Clinics in Liver Disease: Update on Nonalcoholic Steatohepatitis

Sarcopenia and Nonalcoholic Fatty Liver Disease

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KEYWORDS

• Steatosis • Sarcopenia • Loss of muscle strength • Non–liver-related mortality • Myokines • Myosteatosis • Lifestyle modification • Exercise

KEY POINTS

Definition for sarcopenia varies among the studies depending on the following criteria and data availability:

- Sarcopenia has a significant negative impact on survival through an increase in both liver-related and non–liver-related mortality in patients with nonalcoholic fatty liver disease (NAFLD).
- Sarcopenia is associated with loss of type 2 muscle fibers and infiltration of fat, myosteatosis, thought to be a significant risk factor for severe liver disease.
- Muscle is critical for metabolic homeostasis and reduction of chronic inflammation associated with the dual diagnoses of sarcopenia and NAFLD, through insulin resistance, lipolysis, reduction in vitamin D, testosterone, and growth hormone.
- Treatment of the condition includes weight loss, increased activity/exercise, and dietary modification to increase protein intake while reducing energy consumption.
- Efforts to educate patients and health care providers about the importance of sarcopenia in the NAFLD setting is needed for good health outcomes.

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DEFINITION OF SARCOPENIA

Irwin Rosenberg first described the term sarcopenia, which had been derived from the Greek words "sarx" meaning muscle/flesh, and "penia" meaning loss/poverty.[1] Sarcopenia originally was the term designated for age-related skeletal muscle loss. Recently, evidence has accumulated that supports an association between sarcopenia and several chronic conditions including obesity and nonalcoholic fatty liver disease (NAFLD), independent of age. In fact, the term "sarcopenic obesity" has been accepted to reflect this association. Impaired muscle strength and a standardized measure of physical performance, such as ambulation or chair stand test, are also required for the diagnosis of sarcopenia. Although the diagnostic criteria for sarcopenia have varied, a consensus has emerged: loss of skeletal muscle mass is the essential qualification and either muscle strength or physical performance should be evaluated for the diagnosis of sarcopenia (**Table 1**).

On the other hand, methodology and cut-off points vary among the individual criteria. European Working Group on Sarcopenia in Older People (EWGSOP2) recommends measuring appendicular skeletal muscle mass (ASM) using dual-energy X-ray absorptiometry (DEXA), and the cut-off of ASM for sarcopenia is 20 kg for men and 15 kg for women, or ASM divided by height squared (m^2) is 7.0 kg/m^2 for men and 5.5 kg/m^2 for women.[2] Asian Working Group for Sarcopenia (AWGS2019) recommends using DEXA and defines the cut-off of ASM divided by height squared (m^2) as 7.0 kg/m^2 for men and 5.4 kg/m^2 for women. Skeletal muscle index (SMI), which is defined as ASM/body mass index (BMI), is also described in AWGS2019, and the cut-off is 0.789 kg/BMI for men and 0.512 kg/BMI for women.[3] SMI was originally provided in Foundation of Nutritional Institutes of Health (FNIH)[4] to normalize the effect of obesity, and the cut-off for sarcopenia is the same as AWGS2019. Sarcopenia defined by SMI was more closely related to insulin resistance than ASM/height squared in the Korean population.[5] AWGS2019 defined the cut-off for ASM/height (m)^2 obtained by bioelectrical impedance analysis as 7.0 kg/m^2 for men and 5.7 kg/m^2 for women.[3] Imaging modalities including abdominal computed tomography (CT) scan and MRI are used to measure muscle mass. The Japan Society of Hepatology guideline, which was generated to define sarcopenia in chronic liver disease, includes the cut-off of the iliopsoas muscle area at the level of the third lumbar vertebra (measured by CT with the manual trace method) divided by height squared (m^2) as 42 cm^2/m^2 for men and 38 cm^2/m^2 for women.[6] This CT imaging–based procedure is strongly correlated to SMI.[7] For the evaluation of muscle strength, hand dynamometry or grip

Table 1
Recent diagnostic criteria for sarcopenia

	Skeletal Muscle	Strength	Physical Performance
EWGSOP2[2]	✓	✓	+
AWGS2019[3]	✓	✓ (either)	
FNIH[4]	✓	✓	+
JSH[6]	✓	✓	×

Note. Check mark, plus mark, and cross mark individually indicates essential qualification, additional requirement, and not necessary condition.

Abbreviations: AWGS2019, Asian Working Group for Sarcopenia; EWGSOP2, European Working Group on Sarcopenia in Older People; FNIH, Foundation for Nutritional Institutes of Health; JSH, the Japan society of Hepatology.

strength is generally measured. The cut-off for sarcopenia of EWGSOP2 is 27 kg for men and 16 kg for women.[2] In EWGSOP2, the chair stand test (5 times sit-to-stand) can be also used for evaluation of skeletal muscle strength, and the cut-off is 15 seconds. The cut-off of the grip test of AWGS2019 is 28 kg for men and 18 kg for women.[3] For the evaluation of physical performance, gate speed is mostly measured and the cut-off is 0.8 m/s, 1.0 m/s, and 0.8 m/s for EWGSOP2,[2] AWGS2019,[3] and FNIH.[4] EWGSOP2[2] and AWGS2019[3] use the short physical performance battery test, which consists of balance, gait speed, muscle strength, and endurance tests.[8] To date, there is no unified definition for sarcopenia.

The definition of sarcopenia in the studies for NAFLD is inconsistent or incomplete. In the epidemiological studies that retrospectively investigated relatively large cohorts, data availability is limited and either skeletal muscle mass[9] or strength[10] or physical performance[11] is evaluated. At times, skeletal mass was determined using different assessments (eg, DEXA, CT, MRI, or bioimpedance). Therefore, subjects included in these studies never met the full criteria for the diagnosis of sarcopenia. Methodology and the cut-off point for the evaluation of individual qualifications vary among the studies. Moreover, demographics including age, gender, and race are different among the studies. In order to test the pathological association between "conventional sarcopenia" and NAFLD in the research field, a study including the subjects who met the full criteria is probably required. On the other hand, recent studies indicate that hepatic outcome and mortality of NAFLD could be predicted by a single qualification such as skeletal muscle mass or muscle strength.[9,10] Moreover, a recent study identified that not sarcopenia but myosteatosis evaluated by CT imaging and considered to be fat infiltration in the skeletal muscle is highly correlated with liver fibrosis in NAFLD.[12] Efforts to generate sensitive and specific measures for sarcopenia in people with NAFLD that have prognostic value, are feasible, and can be easily used in the clinical setting are needed.

AN ASSOCIATION BETWEEN SARCOPENIA AND MORTALITY

Skeletal muscle plays a crucial role in energy metabolism, and sarcopenia is known as a risk factor for NAFLD. Moreover, several studies including a meta-analysis demonstrated that sarcopenia is associated with significant fibrosis independently of hepatic and metabolic risk factors in patients with NAFLD.[13–16] In addition, Petermann-Rocha and colleagues performed a prospective study of UK Biobank participants and demonstrated that sarcopenia was associated with a higher risk of developing severe NAFLD.[10] These studies suggest that sarcopenia is associated with a poor prognosis in patients with NAFLD.

Recently, several studies have examined the impact of sarcopenia on mortality in patients with NAFLD. By using public data files of the National Health and Nutrition Examination Survey (NHANES), Golabi and colleagues examined the impact of sarcopenia on mortality in patients with NAFLD.[17] Of 4611 participants, a total of 586 subjects died, of whom 251 had NAFLD during a median follow-up of 13.5 years. Among those who died with NAFLD, 33.0% had sarcopenia. Compared with nonsarcopenic NAFLD, sarcopenic NAFLD was significantly associated with a higher risk of all-cause (hazard ratio [HR] 1.78 [1.16–2.73]), cardiac-specific (HR 3.19 [1.17–8.74]), and cancer-specific mortality (HR 2.12 [1.08–4.15]). Sun and colleagues[18] also used the NHANES database. They performed a multivariate model analysis using participants with no NAFLD and no sarcopenia as the reference group. In subjects with both NAFLD and sarcopenia, risks of all-cause and cardiovascular mortality were 1.69 times (95% confidence interval [CI] 1.23–2.31) and 2.17 times (95% CI 1.33–3.54) higher than the

reference group, respectively. However, subjects with nonsarcopenic NAFLD had HRs for all-cause and cardiovascular mortality similar to those of the reference group (no NAFLD and no sarcopenia).[18] Furthermore, Kim and colleagues[19] examined all-cause and cause-specific mortality from sarcopenia using the NHANES database. They found that only in subjects with NAFLD sarcopenia was associated with a higher risk for all-cause mortality, whereas this association was absent in subjects with no NAFLD. Furthermore, sarcopenia was associated with a higher risk for cancer- and diabetes-related mortality among subjects with NAFLD. This association was not noted in subjects with no NAFLD.

In the Asian population, Moon and colleagues[9] investigated the association of sarcopenia and/or NAFLD with mortality using the database of Korean National Health and Nutrition Examination Surveys. They found that NAFLD and sarcopenia additively increased the risk of mortality on an ordinal scale (HR 1.46, 95% CI 1.18–1.81, P for trend = 0.001). The coexistence of NAFLD and sarcopenia increased mortality risk by almost twice as much, even after adjustment for advanced fibrosis (HR 2.18, 95% CI 1.38–3.44). Thus, the results of recent studies indicate that sarcopenia has a significant negative impact on survival through an increase in both liver-related and non–liver-related mortality (Fig. 1).

Histopathology of Sarcopenic Muscle

Studies of tissue pathology in patients with sarcopenia have shown a significant loss of type 2 muscle fibers, more than type 1 fibers. Type 2, or fast-twitch fibers, are associated with muscles that generate bursts of power and fatigue faster than type 1. Data comparing the morphometry of fiber loss in people with osteoporosis (OP), who are likely to have drop out of type 2 muscle fibers and likely to have sarcopenia, as compared with people with osteoarthritis (OA), show significant differences between the 2 groups. Patients with OA showed about 30.00% atrophic fibers with a diameter of less than 30 μm (16.81 ± 1.21% type I and 18.90 ± 1.24% type II), whereas, people with OP had 50.00% atrophic fibers with prevalence of type II fibers affected (19.13 ± 2.07% type I and 29.41 ± 2.56% type II). Controls (CTRL) showed less than 15% atrophic fibers. Similar differences among the 3 groups were found when

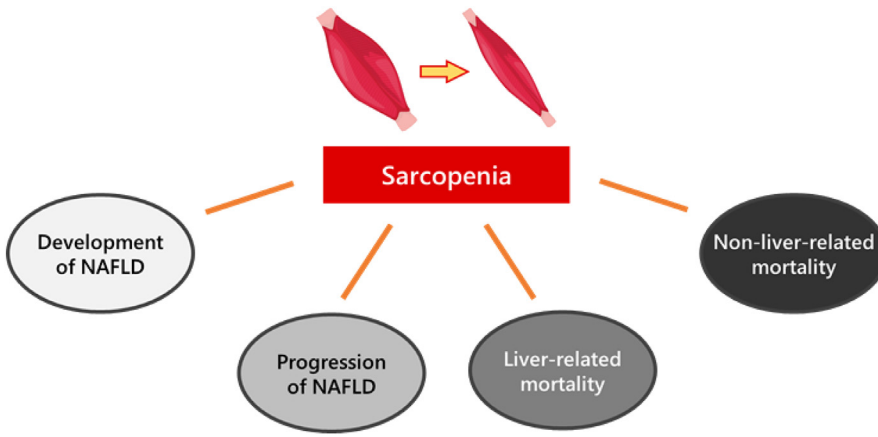

Fig. 1. An association between sarcopenia and NAFLD. Sarcopenia is associated with the development of and progression of NAFLD. Sarcopenia is also associated with both liver-related and non–liver-related mortalities in patients with NAFLD.

immunostaining and other histopathological techniques were used.[20] There was a decrease of BMP2, 4, and 7 expression in patients with OP compared with both OA group and CTRL, suggesting metabolic changes in affected muscle. Others have also found a strong association between sarcopenia and metabolic abnormalities of muscle.[21]

Biochemical and Metabolic Markers Associated with Sarcopenic Nonalcoholic Fatty Liver Disease

Linkages between sarcopenia and NAFLD, NASH, and cirrhosis and other liver diseases are many and complex. Some of this complexity is due to different definitions of sarcopenia and criteria for diagnosis. The earlier discussion in this article has identified a variety of definitions for sarcopenia and the various diagnostic criteria used throughout the world. The field has not yet designated a single set of criteria for diagnosis but there is agreement that a necessary condition for diagnosis of sarcopenia includes loss of skeletal mass. Reports of several investigators suggest there is an inverse correlation between skeletal mass and NAFLD[14] and that this is true even when controlling for obesity (odds ratios [ORs] = 1.55–3.02) or metabolic syndrome (ORs = 1.63–4.00) with p values less than 0.001.[22] Although some report that this relationship holds independent of insulin resistance, many have shown that the loss of skeletal mass is associated with decreased insulin signaling and decreased insulin response (insulin resistance), which has been discussed in recent reviews.[23,24]

There is evidence that people with sarcopenic NAFLD more frequently demonstrate significant liver fibrosis (F2, 46.0 vs 25.0%, $p < 0.001$).[25] Those with sarcopenia have a 2-fold increase in risk for NASH (OR 2.46; 95% CI, 1.35–4.48) and significant fibrosis (OR 2.01; 95% CI, 1.12–3.61).[14] The risk of fibrosis was slightly reduced when adjusted for HOMA-IR and high-sensitivity C-reactive protein but remain significant and supports the view that IR and chronic inflammation are contributors to the severity of liver disease.

Muscle has been shown to be a paracrine, autocrine, and endocrine organ. In its endocrine capacity, it secretes hormone-like products that influence the behavior of several organs. These hormonelike substances are called myokines and have been shown to exert substantial effect on metabolism in the brain, adipose tissue, bone, liver, gut, pancreas, and the vascular bed, among others. They do not always act as proinflammatory cytokines.[26] In its paracrine capacity, these molecules have direct impact on all components of muscle and mitochondria. Investigators recently identified that muscles release cytokines, challenging the belief that adipose tissue is the main source of cytokines, and further, that myokines act directly on organs such as liver and adipose, without having to invoke the central nervous system as the sole source and regulator of hormonal release. The identification of interleukin-6 (IL-6) in plasma during exercise, followed by the presence of IL-1 receptor antagonist and the antiinflammatory cytokine IL-10 supported the hypothesis, which has been confirmed, that humoral factors are released during exercise and are not inflammatory cytokines.[26] In fact, IL-6 may function as an energy sensor during exercise because plasma levels of IL-6 drop if one consumes glucose during exercise.

IL-6 has a significant impact on glucose metabolism.[27,28] IL-6 increased basal glucose uptake and increased insulin-stimulated glucose uptake in vitro. In fact, IL-6 knockout mice have been shown to develop maturity onset diabetes, glucose intolerance, and obesity.[29] The role of IL-6 is still being studied because chronic persistent elevation of IL-6 is associated with inflammation and has been associated with hyperinsulinemia, impaired glucose uptake by skeletal muscle.[30] Explanations for the various roles of IL-6 include the fact that in exercise-induced IL-6 release, levels of

IL-6 increase acutely to up to 100-fold and return to baseline, whereas in chronic conditions, the levels do not increase as steeply or as high and often do not return to baseline. This latter condition is thought to originate from the release of IL-6 from macrophages. In skeletal muscle, however, during exercise IL-6 acts intramuscularly to increase skeletal muscle glucose uptake and fat oxidation and to increase hepatic glucose production and lipolysis in adipose, hence IL-6 does not act as inflammatory myokine, as it is when released from macrophages.[31]

If the data presented earlier are valid, and exercising muscle does release high levels of IL-6, which in its capacity as a hormone facilitates skeletal muscle glucose uptake and promotes insulin sensitivity and fat oxidation, it is plausible that conditions that favor inactivity, sedentary behavior, lack of muscle contraction, and nonexercising muscle promote the opposite. Namely, a low skeletal mass status likely is associated with inefficient glucose uptake by skeletal muscle, insulin resistance, and decreased fatty acid oxidation. This hypothesis may be the link between activity (or lack thereof) and metabolic and inflammatory regulation. Data suggest that sedentary behaviors are also associated with the development of visceral adiposity, myo- and hepatic steatosis.[32]

Myosteatosis, the analogue to fatty liver in muscle, has been identified as a risk factor for more severe liver disease.[33] Muscle composition and specifically muscle fat infiltrate are associated with all-cause mortality in people with NAFLD.[34] Perimuscular fat also affects muscle atrophy. In vitro studies also support an association between inflammation and lipid metabolism as a likely pathogenesis of insulin resistance in skeletal muscle.[35] The perilipin family of proteins is embedded in lipid droplets and functions as a regulator of skeletal muscle lipid metabolism and mitochondrial oxidation. In cultured myocytes, a lipid droplet–associated protein perilipin 2 increases expression of NLRP3 inflammasome, resulting in impaired insulin-stimulated glucose uptake. These results suggest that increased fat accumulation in muscle impairs energy metabolism as well as glucose homeostasis, leading to catabolic status and atrophy of the skeletal muscle. Muscle composition, in particular muscle fat infiltration, also called myosteatosis, is a major determinant not only for muscle strength and function but also for metabolic and liver-related clinical outcomes.[24]

Inflow of fat into muscle may accumulate and thereby exceed oxidative capacity, hence fat accumulates, which blocks GLUT4. GLUT4 is critical for the entry of glucose into cells. When glucose entry is blocked, and fat accumulates in mitochondria, it inhibits mitochondrial respiration, increases reactive oxygen species formation and myocyte toxicity, and may lead to the development of sarcopenia. Intermyocellular adipose tissue (IMAT) and IMCL secrete myostatin, CCL2, TNF-α, IL-1β, and IL-6, thus inducing IR and lipotoxicity, all of which affects liver function.[36]

Fig. 2 displays contributing interactions among visceral fat, hepatic, and muscle factors relevant to the development of the inflammatory and metabolic imbalances seen in sarcopenic NAFLD. The relevant changes in liver physiology are associated with its evolution from normal, healthy tissue to steatosis and steatohepatitis, fibrosis, and cirrhosis; the role of adipose tissues, especially visceral adipose, in promoting sarcopenia and NAFLD, both metabolic and inflammatory; and the profound changes in muscles associated with the development of sarcopenia.

Functional Measures Used in Assessing Sarcopenic Nonalcoholic Fatty Liver Disease

The definition of sarcopenia includes measures of function as well as skeletal mass, and NAFLD is frequently associated with fatigue and low levels of activity.[2] Although

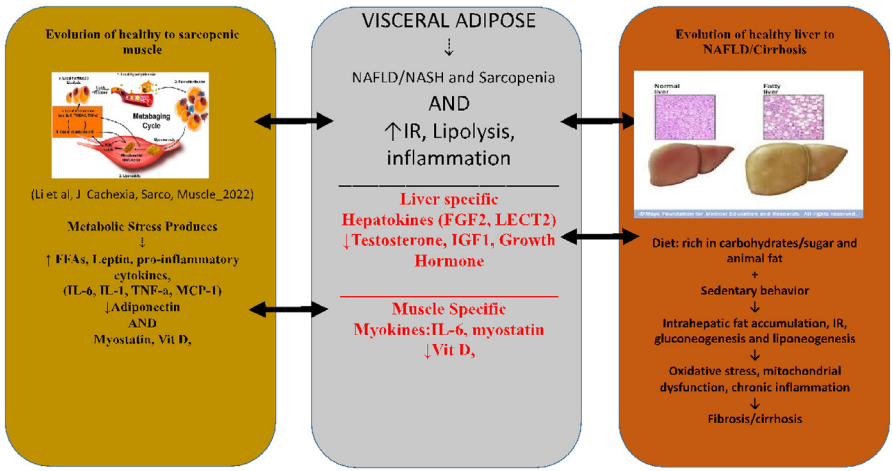

Fig. 2. Contributing interactions among visceral fat, hepatic, and muscle factors relevant to the development of the inflammatory and metabolic imbalances seen in sarcopenic NAFLD.

there is not universal agreement on which functional measures are best used to assess function, many studies include measures of strength and physical performance. Strength measures usually rely on hand dynamometry, used in assessing grip strength and overall physical performance of batteries, such as the Short Form Physical Performance Battery, gait speed, timed up-and-go, and the stair climb power test, among others.[2] These instruments are frequently used both as diagnostic criteria for sarcopenia and also to provide important information about fall risks, which is an important clinical consideration for all with sarcopenia, not only the frail elderly.

The combination of NAFLD and sarcopenia pose substantial risks. Among patients with NAFLD, the presence of sarcopenia was associated with a 78% increase in all-cause mortality. More strikingly, in the NAFLD population, sarcopenia was associated with a 320% increase in cardiac-specific deaths.[17] Furthermore, sarcopenia was associated with a higher risk for cancer- and diabetes-related mortality among those with NAFLD.[19]

It is accepted that dual diagnoses of sarcopenia and NAFLD have impact on mortality. Equally important is that it has significant impact on function and life activity. The relative risk for incident disability in sarcopenic obese subjects was 2.63 (95% confidence interval, 1.19 to 5.85), adjusting for age, sex, physical activity level, length of follow-up, and prevalent morbidity.[37] Compared with women with a healthy body composition and after adjustment for confounders, purely sarcopenic women had no increased odds of having difficulties for all of the physical functions assessed, purely obese women had a 44% to 79% higher odds of having difficulties with most of the physical functions assessed ($P < 0.05$), and sarcopenic-obese women had a 2.60 higher odds of having difficulty climbing stairs and a 2.35 higher odds of having difficulty going down stairs (all $P < 0.05$). These deficits may pose a safety risk to people with sarcopenic obesity.[38]

Additional data have been reported that suggest there is a link among insulin resistance, dementia, sarcopenia, and visceral adiposity.[39] Data have been gathered using a variety of cognitive batteries including the Mini-Mental Status Examination. The hypothetical mechanism for this is that insulin modulates glucose use in the central nervous system through receptors located in the hippocampus and frontal cortex, which has been shown to be proposed to be associated with executive functioning and poor

visual scanning (TMT-A) ($\beta = 11.005$; $P = .02$), poor visual scanning with added cognitive flexibility (TMT-B) ($\beta = 28.379$; $P < .001$), and poor cognitive efficiency.[40,41]

TREATMENT

Data have been reported from NHANES studies that show the activity levels for those with NAFLD who have sarcopenia, as contrasted with those who do not. Among the participants with a diagnosis of NAFLD without sarcopenia, 42% reported being physically inactive and 43% reported practicing the recommended level of activity for a healthy lifestyle. Among the group that had sarcopenia and NAFLD 64% were inactive and only 24% practiced the recommended level of physical activity.[17]

Both NAFLD and sarcopenia are conditions likely to respond to interventions that target weight loss and increased activity. Interventions for treating sarcopenia have been tested mainly in those with age-related sarcopenia; these include aerobic and resistance exercise and nutritional supplements, which has been shown and confirmed over the past 3 decades.[42] Many reports confirm the value of diet and exercise in the treatment of NAFLD. A recent publication of clinical practice guidelines for treatment of NAFLD summarizes the current evidence-based interventions for lifestyle modification in the treatment of NAFLD and provides best practice advice statements to address key issues in clinical management.[43] Recommendations include weight loss and reduction of total carbohydrate, fat, and sugar consumption, coupled with an increase in physical activity.

Although exercise is not an effective strategy for weight loss, it has been shown to help maintain weight loss. It is thought that exercise contributes to improvements in NAFLD and sarcopenia outcomes via a variety of different pathways. It is likely that exercise reduces visceral fat. In a 12-week controlled trial comparing an aerobic exercise intervention with no exercise, as expected, exercise training led to a reduction in visceral adipose tissue mass (probably through lipolysis) and is mediated by the myokine IL-6, which is secreted directly by muscle as a result of exercise. In this setting, IL-6 functions as a hormone, does not function as an inflammatory cytokine, but stimulates glucose uptake and lipolysis. It may also facilitate mobilization of myosteatosis.[44] The outcome of the study was a reduction in NAFLD and improvement in sarcopenia. The combination of progressive resistance training and aerobic exercise results in maximum benefits to weight loss, increase in skeletal muscle mass and strength gain, and improvements in insulin resistance in trials of older individuals aged 60 to –80 years with obesity. The highest muscle gains of up to about 1 kg after 6 months were observed in the resistance exercise group.

Resistance exercise is effective and safe to prevent muscle loss even in old (mean age 87 years) and frail individuals, potentially by also decreasing skeletal muscle apoptosis and improving mitochondrial function and diminishing muscle apoptosis.[45] Treatments for sarcopenia have been shown to be useful, but many investigators indicate that prevention of sarcopenia is more effective. Critical to both treatment and prevention is assessment of what is referred to as “good” protein intake. The issue of what is “good” (or best) source of protein is as yet unresolved. Many believe animal protein is optimal because it is easily digested and absorbed. Many studies have supplemented diet with animal protein (whey) but others believe plant-sourced protein is best. Nonetheless, optimal dietary protein intake, daily 1.0 to 1.2 g/kg with 25 to 30 g of high-quality protein per meal, is what is recommended to prevent sarcopenia. All studies indicate the importance of complete amino acids, branch chain amino acids, and in particular, leucine and cheese and milk protein (whey).[46] Recent studies have demonstrated the value of adding vitamin D to this regimen. A review of several

controlled trials for dietary interventions effective for treating sarcopenia has recently been published.[47]

As of this writing, specific trials to evaluate the best regiment for diet, exercise, and functional outcomes have not yet been reported, but it is very likely that interventions targeting treatment of NAFLD focus on weight loss and increased activity, and efforts to increase muscle mass using resistance and aerobic exercise are likely to have good outcomes in people with sarcopenic obesity.

The substantial challenges to improved health and functional outcomes that face the health care community and patients with this disorder are the following: (1) educating stakeholders about the health risks of sarcopenic NAFLD; (2) establishing generally acceptable diagnostic criteria and readily available tools with which to determine these; and (3) making a commitment to instituting the demonstrated effective lifestyle changes.

CLINICS CARE POINTS

- Definition of sarcopenia: focuses on low muscle strength as a key characteristic of sarcopenia, uses detection of low muscle quantity and quality to confirm the sarcopenia diagnosis, and identifies poor physical performance as indicative of severe sarcopenia.
- Evaluation of sarcopenia should consist of measures of muscle strength, physical function, such as ambulation or sit-to-stand, and appendicular muscle mass.
- The combination of NAFLD and sarcopenia is a risk for all cause mortality and associated with high risk for cancer and diabetes-related mortality. This combination should be screened for.
- Treatment for sarcopenic obesity includes aerobic and resistance exercise, 25-30 g high quality protein per meal and control(if present) of pre-diabetes/diabetes.

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