Changes in nutritional status after liver transplantation

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Abstract
Chronic liver disease has an important effect on nutritional status, and malnourishment is almost universally present in patients with end-stage liver disease who undergo liver transplantation. During recent decades, a trend has been reported that shows an increase in number of patients with end-stage liver disease and obesity in developed countries. The importance of carefully assessing the nutritional status during the work-up of patients who are candidates for liver replacement is widely recognised. Cirrhotic patients with depleted lean body mass (sarcopenia) and fat deposits have an increased surgical risk; malnutrition may further impact morbidity, mortality and costs in the post-transplantation setting. After transplantation and liver function is restored, many metabolic alterations are corrected, dietary intake is progressively normalised, and lifestyle changes may improve physical activity. Few studies have examined the modifications in body composition that occur in liver recipients. During the first 12 mo, the fat mass progressively increases in those patients who had previously depleted body mass, and the muscle mass recovery is subtle and non-significant by the end of the first year. In some patients, unregulated weight gain may lead to obesity and may promote metabolic disorders in the long term. Careful monitoring of nutritional changes will help identify the patients who are at risk for malnutrition or over-weight after liver transplantation. Physical and nutritional interventions must be investigated to evaluate their potential beneficial effect on body composition and muscle function after liver transplantation.

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Key words: Liver transplantation; Sarcopenia; Malnutrition; Obesity; Metabolic syndrome; Outcome; Survival

Core tip: Malnutrition, evidenced by muscle and fat depletion, represents a negative prognostic factor for morbidity and mortality in cirrhotic patients. This factor applies when liver transplantation is indicated. Nutritional depletion, as shown in the general population undergoing major surgery, may influence the outcome and global resource utilisation of liver transplantation. Recently, attention has focused on changes in nutritional status after liver transplantation. While fat mass is easily regained, muscle wasting, when present, is difficult to revert during the first year. The benefits derived from interventional programmes, such as exercise and dietary counselling, must be carefully evaluated in these types of patients.


INTRODUCTION
Liver transplantation has significantly changed the prognosis of end-stage liver disease. Improved immunosuppressive regimens and surgical techniques have progres-
sively modified the outcome of these patients, and the survival rate after liver transplantation is presently 82%, 71% and 61% at one, five and ten years, respectively.

From 2002, the introduction of the Model for End stage Liver Disease (MELD) for prioritising patients in need of new livers has led to a significant reduction in mortality for patients on the waiting list. The utilisation of the MELD score, which is based on the serum concentrations of bilirubin and creatinine and the INR value, favours the transplantation of the sickest patients, in whom complications from cirrhosis are likely to be more severe and life expectancy is likely to be shorter.

Alterations in nutritional status are expected to be frequent in patients with advanced chronic liver disease both of alcoholic and viral origin. These alterations, which may be recognised by more sophisticated methods, even in the early phases of liver cirrhosis, are in fact accelerated by the advanced stages of the disease. Depletions in muscle compartment and fat mass have been demonstrated to contribute to malnutrition in cirrhotic patients. Muscle wasting, which is accompanied by reduced muscle function (a condition defined as sarcopenia), is likely the most relevant feature in these patients. The prevalence of muscle wasting in liver cirrhosis has been reported to range from 10% to 70% according to gender and the severity of liver insufficiency (Table 1). A higher proportion of muscle wasting is generally observed in males, as muscle mass is physiologically lower in women; therefore, sarcopenia is less evident in females. Although less apparent, muscle wasting may be present in obese patients, which is identified as “sarcopenic obesity” and underscores the importance of considering muscle depletion in these types of patients. This observation is relevant because the number of obese patients, with end stage liver disease due to Non Alcoholic Steato Hepatitis, is increasing among those who await liver transplantation.

A reduction in skeletal muscle mass in cirrhotic patients has been suggested to be an independent predictor of survival, quality of life, outcome and response to stress and surgery. The negative predictive role of malnutrition in the outcome from major surgery confirms and extends the observation of the Michigan study. Although many reports have recognised that malnutrition impacts liver transplantation outcomes, it is generally agreed that liver transplant should not be denied even in highly malnourished cirrhotic patients.

By restoring liver function, liver transplantation is expected to ameliorate the patient’s nutritional status. In fact, many metabolic alterations that are involved in causing malnutrition in cirrhotic patients depend on the liver’s inability to regulate energy metabolism and to maintain an adequate protein synthesis. Carbohydrate metabolism is impaired in cirrhosis because of the decreased liver glycogen deposits; transitioning to the fast state is, therefore, rapid in these patients, who need to activate gluconeogenesis to maintain adequate hepatic glucose production. Insulin resistance is also a characteristic in these patients; the low hepatic insulin clearance contributes to this alteration. Lipid turnover is activated due to an enhanced lipolysis, which allows an adequate availability of glycerol for gluconeogenesis and of free fatty acids as alternative energy sources. Protein synthesis is impaired, reducing albumin and other transport proteins (such as lipoproteins). Furthermore, muscle protein catabolism is increased and provides alanine as a substrate for gluconeogenesis. Reduced dietary intake caused by multiple factors is also recognised to contribute to malnutrition in cirrhotic patients. Inadequate food consumption associated with some degree of nutrient malabsorption is responsible for the vitamin and trace element deficiencies, which have been documented in end-stage liver disease in many studies. After liver transplantation, food consumption progressively normalises and contributes to restoring nutritional status and body composition primarily in those patients who were more depleted.

There are few published studies concerning the modifications of the nutritional status after liver transplantation. However, multiple reports have suggested that muscle depletion is not reverted in the first year after liver transplant. A better knowledge of the modification of nutritional status that occurs after liver transplantation could be the departing point for the application of dietary regimens or physical activity programmes targeted at improving nutrition in these patients.

The aim of this review is to examine the recent literature concerning the modifications of nutritional status after liver transplantation. Data concerning the impact of malnutrition on the outcome of liver transplantation were evaluated.

**RESEARCH**

Bibliographic searches were performed using PubMed and Embase for the following words (all fields): “nutrition” (MeSH) or “malnutrition” (MeSH) or “nutritional status” (MeSH) or “protein depletion” (MeSH) or “sarcopenia” (MeSH) or “muscle wasting” (MeSH) and “liver transplantation” (MeSH) or “liver transplant” (MeSH) or “end stage liver disease”. The reference lists in the studies identified during electronic searching were hand-searched to identify additional relevant studies for inclusion in this review. Eligible studies for the review included those that were published as full papers in peer-reviewed journals between 1993 and 2013; however, older studies were utilised, when needed, to support the information concerning the physiopathology of malnutrition in liver disease. Studies published in non-English language were excluded; these non-English studies represented only a small percentage (<5% of total), and, therefore, these excluded studies do not constitute a relevant bias. Preference was given to studies that presented original data, rather than review studies.

**MODIFICATION OF NUTRITIONAL STATUS AFTER LIVER TRANSPLANTATION**

Whereas malnutrition is a common feature in end-stage...
Increased mortality in cirrhotic patients

Protein Index < 0.82 or 2 SDs below the mean value for the controls

No correlation with in-hospital mortality

Prevalence of muscle depletion

Hand-Grip Strength

13.2%

Higher rate of major complications

Mid Arm Muscle Area < 5

Lower survival at 6, 12 and 24 mo

Mid Arm Muscle Circumference

212

Higher rate of hepatic encephalopathy

Hand-Grip Strength 2 SDs below the mean value for the controls

53.2%

No correlation with in-hospital mortality

Hand-Grip Strength

67%

Higher risk of complications

Mid Arm Muscle Circumference

58%

No outcome evaluated

Mid Arm Muscle Circumference at CT scan ≤ 38.5 cm²/m² in women and ≤ 52.4 cm²/m² in men

40%

Increased 3 and 6 mo mortality

Montano-Loza et al[18], 2012

Tandon et al[19], 2012

Merli et al[15], 2006

Table 1 Prevalence of muscle depletion in cirrhotic patients and related outcomes

Ref. | Patients (n) | Definition of muscle depletion | Prevalence of muscle depletion | Outcome associated with muscle depletion
--- | --- | --- | --- | ---
Merli et al[15], 1996 | 1053 | Mid Arm Muscle Area < 5 | 26% | Lower survival in Child A and Child B
Alberino et al[16], 2001 | 212 | Mid Arm Muscle Area < 5 | 25% | Lower survival at 6, 12 and 24 mo
Alvares-da-Silva et al[17], 2005 | 50 | Hand-Grip Strength 2 SDs below the mean value for the controls | 63% | Higher rate of major complications
Campillo et al[18], 2006 | 396 | Mid Arm Muscle Area < 5 | 53.2% | No correlation with in-hospital mortality
Peng et al[19], 2007 | 268 | Protein Index < 0.82 or 2 SDs below the mean protein index for the controls | 51% | No outcome evaluated
Huisman et al[20], 2011 | 84 | Hand-Grip Strength Mid Arm Muscle Circumference | 67% | Higher risk of complications
Fernandes et al[21], 2012 | 129 | Hand-Grip Strength 2 SDs below the mean value for the controls | 69.3% | No outcome evaluated
Montano-Loza et al[22], 2012 | 112 | Lumbar Skeletal Muscle Mass Index at CT scan ≤ 38.5 cm²/m² in women and ≤ 52.4 cm²/m² in men | 40% | Increased 3 and 6 mo mortality
Tandon et al[23], 2012 | 142 | Lumbar Skeletal Muscle Mass Index at CT scan ≤ 38.5 cm²/m² in women and ≤ 52.4 cm²/m² in men | 41% | Increased mortality in cirrhotic patients awaiting liver transplantation
Merli et al[24], 2006 | 300 | Mid Arm Muscle Circumference < 5 | 39% | Higher rate of hepatic encephalopathy

M: Male; F: Female; CT: Computed tomography.

Modifications in body composition after liver transplantation: Sarcopenia overweight and obesity

In 1999, Keogh and co-authors applied dual energy X-ray absorptiometry to assess the changes in bone mineral density and body composition after liver transplantation. The timing of the evaluation of body composition in this study was extremely heterogeneous (range, 3-44 mo after surgery)[37]. While an overall reduction in bone mineral density was observed, body weight increased by 12% after transplantation due to an increase in the fat mass (from 24.1% ± 2.0% to 35.1% ± 1.8%) and a decrease in the fat-free mass (-5.7% ± 1.4%). Similarly, in a small group of 14 unselected patients undergoing liver transplantation, using sophisticated techniques for estimating body composition, a loss of total body fat was reported during the early postoperative period, which was fully regained at 3 mo. In the same group of patients, a depletion in skeletal muscle protein was present after 12 mo[38]. A failure to revert nutritional impairment during the first year after liver transplantation was also documented in a mixed population of 70 cirrhotic and non-cirrhotic patients transplanted between 1997 and 1999. In this retrospective study, 44% of patients were still classified as having some degree of malnutrition one year after transplantation. The presence of malnutrition was associated with a worse nutritional status before transplantation and fat stores (triceps skinfold thickness) remained inadequate in 70% of malnourished patients at the end of the first year[38]. In a prospective cohort study, cirrhotic patients who were severely malnourished while on the waiting list showed further deterioration at 3 mo after transplantation; however, they improved at 6 and 12 mo. Once again, primary changes were observed for fat mass (median triceps skinfold: basal 10.8 mm vs 15.2 mm, 12 mo, P = 0.03), whereas the parameters of muscle mass showed only minor variations (mid-arm muscle circumference: basal 23.4 cm vs 24.0 cm, 12 mo, P = 0.3)[39]. More recently, pre- and post-transplant abdominal muscle and fat area were evaluated in 53 patients, using abdominal CT. The patients were examined at a variable distance from liver...
to a significant increase in fat mass and a slight improvement in lean mass (arm muscle circumference). Similar results were shown in 17 liver recipients followed before transplantation and 12 mo after transplantation. A progressive weight gain characterised by a prevalent increase in fat mass was reported; at the end of the study, the rate of obese patients increased from 11.8% to 29.4%. In a longer follow-up (n = 143 patients, 4 years after liver transplantation), 58% of the patients were observed to be overweight, and 21% were observed to be obese. The multilogistic regression analysis demonstrated that obesity after LT was predicted by a higher BMI before LT and a significant weight gain after LT. Another study showed that in 42 long-term survivors studied at a distance ranging from 18 mo to 100 mo after successful liver transplantation, the mean BMI and the fat mass were significantly higher in transplanted patients compared to 39 patients with liver cirrhosis and a cohort of healthy controls. Studies with a cross-sectional design, however, suffered several limitations: transplanted patients are observed at different times, and long-term survivors are only those patients who exhibited a better outcome after replacement (19.3 ± 9 mo). Of the 66% of sarcopenic patients before LT, only 6% had a reversal of sarcopenia, while 14 of the 20 patients who were not sarcopenic pre-LT developed sarcopenia de novo after LT.

Other studies have primarily focused on the increase in body weight and BMI after liver transplantation, which may lead to a diagnosis of obesity in some patients. A retrospective study in 597 patients transplanted between 1996 and 2001 found that by 1 and 3 years, 24% and 31% of the patients, respectively, showed a BMI > 30 kg/m². However, it should be noted that several of the patients included in that study were already obese before transplantation. Considering only those patients who were not obese at the time of surgery, 15.5% and 26.3% became obese at 1 year and 3 years, thus indicating that overweight and obesity can be recognised as a likely burden after liver transplantation. Gender and the length of steroid therapy (more or less than 3 mo) were not found to be risk factors for the development of overweight and obesity. In a smaller study, 23 patients were followed for 9 mo after transplantation. At the end of the observation period, 87% were classified as overweight or obese due to a significant increase in fat mass and a slight improvement in lean mass (arm muscle circumference). Similar results were shown in 17 liver recipients followed before transplantation and 12 mo after transplantation. A progressive weight gain characterised by a prevalent increase in fat mass was reported; at the end of the study, the rate of obese patients increased from 11.8% to 29.4%. In a longer follow-up (n = 143 patients, 4 years after liver transplantation), 58% of the patients were observed to be overweight, and 21% were observed to be obese. The multilogistic regression analysis demonstrated that obesity after LT was predicted by a higher BMI before LT and a significant weight gain after LT. Another study showed that in 42 long-term survivors studied at a distance ranging from 18 mo to 100 mo after successful liver transplantation, the mean BMI and the fat mass were significantly higher in transplanted patients compared to 39 patients with liver cirrhosis and a cohort of healthy controls. Studies with a cross-sectional design, however, suffered several limitations: transplanted patients are observed at different times, and long-term survivors are only those patients who exhibited a better outcome after replacement (19.3 ± 9 mo). Of the 66% of sarcopenic patients before LT, only 6% had a reversal of sarcopenia, while 14 of the 20 patients who were not sarcopenic pre-LT developed sarcopenia de novo after LT.

Table 2: Mechanisms that cause a reduction in food intake in patients with cirrhosis

<table>
<thead>
<tr>
<th>Mechanism of deficiency</th>
<th>Primary consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced nutrient intake</td>
<td>Unpalatable diet (sodium and water restriction for peripheral oedema and ascites, protein restriction for hepatic encephalopathy)</td>
</tr>
<tr>
<td>Nausea and early satiety</td>
<td>Dysgeusia due to micronutrient deficiencies (zinc or magnesium)</td>
</tr>
<tr>
<td>Frequent compulsory starvation</td>
<td>Anorexic effect caused by increased levels of proinflammatory cytokines (TNFα, IL-1β, IL-6) and leptin</td>
</tr>
</tbody>
</table>

Table 3: Vitamins and trace elements deficiencies in patients with cirrhosis

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Mechanism of deficiency</th>
<th>Primary consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water soluble vitamins</td>
<td>Dietary insufficiency</td>
<td>Wernicke’s encephalopathy and Korsakoff dementia, anemia, asthenia, scurvy</td>
</tr>
<tr>
<td>Complex B and Vitamin C</td>
<td>Intestinal dysmotility</td>
<td></td>
</tr>
<tr>
<td>Fat soluble vitamins</td>
<td>Dietary insufficiency</td>
<td>Risk factor for developing cancer, including hepatocellular carcinoma, night blindness</td>
</tr>
<tr>
<td>Vitamin A (Retinol) and vitamin E</td>
<td>Malabsorption for cholestasis or due to medications (i.e., cholestyramine)</td>
<td>Osteopenia and osteoporosis</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Dietary insufficiency</td>
<td></td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Reduced exposure to UV light</td>
<td>K-dependent coagulation factors deficiency (Ⅱ, Ⅶ, Ⅸ, X)</td>
</tr>
<tr>
<td>Trace elements</td>
<td>Dietary insufficiency</td>
<td>Contribution to impaired glucose tolerance and diabetes, precipitation of hepatic encephalopathy</td>
</tr>
<tr>
<td>Zinc</td>
<td>Malabsorption (intestinal dysmotility)</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>Dietary insufficiency</td>
<td>Loss of muscle strength</td>
</tr>
<tr>
<td></td>
<td>Malabsorption (intestinal dysmotility)</td>
<td></td>
</tr>
</tbody>
</table>

TNF: Tumor necrosis factor α; IL: Interleukin.
transplantation, which represent a relevant selection bias.

All of these data suggested that despite the regain of liver function after liver transplantation and the improvement in body weight after surgery, the alterations in body composition may persist. In particular, muscle depletion seems to persist for at least 12 mo or more.

**FACTORS THAT MAY INFLUENCE NUTRITIONAL MODIFICATIONS AFTER LIVER TRANSPLANTATION**

**Liver gut brain axis**
The common hepatic branch of the ventral vagus is involved in important physiological functions. The afferent and efferent fibres travelling in this branch are crucial for mediating the complex orchestra of biochemical, molecular, and neuronal signals from gut, liver and brain that influence food intake and nutrient homeostasis. The normal hepatic innervations and more specifically, vagus innervation, are lost during transplantation. It has been suggested that the isolation of the liver from the autonomic regulatory control may influence not only nutrient absorption and metabolism, glucose and lipids homeostasis but also appetite signalling and eating behaviour. All of these modifications may contribute to the body composition and weight changes observed in liver transplanted patients.

**Diet**
The majority of the published studies reported a significant increase in dietary intake when the patients were followed after liver transplantation. These changes are particularly evident in those patients following severe dietary restrictions or in those suffering from relevant gastrointestinal symptoms or anorexia before liver transplantation. We observed that calories improved from a median of 27 kcal/kg per day to 32 kcal/kg per day; $P = 0.007$ and proteins from a median of 0.8 g/kg per day to 1.3 g/kg per day; $P = 0.02$ (comparing dietary intake before transplantation and 12 mo after liver transplantation). Similar results were reported by Richardson et al. in 2001, who correlated the high rate of overweight or obesity in liver transplant patients with the increase in energy intake (from $1542 \pm 124$ kcal/d to $2227 \pm 141$ kcal/d), a higher consumption of both proteins and carbohydrates and an approximately doubled intake of fat (from 62 g/d to 102 g/d) compared to pre-transplant.

**Energy metabolism**
Modifications in energy metabolism have been involved in the changes of nutritional status after LT; however, studies reporting resting energy expenditure (REE) measurements have provided controversial results. During the early post-operative period (2-4 wk), several studies showed no significant changes in REE, whereas other studies found that REE was increased to 130% or 142% of the predicted values in the same period. Subsequently (6-12 mo), a persistent hypermetabolism was reported at 6 mo by several authors, whereas others found a reduced REE at 9 mo after liver transplantation. In the latter study, no correlation was observed between body composition, energy expenditure and the immunosuppressive regimen; however, those patients with a reduced energy expenditure showed the higher increase in fat mass. By extending the follow-up to 14 or 32 mo after transplantation, another study found that the increase in energy expenditure normalised only when insulin sensitivity was restored; however, no correlation was found with body weight changes.

Finally, in a more recent study, the large majority (76%) of patients investigated one year after LT were normometabolic. Hypermetabolism after transplantation was significantly associated with hypermetabolism before LT and a higher cumulative dose of prednisonne.

**Immunosuppressive therapy**
Immunosuppressive agents are known to exert metabolic effects, which may be implicated in nutritional changes and body composition modifications after LT. Corticosteroids need attention as they increase appetite and fat deposition and decrease fat oxidation; moreover, they are responsible for increased proteolysis and impaired protein synthesis. Calcineurin inhibitors, such as cyclosporine and tacrolimus, may affect energy metabolism and muscle mass. Cyclosporine was found to be an independent predictor of post transplant weight gain, whereas tacrolimus has been reported to increase energy expenditure. Both cyclosporine and tacrolimus may contribute to the impairment of muscle growth and muscle regeneration by inhibiting calcineurin, which exerts its effects on skeletal muscle differentiation, hypertrophy, and fibre-type determination. Other immunosuppressive agents, such as sirolimus and everolimus, negatively influence muscle mass by inhibiting the mammalian target of rapamycin complex, which is a key regulator of protein synthesis.

**MOLECULAR MECHANISMS OF SARCOPENIA AFTER TRANSPLANTATION**

The majority of the studies dealing with molecular mechanisms of sarcopenia in liver cirrhosis have investigated experimental animal models, such as portacaval shunted rats and biliary duct ligated rats. Few studies have been performed in cirrhotic patients; therefore, definite conclusions could not be drawn. Similarly, the data on the mechanisms of post-transplant sarcopenia are lacking. Interestingly, in 3 subjects who had muscle reduction after transplantation, the mRNA expressions of genes regulating ubiquitin proteasome proteolytic components were unaltered, whereas those of myostatin were significantly elevated. These data suggest that an inhibition of muscle protein synthesis, induced by myostatin, instead of an increase in protein degradation, may play a pivotal role in the pathogenesis of post-transplant sarcopenia.
Increased blood product requirement

Subjective Global Nutritional Assessment

Hand-grip strength

No correlation

More days in intensive care unit

163

Not reported

Parameters used for the assessment of Prolonged ventilator support

Increased incidence of tracheostomy

More days in intensive care unit and hospital

Decreased 5-yr survival after liver transplantation

Figueiredo et al[68], 2010

Anthropometry

Dietary intake

Hand-grip strength

Body composition analysis

Subjective Global Nutritional Assessment

More days in intensive care unit

Increased incidence of infections

Stephenson et al[66], 2001

Anthropometry

Body composition analysis

Subjective Global Nutritional Assessment

100%

Increased blood product requirement

Shahid et al[67], 2005

Hand-grip strength

Not reported

No correlation

de Luis et al[69], 2006

Anthropometry

Body composition analysis

Subjective Global Nutritional Assessment

Not reported

No correlation

Merli et al[64], 2010

Anthropometry

Indirect calorimetry

Dietary intake

Psoas muscle area (CT evaluation)

Not reported

Decreased 1-yr survival

Table 4 Relationship between nutritional status and outcome after liver transplantation

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Patients (n)</th>
<th>Parameters used for the assessment of nutritional status</th>
<th>Prevalence of malnutrition</th>
<th>Outcomes related to malnutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pikul et al[64], 1994</td>
<td>68</td>
<td>Subjective Global Nutritional Assessment</td>
<td>79%</td>
<td>Prolonged ventilator support</td>
</tr>
<tr>
<td>Selberg et al[65], 1997</td>
<td>150</td>
<td>Anthropometry, Body composition analysis, Indirect calorimetry</td>
<td>41%-53%</td>
<td>Increased incidence of tracheostomy, More days in intensive care unit and hospital</td>
</tr>
<tr>
<td>Harrison et al[66], 1997</td>
<td>102</td>
<td>Anthropometry, Dietary intake</td>
<td>79%</td>
<td>Higher risk of infections</td>
</tr>
<tr>
<td>Figueiredo et al[68], 2010</td>
<td>53</td>
<td>Subjective Global Nutritional Assessment, Hand-grip strength, Body composition analysis</td>
<td>87%</td>
<td>More days in intensive care unit, Increased incidence of infections</td>
</tr>
<tr>
<td>Stephenson et al[66], 2001</td>
<td>99</td>
<td>Subjective Global Nutritional Assessment</td>
<td>100%</td>
<td>Increased blood product requirement, More days in hospital</td>
</tr>
<tr>
<td>Shahid et al[67], 2005</td>
<td>61</td>
<td>Hand-grip strength, Anthropometry</td>
<td>Not reported</td>
<td>No correlation</td>
</tr>
<tr>
<td>de Luis et al[69], 2006</td>
<td>31</td>
<td>Anthropometry, Body composition analysis</td>
<td>Not reported</td>
<td>No correlation</td>
</tr>
<tr>
<td>Merli et al[64], 2010</td>
<td>38</td>
<td>Anthropometry, Indirect calorimetry</td>
<td>53%</td>
<td>More days in intensive care unit, Increased incidence of infections</td>
</tr>
<tr>
<td>Englesbe et al[66], 2010</td>
<td>163</td>
<td>Psoas muscle area (CT evaluation)</td>
<td>Not reported</td>
<td>Decreased 1-yr survival</td>
</tr>
</tbody>
</table>

CT: Computed tomography.

NUTRITION AND EXERCISE COUNSELLING

It is conceivable that interventional programmes including dietary and exercise counselling may, in part, correct or completely normalise the nutritional alterations occurring after LT. Specific diet and exercise programmes may prevent the tendency to become overweight or help to obtain an adequate recovery of muscle mass. However, few studies with this goal were conducted. A randomised trial of exercise and dietary counselling after liver transplantation has been recently published. In this study, 151 liver transplant patients were enrolled and randomised into exercise and dietary counselling or usual care. A total of 119 patients completed testing 2, 6 and 12 mo after liver transplantation. Testing included the assessment of exercise capacity through oxygen consumption (VO2) using spirometry, quadriceps muscle strength, body composition by DEXA and a nutritional intake evaluation. The exercise and dietary counselling group showed a greater increase in VO2 peak with respect to controls; however, both groups (exercise and dietary counselling and usual care) presented similar increases in body weight, fat mass and lean mass during the follow-up[61]. Although the dropout rate was small (20%), the authors emphasised that the intervention can be planned only in those patients for whom exercise and dietary counselling can be safely implemented; furthermore, adherence to exercise and nutrition was rated low (37%). The life-style changes should be evaluated after a longer follow-up period.

NUTRITIONAL STATUS AND OUTCOME AFTER LIVER TRANSPLANTATION

Although the modification in nutritional status that occurs after liver transplantation represents a topic that warrants extensive investigation, much information is available concerning the role of nutritional status on the outcome of patients undergoing liver transplantation. Patients with liver disease and malnutrition suffer a higher risk of complications and mortality after surgery[66,67]. Similar findings have been reported in patients undergoing liver transplantation (Table 4)[68,69].

Several studies reported a greater need for blood products during surgery[68], a higher rate of infections[66,67,70] and longer postoperative hospital stay[68,69] and a lower postoperative survival rate[68] in liver recipients affected by severe malnutrition. Recently, the relevant role of malnutrition on survival after liver transplantation was confirmed in a study that focused on muscle wasting[68]. By measuring the cross-sectional area of the psoas muscle on CT scans in 163 liver transplant recipients, a strong association was found between the psoas area and post-transplant mortality (HR = 3.7 per 1000 mm2 decrease in the psoas area; P < 0.0001). The authors suggested that the objective measures of frailty, such as muscle wasting, may have the potential to inform benefit-based allocation models and may help optimise liver transplant outcome.

In contrast, other studies failed to show a correlation...
between the nutritional status and the post-transplant outcome\textsuperscript{[2,30,39]}. In these latter studies, surgical risk, donor risk index, and immunosuppressive therapy could have played a major role in the outcome of liver transplantation and might have blunted the influence of the recipient’s nutritional status.

As muscle wasting is a well-known risk factor that contributes to increasing costs for morbidity and mortality after major surgery in the general population\textsuperscript{[32]}, the specific role of liver disease in this setting might be questioned. Undoubtedly, sarcopenia occurs more frequently in liver disease than in the general population. Furthermore, post-surgical one-year survival was found to be 87% in sarcopenic non-cirrhotic patients\textsuperscript{[31]}, but only 49.7% in sarcopenic cirrhotic patients who are undergoing liver transplantation\textsuperscript{[30]}. Controversies exist concerning the influence of obesity on the outcome of liver transplantation. A higher rate of wound infection was reported in severely obese patients (BMI > 35 kg/m\textsuperscript{2}) who undergo liver transplantation\textsuperscript{[32]}. Additionally, these patients progressed more frequently to early death from multisystem organ failure. These results have been confirmed by analysing a large database including 18,172 transplanted patients, which demonstrated that primary graft non-function, and in-hospital, 1-year and 2-year mortality were significantly higher in the morbidly obese patients (BMI > 40 kg/m\textsuperscript{2})\textsuperscript{[33,34]}. A similar study, using the National Institute of Diabetes and Digestive and Kidney Disease liver transplantation database, found no significant difference in survival across all BMI categories after the BMI correction for ascites\textsuperscript{[35]}. In conclusion, alterations in nutritional status and muscle depletion occur frequently in patients with end-stage liver disease. After liver transplantation, the recovery of muscle mass is challenging. Close monitoring of the modifications in the nutritional status and body composition in liver recipients will help to identify patients at risk for malnutrition or obesity after transplantation. Additional large-scale interventional studies are needed to evaluate whether physical and nutritional interventions after liver transplantation are capable of improving body composition and muscle function.

Malnutrition and severe obesity seem to affect the prognosis of these patients and have an impact on morbidity and mortality after liver transplantation. Recently, sarcopenia has been proposed to be an objective and valid prognostic index of mortality during and after liver transplantation, signalling the importance of severe muscle depletion in the clinical outcome of cirrhotic patients.

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