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ORIGNAL ARTICLE

What is new about diet in hepatic encephalopathy

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Abstract There is a relationship between hepatic encephalopathy (HE) protein malnutrition and muscle wasting. Muscle may play an alternative role in ammonia detoxification. Molecular mechanisms responsible for muscle depletion are under investigation. Specific nutrients may interact to reverse the molecular pathways involved in muscle wasting at an early stage. Training exercises have also been proposed to improve skeletal muscle mass. However, these data refer to small groups of patients. The amelioration of muscle mass may potentially help to prevent HE. The pathogenesis of HE is associated with modifications of the gut microbiota and diet is emerging to play a relevant role in the modulation of the gut milieu. Vegetarian and fibre-rich diets have been shown to induce beneficial changes on gut microbiota in healthy people, with reduction of *Bacteroides spp.*, Enterobacteriaceae, and *Clostridium* cluster XIVa bacteria. By way of contrast, it has been suggested that a high-fat or protein diet may increase Firmicutes and reduce Bacteroidetes phylum. Milk-lysozyme and milk-oligosaccharides have also been proposed to induce a "healthy" microbiota. At present, no studies have been published describing the modification of the gut microbiota in cirrhotic patients with HE as a response to specific diets. New research is needed to evaluate the potentiality of foods in the modulation of gut microbiota in liver disease and HE.

Keywords Cirrhosis · Sarcopenia · Nutrition · Gut microbiota · Vegetables · Fibres

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Malnutrition and HE: what correlation?

Hepatic encephalopathy (HE), together with malnutrition, are among the most frequent complications of liver cirrhosis and upcoming evidence suggests that they may be strictly connected. Indeed, protein malnutrition represents an independent prognostic factor for survival in patients with liver cirrhosis (Merli et al. 1996; Montano-Loza et al. 2012) and is associated with a higher frequency of complications. In a vast series of cirrhotic patients, episodes of hepatic encephalopathy (HE) were reported only in those with a protein-malnutrition diagnosis (Huisman et al. 2011). Furthermore, in a recent prospective study cirrhotic patients with muscle depletion were those at higher risk of both minimal and overt HE (Merli et al. 2013a).

The rationale for the relationship between muscle and HE is based on the role played by muscle in ammonia metabolism. Due to the inability of the failing liver to affect urea synthesis, the muscle plays a crucial role in ammonia detoxification by glutamine synthesis (Olde Damink et al. 2002). Although this metabolic pathway does not result in a definitive ammonia disposal, it has been proposed that muscle depletion may have relevant implications in favouring HE (Wright et al. 2011). From this point of view, amelioration of nutritional status needs to be considered an effective goal to improve the cognitive impairment in these patients. As a consequence, modulation of diet may be considered a promising option when seeking to prevent HE.

European and American Clinical practice guidelines provide clear statements regarding nutritional care in cirrhotic patients (Vilstrup et al. 2014) underlining the fact that the main

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aim of the nutritional support in the presence of liver cirrhosis is to avoid malnutrition and prevent muscle wasting by maintaining an adequate calorie and protein intake. However, in spite of these indications, muscle wasting is still reported in 40–76 % of these patients (Montano-Loza et al. 2012; Giusto et al. 2015; Tandon et al. 2012). It is likely that the dietary approach needs to be associated with something else.

Diet to prevent muscle wasting: should we add something else?

Knowledge concerning the molecular mechanisms involved in muscle wasting has increased, mainly following studies on experimental models, while few data have appeared regarding cirrhotic patients. Myostatin has been shown to play a central role as a negative regulator of muscle mass although controversial results have been published on muscle biopsies from cirrhotic patients (Qiu et al. 2013; Merli et al. 2013b). Experimental models of biliary cirrhosis (Shih-Yi Lin et al. 2004) suggest that the ubiquitin-proteasome system, which becomes hyper-activated in catabolic states associated with muscle depletion, may be involved in skeletal muscle depletion. However, Porto-caval shunt and muscle biopsies from cirrhotic patients seem to suggest that the expression of critical proteasome components such as MuRF1 and atrogin were unaltered, while expression of autophagy markers have been shown to increase significantly (Dasarathy et al. 2004; Dasarathy et al. 2007, Qiu et al. 2012). An opportunity to explore the issue is provided by supplementing the patient's diet with something capable of counteracting the molecular mechanisms involved in sarcopenia.

In a recent paper, Dasarathy et al. investigated the effect of a single oral branched chain amino acid mixture enriched with leucine (BCAA/LEU) on a small group of alcoholic patients with cirrhosis. Muscle biopsies were obtained before and 7 h after BCAA/LEU administration. Although the supplementation did not modify the myostatin expression, autophagy markers decreased while the mammalian target of rapamycin (mTOR), regulating protein synthesis, was activated. These data are interesting because they show the potentially positive effect of BCAA/LEU dietary supplementation on the molecular mechanisms responsible for muscle depletion in liver cirrhosis (Tsien et al. 2015). Nevertheless, the interpretation of the results is limited by the lack of an appropriate control group receiving a comparable nitrogen load.

Another possibility to take into consideration is the association of exercise training and a balanced oral diet. In fact training is known to exert a positive effect on muscle mass even in patients with chronic diseases (Zinna and Yarasheski 2003).

In a recent prospective pilot study by Zenith et al., eight weeks of supervised aerobic exercise training increased muscle mass, expressed as thigh circumference, and reduced fatigue in 8 patients with Child-Pugh class A or B cirrhosis (Zenith et al. 2014). Another recent randomized pilot study including cirrhotic patients, Child-Pugh grade A or B, examined whether an exercise programme combined with leucine supplementation might improve patient outcome over a period of 12 weeks. At the end of the period the authors reported that the intervention group (8 patients) had improved their exercise capacity (evaluated through a 6 min walk test and 2 min step test) and muscle mass (expressed as lower thigh circumference) (Román et al. 2014).

These results, although based on a small series, suggest that a combined diet, nutritional-supplementation and exercise approach may lead to an improvement in skeletal muscle mass in cirrhotic patients.

Whether the amelioration of muscle mass can reduce or even prevent episodes of HE has not been evaluated and needs to be explored by future studies.

The influence of diet on microbiota: one possible mode of HE prevention or treatment

In recent years attention has been focused on gut microbiota and its pathogenic role in the development of systemic inflammation, endotoxemia, and portal vasodilation leading to the main complications involved in liver cirrhosis such as HE (Bajaj et al. 2014). A limited number of studies investigating the gut-liver-brain axis in cirrhosis have proposed that gut microbiome composition may impact on the neurocognitive function (Bajaj 2014; Rai et al. 2015). By sequencing bacterial the 16S rDNA gene from the faeces of cirrhotic patients with and without minimal HE (MHE), Zhang and colleagues observed an abundance of Streptococcaceae and Veillonellaceae in cirrhotic patients vs normal individuals. At the same time, they reported that the gut urease-containing species *Streptococcus salivarius* was present only in cirrhotic patients and not in control subjects. The abundance of *Streptococcus salivarius* was significantly higher in cirrhotic subjects with MHE respect to those without MHE and was found to be correlated with ammonia levels (Zhang et al. 2013). By way of contrast, Bajaj and coauthors, analyzing the stool microbiota of cirrhotic patients with or without overt HE failed to find significant differences. However, when the colonic mucosa microbiota was investigated, these authors observed a number of differences between patients with and without overt HE. Specifically, Firmicutes phylum and members of *Veillonella*, *Megasphaera*, *Bifidobacterium*, and *Enterococcus* genera were higher in the HE group, whereas *Roseburia* was more abundant in the non-HE group (Bajaj et al. 2012).

The identification of a close connection between the gut microbiota, the liver and the brain, together with the

awareness that diet may play a crucial role in the regulation of the gut milieu, led to the hypothesis that modulation of the gut microbiota through changes in the quality of food assumption may be a potential therapeutic target for HE.

One of the first studies, aimed at investigating whether a dietary supplement capable of modulating gut microbiota might prove useful in the treatment of MHE and prevention of overt HE, utilized a probiotic yogurt. The cirrhotic patients were randomized to receive 12 oz of yogurt daily in addition to dietary recommendations to follow for 60 days. MHE improved in a higher percentage of the patients randomized to supplementation and in the same group the occurrence of overt HE was prevented as compared to the non-supplemented patients (Bajaj et al. 2008). Many other studies have utilized the addition of prebiotics, probiotics and symbiotics, defined as functional food components, to daily diet for the management of HE (Amodio et al. 2013).

Vegetarian and fibre-rich diet

Information on the effect of different diets on gut microbiota in liver disease is still not available (Giannelli et al. 2014), however, the idea that diet may represent a reliable alternative therapy in the treatment of HE through modulation of the microbiota is a really fascinating perspective. This working hypothesis provides a new way to explain the positive effects reported for vegetarian diets in patients with cirrhosis and HE (Amodio et al. 2001). In the course of the past few decades it has been claimed that vegetable proteins are better tolerated than animal proteins in cirrhotic patients with HE (Merli et al. 2012). Some of the proposed beneficial effects are the higher intestinal clearance of nitrogen-waste products, due to the high-fibre content which is capable of inducing a greater bacterial mass, a shortened transit time, and a reduced colonic pH entrapping ammonia in the intestinal lumen, a higher ornithine and arginine content, which may facilitate ammonia disposal through the urea cycle, and a lower methionine and tryptophan content compared to animal proteins. Nowadays new evidence suggests that additional benefits of a vegetal-enriched diet may derive from the modulation of gut microbiota. At present, studies evaluating the effects of a vegetable enriched diet on gut microbiota are available only for healthy people. In a study by Zimmer et al., a reduction in *Bacteroides* spp., *Bifidobacterium* spp., *Escherichia coli* and Enterobacteriaceae was observed in fecal samples of patients following a vegetarian/vegan diet vs patients on an omnivorous diet (Zimmer et al. 2011). In a cohort of vegetarian and omnivorous young women in southern India, faecal microbiota was found to be enriched with *Clostridium* cluster XIVa bacteria, specifically *Roseburia* and *E. rectale*, in the omnivorous group (Kabeerdoss et al. 2012). By contrast, other authors failed to report any differences in the microbiota composition of subjects following the these diets (Liszt et al. 2009). The variability of the results provided by the studies available may derive from the heterogeneity of the population and the acknowledge that even a vegetable enriched diet may vary in daily composition, inducing a rapid change in the gut microbiome (David et al. 2014). New and well defined studies on the effect of vegetarian/vegetables-enriched diets on the composition of gut microbiota in cirrhotic patients are needed. The impact of diets rich in whole-grain bread, cereals or rice compared to those comprising white wheat grain have also been investigated. A diet enriched by whole grain products, with high fibre content, seems to induce an increase in Bifidobacteria and a reduction of Bacteroidetes in gut microbiota (Costabile et al. 2008; Martínez et al. 2013; Lappi et al. 2013). The microbiota of children following the low-protein, carbohydrate, "Fiber-based diet", typical of rural countries as opposed to the "protein and polysaccharide-rich diet" typical of the western countries, shows a significant enrichment in Bacteroidetes and a depletion in Firmicutes (De Filippo et al. 2010). Enterobacteriaceae (*Shigella* and *Escherichia* genera) were also significantly lower in the "Fibre-based diet" as opposed to the "protein and polysaccharide-rich diet".

These dietary approaches might provide an interesting opportunity to modulate gut microbiota in cirrhotic patients.

High fat diet

If a beneficial effect on the gut microbiota has been suggested after the introduction of vegetables or fibres, high-fat diet has been shown to induce a shift in the balance between the two major phyla of gut microbiota, leading to an increase of Firmicutes and a decrease of Bacteroidetes (Hildebrandt et al. 2009; Turnbaugh et al. 2009). The administration of cholic acid to rats induced phylum-level alteration in the composition of the gut microbiota with an increase in Firmicutes and a reduction in Bacteroidetes, which are very similar to the changes induced by a high-fat diet (Islam et al. 2011). Given that bile acid secretion increases following a high-fat diet (Reddy 1981), the authors speculated that bile acids might be a determinant of the gut microbiota in response to a high-fat diet (Islam et al. 2011; Yokota et al. 2012). The possible modifications induced by a high-fat diet in cirrhotic patients needs, therefore, also to take the alteration in biliary secretion in these patients into account too.

Specific nutrients improving "healthy microbiota"

Some interesting studies have focused their attention on the influence of specific food constituents on the promotion of "a healthy-microbiota" (Maga et al. 2013; Barile and Rastall 2013). Among these food constituents, milk-lysozyme and milk-oligosaccharides have been investigated. Lysozyme is a

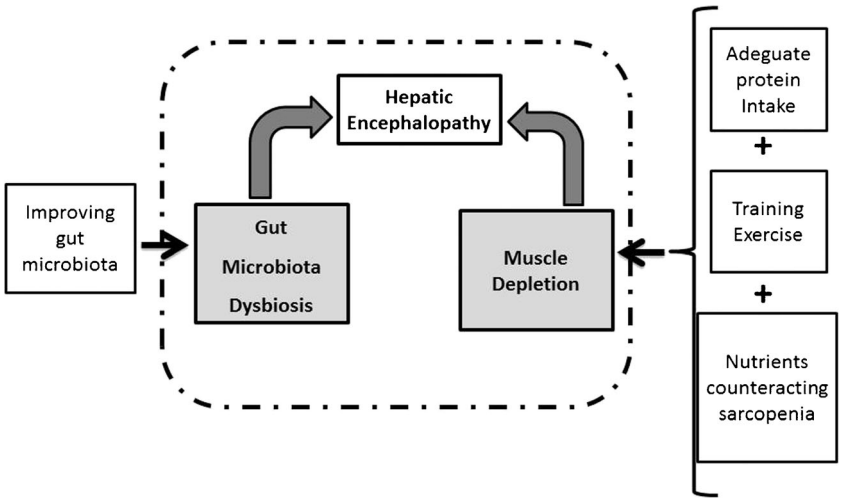

Fig. 1 How can diet contribute to ameliorate hepatic encephalopathy

naturally occurring antimicrobial enzyme found in the tears, saliva, and milk of all mammals that lyses a specific link in the peptidoglycan layer of bacterial cell walls. In an experimental study, milk enriched with **68 %** human lysozyme was used to feed young pigs. This treatment induced an increase in the bacteria associated with gut health (Bifidobacteriaceae and Lactobacillaceae) and a decrease in those associated with diseases (Mycobacteriaceae, Streptococcaceae, Campylobacterales) vs the control-fed group (Maga et al. 2012). This study demonstrated that a single component of the diet, with bioactivity, may change the microbiome composition of the gut. Other studies have investigated the role of Human Milk Oligosaccharides (HMO): HMO are being recognized as a new class of potent bioactive molecules capable of enhancing the growth of Bifidobacteria and Lactobacilli, reducing harmful bacteria such as Clostridia, Enterococci, Eubacteria and Enterobacteria, and preventing bacteria from attaching to target oligosaccharides on the intestinal mucosal surface (Fucosylated and sialylated oligosaccharides) (German et al. 2008; Bode 2012). Recent research has demonstrated that bovine milk contains oligosaccharides that are analogous to HMO and perform a similarly protective role (Zivkovic and Barile 2011). However, fluid bovine milk contains only trace amounts of oligosaccharides; for that reason, in order to increase the concentration of such oligosaccharides, a whey permeate has been produced from bovine milk and has been the subject of recent investigations. Whey permeate, further processed by membrane filtration, may have as much as 10-fold higher total concentrations of free oligosaccharide than bovine milk (Zivkovic and Barile 2011) and may represent a promising alternative as functional food to induce a healthy gut microbiota.

All the data reported suggest that by increasing our understanding we will be able in the future to modulate the gut microbiota through the introduction of specific foods or by adopting specific diets. Fresh research in this field concerning liver patients is required in order to understand how to take advantage of the great potentiality of foods in the modulation of the gut microbiota, in order to provide a therapeutic strategy capable of treating or even of preventing complications such as hepatic encephalopathy in those suffering from cirrhosis.

In conclusion, diet may play a central role as therapeutic support in the treatment and prevention of HE not only by counteracting malnutrition, but also by exerting an effect on others pathogenic mechanisms responsible for HE. Among these, new targets are represented by reversal of sarcopenia and by the modulation of the gut microbiota (Fig. 1).

Conflict of interest The authors declare that they have no conflict of interest.

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