Review

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Sarcopenia and Metabolic Dysfunction-Associated Steatotic Liver Disease: A Narrative Review

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Abstract: The fundamental goal of modern medicine is to increase human life expectancy. Currently, most of the patients in hospitals with different clinical profiles are elderly and senile subjects, with a high incidence of comorbidities, as well as concomitant age-related changes in peripheral tissues. One such change is sarcopenia, a progressive loss of muscle mass, strength, and muscle function that is associated with a high risk of adverse outcomes, leading to an increased risk of disability and death among older adults. The mechanisms of development of sarcopenia are currently being actively studied. This narrative review presents the issues of epidemiology, pathophysiology, and diagnostic criteria for sarcopenia. The relationships between sarcopenia and metabolic dysfunction-associated steatotic liver disease (MASLD) with possible promising directions for the treatment of this comorbid pathology are considered.

Keywords: sarcopenia; metabolic dysfunction-associated steatotic liver disease; diagnostic; treatment

1. Sarcopenia: Where Is the Problem?

One of the fundamental goals of modern medicine is to increase human life expectancy. Currently, most hospitalized patients with different clinical profiles are elderly and senile subjects, with a high incidence of comorbidities, as well as concomitant age-related changes in peripheral tissues. One such change is sarcopenia. Sarcopenia is a syndrome of progressive and generalized loss of mass strength and skeletal muscle function [1,2]. By 2050, sarcoma will become a global problem due to the increased number of elderly and senile people [2], increasing health care costs, morbidity, and disability. In the Organization's report United Nations 2023: "*Don't leave no one left behind in an aging population world*" emphasized that in 2021 the world population there were 761 million people aged 65 years and older, which is 5.9 times more than in 1950, and 2.3 times more, than in 1991. According to the average version of the UN forecast, in the next 30 years, the number of elderly people in the world and old age may increase by another 2.1 times, up to 1664 million people. at the beginning of 2051 [3]. It is well known that all tissues of the human body are formed from digestive substances (nutrients) entering the gastrointestinal tract with food with their further intake into the bloodstream. At different age periods of life in humans, there is a different ratio of the main ingredients of food. Protein requirements in children are significantly higher compared to adults, since proteins (especially animal origin) provide a growing organism child with essential amino acids [4]. In adults, muscle mass also increases is impossible without an adequate supply of protein food. Skeletal muscle is mainly composed of proteins, carrying out metabolic reactions for energy production using glucose and lipids, and is capable of self-repair after physical activity [5]. Human muscle tissue is the main protein pool under conditions of inadequate nutritional support, as well as

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during stressful situations. With prolonged catabolic fasting, exhaustion (or cachexia) develops with loss of muscle and fat mass. During catabolism, muscle protein is used for the needs of the human body as a source of amino acids for remodeling and is used for energy supply through gluconeogenesis. In this case, muscle wasting, physical weakness, and loss of performance develop [4,5]. The first scientific work in the field of studying sarcopenia was an article published in 1931 by the English neurologist M. Critchley, in which age-related changes in muscle tissue were called «senile atrophy» [6]. The term «sarcopenia» was first proposed in 1989 by American professor I. Rosenberg describes the process of loss of skeletal muscle in elderly patients [7]. Recent evidence demonstrates that sarcopenia development is characterized by epigenetic dysregulation of multiple molecular pathways associated with sarcopenia pathogenesis, such as protein remodeling, insulin resistance, mitochondria impairments, and the creation of a systemic, chronic, low-grade inflammation [8]. During sarcopenia, there is a progressive decrease in muscle mass, strength, and function with the development of their exhaustion, the predominance of degradation of muscle protein over its synthesis, and simultaneous increase or preservation of adipose tissue with the development of the phenomenon of sarcopenic obesity. According to some authors, the concept of sarcopenic obesity involves a simultaneous decrease in muscle mass and strength and an increase in fat of more than 25% in men and 38% in women of total body weight according to the results of dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis [9,10]. Sarcopenia leads to a decrease in physical activity and, consequently, an increase in fat mass, while the development of obesity is accompanied by an increase in the production of pro-inflammatory cytokines, dysregulation of leptin and adiponectin secretion, and a decrease in muscle sensitivity to insulin, which further aggravates sarcopenia, as reported in Figure 1.

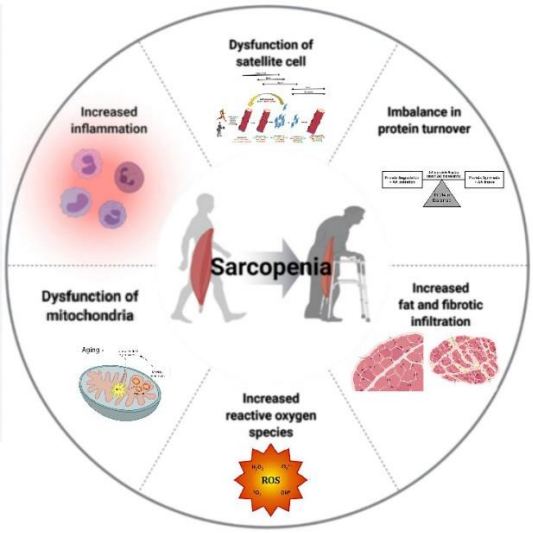

Figure 1. Pathological processes involved in sarcopenia development.

2. Sarcopenia and Systemic Risks

It has been established that patients with sarcopenic obesity have an increased risk of developing cardiovascular pathology and heart failure (23% and 42%, respectively) [11]. There is evidence of a manifold increase in the risk of metabolic syndrome, arterial hypertension, and dyslipidemia in patients with sarcopenic obesity [12]. Thus, using the example of 4252 British men aged 60–79 years, it was demonstrated that sarcopenic obesity is significantly associated with an increase in the overall risk of death by at least two times, including from cardiovascular causes [13]. Sarcopenic obesity is associated with inflammation, and increased risk of fractures, and is observed in patients with visceral obesity, while patients with excessive accumulation of subcutaneous fat have a lower mortality rate, which fits into the concept of the so-called “obesity paradox.” It is worth noting that There are currently more than 500 in the literature articles with conflicting results on the effect of

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obesity on sarcopenia. Conducting large-scale research focused on identifying diagnostic criteria for sarcopenic obesity phenotypes (visceral and subcutaneous) will in the future provide a personalized approach to the treatment and prevention of this state [14]. Until recently, inevitable age-related depletion of muscle mass in elderly, senile, and long-lived people was considered exclusively as a geriatric problem. Due to the aging of the human population, in recent years Consensus documents were adopted on sarcopenia in people of older age groups [1,2,15,16]. The European Working Group on Sarcopenia in Older People (EWGSOP) defines sarcopenia as "a syndrome characterized by progressive and generalized loss muscle mass and strength with an increased risk of adverse events such as disability, deterioration in quality of life and death" [1]. The prevalence of sarcopenia ranges from 5 to 13% in people aged 60–70 years and reaches 50% in persons over 80 years of age [1,2]. A feature of muscle status is its influence on the prognosis for the life of an elderly person. When analyzing 2-year survival in older patients, the greatest prognostic influence was exerted by the grip strength of the hand and the ability to self-service [17]. Low-performance muscle strength and balance disorders identified in study participants significantly increased their risk of future falls. As a person ages, each decade lived until old age increased risk of mortality due to low body weight. The lowest mortality rate among women of advanced and old age was noted with a body mass index (BMI) equal to 31.7 kg/m2, and for men the same age, this figure was 28.8 kg/m2 [18]. Age-related changes in sarcopenia and physical weakness in the elderly are based on inflammatory pathogenesis, immune sensitization, anabolic resistance, and oxidative stress. These phenomena potentiate a sedentary image of life and protein-energy malnutrition due to age-related loss of appetite [19]. Several age-related diseases also lead to sarcopenia (chronic heart failure, chronic obstructive pulmonary disease, chronic kidney disease) [20].

3. Molecular and Pathophysiological Mechanisms of Sarcopenia

Is sarcopenia only a geriatric problem? Today, sarcopenia is diagnosed among middle-aged and young people, and even in children with severe illnesses [20]. Muscle wasting in this case is considered as an inflammatory condition. In some patients, Sarcopenia is accompanied by osteoporosis and obesity with the replacement of muscle tissue by adipose tissue. Myo-steatosis develops with the accumulation of fatty tissue in the muscle structure, which is the result of increased systemic anabolic resistance [5]. Due to myo-steatosis, it develops functional failure of muscles, which increases the risk of mortality [16,19]. Today, primary and secondary sarcopenia are distinguished. Primary (or age-related) Sarcopenia is caused by factors that accompany aging. Sarcopenia that develops with certain conditions (lack of consumption of protein and/or energy, taking glucocorticoids, muscle relaxants, weightlessness) and due to long-term diseases are called secondary [2,21,22]. Sarcopenia can be either a consequence or the cause of various diseases. The pathogenesis of sarcopenia is based on hyperammonemia and a low amount of branched-chain amino acids, harming life patient prognosis [23,24]. Ammonia is involved in the pathogenesis of sarcopenia through mechanisms involving increased expression of myostatin and autophagy markers, which leads to disruption of muscle tissue metabolism and sarcoma. Skeletal muscle replaces the liver as the primary site of ammonia detoxification as a result of modifications of genes encoding key proteins, which are involved in reducing ammonia levels. A vicious cycle occurs in which hyperammonemia causes muscle damage and sarcopenia, limiting the muscle's ability to remove excess blood-borne ammonia, and a vicious circle closes [25,26]. Although muscle tissue is not considered an endocrine organ, muscles are metabolically active [27]. In recent years, more than 650 myokines secreted by muscles, only 5% of which have been studied in detail today [28–31]. During muscle aging, the expression of myokines, in particular interleukin-15 and myostatin, changes, which triggers the development of sarcopenia [15]. Muscle atrophy is characterized by increased protein degradation, where signaling growth factors play an important role. Nuclear factor receptor transcriptions (PPAR) are activated by fatty acids and their derivatives. PPARs regulate genes that are involved in development, metabolism, inflammation, and other cellular processes in various organs PPARs are also expressed in muscle exerting pleiotropic reactions. There are three PPAR isotype (PPAR-α, -β/δ, -γ). Marked high expression of PPAR-α in tissues with efficient catabolism of

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fatty acids, including skeletal muscle. PPARβ/δ is expressed ubiquitously and is the predominant isotype in skeletal muscles, participating in energy metabolism and fiber type switching. PPAR-y is expressed in adipocytes, participating in lipid deposition in muscles and other organs. Taken together, all three PPAR isotypes have important effects on homeostasis muscles. Research in recent years has discovered the relationship between PPARs and the intestinal microbiota since the amount of PPARs changes with the depletion of skeletal muscles during their interaction with intestinal microbiota [5]. Experimental studies on laboratory animals have proven the influence of the luminal microbiota of the intestine on the weight and function of skeletal muscles. Skeletal muscle tur and the content of metabolites in blood serum in mice with sterile intestines significantly differed in the amount of amino acid alanine and glycine, decreased expression of genes encoding proteins involved in assembly and function neuromuscular junctions, from mice with a healthy intestinal microbiome. Intestinal transplant microbiota in germ-free mice increased the volume of muscle mass and functional activity of muscles, which proves the influence of microbiota intestines on the regulation of skeletal muscle mass and function in mice [32]. Experimental models of aging have shown an increase in mucosal permeability in intestines due to age-related changes in the luminal intestinal microbiome. At the same time, the luminal microbiota itself can modulate the phenomenon of "anorexia of aging" [14,19,20,33–35].

4. Sarcopenia Classification and Diagnostic Models

In the 2010 Consensus, the EWGSOP recommended the use of three criteria to diagnose sarcopenia: low muscle mass, determined by computed tomography (CT), magnetic resonance imaging (MRI), two-photon x-ray absorptiometry (DXA) ultrasound examination, bioimpedance analysis to assess the volume of fat and lean body mass, thickness measurement skin-fat fold caliperometry; low muscle strength determined by dynamometry; decreased muscle function, determined chair rise, and speed tests walking [1]. According to the EWGSOP Consensus, there are three stages of sarcopenia: I – pre-sarcopenia, characterized by a decrease in muscle mass without reducing its strengths and functions; II - sarcopenia, characterized by decreased skeletal muscle mass, strength, or functions; III - severe sarcopenia, characterized by a decrease in all three parameters - mass, strength, and muscle function [2,36,37]. Sarcopenia staging is important when choosing treatment and rehabilitation of patients. Recommendations for the diagnosis of sarcopenia were updated in the 2019 EWGSOP-2 consensus [2]. In the EWGSOP-2 sarcopenia diagnostic algorithm, the starting point is the presence of 4 points or more on the SARC-F questionnaire [38]. The main indicator of probable sarcopenia is reduced muscle strength, measured dynamometry [2,26]. The diagnosis is confirmed as reduced muscle mass. With simultaneous decreased muscle mass, strength, and function sarcopenia is considered severe [22]. CT, MRI, assessment of musculoskeletal index (media), as well as ultrasound examination are the diagnostic "gold standards" for assessing muscle mass [39–41]. In the Consensus recommendations, EWGSOP-2 emphasizes that ultrasonic assessment of muscle mass is a reliable and reliable method for identifying sarcopenia in older people with comorbidities [16,36,42,43]. Ultrasound methods for determining muscle mass (for example, measuring the thickness of the rectus abdominis muscle) are more accurate compared to anthropometric methods, as well as greater accessibility than CT, DXA, and bio-impedance analysis, and can be performed by every patient without restrictions, as reported in Figure 2 [44–50].

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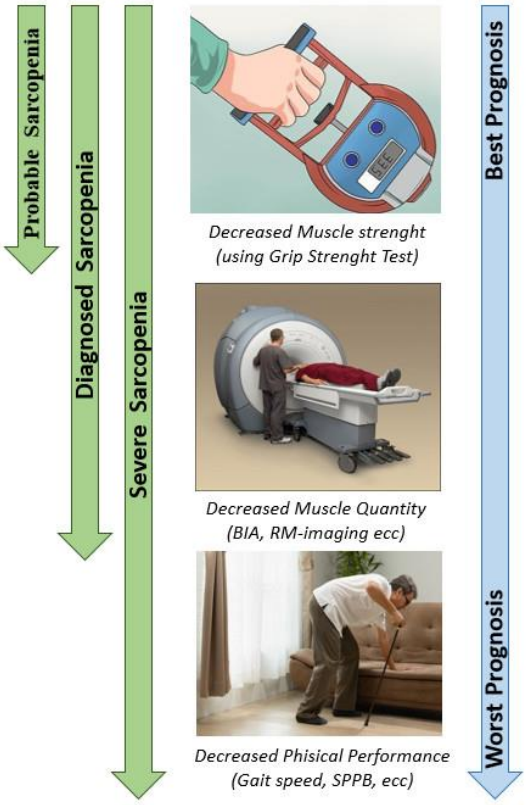

Figure 2. Diagnostic models of sarcopenia.

5. MASLD and Sarcopenia: The Muscles–Liver Axis

To date, enough has been a large number of studies on the effect of sarcopenia on the development of metabolic disorders, including a number on the development of metabolic dysfunction-associated steatotic liver disease (MASLD). This axis based on data «muscles-liver», allows a new way to look at a third of medicinal and non-medicinal approaches to the treatment of MASLD, and provides a convincing rationale for studying skeletal muscle as a therapeutic target for MASLD [51]. MASLD, formerly called non-alcoholic fatty liver disease (NAFLD), is defined as steatotic liver disease in the presence of one or more cardiometabolic risk factors and the absence of harmful alcohol use. MASLD includes steatosis, metabolic dysfunction-associated steatohepatitis (MASH, formerly non-alcoholic steatohepatitis, NASH), fibrosis, liver cirrhosis, and MASH-associated hepatocellular carcinoma (HCC) [52,53]. The prevalence of MASLD is increasing worldwide world, reflecting the current epidemic of obesity with the development of insulin resistance, type 2 diabetes mellitus (T2DM), and metabolic syndrome [54]. 30% of patients with MASLD with compensated cirrhosis reach the stage of decompensation through 8–10 years. The severity of fibrosis in MASLD serves as a predictor of unfavorable outcomes associated with the risk of death and transplantation of the liver [55–57]. Risk factors for the progression of diagnosis of MASLD are age over 50 years, metabolic syndrome (MS), dyslipidemia, insulin resistance (IR), T2DM, arterial hypertension, elevated ferritin levels, and mononucleotide polymorphism of the *PNPLA3* gene [58,59]. The first study to find an association between sarcopenia and MASLD was a 2010 study that found that in individuals with age-related sarcopenia, which is associated with higher BMI and fat mass, there was an increased prevalence of MASLD [60]. Further studies showed that during the aging process, an increase in fat mass and a decrease in muscle mass to an acceleration of metabolic disorders [61]. S. W. Kim *et al.* produced a large-scale work on the relationship between sarcopenia and MASLD, based on national survey data on health and nutrition in South Korea. Patients like obese and non-obese patients showed a significantly higher prevalence of MASLD associated with sarcopenia [62]. Besides, the same study showed that among patients with MASLD,

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the presence of sarcopenia was independently associated with a higher likelihood of progressive liver fibrosis, assessed using non-invasive predictors of fibrosis [62]. Recent studies have shown that sarcopenia is closely associated with obesity and MASH. A causal relationship has been established between sarcopenic obesity and MASH. Although obesity is a major risk factor for MASLD and MASH, some patients with MASLD have a normal BMI. The term "non-obese" refers to people with a normal or overweight BMI. Almost 40% of patients with MASLD do not suffer from obesity, while about 10% of them have a normal BMI (<25.0 kg/m2), and about 30% have an excess weight without obesity (BMI 25.0–29.9 kg/m2). However, the risk of NASH and other metabolic diseases in non-obese patients is no lower than in obese individuals, as they may also develop cardiovascular disease and hepatocellular carcinoma (HCC). At the same time, the pathogenesis of MASLD without obesity remains unclear. One of the possible hypotheses is that loss of skeletal muscle mass reduces the sensitivity and specificity of BMI in diagnosing obesity. Research has revealed a close connection between MASLD and sarcopenia. The prevalence of sarcopenia gradually increases as MASLD progresses. Conversely, sarcopenia increases the risk of developing MASH or liver fibrosis in patients with MASLD and affects mortality from liver cirrhosis. Sarcopenia is also common and occurs in non-obese individuals. In patients with MASLD without obesity, muscle mass, and muscle strength are significantly lower when compared with obese patients. It's important to pay more attention to assessing the condition of skeletal muscles in patients with MASLD and finding effective treatment both for liver disease and for the treatment of sarcoma. Further research is needed to reveal the detailed relationship between sarcoma and MASLD and to propose new ideas for strategies for their treatment. Numerous potential mediators of the muscle-liver axis, include decreased testosterone and hormone levels growth, ammonia, and endotoxemia [63]. Myokine - myostatin, which is a regulator of skeletal muscle mass, also has pronounced hepatic effects. Blockade myostatin in experimental studies not only increased muscle mass in laboratory animals but also protected mice from the development of MASLD and increased sensitivity to insulin [64,65]. Myostatin in early childhood age accelerates the development and growth of adipocytes [66]. The myostatin receptor ACVR2B is also present in hepatic stellate cells, which makes possible the mutual influence of skeletal muscles and the liver. The development of inflammatory changes in the liver of patients with MASLD can stimulate the activation of myostatin and lead to the development of sarcopenia. On the other hand, primary development sarcopenia may indirectly activate stellate cells through myostatin liver. Adiponectin is another potential mediator in the muscle-liver axis. Adiponectin receptors in muscles regulate insulin signaling and enhance the oxidation of fatty acids, which is supposed to be the existence of a cross-link between adiponectin and myostatin [67]. Obesity and inflammation of adipose tissue are accompanied by hypoadiponectinemia. Because myostatin increases mass adipose tissue, and this in turn reduces the secretion of adiponectin, this process can begin in skeletal muscles, affecting both the liver and adipose tissue [51]. Recent work has shown that in patients with nonalcoholic fatty liver disease at the stage of steatosis, a more pronounced hyperammonemia compared with individuals without concomitant liver damage [68]. In 2019 for the first time the Russian Consensus was adopted in the world: "Hyperammonemia in adults" (2019; 2021), reflecting indicated problems in various diseases, including liver diseases [69]. For patients with liver pathology and concomitant sarcopenia, it is important to study the level of ammonia in capillary blood, since in such patients along with the phenomena of hepatic encephalopathy (HE) hyperammonemia is observed [23]. Leptin and other adipokines from adipose tissue increase muscle catabolism and, as a consequence, the development of sarcopenia, the presence of which in MASLD is associated with a high likelihood of progressive liver fibrosis [62,70]. Ammonia (NH3) is formed in the human body as a result of the activity of the intestinal microbiota, as well as the breakdown of proteins and amino acids during physical exercise. Urea synthesis in hepatocytes is the main way to neutralize ammonia. Urea accounts for up to 85% of the total nitrogen excreted from the body. Hence, in patients with obesity and MASLD, disorders occur at all levels: intestinal dysbiosis due to nutritional disorders; decreased tolerance to physical activity with a predominance of decay proteins; and decreased hepatocyte function. HE develops when ammonia levels increase by 1.5–2.0 times due to the toxic effect of ammonia on the fabric brain. This affects the body's adaptation to physical

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activity, as well as the metabolism of skeletal muscles, which leads to the progression of MASLD. Hyperammonemia disrupts the contractile function of skeletal muscles and increases physical weakness even outside depending on the loss of muscle mass, as well as has an important effect on the synthesis of myokines [71]. Ammonia utilization is compensated by muscles' limited periods during intensive physical activity. However, since in inflammatory diseases of the liver skeletal muscles become the main organ accumulating ammonia, increased muscular uptake of ammonia disrupts the contractile response of skeletal muscles [71].

6. Treatments and Future Directions

Skeletal muscle renewal is a slow process, and a temporary decrease in ammonia levels in the blood serum does not necessarily reduce the level of ammonia in muscles or prevent metabolic and molecular disorders. Necessary long-term decline strategy research ammonia levels before this approach can be used to reverse muscle loss mass and disturbances of its contractile function. New, potentially effective methods for reducing muscle ammonia levels include the use of cell-permeable esters alpha-ketoglutarate, which can provide direct reactions with the removal of ammonia in the form of glutamine. Glutamine utilization is an important factor in long-term ammonia management strategies to protect skeletal muscles. As substrates isoleucine and valine were suggested because they can remove one mole of ammonia per mole of amino acids. However molecular and functional answers These interventions have not yet been evaluated in preclinical or clinical studies to reduce muscle ammonia or reduce sarcopenia. New molecular targeting strategies, capable of influencing protein metabolism in skeletal muscles, include the use of myostatin antagonists, direct target activators (mammalian target of rapamycin), antioxidants, and mitochondrial protective agents. However, large-scale preclinical studies are needed on these potential treatment strategies for sarcopenia, before they are transferred to clinical practice [72]. Sarcopenia is detected in almost half of patients with liver cirrhosis. Ammonia is involved in the pathogenesis of sarcopenia in cirrhosis through mechanisms including increased expression of myostatin and autophagy markers, which leads to impaired muscle tissue metabolism and sarcopenia. Skeletal muscle replaces the liver at the primary link of ammonia detoxification as a result of the modification of genes encoding key proteins that participate in reducing ammonia levels during cirrhosis. A vicious circle is formed in which hyperammonemia causes muscle damage and sarcoma, limiting the muscle's ability to remove excess blood-borne ammonia [73,74]. At liver cirrhosis, sarcopenia reduces the quality of life of patients, increases mortality, and increases the risk of HE [26,75,76]. High concentrations of ammonia cause neurotoxicity leading to a neurological disorder known as hepatic encephalopathy. Ammonia is harmful to skeletal muscles. In animal models, excess ammonia, caused by liver failure and portal hypertension, negatively affects muscle protein homeostasis through mechanisms including ATP depletion, nuclear activation factor kappa-B, and activation of myostatin, thereby promoting muscle degradation. Muscle weakness in end-stage liver disease is due in part to high ammonia concentrations, as strategies to reduce ammonia levels in preclinical models of cirrhosis reduce sarcopenia [77]. High ammonia levels in patients with cirrhosis are associated with severe complications and increased mortality, which makes the study of ammonia levels an important laboratory marker and therapeutic target [24]. Hyperammonemia due to hepatocellular dysfunction and portosystemic shunting in cirrhosis, is a mediator of the «muscle-liver» axis and contributes to the development of sarcopenia in this patient category [78]. Hyperammonemia activates proteolysis of skeletal muscles through autophagy, increasing the expression of myostatin, which disrupts protein synthesis in muscles with the formation of sarcopenia [79]. When assessing the effects of non-drug treatment of patients with sarcopenia in association with MASLD the effect of regular physical exercise has been studied in patients. Was found, that in obese subjects with preserved weight skeletal muscle, regular physical exercise was associated with a significantly reduced likelihood of MASLD (46% vs. 55%; $p < 0.001$) [62]. Mitochondrial dysfunction of skeletal muscles promotes muscle atrophy, as well as how disrupted the skeletal muscle substrate is, by expending energy, they contribute to the development and progression of NAFLD. Considering the positive effect of increased physical activity on both hepatic and extrahepatic components of the metabolic syndrome, correction of

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mitochondrial dysfunction of the skeletal muscle is another promising approach for the treatment of metabolic disorders, including MASLD [51]. Elam *et al*. assessed the effect of L-ornithine and L-arginine on endurance and increase in muscle mass in healthy people male volunteers under high physical loads. One-half of them received amino acids (2 g L-arginine and 1 g L-ornithine), and the other half received a placebo. Endurance was assessed volume of muscle mass and destruction rate of muscle-urinary hydroxyproline. Researched, those taking L-ornithine and L-arginine gained significantly more muscle mass (p<0.05), showed greater endurance (p<0.05), and had a significantly lower level of urinary hydroxyproline (p<0.05) than in the control group [51]. The results of other studies also included present data on a significant increase in levels of serum hormone at 45 and 90 minutes after intense anaerobic exercise while taking 170 mg/kg L-ornithine [80]. During drug treatment of patients with NAFLD with loss of muscle mass, the positive effects of the drug L-ornithine-L-aspartate (LOLA). Decline ammonia levels using LOLA increased muscle mass in patients with steatosis, improved cognitive functions, reduced the time of hospital stay, and significantly improved the quality of their lives [81]. An experimental study of muscle changes in a rodent model of MASH was conducted to clarify their internal relationships and explore potential corrective therapeutic agents. LOLA was found to significantly increase lean body mass, grip strength, and mean diameter muscle fibers in mice. This data indicates that the occurrence of MASH precedes sarcopenia in mice treated with a high-fat diet, and associated with steatohepatitis, hyperammonemia may contribute to the pathogenesis of sarcopenia. Overall, LOLA can be an effective drug for both steatohepatitis and sarcopenic obesity, what should happen next is confirmed in groups of patients [63]. LOLA therapy is effective in patients with sarcomas associated with MASLD/MASH. For example, in a study performed on 463 patients with fatty liver, 29% of whom were non-alcoholic, sick treated with oral LOLA for up to 60 days. As a result, a significant decrease in initially elevated liver enzymes. In another randomized clinical trial study, 72 patients received oral LOLA for 12 weeks. Specifically, a significant dose-dependent decrease has been shown in transaminase levels together with a decrease in triglycerides, and an improvement in the liver/spleen ratio. Cases of improved microcirculation in the liver have also been described in patients with MASH who received LOLA. Confirmation of these initial findings of the beneficial effect of LOLA for the treatment of sarcopenia in chronic liver diseases (such as MASLD and cirrhosis) is now required in large, well-controlled studies to demonstrate that LOLA monotherapy is an effective drug for the prevention and treatment of sarcopenia in chronic diseases liver [82]. The use of LOLA in complex therapy of patients with MASH normalizes biochemical activity and reduces atherogenic changes in fractions of serum lipoproteins [51,83]. Ammonia reduction with LOLA simultaneously increased lean body mass in patients with liver pathology [26]. Experimental animal studies models of HE, as well as in patients with liver cirrhosis and hyperammonemia showed that LOLA is effective in reducing circulating ammonia levels and leading to a reduction in the severity of HE. The underlying mechanism involves both the liver and skeletal muscles. Since L-ornithine is a key intermediate of the urea cycle, it can stimulate the conversion of ammonia to urea by periportal hepatocytes. At the same time, ammonia is also removed to a significant extent due to conversion into glutamine predominantly in muscles, since transamination of L-ornithine produces glutamate. Through those two independent mechanisms (urea synthesis in the liver and glutamine synthesis in muscles), LOLA treatment also reduces muscle ammonia, which leads to improved skeletal muscle tone [82]. Ammonia-lowering therapy is clinically approved in patients with cirrhosis and may be prescribed to reduce sarcopenia in liver cirrhosis. Meta-analyses suggest LOLA as an effective ammonia-lowering agent by stimulating residual hepatocyte urea synthesis and muscle glutamine synthesis with the utilization of ammonia in the muscles. In patients with cirrhosis and concomitant sarcopenia synthesis rate muscle protein levels improved significantly after treatment of LOLA [84–86]. Thus, lowering ammonia levels with LOLA increased lean body mass in patients with liver cirrhosis, limiting induced ammonia sarcopenia due to improved synthesis and muscle protein function, improved cognitive function, shortened hospital stay, and significantly reduced mortality, as reported in Table 1 [26,82,87–89]. In patients with cirrhosis with concomitant sarcopenia for treatment in addition to exercise and LOLA are used antibiotics, lactulose, branched-chain amino acids, testosterone, vitamin

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D, zinc, and diet [90]. For example, correction of vitamin D deficit has a favorable effect on muscle mass. Treatment of sarcopenic obesity already established is yet unsatisfactory, although intense and prolonged diets with higher (1.2 g/kg body weight) protein content, and soy isoflavones all look promising [90]. The main purpose of prescribing antibiotics to patients with hyperammonemia and HE is the suppression of urease-producing intestinal microbiota [91]. Preference is given to the non-absorbable antibiotic rifaximin-alpha, whose positive effect on the treatment of hyperammonemia is shown in several clinical studies [90]. In connection with the above, in the future, it seems relevant to further search for cause-and-effect relationships between sarcopenia and MASLD as comorbid diseases, as well as new directions for their diagnosis and treatment methods [92].

Table 1. Summary of different clinical features and potential treatments related to sarcopenia.

Topic	Details	References
Skeletal muscle renewal	• Slow process, temporary decrease in blood ammonia does not necessarily reduce muscle ammonia or prevent metabolic disorders. • Long-term strategies needed.	[72]
Potential treatments	• Alpha-ketoglutarate esters for direct ammonia removal as glutamine. • Use of isoleucine and valine to remove ammonia. • Myostatin antagonists, mTOR activators, antioxidants, and mitochondrial protectors.	[72]
Ammonia and sarcopenia	• Sarcopenia common in liver cirrhosis, with ammonia involved in its pathogenesis. • Ammonia causes muscle damage, impairs protein metabolism, and contributes to sarcopenia.	[23,26,73–79]
Impact of exercise	• Regular physical exercise in obese patients reduces the likelihood of MASLD, improves muscle mass, and reduces sarcopenia.	[51,62]
LOLA	• Effective in reducing ammonia levels, increasing muscle mass, and improving cognitive function in patients with liver disease and sarcopenia. • Confirmed in both animal studies and clinical trials.	[26,51,63,81–89]

Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; LOLA, L-ornithine L-aspartate.

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