

Pathophysiological changes of the liver-muscle axis in end-stage liver disease: what is the right target?

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Abstract

Liver diseases and in particular end stage liver diseases are frequently complicated by muscle modifications that are linked to worse clinical outcome. In addition, recent studies have demonstrated the negative impact of these muscle changes on liver function leading to the hypothesis of a bidirectional relationship referred in the literature as “muscle-liver axis”. In a context of evolution towards a more holistic and less organocentric vision of medicine, studying frailty, myosteatosis and sarcopenia and their underlying pathophysiological mechanisms has led to many publications in the last five years. These studies are describing several pathophysiological mechanisms, highlighting the extremely complex character of this relationship. This review aims to summarize these mechanisms as well as potential therapeutic targets, independently of liver disease etiology. (*Acta gastroenterol. belg.*, 2022, 85, 611-624).

Keywords: muscle, sarcopenia, myosteatosis, end-stage liver disease, myokine, exerkinge.

Background

Muscle changes in end-stage liver disease (ESLD) is extremely frequent and a major contributor to cirrhotic frailty. Frailty could be defined as a global homeostatic disturbance resulting in decreased functional reserves and increased vulnerability to physical stress (1). This term relates to an entire spectrum of physical and functional abnormalities including loss of muscle mass and reduced physical function (sarcopenia). These changes have a major impact on clinical outcomes in ESLD but also in post-liver transplant (LT) outcomes (2-7). Indeed, muscle changes such as sarcopenia in ESLD are correlated to increased all-cause mortality rates independently of liver disease etiology (7,8). Data are also sometimes available for the common causes of chronic liver disease (CLD), namely alcohol-related liver disease (ALD), metabolic dysfunction-associated fatty liver disease (MAFLD) also called non-alcoholic fatty liver disease (NAFLD) and chronic viral hepatitis (9,10).

Skeletal muscle mass is the result of a balance between protein synthesis and proteolysis (11). This process called proteostasis or protein homeostasis is extremely complex and depends on several biochemical mechanisms eventually determining global skeletal muscle mass. Proteostasis can be affected by physiological (aging) or pathological situations leading to **sarcopenia**. Involved signaling pathways and mediators are summarized in

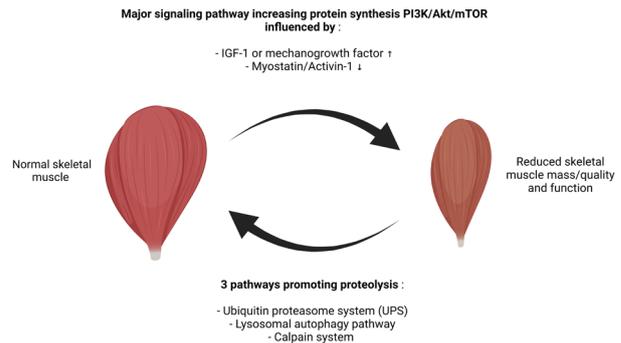


Figure 1. — Summary of signaling pathways and mediators involved in protein homeostasis in the skeletal muscle. Protein synthesis is regulated by two main factors: myostatin inhibits mammalian target of rapamycin-1 (mTOR1) resulting in decreased protein synthesis on the contrary of insulin growth factor 1 (IGF-1) which increases skeletal muscle mass. Proteolysis is induced by three catabolic pathways: ubiquitin proteasome, lysosomal autophagy and calpain systems. PI3K: phosphatidylinositol 3 phosphate. UPS: ubiquitin proteasome system.

figure 1 (12-35). Loss of skeletal muscle mass in cirrhosis is the result of both decreased in protein synthesis and increased proteolysis, mediated by several potential mechanisms (Figure 1).

Defining **sarcopenia** varies according to the scientific literature and the field of interest. Diagnostic criteria include both quantitative and qualitative criteria with low muscle strength, low muscle quantity or quality and low physical performance. However, these criteria have been established based on geriatric cohorts (36,37). Currently there are no specific standardized cut-offs to define sarcopenia in cirrhosis. In ESLD, muscle mass is commonly measured radiologically via computed tomography (CT) of skeletal muscle area (psoas and paravertebral musculature) at the third lumbar vertebrae (L3) (2). Based on this measure, an index, normalized to individual height, is calculated to reflect total skeletal muscle mass: the skeletal muscle index (SMI) (2). Skeletal muscle index sex-specific cut-off values for ESLD have

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been recently investigated and are respectively $< 50 \text{ cm}^2/\text{m}^2$ in males and $< 39 \text{ cm}^2/\text{m}^2$ in females (38). Sarcopenia has been reported with these cut-off values in 40 to 70% of all cirrhotic patients and worsens with the severity of liver disease (39). In practice, however, it is rare to see function tests combined with muscle mass measurement to obtain a diagnosis of sarcopenia. In other reports, independently of these cut-off values, the prevalence of sarcopenia is estimated at 25 to 70% (40-42). A new score, called psoas muscle depletion index (PDI) is proposed, based on psoas area and predicted/estimated psoas area, to remove confounding factors such as age, gender or body weight (43). Other non-irradiating muscle mass assessment techniques exist as standard anthropometric measurements, ultrasound (US) imaging, bioelectrical impedance analysis (BIA) or dual-energy x-ray absorptiometry (DEXA) scanning but appear to be less accurate than CT (44,45).

Recently, a new definition of sarcopenia has been defined in obese patients called **sarcopenic obesity**. This term refers to a disbalance between mean and fat mass characterized by low subcutaneous and high visceral adipose tissue based on absorptiometry or tomography imaging (CT or MRI). However, there is currently a lack of consensus on this definition in clinical studies (46). therefore, we won't discuss further this specific topic.

Physical performance is the second concept included in the definition of frailty. It refers to decrease in both muscle strength and/or function. Many physiotherapy tests exist to assess muscle strength and function. Handgrip strength, peak expiratory flow and knee flexion/extension are performed to evaluate muscle strength. Muscle performance can be assessed through gait speed, six minutes' walk test, handgrip strength, chair stands or short physical performance battery (SPPB) that includes five chair stands, time to walk 4 meters and balance testing (47). Based on these tests, different scoring tools have been developed to assess global frailty: fried frailty index (FFI), clinical frailty index (CFI) and liver frailty index (LFI) (47).

A last concept affecting both muscle mass and function is **myosteatoris**. It is characterized by an excessive accumulation of fat in muscles resulting in an imbalance between lean and fat muscle mass which eventually contributes to the decline in muscle function. The resulting altered muscle function is multifactorial. One of the involved mechanisms is the loss of pennation angle defined by the wrong alignment of muscle fibers and the muscle-force axis secondary to fat infiltrations (48). Myosteatoris is extremely frequent in cirrhosis. Its prevalence is highly associated with hepatic encephalopathy (HE) as well as sarcopenia (49). Its prevalence ranges from 40% in cirrhotic patients without HE to 70% in those with HE. Previous reports have demonstrated that it is an independent risk factor for the development of HE (49,50). It has also a huge impact on clinical outcome of patients with ESLD. Three potential phenotypes of fat deposition are described (51-

53): intermuscular adipose tissue (IMAT), intramuscular adipose tissue and intramyocellular lipid droplets. It affects preferably some muscle groups due to different oxidative capacities. Indeed, oxidative muscles fight more efficiently intramyocellular lipid accumulation by increasing beta-oxidation level producing free fatty acids. On the opposite, glycolytic muscles are facing increased intramyocellular triglyceride storage due to re-esterification of free fatty acids as a consequence of decreased mitochondrial oxidative phosphorylation (54-56). The diagnosis is routinely based on imaging, biopsy being rarely performed. Preferred imaging modality as gold-standard is computed tomography (CT) which highlights muscle fat accumulation though a lower mean muscle radiodensity assessed in Hounsfield Units (HU) (57,58). HU cut-off values are currently not standardized in the context of cirrhosis due to an obvious lack of systematic data. While cut-off values are available from cancer patients' population (59), validated cut-offs are not clearly established for patients with ESLD. A cut-off of 43.14 HU for psoas muscle radiodensity at the level of the fourth to fifth vertebra was evidenced as a good predictor of 12-month mortality in patients with cirrhosis (60). However, it was not the case for predicting post-LT mortality in another study (61). In a recent study on LT patients, a skeletal muscle radiation attenuation (SM-RA) below 41 Hounsfield units (HU) in normal weight patients (BMI up to $24.9 \text{ kg}/\text{m}^2$) and 33 HU in overweight patients ($\text{BMI} \geq 25 \text{ kg}/\text{m}^2$) as been proposed as a criteria for myosteatoris, associated with higher complications rate (62). Adding myosteatoris to the MELD score improves its accuracy in predicting pre-LT mortality (63). The relationship and temporality of the occurrence of sarcopenia and myosteatoris remains unclear (64). Myosteatoris can be present without sarcopenia. However, myosteatoris is extremely frequent in sarcopenic patients with chronic liver diseases (CLD) with a prevalence of up to 93% (65). Interestingly, myosteatoris has been identified as the independent prognostic factor best correlated with the development of severe forms of metabolic dysfunction-associated fatty liver disease, either in preclinical models as a marker of non-alcoholic steatohepatitis (NASH) (66) or in humans with metabolic dysfunction-associated fatty liver disease (MAFLD) in the case of high liver elasticity (67) or NASH on histology (68). This myosteatoris appeared in the absence of sarcopenia (66-68). In the general population, both sarcopenia and myosteatoris are associated with increased mortality (7,69).

Sarcopenia has been previously more studied than myosteatoris and its epidemiology according to cirrhosis etiology is therefore better described (70). In general, independently of liver disease etiology, muscle changes prevalence increases with liver disease severity from non-cirrhotic stages to decompensated cirrhosis (70). There is a strong inverse association between sarcopenia and MAFLD even in non-cirrhotic stages (71). Indeed, sarcopenia is an independent factor

of MAFLD progression through NASH, fibrosis and metabolic-associated complications (72). However, it remains unclear if sarcopenia is a cause or a consequence of MAFLD due to contradictory data on the impact of skeletal muscle mass on liver steatosis. The estimated prevalence of sarcopenia in MAFLD increases through MAFLD progression from 8% in steatosis up to 63% in NASH (73,74).

Sarcopenia is also extremely prevalent in alcohol-related liver disease and is estimated at 60% (75). Its prevalence is also highly correlated to alcohol-related liver disease severity (75). The negative impact of alcohol on skeletal muscle mass is interestingly only mediated by liver disease and thus does not directly contribute to sarcopenia (76). However, it is important to notice that this prevalence might be over-estimated considering the frequent co-existence of alcohol abuse and malnutrition which is also a major risk factor for sarcopenia (77).

Both chronic hepatitis B and C are also associated to sarcopenia in all liver disease stages with an estimated prevalence from 7.1% in non-cirrhotic stages up to 21.9% in decompensated cirrhosis (78). Despite the efficacy of antiviral therapy, no previous study showed skeletal muscle mass improvement after viral eradication in both chronic hepatitis B and C (79).

Concerning myosteatosis, available data in end-stage liver disease only previously focused on non-alcoholic fatty liver disease (MAFLD) and post-liver transplantation whose retained indication was mainly alcoholic cirrhosis and hepatocellular carcinoma (61,62,80). There is therefore an obvious lack of data concerning other cirrhosis etiologies. However, depending on the imaging technique used for myosteatosis assessment, its prevalence ranges from 16% to 82% (65,81). The pathophysiology of sarcopenia and myosteatosis is currently not fully established but previous fundamental studies tend to demonstrate muscle changes not only as stage-related consequences of ESLD but also as provider of liver function decay. This complex bi-directional axis (liver-muscle axis) considers liver but also skeletal muscles as proper endocrine organs which are able to interact via various messengers (hormones, cytokines,...).

The purpose of this review is to summarize the current knowledge and to describe the recently highlighted actors and pathways. The changes detected in cirrhosis can be classified into three broad categories: first, the liver and muscle may be affected by a general deleterious situation; second, the liver may be responsible for muscle disorders; and third, the diseased muscle may affect the condition of the liver (Figure 1). These three possibilities are listed below.

1. The liver and muscle are affected by systemic conditions present in cirrhosis

Beside the muscle-liver axis, many conditions may interfere with these two key-organs and are summarized in figure 2. Several catabolic conditions contribute to

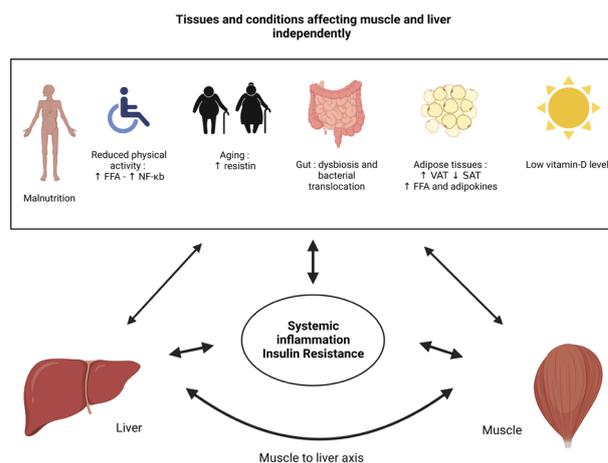


Figure 2. — Summary of potential tissues or catabolic conditions interfering with skeletal muscle and liver in end-stage liver diseases (ESLD) by direct or inflammation-mediated interactions. The temporality of these interactions is dynamic through liver disease stages but also for most of them bidirectional. SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; FFA: free fatty acids; NF- κ B.

systemic inflammation or endotoxemia, and insulin-resistance (IR).

1.1. Malnutrition

This imbalance between caloric uptake and consumption in favor of reduced nutrients storage is highly frequent in ESLD (Figure 2) with an increased prevalence for advanced cirrhotic stages (from 20% in Child-Pugh A to 70% in child-Pugh C) (43,82). It is also a well-known independent prognostic factor in cirrhosis correlated to poorer outcomes (39,43,83). Nutritional assessment in cirrhosis is hence extremely important to improve both liver and muscle function by targeting higher daily calorie, and more specifically, protein goals (83,84). Inadequate intake of food and malabsorption are among frequent causes of malnutrition in cirrhotic patients (figure 2). This condition predominates in alcohol-related liver disease (ALD) due to excessive involvement of alcohol beverages in the daily calorie intake (77).

1.2. Reduced physical activity

A sedentary lifestyle is a major cause of sarcopenia in the elderly (85). In a general context of altered general condition in the cirrhotic patient, increased sedentary lifestyle may also be responsible for sarcopenia. A reduction in activity is directly linked to hepatic fat accumulation and NAFLD pathogenesis mainly by increased fatty acid release from peripheral tissues (86). Its impact on skeletal muscle is mediated by excessive activation of nuclear factor kappa-B (NF- κ B) (Figure 2) involved in stimulating the expression of proteolysis key genes, resulting in altered skeletal muscle (87,88). Gains in physical activity enhance liver function by reducing liver fatty infiltration eventually leading to

reduced hepatic inflammation and fibrosis (89,90). Loss of skeletal muscle mass has been correlated to higher risk for HE in cirrhosis, highlighting the potential preventive role of physical activity on this condition (91).

1.3. Age-related differentiation of muscle stem cells into adipocytes

Aging is associated with a decreased differentiation capacity of muscle stem cells into myocytes leading to preferred adipocyte differentiation. This decreased myogenesis is mediated by several subcutaneous adipose tissue interleukins (secretome) and has been observed in elderly obese patients (Figure 2). Among these interleukins, resistin is highly secreted by subcutaneous adipose tissue (Figure 2) in elderly obese patients (92) and interfere with myogenesis by two pathways. Firstly, resistin activates the NF- κ B resulting in decreasing myotubes' thickness and nuclear fusion. In addition, resistin provides intramyocellular lipid accumulation impairing muscle function by mechanical interaction with myotubes, increasing fatty acid oxidation resulting in increased ATP production (93).

1.4. Dysbiosis and endotoxemia

Changes in the gut microbiota are often presented as causal in the pathogenesis of liver disease (94). However, the gut-liver axis is bidirectional and liver alterations can also cause gut changes (94). This must therefore be interpreted with caution (94). In cirrhosis, altered gut barrier and dysbiosis are frequently found. It has pro-inflammatory consequences by increasing the immune system exposure to bacterial antigens via pathological bacterial translocation (Figure 2) (95). The increased serum level of bacteria and bacterial products including lipopolysaccharides (LPS) or endotoxin interact with toll-like receptors (TLR) and nucleotide-binding oligomerization domain (NOD)-like receptors expressed by several cell types including Kupfer cells and hepatocytes (96,97). Alcohol consumption is particularly associated to increased gut permeability or leaky gut as well as portal hypertension independently (98). It results in increased cytokine expressions by hepatocytes (99). Dysbiosis promotes sarcopenia in advanced age as well as in cirrhosis by reducing gut-microbiota derived micronutrients and promoting systemic inflammation (100). Indeed, those nutrients produced by gut microbiota such as butyrate are important in skeletal mass regulation by anti-inflammatory, energy metabolism enhancement and anti-apoptotic effects (101,102). Acetate, another short chain fatty acid produced by gut microbiota, also fights against muscle changes in ESLD by suppressing ammonia-producing bacterial growth and intestinal ammonia absorption (103,104). Treating dysbiosis has therefore been identified as a potential target for the improvement of skeletal muscle mass (105,106). However, evidence of dysbiosis-related liver damage

has recently come to light. A recent study demonstrated higher prevalence of cytolysin-positive *Enterococcus Faecalis* in patients with alcoholic hepatitis, but also improved liver function, both clinically and biologically, after targeted antibiotic therapy (107). By restoring a healthy microbiome and gut microbial function (108), fecal microbial transplantation (FMT) represents a promising therapy to treat ESLD related complications as HE (109) but also improve liver function (110,111). However, there are currently no data on the impact of FMT on skeletal muscles in cirrhotic patients.

1.5. Low vitamin-D level

Vitamin D deficiency is extremely frequent in ESLD and may contribute to both muscle and liver abnormalities (Figure 2)(112). Low serum vitamin D is more prevalent in patients with MAFLD (113). Vitamin-D plays a key-role in insulin-sensitivity by promoting expression of insulin receptors in several tissues including skeletal muscle, pancreatic beta-cells but also liver. Hence, vitamin-D deficiency is a promoter of insulin-resistance and loss of muscle mass and function (114,115). Furthermore, it may also mediate oxidative stress and systemic inflammation, contributing to liver function decay (116). Vitamin-D supplementation could eventually contribute to preserve liver function by anti-inflammatory mechanisms. This supplementation has been therefore demonstrated to be an effective treatment of sarcopenia in older populations by improving both muscle mass and function (117,118).

1.6. Systemic inflammation

Cirrhosis is associated with systemic inflammation (119) that can directly affect liver homeostasis and muscle wasting (Figure 2). The main cause of this systemic inflammation may be hepatic, namely the cause of CLD (120). However, other actors may play a role, such as endotoxemia from the gastrointestinal tract (see above), visceral adipose tissue expansion, or decreased capacity of subcutaneous adipose tissue storage. Indeed, visceral adipose tissue (pro-inflammatory and releasing free fatty acids directly in the portal vein) plays a deleterious role in liver inflammation and subcutaneous adipose tissue (anti-inflammatory) a rather protective role (121). For these reasons, a high visceral adipose tissue index (VATI ≥ 65 cm²/m²) or a low subcutaneous adipose tissue index (SATI < 60 cm²/m²) are associated with higher rates of cirrhosis related complication. The structure of the adipose tissue also plays a role (122). Low visceral fat density is associated with a higher systemic inflammation (123). High subcutaneous fat density is associated with increased mortality and higher frequency of decompensation in cirrhosis (124). It is hence considered indicative of adipose tissue remodelling with morphological features of tissue fibrosis and inflammatory infiltration leading to adipose tissue dysfunction (124), subcutaneous adipose tissue

eventually losing its likely anti-inflammatory property (121).

1.7. Insulin resistance

Insulin resistance is present in patients with cirrhosis, regardless of the cause of the cirrhosis (120). This is mainly present at the peripheral (muscle) level and not in the liver according to the hyperinsulinemic and euglycemic clamp experiments (120). Among the causes of CLD, MAFLD is of course also associated with insulin resistance, before the development of cirrhosis (125). More simply than with the clamp, insulin resistance can also be evaluated by the homeostasis model assessment of IR (HOMA-IR) (126). The causes of IR are various and may include liver (intra-hepatic inflammation or fibrosis, decreased hepatic glycogenesis) but also digestive, muscle and endocrine changes (increased growth hormone, decreased testosterone) observed in cirrhosis (120). Interestingly, an increased liver expression of alanine aminotransferases (as shown in chronic liver diseases) has recently been shown to be associated with liver alanine catabolism that promotes both hyperglycaemia and muscle wasting (127). IR plays a central role in ESLD related complications but also in liver and muscle functions decay (Figure 2). This vicious circle is defined by insulin inability to regulate glycemia through the loss of physiological response in insulin sensitive tissues including liver and skeletal muscle.

2. From liver to muscle: how can end stage liver disease induce muscle changes?

Cirrhosis can impact the muscle through various mechanisms related to both impaired liver function and portal hypertension. It has been shown that portal hypertension itself was related to sarcopenia, even in the absence of cirrhosis (128). Artu *et al.* have also recently published the positive changes on the muscle and on the subcutaneous and visceral fat composition in a series of patients after transjugular intrahepatic portosystemic shunt (TIPSS) placement (129). The underlying pathophysiology is related to several factors that we will describe here and that are summarized in figure 3.

2.1. Hyperammonemia

Systemic ammonia increases in cirrhosis primarily due to impaired ureagenesis, which is its primary hepatocyte elimination pathway and portosystemic shunting. Hyperammonemia is associated with an increased ammonia uptake by skeletal muscle hypothetically due to an induced overexpression of ammonia transporters (Rh B glycoprotein and Rh C glycoprotein) (130). Its impact on skeletal muscle is mediated by several molecular alterations (Figure 3). Transcriptional upregulation of myostatin is observed by activating a specific NF- κ B signaling pathway (131)

which downregulates mTORC1 signaling and increases adenosine monophosphate (AMP)-activated protein kinase (AMPK)-alpha2 phosphorylation resulting in decreased protein synthesis and increased autophagic proteolysis (Figure 3) (132,133). Increased intramyocellular ammonia in skeletal muscle stimulates cataplerosis of alpha-ketoglutarate. Anaplerosis is the first reaction in the tricarboxylic acid (TCA) cycle and consists in the metabolization of glutamine and glutamate in alpha-ketoglutarate and ammonia by the enzyme glutamate dehydrogenase (GDH) (134). In case of high concentrations of ammonia in the skeletal muscle, the production flow of TCA intermediates decreases to avoid the accumulation of anions within the mitochondrial matrix. The conclusion of this decrease in mitochondrial function is a reduction in ATP synthesis and eventually in protein synthesis (Figure 3) (29). Furthermore, ammonia can, under specific circumstances, inhibit key-enzymes involved in the TCA cycle: oxodehydrogenase, pyruvate dehydrogenase and alpha-KG dehydrogenase (135). This mitochondrial toxicity is also mediated by an increase of reactive oxygen species (ROS) responsible for oxidative damages (29). Hyperammonemia also stimulates skeletal muscle autophagy by this mitochondrial toxicity (Figure 3) (136). Conversely, sarcopenia promotes hyperammonemia and so hepatic encephalopathy. Indeed, skeletal muscle is involved in ammonia metabolism and ammonia serum level reduction by incorporating it into glutamine through glutaminase (137,138).

2.2. Lipotoxicity

Hypercholesterolemia is frequent in ESLD and particularly secondary to cholestatic diseases by decreased enterohepatic cycle, apolipoprotein synthesis or even subcutaneous adipose tissue storage capacity (139). Skeletal muscle is an extremely important organ in fatty acids consumption by mitochondrial dependent beta-oxidation. Increased beta-oxidation of fatty acids leads to increased reactive oxygen species (ROS) which leads to endoplasmic reticulum (ER) stress (Figure 3) (140). Furthermore, intramyocellular lipid accumulation inhibits GLUT-4 translocation which is a major glucose transporter to muscle and adipose tissue contributing to insulin-resistance (Figure 3) (141). It results in decreased ATP production and impaired protein synthesis leading to reduced muscle mass (Figure 3).

2.3. Endocrine disorders

Low serum testosterone in cirrhosis is a consequence of secondary disturbances in the hypothalamic-pituitary-gonadal axis and increased aromatase activity (142). Cirrhosis is associated with central hypogonadism (low level of luteinizing hormone produced by the anterior pituitary gland). Severe systemic disease of any etiology, including liver failure, can downregulate gonadotropin-releasing hormone secretion by the hypothalamus and

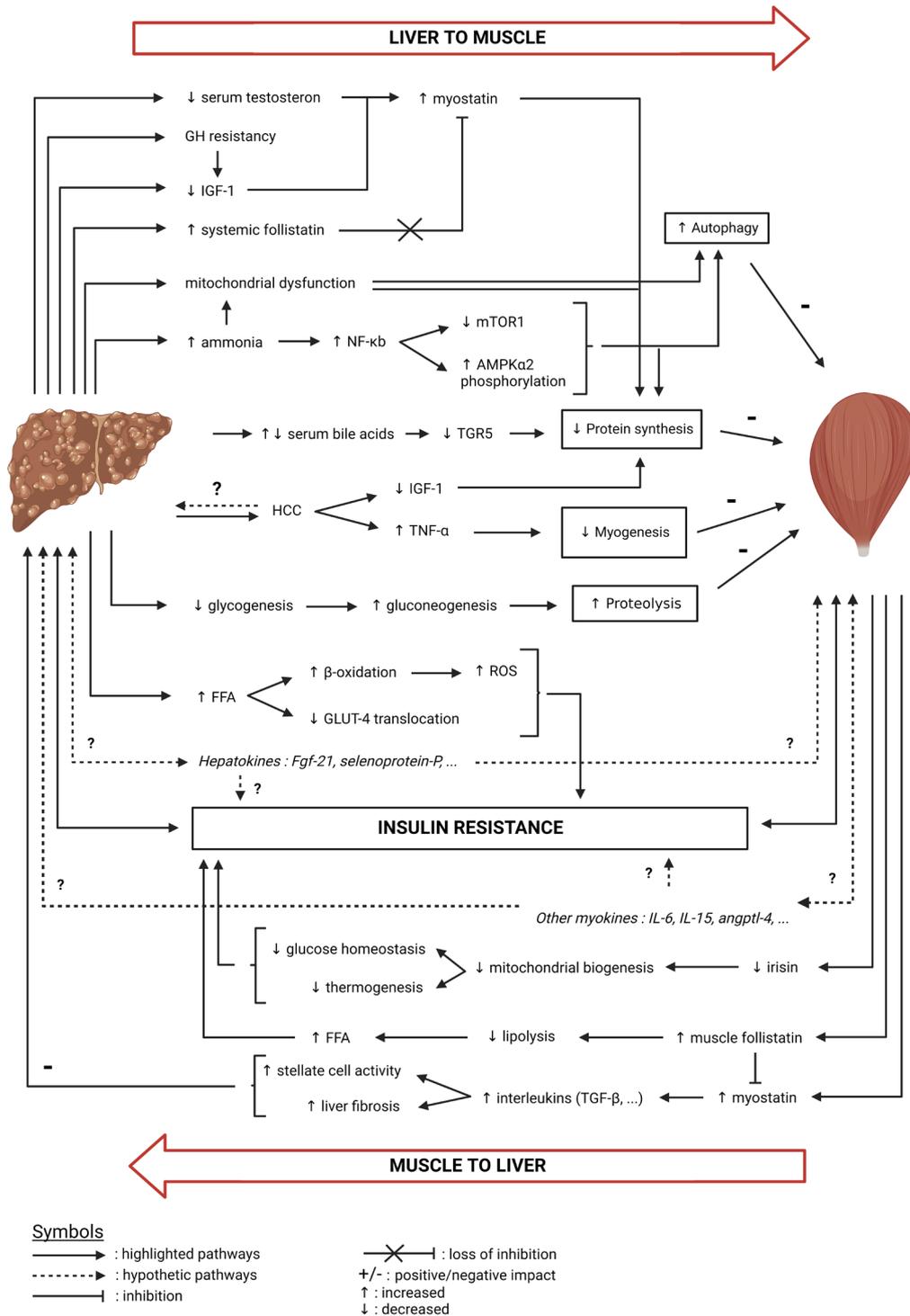


Figure 3. — Highlights of pathophysiological pathways and related mediators involved in muscle changes in ESLD or “liver-muscle axis” and the resulting effect on protein homeostasis and skeletal muscle mass. Demonstrated pathways are represented by continuous arrows. Hypothetical pathways are represented by dotted arrows. mTOR1: mammalian target of rapamycin 1; AMPK α 2: AMP-activated protein kinase alpha-2; GLUT-4: glucose transporter 4; TGR5: G-protein-coupled bile acid receptor 5; TNF- α : tumor necrosis factor - alpha; HCC: hepatocellular carcinoma; NF- κ B: nuclear factor kappa B; GH: growth hormone; IGF-1: insulin growth factor-1; FFA: free fatty acids; ROS: reactive oxygen species. Fgf-21: fibroblast growth factor 21; IL-6: interleukin-6; IL-15: interleukin-15; angptl-4: angiopoietin-like 4; TGF- β : tumor growth factor-beta

lead to secondary testicular failure with low testosterone level. This is partly due to direct effects of inflammatory cytokines produced by the liver (143). Furthermore, androgen receptor binding sites are located on the

myostatin promoter. Low serum androgen contributes then to increased myostatin levels in cirrhosis by losing its inhibition (Figure 3) (144). Importantly, testosterone has an important impact on the muscles, inducing an

increase in muscle strength and volume (143). This led to studies on the impact of testosterone administration in cirrhotic patients. Interventional studies showed positive anabolic effects with increased albumin levels and increased global lean mass but without conclusive evidence of its impact on sarcopenia (145-147).

Furthermore, the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis is also disturbed in cirrhosis. Indeed, the liver is the principal source of IGF-1. In case of decreased serum level of IGF-1 due to cirrhosis, serum level of GH increases secondary to the loss of IGF-1-related negative feedback and leads to GH resistancy (Figure 3). Decreased IGF-1 also increases myostatin levels and hence promotes sarcopenia synergistically with low testosterone levels (Figure 3) (148,149). GH treatment could therefore improve skeletal muscle mass by overcoming GH resistance and hence promoting notably IGF-1 expression (150).

2.4. Altered circulating bile acids

Bile acids are important endocrine mediators (151) independently of their digestive function by interacting with specific receptors expressed in several tissues (152-154) called farnesoid receptor (FXR) and plasma membrane G-protein-coupled TGR5 (Takeda-G-protein-receptor-5) receptor (Gpbar1) (155,156). The main receptor for bile acids expressed by skeletal muscle is TGR5 (157,158). TGR5 activation is a provider of both myocytes' differentiation and skeletal muscle hypertrophy (159). In cirrhosis, bile acids pool globally decreases. Indeed, bile acids synthesis and key hepatic re-uptake in the enterohepatic circulation are decreased and correlated to the degree of hepatocellular insufficiency (160). On the contrary, serum bile acids levels (mainly chenodeoxycholic acid) are increased in peripheral venous blood by portal hypertension and porto-systemic shunting (161,162). The resulting loss of TGR5 stimulation by decreased serum bile acids level leads to skeletal muscle atrophy (Figure 3).

2.5. Accelerated cirrhotic starvation

Cirrhosis is associated with a state of accelerated starvation due to impaired liver glycogen production and storage capacity resulting in a major dependency on gluconeogenesis (Figure 3) (163). Unfortunately, free fatty acids cannot be used for gluconeogenesis in contrast to amino acids whose primary source is skeletal muscle (164). Proteolysis produces both aromatic and branched chain amino acids (BCAA). However, BCAA are the only amino acids catabolized for gluconeogenesis due to the localization of the branched chain ketodehydrogenase (165). Due to this increased consumption, ESLD is associated with an amino acid imbalance characterized by decreased serum BCAA and increased aromatic amino acids (166-168) (Figure 3). Increased protein needs participate to disbalance between caloric intake

and consumption, participating to malnutrition and sarcopenia (figure 3).

2.6. Liver inflammation and hepatokines

Chronic liver inflammation plays a central role in the process leading to cirrhosis. Indeed, the inflammatory process, characterized by parenchymal hepatocyte necrosis and progressive fibrosis, can lead to cirrhosis. An increase in local as well as circulating blood concentrations of pro-inflammatory cytokines (such as tumor necrosis factor-alpha and interleukin-6) is observed in cirrhotic subjects compared to controls (169). Furthermore, there is a positive correlation between TNF- α , IL-6, other inflammatory cytokine levels and the severity of cirrhosis, independently from etiologic factors (170). Alanine aminotransferase level and hepatic alanine metabolism are also correlated with muscle depletion (127). Interestingly, in addition to the "classical" pro-inflammatory cytokines previously mentioned, other chemokines produced by the liver called "hepatokines" (as opposed to adipokines produced by the adipose tissue or myokines produced by the muscle) can act on distant organs (Figure 3). Two hepatokines, selenoprotein-P and fetuin-A, are capable of inducing insulin resistance in peripheral tissues such as the adipose tissue for fetuin-A (171,172) or the muscle for selenoprotein-P (173). Muscle insulin resistance is associated with myosteatosis (174). Higher serum concentrations of fibroblast growth factor 21 (Fgf21), which is also expressed by adipose tissues, are also found in cirrhotic patients with sarcopenia independently of liver function and portal hypertension (175,176). The elevated level of Fgf21 might therefore be promoted by adipose tissue rather than the liver itself. This hypothesis is reinforced by the high correlation between steatosis, necro-inflammation, fibrosis and Fgf21 serum level in MAFLD and chronic hepatitis C (177-179). Fgf21 is able to induce muscle atrophy via inhibition of protein synthesis and stimulation of autophagy (180,181). Follistatin is a glycoprotein inhibiting 21 members of TGF-beta superfamily including myostatin and activin-1 by antagonizing the related-receptors, leading to increased protein synthesis and skeletal muscle hypertrophy (182-185). Its secretion is upregulated by a high glucagon-to-insulin ratio (186). Follistatin is expressed by almost all tissues including liver which is the main actor in the production of circulating follistatin as well as skeletal muscle. This hepatic production contributes to prevent atrophic effects of myostatin and activin-1 on skeletal muscle. However, follistatin is also implicated in the insulin-resistance process (figure 3) especially by its interaction with white adipose tissue as demonstrated in mouse models and patients with type 2 diabetes (187). Furthermore, serum follistatin-levels are well correlated to HbA1c level and the risk of developing type 2 diabetes (133). The resulting effect is a decreased insulin-inhibited white adipose tissue lipolysis and increased serum levels of FFA (figure 3) (185).

2.7. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is unfortunately frequent in ESLD and associated to worsened outcomes (188). Cancer-related sarcopenia named cachexia is multi-factorial and related to malnutrition, secretion of specific pro-cachexia cytokines, adipose tissue depletion by increased lipolysis or even cardiac muscle atrophy (189). The association between sarcopenia and poorer hepatocellular carcinoma related prognosis has been previously well demonstrated with increased all-cause mortality and even higher tumor recurrence rates (190,191). Hypothetical muscular mechanisms are reduced secretion of insulin-like growth factor (IGF-1) and increased activity of TNF-alpha system (Figure 3) (192). However, the impact of primary liver cancer on liver function is less clear (Figure 3). Indeed, cases of liver function improvements in patients with unresected hepatocellular carcinoma and ESLD have been reported, as well as liver function worsening in Child-Pugh A cirrhosis after HCC resection (193). This “compensation” would be mediated by increased energy metabolism associated with the cancer cells, which would restore partially basal metabolic rates (193).

3. From the muscle to the liver: how damaged muscle can contribute to the deterioration of the liver?

As described above several factors can interact with proteostasis and lead to sarcopenia. Few studies tend to demonstrate that muscle alterations could precede and eventually participate to liver function decay leading to the hypothesis of a bidirectional muscle - liver axis. Proteostasis is the balance between protein synthesis and proteolysis in the skeletal muscle. It involves the secretion of various factors that can interact with other tissues or organs. As described in figure 1 protein synthesis in the skeletal muscle is influenced by mediators activating the key signaling pathway phosphatidylinositol-3 kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR). Firstly, myostatin, a member of tumour growth factor beta (TGF β) superfamily or its homologue activin A inhibit mTOR1 (mammalian target of rapamycin complex 1) signaling pathway resulting in increased proteolysis (12,13). Secondly, IGF1 (insulin like growth factor 1) or mechanogrowth factor increases protein synthesis by recruiting the IGF 1/PI3K/Akt signaling cascade but also by inhibiting the proteolytic action of FOXO transcription factors (FOXO 1, 3 and 4) (29,30).

On the other hand, three major pathways regulate proteolysis in skeletal muscle (Figure 1). Firstly, ATP-dependent ubiquitin proteasome system (UPS) is the main proteolytic system (14,15,35). -Degrading proteins are targeted by 26S proteasome through covalent attachment of a multi-ubiquitin chain. This ubiquitination process is highly dependent of the E3 ubiquitin ligases involving two muscle ligases called atrogen-1 or muscle atrophy F-box (MAFbx) and muscle ring finger-1 (MURF-1) (16).

Those two enzymes are highly expressed in cirrhosis (17). Secondly, lysosomal autophagy pathway is the result of a dynamic enzymatic process leading to autophagosome formation responsible for degrading proteins (18). This catabolic pathway is highly depending on AMPK and mTORC1 as described above. AMPK has a catabolic function by regulating the TCA cycle flux to increase ATP production and decrease ATP consumption (19-21). Lastly, calpains are calcium-dependent non-lysosomal cysteine proteases expressed in skeletal muscles and activated by intracellular calcium (22,23,25).

Beside its role in energy and carbohydrate metabolism, skeletal muscle interacts with several tissues by secreting mediators called myokines. These myokine secretion profiles depend on physical activity. If a muscle to liver axis is demonstrated in cirrhosis, then improving skeletal muscle mass and function could therefore enhance liver function or prevent functional deterioration. These specific pathways involved in this bidirectional relationship between liver and skeletal muscle mass are summarized in figure 3.

3.1. Elevated myostatin level

Myostatin, as seen above, is extremely important in proteostasis by inhibiting protein synthesis and reducing eventually muscle mass (Figures 1 and 3). Its serum level has been reported to be up to four times higher in cirrhotic patients (133). In MAFLD, myostatin has demonstrated impairing skeletal muscle protein synthesis but also activating protein degrading via UPS (194). Repressing myostatin expression in mouse models is therefore associated with improvements in global skeletal muscle mass, insulin sensitivity and liver insulin sensitivity as well as reduced liver fat (195). A regression of muscle inflammation, detected in particular by a decreased macrophage marker F4/80, is demonstrated in these animals without functional myostatin (195). Macrophagic recruitment to the muscles occurs indeed in the presence of myosteatosis and muscle insulin resistance (174). However, in these animals without functional myostatin, hepatic F4/80 levels are unchanged (195). Myostatin would also be involved in liver fibrosis by its interaction with hepatic stellate cells and increased systemic inflammation by promoting expression of interleukins as transforming growth factor-1 (TGF-beta1) (196) These cell culture experiments indicate that a myokine could be involved in liver fibrosis development.

3.2. Low irisin level?

Irisin is mainly expressed and secreted by skeletal muscle (197). Irisin and its precursor fibronectin type III domain-containing protein 5 (FNDC 5) are key-myokines involved in glucose metabolism mainly by inducing mitochondrial biogenesis. Irisin upregulates browning genes in subcutaneous adipose tissue via p38MAPK and ERK signaling pathways and by upregulation of

uncoupling protein 1 (UCP-1) (198-200). It results in increased energy expenditure by thermogenesis (199). Furthermore, irisin plays also an autocrine-role on skeletal muscle improving glucose homeostasis. Irisin expression is particularly reduced in obesity and participate to insulin-resistance process in MAFLD (figure 3)(200,201). Other effects of irisin on the liver are possible but not described. Irisin concentration were also correlated with muscle surface measured at the third lumbar level (202). However, in a recent study, a decrease in irisin levels was found in relation to age but not in relation to cirrhosis or ESLD or the presence of sarcopenia (197).

3.3. Others

There are many mediators described as both hepatokines and myokines, the levels of which may vary in sarcopenia or myosteatosis. These include, for example, follistatin, FGF21, myonectin, angiopoietin-like protein 4, IL-6 or interleukin-15 (IL-15) (203,204). The effects of the muscle form of those proteins on the liver condition need to be characterised (Figure 3). As explained above, exercise can modulate the secretion of these myokines and lead to remote effects, for example on adipose tissue or the liver (204). For this reason, the term “exerkines” is now used to describe molecules released into the circulation that have a systemic effect (205). These exerkines can be transported in extracellular vesicles, such as apoptotic bodies, microvesicles or exosomes (205). Interesting data suggest that exosomes secreted by skeletal muscle may play a role not only in skeletal muscle function but also in inter-organ communication in different pathologies (206).

Opportunities for the future: better understanding as a diagnostic and therapeutic tool?

Muscle-liver axis is extremely complex due to the multitude of potentially involved biochemical mechanisms but also other tissues interfering in this relationship as adipose tissue or gut. Furthermore, some actors are ubiquitously expressed but their role may differ, as illustrated in this review, depending on the producing tissue. Recently highlighted actors involved in these mechanisms regardless of the ESLD etiologies where described in this review. Nevertheless, they probably differ depending on etiology as well as stages of liver diseases. Indeed, cirrhosis is associated with changes in body composition as a result of the progression of liver function impairment. The burning questions that persist are the temporal and causal link between these two key actors and, at present, although the liver appears to play a dominant role in muscle abnormalities, it is not impossible that specific factors produced by the muscle play a toxic role on the liver. Similarly, the muscle or certain myokines or exerkines could be identified as therapeutic targets. Hence, the hypothesis of a

simple bidirectional axis may be irrelevant and further experimental and clinical experimentations are required to highlight potential future involved mediators and pharmacological targets. Pending these results, muscle assessment of patients with cirrhosis is recommended and the benefit of general interventions such as physical activity should be further investigated.

Abbreviations: AMPK: adenosine monophosphate-activated protein kinase; ESLD: end-stage liver disease; CT: computed tomography; LT: Liver transplantation; HU: Hounsfield unit; HE: hepatic encephalopathy; NASH: non-alcoholic steatohepatitis; NF- κ B: nuclear factor kappa-B; MAFLD: metabolic dysfunction-associated fatty liver disease; CLD: chronic liver disease; mTOR1: mammalian target of rapamycin receptor 1; GH: growth hormone; IGF1: insulin like growth factor 1; UPS: ubiquitin proteasome system; FOXO: forkhead box protein O; FFA: free fatty acids; TCA: tricarboxylic acid; ROS: reactive oxygen species; BCAA: branched chain amino acids; TNF- α : tumor necrosis factor-alpha

Conflict of interest

None of the authors have conflict of interest regarding this work.

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