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Review Article

Sarcopenic Obesity: Time to Meet the Challenge

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Keywords

Obesity · Sarcopenia · Skeletal muscle

Abstract

The prevalence of overweight and obesity has reached epidemic proportions worldwide due to increasingly pervasive obesogenic lifestyle changes. Obesity poses unprecedented individual, social, and multidisciplinary medical challenges by increasing the risk for metabolic diseases, chronic organ failures, and cancer as well as complication rates in the presence of acute disease conditions. Whereas reducing excess adiposity remains the fundamental pathogenic treatment for obese individuals, complex metabolic and lifestyle abnormalities as well as weight reduction therapies per se may also compromise the ability to preserve muscle function and mass, especially when chronic disease co-exists with obesity. Emerging evidence

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indicates that low muscle mass and quality have a strong negative prognostic impact in obese individuals and may lead to frailty, disability, and increased morbidity and mortality. Awareness of the importance of skeletal muscle maintenance in obesity is however low among clinicians and scientists. The term ‘sarcopenic obesity’ has been proposed to identify obesity with low skeletal muscle function and mass, but its utilization is largely limited to the aging patient population, and consensus on its definition and diagnostic criteria remains insufficient. Knowledge on prevalence of sarcopenic obesity in various clinical conditions and patient subgroups, on its clinical impacts in patient risk stratification, and on effective prevention and treatment strategies remain therefore dramatically inadequate. In particular, optimal dietary options and medical nutritional support strategies to preserve muscle mass in obese individuals remain largely undefined. The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) recognize and indicate obesity with altered body composition due to low skeletal muscle function and mass (sarcopenic obesity) as a scientific and clinical priority for researchers and clinicians. ESPEN and EASO therefore call for coordinated action aimed at reaching consensus on its definition, diagnostic criteria, and optimal treatment with particular regard to nutritional therapy. We are convinced that achievement of these goals has a strong potential to reduce the burden of morbidity and mortality in the rapidly increasing obese patient population.

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Introduction: What We Know

Obesity Epidemic

Obesity is a disease characterized by increased adiposity with negative impact on patient health, and it is commonly diagnosed by body mass index (BMI) above 30 kg/m² (or above 27.5 kg/m² in specific ethnic groups). Its prevalence has rapidly increased worldwide over the last three decades, largely due to combined genetic predisposition and profound lifestyle changes including sedentary habits and high-calorie dietary intake [1–3]. In many parts of the world, overweight (BMI > 25 kg/m²) and obese individuals currently account for a majority of the population [3–6]; the proportion is substantially higher in middle- and elderly age groups [7, 8]. This unprecedented shift in body weight paradigms has posed dramatic individual, social, economic and healthcare challenges. Obesity is a strong risk factor for metabolic diseases such as metabolic syndrome and type 2 diabetes as well as atherosclerosis and cardiovascular events [9, 10]. In addition, obese individuals are at higher risk for many chronic and acute diseases involving end-stage organ failures, cancer, and infections [9–12]. For example, overweight and obese patients carry an at least 70% higher risk for coronary disease and a 20–50% higher risk of developing wound infections after colorectal surgery compared to normal-weight patients [13]. Liver steatosis, cirrhosis, and cancer becomes a raising challenge for patients with long-standing obesity [14]. All the above conditions may lead to acute complications and hospitalizations.

Obesity and Skeletal Muscle

Reducing excess adiposity remains the fundamental pathogenic treatment for obese individuals [15, 16]. Complex metabolic and lifestyle abnormalities [17–22] as well as weight reduction therapies per se [23] may however also compromise the ability to preserve muscle function and mass. Skeletal muscle changes are not uniformly observed in obese individuals, and heterogeneous phenotypes may contribute to their underestimation. Indeed a positive association between BMI and lean body mass has been reported in general population studies

[23], and moderate increments in skeletal muscle mass may occur in obesity as a consequence of higher postural and ambulatory muscle work as well as potential direct anabolic effects of higher dietary intake of calorie proteins. It is however increasingly clear that profound skeletal muscle metabolism changes may occur in obesity and may lead to altered body composition with higher fat mass and substantial impairment of muscle mass and quality [24–27]. Various complex interrelated mechanisms may contribute to these changes.

Metabolic and Lifestyle Changes

- (1) *Primary Metabolic Abnormalities*: Clustered metabolic derangements including systemic and muscle oxidative stress, inflammation and insulin resistance may occur in obesity [17–20] due to various causes that primarily include i) excess nutrient availability and tissue delivery, particularly saturated fat [28] and glucose [29] as well as ii) adipose tissue dysfunction upon activation of maladaptive responses in the presence of enhanced demand for lipid storage [30]. These alterations are at least in part causally interrelated and have a strong muscle-catabolic potential [31]; they can also promote a typical ‘anabolic resistance’ state in skeletal muscle, meaning that the response of muscle protein synthesis to nutrients is blunted [24–27].
- (2) *Ectopic Muscle Fat Accumulation*: Muscle lipid accumulation commonly occurs [30] as a result of insufficient adipose tissue expansion in the face of excess lipid availability [32]; convincing evidence has long demonstrated the close association of skeletal muscle lipid content with tissue and systemic insulin resistance [30, 33]. Mechanisms mediating metabolic lipotoxicity are complex and appear to include direct pro-oxidative and inflammatory activities [28] as well as accumulation of metabolically toxic lipid moieties such as diacylglycerol and ceramides [34]. Recent evidences show that ectopic lipid deposition may also compromise muscle protein turnover [35].
- (3) *Mitochondrial Dysfunction*: Mitochondrial changes are not invariably observed in obese skeletal muscle until relatively late stages [21, 22]. Their onset may however exacerbate oxidative stress and related metabolic cascades leading to insulin resistance and catabolism [21, 22]. Potential reduction in ATP production may also directly result in low muscle strength and endurance capacity.
- (4) *Stem Cell Dysfunction*: Functionally altered muscle stem cells that may undergo adipocyte differentiation are increasingly described in the context of complicated obesity and muscle fat accumulation [36–38], and their potential relevant role in limiting skeletal muscle mass maintenance has been proposed.
- (5) *Physical Inactivity*: Low physical activity is one fundamental contributor to positive energy balance [22]. Progressive reduction of physical activity is further observed with disease progression due to worsening obesity and its joint and musculoskeletal complications [22], with direct negative impact on muscle protein turnover and muscle oxidative and performance capacity [39, 40].

Comorbidities and Treatment

- (1) *Cardiometabolic Complications*: Complications such as metabolic syndrome or overt type 2 diabetes and hyperglycemia are associated with enhanced oxidative stress, pro-inflammatory changes, and mitochondrial dysfunction [21, 29] that commonly cause catabolic abnormalities and may independently further muscle alterations. Altered tissue perfusion in the presence or absence of clinically relevant atherosclerotic disease as well as epicardial fat enlargement may also cause metabolic complications by enhancing ROS production and their negative metabolic impact [41, 42].
- (2) *Chronic and Acute Complications*: Obesity directly enhances the risk for, or may be associated with chronic organ failure syndromes and chronic diseases (including chronic

heart failure, chronic kidney disease, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, and cancer) as well as their acute complications [10–12]. All of the above events and conditions may result in heterogeneous sources of inflammation and oxidative stress [43–48] while impairing spontaneous physical activity, thereby synergistically enhancing muscle loss and dysfunction [49].

- (3) *Surgical and Medical Treatment*: Bariatric procedures are becoming increasingly common and almost invariably lead to skeletal muscle catabolism, at least in the initial rapid weight loss phase, characterized by profoundly negative energy balance [50]; low- or very-low-calorie diets are associated with similar qualitative changes although to less pronounced degrees [23, 51].

A multifactorial network of clustered alterations therefore appears to occur in obesity that may account for skeletal muscle derangements. While these changes are not inevitable, they become increasingly likely in patients with longer obesity duration, complications, and comorbidities as well as in elderly individuals that may undergo muscle changes also due to aging per se [52]. Most mechanisms directly reduce muscle anabolism, thereby reducing muscle mass as previously described [24–27]. In addition, several alterations have a negative impact on muscle quality in terms of strength per muscle unit and endurance capacity. The latter include muscle fat accumulation that reduces muscle density and quality with lower contractile protein content per unit tissue [35, 53, 54], mitochondrial dysfunction that may cause impaired ATP production, and maximal oxygen consumption leading to both reduced strength and endurance [21]. Physical inactivity that reduces muscle mass, mitochondrial biogenesis and function, and tissue lipid oxidation, also leads to reduced strength and endurance potentially enhancing tissue and systemic inflammation and oxidative stress [39, 40, 55].

Skeletal Muscle Changes and Outcome

A profound negative clinical impact of low skeletal muscle function and mass is unequivocally emerging in many disease conditions and in aging [52, 56, 57]. A similar negative impact is also emerging in obesity despite potential difficulties in identifying and defining muscle changes within the obese phenotype [58–60]. Available studies indeed described muscle changes through heterogeneous definitions and methodologies including body composition analysis, muscle strength, or cardiorespiratory fitness and physical capacity [61–64]. With this limitation in mind, obese individuals with low muscle mass or functional parameters had higher risk of developing frailty and disability, and therefore poor quality of life [65, 66]. Risk for frailty and disability in obese individuals with low muscle function and mass has been reported to be significantly higher than that observed in non-obese counterparts with similar muscle alterations [65]. This could appear as contradictory to the so-called ‘obesity paradox’, but it means that obesity does not protect from chronic disease-related mortality when it is associated with sarcopenia. Indeed low or declining muscle mass is emerging as a negative prognostic factor associated with higher morbidity and mortality in obese patients with chronic diseases [67, 68]. Obese individuals with gastrointestinal cancers and low muscle mass accordingly had higher risk of dying than matched obese patients without muscle abnormalities [68]. In obese heart failure patients, low physical capacity also predicted poor outcome [62]. In chronic kidney disease patients, direction of changes in muscle mass was the major determinant of survival independently of direction of changes of total body weight [70]. We conclude that i) available evidence, despite limitations and heterogeneity, points towards an important role of skeletal muscle changes with altered function and mass in negatively modulating obese patient morbidity and mortality; and that ii) preventing and/or treating muscle changes has therefore relevant potential to improve obesity-associated morbidity and mortality.

Table 1. The following areas are identified as suffering from limitations in knowledge and/or consensus and are proposed for focused, coordinated action in obese individuals with low muscle function and mass

Sarcopenic obesity: limitations and needs

Basic knowledge
Diagnostic tools
Diagnostic criteria
Prevention and treatment
Patient subgroup and clinical settings definition

Where We Are – Sarcopenic Obesity: Limitations and Needs

Low muscle function and mass are currently addressed in obese individuals under the definition of sarcopenic obesity. The latter is based on the originally geriatric concept of sarcopenia, i.e. the age-associated combination of declining muscle mass and function (particularly muscle strength) [52]. A definition of primary, age-associated sarcopenia and corresponding diagnostic criteria have been proposed [52], but relevant methodological issues and clinical thresholds for defining criteria remain under debate. The current definitions of sarcopenic obesity combine sarcopenia, as defined through variable criteria, with the presence of obesity either defined as BMI > 30 kg/m² or by adiposity levels [61, 71–73]. We believe that these concepts and available results represent important starting points, but do not currently allow for satisfactory patient identification, clinical stratification, and thus treatment. As a direct consequence, awareness of the relevance of skeletal muscle maintenance in obesity remains inadequate among researchers and clinicians. We specifically identify the following limitations and needs (table 1).

Basic Knowledge

- *Limitations:* Although several mediators and metabolic pathways involved in the onset of skeletal muscle catabolism and anabolic dysfunction have been elucidated, knowledge remains incomplete.
- *Needs:* Research should continue to elucidate fundamental issues in terms of molecular and endocrine mediators regulating skeletal muscle function and mass as well as amino acid metabolism, with particular regard to cross-talk and interactions between skeletal muscle and adipose tissue also at stem cell level. Additional important areas include mediators of positive effects of exercise, the role of gut hormonal systems and microbiota metabolism and their nutritional regulation in altering skeletal muscle homeostasis with potential muscle-catabolic systemic alterations [74], the role of brain regulation of physical and skeletal muscle activities [75]. Also importantly, research should aim at elucidating potential disease-specific mechanisms that could interact with obesity in regard to negatively affecting muscle function and mass in the presence of various complications and comorbidities.

Patient Groups and Clinical Settings

- *Limitations:* The concept of sarcopenia and sarcopenic obesity have been primarily defined and applied in geriatric populations [8, 52, 65]. Although the parallel concept of secondary sarcopenia was introduced to refer to all-cause early onset of muscle loss and dysfunction, we are convinced that substantial work is needed to enhance awareness of the strong risk for muscle changes in obese individuals at any age.
- *Needs:* Awareness of the risk of muscle changes should be particularly promoted at any age for obese individuals in the presence of metabolic complications, chronic comorbidities,

acute or critical illness, and following bariatric surgery or hypocaloric diet. Disability and frailty may occur in obese geriatric and non-geriatric patients and should be evaluated through medical history and clinical assessment in obese individuals at risk for, or already presenting with, clinical comorbidities. It should also be pointed out that patient characteristics and therapeutic needs for low muscle function and mass may vary substantially in different settings; this fundamental issue should be appropriately recognized and addressed.

Diagnostic Tools

- *Limitations:* As mentioned above, identification of diagnostic tools to measure skeletal muscle and fat mass as well as skeletal muscle function has proven generally problematic, particularly in terms of combining precision, safety, and routine applicability in clinical practice. It should be pointed out that simple anthropometric measurements may be biased in obese individuals by confounding adipose depots. Radiological methodologies that include nuclear magnetic resonance spectroscopy, selected CT scans or dual energy X-ray absorptiometry (DEXA) have been considered potentially most accurate but are not readily available and may involve X-ray exposure [64]. Bioelectrical impedance analysis has been considered and proposed as a potential acceptable compromise in terms of invasiveness, accuracy, and applicability in the absence of confounding fluid balance abnormalities [76, 77]. Functional measures also are heterogeneous and include hand-grip, knee extensor strength, and various mobility measurements involving postural or walking tests [64].
- *Needs:* There is obviously no ideal methodology to simultaneously achieve maximal precision, safety, and routine applicability. Since the latter is ultimately sought, surrogate markers may have to be accepted as reasonable compromises (e.g. as similarly applied for waist circumference relative to abdominal visceral fat). To reach larger consensus on diagnostic tools, homogeneous datasets should be ideally evaluated or created to identify gold standard techniques and corresponding acceptable, readily applicable surrogate markers. Although apparently adding to complexity, such efforts should also aim at evaluating homogeneous patient groups, and potential different optimal approaches in different patient groups should be considered.

Diagnostic Criteria

- *Limitations:* Diagnostic criteria for obesity with low muscle function and mass currently suffer from lack of widespread consensus on diagnostic tools and related difficulties in comparing different outcome measures in different studies [61, 71–73]. Normalization of available outcomes into indexes attempting to normalize measured information may be appropriate, but it also may result in enhanced variability. Application of different criteria to identify sarcopenic obesity may therefore currently lead to substantially and, unfortunately, clinically unacceptable variable prevalence levels.
- *Needs:* Overcoming lack of consensus will likely require further evaluation or creation of databases that should be ideally acquired in the context of homogeneous methodologies and designs. Systematic efforts to integrate measurements of both muscle and fat mass and their relationships, as well as their body distribution, in the concept of sarcopenic obesity are also missing [77, 78]. We believe that such efforts should also be undertaken, based on evidence of fundamental pathogenetic inter-relationships between adipose and skeletal muscle mass, distribution, and function.

Prevention and Treatment

- **Limitations:** Under the above-described conditions it is perhaps not surprising that prevention and treatment of low muscle function and mass in obese individuals are both difficult and under-implemented. Multimodal therapeutic strategies should include physical activity and nutrition [79–82] that should in turn offers adequate high-quality protein intake [83, 84] or protein / amino acid administration in patients in need of medical nutrition [83–85]. As previously discussed, heterogeneity in patients groups, treatment protocols, and outcome measures make it difficult to compare and interpret study results. Use of nutraceuticals to stimulate anabolism beyond anabolic resistance has also been advocated and tested, but variable protocols, treatment duration, and dose prevent final conclusions on their efficacy [86].
- **Needs:** Identification of optimal prevention and treatment modalities aimed at preserving and increasing skeletal muscle function and mass in obesity is of urgent priority, and potential use of nutraceuticals besides optimal macronutrient composition should be specifically addressed [86]. It should however be pointed out that, despite gaps and limitations in knowledge, a large and growing body of evidence provides strong support for an association of protein and amino acid intake as well as skeletal muscle anabolism with maintenance of lean body mass [83, 84]. It therefore seems that routinely recommending and ensuring adequate protein intake of 1 g/kg ideal body weight per day as recommended intake in healthy non-geriatric populations is reasonable and safe, with higher amounts for high-risk patient groups in the absence of contraindications (see paragraph below). We also need to emphasize that exercise training or physical therapy have repeatedly been proven effective in improving muscle function and mass, and appropriate and safe exercise levels relative to the level of comorbidities and disabilities should be routinely recommended in obese patients [80–82].

Current Approach – What We Can Do

We are aware that existing limitations in current approaches to obese individuals with low muscle function and mass must not limit our efforts to provide the best possible clinical assessment and treatment. We propose the following approaches:

- **Awareness:** We believe that risk of skeletal muscle loss and dysfunction should be considered in obese patients, particularly in the presence of advanced age (>65 years) or when concomitant metabolic complications, chronic diseases, or acute complications occur. Efforts should be made to monitor skeletal muscle function and mass and to prevent or minimize its loss in patients undergoing bariatric surgery procedures, with particular regard to malabsorptive ones, and in those undergoing hypocaloric dietary treatment particularly in the presence of advanced age and/or comorbidities. It may also concern patients recovering from critical illness or after long immobilization as in ICU [48], as well as patients suffering from specific endocrine disorders (diabetes, hypogonadism, Cushing syndrome, or long-term glucocorticoid treatment).
- **Assessment – Skeletal Muscle Function and Mass, Functional Status and Disabilities:** When loss of skeletal muscle mass and/or function is suspected or appears likely based on medical history and examination, clinical assessment should include measurement of body composition and muscle strength by available techniques, such as bioelectrical impedance analysis, handgrip test or walking test. Such information may be useful not only for identification of muscle changes but also for longitudinal patient monitoring over time. We support the concept that global assessment of obese individuals should include functional status, particularly in the presence of complications and comorbidities.

- The recently proposed Edmonton obesity staging system [87] provides a potential example of staging tools including disability assessment that may in turn largely reflect loss of skeletal muscle function and mass. Presence of components of frailty could also be assessed to the same purpose not only in elderly individuals but in all at-risk patients.
- *Prevention and Treatment – Nutrition and Physical Activity:* In patients with clinical evidence for loss of skeletal muscle function and mass or in those with at-risk conditions such as metabolic complications, chronic and acute disease and advanced age as well as in those undergoing weight loss programs, treatment should be associated with precautions to prevent, limit, or treat skeletal muscle alterations. Such approaches should include nutritional care and physical exercise. Based on available evidence [83, 84], adequate protein intake of 1 g/kg ideal body weight per day should be provided in healthy non-geriatric individuals. In addition, higher protein intakes are increasingly recommended by guidelines and expert groups for high-risk patients. The latter include aged individuals and hemodialysis patients [83]. Obese ICU patients undergoing acute metabolic stress with likely substantial muscle loss and weakness have been specifically addressed in recent guidelines with recommendations of very high protein intakes of up to 2.2 g/kg day through medical nutritional support [84]. Hypocaloric diets with unbalanced macronutrient composition and higher protein levels are considered acceptable by recent guidelines [15, 16] and could become more routinely recommended particularly in patients with low muscle function and mass in need to undergo weight loss treatment, or in those at higher risk of developing such changes during weight loss. Oral protein supplements should be considered when sufficient dietary intake is not possible [88]. As previously anticipated, appropriate and safe exercise levels relative to comorbidities and disabilities should be routinely implemented. Physical support rehabilitation should finally be implemented whenever possible according to patient status [89].

Conclusion: A Call for Action

The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) recognize and indicate obesity with altered body composition due to low skeletal muscle function and mass (sarcopenic obesity) as a scientific and clinical priority. ESPEN and EASO therefore call for coordinated action aimed at increasing awareness on this topic among researchers and clinicians, and at promoting research and initiatives aimed at reaching evidence-based consensus on diagnostic tools, definition, and diagnostic criteria as well as optimal treatment. ESPEN and EASO aim at directly contributing by promoting the topic in workshops, meeting sessions and educational initiatives, by fostering networking and collaboration among interested scientists and experts, and by promoting awareness and disseminating evidence on best available diagnostic tools and on treatment options with particular regard to diet and medical nutritional support. We are convinced that achievement of these goals has a strong potential to reduce the burden of morbidity and mortality in the dramatically increasing obese patient population across all medical specialties.

Disclosure Statement

The authors have no conflicts of interest to declare relative to the current work.

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