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Sarcopenic obesity research perspectives outlined by the Sarcopenic Obesity Global Leadership Initiative (SOGLI) – proceedings from the SOGLI Consortium meeting in Rome November 2022

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Summary

The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) launched the Sarcopenic Obesity Global Leadership Initiative (SOGLI) to reach expert consensus on a definition and diagnostic criteria for Sarcopenic Obesity (SO).

The present paper describes the proceeding of the Sarcopenic Obesity Global Leadership Initiative (SOGLI) meeting that was held on November 25th and 26th, 2022 in Rome, Italy. This consortium involved the participation of 50 researchers from different geographic regions and countries.

The document outlines an agenda advocated by the SOGLI expert panel regarding the pathophysiology, screening, diagnosis, staging and treatment of SO that needs to be prioritized for future research in the field.

Key words: sarcopenic obesity, obesity, sarcopenia, consensus

Introduction

The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) launched the Sarcopenic Obesity Global Leadership Initiative (SOGLI) to reach an expert consensus on the definition and the diagnostic criteria for Sarcopenic Obesity (SO) (1-3). The jointly appointed international expert panel proposed that SO is defined as the co-existence of excess adiposity and low muscle mass/function (4, 5). The diagnosis of SO should be considered in at-risk individuals who screen positive for co-existing surrogate markers of excess adiposity, such as elevated body mass index (BMI) or waist circumference (WC), and factors suggestive of low skeletal muscle mass and function (accepted risk factors, clinical symptoms, or validated questionnaires). Diagnostic procedures should initially include assessment of skeletal muscle function, followed by the assessment of body composition where the presence of excess adiposity and low skeletal muscle mass or related body compartments (fat-free mass, lean mass, appendicular lean mass) would confirm the diagnosis of SO. Individuals with SO should be further stratified into Stage I in the absence of clinical complications, or Stage II if SO is associated with complications linked to altered body composition or skeletal muscle dysfunction. To study the predictive value, treatment efficacy, and clinical impact of this new SO definition (4, 5) ESPEN and EASO encouraged prospective cohort studies and clinical trials in addition to secondary analysis of existing datasets. The aim of the present document is to outline future research agenda laid forth and advocated by the panel that should be prioritized in the SO field. The present paper represents the proceeding of the Sarcopenic Obesity Global Leadership Initiative (SOGLI) event that was held in November 2022 in Rome (Italy) and that involved 50 researchers from different research areas, coming from different geographic regions and countries.

a. Pathophysiology of sarcopenic obesity

SO is characterized by the combination of obesity, defined by high body fat percentage or fat mass index (FM in kg/m^2), and sarcopenia, defined as low muscle function accompanied by low skeletal muscle mass. In several conditions, including aging as well as chronic diseases across the lifespan, SO has been associated with poorer health outcomes than sarcopenia and obesity alone. SO therefore needs to be considered as a unique clinical condition, as its effect on clinical outcomes differ from those associated with obesity or sarcopenia per se. Early evidence suggests that SO can reduce a patient's quality of life to a larger extent than sarcopenia, obesity or even the sum of their separate effects (6). This is due to the existence of: 1) negative interaction and vicious cycling between body fat mass (FM) accumulation/dysfunction and the loss of skeletal muscle mass and function; and, 2) negative clinical interactions between obesity and sarcopenia, leading to synergistically higher risk for metabolic disease and functional impairment in SO compared to those caused by cumulative risk from each condition (7, 8). The consensus on SO (4, 5) supported that current definitions of obesity and sarcopenia should not be automatically applied to define SO. In

particular, sarcopenia has been defined as low skeletal muscle function and mass (appendicular lean mass in age related primary sarcopenia) (9), but muscle changes should be considered in the context of obesity and related to high fat and total body mass. Further research on the role of each factor and mechanism in SO, as well as on their interactions may lead to better understanding of the complex pathophysiology of this condition, with the potential to favour improved tools and define new targets for identifying and treating subjects at higher risk.

Suggestions for future research

1. The role of hormonal status on the pathogenesis and the pathophysiology of SO needs to be explored in detail. Hypercortisolism has been suggested as a clinical model for SO (10), testosterone deficiency contributes to loss of muscle and bone as well as fat accumulation (11); impairment of the GH/IGF-1 axis may be associated to the risk of the development of SO and ectopic fat deposition in the liver (12).
2. Definition and differentiation of primary from secondary SO should represent a topic for future research. Primary SO is related to aging as a cluster of risk factors for inevitable, progressive muscle loss with fat accumulation, or to sedentary lifestyle and poor dietary intake, or to direct negative impact of adipose tissue-induced inflammation on muscle mass. Secondary SO is due to the simultaneous presence of obesity as potential accelerating factor, and acute or chronic diseases which may provide the major pathophysiological background for the condition, with vicious cycling leading to muscle catabolism, low physical activity, poor dietary intake and gain of FM. The relevance of differentiating primary from secondary SO still needs to be assessed, and a clinical definition and approach could result from future research. The relevance of a healthy dietary pattern with adequate intake of proteins and other nutrients (e.g., vitamin D, magnesium), with probably different requirements for healthy aging or in the context of specific diseases, should however be considered as an urgent research goal. Moreover, as aging is also frequently associated with the onset and progression of chronic diseases (13), distinguishing the relative contribution of these two factors to SO may be challenging in older people. In this context, while differentiating chronological from biological age may be considered as a strategy to better identify primary vs. secondary SO, currently no cut-point values or universally accepted parameters are available to this aim. Nevertheless, robust evidence shows that senescent cells are associated to an aged-like inflamed niche that mirrors inflammation associated with ageing and delays regeneration (14). Furthermore, limiting senescence with senolytics ameliorates muscle wasting and strength in an experimental model of chronic disease (15).

3. Assessing metabolic perturbations in adipose tissue and skeletal muscle, as well as the interorgan crosstalk in patients with SO, is necessary to identify key pathways involved in the development of SO. Sarcopenia indeed contributes to lower physical activity and energy expenditure, possibly favouring increased adiposity with a resulting vicious cycle including muscle fat deposition. The specific role of muscle lipid deposition, both intramuscular and intramyocellular, in the onset and progression of SO should also be addressed, as it may promote lipotoxicity, with pro-inflammatory cascade and oxidative stress, altered mitophagy and mitochondrial dysfunction, impaired insulin signalling, and loss of muscle mass and function (16, 17). As several studies show that obesity is associated with muscle anabolic resistance (18, 19), further studies should also better clarify the potential relevance of these mechanisms in SO development.
4. Evidence shows that weight loss induced by several causes, including hypocaloric diets, bariatric surgery, medications, and chronic diseases involve the loss of both fat and muscle mass~~es~~, as well as muscle function. Subsequent weight regain may result in an unfavourable shift in body composition with relatively larger increases in fat mass compared to lean mass (20). Further research should focus on the identification of effective strategies, including combinations of exercise and nutrition interventions, to counteract muscle mass loss during weight loss and to prevent excessive FM weight gain or prevent the development of SO during weight regain. The preservation of muscle mass and function during weight loss is particularly relevant, since muscle is needed to adopt and implement exercise as an intervention against fat regain, such as in the case of visceral fat accumulation after bariatric surgery.
5. Derangements in neuromuscular junction (NMJ) efficiency have been previously demonstrated in obesity-independent, age-related sarcopenia (21). Whether NMJ alterations contribute mechanistically to SO needs to be elucidated in future research. Age-related loss of innervation, contributing to sarcopenia (22) and obesity-related defects at NMJ (23) have been indeed reported, but no studies are currently available on the nerve-muscle crosstalk in SO. Recently, denervation has been spotlighted to occur in inflammatory-based muscle wasting conditions such as cancer cachexia (24, 25), where fat has been shown to contribute to the chronic inflammation (26) similarly to what observed in SO (27).
6. The emerging role of potential negative interactions and cross-talk between bone and muscle and adipose tissue should be further analysed. Osteopenia-osteoporosis, sarcopenia and fat accumulation with overweight or obesity are commonly associated in the aging process. Furthermore, recent evidence suggests interconnection of these syndromes, with overlapping pathophysiological features (28).

7. The role of the variations in daily energy expenditure (EE) in the pathogenesis of SO should be better analysed. Fat-free mass accounts for up to ~70% of inter-individual variance in daily EE in non-exercise conditions; any sarcopenia-related changes in lean mass may induce changes in the rate of energy expenditure. It has been shown that reduced daily EE predicts future weight gain (29), indicating the relevance of EE in body weight homeostasis. The rate of whole-body EE can be accurately and continuously measured over 24 hours inside the metabolic chamber.
8. Sex differences must be considered while investigating the pathophysiology of SO, since further insights on this issue will certainly impact on the screening and diagnosis of SO in the future. Sex differences in body fat distribution are well established (30). These determine differences in responses to diet (31), metabolism (32), and disease states (33). At the same time, men have larger muscle mass and more glycolytic muscle fibers than women. Sex differences are reported in the development of muscle atrophy: men are more prone to inflammation-mediated atrophy, such as in cachexia, while women are more sensitive to disuse atrophy (34). The fast, glycolytic fibers undergo more pronounced atrophy in cachexia, while the slow, oxidative fibers undergo more pronounced atrophy in disuse. This indicates sex-dependent differences in the onset and development of fiber atrophy (34, 35).

b. Screening for sarcopenic obesity

Screening for SO is based on concomitant presence of high BMI or WC with ethnicity-specific cut-points (36-44) (table 1) and surrogate indicators potential sarcopenia indicators (e.g., clinical symptoms, existing risk factors or validated questionnaires (such as SARC-F in older subjects) (45, 46). The panel proposes adopting cut-points provided by WHO for BMI (38, 44) and the references given by National Institute of Health and Misra et al. for WC, respectively for Caucasian and Asian populations respectively (36, 41, 47). The panel strongly supports the idea that SO screening should be differentiated from diagnosis. Screening should ideally be simple, relying only on easily available instruments that are routinely available in primary care settings. Screening might be setting-specific (e.g., geriatric clinics, oncology departments, etc). Moreover, it should be adopted by health care professionals and patients and be cost-effective (48). The aim of SO screening entails to refer individuals identified at potential risk for further assessment and diagnosing. Rising awareness on the importance of SO in both professionals and the population at large is essential for effective population screening.

Suggestions for future research

1. <u>Waist circumference</u>
    a. Definitions of obesity that are based on BMI cut-points (table 1) are the most widely accepted. However, given the relevance of FM distribution on clinical outcome, additional

evidence should be gathered on the role and relevance of WC, and its relationship with BMI, with respect to SO screening. Further investigation could also assess whether WC could be used to identify a higher risk of SO in subjects with overweight/normal BMI (49, 50).

b. The validity of simple anthropometric equations including WC [e.g., relative fat mass – RFM = 64 - (20 × height/waist circumference) + (12 × sex)] may be evaluated. RFM has been shown to better predict whole-body fat percentage, measured by DXA, among women and men of different ethnicities (51).

c. The ability of WC to differentiate subcutaneous from visceral fat deposition and depots should be improved. WC shows a stronger association with Subcutaneous Adipose Tissue (SAT) than with Visceral Adipose Tissue (VAT), which is more strongly linked to metabolic abnormalities (52). Adjustment of WC to subcutaneous fat thickness (in relation to age) may contribute to reliable estimate of VAT (53). Sagittal abdominal diameter may represent an option for WC that may better indicate visceral fat (54).

d. Normative sex-, ethnicity- and age-specific cut points for BMI and WC to better define visceral obesity should be selected (Table 1) with subsequent prospective cohort studies to test their validity.

e. Potential changes in predictive value from use of continuous vs broad categorical variables should be verified. The association between WC and adverse health risk varies across BMI categories, and using the same WC threshold values for all BMI categories may lead to the loss of important information that affects the ability of WC to predict morbidity and mortality (55).

f. Potential clinical value of adjusting WC for BMI or other factors in order to improve its association with morbidity and mortality should be analysed. In particular, waist-to height ratio may be a reliable and accurate screening tool, as it proved to be for cardiometabolic risk factors in adults (56). However, optimal biological/allometric scaling (the change in relation to proportional changes in body size) for WC in the context of SO remains undefined (57). In general, WC and derived indexes could be as important or even more informative than BMI in persons with lower BMI levels, where elevated WC is more likely to be directly associated with visceral adiposity and increased cardio-metabolic risk) (55).

g. The best protocol for measurement of WC [at the level of iliac crest (NIH) or midpoint between the last rib and iliac crest (WHO) or immediately below the lowest rib at the narrowest waist (ASM)] should be defined. Standardized and harmonized WC assessment protocols are needed given the large inter-assay variability (10–20% in females and 6–10% in males) (52).

2. Muscle function screening

a. Predictive value of SARC-F questionnaire (45, 46) for SO screening should be further assessed. All items included in SARC-F refer to disability potentially related to muscle function (strength, assistance walking, rise from a chair, climbing stairs and history of falls) and might therefore provide a screening tool for SO as well. However, whether SARC-F is a good screening test in persons younger than 65 years and in subjects with obesity is substantially less investigated. Studies have suggested that the sensitivity of SARC-F may be improved by adding calf-circumference (CC) and further validation is needed for this model (58).

Table 1 Cut-points of body mass index (BMI) and waist circumference (WC) for Sarcopenic Obesity screening (as proposed in different study populations)

Parameter	Cut-points	Methods	Sample characteristics	Sample size	References
BMI	≥30 Kg/m^2	Consensus statement based on association of BMI with mortality	/	/	(44)
	≥27.5 Kg/m^2	Consensus statement based on association of BMI with health risks, high risk of type 2 diabetes and cardiovascular disease in Asian population	Asian	/	(59)
	≥28 Kg/m^2 for M ≥24 Kg/m^2 for F	Predictive value (sensitivity and specificity) and ROC analysis to identify cut-points relative to percent body fat	Mixed ethnicity (White, Black, Hispanic, "Other"), M and F, ≥18y	1393	(42)
	≥25 Kg/m^2	Predictive value (sensitivity and specificity) and ROC analysis to identify cut-points relative to percent body fat	Mixed ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and "Other"), M and F, ≥60y	4984	(37)
	≥25 Kg/m^2	Predictive value (sensitivity and specificity) and ROC analysis to detect subjects with multiple risk factors (hyperglycemia, dyslipidemia, hypertension)	Asians, M and F, 20–84y	1193	(39)

WC	≥102 cm for M ≥88 cm for F	Predictive value (sensitivity and specificity) and ROC analysis to detect subjects with BMI ≥30 kg/m^2	Caucasian, M and F, 25–74y	1918	(40)
	2 levels I: ≥90 cm for M ≥80 cm for F; II: ≥102 cm for M ≥88 cm for F	Consensus statement on sex-specific cut-points to identify increased relative risk for the development of obesity-associated risk factors in most adults with a BMI of 25 to 34.9 kg/m^2	/	/	(36)
	2 levels I: ≥78 cm for M ≥72 cm for F; II: ≥90 cm for M ≥80 cm for F	Predictive value (sensitivity and specificity) and ROC analysis to detect cut-points associated with the presence of at least one cardiovascular risk factor	Asian-Indian, M and F, >18y	2050	(41)
	Optimal thresholds: 97.6cm for M 87.4cm for F	Predictive value (sensitivity and specificity) and ROC analysis to identify cut points relative to percent body fat	Mixed ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and Other), M and F, ≥60y	4984	(37)
	Optimal cut-points	Predictive value (sensitivity and specificity) and ROC analysis to identify cut points associated to	Mixed ethnicity (Caucasian, Asian, Asian-Indian, African-	61 studies	(43)

	ranged from: 72.5 to 103cm for M 65.5 to 101.2cm for F	health outcomes	American, White American, Hispanic, Other), M and F, ≥18y	reviewed	

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c. Diagnosis of sarcopenic obesity

The diagnosis of SO will be performed, according to the consensus algorithm, in two steps by sequentially assessing:

1) Skeletal muscle functional parameters: the panel supports the use of skeletal muscle strength [e.g., hand-grip strength (HGS), or chair-stand test (5-time sit-to-stand test; 30s chair stand test)].

2) Body composition: the panel supports dual-energy x-ray absorptiometry (DXA) as first choice, or bioelectrical impedance analysis (BIA) as an alternative. Computerized tomography (CT) or magnetic resonance imaging (MRI) should be used when possible, e.g. in patients undergoing these diagnostic procedures for other diagnostic reasons.

The panel further supports the use of cut-points provided by Dodds et al. (60) and Auyeung et al. for HGS (61), respectively for Caucasian and Asian populations, with reference ranges provided by Gallagher et al. for FM (62), by Janssen et al. for SMM/W (63) and by Levine et al. for ALM/W (64).

Suggestions for future research

1. <u>Skeletal muscle functional parameters:</u>
    a. Further definition of normative sex-, ethnicity- and age-specific cut points are needed (table 2) (47, 60-96). In particular, since sarcopenic obesity may be present also in younger people, age-specific cut-off points should be investigated and established for this age group (96).

       The use of an approach based on the concept of the minimum clinically important difference (MCID) on outcomes (97, 98), could be used as a criterion to aid cut-points definition. This represents the smallest improvement considered worthwhile for a patient.
    b. Evaluating whether hand-grip strength (HGS) and other functional parameters should be adjusted to body weight, height or BMI is also relevant. In previous studies, HGS per se was not associated with features of the metabolic syndrome, in contrast to HGS/body weight and HGS/BMI which showed a significant association. This suggests that adjusted parameters may be better suitable to identify the presence of metabolic complications of sarcopenia in SO (99, 100). Similar to WC, the best allometric scaling (considering how morphological/physiological traits or processes scale with one another) for HGS in the presence of SO needs to be thoroughly clarified (101). Finally studies on ALM/BMI suggest that body size and potentially fatness influence the association between lean mass and weakness as it happens in SO (102).
    c. The opportunity to refer to lower as opposed to upper limb strength for the diagnostic procedure should be considered. A greater decline in lower compared to upper limb

strength is commonly observed (103), suggesting potential higher sensitivity. Importantly, its specificity may be limited by potential confounding factors and comorbidities that may affect test results, such as osteoarthritis of the knee which is frequently observed in patients with obesity (104). Cognitive impairment as well as social and psychological limitations could also interfere. Moreover, among lower limb strength tests, some, such as the knee extension strength test, are not easily available in non-specialized centres. Gait speed or chair to stand tests could provide a simpler alternative. Walking speed is reported to be a valid, reliable, sensitive measure appropriate for assessing and monitoring functional status and overall health in a wide range of cohorts (105). Differences have been outlined by some authors who distinguish the chair stand test (along with HGS) as an indicator of skeletal muscle strength from gait speed as an indicator of physical performance (used to determine severity of sarcopenia) (106).

d. Potential use/preference of specific functional tests for selected patient groups should be addressed. It may also be relevant to validate, by correlation with biochemical or clinical parameters specific for SO, the best fit of different types of functional tests (e.g., HGS vs gait speed) with the clinical outcomes. Studies should aim at selecting tests that best represent muscle-specific functional deficiencies of SO or of specific groups of SO patients.

e. Possible continuous variable risk assessment values, not based on cut-points, should be identified and evaluated. Z-score or percentiles distribution for individual strength (or other measurements) compared to the reference population, could allow attribution of specific risk scores for SO. This approach would also allow quantitative monitoring of SO risk in the same individual over time, thus potentially contributing to the identification of individuals with fast progression. This can help to better prioritize treatments to patients at higher risk for negative outcomes.

f. A more complete assessment of mobility should also be considered, with combined composite scores integrating functional parameters, lifestyle assessment [Instrumental Activities of Daily Living questionnaire, naturalistic real-life measurements (e.g., actigraphy of physical activity level], mood and social aspects and other parameters that could influence mobility. The possibility to increase the relative importance of tests related to quality of life (due to reduced mobility) compared to purely functional tests (such as the measure of muscle force) should be finally considered.

2. <u>Body composition</u>

a. Further definition of normative sex-, ethnicity-, and age-specific cut-points is needed.

b. Despite pathophysiological interactions that lead to vicious cycles with potential mutual synergistic worsening of obesity and sarcopenia, there is currently insufficient clinical data

to suggest and support an integrated index for SO definition that simultaneously accounts for body fat and muscle mass. The definition of a single composite criterion for SO diagnosis including both FM and muscle measurements (e.g., VAT/ALM) should however be sought and validated (107).

c. The validity of absolute vs relative reduction of muscle mass (fat mass and lean mass or skeletal muscle mass normalized by height^2) (108) should be verified. In absolute terms, high body fat in obesity may result in a relative reduction of skeletal muscle mass (% skeletal muscle mass/body weight), also in the absence of absolute skeletal muscle loss. A relative reduction in skeletal muscle mass could therefore merely result from higher body fat. Individuals with obesity may conversely have comparable or even higher absolute skeletal muscle mass relative to non-obese counterparts, due to higher overall body mass and potentially higher related muscle workload in daily physical activity (109, 110). Moreover, a relative reduction of muscle mass in the presence of high total body mass and FM may have relevant clinical and functional impact even in the absence of absolute muscle mass loss (44, 111).

d. The clinical impact of lower or inadequate muscle strength and performance in individuals with normal or near-normal muscle mass should be assessed (112).

e. Segmental body composition analysis has provided reliable information about body composition in different studies (113). The validity of specific muscle areas, as surrogate of whole body muscle mass for prediction of clinical outcomes, should be further analysed and validated (114, 115).

f. The validity of specific muscle anthropometric measurements as surrogate of muscle mass for prediction of clinical outcomes in persons with obesity should be defined. Limited data is currently available on use of calf circumference (CC) in SO, mainly highlighting the need to standardize the procedure (116). Whether CC in SO is a muscle mass index, or a subcutaneous fat index or both should be better clarified. A Potentially improved predictive value of surrogate muscle measurements for clinical outcomes has however been reported when simple adjustment factors have been used (117-122), for example for BMI or other adiposity proxies, which deserves further investigation.

g. Specific standard procedures for surrogate measurements should be better defined (including patient position, dominant side evaluation, measurement site, number of repeated measures, use of mean or maximum of measurements).

h. The opportunity to use specific cut-points values for specific conditions, such as aging or chronic diseases and their validation vs. outcomes, is a potentially important issue that should be further evaluated.

i. Skeletal muscle quality should be considered. Skeletal muscle quality may be profoundly altered in people with obesity, particularly in terms of ectopic fat deposition (e.g., myosteatosis) which may be highly prevalent in the presence of excess body fat. Myosteatosis is indeed recognized to be negatively associated with skeletal muscle mass and strength (muscle quality), as well as with mobility and systemic metabolic derangements, including insulin resistance and type 2 diabetes, thereby being of prognostic relevance (27, 123, 124). Moreover, under conditions of oxidative stress and chronic inflammation, myoblasts with muscle regenerative function may transdifferentiate into myofibroblasts, which secrete a large amount of extracellular matrix components such as collagen to promote skeletal muscle fibrosis (125). Definition and tools to assess muscle quality in clinical practice remain however elusive and should represent an open research topic.

The role of changes in body fluids (dehydration and edema) in hampering the assessment of muscle mass should be considered. Studies performed in subjects with BMI ≥35 kg/m^2 revealed conflicting results, with ~~an~~ overestimation of body fat or fat-free mass using BIA methodology due, in particular, to modifications of hydration status; changes in plasma sodium concentrations after variable water intake may also conversely affect BIA measurements whereas hyper-hydration may cause underestimation of total body water (TBW) (126-128).

j. Obesity-specific adjustments in BIA equations may improve the accuracy of body composition estimation in these patients (129). Similarly, acute water ingestion before a DXA analysis (500 ml) significantly influences body composition (by inflating expanding fat free mass and reducing percent body fat) (130).

k. Upper sex-specific cut-points of 40% for female and 30% for male have been proposed as best predictors of mortality with regards to body fat in the NHANES sample (American population) using DXA (95). Woolcott et al. (51) developed a calculated % FM parameter defined as relative FM based not on body composition assessment, but rather calculated using height and waist circumference. These proposed parameters and values need to be validated in populations with different ethnicities and using different methods for % FM assessment.

l. Specific equations for the assessment of SMM/W (total skeletal muscle mass adjusted by weight) using BIA especially in individuals with BMI > 34 kg/m^2 (129) should be validated, also considering the potential need for age or disease specific BIA equations (131). Potential use of BIA electrical output values should be evaluated since they can potentially allow for better data comparison and help reduce complexity and variability related to the

use of different equations. Phase angle, a variable directly available from BIA electrical measurements that is independent from equation-related output, is a validated proxy for muscle mass and function (132, 133). Moreover different studies have highlighted the potential of bioelectrical impedance vector analysis (BIVA) in the analysis of body composition and in particular in subjects with SO (134, 135).

m. Selected modified or relatively new methodologies (e.g., segmental BIA; iDXA and visceral fat DXA-analyser; MRI and D3-creatine dilution (136), ultrasound (137, 138) should be validated for the assessment of body composition in particular in subjects with SO.

n. The potential relevance for clinical use of data from easily available, patient-operated devices, including for example smartphone apps for body scanning and anthropometric measurements and home scales with BIA capabilities should also be assessed.

Table 2. Cut-points values for Sarcopenic Obesity diagnosis (as proposed in various studies)

Parameter	Cut-points	Method	Sample characteristics	Sample size	References
Skeletal muscle function					
HGS	< 27 Kg for M < 16 Kg for F	HGS ≤ 2.5 SD below the gender-specific peak mean	Caucasian, M and F ≥ 5y	49964 (data from 12 studies)	(60)
	< 35,5 Kg for M < 20,0 Kg for F	CART and ROC/AUC models to identify cut points associated with adverse clinical outcomes such as mortality, falls, self-reported mobility limitation, and hip fracture	Mixed ethnicity, M and F ≥ 65y	12984	(66,67)
	<30 Kg for M <20 Kg for F	2 SD below the mean of the healthy young-adults group functional outcomes (walking speed ≤ 0.8 m/s; self-reported inability to walk for 1 km)	Caucasian , M and F, 20-102y (RG 20-29y)	1030 (RG 47)	(47)
	<26 Kg for M < 16 Kg for F	Consensus statement identifying cut-points corresponding to a mobility impairment expressed by physical performance tests such as slow walking (gait speed ≤ 0.8 m/s)	Mixed ethnicity, M and F, ≥65y	26625 (data from 9 studies)	(65)
	<28 Kg for M <18 Kg for F	Lowest quintile of the general Asian older population	Asian, M and F, ≥65y	26344 (data from 8	(61)

				cohorts)	
	Normative values based on gender, age, height, right/left side	<5th percentile of the general population aged between 39 and 73 years in 2006 to 2010 from across the United Kingdom	Caucasian, M and F, 39-73y	224830 (r) 224852 (l)	(79)
	26.6 ± 8.3 kg (low LMI) 34.6 ± 13.7 kg (normal LMI)	< LMI 17 kg/m^2 for men and 15 kg/m^2 for women	Caucasian, M and F, 48.8±9.6 y	817 (364 M, 453 F)	(96)
Knee extension strength test	<18 Kg for M <16 Kg for F	Predictive value (sensitivity and specificity) and ROC analysis to identify cut points based on percentage of normalized gain of mobility index (MI) derived from a questionnaire about activity of daily living	Asian, M and F ≥60y	950	(68)
	Strength/W (Kg/Kg) <0.40 for M <0.31 for F	Predictive value (sensitivity and specificity) and ROC analysis to identify cut points relative to the presence of functional limitation	Caucasian, M and F, ≥60y	947	(75)
	< 390.9 N/dm for M <266.4 N/dm for F	2 SD below the mean for the sex-specific RG (healthy young adults)	Caucasian, M and F, 20-102y (RG 20-29y)	1030 (RG 27)	(47)
5 times Sit-to-Stand Chair test	≥17 s	< 21.3 percentile of well-functioning older persons population	Mixed ethnicity, M and F, 70-79y	3024	(71)

30 s Chair Stand Test	60-64y: 15 for F, 17 for M; 65-69y: 15 for F, 16 for M; 70-74y: 14 for F, 15 for M; 75-79y: 13 for F, 14 for M; 80-84y: 12 for F, 13 for M; 85-89y: 11 for F and M; 90-94y: 9 for F and M	normative values across 5 years age ranges (outcomes: moderate functional ability as defined by CPF scale questionnaire and % of decline in physical performance)	Caucasian, M and F, ≥60y	2140	(77)
Body composition					
FM%	20-39y: >39% for F, >26% for M (Caucasians); >40% for F, >28% for M (Asians); >38% for F, >26% for M (African-Americans) 40-59 y: >41% for F, >29% for M (Caucasians); >41% for F, >29% for M (Asians);	Multiple regression model considering FM as outcome variable and BMI, sex, age and ethnicity as predictor variables	Asian, African-American, Caucasian, M and F, Adults	1626	(62)

	>39% for F, >27% for M (African-Americans); 60-79y: >43% for F, >31% for M (Caucasians); >41% for F, >29% for M (Asians); >41% for F, >29% for M (African-Americans);				
	>38% for F >27% for M	Percentage of body fat greater than the sex-specific median	Hispanic and non-Hispanic white, M and F, older people	808	(70)
	>37.2%for F >29.7% for M	Highest sex-specific quintile	Asian, M and F, ≥65y	1731	(72)
	>40.7% for F >27.3% for M	> 60th percentile of body fat of the study population	Caucasian, M and F, ≥60y	992	(69)
	>42.9% for F	2 highest quintiles of the study population	Caucasian, F, 67-78y	167	(80)
	>40.9% for F >30.33% for M	2 highest quintiles of the study population	Caucasian, M and F, 65-92y	2747	(76)
	>20.21% for M	2 highest quintiles of the young RG	Asian, M and F, 20-88y	591	(73)

	>31.71% for F		(RG 20-40)	(145 RG)	
	>25.8% for M >36.5% for F	2 highest quintiles of the study population	Asian, M and F, ≥40y	309	(74)
	>25% for M >32% for F	Expert opinion of the American Society of Bariatric Surgery	/	/	(78)
	RFM (derived from the ratio of h to WC) ≥40% for F ≥30% for M	Multiple regression model considering FM as outcome variable and BMI, education level, smoking status, sex and ethnicity as predictor variables	Mixed ethnicity, M and F, ≥20y	31008	(95)
	Highest two quintiles: 36.2 ± 3.8% for F 20.5 ± 3.3% for M	Highest two quintiles of FM% estimated using predictive equation including WC, hip circumference, triceps skinfold and gender [51]	Mixed ethnicity (non-Hispanic whites, non-Hispanic blacks, Mexican Americans), M and F, ≥70y	2917	(85)
SMM/W (BIA or DXA)	CLASS I of Sarcopenia (1-2 SD): 31.5-37% for M 22.1-27.6% for F; CLASS II of Sarcopenia (< 2 SD):	Class I: SMM/W within -1 to -2 SD of young adult values Class II: SMM/W -2 SD of young adult values	Mixed ethnicity, M and F, 18-39y	6414	(63)

	<31.5% for M <22.1% for F				
	CLASS I of Sarcopenia (1-2 SD): 42.9-38.2% for M 35.6-32.2% for F; CLASS II of Sarcopenia (< 2 SD): <38.2% for M <32.2% for F	Class I: SMM/W within -1 to -2 SD of young adult values Class II: SMM/W -2 SD of young adult values.	Asian, M and F, ≥40y (RG 18-40y)	309 (273 RG)	(74)
	CLASS I of Sarcopenia (1-2 SD): 27-23% for F CLASS II of Sarcopenia (< 2 SD): <23% for F	Class I: SMM/W within -1 to -2 SD of young adult values Class II: SMM/W -2 SD of young adult values	Caucasian, F, 20-50y (RG)	120 (RG)	(80)
ALM/W (DXA)	<29.9% for M <25.1% for F	1 SD below the sex specific mean for young adults	Asian, M and F, mean age 28.4 ± 3.1 and 26.3 ± 2.6	70 (RG)	(92)
	<30.1% M <21.2% F	1 SD below the mean of a young population RG	Asian, M and F, ≥ 40y (RG 20-39y)	10118 (5944 RG)	(81)
	<30.65% for M <23.9% for F	1 SD below the mean of a healthy young RG	Asian, M and F, ≥ 65y (RG 20-39y)	3483 (4192 RG)	(82)

< 25.7% for M < 19.4% for F	2 SD below the mean of a healthy young RG	Mixed ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, "other"), M and F, ≥ 60y (RG 18-59y)	4984 (10877 RG)	(64)
<30.3% for M <23.8% for F	1 SD below the mean of a healthy young RG	Asian, M and F, ≥ 20y (RG 20-39y)	11521 (4987 RG)	(83)
< 32.5% for M < 25.7% for F	1 SD below the mean of a healthy young RG	Asian, M and F, ≥ 60y (RG 20-39y)	2943 (2781 RG)	(84)
< 29.53% for M < 23.2% for F	2 SD below the mean of a healthy young RG	Asian, M and F, ≥60y (RG 20-39y)	2221 (2269 RG)	(86)
<31.3% for M <24.76% for F	1 SD below the mean of a healthy young RG	Asian, M and F, ≥40y (RG 20-39y)	3320	(87)
<32.2% for M <25.6% for F	Class I: within -1 to -2 SD of the healthy young adult values Class II: 2 SD below the mean of the healthy young adult values	Asian, M and F, ≥20y (RG 20-39y)	10485 (2513 RG)	(89)
<29.5% for M < 23.2% for F	2 SD below the mean of a healthy young RG	Asian, M and F, ≥50y (RG 20-40y)	3169 (2392 RG)	(88)
< 26.8% for M	2 SD below the mean of the young RG	Asian, M and F, ≥50y (20-40y	2893	(90)

	< 21% for F		RG)	(2113 RG)	
	< 32.2 for M < 25.5% for F	2 SD below the mean of the young RG	Asian, M and F, ≥20y (RG 20-30y)	15132 (2200 RG)	(91)
	< 44% for M < 52 % for F	1 SD below the mean of the young RG	Asian, M and F, ≥60y (RG 20-39y)	1433 (1746 RG)	(93)
	< 28.27% for M < 23.47% for F	2 SD below the mean of the young RG	Caucasian, M and F, 18-65y (RG 20-39y)	727 (222 RG)	(94)

Legend: 6MWT 6 minutes walking test, **ALM** appendicular lean mass**, AUC** area under the curve, **BIA**, bioelectrical impedance analyses, **BMI** body mass index, **CART** Classification and Regression Tree model, **CPF** Composite Physical Function, **DXA,** dual-energy X-ray absorptiometry, **FM** fat mass, **HGS** hand grip strength, **LMI** lean mass index, **mPPT** modified physical performance test, **RFM** relative fat mass, **RG** reference group, **ROC** Receiver operating characteristic, **SD** standard deviation, **SMM** skeletal muscle mass, **TMSE** Thai mental state examination, **W** weight, **WC** waist circumference,

d. Staging and overall structure of the algorithm

When the diagnosis of SO is established, a two-level staging is proposed, based on the presence or absence of complications (e.g., metabolic cardiovascular and respiratory diseases, or disabilities resulting from high FM and-or low muscle mass). This will aim at stratifying patients based on SO severity. SO stages were defined as follows (4, 5):

STAGE I: No complications attributable to altered body composition and skeletal muscle functional parameters;

STAGE II: Presence of at least one complication attributable to altered body composition and skeletal muscle functional parameters.

Suggestions for future research

1. The predictive value of the proposed algorithm in younger subjects should be directly assessed. Younger persons with SO may have a relative low muscle mass for their age but still relatively preserved muscle function. Moreover, in younger persons functional parameters may not be the primary clinical outcome of interest, particularly in secondary sarcopenia (e.g., patients with cancer or other chronic conditions, or hospitalised), and it is unknown whether temporary SO in younger individuals impacts long-term clinical outcomes and recovery.
2. The possibility to consider global as opposed to muscle-specific outcomes (e.g., lower quality of life related to impaired mobility, institutionalization, disability) as markers of severity of SO, and their inclusion in SO staging needs to be carefully evaluated since they may not be necessarily associated with (or only with) SO, but they may be clinically most relevant SO outcomes in older adults (139).
3. Use of big data analysis and artificial intelligence to aid the identification of other potential important parameters associated with SO, and to contribute to better define cut-points for SO diagnosis and identification of patients at higher risk of poor outcome, may represent a relevant topic for future research.

e. Prevention and treatment strategies for sarcopenic obesity

Treatment of SO is an important clinical challenge due, in particular, to the different phenotypic characteristics and to the different etiopathogenetic pathways leading to SO. Lifestyle interventions, including dietary intervention and optimal protein intake, as well as physical activity/exercise, are hallmarks in the treatment of SO (6). Because of the many pathological and clinical interactions between sarcopenia and obesity, as outlined above, treatment and prevention strategies may also not simply be a combination of known strategies to treat obesity and/or sarcopenia alone. Furthermore, certain treatment strategies for obesity may even be harmful for sarcopenia or vice-versa: intentional weight loss in older adults with obesity has been shown to improve morbidity and physical function (140), but weight loss may also lead to loss of muscle mass, which may worsen sarcopenia and hamper physical function. Although few clinical trials specifically focused on SO (141-144) have been performed, a personalized multidisciplinary approach combining nutritional, physical, psychological, pharmacological and surgical components seems to represent the best treatment of SO. Finally, the panel of experts underlined and agreed on the need to correctly define and diagnose SO before treatment.

Suggestions for future research

1. How clinical stratification proposed in the Consensus algorithm may influence the treatment of subjects with SO and the potential benefits of a more aggressive approach in subjects with higher clinical severity and risk for poor outcomes should be evaluated.
2. Primary and secondary SO may have different clinical and functional characteristics that should be independently investigated and better defined. Specific treatment strategies to address underlying pathophysiological mechanisms may be eventually needed.
3. Several endocrine disorders [hypercortisolism (10), testosterone deficiency, impairment of GH/IGF-1 axis, adult GH deficiency] including the endocrine consequences of various diseases (e.g., cirrhosis, COPD) are associated with SO. Treatment of SO in these conditions requires further specific investigation that may potentially lead to specific recommendations (145-147).
4. How functional characteristics of subjects with SO may influence treatment protocols (in particular the intensity and volume of physical exercise), and how aerobic and resistance treatment approaches can be combined need to be assessed. The evaluation of the efficacy of single and combined treatment options in different age groups or in patient groups with different levels of fitness may help identify the best strategies that can be used to optimise outcomes.
5. The efficacy of previously proposed approaches to treat obesity (notably caloric restriction, physical activity, pharmacological and psychological protocols, bariatric surgery) and sarcopenia [exercise and functional rehabilitation, adequate protein intake (including the most appropriate amount, timing and type of protein in the diet and its interactions with exercise), nutrient supplementation

(e.g. Vitamin D, whey protein, branched chain amino acids), pharmacological treatment] need to be validated and confirmed in subjects with SO. In particular, strategies to better preserve muscle mass during weight loss need to be identified. Both aerobic and resistance exercise, separately, or in combination, have been shown to improve functional status with concomitant caloric restriction in older adults with obesity, while synergistic improvements in physical function has been observed with both types of exercise (148). However, the potential combined role of other factors and treatments, including dietary aspects, still need to be fully addressed. In particular, more emphasis should be placed on studying forms of personalized physical exercise, which should take into account not only the different roles it plays in the treatment of SO (i.e. increase energy expenditure, maintain muscle mass) but also its coordination with other therapeutic strategies.

6. Novel medications (GLP-1, GIP, glucagon agonists) hold great promise for the treatment of obesity by allowing weight reductions above 15% (149). Assessment on the effects of these emerging treatments on lean mass changes as well as other specific components of the SO phenotype will likely become an important priority in order to allow for safe utilization in persons with, or at risk for SO.
7. Treatment of obesity by nutritional, pharmacological or surgical intervention leading to a reduction in fat mass and in fat free mass will also induce changes in energy metabolism (i.e., adaptive thermogenesis), thereby influencing daily energy balance (energy intake and energy expenditure) and future changes in body composition (150). A better understanding of the interplay between energy intake and energy expenditure will help to identify the best therapies aimed at preserving muscle mass over time.
8. Medications or nutritional formulations recommended to counteract sarcopenia may also be effective in the context of increased adiposity and SO, in terms of pharmacological lipophilic behaviour and compartment distribution, but this hypothesis should be directly tested in future clinical studies. In particular, muscle-anabolic therapeutic approaches considering nutritional supplementation (e.g., aminoacids, isoflavones), pharmacological/hormonal treatment (e.g., oestrogen, testosterone, selective androgen receptor modulators, recombinant human growth hormone (151), anamorelin, myostatin inhibitors, vitamin K), senolytic agents (152) or mesenchymal stem cells provided conflicting results and require further research. Finally, the efficacy of new treatments focused on muscle [e.g., antibody blockade of activin type II receptor (ActRII) signaling, which stimulates skeletal muscle growth] potentially leading to improvements in fat mass reduction and metabolic markers should be verified in the management of SO (153).

Conclusion

This document summarizes the result of the work carried out in recent years, in the context of the EASO ESPEN initiatives, by the SOGLI expert panel, leading to a meeting that took place in Rome in November 2022. In the context of other recently-published documents (systematic review of literature concerning SO, and ESPEN-EASO consensus on definition and diagnostic criteria) it proposes a starting point for research aimed at improving knowledge and clinical practice in SO.

At the moment the validation of the ESPEN-EASO criteria for SO screening and diagnosis using already available data from merging datasets (from Italy, Czech Republic, Finland, Poland) and from different epidemiological studies [Sarcopenia & Physical fRailty IN older people (SPRINTT), National Health and Nutrition Examination Survey (NHANES), National Health and Aging Trends Study (NHATS), Baltimore Longitudinal Study of Aging (BLSA)] is ongoing. We aim at producing results to be presented and discussed at the next SOGLI meeting that we are planning for fall 2023 where the many researchers interested in SO will be able to discuss their ideas and data, and kick off new initiatives.

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