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REVIEW

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"Bioelectrical impedance analysis in managing sarcopenic obesity in NAFLD"

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Abstract

Introduction: Sarcopenic obesity and its association with nonalcoholic fatty liver disease (NAFLD) is under-recognized by many healthcare providers in Western medicine due to the lack of awareness and diagnostic guidelines. The result is delayed recognition and treatment, which leads to further health deterioration and increased healthcare costs. Sarcopenic obesity is characterized by the presence of increased fat mass in combination with muscle catabolism related to chronic inflammation and/or inactivity. Previous research has recommended evaluating body composition and physical function performance to adequately diagnose sarcopenic obesity. Body composition analysis can be performed by imaging applications through magnetic resonance imaging, computed tomography, and dual-energy x-ray absorptiometry. Due to the cost of each device and radiation exposure for patients as evidenced in all three modalities, bioelectrical impedance analysis offers a noninvasive approach capable of providing quick and reliable estimates of lean body and fat mass.

Methods and Results: This review analyzes the current evidence-based literature, indicating a lower skeletal muscle mass and increased visceral adipose tissue correlation to the advancement of fibrosis in fatty liver disease.

Conclusion: Given the substantial promising research conducted in predominantly Asian populations regarding body tissue distribution and NAFLD, additional prospective research is needed to extend these findings in Western populations.

KEYWORDS
bioimpedance, body composition, fatty liver disease, NASH, obesity, sarcopenia

1 | INTRODUCTION

In recent years and throughout the world, obesity has become a significant public health issue secondary to its adverse impact on health, longevity, quality of life (QOL), and healthcare costs. Increased public and provider awareness of obesity has enhanced the focus on obesity-related comorbid diseases, such as nonalcoholic fatty liver disease (NAFLD).[1] NAFLD is classified as a spectrum of diseases ranging from steatosis to nonalcoholic steatohepatitis (NASH) to cirrhosis.[2] Sarcopenia, which translated from Greek means "poverty of flesh," 3 involves adverse alterations in muscle mass and function which can complicate obesity and NAFLD resulting in additional morbidity. Potential consequences of sarcopenia include physical disability, impaired QOL, falls, osteoporosis, fatty liver disease, cardiovascular disease (CVD), metabolic syndrome, and immunosuppression.[4] To date, a concise and unified assessment of sarcopenia is lacking.

Sarcopenic obesity is characterized by the presence of increased fat mass in combination with muscle catabolism related to chronic inflammation and/or inactivity.[5] Since obesity and NAFLD are strongly associated and may be independent risk factors for sarcopenia,[6] early recognition of these conditions, provider awareness, and the development of management strategies are needed.

Bioelectrical impedance analysis (BIA), originally used to estimate total body water, is a common clinical assessment tool to estimate fat-free and fat mass.[7] In this original two-compartment model, fat-free mass would be classified as protein, minerals, and body water. BIA technology has evolved to provide estimates of whole body and visceral adipose tissue as well as segmental muscle mass.[8] There is limited research in assessing the fat distribution, by BIA, in patients with sarcopenic obesity. Due to the low operating cost and noninvasive approach, BIA may be a suitable resource to assess body composition changes over time to diagnose sarcopenic obesity and NAFLD.

Current guidelines from the American Society of Parental and Enteral Nutrition (ASPEN) rely predominantly on history and physical examination to define malnutrition, while the definitions of sarcopenia, sarcopenic obesity, and utility of bioimpedance are not standardized.[9,10] Therefore, the purpose of this review is to detail the current information regarding the clinical presentation, prevalence, pathogenesis, diagnostic criteria for body composition assessment, and efficacy of treatment for sarcopenic obesity in the setting of NAFLD.

2 | DEFINITIONS OF OBESITY, NAFLD, AND SARCOPENIA

The limitation with the use of BMI as a measure of obesity is BMI does not indicate the proportions of adipose tissue and lean body mass.[11] Further, BMI does not identify fat distribution, nor accurately predicts the risk of comorbidities and association with metabolic syndrome, which is defined as a group of metabolic diseases including obesity, hypertension, hyperglycemia, and hyperlipidemia.[4,11,12] Increased visceral adipose tissue (VAT) is associated with metabolic syndrome and cardiovascular risk, which is why both the American Heart Association (AHA) and the National Heart Lung and Blood Institute utilize waist circumference (WC) in defining metabolic syndrome. Excess caloric intake contributes to the accumulation of VAT, which further exacerbates the lipolytic activity shifting to an inflammatory phenotype. This inflammatory response results in the production of inflammatory cytokines and free fatty acids (FFA) into the portal venous system. Cumulatively, this adversely affects hepatic metabolism by promoting hepatic lipid accumulation and ultimately NAFLD.[12]

NAFLD is defined as macrovesicular lipid accumulation in the absence of significant alcohol use and is a spectrum of variants including nonalcoholic fatty liver (NAFL), NASH, and different stages of fibrosis.[2] NAFL requires the presence of at least 5% hepatic steatosis with no evidence of hepatocyte injury identified by ballooning or fibrosis. NASH involves inflammation and hepatocyte injury, and fibrosis stages include F0 without any fibrosis to F4 cirrhosis or advanced scarring.[2]

Several expert committees have proposed different definitions and criteria to classify sarcopenia.[13] The European Society for Parental and Enteral Nutrition and the International Working Group on Sarcopenia identify sarcopenia as a loss of both muscle strength and mass, predominantly in the elderly community.[14,15] The Society of Sarcopenia, Cachexia and Wasting Disorders emphasized the difference between frailty and sarcopenia, in which sarcopenia causes limited mobility and muscle mass loss.[16] In addition, the new guidelines by European Working Group on Sarcopenia in Older People (EWGSOP) underline that sarcopenia is not only a disease of the elderly and provides a clear algorithm with separate cut-off points for men and women in physical function measures such as grip strength, muscular endurance, and gait speed along with appendicular skeletal muscle mass (ASM).[17]

Sarcopenic obesity was first defined by Baumgartner as ASM/ht^2 < 2 SD of a younger sex-specific mean with a concurrent relative body fat of ≥27% in men and ≥38% in women.[18] Later, a weight-based method was developed to define sarcopenia as ASM/weight × 100.[19] However, since definitions were applied for age-related skeletal muscle wasting and weakness,[20] there is a need for a new definition that incorporates functional assessment within the setting of chronic diseases such as NAFLD with obesity and sarcopenia.

3 | PREVALENCE OF NAFLD AND SARCOPENIC OBESITY

Currently, NAFLD is the most common cause of liver disease in the Western world.[21,22] NAFLD is prevalent in 25% of the general population and 75% in adults with obesity or type 2 diabetes mellitus (T2DM).[2,23] In the United States, the incidence of NAFLD is expected to grow as the population of adults with obesity continues to rise. The current literature indicates up to 95% of individuals with Class III

obesity have NAFLD.[24,25] Therefore, NAFLD should be suspected in patients with obesity for early clinical diagnosis and appropriate management.

The prevalence of sarcopenia varies depending on the definition utilized and the population studied. Using EWGSOP criteria, a Chilean cohort of 1006 nondisabled, community-dwelling individuals ≥60 years of age indicated a prevalence of sarcopenia of 19.1%. Of note, only 2% of adults with obesity (35.9% of the cohort) were also identified as sarcopenic.[26] Initially, sarcopenia was thought to be a disease only associated with aging. However, further research analysis showed the prevalence of sarcopenia and other chronic medical conditions. Utilizing data from the National Health and Nutrition Examination Surveys 1999–2004, a study conducted in the United States determined that the prevalence of sarcopenia in men was 16% and in women 19.3%.[27] A recent meta-analysis on the prevalence of sarcopenia in comorbid diseases highlighted an association of sarcopenia with CVD (31.4%), dementia (26.4%), T2DM (31.1%), and respiratory diseases (26.8%) in a cohort of 17,206 individuals.[28]

Most sarcopenic obesity studies were conducted in east Asian countries. In a Korean longitudinal study, the prevalence of sarcopenic obesity defined by visceral fat area (VFA) 100 cm^2 and ASM/Ht^2 was determined to be 16.7% in men and 5.7% in women.[29] However, when utilizing ASM/Wt, the prevalence increased to 35.1% in men and 48.1% in women. Thus, utilization of the weight-based method to define sarcopenic obesity identified patients with increased risk of metabolic syndrome when compared to patients with obesity only. Although there have been separate prevalence studies on NAFLD and sarcopenic obesity as discussed above, there has yet to be any epidemiological study conducted on adults with sarcopenic obesity and NAFLD.

4 | ETIOLOGY OF NAFLD AND SARCOPENIC OBESITY

4.1 | Pathogenesis of sarcopenia and obesity

As with NAFLD, there are many factors which contribute to loss of muscle mass and muscle function. Aging is associated with increases in visceral fat secondary to reductions in physical activity and basal metabolic rate without a decline in energy intake. Age is also associated with changes in multiple trophic effects on muscle which results in progressive loss of muscle mass and function. Loss of muscle mass and function result in a more sedentary lifestyle and a reduction in energy expenditure, favoring increase of fat mass resulting in a vicious cycle.

The proinflammatory secretory phenotype associated with caloric excess, obesity, and dysfunctional adipose tissue is thought to be the cause of the chronic low-grade inflammation associated with obesity. Proinflammatory cytokines such as TNF-α and IL-6 have been found to be positively associated with fat mass and negatively associated with muscle mass.[30–32] Inflammatory mediators also result in high levels of circulating FFA and insulin resistance via alteration in the function of the insulin receptor, contributing to infiltration of fat into muscle. In a rodent model, aging and obesity were associated with insulin resistance, accumulation of lipid products (ceramide deposition) in muscle, and reduced protein synthesis.[33]

4.2 | Muscle cell function

Aging is associated with numerous biochemical and cellular alterations in muscle, which affect muscle function and can adversely affect physical status and QOL. Muscle mass declines by 3%–8% per decade after the 30th year.[34] Loss of skeletal muscle mass is accompanied by a progressive decline in absolute strength, averaging a decrease of 10%–15% per decade, with significant decreases of skeletal muscle strength of 25%–40% per decade beyond the 70th year.[35] For most healthy adults, there is a positive correlation between total body strength and skeletal muscle mass.[36] However, in adults with sarcopenia there are progressive changes within skeletal muscle, which reflect a decline in motor neuron health,[37] increased muscle fiber denervation within the motor unit,[38] atrophy of type II skeletal muscle fibers,[39] and reductions in satellite cell content and apoptosis.[40] All these changes contribute to reduced skeletal muscle mass and strength.

Forces of each skeletal muscle contraction are also dictated by the composition of each muscle fiber. Muscle fiber types are categorized based on oxidative capacity, myosin heavy chain structure, force production, and metabolic pathway.[41] Fiber types are typically classified as slow-twitch (Type I), fast twitch oxidative-glycolytic (Type IIa), and fast twitch glycolytic (Type IIx).[42] Of these groupings of muscle fibers, Type II fibers are characterized as having a higher force production and lower fatigue threshold, whereas Type I fibers are regarded as having a higher oxidative capacity and decreased force production. Adults with obesity have a greater preservation of the fast twitch glycolytic Type IIx fibers in comparison to Type I fibers.[43–45] Despite the recognition of muscle fiber types and function in sarcopenia and obesity individually, little is known regarding the overall distribution of fiber types in sarcopenic obesity.

4.3 | Pathogenesis of NAFLD

Fat accumulates in the liver when there is an imbalance between FFA delivery to the liver, liver fat synthesis, liver fatty acid oxidation, and liver fat export as secretion of very low-density lipoproteins. Until recently, simple steatosis was thought to be a benign condition and about 15% of adults with NAFLD undergo a "second hit" phenomenon in which an inflammatory response to the fat-laden hepatocytes results in liver cell injury, death, and fibrosis. Recent evidence suggests that simple steatosis can progress to NASH as early as 6 months to a year from diagnosis.[46,47]

While the pathogenesis of NAFLD remains under investigation, current evidence suggests a multifactorial etiology with insulin

resistance playing a critical role and involving alterations in adipocyte function and the intestinal microbiome. Dietary excess leads to abnormal enlargement of adipocytes and a shift in adipocyte secretory activity with release of inflammatory mediators TNF-α and IL-6.[48] The proinflammatory phenotype in adipose tissue results in deregulation of lipolysis and enhanced release of FFA.[49]

In obesity, alterations in the gut microbiome, gastrointestinal permeability and associated bacterial overgrowth result in absorption of proinflammatory molecules, such as lipopolysaccharide.[50] These ligands, together with FFA from VAT, are released into the portal vein, stimulate proinflammatory signaling, activate Kupfer cells, and augment uptake of FFA into hepatocytes.

As a result of insulin resistance, high levels of circulating FFA accumulate in the liver and convert to hepatic triglycerides via de novo hepatic lipid synthesis.[50] The accumulation of lipid metabolites in the liver lead to mitochondrial dysfunction, oxidative stress, and the release of reactive oxygen species.[50,51] In individuals with genetic predisposition, the sum of these alterations results in a state of chronic hepatic inflammation.

4.4 | Endocrine factors

Aging is associated with an increase in fat mass from 20% to 40% between ages 20 and 80 years 51 Since insulin is an anabolic hormone, insulin resistance in muscles is associated with net protein catabolism. Increased adiposity not only exacerbates insulin resistance, but associated increases in plasma FFA leads to a reduction in both insulin-like growth factor 1 (IGF-I) and growth hormone,[52] further compromising protein synthesis and thus contributing to sarcopenia.

Testosterone promotes muscle cell regeneration via satellite cell activation, increases the amino acid utilization in skeletal muscle and androgen receptor expression, thereby improving the total muscle protein synthesis.[53] This is directly achieved by increased IGF-1 expression. In addition, testosterone has anti-inflammatory effects.[54,55] With obesity, there is increased aromatization of testosterone to estrogen. This decrease in testosterone combined with increased proinflammatory TNF-α and IL-6 creates a milieu for loss of muscle mass.[55]

5 | QUALITY INDICATORS FOR SARCOPENIC OBESITY & NAFLD

5.1 | Body composition

In the objective assessment of adults suspected of sarcopenic obesity, a quantitative measurement of muscle mass and fat and distribution is critical. Human tissue composition may be assessed at the atomic, molecular, cellular, tissue-organ, and whole-body levels.[56] For sarcopenic obesity, most research has been conducted at the tissue-organ and whole-body level. Imaging applications such as magnetic resonance imaging (MRI) and computed tomography (CT) are regarded as the benchmark for regional adiposity, yet these techniques pose many challenges for practicing clinicians. Limitations include availability of trained personnel, appropriate referral procedures, and cost. In the absence of these imaging applications, providers can also obtain measurements of body composition through Air-Displacement Plethysmography (ADP), Dual-energy X-ray absorptiometry (DEXA), or BIA. In adults with severe obesity, a strong correlation exists in the estimation of adipose tissue among BIA and the reference methods of DEXA[57,58] and ADP.[59] Although DEXA is widely regarded as the superior modality for body composition assessment, obtaining measurements via DEXA poses some restrictions when assessing this patient population. Body habitus presents limitations on the spectrum of patients that can be accurately scanned due to the dimensions of the scanning table as well as the distance between a patient's mid-section and the scanning x-ray detector. Furthermore, DEXA is regarded as a more tedious procedure which could impact the amount of time a clinician has to complete their assessment and treatment plan for their patients. With the evolution of BIA technology over the past few decades, most BIA scans can be completed in under one minute. As evidenced in the prior studies reflecting upon the agreement of adiposity measured in both DEXA and BIA for the adult population with obesity, the implementation of BIA in clinical practice to assist in the screening of suspected individuals with sarcopenic obesity might be a more practical solution for providers to independently receive quick and reliable results in terms of body composition.

With body composition analysis emerging as the gold standard for the quantitative evaluation of lean body and fat mass, criterion for the assessment of sarcopenic obesity with this approach needs standardization. In sarcopenic obesity, the expanding visceral fat mass with obesity leads to the release of inflammatory adipokines and metabolic dysfunction, which are associated with loss of muscle mass and function.[60,61] While there have been theories regarding mechanisms for the progression of sarcopenic obesity, little is known regarding the stratification for sarcopenia based on body composition analysis in the presence of NAFLD. A consensus is needed to define body composition criteria predisposing to the development of NAFLD. Table 1 summarizes the characteristics of studies addressing the relationship between adiposity, NAFLD, and more progressive forms of NAFLD.

Koda et al.[62] studied 125 adults and identified alanine aminotransferase (ALT), visceral fat, and serum albumin as independent predictors of hepatic steatosis, with visceral fat yielding the strongest relationship. Excess visceral adipose tissue and the presence of NAFLD was further confirmed by Park et al.[63] and Ko et al.[64] along with elevated triglycerides, WC, fat mass, and BMI as factors associated with the presence of NAFLD.

In a study of histologic severity of NAFLD variants (grade 0–3 for steatosis, necroinflammation, ballooning degeneration, and grade 0–4 for fibrosis), increased visceral fat, and insulin resistance were found to be risk factors for the presence of NASH (Table 1).[65] In another study of liver histology in 38 adults, visceral fat was

independently associated with hepatic inflammation and fibrosis.[66] Eguchi et al. 67 called attention to the importance of assessment of VFA and relationship to the progression of NASH by showing that VFA is higher in adults with advanced NASH. In a study of 324 NAFLD biopsy proven adults, it was identified that VAT is independently associated with NASH or fibrosis.[68] Conversely, in a small study of 21 Indian adults with biopsy proven NAFLD found that both subcutaneous and total adiposity are significantly associated with NAFLD severity when assessed with the NAFLD activity score.[69]

In a 6-year longitudinal study, Kim et al. 70 obtained CT images of abdominal fat, while performing laboratory tests of hepatic function and abdominal ultrasonography to identify the presence of liver fat. The study identified 288 cases of NAFLD with 159 of the 288 adults showing NAFLD regression during the study interval. The findings suggested that the volume of visceral fat is associated with progression of NAFLD, whereas higher concentrations of subcutaneous adipose tissue was associated with regression. Additional support for the association between visceral fat and NAFLD is provided by the Golestan Cohort Study of 109 adults with NAFLD assessed by ultrasound and MRI who underwent imaging and anthropometric study of body fat distribution.[71] This study identified a significant association of NAFLD with visceral adiposity but not with subcutaneous adiposity.

A quantitative measure of skeletal muscle mass is now widely accepted as an important component of the assessment of sarcopenia. Most evaluations of skeletal muscle mass are based on appendicular skeletal muscle relative to either weight[19] or height.[72] Current studies exploring the relationship between the quantitative assessment of skeletal muscle and NAFLD are summarized in Table 2.

Hong et al. 6 measured skeletal muscle mass utilizing DEXA and calculated the skeletal muscle index (SMI) in 452 adults who also underwent CT scan for assessment of NAFLD based on the liver attenuation index (LAI). A multiple logistic regression analysis determined that subjects in the lowest SMI quartile posed the highest adjusted risk for NAFLD compared to subjects in the fourth quartile. In a cross-sectional study, using the Korea National Health and Nutrition Examination Surveys, Lee et al. 73 also identified that lower SMI is associated with NAFLD. Further analysis demonstrated that both sarcopenic and sarcopenic obese subjects had significant incidences of NAFLD. Additionally, sarcopenia was significantly associated with the degree of fibrosis in NAFLD. A 7-year longitudinal study supported the association of a higher prevalence of NAFLD in the lower quartiles of SMI. The longitudinal follow-up also demonstrated that an increase in skeletal muscle mass over one year was associated with a significant reduction in the development of NAFLD.[74]

Choe et al. 75 also confirmed the association of low levels of SMI utilizing CT analysis of skeletal muscle mass with NAFLD. Most studies attempting to define the association between SMI and NAFLD have utilized a weight based SMI [skeletal muscle mass (kg)/total body weight (kg)]. A few investigators introduced a height-based index of SMI [absolute skeletal muscle mass (kg)/height (m^2)]. As evidenced by Peng et al. 76 utilizing only weight-based skeletal muscle models in adults with high BMI scores can create bias on the detection of sarcopenia in NAFLD due to the abundance of adipose tissue.

Several recent studies demonstrated an association between sarcopenia and NAFLD severity.[77–79] One study utilizing data from the third national health and nutrition examination survey (NHANES III) found that sarcopenia was more prevalent in subjects with NAFLD and is an independent predictor of advanced fibrosis in Western populations.[80]

To date, most of the research regarding the role of body composition on the detection and prognosis of NAFLD examined the role of sarcopenia or adiposity as the primary factor. Limited research has been conducted on the simultaneous role of both adipose tissue and skeletal muscles relationship to NAFLD. Table 3 outlines the studies that evaluated both adiposity and sarcopenia and in relation to NAFLD.

To address both the extent of visceral adiposity, skeletal muscle mass and the association with NAFLD progression, Moon et al. 81 identified an inverse relationship between skeletal muscle mass and VFA when correlated to the fatty liver index. The findings suggested that increases in skeletal muscle relative to total body weight may be an important factor that may contribute to the prevention of NAFLD. Additional data also supports an inverse relationship between the visceral adiposity and skeletal muscle mass in relation to NAFLD progression.[82] In one of the few longitudinal studies examining the age-related effects of body composition on sarcopenia and the development of NAFLD, Lee et al. 83 identified 591 of 4398 subjects who developed NAFLD over a 10-year period. Increases in WC, BMI, fat mass, and body weight were identified as associated factors. In addition, a decrease in skeletal muscle mass was also associated with development of NAFLD.

Utilizing data taken from the Wellness Living Laboratory study, Hsing et al. 84 identified 476 participants with NAFLD. This study utilized the android fat ratio [(AFR) total android fat mass (g)/total fat mass (g)] to assess adiposity distribution. Android body phenotypes are those where most of the adipose tissue is distributed within the trunk and upper body which is commonly seen in adult males with obesity. The study established a significant relationship between AFR and NAFLD risk and demonstrated that a higher SMI had a significant inverse relationship with NAFLD risk. Lastly, in a retrospective study of larger cohort (n = 5989), Chung et al. 85 observed a higher prevalence of NAFLD in sarcopenic as well as sarcopenic-obese subjects.

5.2 | Physical function status

Diminished skeletal muscle mass relative to total body weight has been shown to impact physical activity, increase risk for falls, decrease functional capacity, and thus adversely affect activities of daily living. This phenomenon was first reported in 2004 when those with sarcopenic obesity were found 2–3 times more likely to have a

diminished ability to perform instrumental activities of daily living (IADL).[86] The inability to carry out activities of daily living exacerbates the vicious cycle of accumulation of excess adipose tissue while perpetuating the degradation of skeletal muscle. Therefore, healthcare providers should be cognizant of the importance of tests of physical function to compliment body composition assessment in evaluating the clinical significance of sarcopenic obesity.

In the clinical setting, evaluating physical function should encompass a spectrum of functional assessments to determine the quality of muscular strength and functional ability. In sarcopenic and sarcopenic obese populations, hand-grip strength assessed via hand dynamometry, correlates with total body strength.[87,88] Clinicians should familiarize themselves with the recommendations and test protocol for hand-grip strength assessment set forth by the American Society of Hand Therapists.[89]

When assessing the severity of sarcopenia in adults, hand-grip strength measurement should be complimented with additional measures of physical function. These can include gait speed, muscular power, balance, and cardiorespiratory endurance. Physical Medicine & Rehabilitation providers and kinesiotherapists may also be consulted to diagnose and monitor treatment. For clinical reference, a comprehensive review on physical function assessments is covered by Beaudart et al.[90]

6 | IMPACT OF SARCOPENIC OBESITY & NAFLD ON HEALTH OUTCOMES

6.1 | Disability and mortality with sarcopenic obesity

Sarcopenia causes frailty including weakness, falls, immobility, functional decline, and institutionalization. In combination with sarcopenia, the rise in the prevalence of obesity may add additional risk factors to poor health outcomes.[91] Adults with sarcopenic obesity are more likely to develop disability and lower QOL when compared to purely sarcopenic or nonsarcopenic obese adults. A cross-sectional study[92] showed that when compared to purely sarcopenic or nonsarcopenic obese group, women with sarcopenic obesity had more difficulty performing physical activities such as climbing, stair descending, and rising from a chair or bed. Similarly, of the three aforementioned groups, individuals with sarcopenic obesity had the lowest mean gait speed, hand grip strength, and demonstrated the highest fall risk.[93] Baumgartner et al. 86 also demonstrated increased risks of disability and reduced mobility with an expanded fat mass. In addition to physical disability, a cross-sectional study[94] suggested sarcopenic obesity was associated with lower QOL and negative psychological effects including stress, depression, and suicidal ideation.

There is limited longitudinal data which addresses the mortality risk associated with sarcopenic obesity. A meta-analysis study by Zhang et al. 95 included 23 prospective cohort studies looking at adults with mean age 50–82.5 years, which showed higher all-cause mortality risk in the sarcopenic obese group among community-dwelling adults and hospitalized adults compared to nonsarcopenic nonobese group. Likewise, Baumgartner et al. 86 showed that a decrease in IADL was significantly associated with increased mortality. Van Aller et al. 96 showed that for age 50–70 years compared to age 70 years and older, mortality is increased in sarcopenic obese group. Despite the high prevalence of sarcopenia and sarcopenic obesity in men compared to women, all-cause mortality risk (most commonly due to CVD) were higher in women with sarcopenia, independent of obesity.[91]

6.2 | NAFLD mortality

NAFLD affects extrahepatic organ systems including, but not limited to, the cardiovascular, endocrine, and renal systems. NAFLD is associated with increased prevalence and incidence of CVD, chronic kidney disease (CKD) (20%–55%), and T2DM (10-18%) with the most common causes of death from CVD.[97] In hospitalized adults with T2DM, NAFLD is also associated with an increased risk of atrial fibrillation[98] and all spectrums of heart block.[99] Elderly adults admitted with acute heart failure who were diagnosed with NAFLD during the hospital stay were five times more likely to be readmitted within 1 year for mostly cardiac reasons.[100]

7 | TAILORED TREATMENT OPTIONS FOR ADULTS WITH SARCOPENIC OBESITY AND NAFLD

7.1 | Current guidelines and emerging treatments

In 2018, the International Conference on Frailty and Sarcopenia Research (ICFSR) developed screening, diagnosis, and management guidelines. In addition to developing guidelines for screening and diagnosis, there were some recommendations regarding treatment.[101] Sarcopenia requires a multifaceted management involving supervised intake of quality nutrients and resistance exercise. The evidence remains inconclusive regarding the efficacy of anti-inflammatory and anabolic medications.[101] Adequate protein intake is critical to the restoration of muscle mass and function. Daily recommended protein intake is 1–1.2 g/kg/day instead of 0.8 g/kg/day for adults with age-related sarcopenia >65 years. In addition, there is evidence supporting the addition of Vitamin D to an adequate diet in males >64 years of age, resulting in increased postprandial protein synthesis and muscle mass.[102] The ICFSR, however, does not endorse the supplementation of Vitamin D given insufficient evidence.[101] Dietary supplementation with omega-3 or monounsaturated fatty acids can be therapeutic in the management of sarcopenia to decrease insulin resistance, prevent fat mass increase, and allow for an overall improved protein anabolism, muscle mass and function.[103]

Recent evidence supports specific dietary recommendations for treatment of NAFLD. Medium-chain triglycerides (MCT) consisting of 6–12 carbon chains reduce steatosis compared to long-chain.[104,105] MCTs enter hepatocytes and mitochondria by direct absorption into

the hepatic portal vein and do not rely on the typical fatty acid transport system. This unique absorption allows easy storage, metabolism and degradation by direct thermogenesis without any additional energy or stress to the liver.[104]

7.2 | Physical activity

Physical activity has been widely examined with acute and chronic exposure for a multitude of medical ailments and is regarded as an independent therapeutic agent for sarcopenia, obesity, and NAFLD. However, in adults with sarcopenic obesity and NAFLD, the benefits of structured exercise warrant further investigation as weight loss alone is perceived responsible for improvements in NAFLD. Current recommendations suggest a weight loss reduction of 7%–10% in bodyweight to yield improvements in NAFLD, NASH, and fibrosis.[106] However, several systematic reviews have shown beneficial effects of exercise on NAFLD independent of weight loss.[107–109]

The mechanisms underlying the effects of physical exercise on hepatic fat mobilization are unknown. Exercise improves insulin sensitivity, FFA oxidation, and reduces oxidative stress, thereby ameliorating mitochondrial dysfunction in the liver.[110] Furthermore, physical exercise, frequency, duration, and relative intensity can reduce intrahepatic fat content and improve NAFLD. A systematic review by Hashida et al. 111 explored the effects of exercise on NAFLD. The conclusion was both aerobic and resistance exercises reduce hepatic steatosis with no significant difference in frequency, duration, or length of exercise intervention. Based on this review, aerobic exercise is beneficial for adults with NAFLD at an intensity of 4.8 metabolic equivalents (METs) for 40 min per session, three times per week for 12 weeks. Resistance exercise is recommended at an intensity of 3.5 METs for 45 min per session, three times per week for 12 weeks. Glass et al. 112 further suggests an intensity of 46%–90% of VO_2 Max eliciting a moderate-vigorous effect for aerobic exercise. Strength training or hypertrophy driven protocols on non-consecutive days, developed by the American College of Sports Medicine (ACSM), were also recommended for resistance exercise.

In adults with sarcopenic obesity, participation in a regular exercise regimen may be arduous due to impaired function status and physical deconditioning. Guidelines set forth by the WHO,[113] ACSM, and AHA[114] recommend adults to accrue 150 min per week of moderate intensity aerobic exercise with engagement of resistance training on 2 or more days per week. A meta-analysis evaluated the concurrent or independent effects of exercise on sarcopenic obesity in adults. Findings of the study suggest overall reduction in bodyweight occurred with aerobic exercise, while reduction in body-fat percentage were most prominent in both aerobic and resistance exercise or resistance exercise.[115]

While specific guidelines for physical activity remain limited in adults with sarcopenic obesity, a recent publication[116] highlighted recommendations on the initial exercise prescription including steps of progression in both exercise domains for adults with sarcopenic obesity.

7.3 | Bariatric surgery

Bariatric surgery is an additional option for individuals with a BMI ≥40 kg/m^2 or a BMI ≥35 kg/m^2 with an obesity-related medical comorbidity. Yielding an average weight loss of 27%–35% of initial body weight, bariatric surgery can ameliorate obesity-related diseases such as T2DM, hypertension, obstructive sleep apnea, and NAFLD.[117] However, in the first 3 postoperative months, lean body mass (LBM) loss makes up 16%–31% of the weight loss, drawing into question whether bariatric surgery will further exacerbate sarcopenia.[117,118] Contrary to this concern, Kulovitz et al. 119 showed no difference in LBM loss following a 15% weight loss achieved by RYGB ($n = 24$) versus a medically directed weight loss program ($n = 24$). Over the course of 1 year, both groups experienced approximately 24% LBM loss and similar overall changes in body composition. Another study demonstrated that 5 years after bariatric surgery, LBM and muscle mass were maintained or decreased minimally beyond the initial loss.[117]

In efforts to preserve muscle mass loss associated with bariatric surgery, the American Society for Metabolic and Bariatric Surgery (ASMBS), the American Association of Clinical Endocrinologists (AACE), and the Obesity Society (TOS) have established guidelines for protein intake, recommending 60–90 g of protein per day. However, in adults with sarcopenic obesity and NAFLD, the beneficial effects of structured exercise warrant further investigation as weight loss alone is perceived responsible for improvements in NAFLD. After surgery, meeting the recommended protein intake requirements can be difficult for a variety of reasons, including restricted food intake, vomiting, food intolerances, and food aversions.[120–122] To ensure adequate nutrition postoperatively, the ASMBS, AACE, and TOS recommend that individuals follow with a multidisciplinary team made up of physicians, dietitians, and behavioral specialists.[123]

While data is limited on the number of adults with sarcopenic obesity seeking bariatric surgery, 95% or more adults undergoing bariatric surgery have a diagnosis of NAFLD.[2] Studies have consistently shown improvement in steatosis and steatohepatitis in most adults following bariatric surgery. Complete resolution of steatosis, inflammation, ballooning, and fibrosis has been cited to be 66%, 50%, 76%, and 40%, respectively.[124] Roux-en-Y gastric bypass has greater positive impact on the histological features of NAFLD compared to vertical sleeve gastrectomy or gastric banding.[124,125] Following bariatric surgery, the improvement of NAFLD has been linked to metabolic effects of insulin sensitivity, reduction of systemic inflammation, alterations in gut hormones, decreases in the proportion of obesogenic gut microbiota, and significant reduction in fat mass.[126]

7.4 | Anabolic medication

Selective androgen receptor modulators (SARMs), testosterone agonists, and myostatin inhibitors are a few of the current efficacious anabolic medications in adults with sarcopenia. In phase II clinical trials of both cancer and noncancer older adults, SARMs increased muscle mass and function.[127] The data regarding testosterone-mediated

increases in muscle strength and function is controversial. Some studies find mobility and muscle strength are not improved,[128] whereas others find the opposite.[129] This discrepancy among studies is likely due to increased lean mass after testosterone or growth hormone therapy and does not correlate directly to increased functional ability.[130,131]

Myostatin inhibition via monoclonal antibody has also been tested in animal models. Myostatin is a protein found in skeletal muscles that limits muscle growth. Myostatin is increased in adults with increased total adipose tissue.[132] Studies suggest myostatin inhibition improved muscle mass, strength, and resistance to obesity.[133,134] However, the role of myostatin, specifically in adults with sarcopenic obesity, needs to be studied further.

8 | FUTURE RESEARCH

Over the years, research in BIA has continued to grow across different disciplines of medicine. Given the ability of BIA to capture objective data on tissue distribution within the human body, clinicians now have insight into how this tool can be used to monitor sarcopenic obesity. As various BIA devices become affordable and available, the utilization of the devices may increase. Given the substantial promising research conducted in Asian populations regarding body composition assessment and NAFLD, additional research is needed to extend these findings in Western populations. The material reviewed here argues for additional prospective study of the proportion of skeletal muscle and fat mass, which is related to the presence and progression of NAFLD in Western populations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Study coordination and design, literature search, writing and revision of the manuscript, and approval of the final version: David J. Hanna, Scott T. Jamieson, Christine S. Lee, Christopher A. Pluskota, Nicole J. Bressler. Revision of the manuscript, and approval of the final version: Peter N. Benotti, Sandeep Khurana, David D. K. Rolston, Christopher D. Still.

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Appendix

TABLE 1 Characteristics of studies evaluating relationship between adiposity & NAFLD

Author(s)	Year	Country	Sample size	Adiposity Assessment	NAFLD Diagnosis	Main findings
Koda et al.	2007	Japan	• 125 adults (cross-sectional) • 25 adults (longitudinal)	• %BF by BIA • VFT by US • SFT by US with electronic calipers	• US for presence of steatosis	ALT, VFT, and serum albumin are independent factors predicting hepatic steatosis ($r = 0.591$, $r^2 = 0.349$)
Sobhonslidsuk et al.	2007	Thailand	• 30 adults (NASH) • 30 adults (control)	• BC by BIA • Total & regional body fat by DEXA • SFA & VFA by CT	• Liver biopsy • Histology by brunt criteria	VFA > 158 cm^2 (OR 18.55, 95% CI: 1.60–214.67; $p = 0.019$) and HOMA-IR > 2.8 (OR 20.98, 95% CI: 3.22–136.62; $p < 0.001$) were independent predictors of NASH
Park et al.	2008	South Korea	• 177 living liver donors	• SAT & VAT by CT	• Liver biopsy	VAT (OR 1.031, 95% CI: 1.013–1.048, $p < 0.01$) and TG (OR 1.012, 95% CI: 1.004–1.020, $p < 0.01$) were classified as independent risk factors for hepatic steatosis.
Van der Poorten et al.	2008	Australia	• 38 adults	• Visceral & subcutaneous abdominal fat volume by MRI	• Liver biopsy • Histology by brunt criteria	Visceral fat is an independent predictor of advanced NASH (OR 2.1, 95% CI: 1.1–4.2, $p = 0.05$) and fibrosis (OR 2.9, 95% CI: 1.4–6.3, $p = 0.006$)
Eguchi et al.	2011	Japan	• 550 adults • 74 adults (biopsy proven)	• VFA by BIA (550 subjects) • VFA by CT (74 subjects)	• Liver biopsy • Histology by brunt criteria	VFA in adults with stage 3-4 NASH was greater than in patients with stage 1-2 NASH ($p < 0.05$)
Choudhary et al.	2012	India	• 21 adults	• VATV, SATV, TATV by CT	• Liver biopsy • Histology by NAS	SATV [$r = 0.51$, ($p = 0.01$)] & TATV [$r = 0.47$, ($p = 0.03$)] had a significant correlation with severity of liver disease determined by NAS
Yu et al.	2015	South Korea	• 324 adults (NAFLD) • 132 adults (control)	• SAT & VAT by CT	• Liver biopsy • Histology by brunt & Kleiner criteria	VAT independently associated with NASH (OR 1.17, 95% CI: 1.05–1.32) & NAFLD with significant fibrosis (OR 1.21, 95% CI: 1.07–1.37)
Radmard et al.	2016	Iran	• 109 adults (NAFLD) • 92 adults (control)	• SFA & VFA by MRI	• MRI for presence of steatosis	VFA is significantly associated with NAFLD ($p < 0.001$).

(Continues)

TABLE 1 (Continued)

Author(s)	Year	Country	Sample size	Adiposity Assessment	NAFLD Diagnosis	Main findings
Kim et al.	2016	South Korea	• 3718 adults (baseline) • 2017 adults (at time of follow-up) [median = 4.43 years]	• VAT & SAT by CT	• US for presence of steatosis	Increasing VAT area had a higher incidence of NAFLD (HR 2.23, 95% CI: 1.28-3.89, $p = 0.002$). Increases in SAT from baseline was significantly associated with regression of NAFLD (HR 2.30, 95% CI: 1.28–4.12, $p = 0.002$)
Ko et al.	2017	China	• 2759 adults	• %BF, VFA by BIA	•US for presence of steatosis	Mild-severe NAFLD had a statistically significant relationship to increased WC, BMI, FBG, TG, SBP, DBP, %BF & VFA ($p < 0.05$)

Abbreviations: %BF, body-fat percentage; ALT, alanine aminotransferase; BC, body composition; BIA, bioelectrical impedance analysis; CI, confidence interval; CT, computed tomography; DBP, diastolic blood pressure; DEXA, Dual-energy X-ray absorptiometry; FBG, fasting blood glucose; HR, hazard ratio; HOMA-IR, homeostatic model assessment of insulin resistance; MRI, magnetic resonance imaging; NASH, nonalcoholic steatohepatitis; NAS, nonalcoholic fatty liver disease activity score; OR, odds ratio; SAT, subcutaneous adipose tissue; SATV, subcutaneous adipose tissue volume; SBP, systolic blood pressure; SFA, subcutaneous fat area; SFT, subcutaneous fat thickness; TATV, total adipose tissue volume; TG, triglyceride; US, abdominal ultrasonography; VAT, visceral adipose tissue; VATV, visceral adipose tissue volume; VFA, visceral fat area; VFT, visceral fat thickness; WC, waist circumference.

TABLE 2 Characteristics of studies evaluating relationship between skeletal muscle & NAFLD

Author(s)	Year	Country	Sample size	Skeletal muscle assessment	NAFLD diagnosis	Main findings
Hong et al.	2014	South Korea	• 452 adults	Quantity: • SMI_{WT} by DEXA • COV, 39.8% men, 34.1% women • Quality: • No assessment	• CT • LAI	Lower SMI values have a higher risk associated with the presence of NAFLD (OR 5.16, 95% CI: 1.6–16.33)
Lee et al.	2015	South Korea	• 15,132 adults	• Quantity: • SMI_{WT} by DEXA • COV, 32.2% men, 25.5% women Quality: • No assessment	NAFLD: • HSI • Comprehensive NAFLD score, • NAFLD liver fat Advanced fibrosis: • BARD • FIB-4	SMI had a negative relationship with all prediction scores of NAFLD ($p < 0.001$). Lower SMIs are associated with advanced fibrosis per BARD and FIB-4 (ORs 1.83 & 1.69; $p < 0.001$)

TABLE 2 (Continued)

Author(s)	Year	Country	Sample size	Skeletal muscle assessment	NAFLD diagnosis	Main findings
Petta et al.	2016	Italy	• 225 adults	Quantity: • SMI_{WT} by DEXA • COV, ≤37% men, ≤28% women Quality: • No assessment	• Liver biopsy • Histology by Kleiner criteria	Severe liver fibrosis had a significant relationship in patients with sarcopenia (48.3%) to those without sarcopenia (20.4%) $p < 0.001$
Koo et al.	2017	South Korea	• 309 adults	Quantity: • SMI_{WT} by BIA • COV, <29.0% men, <22.9% Quality: • No assessment	• Liver biopsy • Histology by blunt criteria • Liver stiffness by fibroscan	Increasing NAFLD severity has a significant relationship with ASM ($p < 0.001$). Fibrosis (≥F2) was significantly higher in sarcopenic (45.7%) than in nonsarcopenic subjects (24.7%) $p < 0.001$.
Kim et al.	2018	South Korea	• 10,534 adults (no baseline NAFLD) • 2631 adults (baseline NAFLD)	Quantity: • SMI_{WT} by BIA • No COV listed for sarcopenia Quality: • No assessment	• HSI	NAFLD was significantly lower in subjects with higher SMI baseline values than those with lower SMI ($p < 0.001$). Increasing SMI over 1 year had a significant risk reduction in development of NAFLD (AHR = 0.79, 95% CI: 0.67–0.93).
Choe et al.	2018	South Korea	• 1828 adults	Quantity: • SMI_{HT} by CT • COV, 8.3 kg/m^2 men, 7.47 kg/m^2 women Quality: • No assessment	• US for presence of steatosis	Increasing severity of sarcopenia from mild-severe is associated with risk of NAFLD (OR 1.45, 95% CI: 1.09–1.92) versus (OR 2.51, 95% CI: 1.16–5.56)
Wijarnpreecha et al.	2019	United States	• 11,325 adults	Quantity: • SMI_{WT} by BIA • COV, 37.0% men and 28.0% women) Quality: • No assessment	• US for presence of steatosis • Fibrosis severity by NFS criteria	NAFLD was more prevalent in sarcopenic (46.7%) versus non-sarcopenic adults (27.5%) $p < 0.001$). Independent of lifestyle and metabolic risk factors, sarcopenia was associated with higher indices of advanced fibrosis (OR 1.79, 95% CI: 1.18–2.72).

(Continues)

TABLE 2 (Continued)

Author(s)	Year	Country	Sample size	Skeletal muscle assessment	NAFLD diagnosis	Main findings
Peng et al.	2019	United States	• 2551 adults	Quantity: • SMI_{HT} by BIA • COV, <10.76 kg/m^2 men, <6.75 kg/m^2 women • SMI_{WT} by BIA • COV, <37.0% men, <28.0% women Quality: • Gait speed • COV, ≤0.8 m/s	• US for presence of steatosis and HSI for hepatic parenchyma grade of steatosis	SMI height model signified an inverse relationship between severe hepatic steatosis and SMI (OR 0.63; 95% CI: 0.46–0.87). The opposite relationship was observed when SMI was paired with weight (OR 1.73, 95% CI: 1.31–2.28)
Kang et al.	2019	South Korea	• 10,711 adults	Quantity: • LSMM-BW by BIA • COV, <29.0% men, <22.9% women) • LSMM-BMI by BIA • COV <0.789 men, <0.512 women Quality: • No assessment	• US for presence of steatosis • Fibrosis severity by NFS & FIB-4 criteria	Low skeletal muscle mass is an independent risk factor for liver fibrosis per low COV (OR 1.64, 95% CI: 1.34–1.99) and high COV (OR 2.68, 95% CI: 2.38–5.59 on NFS. The association between low skeletal muscle mass and low COV for FIB-4 was maintained after adjustment of metabolic factors examined (OR 1.26, 95% CI: 1.03–1.54)

Abbreviations: ASM, appendicular skeletal muscle; AHR, adjusted hazard ratio; BIA, bioelectrical impedance analysis; CI, confidence interval; COV, cut-off value; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; FIB-4, Fibrosis 4; HSI, hepatic steatosis index; LAI, liver attenuation index; NAFLD, nonalcoholic fatty liver disease; NFS, Nonalcoholic fatty liver disease fibrosis score; OR, odds ratio; LSMM-BW, low skeletal muscle mass by bodyweight; LSMM-BMI, low skeletal muscle mass by BMI; $SMI_{HT,}$ skeletal muscle index by height; SMI_{WT} skeletal muscle index by bodyweight, US, abdominal ultrasonography.

TABLE 3 Characteristics of studies evaluating relationship between skeletal muscle, adiposity, and NAFLD

Author(s)	Year	Country	Sample size	Body composition assessment criteria	NAFLD diagnosis	Main findings
Moon et al.	2013	South Korea	• 9565 adults	• SMI_{WT} by BIA • No COV listed for sarcopenia • VFA by BIA • SVR (skeletal muscle/ visceral fat ratio)	• FLI	An inverse relationship was noted among SMI ($r = -0.56$) and SVR ($r = -0.41$) when compared against FLI. VFA produced a strong correlation compared to FLI ($r = 0.73$).
Shida et al.	2018	Japan	• 337 adults (NAFLD) • 106 adults (control)	• SMM by BIA • VFA by BIA • SV (skeletal muscle/ visceral fat ratio)	• US for presence of steatosis • fibrosis severity by fibroscan	Decreased SV ratio indicated a risk factor for moderate to severe fat accumulation in the liver (Q_4: 1, Q_3: 1.37, Q_2: 1.81, Q_1: 1.89) similarly, decreased SV ratio indicated a risk factor for advanced fibrosis (Q_4: 1, Q_3: 1.00, Q_2: 2.18, Q_1: 3.64)
Lee et al.	2019	South Korea	• 4398 adults	• SMI_{WT} by BIA • Total adiposity by BIA	• US for presence of steatosis	Low ASM and higher total body fat increased the risk for NAFLD among men and women $p < 0.001$.
Hsing et al.	2019	China	• 3589 adults	• SMI_{WT} by DEXA • COV, 29.2% men, 25.1% women • AFR by DEXA	• FLI	AFR (>0.1) had a significant relationship with NAFLD (OR 22.9, 95% CI:, 14.3–29.7), nonsarcopenic subjects yielded a significant inverse relationship with NAFLD (OR 0.2, 95% CI: 0.1–0.2).
Chung et al.	2019	South Korea	• 5989 adults	• SMI_{WT} by BIA • COV, <29.0% men, <22.9% women • VFA by CT	• US for presence of steatosis	NAFLD prevalence was higher in sarcopenic (69.5%) than in nonsarcopenic subjects (36.5%) $p < 0.001$. NAFLD was also higher in sarcopenic obese (75.3%) than obese (62.8%) subjects $p < 0.001$.

Abbreviations: ASM, appendicular skeletal muscle mass; AFR, android fat ratio; BIA, bioelectrical impedance analysis; CI, confidence interval; COV, cut-off value; CT, computed tomography; DEXA, Dual-energy X-ray absorptiometry; FLI, fatty liver index; NAFLD, nonalcoholic fatty live disease; OR, odds ratio; Q, quartile; $SMI_{WT,}$ skeletal muscle index by bodyweight; SMM, skeletal muscle mass; SVR, skeletal muscle to visceral fat ratio; SV, skeletal muscle to visceral fat ratio; US, abdominal ultrasonography; VFA, visceral fat area.