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ОСОБЕННОСТИ ВЕДЕНИЯ БОЛЬНЫХ С НАЖБП И САРКОПЕНИЕЙ

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Features of Management of Patients with NAFLD and Sarcopenia

Резюме

С учетом роста заболеваемости неалкогольной жировой болезнью печени (НАЖБП) и демографического старения населения саркопения стала рассматриваться как одно из патологических состояний, участвующих в развитии и прогрессировании НАЖБП. Установлено, что НАЖБП и саркопения связаны с резистентностью к инсулину и атрофией скелетных мышц как органа-мишени инсулина. В патогенезе НАЖБП участвуют воспалительные цитокины с последующим распадом белков скелетных мышц, адипонектин, низкий уровень которого приводит к снижению чувствительности к инсулину, оксидативный стресс с активацией катаболических процессов и развитием атрофии мышц. Прогрессирование саркопении при НАЖБП является прогностическим фактором и увеличивает риск смертности. Саркопения, преимущественно возникающая за счет снижения мышечной массы, в сочетании с увеличением висцерального жира, достаточно часто приводит к саркопеническому ожирению и при НАЖБП увеличивает риск сердечно-сосудистых заболеваний. Гипераммониемия, аномальная микробиота кишечника, липидные факторы также способствуют развитию саркопении у пациентов с НАЖБП. Учитывая общие патогенетические механизмы, указывающие на двунаправленную связь между саркопенией и НАЖБП, мультидисциплинарный подход к ведению больных с НАЖБП и саркопенией в настоящее время представляется наиболее оптимальным. Современные концептуальные стратегии направлены на раннюю диагностику НАЖБП и саркопении, оздоровление образа жизни таких больных, поиск эффективных лекарств, комплексное персонализированное лечение, профилактику прогрессирования данных заболеваний и их осложнений.

Ключевые слова: *неалкогольная жировая болезнь печени, саркопения, ожирение, мышечная масса, мышечная сила, мышечная функция*

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Abstract

Nowadays non-alcoholic fatty liver disease (NAFLD) and sarcopenia are actually considered as one of the pathological condition with involvement into development of pathology of liver and skeletal muscles. Scientists of different countries found that sarcopenia is associated with insulin resistance and skeletal muscle atrophy as an insulin target organ. Spredly known many cytokines of inflammation with variable affection of skeletal muscle proteins, low level of adiponectin, decreased insulin sensitivity, oxidative stress with activation of catabolism leading to muscle atrophy are involved into complicated pathogenesis of NAFLD. Progressive sarcopenia associated with NAFLD is prognostic factor and can increase the risk of mortality. Sarcopenia, which due to decreased skeletal muscle mass and increased visceral fat, very often provokes development of sarcopenic obesity and NAFLD. Hyperammonemia, abnormal intestinal microbiota, lipid factors also contribute to the development of sarcopenia in patients with NAFLD. Given the common pathogenetic mechanisms indicating a bidirectional relationship between sarcopenia and NAFLD, a multidisciplinary approach to

the management of patients with NAFLD and sarcopenia could be the most optimal. Modern strategies are aimed at early diagnosis of NAFLD with sarcopenia, optimizing the lifestyle of these patients, searching for effective drugs, personalizing treatment and prevention of the progression of these diseases and their complications.

Key words: *non-alcoholic fatty liver disease, sarcopenia, obesity, skeletal muscle mass, muscle strength, muscle function*

Conflict of interests

Co-author of the article Statsenko M.E. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Statsenko M.E. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

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AOP — antioxidant protection, ROS — reactive oxygen species, WHO — World Health Organization, HCC — hepatocellular carcinoma, DHEA — dehydroepiandrosterone, IR — insulin resistance, CT — computed tomography, CPK — creatine phosphokinase, HDL — high-density lipoproteins, MS — metabolic syndrome, MRI — magnetic resonance imaging, NAFLD — non-alcoholic fatty liver disease, NASH — non-alcoholic steatohepatitis, LPO — lipid peroxidation, RCTs — randomised controlled trials, DM2 — type 2 diabetes mellitus, TG — triglycerides, UDCA — ursodeoxycholic acid, LC — liver cirrhosis, ANGPTL4 — angiopoietin-like protein 4, ASM — appendicular skeletal muscle mass, ASMM — appendicular skeletal muscle mass measurement, BIA — bioelectrical impedance analysis, CRP — C-reactive protein, CX3CL1 — monocyte chemoattractant protein 1, DXA — dual-energy X-ray absorptiometry, EMA — European Medicines Agency, EWGSOP — European Working Group on Sarcopenia in Older People, FDA — Food and Drug Administration (USA), IGF1 — insulin-like growth factor 1, IL-6 — interleukin 6, SARC-F — Strength, Assistance with Walking, Rising from Chair, Climbing Stairs, and Falls, SARM — synthetic androgen receptor modulators, SMM — skeletal muscle mass, SPPB — Short Physical Performance Battery, TNF-α — tumor necrosis factor α, TUG — walking time test, TWEAK — TNF-like weak apoptosis inducer, VEGF — vascular endothelial growth factor

This article represents the analysis of literature in ELibrary, PubMed reference databases concerning publications in 2007–2023.

Non-alcoholic fatty liver disease (NAFLD) is currently defined as the most common chronic liver disease that includes steatosis, non-alcoholic steatohepatitis (NASH) with fibrosis, liver cirrhosis (LC), and hepatocellular carcinoma (HCC). Prior studies have demonstrated that NAFLD increases the risk of cardiovascular diseases, cancer, type 2 diabetes mellitus (DM2) [1–3]. Sarcopenia has been deemed the progressive disease associated with DM2, metabolic syndrome (MS), liver diseases, and cardiovascular diseases [6–8]. A common combination of NAFLD and sarcopenia can be considered two interdependent conditions associated with aging, systemic inflammation, and insulin resistance (IR) [8].

The term „sarcopenia" meaning age-related muscle mass loss was introduced into practice by I. Rosenberg in 1989. In 2000, R.N. Baumgartner proposed the term „sarcopenic obesity", i.e. the condition characterised by the combination of excessive adipose tissue in the body and decreased muscle amount, decreased muscle strength, and impaired muscle function [5].

In 2010 and 2019, European Working Group on Sarcopenia in Older People (EWGSOP) developed and published diagnostic criteria, which made sarcopenia a widely renowned disease [6, 7].

The prevention of sarcopenia and its detection in the presarcopenia stage in patients with NAFLD is an up-to-date objective of modern medicine. It has been shown that the risk of NAFLD in patients with sarcopenia is increased more than 5-fold, regardless of the presence of obesity [8, 9]. S. Petta et al. detected a linear incremental growth of the sarcopenia & fibrosis (especially severe fibrosis, F3–F4) severity association. Significant associations have also been proven for sarcopenia and NASH, sarcopenia and steatosis severity. The prevalence of sarcopenia in the European population with hepatic fibrosis depending on its severity is as follows: F0 — 22.2 %, F1 — 34.9 %, F2 — 43.7 %, F3 — 66.6 %, F4 — 60.0 %. With that, the prevalence of severe fibrosis along with sarcopenia was higher both in patients with visceral obesity (46 % vs. 30.9 %) and in patients without obesity (44.4 % vs. 7.1 %, respectively) [10].

The association between sarcopenia prevalence and steatosis severity has been detected in the Asian population. Sarcopenia was observed in healthy subjects from the control group without NAFLD (~8–22 %), in patients with NAFLD (~18–38 %) and NASH (~35–63 %). A high incidence of NASH with fibrosis (46 %) was also detected in patients with sarcopenia compared to those without it (25 %), as well as with a higher risk of NASH (2.5-fold) and significant fibrosis in patients with NAFLD, regardless of obesity and IR [11–14].

Diagnostic aspects of NAFLD and sarcopenia

In NAFLD, fat is detected in over 5 % of hepatocytes in patients not abusing alcohol (< 20 g/day for females, < 30 g/day for males), while the severity varies from simple steatosis to steatohepatitis, progressive fibrosis and LC. Liver biopsy is currently considered the „golden"

standard of NAFLD diagnosis despite limitations concerning the sample variability, invasiveness, and high costs.

Multiple non-invasive biomarkers, serum markers, imaging methods are mainly intended to detect steatosis, NASH, or severe fibrosis. Currently US examination is proposed as a screening method for the diagnosis of steatosis in the target population, while the diagnosis of NAFLD requires the exclusion of other steatosis causes in chronic liver diseases. Progressive fibrosis is important in the NAFLD diagnosis; this can be excluded using the NAFLD Fibrosis Score, FIB-4 score, or with transient elastography. The most reliable diagnostic methods are represented by magnetic resonance imaging, enabling the accurate steatosis evaluation or determining the fibrosis stage, although they are still not applicable in routine practice [3].

The updated consensus document EWGSOP2 presented in 2019 defines sarcopenia as a progressive and generalised disease of skeletal muscles characterised by the decreased muscle strength, mass, and physical ability. The main attention is paid to low muscle strength as a key criterion for the diagnosis of sarcopenia, with the addition of evaluating muscle amount and quality to confirm the diagnosis. Severe sarcopenia is diagnosed in the presence of all three criteria: low muscle strength, low muscle amount or quality, and decreased physical ability. Sarcopenia is divided into acute and chronic forms: an acute condition spans for less than 6 months, while the chronic form lasts ≥ 6 months [6, 7].

In clinical practice, the diagnosis may start from the detection of symptoms, i.e. frequent falls, weakness sensation, slowed walking rate, and difficulties when rising from a chair. In such cases, further testing for sarcopenia is recommended. To screen for sarcopenia, EWGSOP2 proposes the SARC-F (Strength, Assistance with Walking, Rising from Chair, Climbing Stairs, and Falls) questionnaire, enabling patients to assess their limitations of daily activities independently. The questionnaire consists of five items and serves as a simple tool for the detection of sarcopenia risk in clinical conditions. EWGSOP2 specifically denotes a high SARC-F validity, its sensitivity from low to moderate, and very high specificity for the prognosis of low muscle strength with ≥ 4 points [6, 7].

As an alternative, a more formal tool is proposed for the detection of sarcopenia cases in clinical populations — this Ishii test is based on three variables: age, grip force, and calf circumference. Functional tests are more informative in the muscle strength assessment. „Rise from a chair" test defines the time within which a patient can rise from a chair five times without using arms (it is usually over 15 s in sarcopenia) [6, 7].

Based on EWGSOP2 guidelines, the amount of skeletal muscles is assessed as their total mass (SMM), as well as the mass of appendicular skeletal muscles. Magnetic resonance imaging (MRI) and computed tomography (CT) are defined as a golden standard for the non-invasive evaluation of the skeletal muscle amount or mass according to the latest EWGSOP2 guidelines; nevertheless, in the majority of cases these methods are not widely used due to high equipment costs and the absence of highly qualified staff. As noted by EWGSOP2, dual-energy X-ray absorptiometry (DXA) is more frequently preferred to measure the appendicular skeletal muscle mass (ASMM) [6, 7].

Normal values for the appendicular skeletal mass (ASM) (DXA) are as follows: males > 7.26 kg/m^2, females > 5.76 kg/m^2.

Bioelectrical impedance analysis (BIA) does not measure the muscle mass directly, but rather assesses the muscle mass based on the electric conductivity of the whole body [6, 7].

Physical ability may be tested using the 4-meter walking speed, Short Physical Performance Battery (SPPB), walking time test (TUG), 400-meter walking test [6, 7].

Reference values for physical ability tests are as follows:

- 4-meter walking speed < 6 seconds is considered normal;
- SPPB test ≥ 10 points defines the well-fit physical form;
- TUG test < 10 seconds is considered normal;
- 400-meter walking test < 6 minutes is considered normal.

Muscle quality may be evaluated using the phase angle measured using BIA [6, 7].

The ultrasound method is recommended to measure the muscle amount and quality [6, 7].

The search for laboratory biomarkers of the muscle mass loss is considered perspective, requiring further studies.

Testing ammonia levels in patients with NAFLD and concomitant sarcopenia is important, as sufficient scientific data demonstrate that hyperammoniemia is an important factor of the impaired contractile skeletal muscle function [15]. Multiple studies have demonstrated that ammonia synthesis in hepatocytes is the main route of ammonia neutralisation. NAFLD with the impaired hepatocyte function promoting intestinal dysbiosis leads to the decreased tolerance to physical loads and hyperammoniemia. With that, skeletal muscles become the main organ accumulating ammonia, which impairs the contractile response of skeletal muscles. Leptin and other adipokines from the adipose tissue enhance the muscle catabolism and progressive hepatic fibrosis, which also makes the analysis of adipokines important when studying patients with sarcopenia and NAFLD [16] (Figure 1).

Increased blood cortisol levels may leads to insulin resistance (IR), metabolic syndrome (MS), increased levels of specific cytokines, and obesity. Consequently, cortisol may be a potential biomarker of sarcopenia and NAFLD.

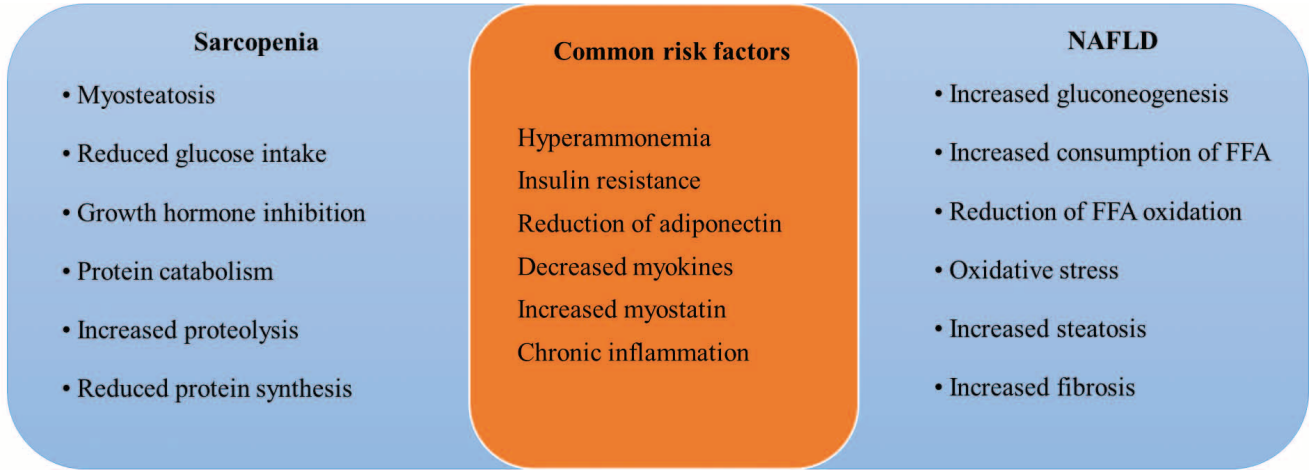

Figure. *Interaction between pathogenesis of sarcopenia and NAFLD.*
List of abbreviations: FFA — free fatty acids

Sufficiently significant data from studies demonstrate that skeletal muscles, liver, and adipose tissue exhibit variable activity (endocrine, autocrine, and paracrine) [17]. Secretion of cytokines and other signal molecules forms the basis of molecular crossover interactions in the „muscle-liver-adipose tissue" system, with cortisol acting as a key modulator. Chronic inflammation is considered a result of increased plasma levels of pro-inflammatory mediators, e.g. tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) [18]. Other circulating agents, i.e. TNF-like weak apoptosis inducer (TWEAK), IL-18, insulin-like growth factor 1 (IGF1), insulin, leptin, adiponectin, have been confirmed to be associated with sarcopenia and NAFLD — thus, they can be considered potential markers [19, 20]. Besides, the developing oxidative stress and accumulation of reactive oxygen species (ROS), trending to increase with age, cause severe lesions of the skeletal muscle cells, also participating in the NAFLD pathogenesis [19, 20]. Thus, testing for lipid peroxidation (LPO) and antioxidant protection (AOP) system may be important in patients with NAFLD and sarcopenia.

Actual issues of NAFLD and sarcopenia prevention and treatment

Non-drug aspects of NAFLD and sarcopenia treatment

According to modern national and European guidelines, a reconvalescent lifestyle is

feasible, which presumes a healthy diet, sufficient physical activity, body weight normalisation as a basis for the treatment and prevention of NAFLD, IR; this is especially important both for sarcopenia and „sarcopenic obesity" [3, 6, 7, 17, 21–24]. Guideline preferences focus on the Mediterranean diet, specifically counting the calories, with the optimal balance of vegetables, fruits, seafood, monounsaturated fatty acids, ω-3,6,9-polyunsaturated fatty acids, various plant fibers, and products with a low glycemic index. The diet also presumes rational limitation of sweet beverages and simple carbohydrates, increased amounts of insoluble dietary fibers to decrease the risk of hepatic steatosis and the risk of associated metabolic disorders [3, 21–24].

According to many studies, the efficacy of the Mediterranean diet has been demonstrated in the treatment of NAFLD with a sufficiently high degree of significance regarding the improvement in steatosis, inflammatory processes, and insulin resistance. However, its effects on the hepatic fibrosis degree remains less significant [21–24]. In overweight patients, World Health Organization (WHO) and European Liver Association guidelines define the necessity of the steady smooth weight decrease (no more than 0.5–1.0 kg per week). Many authors underline that weight loss > 5 % may decrease the hepatic liver amount, 7–10 % — may decrease the inflammation, and > 10 % — may decrease fibrosis. Quick weight loss is undoubtedly dangerous regarding the steatohepatitis and fibrosis progression, as well as a more significant LPO/AOP imbalance, which can lead to the deteriorated condition in sarcopenia [22–24].

Patients with NAFLD, but without obesity are recommended to lose weight moderately (3–5 %) to achieve the disease remission [24].

Physical activity is recommended in the form of predominantly aerobic, to the lesser extent — strength training both in NAFLD and sarcopenia, accounting for the individual approach. Physical activities should correlate to the NAFLD and sarcopenia stage, as well as with concomitant diseases. Exercises should be selected strictly individually.26 With that, one should account for the patient preferences, which will increase his/her compliance. It has been detected that physical exercises in the adequate scope arranged constantly lead to the improved histological signs in NASH even if the body weight has not decreased significantly. Besides, the physical activity

option proposed above promotes the decreased serum cholesterol levels**5** [21]. This is specifically important in the treatment of sarcopenic obesity.

It has been shown that physical activity is an efficient method of maintaining the normal function of muscles and the cardiovascular system. The combination of aerobic and strength exercises may be considered as a therapeutic strategy in patients with primary or secondary sarcopenia [7].

As physical abilities vary in different patients, it is important to use the personalised approach to each patient when selecting the physical exercise program. Electrical myostimulation and vibration have been proposed in patients with sarcopenia on a prolonged bed regimen as new therapeutic interventions. However, additional studies are required to determine their efficacy.

It has been established that the use of several diets (Mediterranean, Scandinavian) are associated with the improved physical functions and the decreased sarcopenia risk. One should thoroughly and individually weigh the risks and advantages before administering diets to decrease the weight in elderly persons with obesity due to the risk of muscle mass loss in them. When losing weight, to achieve the target loss of approximately 5–10 % from the primary body weight within 6 months, using protein in the amount at least 1.0 g/kg of body weight and fluid in the amount of at least 1.6–2.0 L of water daily will be required. Dietary regulations in patients with sarcopenia should provide them with sufficient calories, guarantee the adequate consumption of nutrients according to the individual features (age, sex, treatment, physical activity level) [25–28].

Drug aspects of NAFLD and sarcopenia treatment

No drugs have been currently approved for the treatment of NAFLD and sarcopenia [3, 6, 7, 21–23]. Therapeutic approaches for the combination of NAFLD and sarcopenia may be implemented via the increased tissue insulin sensitivity and decreased hepatic lesions.

Omega-3,6,9-polyunsaturated fatty acids are proposed for use in the treatment of NAFLD and sarcopenia. Currently these drugs are considered the first line in the treatment of hypertriglyceridemia in patients with NASH [22].

It is feasible to use statins to decrease cardiovascular risks in patients with NAFLD.

Statins decrease levels of cytolytic liver enzymes, decrease inflammation and steatosis in patients with NAFLD. Rosuvastatin is somewhat better to recommend, as it is the safest and most efficient. Antiangiogenic and antineoplastic effects define the preventive direction of lipophilic statin effects [29, 30].

Potential statin properties promoting sarcopenia may be associated with mechanisms mediated by infammatory processes, apoptosis, disorders in the ubiquitine-proteasome system, as well as with changes in insulin-like growth factor 1 and myostatin levels [31].

Increased triglyceride (TG) levels in blood may be adjusted with fibrates. Fenofibrate is an optimal representative of this drug group [23, 28]. This drug increases the insulin sensitivity of tissue receptors. In turn, this prevents lipid accumulation in muscles and the liver.

Fenofibrate as monotherapy or in combination with statins improves the atherogenic lipid serum profile, significantly decreasing TG levels, while increasing high-density lipoprotein (HDL) levels. Besides, it exhibits anti-inflammatory and antithrombotic effects, simultaneously improving the endothelial function, especially in patients with MS and DM2 [32].

Muscular complications, i.e. myalgia, myopathy, and rhabdomyolysis with increased creatine phosphokinase (CPK) levels, are considered the most common effects of statins and fibrates; they become the main causes for the adjustment of initial treatment with these drugs in sarcopenia [33, 34].

It is interesting to note that the daily tocopherol dose (vitamin E) dose of 800 mg positively affects histological parameters in NAFLD, including the improvement in balloon dystrophy, steatosis, and inflammatory processes. However, no improvement is detected in the hepatic fibrosis setting. At the same time, one should pay attention to the potential procarcinogenic tocopherol effects in doses ≥ 800 mg/day, which were detected in the context of prostatic cancer. The dose of 400 mg/day is considered optimal [3, 35]. The association between this drug and the muscle tissue condition is being actively analysed.

Tocopherol in combination with ursodeoxycholic acid (UDCA) is used in the treatment of patients with NAFLD. The efficacy of this combination is associated with decreased serum transaminase levels, decreased steatosis and hepatic inflammatory processes in NASH. The concomitant use of these drugs promotes the decreased hepatocyte apoptosis and improved hepatic histology. Besides, blood adiponectin levels restore, which is associated with metabolic and cytoprotective effects [36].

UDCA demonstrates a wide spectrum of pleiotropic effects, which promote its efficacy in the treatment of NAFLD. In particular, it possesses antioxidant, antifibrotic, and cytoprotective properties in hepatocytes. Besides, UDCA normalises apoptotic processes: if the apoptosis level was high, it promotes the decrease, though it can activate the process if apoptosis was lacking. This UDCA feature is the key for its anticarcinogenic effects. UDCA use also leads to the decreased aggressive effects of toxic bile acids on hepatocytes. When using UDCA at the NASH stage, functional hepatic parameters improve in patients with NAFLD. Besides, UDCA affects insulin resistance, which is one of the main pathogenetic mechanisms of NAFLD and metabolic syndrome.

UDCA therapy in patients with NAFLD significantly decreases lipotoxicity signs, steatosis, and even hepatic

fibrosis. UDCA promotes decreased insulin resistance, normalised lipid profile, and provides positive effects on metabolic processes [23, 36, 37].

Several effects (inhibition of serotonin, bradykinin, histamine inflammatory reactions; decreased vascular permeability; anti-kinin, antiproliferative effects) define the anti-inflammatory properties of glycyrrhizinic acid. Glycyrrhizinic acid inhibits protein kinase C, which blocks CD4+ leukocyte receptors, implementing pseudo-corticoid effects. Antioxidant properties of glycyrrhizinic acid are associated with its ability to block LPO processes. The mechanism of this inhibition includes 5-lipoxygenase phosphorylation [23]. Besides, glycyrrhizinic acid interacts with prostaglandin E2, a prooxidant. All these effects have significant effect in the treatment of NAFLD and sarcopenia.

Randomised controlled trials (RCTs) aimed at evaluating the efficacy of using cholecalciferol (vitamin D) orally for the treatment and prevention of sarcopenia demonstrated ambiguous results. Currently no sufficient evidence confirms its efficacy in the treatment of sarcopenia [38].

As of today, no drug product is approved for the treatment of sarcopenia, including testosterone. Currently the administration of testosterone is feasible only in patients with the established cause of hypogonadism, as it improves the muscle mass and strength in patients with hypogonadism [39, 40]. The addition of testosterone is efficient to improve the muscle mass and muscle strength only in elderly patients with variable hypogonadism degrees. However, the efficacy of testosterone concerning the physical ability is very low [40].

Besides, no positive estrogen effects have been demonstrated in the treatment of sarcopenia. It has been shown that estrogens do not significantly affect muscle mass and strength. Thus, estrogen benefit in females with sarcopenia is mild; with that, estrogen therapy is associated with a higher risk of breast cancer. This issue is an important limitation regarding estrogen therapy in patients with sarcopenia and NAFLD [40].

Dehydroepiandrosterone (DHEA) is synthesised in males and females, having the ability to increase testosterone levels. Only several small and relatively short RCTs analysed DHEA effects on sarcopenia [41], which proves that further studies are required.

Synthetic androgen receptor modulators (SARM) do not bond with corticosteroid and progesterone receptors, but are characterised by a high variability of regulatory androgenic receptor properties. This enables them to affect skeletal muscles without androgenic effects. However, additional studies are required. Currently no synthetic androgen modulator has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [42].

Several studies have demonstrated that peripheral β2-receptor agonist, salbutamol, usually administrated in chronic obstructive pulmonary disease and asthma, improves the protein metabolism rate in skeletal muscles with a positive protein synthesis balance. Despite the potential therapeutic benefit in muscle atrophy, salbutamol or other highly selective β2-agonists have never been analysed in patients with sarcopenia [42].

Metformin and other prospective molecules, e.g. exerkines (interleukin-6, TNF-α, interleukin-15, fibroblast growth factor 21, irisin, apelin, etc.) or xenolytics (dazatinib, quercetine, ruxolitinib, etc.) are currently analysed in preclinical studies for the prevention of muscle mass, strength, and physical ability losses [43–45].

The intestinal microbiome affects the amino acid absorption [46]. This means that a microbiome may promote sarcopenia. In the future, after corresponding RCTs, the intestinal microbiome correction may become a new direction in the treatment of sarcopenia.

Probiotics and prebiotics may become new tools in the treatment of sarcopenia. The studies of bacterial quorum-sensitive peptides, e.g. iAM373, produced by E. faecalis have detected a potentially new sarcopenia inducer both in animals and humans [47], which requires additional analysis.

Thus, there is still very little evidence of efficient drug use for the treatment or prevention of sarcopenia. Unless current studies (large-scale Phase 3 RCTs, in particular) confirm the drug efficacy in the context of sarcopenia, lifestyle modification, including adequate physical exercises and quality food, will remain the sole recommendation for this indication.

Prophylactic aspects of NAFLD and sarcopenia evolution

Based on the data from randomised controlled trials (RCTs) concerning sarcopenia prevention, EWGSOP2 recommends the concept of maximum muscle mass increase in young persons, its preservation in the middle age, and minimising losses in the elderly [7]. Physical activities are considered as the basis for both primary and secondary sarcopenia prevention. In physical activities, the production of pro-inflammatory cytokines decreases, along with the increased synthesis of muscle protein, production of pro-inflammatory cytokines, and glucose consumption — that decreases the risk of NAFLD and sarcopenia progression. Physical exercises stimulate myocytes to produce myokines, enhancing muscle innervation and angiogenesis, satellite cell proliferation and differentiation. Regarding the bone tissue, physical exercises activate osteocytes to produce osteokines, promoting mitochondrial biogenesis and (indirectly) the muscle tissue growth.

The role of inflammatory cytokines and chemotactic proteins, e.g. monocytic chemotactic protein 1 (CX3CL1), in trained muscles presumes the attraction of immune cells and facilitation of their migration and infiltration into muscles; simultaneously, the product

of IL-10 and IL-1 receptor antagonist switches the pro-inflammatory reaction to anti-inflammatory [48]. This leads to decreased levels of several inflammatory cytokines participating in systemic inflammatory reactions [48, 49]. In addition to the localised release of the vascular endothelium growth factor (VEGF), the levels of associated extracellular matrix proteins, 61/CNN1 cysteine-rich angiogenic protein, and /CNN2 connective tissue growth factor along with IL-8 increase after exercises, and these molecules play an important role in skeletal angiogenesis, activating the endothelial cell proliferation, capillary tube organisation, and extracellular matrix remodeling. The production of angiopoietin-like protein 4 (ANGPTL4) in trained muscles enhances angiogenesis in skeletal muscles to an even larger extent, also increasing vascular permeability and lipid metabolism in muscles. These secretory angiogenic factors cause enhanced angiogenic effects in muscles, enabling a larger amount of blood to enter muscles with a more efficient delivery of nutrients into the muscle tissue — this is an important function in the prevention and delay of sarcopenia progression [49, 50].

Currently the issue of developing therapeutic & diagnostic algorithms for combined NAFLD and sarcopenia phenotypes is still not resolved. Undoubtedly, this topic will form the basis of prospective studies.

Conclusion

1. A clear association has been detected between NAFLD and sarcopenia. The prevalence of sarcopenia increases with NAFLD progression, and, vice versa, sarcopenia increases the risk of NASH and/or liver fibrosis in patients with NAFLD, affecting the mortality in LC. Physicians should assess the association between sarcopenia and NAFLD. Sarcopenia may be a potentially treatable condition. Specific therapeutic recommendations have still not been defined for patients with sarcopenia and NAFLD. No algorithm exists for the management of such patients.

2. It is feasible to actively screen patients with NAFLD for sarcopenia, assessing their muscle strength, force, and function.

3. The multidisciplinary approach for patients with NAFLD and sarcopenia should include the participation of not only a gastroenterologist, endocrinologist, cardiologist, and gerontologist, but also a physical therapist, dietician, and nutrition specialist. The treatment efficacy may require an individual approach, combination of drug and non-drug interventions accounting for the NAFLD and sarcopenia staging, as well as concomitant diseases and possible complications. The alertness concerning concomitant sarcopenia in patients with NAFLD is important to prevent the disease progression and to decrease the risk of remote negative results when selecting the optimal time for the start of therapeutic interventions.

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