REVIEW

Sarcopenic obesity in fatty liver

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Purpose of review
Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steato hepatitis have an increasing prevalence among liver diseases. Overweight and obesity are frequently associated conditions in patients with fatty liver. Skeletal muscle mass depletion may also coexist with chronic liver disease even in obese patients. This review will focus on the relationship between sarcopenic obesity and fatty liver.

Recent findings
Obesity and sarcopenia are frequently encountered in patients with NAFLD. Adipose tissue is able to release molecules (adipokines) that regulate lipid metabolism, interact with insulin sensitivity and may contribute to induce fibrogenesis in the liver. Skeletal muscle tissue is able to secrete myokines regulating muscle metabolism and insulin sensitivity. Myokines perturbation has been reported to influence adipose tissue mass and fat deposition in the liver. Sarcopenia has been reported as independent risk factor for the development of NAFLD, and for a more severe liver fibrosis in patients with NAFLD.

Summary
The interaction between skeletal muscle, adipose tissue and the liver may play a role in the development of NAFLD. Sarcopenia and sarcopenic obesity are risk factors for the development of fatty liver and associated with more severe liver fibrosis. Management is not standardized, but dietary counseling and physical training have been proposed as promising strategies. Bariatric surgery may be considered in patients with severe 'resistant' obesity.

Keywords
insulin resistance, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, sarcopenia, sarcopenic obesity

SARCOPENIC OBESITY AND NONALCOHOLIC FATTY LIVER DISEASE: THE MAGNITUDE OF THE PROBLEM

In the last decade, nonalcoholic fatty liver disease (NAFLD) is becoming the most common cause of chronic liver disease and liver failure in Western countries [1]. The prevalence of NAFLD is estimated to range between 20 and 30% in the general population, about 30% of these patients will develop a nonalcoholic steato hepatitis (NASH) and 30–40% of them will progress into liver fibrosis and cirrhosis [2]. A recent meta-analysis analysis of studies involving more than 8.5 million people from 22 different countries showed that more than 80% of patients with NASH are overweight or obese [3]. At the same time some studies reported a higher prevalence of sarcopenia, a condition of progressive and generalized loss of muscle mass and strength, in patients affected by NAFLD [4▪▪,5▪▪]. It is still under debate if these conditions, 'fat gain' and 'muscle loss', may be involved among the causes of liver fat accumulation or if they should be considered mainly a bystander. Significantly, in some of these patients skeletal muscle loss and increase in adipose tissue may even coexist, evolving to the scenario of the so called *sarcopenic obesity*.

The term *sarcopenic obesity* was firstly introduced by Baumgartner *et al.* in the elderly population, describing an interplay between obesity and sarcopenia related to progressive sedentarism and physical inactivity and a consequent reduction of energy expenditure. The first observation that sarcopenia, and eventually *sarcopenic obesity,* could be involved in NAFLD came from a large population study, the Korean Sarcopenic Obesity Study [6]. The authors examined 452 apparently healthy adults enrolled in a prospective observational cohort study. The presence of sarcopenia was associated with an increased risk of developing NAFLD. *Sarcopenic obesity* has been also reported in patients affected by advanced

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KEY POINTS

- Prevalence of sarcopenic obesity and NAFLD is increasing and a possible interplay of the two conditions is suggested.
- A muscle–liver–adipose tissue axis is proposed as a common pathophysiological background.
- Sarcopenic obesity may accelerate liver fibrosis in patients with fatty liver.
- Treatment of sarcopenic obesity through nutritional counseling and an increase in physical activity is advisable in patients with NAFLD.
- Patients with severe obesity undergoing bariatric surgery may improve liver fibrosis.

chronic liver disease and has gained remarkable interest being associated with higher mortality in patients with liver cirrhosis [7▪,8,9].

DEFINITION OF SARCOPENIC OBESITY

A consensus definition for *sarcopenic obesity* is lacking and should derive from the knowledge of how to diagnose patients with sarcopenia and obesity. The European Working Group on Sarcopenia in Older People consider sarcopenia in presence of alteration of both muscle mass and strength, however, more commonly, sarcopenia is diagnosed taking account the muscle mass only. When a computed tomography (CT) scan, performed as for other indication, is available sarcopenia is evaluated through the skeletal muscle index (SMI) by measuring the total abdominal muscle area at L3 [10,11].

CT scan is also able to inform about the proportion of intermuscular and intramuscular fat, the so-called myosteatosis [8]. Myosteatosis increases with age and adiposity and it is associated with metabolic abnormalities, decreased strength and mobility [8,12]. In patients with advanced liver disease myosteatosis is associated with a decreased muscle function and worse median survival [8].

If a CT scan is not available, the evaluation of the appendicular SMI (ASMI) by dual energy x-ray absorptiometry could be a possible alternative. bioelectrical impedance analysis (BIA) and anthropometry are other complementary tools that can be utilized by trained staff. All these methods need to apply threshold values derived from a sex and age matched population. For CT-SMI threshold values were derived from inactive oncologic patients or from a population of patients with liver disease listed for liver transplantation according to their mortality [13] ASMI, BIA, and anthropometric normal values are generally available.

Obesity is defined by a BMI of at least 30 kg/m^2 in white populations and at least 25 kg/m^2 in Asian population, with further subclasses into Class I (30–34.9 kg/m^2), II (35–39.9 kg/m^2), and III ($\geq$40 kg/m^2) obesity [14]. However, BMI does not give information about the relative proportions of fat and lean body mass. Considering a similar BMI, women have a higher proportion of adipose tissue while men have a higher proportion of lean muscle mass; furthermore, fat accumulation translates into increased subcutaneous adipose tissue (SAT) in women and in increased visceral adipose tissue (VAT) in men. Therefore, the evaluation of SAT and VAT would be more appropriate, when possible, to better characterize these patients. For instance, the deleterious effects of obesity, including the development of NASH, are strongly associated with an increased VAT [15,16]. VAT compared with SAT is richer in cells, particularly large adipocytes, which are metabolically active, as well as inflammatory and immune cells therefore, it is important to distinguish these two components. However, VAT and SAT can be evaluated only through cross-sectional CT scan.

THE MUSCLE–LIVER–ADIPOSE TISSUE AXIS

NAFLD and sarcopenic-obesity share a similar pathophysiological background. Common findings in both these conditions are: increased proinflammatory markers, decreased physical activity, reduced protein intake, disease-related reduction in testosterone and growth hormone levels [17▪]. The possible interplay between adipose tissue, muscle mass, and liver, leading to *sarcopenic obesity* and NAFLD is shown in Fig. 1.

The pathogenesis of sarcopenic obesity in liver disease is multifaceted and further research is required to clarify both clinical and molecular aspects and to identify the mechanism of interplay among muscle, liver, and adipose tissue [4▪▪,18,19].

Until recently, adipose tissue has been mainly considered as an energy storage deposit, but in recent years this view has been largely modified. Indeed adipose tissue has been found to be able to release proteins, hormones, cytokines, and growth factors. These molecules, also known as adipokines, may act through autocrine-pathways that regulate lipid accumulation and adipocyte differentiation. In particular, adiponectin, ameliorates insulin sensitivity, and its reduction in obesity contributes to insulin resistance and glucose intolerance [20]. Moreover, being adiponectin an antisteatotic, anti-inflammatory and antifibrotic adipokine, low

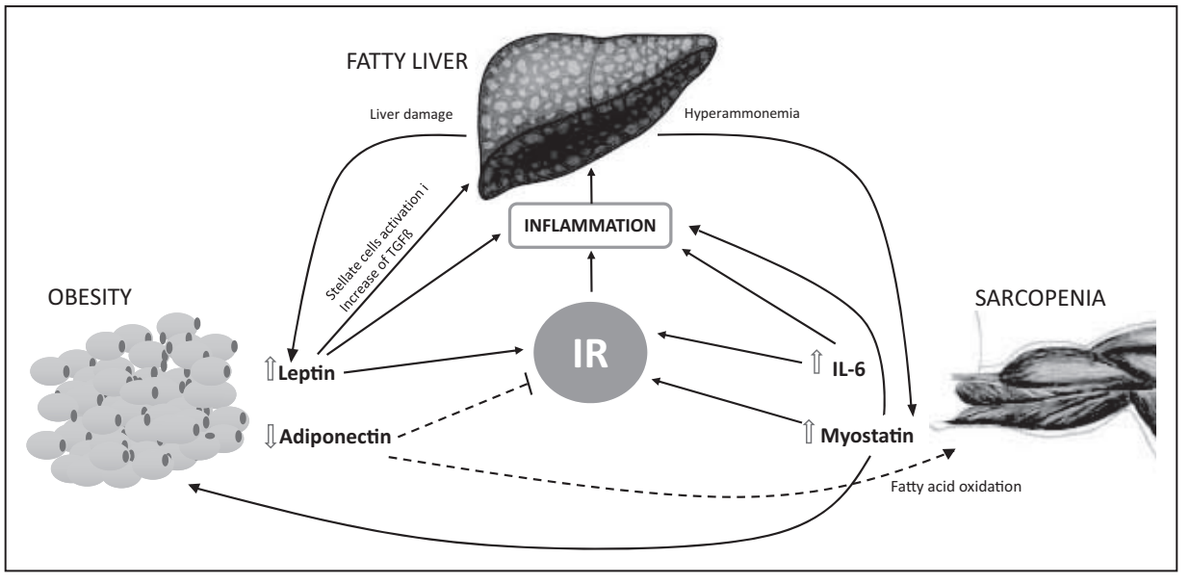

FIGURE 1. A muscle–liver–adipose tissue axis has been suggested as a possible cause of sarcopenic obesity and nonalcoholic fatty liver disease interplay. In obesity there is a reduction in adiponectin and an increase in leptin levels that contribute to reduced insulin sensitivity and glucose intolerance, increased inflammation and sarcopenia. At the same time leptin may induce the activation of hepatic stellate cells and these cells are involved in liver fibrosis. Activated hepatic stellate cells are also able of producing leptin causing the persistence of high levels. Liver disease may also contribute to sarcopenia through hyperammoniemia, high levels of myostatin induce proteostasis in skeletal muscle. Myostatin also increase adipose tissue mass and decreases adiponectin secretion. IL-6 contributes to inflammation and glucose intolerance. IR, insulin resistance; TGFβ, transforming growth factor β.

adiponectin levels may predispose to fatty liver and advanced hepatic injury [20,21]. Leptin, being a mitogenic substance that stimulates activated hepatic stellate cells division and enhances the synthesis of inflammatory and profibrogenic factors in these cells, also contributes to fibrogenesis in chronic liver diseases. At the same time, activated hepatic stellate cells are capable of producing leptin, and this is supposed to further maintain the mechanism leading to liver fibrosis [22]. Finally, leptin also induces an increased synthesis of transforming growth factor β (TGFß) in Kupffer cells, which contributes to fibrosis progression.

Skeletal muscle can also be seen as an endocrine organ secreting various myokines [23]. A number of animal studies have shown that myostatin, a TGFß superfamily member, which was originally discovered as a regulator of skeletal muscle mass, above the role of regulating skeletal muscle metabolism, has also significant hepatic effects. Blocking myostatin causes not only an increase in muscle mass, but also improves insulin resistance and protects animal models from the development of fatty liver [24,25]. It has been reported that adiponectin receptors in muscle are involved in the regulation of insulin signaling and are able to increase, at the same time, fatty acid (FA) oxidation; however the adiponectin–myostatin cross-talk has never been proven in details [26]. Since myostatin increases adipose tissue mass, and this, in turn, decreases adiponectin secretion, it can be speculated that the liver–muscle–adipose tissue perturbation may begin in the skeletal muscle and act on both liver and adipose tissue. IL-6 is another myokine that potentially regulates hepatic FA oxidation via an adenosine monophosphate-activated protein kinase dependent mechanism. Secretory and signaling perturbations of other myokines (myonectin and irisin) that regulate lipid and glucose metabolism have been suggested to contribute to the development of insulin resistance and fatty liver [27] in patients with NAFLD.

THE IMPACT OF SARCOPENIC OBESITY IN NONALCOHOLIC FATTY LIVER DISEASE AND LIVER CIRRHOSIS

In elderly people, sarcopenic obesity is associated with a worse prognosis in terms of increased risk of metabolic and cardiovascular disease, increased healthcare costs and mortality [28–30]. Obesity, via insulin resistance and systemic inflammation, is associated with a worse prognosis and higher fibrosis in patients with NASH [1,31]. However, recent studies have shown that also sarcopenia is

related to the progression of NAFLD-related fibrosis [32▪▪]. Petta *et al.* examined 225 patients with histological diagnosis of NAFLD and documented that the prevalence of sarcopenia was independently associated with the severity of fibrosis, being severe fibrosis (F3–F4) more than doubled in sarcopenic patients (48.3 vs. 20.4% in fibrosis ≤F2, $P < 0.001$). Furthermore, this study confirmed a correlation between obesity and sarcopenia [4▪▪]. Hong *et al.* [6] demonstrated a higher risk of NAFLD in those with lower muscle mass after adjusting for confounding factors such as insulin resistance and inflammation. The individuals with sarcopenia presented a higher prevalence of metabolic syndrome, higher C-reactive protein levels, and higher body fat mass when compared with those without sarcopenia. Similar results were reported in another study [33]. More recently, Lee *et al.* [34] observed that sarcopenia was associated with significant liver fibrosis in patients with NAFLD (odds ratio 0.52–0.67; $P < 0.01$), independently of obesity and insulin resistance. However, it is important to highlight that in this study liver fibrosis was assessed through noninvasive scores such as Forns, fibrosis-4 index, and NAFLD fibrosis score. These data were confirmed in a recent study conducted by Koo *et al.* in which 309 patients were evaluated. A multivariate analysis adjusted for age, sex, BMI, hypertension, diabetes, and smoking status demonstrated that in the group of biopsy-proven NAFLD, patients with sarcopenia were more likely to develop NASH than those without sarcopenia [odds ratio, 2.28; 95% confidence interval (CI), 1.21–4.30] [6].

Sarcopenia and obesity are well known negative prognostic factor in liver cirrhosis [10,35,36]. Existing studies in cirrhosis are limited, but they have reported a quite high prevalence of sarcopenic obesity, from 5 to 35%, and an association with worse prognosis and increased mortality [8,9,37]. A further study documented a worse prognosis in patients with sarcopenic obesity awaiting liver transplantation, the same study showed that patients with NASH have a six-fold increase risk of sarcopenic obesity [37].

THE MANAGEMENT OF SARCOPENIC OBESITY

Though novel approaches are under investigation, there is, at present, no consensus for the treatment of sarcopenic obesity in patients with liver disease. Reasons for the lack of effective therapies are incomplete understanding of the underlying mechanisms of sarcopenia in liver disease and lack of sensitive and specific biomarkers for the diagnosis. For this reasons therapies have been mainly based on deficiency of replacement rather than on mechanistic targets. The management of obesity, in patients with liver disease, is currently based on weight loss and modifications of lifestyle. The most important proposed strategies are therefore nutritional therapy, and increased physical activity. When patients are severely obese bariatric surgery is also a possible option.

Nutritional therapy

Weight loss has been reported as a keystone element for the improvement of the histological features of NASH [38,39]. The best therapeutic approach is based on energy restriction obtained with a low calorie (1200–1600 kcal/day), low fat (<10% of saturated FA) and low carbohydrate diet (<50% of total kcal) [40]. Considering that weight loss following caloric restriction in overweight/obese patients results in fat mass loss (75% of the loss) and muscle mass loss (around 25%), very low-calorie diets are inappropriate in liver disease patients who are likely to be also sarcopenic. A 5–10% weight loss is the target of most lifestyle interventions. To avoid the loss of muscle mass, which is certainly harmful in patients with sarcopenia and liver disease, adequate protein intake has been recommended [41]. In older individuals, a minimum protein intake of 25–30 g per meal has been suggested for optimal muscle protein synthesis. In cirrhotic patients, to prevent the state of 'accelerated starvation,' patients should avoid fasting for longer than 4–6 h. Evidence supports small frequent meals and the use of a late night snack containing at least 50 g of complex carbohydrates as well as a source of protein [42].

Exercise

To increase energy expenditure and prevent muscle mass loss, physical activity should be always implemented in patients with sarcopenic obesity. In elderly people with sarcopenic obesity a multicomponent intervention has been proposed to obtain weight reduction and increased physical activity through counseling for changing lifestyle [43].

In NAFLD an exercise-oriented meta-analysis showed improvement in steatosis, even if the level of exercise is below that recommended for the management of obesity and even in presence of minimal or no weight loss [44]. Two other meta-analyses demonstrated exercise-related improvement of liver function and steatosis [45▪,46]. Notably, one of these studies reported that exercise was more beneficial in severely obese individuals and confirmed that the effect was not associated with the intensity of the intervention (number and duration of sessions, and period of training intervention) or the alteration in diet [46].

In liver cirrhosis, some studies suggested a beneficial effect of exercise training associated with branched chain amino acids supplements in improving nutritional status [47▪]. A small randomized pilot trial, while giving leucine supplements 10 g/day orally for 12 weeks in all participants, proposed exercise training in eight and no physical intervention in nine cirrhotic patients (controls). Lower thigh circumference and the 6-min walking test both improved significantly ($P = 0.01$) only in those cirrhotic patients who combined exercise training with Leucine supplements [48].

Bariatric surgery

In patients with 'resistant' obesity, bariatric surgery has proven to be effective for achieving sustained weight loss and can reverse risk factors that contribute to the pathogenesis of NAFLD, including dyslipidemia, insulin resistance, and inflammation, making it a promising treatment option for NAFLD. A recent systematic review and meta-analysis examining data from 32 cohort studies comprising 3093 biopsy specimens, found that patients' mean NAFLD activity score was reduced significantly after bariatric surgery (mean difference, 2.39; 95% CI, 1.58–3.20; $P < 0.001$) [19].

There are limited data on the effect of bariatric surgery in patients with sarcopenic obesity. The risk of excessive loss of muscle mass exists, especially if weight loss is rapid and if bariatric surgery is not followed by a regular exercise program [49]. Since there is no available randomized controlled trial for bariatric surgery in patients with sarcopenic obesity, the best evidence to date comes from a 12-month prospective cohort study in which the effect of bariatric surgery (gastric bypass or sleeve gastrectomy) was evaluated in a cohort of morbidly obese patients comparing sarcopenic with nonsarcopenic patients [50]. Bariatric surgery resulted in similar weight loss and similar improvement in comorbidity (i.e., type 2 diabetes mellitus, NAFLD, hypertension, dyslipidemia, obstructive sleep apnea syndrome, and arthritis) in both groups. Notably, muscle mass was not different between groups 12 months after surgery, thus implying that sarcopenic patients did not lose more muscle mass despite similar weight loss.

In conclusion, sarcopenic obesity and NAFLD are strictly correlated and the interrelation between muscle, adipose tissue, and liver, results in a vicious circle in which sarcopenia, obesity, and liver disease, contribute one to the other. Sarcopenic obesity is a negative prognostic factor in patients with NAFLD therefore this condition needs to be identified and possibly treated. Dietary and lifestyle counseling are, at present, the main recommended approach. In severely obese patients bariatric surgery needs to be considered.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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