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Improving the prognosis before and after liver transplantation: Is muscle a game changer?

Goffaux A *et al*. Cirrhosis, muscle condition and prognosis

Abstract

Liver transplantation (LT) is currently the only curative treatment option for selected patients with end stage liver disease or hepatocellular carcinoma. Improving waiting list-mortality, post-transplant morbidity and mortality and refining the selection of the patients remain our current central objectives. In this field, different concepts dealing with nutrition and the muscle such as sarcopenia, malnutrition, frailty or myosteatosis have emerged as possible game changers. For more than a decade, many prospective studies have demonstrated that sarcopenia and frailty are major predictive factors of mortality in the waiting list but also after LT. Malnutrition is also a well-known risk factor for morbidity and mortality. Muscle composition is a newer concept giving insight on muscle quality which has also been shown to be linked to poorer outcome. Each of these terms has a precise definition as well as pathophysiological mechanisms. The bi-directional liver-muscle axis makes sense in this situation. Defining the best, easy to use in clinical practice tools to assess muscle quality, quantity, and function in this specific population and developing quality prospective studies to identify interventional strategies that could improve these parameters as well as evaluate the effect on mortality are among the important challenges of today.

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Core Tip: Patients suffering from end stage liver disease currently have liver transplantation as only curative treatment. In order to improve the pre and post transplantation management of patients, muscle related concepts such as sarcopenia, myosteatosis, frailty and malnutrition could be important potential game changers. Considering a bidirectional axis between the muscle and the liver, it is therefore justified to characterize the condition of the muscles adequately and to identify

interventional strategies that could improve both muscle parameters and patient survival.

INTRODUCTION

To date, despite medical developments in knowledge and drug treatments, liver transplantation (LT) remains the only curative treatment option for selected patients with acute liver failure, end-stage liver disease (ESLD), liver cancer and acquired or genetic metabolic liver disease[1]. ESLD is the most frequent indication for LT with alcohol-related liver disease as the main etiology[2]. Other common etiologies are metabolic dysfunction-associated fatty liver disease (MAFLD) and viral hepatitis[3,4]. Autoimmune related liver diseases and cholestatic diseases are rarer indications in Western countries. The epidemiology of LT has changed over the last twenty years since the selection of patients suffering from hepatocellular carcinoma (HCC) with the Milan criteria and the progressive eradication of hepatitis C virus since the universal use of direct-acting antivirals[5]. MAFLD is probably becoming one of the main indications for LT in parallel with the epidemic of overweight in Western countries. This disease can coexist with other causes and act as an important co-factor. This specific population represents a series of challenges in the pre-, peri- and post-transplant settings, due to the presence of medical comorbidities that include obesity, type 2 diabetes and cardiovascular risk factors[6,7].

For years, graft allocation has been based on the model for end-stage liver disease (MELD) score that has been used to predict three-months mortality on the waiting list. The use of the MELD score has led to a better selection of patients requiring LT but also to a reduction in waiting time and a reduction in mortality on the waiting list[8]. However, the score suffers from several limitations: Patients with cholestatic liver diseases, severe portal hypertension as well as those with hepatic encephalopathy are disadvantaged due to a preserved synthesis function which does not reflect the severity of the disease and the related morbi-mortality. Another major limitation is the absence of assessment of malnutrition and more specifically of sarcopenia[8-10]. Abnormalities of

body composition are frequently found in patients with chronic diseases such as cirrhosis. Interestingly, there is a close relationship between the skeletal muscle compartment and liver function (Figure 1)[11].

In the field of chronic liver disease (CLD) and particularly ESLD and LT, different concepts have emerged and are commonly used, such as sarcopenia, malnutrition, frailty or myosteatosis[12]. They affect between 40%-70% of cirrhotic patients with important clinical outcomes. They have been evaluated independently in different studies and it is confirmed that they are robust predictors of poor outcomes[13]. This fragile population is at increased risk of hepatic decompensation, reduced quality of life, increased risk of infection, and prolonged hospitalization. It leads to a higher morbidity and mortality[14,15]. Adding the concept of frailty on the waiting list prioritization specifically helps a population that is listed with low priority based on a low MELD score (< 15). While adding muscle surface to the MELD score had limited added value for organ allocation in a global cirrhotic population, this measurement is highly correlated with waiting list mortality in patients with low MELD score (< 15)[16]. It is therefore important to define the best tools to evaluate these functional concepts in the field of liver diseases and LT[13].

Understanding these different concepts and their implications in our clinical practice is of major interest to improve the management of our patients. There is clearly a certain overlap in these definitions, but it is important to understand them separately to develop tailored behavioral interventions and targeted pharmacotherapies for these conditions[17]. It is necessary to clearly define the gold standard of sarcopenia management with standardized cut-offs for this specific cirrhotic population. These clear definitions will allow us to evaluate the impact of interventions on patients' outcome[13]. We then review the pathophysiology of cirrhosis-related sarcopenia and myosteatosis, provide a narrative review of the major studies on the subject, and discuss the tools available for muscle assessment and treatment.

DEFINITIONS OF COMMONLY USED YET DISTINCT CONCEPTS

As explained above, various terms are now frequently used in the field of CLD, sometimes incorrectly or inappropriately. However, they have a precise definition.

Malnutrition

Malnutrition can be defined as, a state resulting from an insufficient intake of nutrients or an imbalance in essential nutrients and/or in their utilization. This imbalance will have a deleterious impact on the body composition and body cell mass that could lead to diminished physical and mental function, as well as impaired clinical outcome from disease. Malnutrition has multiple causes combined or take alone which are starvation, disease such as CLD and aging[18]. It is also important to note that malnutrition can affect the entire body mass index (BMI) spectrum from obese to anorexic[17]. Different clinical scores exist to estimate the presence of malnutrition, such as the nutritional risk score or the Global Leadership Initiative on Malnutrition criteria. Malnutrition is associated with increased mortality in cirrhotic patients[19].

Sarcopenia

The term sarcopenia comes from the Greek, and literally means the "loss of flesh". Sarcopenia is characterized by 3 components: Decreased muscle mass, decreased muscle strength as well as decreased physical performance[20]. Initially, sarcopenia was described as associated with aging. The term is now also used in association with chronic diseases such as cirrhosis[12]. Nevertheless, even today, the criteria to be included as well as the cut-off values are still discussed. The diagnosis of sarcopenia is still complicated today as the criteria can be so variable, especially in obese people[21]. Cutoffs for muscle mass depletion exist but are still currently under debate. Nevertheless, the use of muscle area measurement at the level of the third lumbar vertebra on a computed tomography (CT) slice is recognized as acceptable by relating the muscle area to the patient's height squared [skeletal muscle index (SMI)]. By extension, the term sarcopenia is often used based on the sole criterion of low muscle area. Sarcopenia is then defined when SMI is < 41 cm^2/m^2 for a woman and < 53

cm²/m² for a man in the field of obesity[22] or < 39 cm²/m² for a woman and < 50 cm²/m² for a man in the field of ESLD[23]. In the field of liver diseases, this measure is particularly interesting because it is little affected by hydro-sodium retention. Measurement of the brachial circumference (BC) or mid-arm muscle circumference and arm strength using the hand dynamometer are other frequently used techniques.

Myosteatosis

Myosteatosis can be defined as the ectopic accumulation of fat in the muscle. This increased accumulation around and within the myocyte can lead to an impairment of normal physiological function. We will therefore speak of intra and extra cellular fat. It can be estimated on the basis of the decrease in muscle density on an ultrasound image or a CT scan section for example[24,25]. A skeletal muscle radiation attenuation below 41 Hounsfield units (HU) in normal weight patients (BMI up to 24.9 kg/m²) and 33 HU in overweight patients (BMI ≥ 25 kg/m²) could be used[24]. Muscle density can also be related to the muscle surface to give an idea of the absolute amount of intramuscular fat[26]. This led to the following parameters: The skeletal muscle density index (SMDI)[27] and the skeletal muscle fat index (SMFI) described in patients with MAFLD without ESLD[26,28]. Different groups of patients are compared in clinical studies, but pathological cut-offs for SMDI or SMFI are not yet defined[26-28]. Finally, imaging allows us to assess the homogeneous or heterogeneous distribution of fat in the muscle. This parameter can be associated with certain pathological conditions[29].

Frailty

Defined in the field of geriatrics, frailty is considered a metabolic syndrome associated with a decrease in physiological reserves and an increase in vulnerability to stress factors. In the case of cirrhosis, the stressors are variable, ranging from a dysfunction in protein synthesis to muscle toxicity. A reproducible and objective assessment of patients with liver disease is offered by several simple, non-invasive tests. For example,

based on the results of handgrip, sit to stand and balance tests, the liver frailty index (LFI) can be calculated. A patient is considered frail if the score is between 4.5 and 6[15].

Physical exercise

Physical exercise is defined as activity requiring physical effort, performed specifically to maintain or improve health and fitness. The term is therefore relevant to physical activity interventions offered to patients with CLD to improve their condition. The data available so far concern patients with compensated liver disease, with no separate results for patients with ESLD[30]. An increase in functional capacity, strength and muscle mass is noted in these patients with compensated cirrhosis subjected to physical exercise for 12 wk and compared to a group of patients with relaxation activity[31]. In patients awaiting LT, specific protocols are being evaluated (NCT04604860, NCT05061576, NCT05237583, *etc.*). The type (endurance and/or resistance), duration and frequency should be determined, bearing in mind that these programmes must be adapted to the patients' situation (safety, absence of contraindications).

PATHOPHYSIOLOGICAL BASIS OF SARCOPENIA AND MYOSTEATOSIS IN END STAGE LIVER DISEASE

Several mechanisms exist that link sarcopenia to CLD and ESLD. Nevertheless, these exact mechanisms are mostly not well known. Sarcopenia is often a feature of malnutrition. The reasons for this malnutrition, in the case of cirrhosis, are multiple and often result from the combination of several factors (Figure 1)[32]. The first factor in the context of CLD and cirrhosis is the presence of a hypermetabolic status, resulting from chronic inflammation and altered gut barrier function[33]. Low liver glycogen content induces muscle protein catabolism for blood glucose maintenance[34]. In addition, ascites present in cirrhotic patients may be responsible of an increase of energy expenditure and therefore increase the catabolism of protein[35]. Partly due to the pro-inflammatory environment, patients with cirrhosis and HCC showed accelerated sarcopenia[36]. Second, the hyperammonemia level is also increased due to its poor

elimination because of a pathological architecture of the liver. The consequence of this increase will be the activation of myostatin and consequently the inactivation of protein synthesis which will lead to sarcopenia. Third, inadequate intake of micro and macronutrients can be due in cirrhotic patients to loss of appetite (dysgeusia, cytokines), prolonged gastric emptying or a restrictive diet (sodium and protein) for example. The sedentary lifestyle is probably the most obvious factor in sarcopenia. Indeed, a study showed that one of the causes of sarcopenia in the elderly was partly due to lack of physical exercise[20]. It is therefore easy to think that decompensated cirrhotic patients with high frailty and malnutrition may also suffer from a lack of physical activity aggravating their sarcopenia even more. Fourth, cirrhosis is associated with some degree of cholestasis. An increase in bile acids related to deregulation of the enterohepatic cycle (also due to the dysbiosis associated with cirrhosis) is observed. These have a potentially toxic effect, particularly on the muscle that expresses some bile acid receptors, inducing muscle atrophy[37]. Malabsorption in the context of cirrhosis also plays an important role. A decrease in bile excretion will result in a decrease in the reabsorption of lipids and certain lipo-soluble vitamins. Altered intestinal motility as well as changes in the composition of the gut microbiota will also affect nutrient absorption and utilization[33]. Finally, in cirrhotic patients, a decrease of testosterone levels has been associated with a decrease of muscle mass that could favor sarcopenia[34].

The mechanism through which myosteatosis occurs is still not well understood. Myosteatosis is a well-known characteristic of patients with CLD due to MAFLD[27]. Cirrhotic patients are also characterized by muscle insulin resistance, regardless of the cause of the cirrhosis[34]. This insulin resistance status may also be responsible for myosteatosis[34]. Other proposed mechanisms include hyperammonemia (inducing impaired mitochondrial oxidative phosphorylation and decreased lipid oxidation in muscle), decreased lipid storage capacity within the subcutaneous adipose tissue and age-related differentiation of muscle stem cells into adipocytes[38].

WHY IS IT IMPORTANT TO CONSIDER THE MUSCLE IN A LIVER TRANSPLANT SETTING?

To assess physical activity, muscle function, composition and mass, several tools exist. It is important to note that many tests, questionnaires and radiological methods are possible. A non-exhaustive list of these tools is presented in Table 2 with their advantages and disadvantages. Some of them have been included in a recent review manuscript[50]. It is interesting to note that patients' baseline physical activity can be assessed by questionnaire or objective measurement (Table 2). Easy tests are possible in consultation or at the patient's bed, such as measuring BC or handgrip strength. Tests that are more complex to implement in routine practice are also available, such as the 6-min walk test (6MWT), which correlates well with survival in patients awaiting LT[51], or isokinetic testing, the detailed results of which have given interesting information in other diseases such as type 2 diabetes[29]. Finally, among imaging techniques, the same dilemma exists between easier and less expensive techniques (such as ultrasound)[52,53] and time-consuming but probably more objective and reproducible techniques [such as CT or magnetic resonance imaging (MRI)][41] (Table 2).

HOW TO EVALUATE THE MUSCLE IN ROUTINE PRACTICE?

To assess physical activity, muscle function, composition and mass, several tools exist. It is important to note that many tests, questionnaires and radiological methods are possible. A non-exhaustive list of these tools is presented in Table 2 with their advantages and disadvantages. Some of them have been included in a recent review manuscript[50]. It is interesting to note that patients' baseline physical activity can be assessed by questionnaire or objective measurement (Table 2). Easy tests are possible in consultation or at the patient's bed, such as measuring BC or handgrip strength. Tests that are more complex to implement in routine practice are also available, such as the 6MWT, which correlates well with survival in patients awaiting LT[51], or isokinetic testing, the detailed results of which have given interesting information in other diseases such as type 2 diabetes[29]. Finally, among imaging techniques, the same

dilemma exists between easier and less expensive techniques (such as ultrasound)[52,53] and time-consuming but probably more objective and reproducible techniques (such as CT or MRI)[54] (Table 2).

HOW TO IMPROVE THE MUSCLE IN CLINICAL PRACTICE?

It is well defined that malnutrition plays a major role in the prognosis of the cirrhotic patient and that the resulting loss of muscle mass is a real complication of cirrhotic disease with a significant impact on the morbidity and mortality of these patients. All patients with CLD should be evaluated for nutrition and sarcopenia at the time of diagnosis and then regularly at least annually for compensated cirrhosis and every 8-12 wk for decompensated cirrhosis[17]. The ultimate goal of the medical practitioner is the prevention of the occurrence of complications that may result from sarcopenia and undernutrition. Nevertheless, although there is no clear evidence for an appropriate guideline for patients at present, the current management in transplant centers is that patients with cirrhosis who are placed on the list benefit from efforts by the multidisciplinary team to try to preserve muscle mass and function, through the interventions of dieticians (screening for undernutrition, implementation of standard nutritional measures, early oral intake) and physical therapists (mobilization)[54]. However, it is not yet proven that we are able to slow down the progression of complications or reverse advanced situations *via* muscle targeted interventions[13]. There are two main options, non-exclusive: Dietary interventions and physical activity. Additional specific pharmacological measures are under investigation.

The current nutrition guidelines for patients with CLD recommend a weight-based daily caloric intake of at least 35 kcal/kg/d with a protein intake of 1.2-1.5 g/kg/d[18]. These recommendations are derived from data assessing energy expenditure (indirect calorimetry). They are difficult to achieve in routine practice. Protein intake is easily found in staple foods such as meat and vegetables. Several studies have analyzed the benefit of branched-chain amino acid (BCAA) supplementation but the results of these data are contradictory. While some authors suggest that BCAA improve hepatic

encephalopathy and muscle mass[55], a meta-analysis shows that there is no effect on mortality and nutritional parameters[56]. Because of these contradictions and the limitations of clinical studies, BCAA supplementation is not currently recommended. Prolonged periods of fasting should be avoided in cirrhosis and it is important to favor split meals associated with a late evening snack or an early morning breakfast[17]. Oral nutritional supplements given before bedtime showed a muscle benefit in Child A patients but not Child B or C[57]. If not achieved *via* oral route, energy intake *via* enteral nutritional supplementation may be considered to achieve targets.

Beside these nutritional recommendations, physical activity improvement is also important. The latest recommendations propose to assess frailty and/or sarcopenia with standardized tools in order to define a personalized approach for the sarcopenic patient. This personalized activity prescription is guided by the principles of frequency-intensity-time-type: A combination of aerobic exercise that improves cardiorespiratory endurance and resistance exercise that improves strength and skeletal muscle mass[17]. Personalized physical activity allows patients to improve their cardiopulmonary capacity and quality of life. Unfortunately, current randomized controlled data are limited by small samples of well-compensated cirrhosis patients (mean MELD = 10)[31,58]. Despite these promising results, there are no randomized controlled studies with patients with ESLD or a waiting list for LT. It is therefore not currently possible to conclude whether a personalized physical activity program would improve the outcomes in the waiting list and post-LT surgery.

Several randomized controlled trials evaluating the benefit of nutritional and/or physical exercise on muscle mass (SMI) and frailty (LFI) pre- and post-LT would help to answer these uncertainties. Finally, pharmacological treatments are being studied to treat sarcopenia (hormone replacement therapy such as testosterone or growth hormone, ammonia reduction and myostatin inhibition)[59].

CONCLUSION

Malnutrition, sarcopenia and frailty are very common in patients with cirrhosis, especially in cases of disease requiring organ transplantation. Bi-directional pathophysiological links exist between muscle and liver that underlie this association. This highlights the interest of prospective studies comparing the different tools at our disposal to evaluate the cirrhotic patient as well as translational studies to understand these mechanisms and find a possible therapeutic or diagnostic target. Through a better understanding of mechanistic links, the muscle can become a game changer. A better understanding of the situation will also allow to prioritize fragile patients who need a faster LT or to identify negative factors in certain recipients in whom the situation would be irreversible post-LT and deleterious to the graft. Interventional strategies (nutritional, physical exercise and pharmacological treatments) are also being evaluated. The rationale for their efficacy is clear, even if at this ESLD, evidence of their impact on reducing pre-LT and post-LT mortality is lacking, as well as a precise characterization of the protocols to be implemented. Again, quality prospective studies will be able to answer this question.

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