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Sarcopenia in alcoholic liver disease: clinical and molecular advances

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Abstract

Despite advances in treatment of alcohol use disorders that focus on increasing abstinence and reducing recidivism, alcoholic liver disease is projected to be the major cause of cirrhosis and its complications. Malnutrition is recognized as the most frequent complication in alcoholic liver disease (ALD) and despite the high clinical significance, there are no effective therapies to reverse malnutrition in ALD. Malnutrition is a relatively imprecise term and sarcopenia or skeletal muscle loss, the major component of malnutrition, is primarily responsible for the adverse clinical consequences in patients with liver disease. It is, therefore, critical to define the specific abnormality (sarcopenia) rather than malnutrition in ALD, so that therapies targeting sarcopenia can be developed. Skeletal muscle mass is maintained by a balance between protein synthesis and proteolysis. Both direct effects of ethanol and its metabolites on the skeletal muscle and the consequences of liver disease result in disturbed proteostasis (protein homeostasis) and consequent sarcopenia. Once cirrhosis develops in patients with alcoholic liver disease, abstinence is unlikely to be effective in completely reversing sarcopenia, since other contributors including hyperammonemia, hormonal and cytokine abnormalities aggravate sarcopenia and maintain a state of anabolic resistance initiated by ethanol. Cirrhosis is also a state of accelerated starvation, with increased gluconeogenesis that requires amino acid diversion from signaling and substrate functions. Novel therapeutic options are being recognized that are likely to supplant the current “deficiency replacement” approach and instead focus on specific molecular perturbations, given the increasing availability of small molecules that can target specific signaling components. Myostatin antagonists, leucine supplementation, and mitochondrial protective agents are currently in various stages of evaluation in preclinical studies to prevent and reverse sarcopenia, in cirrhosis in general, and alcoholic liver disease, specifically. Translation of these data to human studies and clinical application requires priority for allocation of resources.

Introduction

Alcohol is the most frequently used socially acceptable hepatotoxin (McCullough et al., 2011). The spectrum of alcoholic liver disease, the most recognized clinical consequence of alcohol abuse, includes alcoholic steatosis, steatohepatitis and cirrhosis. Malnutrition, one of the most frequent complications of alcohol abuse occurs in all stages of alcoholic liver

disease(Mendenhall et al., 1984, Mendenhall et al., 1986, Mendenhall et al., 1993, Mendenhall et al., 1995a, Mendenhall et al., 1995b). Malnutrition contributes to adverse outcomes at all stages of ALD(Mendenhall et al., 1984, Mendenhall et al., 1986), and despite the high clinical significance, there are currently no universally recognized effective therapies to prevent or reverse sarcopenia(Dasarathy, 2012). It is critical to recognize that skeletal muscle loss, or sarcopenia, is the major component of “malnutrition in liver disease”, and this is discussed in the next section. In ALD, hepatocellular dysfunction and portosystemic collaterals, as well as alcohol directly, or its metabolites, result in skeletal muscle loss(Thapaliya et al., 2014, Tsien et al., 2015, Preedy and Peters, 1988b, Preedy and Peters, 1989, Pacy et al., 1991, Preedy et al., 1992, Sneddon et al., 2003) by reduced protein synthesis and anabolic resistance, or impaired response to nutritional interventions(Preedy and Peters, 1988a, Pacy et al., 1991, Preedy et al., 1992, Sneddon et al., 2003, Tsien et al., 2015, Qiu et al., 2012, Qiu et al., 2013, Thapaliya et al., 2014). Even though skeletal muscle consequences of alcohol may reverse after complete abstinence, recovery is usually incomplete and may be related to the underlying liver disease(Peters et al., 1985, Estruch et al., 1998). This sometimes makes it difficult to dissect the contribution of liver disease from that of alcohol or its metabolites on sarcopenia. Understanding the pathogenesis and molecular mechanisms of skeletal muscle consequences of alcohol and ALD are, therefore, likely to provide novel therapeutic targets reversing sarcopenia, with improvement in outcomes of these patients. Alcohol use disorders in general, and ALD in particular, are also accompanied by micronutrient deficiencies, but these will not be discussed in this review, where the focus will be on skeletal muscle loss. Interested readers are referred to a recent review focused on the nutritional consequence of alcoholic liver disease and the potential effects of nutrition on alcoholic liver disease beyond sarcopenia(Dasarathy, 2016b) while the focus of this review is primarily on sarcopenia in alcoholic liver disease.

Terminology and measurement instruments to diagnose malnutrition and sarcopenia in liver disease

Malnutrition is defined in the Miriam Webster dictionary as “*faulty nutrition due to inadequate or unbalanced intake of nutrients or their impaired assimilation or utilization*”. However, clinically, the term malnutrition was widely used in patients with alcohol abuse, those with ALD and cirrhosis to refer to a clinical syndrome of weight loss, muscle wasting or weakness, usually with micronutrient deficiencies rather than impaired intake of nutrients(Dasarathy, 2016b, McClain et al., 2011). Even though it is widely recognized that sarcopenia is the major component of malnutrition, a number of methods to define malnutrition have added to the difficulty in interpreting and comparing studies from different investigators(Merli et al., 1987, Kalafateli et al., 2016, Dasarathy and Merli, 2016). A number of measures have been used to diagnose malnutrition in the past and include: serum albumin is a hepatic synthetic function; lymphocyte functions are responses of the immune system; anthropometry and subjective global assessment include both fat and muscle mass(Caregaro et al., 1996, Merli et al., 1987) making it difficult to determine what truly constitutes clinical “malnutrition”. Increasingly, investigators and clinicians are using the term sarcopenia that refers to the clinical syndrome of muscle loss instead of the term “malnutrition” in patients with liver disease in general and ALD in particular that allows for comparisons of data across different populations(Dasarathy, 2016a, Kalafateli et al., 2016,

Hara et al., 2016, Sinclair et al., 2016, Carey et al., 2017, Merli et al., 2013, Giusto et al., 2015, Dasarathy and Merli, 2016). Imaging and dual energy X-ray absorptiometry are being used as more reliable measures of muscle mass (Giusto et al., 2015, Tsien et al., 2013). Another term that was commonly used was alcoholic myopathy that also sometimes referred to muscle injury rather than muscle loss (Urbano-Marquez et al., 1989). Even though skeletal muscle injury or rhabdomyolysis can occur during acute alcohol intoxication likely due to the direct effects of alcohol or its toxic metabolite, acetaldehyde, a much more frequent consequence is skeletal muscle loss due to or accompanying the hepatic injury due to alcohol (Urbano-Marquez et al., 1989, Estruch et al., 1998). In fact, other than in animal models, most human studies do demonstrate varying degrees of liver injury even with modest alcohol consumption (Becker et al., 1996) and it can be difficult to determine if the skeletal muscle effects are a direct effect of ethanol and/or due to the accompanying liver disease. Furthermore, in children, malnutrition has been more precisely defined as predominantly protein deficiency or *kwashiorkor* and a combined protein-calorie malnutrition or *marasmus* (Waterlow, 1972). In adults, on the other hand, malnutrition has been used to refer to a number of clinical conditions with a common underlying factor of loss of protein or skeletal muscle mass (Detsky et al., 1987, Merli et al., 1987, Carvalho and Parise, 2006, Dasarathy, 2016b, Dasarathy, 2016a). Due to the increasing prevalence of sarcopenic obesity with greater loss of muscle than fat mass, quantifying or defining protein deficiency becomes difficult unless sophisticated research tools are used to quantify whole body protein content (Hara et al., 2016). Instead, there is increasing focus on the skeletal muscle as a measure of whole body protein adequacy (Merli et al., 1987, Giusto et al., 2015, Dasarathy and Merli, 2016). One potential reason for the continued use of “malnutrition” in liver disease instead of the more precise term, “sarcopenia” has been the lack of precise cut off values to define the sarcopenic population. Publications that define cut off values of muscle area on imaging have resulted in more widespread use of sarcopenia rather than malnutrition (Carey et al., 2017, Montano-Loza et al., 2012).

Energy metabolism is another component of nutritional assessment, and fat mass is the major body store of energy. Loss of fat mass and/or disordered energy metabolism is also major components of malnutrition (Peng et al., 2007, Muller et al., 1999, Glass et al., 2012, Glass et al., 2013). These factors have confounded the use of precise and standardized terminology to define malnutrition in adult subjects in general, and due to ALD in particular. In the past, we have suggested that malnutrition in liver disease included interrelated but distinct components: skeletal muscle loss, disordered energy metabolism and micronutrient deficiency (Periyalwar and Dasarathy, 2012). The major component of malnutrition in liver disease, skeletal muscle loss, was sarcopenia of liver disease (Dasarathy et al., 2011). The term “sarcopenia” is derived from the Greek words, “sarcos” refers to flesh and “penia” means deficiency. This term was initially almost exclusively restricted to refer to the age related decline in muscle mass and function (Rosenberg, 1997). Even though our initial use of this term sarcopenia of liver disease caused much angst amongst those investigating muscle loss of aging, the term sarcopenia is now extensively used in the liver, lung and cardiac literature. A distinction between primary sarcopenia, the loss of muscle mass and strength that accompanies aging, and secondary sarcopenia that occurs in disease states is now being recognized (Santilli et al., 2014). Other terms that have been used to describe

malnutrition include cachexia that is loss of both fat and muscle mass and pre cachexia, that is a milder form of reduction in both fat and muscle mass(Muscaritoli et al., 2010). Finally, with the increasing epidemic of obesity and related non-alcoholic fatty liver disease underlying or compounding ALD, these patients continue to lose muscle mass disproportionately compared to fat loss(Dasarathy et al., 2014). The classical phenotype of the “wasted” alcoholic patient may therefore become infrequent over time due to the ongoing obesity epidemic, but a recent report did not show a change in BMI over time in alcoholic liver disease(Singal et al., 2013) suggesting that clinical evidence of muscle loss continues to remain overt in these patients. These observations clearly show that there is an urgent need for precise definitions of specific components of malnutrition in patients with liver disease in general, and alcoholic liver disease in particular. Interestingly, despite the potential for disparity between studies, most studies published to date on malnutrition in liver disease use methods that primarily focus on muscle loss(Merli et al., 1987, Dasarathy and Merli, 2016, Mendenhall et al., 1984, Caregaro et al., 1996, Peng et al., 2007).

We have emphasized that the term “malnutrition in liver disease” be replaced by specific components, so that the patient populations being studied are comparable across studies(Dasarathy, 2012, Periyalwar and Dasarathy, 2012). Such an approach is likely to allow comparisons of data across publications with greater reliability. Since the major clinical consequence of malnutrition is sarcopenia or skeletal muscle loss and this review will focus on skeletal muscle loss in ALD. Unlike in the aging literature, where muscle weakness is an integral part of sarcopenia(Rosenberg, 1997, Muscaritoli et al., 2010), a number of factors besides loss of muscle mass including impaired muscle mitochondrial function(Bonet-Ponce et al., 2015) and bioenergetics, as well as the neurological consequences of alcohol(Nelson et al., 1979) can affect fatigue and muscle weakness in alcoholic liver disease and hence these will only be reviewed briefly.

Epidemiology of malnutrition, specifically muscle loss or sarcopenia in alcoholic liver disease

Variability in investigators using different instruments to measure and then define malnutrition affects the prevalence of nutritional disorders in liver disease(Caregaro et al., 1996). Sarcopenia, the major component of malnutrition in liver disease, is the most frequent complication in cirrhosis and also in patients with milder forms of ALD(Dasarathy, 2016b). Based on published data on nutritional assessment in ALD, most of which use measures that assess muscle mass by different methods, despite some heterogeneity, one can conclude that nearly 60% of patients with ALD suffer from varying degrees of muscle loss.(Table 1) (Koehn et al., 1993, Lolli et al., 1992, Mendenhall et al., 1986, Roongpisuthipong et al., 2001, O’Keefe et al., 1980, Caregaro et al., 1996, Mendenhall et al., 1995a, Mendenhall et al., 1994, Tai et al., 2010, Carvalho and Parise, 2006, Singal et al., 2013, Teiusanu et al., 2012, DiCecco et al., 1989, Thuluvath and Triger, 1994, Sarin et al., 1997, Chang et al., 2003, Narayanan et al., 1999, Huisman et al., 2011, Tandon et al., 2012, Panagaria et al., 2006). The largest data comes from the classical studies in patients with alcoholic hepatitis at the Veterans Affairs hospitals(Mendenhall et al., 1984, Mendenhall et al., 1986, Mendenhall et al., 1993, Mendenhall et al., 1995a, Mendenhall et al., 1995b). Detailed nutritional assessment using state of the art methods available at that time suggested that

muscle loss was indeed the major component of malnutrition in ALD(Peng et al., 2007). The frequency of muscle loss worsens with severity of liver disease and may be due to higher alcohol consumption, greater metabolic and molecular perturbations with worsening severity of liver disease, or a confounding effect of these(McClain et al., 2011, Mendenhall et al., 1986, Lolli et al., 1992, Lolli et al., 1994, Roongpisuthipong et al., 2001, Dasarathy et al., 2014). There are conflicting reports of greater severity of malnutrition, primarily quantified by muscle mass, in patients with ALD, compared to those without a significant component of alcohol consumption as referred to in Table 1(O'Keefe et al., 1980, DiCecco et al., 1989, Lolli et al., 1992, Lolli et al., 1994). This may be due to the varying contributions of the duration of abstinence, cholestasis that also worsens muscle loss, method used to define muscle loss and malnutrition, given the difficulty in precise quantification of muscle mass during anthropometric measures, and differences in nutritional support provided. However, a review of existing publications on the prevalence of malnutrition in different etiologies of liver disease does suggest that patients with alcoholic liver disease generally have greater severity of malnutrition than those with non-alcoholic liver disease (Table 1). The prevalence of sarcopenia derived from previous publications using anthropometric measures suggests a higher prevalence in alcoholic hepatitis than that in cirrhosis, but this may be due to the acute inflammatory response in patients with severe alcoholic hepatitis(Mendenhall et al., 1986, Mendenhall et al., 1995b, Singal et al., 2013).

Clinical Significance

Of the various recognized complications of alcohol use disorders and alcoholic liver disease, malnutrition, primarily sarcopenia, is the most frequent consequence that adversely affects clinical outcomes(Mendenhall et al., 1984, Mendenhall et al., 1986, Mendenhall et al., 1993, Mendenhall et al., 1995a, Mendenhall et al., 1995b, Carvalho and Parise, 2006). In patients with liver disease, survival, development of other complications of liver disease including ascites, infection and encephalopathy, and quality of life are all adversely affected by malnutrition, primarily sarcopenia(O'Keefe et al., 1980, Merli et al., 2010b, Merli et al., 2010a, Kalafateli et al., 2016, Merli et al., 2013). Interestingly, unlike other complications of cirrhosis that are reversed after liver transplantation, sarcopenia does not improve or in many instances, worsens after transplantation(Tsien et al., 2014, Dasarathy, 2012, Dasarathy, 2013). Even though these adverse consequences have not been specifically evaluated with respect to etiology of liver disease, except in acute alcoholic hepatitis, sarcopenia worsens clinical outcomes in the large population of cirrhotic patients without, as well as in those after liver transplantation(Dasarathy, 2013, Tsien et al., 2014). In addition to the evidence that sarcopenia worsens clinical outcomes(Tandon et al., 2012, Montano-Loza et al., 2012, Merli et al., 2010b, Merli et al., 2010a, Merli et al., 2013), there is also emerging evidence that reversal of muscle loss improves clinical outcomes supporting the need for developing strategies to reverse sarcopenia to improve clinical outcomes(Tsien et al., 2013). The interested reader is referred to a number of recent reviews and original publications that have addressed these issues(Tandon et al., 2012, Montano-Loza et al., 2012, Dasarathy, 2012, Periyalwar and Dasarathy, 2012, Dasarathy, 2013, Tsien et al., 2013, Dasarathy, 2014, Dasarathy and Merli, 2016, Dasarathy, 2016b, Dasarathy, 2016a). Unfortunately, despite the high clinical significance, there are no effective or established therapies to reverse sarcopenia in cirrhosis, primarily because the mechanisms are poorly understood(Dasarathy,

2012). In the next section, an overview of the recent advances in our understanding of sarcopenia in alcoholic liver disease will be provided.

Mechanisms of sarcopenia in alcoholic liver disease

A combination of liver disease and direct effects of ethanol contribute to skeletal muscle loss in alcoholic liver disease (Table 2). Interestingly, the primary organs for ethanol metabolism are believed to be the liver and brain, but there is evidence to suggest that ethanol is also metabolized in the skeletal muscle (Thapaliya et al., 2014, Estonius et al., 1993b, Estonius et al., 1993a, Estonius et al., 1996). It may sometimes be difficult to dissect the clinical and pathophysiological effects of the underlying liver disease and its consequences from the direct effects of ethanol (and/or its metabolites) on skeletal muscle proteostasis.

Additionally, synergistic adverse effects of liver disease and ethanol or its metabolites could contribute to sarcopenia.

Direct effects of ethanol or its metabolites

Evidence of ethanol metabolism in the skeletal muscle includes the expression of alcohol metabolizing enzymes and cellular and tissue responses to alcohol and aldehyde dehydrogenase inhibitors. These data suggest a direct effect of ethanol on muscle proteostasis and consequent sarcopenia (Korsten et al., 1975, Uppal et al., 1991, Thapaliya et al., 2014). Ethanol feeding or exposure in animal models results in impaired protein synthesis (Preedy and Peters, 1988b, Preedy and Peters, 1989, Pacy et al., 1991, Preedy et al., 1992, Hong-Brown et al., 2001, Lang et al., 2003, Sneddon et al., 2003, Lang et al., 2004b, Fernandez-Sola et al., 2007, Steiner and Lang, 2014, Tsien et al., 2015). Whole body protein turnover studies in human patients with stable alcoholic cirrhosis show impaired protein synthesis in the postabsorptive and postprandial phases suggesting a state of “anabolic resistance” (Lang et al., 2003, Sneddon et al., 2003, Steiner and Lang, 2014). Anabolic resistance is defined as suboptimal stimulation of protein synthesis despite adequate nutrient or protein intake (Rennie, 2009) and contributes to decreased muscle protein synthesis. However, for loss of muscle mass to occur, reduced protein synthesis alone is not enough and an increased protein breakdown or proteolysis is necessary. The ubiquitin proteasome pathway, believed to be the major mechanism of skeletal muscle proteolysis, is either unaltered or decreased by ethanol and in alcoholic liver disease (Koll et al., 2002, Thapaliya et al., 2014). Instead, skeletal muscle autophagy is increased and contributes to loss of muscle mass (Thapaliya et al., 2014, Tsien et al., 2015, Bonet-Ponce et al., 2015). Even though autophagy is believed to be a cellular adaptive response to eliminate damaged organelles and cytotoxic cellular proteins, unregulated autophagy with ethanol exposure contributes to muscle loss (Thapaliya et al., 2014). These observations show that ethanol induced impaired protein homeostasis or proteostasis due to the imbalance between protein synthesis and autophagic proteolysis results in muscle loss.

The molecular pathways that regulate skeletal muscle mass target both protein synthesis and autophagy (Periyalwar and Dasarathy, 2012). A number of investigators have shown that mammalian target of rapamycin complex 1 (mTORC1) is inhibited by ethanol or its toxic metabolite, acetaldehyde (Lang et al., 2003, Lang et al., 2004b, Steiner and Lang, 2014). mTORC1 stimulates protein synthesis via downstream signaling molecules, P70S6 kinase

and 4 E binding protein 1. Ethanol exposure inhibits mTORC1 and its signaling targets with reduction in protein synthesis (Lang et al., 2003, Steiner and Lang, 2014). In addition to stimulating protein synthesis, mTORC1 also suppresses autophagy (Laplanche and Sabatini, 2012). Consistently, ethanol exposure also simultaneously increases autophagy with perturbed proteostasis (Thapaliya et al., 2014). The mechanism by which ethanol inhibits mTORC1 signaling is of great interest. Both Akt/PKB1 and AMPK, that are upstream regulators of mTORC1, are potential targets of ethanol-induced regulation (Laplanche and Sabatini, 2012). Despite initial reports in hepatocytes that ethanol phosphorylates and activates AMPK in hepatocytes (Nammi and Roufogalis, 2013), more recent data show that dephosphorylation results in reduced AMPK activation in alcoholic liver disease (You et al., 2004, Liangpunsakul et al., 2010). Since dephosphorylation is context dependent, whether a similar mechanism occurs in the skeletal muscle needs to be determined. In myoblasts, ethanol has been reported to activate AMPK (Hong-Brown et al., 2012) but in preliminary studies, surprisingly, we have observed that AMPK activation is decreased in myotubes and muscle tissue from mice fed ethanol, suggesting dephosphorylation of mTORC1 and AMPK by a protein phosphatase mediated mechanism (Gangarao Davuluri, 2015). Impaired mTORC1 signaling occurs during fasting and AMPK activation is decreased in the fed state, so that a combination of impaired mTORC1 and AMPK can be considered to be a “pseudofed” state induced by ethanol, as opposed to a “pseudofasted state” when both mTORC1 and AMPK are activated in response to the drug, olanzapine (Schmidt et al., 2013). Whether these molecular effects are mediated by the direct effects of ethanol, its metabolites acetaldehyde or acetate, or indirectly by metabolic perturbations including redox changes (Fernandez-Sola et al., 2007), mitochondrial dysfunction (Bonet-Ponce et al., 2015), and oxidative stress, are currently areas of intense investigation. Ethanol results in impaired skeletal muscle mitochondrial function and consequent generation of reactive oxygen species that in turn can activate autophagy (Bonet-Ponce et al., 2015, Mansouri et al., 2001, Haida et al., 1998). Impaired mitochondrial function results in lower ATP generation that impairs protein synthesis because of mRNA translational is one of the most energy intense cellular processes (Roux and Topisirovic, 2012). Combined, these data show that ethanol and/or its metabolites causes metabolic, biochemical, and molecular perturbations in the skeletal muscle, with consequent impaired proteostasis.

Hyperammonemia of cirrhosis

Another potential mechanism that has been understudied is the impact of liver disease on sarcopenia in alcohol abusers and alcoholic liver disease. In cirrhosis, hyperammonemia is a consistent abnormality with increased ammonia uptake by the skeletal muscle and elevated muscle ammonia concentrations (Shangraw and Jahoor, 1999, Qiu et al., 2013, Ganda and Ruderman, 1976, Lockwood et al., 1979). Ammonia impairs skeletal muscle proteostasis by impaired muscle protein synthesis and increased muscle autophagy (Qiu et al., 2012, Qiu et al., 2013). Acetaldehyde, a cytotoxic ethanol metabolite, impairs ornithine transcarbamylase, the critical rate-limiting enzyme in ureagenesis in hepatocytes (Holmuhamedov et al., 2012). Therefore, in patients with alcoholic liver disease, hepatic ureagenesis can be impaired even without severe hepatocyte dysfunction or portosystemic shunting. The additive effect of ethanol and ammonia on skeletal muscle may be responsible for previous reports of severe muscle loss and malnutrition in alcoholic liver disease (1994, Mendenhall et al., 1986).

Whether hepatic ureagenesis is worse and skeletal muscle uptake of ammonia is greater in alcoholic liver disease is currently unknown.

Endocrine abnormalities

Cirrhosis is associated with a number of endocrine abnormalities including hypogonadism (Green, 1977, Castilla-Garcia et al., 1987). Low testosterone is believed to be secondary to increased aromatase activity (Dasarathy et al., 2006). Additionally, ethanol directly results in testicular dysfunction (Green, 1977, Villalta et al., 1997). Since testosterone is an anabolic hormone, the additive effects of cirrhosis and ethanol intake on hypogonadism can contribute to more severe muscle loss in alcoholic liver disease, especially in men. Impaired growth hormone secretion or loss of circadian patterns can also contribute to muscle loss (Hattori et al., 1992, Santolaria et al., 1995). Growth hormone has multiple effects on skeletal muscle, including inducing insulin like growth hormone 1 and inhibiting myostatin, both of which stimulate protein synthesis and muscle growth (Hattori et al., 1992, Santolaria et al., 1995, Liu et al., 2003). However, clinical studies have yet to demonstrate consistent safety and efficacy of growth hormone therapy in cirrhosis (Moller et al., 1994, Donaghy et al., 1997).

Intestinal dysfunction

Both alterations in gut microbiome (Bull-Otterson et al., 2013, Engen et al., 2015) and loss of epithelial cell tight junctions due to ethanol (Dunagan et al., 2012), can result in alterations in circulating cytokines and lipopolysaccharides (Bala et al., 2014), both of which can directly result in impaired skeletal muscle proteostasis by a number of mechanisms and consequent sarcopenia (Gordon et al., 2013).

Energy expenditure in liver disease and sarcopenia

Cirrhosis is a state of accelerated starvation as shown by reduced respiratory quotient, the ratio of oxygen consumed to carbon dioxide produced, including that in abstinent patients with alcoholic cirrhosis (Peng et al., 2007, Glass et al., 2013). In the post prandial or fed state, carbohydrates and glucose become the primary substrate for oxidation and energy generation, yielding an RQ close to one (Glass et al., 2012). With time, a post absorptive or fasted state sets in, with a gradual transition to fatty acids as a dominant substrate for oxidation with a reduction in RQ in human patients with cirrhosis (Tsien et al., 2012). In the fasted state, even though fatty acids are oxidized by a number of tissues instead of glucose, the metabolic response also included increased gluconeogenesis. Since fatty acid carbon is not used for gluconeogenesis the primary carbon source is from amino acids (Landau et al., 1993, Owen et al., 1981). In alcoholic liver disease, we and others have reported an increased autophagy and decreased proteasome-mediated proteolysis that occurs in the muscle (Thapaliya et al., 2014, Bonet-Ponce et al., 2015). Repeated and frequent fasting results in recurrent proteolysis and the anabolic resistance results in impaired protein synthesis during the next fed state, resulting in incomplete restoration of protein stores culminating in muscle loss in human cirrhotic patients (Tsien et al., 2012). This is supported by our observation that reduction in RQ is associated with severity of sarcopenia in cirrhosis (Glass et al., 2013). The pathways in alcoholic liver disease that contribute to sarcopenia are summarized in Figure 1.

Diagnosis of sarcopenia in alcoholic liver disease

A number of strategies have been used to quantify skeletal muscle mass in patients with liver disease (Dasarathy and Merli, 2016). These methods are based on different principles, but most do not measure skeletal muscle mass directly or precisely. Of the various methods used clinically, subjective global assessment and anthropometric measures both rely on muscle loss as the major component of malnutrition (Detsky et al., 1987, Roongpisuthipong et al., 2001, Tai et al., 2010). Dual energy X-ray absorptiometry and bioelectrical impedance analysis quantify lean body mass that is not automatically translated to muscle mass. Increasingly, image analysis of computed tomographic scans and ultrasound measurement of thigh muscle thickness have gained interest due to the relative simplicity and efficiency in quantifying whole body muscle mass from single sections (Giusto et al., 2015, Tsien et al., 2013). Based on current data, in patients with liver disease, due to the frequent use of computed tomography of the abdomen as part of routine clinical evaluation, image analysis can be used to quantify muscle mass. Serial CT scan results can also be used to quantify changes in muscle area over time (Tsien et al., 2013). In vitro neutron activation is a relatively infrequently used method to quantify whole body protein content, but only 50–60% of protein is localized to the skeletal muscle (Peng et al., 2007).

Muscle strength is considered to be a component of sarcopenia of aging (Rosenberg, 1997) but since the term sarcopenia refers to loss of muscle mass and not function, contractile dysfunction in liver disease is considered separately. In patients with liver disease, grip strength is consistently lower than in controls (Alvares-da-Silva and Reverbel da Silveira, 2005). However, there is some concern that grip strength may not be the best method to measure deconditioning and predicting risk of falls due to muscle loss. Instead, thigh muscle strength, walk speed, sit to stand test and thigh extension are believed to be better measures of deconditioning or frailty (Dunn et al., 2016b, Dunn et al., 2016a, Tapper et al., 2015, Lai et al., 2016, Yadav et al., 2015). Even though there are reports that ethanol impairs muscle strength directly, it is difficult to measure contractile function in vivo in humans in an inebriated state. Muscle loss is associated with weakness and the combination of ammonia-induced muscle loss and impaired contractile function with ethanol-induced muscle loss result in a worse clinical course in patients with alcoholic liver disease (McDaniel et al., 2016).

Clinical consequences

Sarcopenia is one of the most frequent complications of cirrhosis (Dasarathy, 2012). Both impaired contractile function and loss of skeletal muscle mass in alcoholic liver disease contribute to adverse clinical outcomes. Patients with alcoholic liver disease during the entire clinical spectrum, from steatosis to cirrhosis, have evidence of skeletal muscle loss, the severity of which depends on the degree of the underlying liver disease and whether there is ongoing alcohol abuse (Mendenhall et al., 1984, Peters et al., 1985, Mendenhall et al., 1986, Urbano-Marquez et al., 1989, Lolli et al., 1992, Mendenhall et al., 1993, Mendenhall et al., 1994, Thuluvath and Triger, 1994, Mendenhall et al., 1995a, Caregaro et al., 1996, Roongpisuthipong et al., 2001, Panagaria et al., 2006, Singal et al., 2013). Sarcopenia in patients with cirrhosis, including alcoholic liver disease, worsens survival and quality of life (Periyalwar and Dasarathy, 2012, Shiraki et al., 2013). Additionally, other

complications, including encephalopathy and infections, are more severe in cirrhotic patients with sarcopenia than those without (Merli et al., 2013). Interestingly, due to excellent clinical outcomes after liver transplantation, a definitive curative procedure is now available, albeit to a minority of patients with alcoholic cirrhosis (Singal et al., 2012). However, post liver transplant outcomes are worse in sarcopenic patients than those with relatively preserved muscle mass (Selberg et al., 1997, Periyalwar and Dasarathy, 2012). Furthermore, the majority of patients with cirrhosis are not liver transplanted and muscle loss adversely affects their clinical outcomes (Dasarathy, 2012). Since only a small fraction of cirrhotics undergoes transplantation, ammonia dependent muscle loss adversely affects clinical outcome in most patients. Transplanted patients still lose muscle mass, but this is via a different mechanism, possibly related to immunosuppression, as suggested by us earlier (Tsien et al., 2014). These data show the high clinical significance of sarcopenia in alcoholic cirrhosis. Since muscle loss does not reverse after transplantation and in fact, worsens in the majority of patients, definitive therapies are urgently needed to prevent and reverse muscle loss before transplantation (Tsien et al., 2014, Dasarathy, 2013).

Therapy of Sarcopenia in alcoholic liver disease

Recent reviews have described the management strategies for sarcopenia in alcoholic liver disease (Dasarathy, 2016b, McClain et al., 2011, Rossi et al., 2015). In addition to abstinence, there are no other effective therapies to prevent or reverse sarcopenia in liver disease in general and alcoholic liver disease, specifically. This is probably related to “deficiency replacement” being used as the major therapeutic approach. This principle involves replacing any identified deficiency without determining the underlying mechanism for the defect. Most interventions to reverse sarcopenia in cirrhosis use this approach and have been generally not effective, possibly because of a non-mechanistic treatment strategy. Ethanol ingestion and alcoholic liver disease are states of anabolic resistance, at least by the molecular studies (Lang et al., 2003, Steiner and Lang, 2014, Tsien et al., 2015) and reduced muscle protein synthetic response to protein or nutrient intake (Hong-Brown et al., 2001, Lang et al., 2003, Lang et al., 2004b, Frost et al., 2005). Therefore, identifying the molecular and metabolic mechanisms of sarcopenia and therapies to overcome anabolic resistance will provide mechanistic approaches to treat sarcopenia in alcoholic liver disease including ammonia lowering measures, mitochondrial protection and high dose leucine supplementation (Davuluri et al., 2016b, Davuluri et al., 2016a, Kumar et al., 2017, Tsien et al., 2015).

Abstinence

In addition to liver injury by multiple mechanisms, ethanol and its metabolites also induce a state of anabolic resistance by inhibiting mTORC1 signaling (Lang et al., 2003, Hong-Brown et al., 2012, Tsien et al., 2015). The most important intervention to reverse alcohol-induced target organ damage is, therefore, abstinence followed by targeted interventions to reverse muscle loss and is the current strategy to prevent and treat sarcopenia in alcoholic liver disease (Peters et al., 1985). Given the high recidivism rates in patients with alcohol abuse disorders (Miller et al., 2015), this is a difficult goal to achieve in the majority of patients. However, cognitive therapy, supported by pharmaceutical measures to promote abstinence, should be an integral part of managing sarcopenia in alcoholic liver disease. A number of

reviews have discussed this approach(Miller et al., 2015, Lee and Leggio, 2014, Johnson, 2010).

Nutritional supplementation

As mentioned earlier, strategies to overcome anabolic resistance in alcoholic liver disease are likely to be beneficial in treating sarcopenia in these patients. Increasing understanding of the molecular perturbations due to ethanol, its metabolites and ammonia have allowed the development of targeted therapies, but nutritional supplementation alone is unlikely to be of benefit, since only deficiency replacement is being addressed. This is shown in multiple recent systematic reviews on nutritional supplementation in patients with liver disease, including ALD and alcoholic hepatitis(Antar et al., 2012, Fialla et al., 2015, Koretz et al., 2012, Koretz, 2014).

Protein supplementation

Since protein restriction is no longer considered appropriate in cirrhosis except in very specific situations, daily intake of 1.5 g.kg-1.d-1 is now standard of care and recommended by the ESPEN(Plauth et al., 2006). Reduced tolerance of animal proteins, due to the high aromatic amino acid content, and the low nitrogen retention of plant proteins, remain concerns(Uribe et al., 1982). Recommending a third of the protein intake in the form of dairy protein (casein), a third from plant sources (rich in branched chain amino acids) and a third from animal protein (high quality) is one approach for the management of patients with cirrhosis(Dasarathy, 2014, Dasarathy, 2016b). Even though there are individual studies that have suggested a beneficial role, systematic reviews and metaanalyses have shown lack of efficacy of nutritional supplementation with protein or calories(Puri and Thursz, 2016).

Amino acid supplementation

Even though branched chain amino acids (BCAA) have been used with reported benefits, neither acute nor chronic administration for hepatic encephalopathy resulted in improved nutritional status(Dasarathy, 2012). Even though in preclinical studies, leucine resistance was reported with ethanol(Lang et al., 2003), recently a single dose of leucine-enriched BCAA showed reversal of molecular perturbations in the skeletal muscle of patients with alcoholic cirrhosis(Tsien et al., 2015). A subsequent study showed that hyperammonemia of liver disease results in sequestration of leucine and potentially other BCAA in the mitochondria for anaplerotic flux and administering large doses of leucine and potentially, isoleucine, can improve muscle loss(Davuluri et al., 2016b). These are very recent studies and need to be developed further before being implemented in routine clinical practice.

Late evening snack

Since the longest period of fasting is at night, a number of studies have shown that a late evening protein snack shortens the post absorptive phase and by avoiding accelerated starvation, improves lean body mass(Periyalwar and Dasarathy, 2012, Tsien et al., 2012, Plank et al., 2008). Another dietary modification is to ensure that patients eat breakfast with high protein content(Vaisman et al., 2010). The combination of a high protein snack before

bedtime and a protein rich breakfast will result in the most reduction in postabsorptive phase and consequent loss of muscle mass(Tsien et al., 2012).

Enteral and parenteral feeding

A number of studies have evaluated aggressive enteral and parenteral nutrition in hospitalized patients with alcoholic liver disease, with limited or no benefits(Antar et al., 2012, Dupont et al., 2012, Fialla et al., 2015, Moreno et al., 2016, Puri and Thursz, 2016). The primary outcome measure was survival, while other outcome measures, including gain in weight, showed improvement in some studies. Encouraging oral feeding is perhaps the best strategy to improve muscle mass in alcoholic liver disease.

Hormone replacement

At least in male patients with cirrhosis, testosterone supplementation has been reported to improve muscle mass(Sinclair et al., 2016). However, the effect of increased aromatase activity may blunt the beneficial effects of testosterone administration in cirrhosis with portosystemic shunting(Gordon et al., 1979, Dasarathy et al., 2006). Adding oxandrolone to calorie supplementation in alcoholic liver disease resulted in improvement in nutritional parameters but not survival(Mendenhall et al., 1993).

Emerging therapies

Novel therapeutic strategies being developed include those targeting skeletal muscle mitochondrial dysfunction and generation of reactive oxygen species, myostatin antagonists, long-term ammonia lowering therapy, and autophagy regulators(Cohen et al., 2015, Qi et al., 2013, Lang et al., 2004a). These agents have shown promising results in preclinical studies, but have yet to be established as therapies for human patients. These agents are not specific for alcoholic liver disease, but have been studied in models of liver disease with sarcopenia.

Exercise and physical activity

Patients with cirrhosis have both sarcopenia and deconditioning or frailty that worsen clinical outcomes(Dunn et al., 2016b, Dunn et al., 2016a). Improvement in muscle mass alone is insufficient to increase contractile function. As mentioned earlier, ammonia impairs muscle contractile function and worsens muscle fatigue, both of which restrict exercise capacity(McDaniel et al., 2016). Importantly, exercise increases ammonia generation that can increase myostatin expression, impair mitochondrial function, and decrease contractility(Rush et al., 1995, McDaniel et al., 2016, Qiu et al., 2012, Qiu et al., 2013). Even though endurance exercise has been shown to be beneficial in cirrhosis, lower exercise tolerance and consequences of increased muscle ammoniogenesis during activity may limit the benefits, unlike that in healthy subjects where hepatic ureagenesis is not decreased(Didsbury et al., 2013, Jones et al., 2012). There are no specific recommendations for exercise in alcoholic liver disease, but in patients with liver disease, endurance exercise improves aerobic capacity. Resistance exercise increases muscle mass, but has the potential risk of increasing portal pressure, a risk factor for variceal bleeding, that should be taken into consideration before recommendations are made.

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Summary

- Skeletal muscle loss or sarcopenia is a major complication of alcoholic liver disease.
- Sarcopenia adversely affects clinical outcomes including survival, quality of life, other complications of liver disease, and post liver transplant outcomes.
- Direct effects of ethanol and its metabolites, as well as the consequences of cirrhosis, including hyperammonemia, contribute to the pathogenesis of sarcopenia.
- Anabolic resistance in alcoholic cirrhosis is mediated by impaired mTORC1 signaling.
- Late evening snack, breakfast and frequent meals have the potential to reduce the development and progression of sarcopenia.
- Therapeutic goals include an improvement in skeletal muscle mass, as well as contractile function.

Figure 1.

Table 1
Comparisons of malnutrition, specifically, muscle loss in alcoholic versus non-alcoholic liver disease.

Author/year	Measure used	Number of subjects	Disease	Conclusion
O'Keefe 1980[1]	Anthropometrics	156	Cirrhosis	49–55% prevalence; alcoholic little worse than non alcoholic
Mendenhall 1986[2]	Anthropometrics	252	Alcoholic hepatitis	3–64% malnutrition, primarily muscle mass. Degree of muscle loss worsens with increasing severity of liver disease. No non-alcoholic patients.
DiCecco 1989[3]	Anthropometrics	74	Cirrhosis	Alcoholic worse than non-alcoholic.
Lolli 1992[4]	Anthropometric		Cirrhosis	Males greater muscle loss; No difference between alcoholic and non alcoholic.
Koehn 1993[5]	Cross sectional; anthropometric	93	Inpatients with alcohol use disorder compared with non-alcoholic patients.	Triceps skinfold thickness less in alcohol use patients.
Italian multicenter 1994[6]	Anthropometrics	1402	Cirrhosis	Alcoholic greater severity and prevalence of muscle loss than non-alcoholic.
Thuluvath 1994[7]	Anthropometrics	132	Cirrhosis	35% cirrhosis has muscle loss. Alcoholic and non-alcoholic similar.
Mendenhall 1995[8]	Anthropometrics, laboratory	666	Alcoholic hepatitis	62% prevalence in alcoholic hepatitis; 100% in severe disease.
Caregaro 1996[9]	Anthropometrics	120	Cirrhosis	34% prevalence; Alcoholic similar to non-alcoholic.
Satin 1997[10]	Anthropometrics	215	Cirrhosis, non cirrhotic liver, healthy controls	Lower lean body mass in cirrhosis. alcoholic similar to non-alcoholic.
Narayanan 1999[11]	Anthropometrics	60	Cirrhosis	Muscle loss greater in alcoholic than non-alcoholic.
Roongpisuthipong 2001[12]	Anthropometrics	60	Cirrhosis	22–45% prevalence; alcoholic worse than non-alcoholic cirrhosis
Chang 2003[13]	Anthropometrics	66	Cirrhosis	Only fat mass less in alcoholic than non-alcoholic.
Carvalho 2006[14]	Anthropometrics	300	Cirrhosis	75.3% malnutrition, primarily muscle loss. Alcoholic worse than non-alcoholic.
Panagaria 2006[15]	Anthropometrics, creatinine-height index	81	Cirrhosis	Muscle loss in alcoholic more severe and prevalent than non-alcoholic.
Tai 2010[16]	Anthropometrics	36	Cirrhosis	Alcoholic cirrhosis worse muscle loss than non-alcoholic.
Huisman 2011[17]	Anthropometrics	84	Cirrhosis	67% prevalence; no difference between alcoholic and non-alcoholic.
Tandon 2012[18]	CT image analysis	142	Cirrhosis	41% muscle loss. No effect of etiology.
Teiusanu 2012[19]	Anthropometrics	176	Cirrhosis	Alcoholics worse than non-alcoholic.
Singal 2013[20]	Anthropometrics	261	Cirrhosis	84% prevalence. Anthropometrics and grip strength worse in alcoholic.

Cirrhotic patients included both alcoholic and non-alcoholic patients. Anthropometric measures quantified skeletal muscle mass.

Table 2

Factors contributing to sarcopenia in alcoholic liver disease.

Clinical symptom	Pathophysiological mechanism
Poor oral intake	Dysgeusia due to micronutrient deficiency Alcohol use disorder, inebriation-decreased dietary intake
Anorexia	Cytokine release Endotoxemia-gut dysbiosis, leaky gut epithelial barrier Ascites-early satiety Gut dysmotility due to portal hypertension
Maldigestion, malabsorption	Pancreatic insufficiency Intestinal epithelial cell dysfunction Portal hypertensive enteropathy
Decreased protein synthesis	Anabolic resistance of alcohol Hyperammonemia
Dysregulated muscle autophagy	Acetaldehyde Hyperammonemia