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Muscle quality as a diagnostic criterion for sarcopenia and sarcopenic obesity: a literature review

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Declaro para os devidos efeitos ter atuado com integridade na elaboração deste Trabalho de Projeto, atesto a originalidade do trabalho, confirmo que não incorri em plágio e que todas as frases que retirei de textos de outros autores foram devidamente citadas ou redigidas com outras palavras e devidamente referenciadas na bibliografia.

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(Inês Margarida Santos Aguiar)

Trabalho apresentado à Universidade Fernando Pessoa como parte dos requisitos para obtenção do grau de licenciado em Ciências da Nutrição.

Orientadora:
Professora Doutora Ana Sofia Sousa

I. Dedicatória

Aos meus pais, pelo apoio incondicional e pelo incentivo demonstrado ao longo do meu percurso.

À Sónia e à Joana, por terem sido colegas excecionais cujo apoio fez toda a diferença.

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II. Index

III. Figure Index

IV. List of abbreviations

AWGS – Asian Sarcopenia Working Group for Sarcopenia

BIA – Bioelectrical Impedance Analysis

BMI – Body Mass Index

CHAMP – The Concord Health and Ageing in Men Project

CT – Computed Tomography

DXA – Dual X-ray Absorptiometry

EWGSOP – European Working Group on Sarcopenia in Older People

EWGSOP2 - Sarcopenia: Revised european consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People

FNIHSP – Foundation for the National Institute of Health Sarcopenia Project

IMAT – Intermuscular Adipose Tissue

IWGS – International Sarcopenia Working Group on Sarcopenia

MRI – Magnetic Resonance Imaging

Muscle quality as a diagnostic criterion for sarcopenia and sarcopenic obesity: a literature review

Qualidade muscular como critério de diagnóstico para a sarcopenia e obesidade sarcopénica: revisão bibliográfica

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Resumo

A qualidade muscular foi recentemente associada à sarcopenia. No entanto, já é reconhecida como um critério que pode confirmar a presença de sarcopenia e de obesidade sarcopénica. O objetivo desta revisão da literatura é apresentar uma visão geral atualizada quanto às evidências atuais sobre a qualidade muscular como um critério de diagnóstico para a sarcopenia e obesidade sarcopénica.

A PubMed foi a base de dados eleita para a procura de evidência onde foram aplicados os seguintes critérios de inclusão: artigos desde 2010; em humanos; com idioma em português, inglês ou espanhol.

A qualidade muscular é essencial para a função muscular especialmente com o avanço da idade. A deterioração da qualidade muscular pode preceder a perda de massa muscular, portanto, a avaliação desse parâmetro pode ser benéfica para a identificação precoce de sarcopenia ou obesidade sarcopénica.

Embora a qualidade muscular tenha o potencial de ser um critério relevante no diagnóstico dessas condições, apresenta algumas limitações, como o recurso a ferramentas sofisticadas e de acesso limitado, alto custo, exposição à radiação e necessidade de profissionais altamente qualificados, o que prejudica a aplicação mais ampla dessas técnicas na prática clínica.

Em conclusão, a avaliação da qualidade muscular é um parâmetro promissor para o diagnóstico de sarcopenia e obesidade sarcopénica, principalmente em estadios iniciais. Porém, mais estudos são necessários relativamente à qualidade muscular como critério diagnóstico para sarcopenia e obesidade sarcopénica, uma vez que ainda não existe um método adequado para a aplicação por rotina na prática clínica.

Palavras-chave: Qualidade muscular; Sarcopenia; Obesidade sarcopénica

Abstract

Muscle quality has been recently associated with sarcopenia. However, it is already recognized as a criterion that can confirm the presence of sarcopenia and also sarcopenic obesity. The purpose of this literature review is to present an updated overview on the current evidence regarding muscle quality as a diagnostic criterion for sarcopenia and sarcopenic obesity.

PubMed was the database elected for the search of evidence and the following inclusion criteria were applied: articles since 2010; in humans; with language in Portuguese, English or Spanish.

Muscle quality is vital to muscle function later in life and it actually decreases with age. The deterioration of muscle quality may precede the loss of muscle mass, therefore the assessment of this parameter can be beneficial for early identification of sarcopenia or sarcopenic obesity.

Even though muscle quality has the potential to be a relevant criterion in the diagnosis of this conditions, it presents some limitations such as the need for sophisticated tools that are of limited access, besides high cost, exposure to radiation and the need for highly qualified professionals, which impairs the wider use of these techniques in clinical practice.

In conclusion, muscle quality assessment is a promisor parameter for the diagnosis of sarcopenia and sarcopenic obesity, particularly in early stages of these conditions. However, more research is needed concerning muscle quality as a diagnostic criterion for sarcopenia and sarcopenic obesity, since there is still no suitable method for routine use in clinical practice.

Keywords: Muscle quality; Sarcopenia; Sarcopenic obesity

1. Introduction

Sarcopenia was firstly described by Irwin Rosenberg in1989, as an age-related decrease of muscle mass (1, 2). Since then, there was not a consensual definition for this condition (3) until 2010 when the European Working Group on Sarcopenia in Older People (EWGSOP) released a consensus. In this consensus, sarcopenia is defined as a syndrome characterized by loss of skeletal muscle mass and strength which also provides a risk of negative outcomes such as physical disability, poor quality of life and death (4,5). According to the EWGSOP consensus, sarcopenia is considered 'primary', or age-related, when no other cause is evident but aging itself, or considered 'secondary' when one or more other causes are perceptible (3).

In 2018, EWGSOP released an updated consensus (EWGSOP2), and considered sarcopenia as a muscle disease, characterized by low muscle strength. Moreover, the role of low muscle mass as a criterion for sarcopenia was overtook by muscle strength (6 ,7, 8, 9) since muscle strength seems to be a better predictor for adverse outcomes than muscle mass (6, 7, 8, 10). Besides low muscle strength, sarcopenia is also characterized by low muscle quantity or quality and low physical performance (11).

Sarcopenia is frequent among older adults. However this condition can also affect younger adults, since its development can occur earlier in life (11).

According to the latter EWGSOP definition of sarcopenia, this condition can be considered acute when it has lasted less than 6 months and is usually related to an acute injury or illness, or it can be considered as a chronic state when lasts 6 or more months, associated with chronic and increasing states that can escalate the risk of mortality (11).

The negative outcomes associated with sarcopenia such as, mobility disorders, increased risk of falls, impaired ability to perform activities of daily living, disabilities, loss of independence and increased risk of death resulted from sarcopenia (3), have stimulated the development of studies about its prevalence and management (3,11, 12, 13, 14, 15).

Besides being associated with negative health outcome, sarcopenia is also a risk factor for other diseases. Indeed, sarcopenia increases the risk of physical limitation and subsequent disability and is frequently associated with poor endurance, physical inactivity, slow gait speed and decreased mobility (16).

Several underlying mechanisms such as, protein synthesis, proteolysis, neuromuscular integrity and muscle fat content have been linked to the development of

sarcopenia, even though not all of them have been fully elucidated (14). The contribution of the different mechanisms that can lead to sarcopenia may differ over time and from an individual to another (3). Understanding the mechanisms underlying sarcopenia is crucial for the development of strategies for the prevention and treatment of this disease (14).

The EWGSOP2 introduced a new criterion for the diagnosis of sarcopenia – muscle quality. Muscle quality expresses muscle's ability to function and it is usually described as muscle strength or power per unit of muscle mass (17, 18).Thus this criterion refers both to micro- and macroscopic changes in muscle architecture and composition, and when those changes are damaging they may affect muscle performance both functionally and physiologically, increasing the risk of sarcopenia (11, 19).

Probable sarcopenia is identified by low muscle strength and the presence of sarcopenia, is confirmed by low muscle quantity or quality. When there is low muscle strength, low muscle quantity or quality and also low physical performance, sarcopenia is considered severe possibly leading to the development of several other diseases, such as cardiac disease, respiratory disease and even death (11) (Figure 1).

Muscle quality is affected in sarcopenia. However, because of technological limits - high costs and limited availability of equipment -, both muscle quantity and muscle quality remain problematic as primary criteria for the diagnosis of sarcopenia (20, 21, 22). Instruments and methods to appraise muscle quality are developed and clarified in the future, thus muscle quality is expected to grow in importance as a defining characteristic of sarcopenia (11).

Currently, despite the two EWGSOP published consensus there are still issues regarding the diagnosis of sarcopenia. In fact there have been several techniques recommended for the assessment of the different parameters and also several cut-offs which impair a homogeneous methodology for the identification of sarcopenia both in research field and clinical practice (11). Anthropometric measurements, such as mid-upper arm circumference, calf circumference, and skin fold thickness, are not routinely recommended for the diagnosis of sarcopenia but the EWGSOP2 provides recommendations for cut-off points for different parameters to increase harmonization of sarcopenia studies (11).The commonly used diagnostic criteria for epidemiological research and also for clinical practice include the Baumgartner diagnostic criteria (23),the International Working Group on Sarcopenia (IWGS) (24), the Asian

Sarcopenia Working Group for Sarcopenia (AWGS) (25) and the Foundation for the National Institutes of Health Sarcopenia Project (FNIHSP) (26). All these criteria, except from Baumgartner, include the assessment of muscle quality, muscle strength and muscle function.

In conditions such as malignancy, rheumatoid arthritis and aging, lean body mass is lost while fat mass may be preserved or even increased. The loss in muscle mass and the decrease of muscle quality may be associated with increased body fat so that a normal weight can coexist with marked weakness. This condition is named sarcopenic obesity (16).

Sarcopenic Obesity

Obesity represents a severe health threat and is a major risk factor for metabolic and cardiovascular morbidity and mortality (27). The prevalence of obesity in middle-aged and older adults has doubled since 1980, and it continues to increase worldwide (27).

The term sarcopenic obesity was first introduced by Baumgartner (28) and is defined by a combination of sarcopenia and obesity. Thus it refers to an obesity disease accompanied by low skeletal muscle quality, strength and/or function, which is more usual in the elderly and seriously affects quality of life. This syndrome can lead to falls, unstable walking, balance disorders and fractures in the elderly (29).

Obesity aggravates sarcopenia outcomes, increases the infiltration of fat into muscle which affects directly the muscle's quality, lowers physical function and increases risk of mortality (30, 31, 32, 33).

With aging, lean body mass decreases, while fat mass increases preferentially in the intra-abdominal area, even in relatively weight-stable, healthy individuals (16). Obesity and sarcopenia may potentiate each other and act synergistically causing physical impairment, metabolic disorders and mortality (16).

Sarcopenia reduces physical activity, which leads to decreased energy expenditure and increases the risk of obesity (34). In contrast, an increase in visceral fat induces inflammation, which contributes to the development of sarcopenia (35). It has been considered that sarcopenic obesity may have a greater impact on metabolic diseases and cardiovascular morbidity and mortality than either sarcopenia or obesity alone (27, 36).

Since EWGSOP (3) first proposed the comprehensive diagnostic criteria and stages of sarcopenia in 2010, the diagnosis of sarcopenic obesity is not limited to the evaluation of muscle mass combined with obesity, but includes the comprehensive evaluation of muscle strength, muscle quantity and muscle quality, and is determined in combination with obesity (3).

Sarcopenic obesity is a relatively new concept that has become increasingly important in the aging population. However, several different definitions of sarcopenia limit the identification of sarcopenia and sarcopenic obesity and their association with metabolic disorders and cardiovascular disease (37).

Muscle quality has been recently associated with sarcopenia as an emerging criterion that can confirm the diagnosis of sarcopenia and also sarcopenic obesity (11). Therefore, the purpose of this literature review is to present an updated overview on the current evidence regarding muscle quality as a diagnostic criterion for sarcopenia and sarcopenic obesity.

2. Methods

To carry out the present literature review, PubMed was the database elected for the search of evidence and information. The terms used during the search were "muscle quality and sarcopenia" and "muscle quality and sarcopenic obesity". The following inclusion criteria were applied: articles since 2010; in humans; with language in Portuguese, English or Spanish. The articles that, after a reading of the title and abstract, didn't addressed the subject of this review were also excluded.

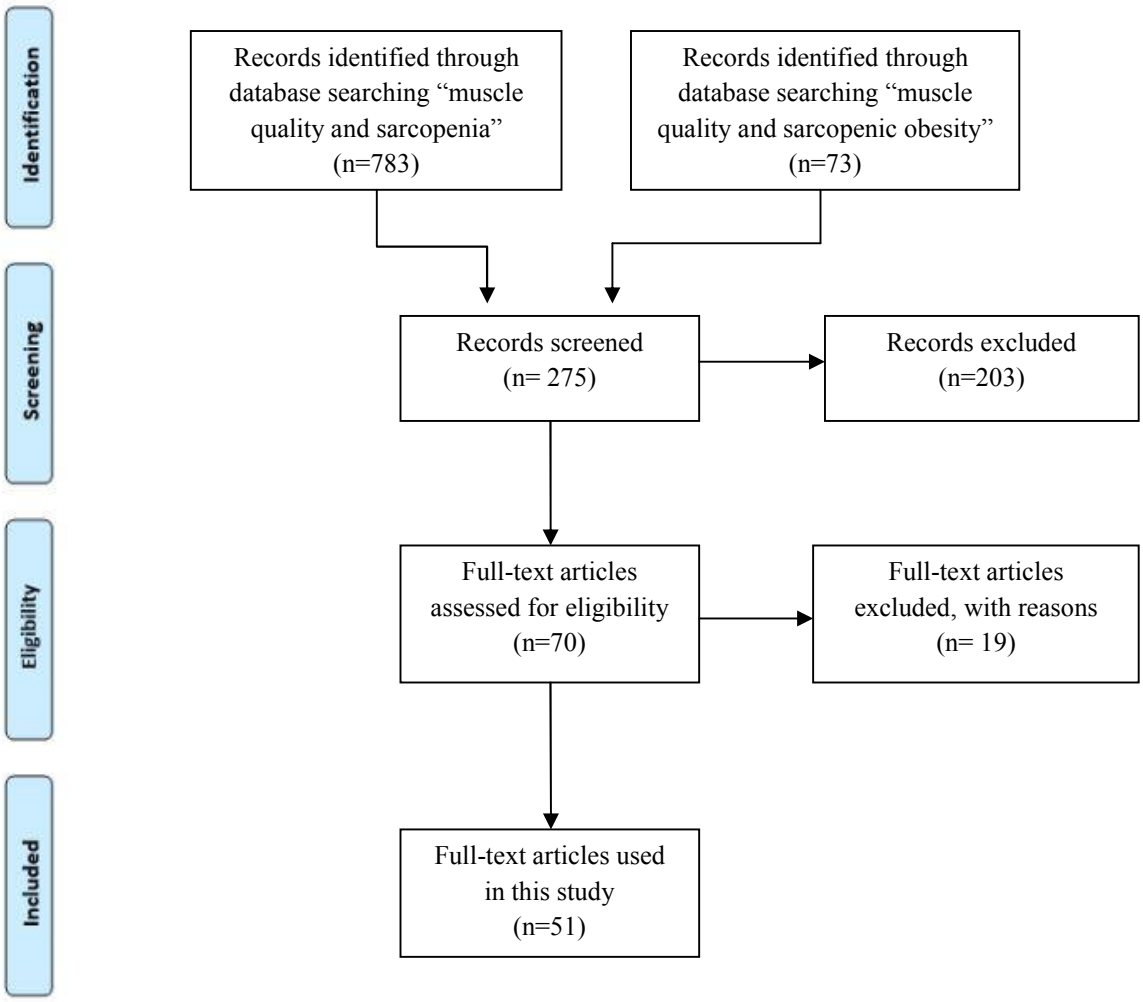

Fig.1 – PRISMA flow diagram (Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71)

3. Muscle Quality

Muscle quality is a term that has been recently associated with sarcopenia. The European Working Group on Sarcopenia in Older People (EWGSOP2) proposed the necessity to include muscle quality assessments for a diagnostic tool in sarcopenia, since muscle quality could be used effectively to identify individuals at risk of impaired mobility (11).

Muscle quality has most frequently been defined in terms of relative strength or muscle composition (19). Essentially, muscle quality reflects muscle's ability to function (19). This parameter is vital to muscle function later in life and it actually decreases with age (18).

The reason muscle quality can be considered a strong surrogate marker for sarcopenia is because it quantifies the function of muscle mass and muscle strength as a single unit regarding all the underlying factors of the muscle function such as composition, architecture, type of muscle fibers and also the lipid content (38).

Cohort studies demonstrate that muscle mass is positively associated with muscle strength (39, 40) and that low muscle strength is associated with increased risk of impairment (41, 42). Otherwise, it is presumed that individuals with higher muscle mass are, therefore, stronger, and that they are less likely to develop physical impairments (43). However, although muscle mass may be a major contributor to the production of strength, variations in one or more of the characteristics underlying muscle strength may explain why individuals with similar muscle mass do not necessarily have similar muscle strength and, consequently, do not have similar risks of having impairments (43).

Neural factors can partly contribute to the dissociation between muscle mass and muscle function (44, 45). However most of this dissociation may possibly be elucidated by muscle-specific factors, besides muscle quantity, and variations in its intrinsic capacity to generate strength, *i.e.*, its quality. Although muscle quality is commonly simply calculated as the ratio of muscle strength or power per unit of muscle mass, it actually includes several muscle features such as the lipid content (46), as well as the ability of connective tissues to transmit the strength fabricated by contractile tissues, which influences the quality of the muscle (47).

When compared with muscle mass or strength, the muscle´s ability to function represented by muscle quality has potential to be a predictor of functional capacity (48). The Concord Health and Ageing in Men Project (CHAMP) study showed that, muscle quality or muscle strength, was a strong marker of disability and physical function since it was found to be the most useful indicator of age-related changes in muscle (49).

According to the "Health, Aging, and Body Composition" study (50), where data from 2307 men and women was collected, an increase in fat mass was positively associated with muscle mass and muscle strength but was negatively associated with muscle quality. In fact, higher muscle mass or muscle strength with excess fat may impair muscle quality, which may misclassify sarcopenic or sarcopenic obese patients as non-sarcopenic patients since muscle strength and muscle mass are usually the first parameters to be evaluated (38).

As reported by the results of three previous studies (43, 48, 51), muscle mass is inversely associated with muscle quality in young and also elderly persons. The inverse association that was observed between muscle mass and muscle quality indicates that the organization of the factors involved in muscle quality is negatively influenced by muscle mass itself. Therefore, higher muscle mass compromises this organization and, consequently, its own quality (43).

3.2 Fat Infiltration in the Muscle

Muscle quality has been shown to decline continuously with age, potentially as a result of neurological derangements, fat infiltration, and proportion of type II muscle fiber (52, 53) – that can be divided in to type IIA and type IIB fibers. The type IIA (fast oxidative fibers) can produce relatively high amounts of tension and do not fatigue quickly (54). They are used primarily for movements, such as walking. The type IIB (fast glycolytic fibers), unlike the others, fatigue quickly and are used to produce rapid, forceful contractions to make quick, powerful movements (54).

Age-related changes in body composition can affect muscle performance both functionally and physiologically. Physiologically, with aging the density of skeletal muscle reduces, indicating lipid accumulation in the muscle which can actually derange muscle functioning (19).

The fat infiltration in the muscle or intermuscular adipose tissue (IMAT) has emerged as an important factor supporting muscle quality and also may be a predictor of

muscle function in older adults (55). IMAT is typically the general definition of fatty infiltration in the muscle referring to storage of lipids in adipocytes underneath the deep fascia of the muscle. This includes the visible storage of lipids in adipocytes located between the muscle fibers, also termed intramuscular fat, and also between muscle groups, intermuscular fat (56).

A reduction in the number of mitochondria and elevated production of reactive oxygen species occur in muscle following the deposition of intramyocellular lipids (57). This process can impair muscle function and might reduce the oxidative capacity of the muscle (57).

A consistent body of evidence supports IMAT as a notable predictor of both muscle and mobility function in older adults suggesting that increased IMAT may at least partially explain a loss of strength and mobility seen with aging (56). Older adults with higher levels of IMAT in the legs have lower muscle strength as well as muscle quality (56).

The relationship of increased levels of IMAT and decreased strength and muscle quality is reported in multiple studies in the thigh and calf muscles, in healthy elders, and in adults with comorbid conditions including diabetes (58). Several authors have implied that IMAT is an unavoidable consequence of aging as several studies have reported significant positive relationships between aging and IMAT (56, 59).

Since IMAT is in close proximity to the muscle fibers, it is possible that IMAT may interact with muscle fibers through a still unknown pathway leading to muscle dysfunction and insulin resistance (58). The link between IMAT and insulin resistance could be theoretically attributed to the association of IMAT and body mass index (BMI). Generally, as BMI increases so does IMAT and this will lower the quality of the muscle increasing the risk of sarcopenia and/or sarcopenic obesity (58).

Muscle dysfunction, *i.e.*, decreased muscle strength and muscle quality, may lead to further inactivity and increased levels of IMAT precipitating a cycle of increased IMAT, insulin resistance and muscle dysfunction (58).

3.3 Assessment of Muscle Quality in Sarcopenia and Sarcopenic Obesity

Although several methods, such as DXA, BIA and MRI have been used for the assessment of muscle quality, CT represents the gold standard and the most accurate imaging method to provide an exact measurement of total cross-sectional area, muscle density, and intramuscular adipose tissue. CT is characterized by being a fast imaging method that uses X-rays for an indirect measurement of IMAT based on the tissue density of an area (60).

CT was actually the first method introduced that could quantify whole-body and regional skeletal muscle mass with high precision (60).

Particularly, age-related muscle loss is predominantly detected at the specific body site - thigh muscle - and the assessment of site-specific muscle quality such as thigh muscle is critical to determine functional mobility as well as healthy life expectancy (61, 62). Although CT is widely used as the gold standard for diagnosis, this tool was not frequently used in primary diagnosis and treatment because of high costs and limited availability of equipment.

Nevertheless, with ever-increasing requirements to assess the architecture and tissue composition in sarcopenia and to identify this condition in preliminary diagnosis, high-resolution CT is predicted to be generally utilized in future clinical practice and in research areas (48).

Muscle biopsy is also a procedure that can be used in assessing muscle quality. This is a procedure normally indicated in the diagnosis of diseases involving muscle tissue. Part of the tissue and cells from a specific muscle are removed and viewed microscopically (63). This procedure grants the analysis of muscle fibers, capillaries and satellite cells which can tell us if the muscle quality is compromise (64). However, muscle biopsy is an invasive technique so it´s not commonly used in clinical practice, particularly for the diagnosis of sarcopenia and sarcopenic obesity (63).

There is also evidence showing that changes in specific sites of the muscle quality, thigh muscle, have been associated with impaired mobility and other chronic diseases (48, 65). The major findings in a previous study indicated that sarcopenic participants exhibited lower site-specific thigh muscle quality including parameters such as, total muscle volume, isometric muscle strength, and intramuscular adipose tissue in comparison with non-sarcopenic participants. Alongside weak functional fitness level, poor muscle quality is often identified in older adults with sarcopenia which emphasizes

The potential usefulness of muscle quality assessment in the identification of this syndrome (48).

Muscle quality at the upper and lower body might be estimated using strength measures and apply as a practical prognostic tool, bypassing some limitations of techniques such as CT (18). Individuals with low 'estimated' muscle quality may then be referred for DXA imaging as necessary to confirm or exclude the presence of sarcopenia or sarcopenic obesity (18).

3.3.1Advantages of the assessment of muscle quality in sarcopenia and sarcopenic obesity

Muscle quality reflects several muscle characteristics which can allow a thorough assessment of the presence of sarcopenia or sarcopenic obesity (43).

Muscle quality is a reliable marker of functional capacity - and actually quantifies muscle mass and muscle strength as a single unit (38). Also, the deterioration of muscle quality may precede the loss of muscle mass. Therefore, in clinical practice, the assessment of muscle quality can be beneficial for early identification of sarcopenia or sarcopenic obesity (66).

In general, muscle quality assessment is a very specific and informative parameter, allowing the identification and even the prevention of sarcopenia and/or sarcopenic obesity.

3.3.2 Limitations of muscle quality in sarcopenia and sarcopenic obesity

Even though muscle quality has the potential to be a relevant criterion in the diagnosis of sarcopenia and sarcopenic obesity, this parameter presents several of limitations. The techniques for assessing muscle quality, particularly CT, are invasive and requires sophisticated tools that are of limited access, besides high cost, exposure to radiation and the need for highly qualified professionals, which impairs the wider use of these techniques in clinical practice (14, 43).

4. Discussion

Muscle quality reflects the muscle's ability to function and it is defined as muscle strength or power per unit of muscle mass. Not with standing this, no consensus definition of muscle quality presently exists. Moreover, there are still many gaps in the information on this parameter as a diagnostic criterion for sarcopenia and sarcopenic obesity.

The majority of current studies on muscle quality focus on older adults aged 65 years. Thus, more research involving other age groups would be enlightening since muscle quality may be used in early identification of sarcopenia and sarcopenic obesity. Currently, data on the primary determinants of muscle quality in middle-aged adults are also scarce (17).

The development of muscle quality assessment tools that encompasses muscle quality and which is sensitive to small changes within muscle that precede a diminish in muscle function would allow to identify the risk of sarcopenia or sarcopenic obesity (17). Non-invasive imaging of muscle such as imaging methods may identify multiple factors related to muscle quality, namely composition, size, intramuscular lipid and fibrosis in the research setting. However, because of the high-cost, these methods are not suitable to assess muscle quality for routine in clinical practice (17).

Nevertheless, a multi-dimensional approach of the factors that contribute to muscle quality, may lead to improved efforts in identifying risk factors and developing effective treatments for functional impairments.

By measuring muscle quality, strategies such as the use of emerging technology or alternative measurements (e.g strength measures) to early identify individuals at 'high risk' of functional decline can be developed and more intensive care and interventions can be executed. Moreover the widespread use of muscle quality as a diagnosis criterion would allow a more robust definition of sarcopenia or sarcopenic obesity.

In conclusion, muscle quality assessment is a promisor parameter for the diagnosis of sarcopenia and sarcopenic obesity, particularly in early stages of these conditions. However, more research is needed concerning muscle quality as a diagnostic criterion for sarcopenia and sarcopenic obesity, since, although there are several

available techniques for the assessment of this parameter, there is still no suitable method for routine use in clinical practice.

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6. Figures

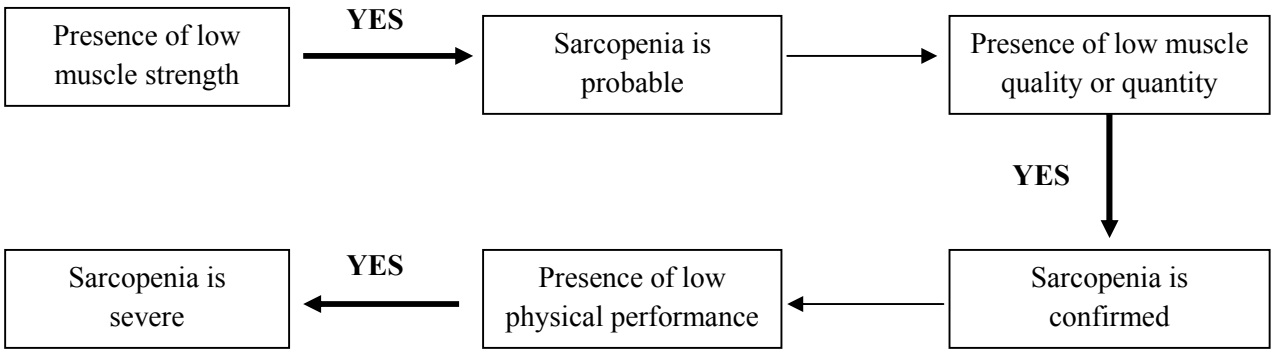

Fig.2 – Algorithm for case-finding, making a diagnosis and quantifying severity of sarcopenia in practice, adapted from EWGSOP2 (11)