein intake and amount of lean mass (36). However a Cochrane review (37) found no consistent effect of supplements on functional measures relevant to sarcopenia. The quantity and composition of dietary protein for the prevention and treatment of sarcopenia therefore remains unclear.

The current widespread interest in diseases potentially related to vitamin D deficiency (38) includes sarcopenia. Evidence supporting a role for vitamin D includes the fact that polymorphisms in vitamin D have been linked to muscle strength (39); also frailty (a condition which has some overlap with sarcopenia) has been shown to be associated with vitamin D deficiency (40). As with protein supplementation, intervention trials of the effect of vitamin D on strength and physical performance have shown mixed results, however (41). Given that vitamin D deficiency is prevalent in older people, further trials to clarify its role in sarcopenia are therefore warranted.

The accumulation of reactive oxygen species (ROS) in older age is recognised to have a role in muscle wasting, although the precise forms of ROS responsible and their interactions are not fully understood (42). This in turn makes it difficult to know which specific antioxidants are likely to be of benefit as supplements and there have been few trials. There is evidence from observational studies that those with higher overall antioxidant status have better physical function as well as attenuated decline in measures such as walking speed (43).

In summary, a common finding across the three types of dietary intervention is a mismatch between the findings from observational and intervention studies. One possible explanation for this is the tendency for intake of dietary components to be highly correlated with one another (44); hence the association between one marker of a healthy diet and physical function may be confounded by other components. Indeed there is some evidence linking 'healthy' diets, containing wholemeal cereals and greater amounts of fruit and vegetables, to greater muscle strength in older people (32). An important area for further research is therefore the potential of whole-diet interventions, which attempt to change dietary patterns rather than focussing on specific nutrients in isolation.

Medication

Sarcopenia is now a major focus for drug discovery. This follows in part from the fact that although resistance training has been shown to be effective, many older people may be unable or unwilling to exercise at the required intensity. One area which has been explored is hormone administration (45). Growth hormone has been shown to increase muscle mass but not clearly alter functional outcomes and is therefore of questionable benefit. This highlights the challenge of choosing outcome measure(s) for trials in sarcopenia (25). Testosterone supplementation has been found to increase both muscle mass and strength in men but has now been linked to adverse cardio-vascular events (46). A current area of interest is in drugs affecting the renin-angiotensin system, and whether these might have direct effects on muscle. An observational study initially suggested that ACE (angiotensin converting enzyme) inhibitors might be of benefit for physical function (47), a finding subsequently confirmed in a trial showing improved six minute walk time in those given perindopril (48,49). A similar effect was not seen with

a trial of spironolactone (50), and neither has either of these drugs yet shown a benefit in terms of outcomes more traditionally related to sarcopenia.

FUTURE DIRECTIONS FOR RESEARCH AND CONCLUSIONS

There are multiple areas of research which should increase our understanding of sarcopenia and its management. These include an increased understanding of the molecular and cellular mechanisms which underlie this condition, drawing from both human (51) and animal studies (52). Such studies have the potential to identify novel therapeutic targets as well as monitor and predict responses to treatment. There is also the life course approach as shown in figure 2, which recognises that function in older age is the product of a peak in early adult life and subsequent decline, both influenced by a range of factors operating across the whole of life including early influences (53,54). Finally there is further potential to explore whether nutritional supplementation and resistance training might be combined to produce synergistic effects (55).

In conclusion, this review has covered recent developments in the diagnosis and treatment of sarcopenia, a syndrome comprising loss of muscle mass and function. The development of consensus definitions for sarcopenia has helped to inform clinical assessment of patients as well as recruitment into trials. At present, progressive resistance training is the most well studied intervention for sarcopenia. Research into this condition is expanding exponentially and will hopefully deliver benefits for older people with established sarcopenia, as well as considering how we might be able to intervene earlier in the life course to prevent its occurrence.

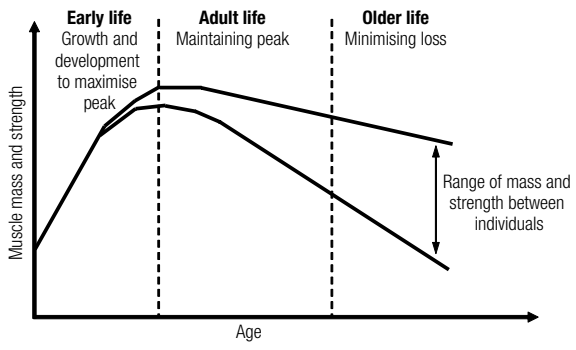

Figure 2. A life course approach to sarcopenia (31).

Acknowledgements: none.

Funding statement and competing interests: Richard Dodds is supported by a Wellcome Trust Fellowship (Grant number WT099055AIA).

Disclosure: no potential conflict of interest relevant to this article was reported.

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