L-ornithine L-aspartate for the Treatment of Sarcopenia in Cirrhosis: Potential Impact on the Outcome of Liver Transplantation

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ABSTRACT
Sarcopenia is a serious complication of cirrhosis with a significant negative impact on pre-transplant wait-list survival as well as post-transplant outcome and health-related quality of life. Preclinical studies demonstrate that ammonia toxicity is directly implicated in the pathogenesis of sarcopenia in cirrhosis via mechanisms involving increased expression of myostatin as well as markers of muscle autophagy. Paradoxically, in cirrhosis, it has been established that skeletal muscle replaces liver as the primary ammonia-detoxifying site, as a consequence of the induction of genes coding for glutamine synthetase and for an ammonium transporter protein. These molecular transformations give rise to a vicious cycle whereby hyperammonemia resulting from impaired hepatic ammonia removal in cirrhosis causes muscle damage and sarcopenia. This, in turn, reduces the capacity of muscle to remove blood-borne ammonia and the cycle is initiated. L-ornithine L-aspartate (LOLA) is an ammonia-lowering agent with newly-identified hepato-protective properties resulting in improvements in circulating transaminases, bilirubin, prothrombin times and MELD scores. Preliminary reports also suggest that LOLA may result in improved hepatic microcirculation via a nitric oxide-related mechanism. Treatment of cirrhotic patients with LOLA limits sarcopenia in cirrhosis due to its effective ammonia-lowering properties leading to improved muscle protein synthesis and function. Consequently, in addition to its well-established efficacy for the treatment of encephalopathy, LOLA has the potential to prevent sarcopenia leading to improvement in liver transplantation outcomes in patients with cirrhosis.

Keywords: L-ornithine L-aspartate, Sarcopenia, Liver transplantation, Ammonia, Cirrhosis, Running Head: LOLA for Sarcopenia and Transplantation

Introduction
Sarcopenia or loss of skeletal muscle mass is a common complication of cirrhosis where it is associated with a poor prognosis with negative impact on survival and health-related quality of life [1]. Median 6-month survival rates for sarcopenic patients with cirrhosis are significantly lower compared to non-sarcopenic patients. Sarcopenia is also associated with increased morbidity and mortality both before and after liver transplantation [1,2]. The presence of sarcopenia is also a predictor of other complications of cirrhosis such mortality and sepsis after living donor liver transplantation [3] and hepatic encephalopathy (HE) [4].

Nutritional supplementation has, until recently, been the focus for therapeutic initiatives for sarcopenia in cirrhosis. However, these approaches have not been consistently effective due in part to the fact that the underlying metabolic and molecular disturbances characteristic of sarcopenia in cirrhosis are largely unaffected by nutritional supplements [1].

Pathogenesis of Sarcopenia in Cirrhosis: Evidence that Ammonia Plays a Key Role
In chronic liver diseases, the capacity for ammonia removal by the liver due to urea synthesis (periportal hepatocytes) or glutamine production (perivenous hepatocytes) is seriously impaired. Under these circumstances, skeletal muscle takes on a predominant role for ammonia removal, a process that occurs exclusively via glutamine...
synthesis rather than incorporation into urea since muscle cells do not express all constituent enzymes of the urea cycle. Neurobiological and neuroimaging studies reveal that hyperammonemia plays a major role as mediator of the liver-muscle axis [1] and, consequently, in the pathogenesis of sarcopenia in cirrhosis.

**Muscle ammonia removal in cirrhosis**

Arterio-venous (A-V) differences for ammonia measured across the forearm of patients with decompensated cirrhosis reveal significant decreases in patients with sarcopenia [5]. A-V differences for glutamine in these patients are concomitantly increased several fold consistent with the notion that muscle plays a key role for the disposal of ammonia in patients with cirrhosis and that a major fraction of ammonia taken up by muscle is released as glutamine. These findings were confirmed in a study of the dynamics of ammonia metabolism in patients with cirrhosis using $^{13}$NH$_3$ where significant metabolic trapping of ammonia by muscle was observed [5]. Molecular studies in experimental animals with chronic liver failure suggest that this alternative pathway for ammonia removal implicating skeletal muscle is facilitated by post-translational induction of the gene coding for glutamine synthetase (GS) [6]. Increases in expression of ammonia transporters may also be implicated [7]. Given the evidence that muscle becomes the major pathway for ammonia removal in cirrhosis, it is evident that sarcopenia would likely result in worsening of hyperammonemia and this is indeed what has been generally observed [1,5].

**Sarcopenia and ammonia in cirrhosis: mechanisms**

Results of recent investigations suggest that ammonia per se is implicated in the pathogenesis of sarcopenia in cirrhosis. Mechanisms involved include the transcriptional upregulation of myostatin [1] and direct inhibitory effects of ammonia on muscle protein synthesis [8] as well as the induction of autophagy in muscle cells [9]. The in vitro exposure of myotubes to millimolar concentrations of ammonia results in decreased myotube diameters together with decreases of protein synthesis and increased expression of markers of autophagy [8]. Removal of the ammonia from these preparations results in significant attenuation of these effects.

Moving on to an in vivo preparation characterized by chronic hyperammonemia, the end-to-side portacaval-shunted rat, it was demonstrated that, one week post surgery, lean body mass, grip strength, muscle mass and muscle fibre diameter were all significantly reduced compared to controls [8]. Moreover, muscle changes were correlated with increases of both blood and muscle ammonia concentrations.

Based upon the above findings from in vitro and in vivo studies, it is now postulated by the author of the present review that a vicious cycle occurs in cirrhosis [10] whereby hyperammonemia resulting from impaired hepatic removal of ammonia causes severe muscle dysmetabolism, impaired protein synthesis and autophagy characteristic of sarcopenia. This impairment of muscle function and the consequent loss of the alternative pathway for ammonia removal by muscle then results in worsening of hyperammonemia and the cycle is underway (Figure 1). The presence of such a cycle provides a plausible explanation for the well-established clinical observation that severe muscle wasting has a significant negative impact on post-transplant outcomes.

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**Figure 1:** Schematic representation of the vicious cycle by which hyperammonemia in cirrhosis resulting from diminished hepatic ammonia removal and portal-systemic shunting of venous blood results in muscle damage characterized by impairment of proteostasis and evidence of autophagy, the hallmarks of sarcopenia. Treatment with LOLA results in attenuation of hyperammonemia leading to reduction of muscle sarcopenia and restoration of muscle glutamine synthesis, a key mechanism implicated in the lowering of blood ammonia in cirrhosis.

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Given the key role of hyperammonemia in the pathogenesis of sarcopenia in cirrhosis described above, treatments aimed at the effective lowering of blood ammonia could offer an approach for the effective management and treatment of sarcopenia in cirrhosis.

**Benefit of L-ornithine L-aspartate for the Treatment of Sarcopenia in Cirrhosis**

Studies in both experimental animal models of HE [11] as well as in patients with cirrhosis and hyperammonemia [12] have consistently shown that L-ornithine L-aspartate (LOLA) is effective for the lowering of circulating blood ammonia via mechanisms involving both the liver and skeletal muscle. L-ornithine stimulates the conversion of ammonia to urea by residual periportal hepatocytes whereas ammonia is removed via increased conversion to glutamine by the muscle [5,11] via GS. Transamination of L-ornithine provides glutamate, the obligate substrate for GS.

Via these two independent mechanisms, LOLA treatment has been shown to lower blood and muscle ammonia resulting in improved skeletal muscle phenotype and function [8]. The effective use of LOLA for the reduction of circulating ammonia in patients...
with cirrhosis was confirmed in a recent systematic review and meta-analysis [13].

Treatment of portacaval-shunted rats with LOLA together with the antibiotic rifaximin (in order to maximize ammonia removal) results in significant improvements in lean body mass, grip strength, skeletal muscle mass and muscle fibre diameters as a function of marked reductions in circulating and skeletal muscle ammonia concentrations [8]. Moreover, protein synthesis rates in gastrocnemius muscle that were significantly reduced following portacaval shunting were significantly improved by the ammonia-lowering strategy.

In a metabolic study of 16 patients with cirrhosis and sarcopenia randomized to receive LOLA or placebo, muscle protein synthesis rates measured in percutaneous biopsies of anterior tibialis muscle, improved significantly in the LOLA treatment group [14]. The findings from this study also demonstrated improvement of muscle protein synthesis in response to feeding following LOLA treatment.

In a subsequent study, 34 patients with cirrhosis were randomized to receive LOLA or placebo and markers of muscle function including handgrip strength and skin fold thickness were recorded. A biceps skin fold thickness assessment revealed a significant gain of 1.5 mm in the LOLA group compared to a loss of 1.0 mm in placebo [15]. Given the established role of skeletal muscle for ammonia removal in cirrhosis, it is likely that the ammonia-lowering properties of LOLA in patients with cirrhosis result, at least in part, from its beneficial effects on sarcopenia.

Impact of LOLA on Liver Transplant Allocation and Outcomes in Patients with Cirrhosis

Liver transplant allocation currently relies heavily on the use of the Model for End-stage Liver Disease (MELD) scoring system that predicts wait list survival and has been shown to result in decreased mortality in transplant candidates by directing organs to the most seriously ill patients [16]. An illustration of the impact of sarcopenia on pre-transplant survival was provided by an imaging study of cross-sectional areas of muscle at the 3rd lumbar vertebra of wait-listed candidates [17]. Sarcopenia was present in 41% of cases and higher wait-list mortality was significantly correlated with sarcopenia [HR: 2.36, 95% CI: 1.23-4.53] with the greatest effect in patients with low MELD scores.

There is an increasing body of evidence to suggest that LOLA has direct hepato-protective properties in cirrhosis [18]. Evidence is multi-dimensional and is based on the results of clinical trials in which LOLA was shown to result in improvements of circulating liver transaminases, bilirubin and prothrombin times [19-21]. Improvements in MELD scores were also reported in LOLA-treated patients with cirrhosis (Table 1) where improvements in liver function were accompanied by significant reductions in circulating ammonia and improvements in cognitive function/HE [19].

Alternative (or additional) mechanisms have been proposed to explain these hepatoprotective properties of LOLA including improvements in hepatic microcirculation due to increased synthesis of nitric oxide (NO) [22,23] resulting from increased synthesis of L-arginine, the obligate substrate for nitric oxide synthase. While further studies are required to confirm that NO is implicated in the pathogenesis of sarcopenia in cirrhosis, it is interesting to note that increased NO production in muscle leading to the S-nitrosylation of calpain results in slowing of sarcopenia in aging [24]. Whether or not a similar mechanism occurs in cirrhosis-related sarcopenia awaits the results of ongoing investigations.

Conclusions

Inter-organ trafficking of ammonia is modified in cirrhosis whereby the normal removal of ammonia by the liver as urea or glutamine gives way to its incorporation into glutamine by skeletal muscle. This metabolic adaptation results from the post-translational induction of muscle GS together with increased expression of ammonia transporters in muscle. Paradoxically, ammonia has been shown to have deleterious effects on muscle protein synthesis and may also result in autophagy. Together, these processes constitute sarcopenia.

As a result of this sequence of events, a vicious cycle is created whereby hyperammonemia causes muscle damage (sarcopenia) that limits the capacity of muscle to fulfil its alternative ammonia-lowering function in cirrhosis. Evidence for the existence of this cycle involving the liver-muscle axis is predicated on the results of experiments using in vitro techniques as well as in preclinical and preliminary clinical investigations.

LOLA has the capacity to restore muscle protein synthesis in patients with cirrhosis. The mechanism by which LOLA is beneficial for the treatment of sarcopenia in cirrhosis relates primarily to its ammonia-lowering action. In addition, LOLA has hepatoprotective properties mediated via the transformation of L-ornithine into key substrates including glutamine, glutathione (an anti-oxidant) and L-arginine, the substrate for nitric oxide synthase, the enzyme responsible for NO production.

Confirmation of the preliminary clinical observations of beneficial effects of LOLA on sarcopenia in cirrhosis awaits the results of adequately-powered, well-controlled randomized clinical trials.

References


Table 1: Effects of LOLA compared to placebo on 6-month progression rate to OHE and on Child-Pugh and MELD scores.

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<th>Placebo</th>
<th>LOLA</th>
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<tr>
<td></td>
<td>Day 0</td>
<td>Day 60</td>
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<tr>
<td>OHE at 6 months</td>
<td>38%</td>
<td>5%</td>
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<tr>
<td>Child-Pugh</td>
<td>7.6±2.06</td>
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<td>MELD</td>
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