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REVIEW

Role of the diet as a link between oxidative stress and liver diseases

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Abstract

Oxidative stress is caused by an imbalance between the production of reactive oxygen (free radicals) and the body's ability (antioxidant capacity) to readily detoxify the reactive intermediates or easily repair the resulting damage. An adequate diet, characterized by daily intake of foods associated with improvements in the total antioxidant capacity of individuals and reduced incidence of diseases related to oxidation, can modulate the degree of oxidative stress. In fact, diet-derived micronutrients may be direct antioxidants, or arecomponents of antioxidant enzymes, leading to improvement of some indicators of hepatic function. However, although their increased dietary intake might be beneficial, literature data are still controversial. This review summarizes what is known about the effects of diet nutrients on oxidative stress, inflammation and liver function. Moreover, we have analyzed: (1) the main nutritional components involved intheproduction and/or removal of free radicals; and (2) the role of free radicals inthe pathogenesis of several hepatic diseases and related comorbidities.

Key words: Nutrition; Micronutrients; Macronutrients; Liver disease; Oxidative stress

Core tip: Nutritional intake is a fundamental determinant of health. Recently, it has been observed that dietary supplementation has hepatoprotective and anti-oxidant effects. The aim of this review was to summarize the molecular changes promoted by diets and to underline the relationship between diet, oxidative stress and liver disease.

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INTRODUCTION

Dietary elements have long been known to play a critical role in the physiological or pathological response to tissue inflammation and oxidative stress (OS). Accordingly, deficiency or excessive production of most dietary nutrients can impair the balance between the anti- and pro-oxidant agents, also causing liver diseases. Although few studies have evaluated the histological signs in hepatic diseases after adequate and/or inadequate dietary intake[1,2], the involvement of nutrition and OS in the pathogenesis of liver dysfunction has been assessed[1,3,4]. In fact, specific micro- or macro- nutrients may play a critical role in liver cell integrity, influencing fibrosis, inflammation, and degree of liver steatosis caused by OS. Therefore, it is useful to understand the underlying mechanism for the production and removal of free radicals (FR) and/or other reactive species. FRs, including superoxide anions, hydroxyl radicals, and hypochlorous acid, show "two faces" in biology. They may be released in the liver as a consequence of physiological (*e.g.*, signal transduction, gene transcription, phagocytosis, hepatic detoxification, and metabolic pathways) and pathological conditions (*e.g.*, inflammation and necrosis)[5-7]. The impairment of antioxidant defense mechanisms (*e.g.*, superoxide dismutase, catalase and glutathione peroxidase, and glucose 6-phosphate dehydrogenase) could permit enhanced free radical–induced tissue damage. Therefore, reactive oxygen species (ROS)-mediated injury to membranes, proteins, DNA and RNA, generation of pro-inflammatory cytokines, activation of spindle cells, and finally fibrogenesis can occur[8,9]. The main targets of OS are the endoplasmic reticulum (ER) and mitochondria.

The ER regulates the synthesis and release of membrane proteins. The maintenance of its function requires high concentrations of intra-ER Ca^{2+}. Several injuries induce a decrease in physiologically high intra-ER Ca^{2+} levels that result in impaired ER function, also known as "ER stress", promoting apoptosis, hepatic stellate and Kupffer cells recruitment, and synthesis of inflammatory cytokine-inducible factors[10].

Although mitochondria can control the oxidative balance, under continuous stressful stimuli they collapse and become producers of oxidative damage[11]. In fact, mitochondrial fatty acids are normally transferred to the β-oxidation pathway. Fatty acid overload can lead to an imbalance between increased delivery of electrons to the respiratory chain and their decreased outflow from this chain, causing accumulation of ROS and peroxidation products. Thus, mitochondria represent the main source of ROS. Furthermore, ROS attack mitochondrial DNA and promote accumulation of DNA mutations, which, in turn, lead to further ROS synthesis[11]. Additionally, by inducing collagen gene expression, lipid peroxidation products can stimulate fibrogenesis and apoptosis. The released apoptotic bodies can activate hepatic stellate cells and convert them, through transforming growth factor beta 1, platelet-derived growth factor and endothelial growth factor, into myofibroblasts. Moreover, apoptotic bodies can also stimulate Kupffer cells to generate ROS, which further enhance apoptosis, and the release of cytokines and chemokines that contribute to the activation of hepatic stellate cells into myofibroblasts[12]. Myofibroblasts, through nicotinamide adenine dinucleotide phosphate (NADPH), can also induce the ROS synthesis, and the release of adhesion molecules for T lymphocytes and natural killer T-cells. Finally, myofibroblasts generate an extracellular matrix resistant to degradation mediated by metalloproteinases[13].

The consequence of these numerous interactive cellular and molecular pathways is to perpetuate and to enhance hepatic tissue injury. Specific dietary nutrients can interfere in the aforementioned pathways, potentially modulating the conversion of highly reactive FR to relatively inert radicals.

NUTRITION AND HEPATIC OXIDATIVE STRESS

Literature data support the usefulness of anti-oxidant activities of micro- and macro- nutrients to prevent many human diseases (*e.g.*, neoplasia, inflammation, autoimmune diseases). On the other hand, growing evidence suggests that hypo- and hyper-nutrition are associated with a higher likelihood of cellular oxidation[14], mediated by specific nutrient pathways.

Here, we discuss the role of micro- and macro-nutrients intake on the development hepatic disease.

Proteins

Proteins, including amino acids (*e.g.*, arginine, citrulline, glycine, histidine, and taurine), small peptides (carnosine), and nitrogenous metabolites (*e.g.*, creatine and uric acid) directly scavenge ROS and also inhibit inducible-nitric oxide synthase (iNOS) expression in various cell types, including hepatocytes[15]. However, when the capacity of this antioxidant system decreases, the level of inactivated ROS rises. ROS-mediated modification might alter both protein structure and function. OS may induce reversible and irreversible changes in proteins. Reversible alteration, generally involving cysteine, can modulate the function of a protein. Irreversible modification, usually lysine, results in a permanent loss of function and may contribute to the degradation and the accumulation of proteins into cytoplasmic inclusions[16]. Moreover, oxidized proteins are highly susceptible to proteolytic attack by proteasomes. Thus, a dietary deficiency of protein is associated with decreased synthesis of antioxidant enzymes and an increased superoxide anion release. Likewise, protein malnutrition can also cause steatosis, modulating the expression of lipolysis and lipid utilization genes in liver[17]. Proteins are involved in several mechanisms of hepatic fat storage. In fact, an adequate protein diet was associated with: (1) major metabolic rates and mitochondrial oxygen consumption; (2) increased β-oxidation of fatty acids; and (3) elevated

bile acids levels which, in turn, inhibit lipogenesis[18]. Finally, proteins in the hepatic tissue, produce a large amount of energy.

In animal models, it has been reported that insufficient protein intake causes a deficiency of micronutrients (zinc) and serum albumin levels[14,19]. In fact, plasma free iron values are elevated in malnourished patients. Some studies suggested that the increased tissue free iron concentrations likely result from low concentrations of hepatic iron-binding proteins (ferritin, transferrin, and lactoferrin)[20].

An increment in dietary protein content has been noted to prevent the likelihood of liver fat accumulation in excessive fat intake in humans[21].

However, recently, an increased protein intake has been shown to stimulate the generation of ROS, and lipid peroxidation in human polymorphonuclear leukocytes and mononuclear cells[22].

For these reasons, a high-protein and low-carbohydrate diet is not typically used in children because of their low energy intake, which might compromise the child's growth[23]. However, this type of diet is preferred, for a short time, to induce a rapid weight loss in obese children affected by non-alcoholic fatty liver disease (NAFLD)[23].

In conclusion, although the exact mechanism remains to be elucidated, an adequate quality and quantity of protein intake might be helpful in fatty liver disease.

Carbohydrates

Epidemiologic studies have implicated foods containing high concentrations of carbohydrates in the etiology of liver diseases. In fact, high carbohydrate intake, by activation of specific transcription factors, promotes hepatic steatosis and insulin resistance. The most common simple carbohydrates, glucose and fructose, can result in relatively high glycemic index values. High glycemic index foods stimulate excessive and prolonged insulin secretion, which increases deposition of fats and leads to major serum non-esterified free fatty acid values into circulation and in the hepatocytes mass. According to these findings, subjects affected by hepatic disease should avoid high carbohydrate intake, especially fructose[24], which, by inducing depletion of ATP, causes arrest in protein production, favors inflammatory proteins release, alters endothelial function, and stimulate OS[25]. Several adult studies have found links between higher consumption of total carbohydrates and NASH and the metabolic syndrome. Although fructose's role in human NAFLD is unknown, it is hypothesized that in addition to OS, lipid peroxidation, cytokine activation, nitric oxide (NO) and ROS, endogenous toxins of fructose metabolites can further lead to hepatic fat accumulation[26]. Fructose promotes intestinal permeability leading to portal overload of endotoxins, pro-inflammatory factors (Tumor Necrosis Factor-alpha: TNF-α), and fatty acids in the liver[27].

Lower serum HDL levels and higher triglyceride values were previously associated with major fructose intake in children affected by NAFLD[27]. Moreover, mineral deficiency, metabolic imbalance, and higher release of ROS can further favor fructose-induced NAFLD[27]. Recently, a study in normal-weight and overweight children showed that total fructose intake was the only dietary factor that significantly predicted low-density lipoprotein particle size[28].

However, it has been also reported that changes in the quality of carbohydrates intake did not influence hepatic functionality. In fact, isocaloric exchange of fructose for other carbohydrates seems not induce NAFLD changes in healthy subjects[29].

Lipids

Fat is an important component of the normal human diet. It is a source of energy and provides essential fatty acids and fat-soluble vitamins. However, saturated fatty acids (SFAs) and polyunsaturated fatty acids (PUFAs) can have adverse effects on human health. Although SFAs promote OS-resistant states in the liver and protect it against OS[30], studies have demonstrated that SFAs are more toxic than unsaturated fats. High SFA intake leads to a proinflammatory status resulting from an imbalance in lipid signaling pathways and increased production of inflammatory cytokines (*e.g.*, TNF-α, IL-6)[31]. Moreover, SFAs promote endoplasmic reticulum stress as well as hepatocyte injury. In fact, accumulation of SFAs in the liver leads to impaired mitochondrial metabolism and increased markers (ROS) related to endoplasmic reticulum stress. This latter, in turn, contributes to hepatic apoptosis progression[32].

The accumulation of SFAs in the hepatocytes can promote apoptosis by intrinsic and extrinsic pathways. The intrinsic pathway of cell death includes: (1) ROS-induced stress that affects the endoplasmic reticulum, mitochondrial membranes, and lysosomes; and (2) lipid peroxidation that increases the serum ROS levels[33]. The extrinsic pathway is mediated by death ligands, such as Fas (a key death receptor belonging to the TNF-receptor family) and TRAIL (TNF-related apoptosis-inducing ligand), which subsequently stimulate TNF-α production. TNF-α consequently induces the upregulation of pro-apoptotic molecules and, finally, cell death[34].

If overeating SFA promotes hepatic damage and visceral fat storage, an excess energy from PUFA may contribute to perpetuate liver injury. PUFAs are essential fatty acids, which are crucial for normal growth and health, and are not synthesized in the body of mammals. PUFAs exhibit anti-inflammatory action by suppressing pro-inflammatory cytokine production, macrophages and hepatocytes[35]. ω-6 PUFAs (*e.g.*, linoleic acid, alpha-linoleic acid, and arachidonic acid) contribute to the regulation of fatty acid synthesis and oxidation in the liver. However, high intake of ω-6 PUFAs may increase lipid peroxidation, iNOS expression, FR production and oxidative DNA damage in many cell types such as macrophages, muscle and liver cells. Higher fatty acids levels in portal or systemic circulation promote

visceral and hepatic fat deposits, mediated by decreased synthesis of lipoproteins and export of lipids from the liver. Subsequently, liver fatty infiltration may also cause decreased fatty acid oxidation and hepatic steatosis[36]. ω-3 PUFAs (*e.g.*, α-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid) inhibit lipogenesis and stimulate fatty acid oxidation in the liver[23]. In rodents, ω-3 PUFAs may influence body composition and obesity. Major intake of ω-3 PUFAs may decrease fat accumulation, mainly visceral fat, and reduce body weight when already obese[37]. It has been suggested that ω-3 PUFAs may activate a metabolic change in adipocytes, including increased β-oxidation, suppressed lipogenesis, decrease fat accumulation and higher apoptosis. Additionally, ω-3 PUFAs seem to reduce prostaglandin synthesis, even more than ω-6 PUFAs[38].

Liver-specific responses, such as regulation of blood glucose homeostasis, sinusoidal blood flow within the liver, properties of the trans-endothelial barrier within the liver, synthesis and release of important other mediators like cytokines, growth factors or NO, and liver fibrogenesis, are mediated or regulated by prostaglandin E2 (PGE2)[39]. Appropriate PGE2 levels are generated through the activation of constitutive cyclooxygenase-1 (COX-1) in hepatocytes. PGE2 plays a crucial role in liver pathophysiology *via* essentially hepatoprotective functions, such as inhibiting the generation of ROS, preventing leukocyte migration, improving hepatic insulin and lipid metabolism and regulating the production of inflammatory cytokines[40]. On other hand, PGE2 also induces the expression of inflammatory cytokines, which can, in turn, enhance the production of ROS[41].

Previously, certain authors[42] suggested that ω-3 PUFAs combines with the specific site on the COX-1 enzyme that converts ω-6 PUFAs into prostaglandins. Moreover, they can also act as the precursor of prostaglandins; however, their activity is 2–50 times lower than the prostaglandin produced by ω-6 PUFAs. It has also been observed that ω-3 PUFAs influence the synthesis of inflammation resolution mediators by neutrophils[43]. In animals, the anti-inflammatory effect was correlated with overexpression of antioxidant genes (glutathione-S-transferases, uncoupling protein-2 and Mn-SOD)[44]. In humans, however, data are controversial. An insufficient ω-3 PUFAs intake was promotes susceptibility to hepatic inflammation in children with NAFLD[45]. Although it has been reported thatω-3 PUFAs ameliorate hepatic circulation, mediated by suppression of local and systemic proteins, including high-mobility group box 1 (HMGB1)[46-48], an adequate dietary intake of ω-3 PUFA did not reflect systemic pro-inflammatory cytokines and protein levels[49].

It has been reported that diet integration with ω-3PUFAs might facilitate hepatic metabolic adaptation from in utero nutrition to the postnatal diet, by increasing fatty acid oxidation and modifying glucose and amino acids to anabolic pathways[50]. In addition to normocaloric/normolipidic diet, ω-3 PUFAs treatment correlated with the best metabolic parameters results (lower rise of serum triglycerides, glycemia, and cholesterol levels in serum) and reversed the liver histopathological results[51]. Recently, Chahal *et al*[37] assessed that ω-3 PUFAs supplementation was not significantly effective in treating hypertriglyceridemia in pediatric patients. Although the mechanism remains unclear, it has been proposed that ω-3 PUFAs, in addition to total parenteral nutrition and weight reduction therapy[52], reverse or improve abnormal liver tests in children[53]. To date, studies are insufficient regarding the types, amount, and duration of the intake of PUFAs in children[54].

Vitamins

Many vitamins play an important role in preventing radical induced cytotoxicity by inhibition of iNOS activity, its gene transcription and nitric oxide (NO) production. Vitamins also directly scavenge ROS and upregulate the activities of antioxidant enzymes[15].

Among them, vitamin E (α-tocopherol) is thought to be one of the most important micronutrients that inhibit ROS-induced release of lipid peroxyl radicals, protecting cells from pro-oxidants and OS. Vitamin E, acting as a chain-breaking antioxidant, prevents the propagation of FR in membranes and in plasma lipoproteins. When peroxyl radicals are formed, these quickly react with vitamin E (Vit EOH). The hydroxyl group of tocopherol reacts with the peroxyl radical to form the corresponding lipid hydroperoxide and tocopheryl radical (Vit E-O). This latter, by binding vitamin C, returns vitamin E to its reduced state[55]. The interaction of vitamins E and C has led to the hypothesis of the "antioxidant network", also knows as "vitamin E recycling", by which the antioxidant function of oxidized vitamin E is continuously restored by other antioxidants[56]. During phlogosis, this mechanism also reduces mast cell activation. Mast cells are activated by oxidized lipoproteins, resulting in increased expression of inflammatory cytokines and suggesting the reduction of oxidation of low-density lipoprotein by vitamin E[57]. Therefore, a dietary deficiency of vitamin E reduces the activities of antioxidant enzymes, (such as liver GSH peroxidases, glutathione reductase, and catalase) and leads to increased hepatic lipid peroxidation. Fortunately, all these negative effects can be reversed by dietary vitamin E supplementation[58]. However, the efficacy of vitamin E remains controversial in the treatment of liver diseases, including NAFLD. Several experimental studies assessed the potential protective role of vitamin E and showed that it improves the clinical symptoms of NAFLD[59], enhances glucose metabolism[60], and correlates with lower serum transaminase levels[61]. Moreover, Vitamin E, decreases histopathological damage (including degree of steatosis, inflammation and fibrosis) in adults and children[62-64]. However, other authors did not confirm these data[65-67].

Currently, randomized controlled trials in children

have not demonstrated uniformly the beneficial effects of vitamin E on the long-term outcome of NAFLD patients. The TONIC trial did not find a significant correlation between the vitamin E and control groups in improving serum alanine aminotransferase levels, steatosis or hepatic inflammation. However, increased resolution of hepatocyte ballooning was observed in the vitamin E subjects[64].

In humans, vitamin C, a water-soluble electron donor, plays a protective role against FR-induced OS. Vitamin C inhibits peroxidation of membrane phospholipids and acts as a scavenger of FR (superoxide, singlet oxygen, and hydroxyl radicals) and is also required for one-electron reduction of lipid hydroperoxyl radicals *via* the vitamin E redox cycle[67]. Vitamin C prevents hepatic storage of 8-hydroxydeoxyguanosine, a marker of DNA injury, and hinders hepatocellular growth. Moreover, vitamin C arrests bacteria internalization and translocation by increasing the transepithelial membrane resistance[68] and enhancing the ability of neutrophils to kill bacteria. In the presence of bacteria, ascorbate levels in neutrophils increase to protect these cells against damage by ROS that they previously produced[69].

In an experimental model, ascorbate's anti-fibrotic action, attributed to decrease in the oxidative stress, hepatic stellate cells activation, cytotoxicity and mRNA expression of fibrotic genes, has been also been reported[70]. The aforementioned positive effects of vitamins could provide a rationale for dietary vitamin C intake in individuals. However, the supplementation of vitamin C as further liver treatment is still controversial. A Cochrane database meta-analysis, analyzing six trials that used a combination of selenium, vitamin C and vitamin E to evaluate their effects on the NAFLD, found no evidence to support or refute them as useful treatments[71]. Intervention studies with vitamin C have shown no change in markers of oxidation or in clinical benefit. In fact, in children, authors reported no additional effects of using vitamin C or E on weight loss and a possible histological improvement in patients affected by NAFLD[1,72]. Perhaps these controversial data are related to different administration doses. Dose concentration studies of vitamin C in healthy people showed a sigmoidal relationship between oral dose and plasma and tissue vitamin C concentrations. Hence, optimal dosing is critical for intervention studies using vitamin C[73].

Vitamin B12 is an essential cofactor that plays important roles in one-carbon metabolism, which is required for the maintenance of intracellular DNA synthesis and methylation. In fact, vitamin B12, serving as a cofactor for methionine synthase, cystathionine synthase, and cystathionase, and as a substrate (5-methyltetrahydrofolate) for methionine synthase, helps to reduce the risk of OS-mediated homocysteine[74]. The liver is the principal storage site of vitamin B12. Consequently, serum Vitamin B12 levels reflect liver function. In fact, it has been reported that vitamin B12 and hepatic enzyme serum levels are correlated, especially in alcohol-dependent liver disease[74].

Vitamin B12, through epigenomic mechanisms related to imbalanced acetylation/methylation, influences cell proliferation, differentiation and apoptosis. In addition, vitamin B12, by ER stress stimulation, impairs fatty acid oxidation and energy metabolism in the liver[75]. Therefore, increased serum vitamin B12 levels have been attributed to the release of the vitamin from the liver during hepatic necrosis and decreased hepatic synthesis of trancobalamine II, an essential element for tissue binding of vitamin B12[75].

Minerals

Studies on most micronutrients are complicated by the fact that the nutrients have several roles.

Selenium, a cofactor of numerous enzymes (*e.g.*, glutathione peroxidase, selenoprotein P, and other selenoproteins) has a protective role against peroxidative and/or FRs damage and mitochondrial dysfunction[76]. In humans, deficiency of selenoproteins causes liver necrosis and hepatic cell death by OS. Furthermore, low serum selenium levels have been found in patients with chronic liver disease[77].

Magnesium is involved in ATP-mediated reactions. Deficiency of dietary magnesium reduces glutathione reductase activity, and results in generation of ROS and increased susceptibility to lipid peroxidation, and marked lesions in tissues (*e.g.*, skeletal muscle, brain, and kidney)[78].

Manganese is a component of several enzymes involved in fatty acid and cholesterol biosynthesis, as well as mitochondrial pathways. Manganese is a cofactor for a number of enzymes important for intermediary metabolism, including the hepatic urea cycle enzyme arginase. There are few well-described cases of manganese deficiency in the medical literature[14] and how manganese affects normal metabolism in the liver remains unclear[79].

Copper, zinc and manganese are indispensable metals for the activities of Cu, Zn-SOD and Mn-SOD, respectively[80].

The liver plays an important role in the disposition of copper, which can be used for protein and energy production. Consequently, abnormal copper metabolism can also cause oxidative damage and hepatotoxicity. Mitochondria are the first responders involved in copper homeostasis. In an animal model, Cu^{2+} induced a concentration and time-dependent rise in mitochondrial ROS formation, lipid peroxidation, cytochrome c expulsion, mitochondrial swelling and collapse, and finally cell death signaling. Interacting with respiratory complexes (Ⅰ, Ⅱ, and Ⅳ), Cu^{2+} causeddecreases the ATP concentration and the ATP/ADP ratio mitochondria, favoring liver toxicity[81]. Synthesis of ROS, tissue failure and hepatocyte death are also observed in human disease progression, such as un Wilson disease (WD). Liver damage in WD appears to involve two

different pro-oxidants mechanisms: synthesis of ROS, mediated by the Haber-Weiss reaction[82], and apoptosis through the activation of acid sphingomyelinase and consequent production of ceramide[83,84].

The liver plays a central role in zinc homeostasis, removing it from albumin in the blood and distributing it to the body as needed. Zinc acts as an essential cofactor for enzymes that are necessary to counteract hepatic OS[85]. Cirrhotics show increased urinary zinc loss and can become zinc deficient[77].

Liver is an important site for iron, a cofactor for important biological biochemical reactions, including the transport of oxygen and electrons *via* cells, oxidative phosphorylation, energy production, DNA synthesis, cell growth or apoptosis and gene expression[20]. However, iron's bioavailability is limited because its accumulation can enhance OS and related toxic effects. Therefore, iron deficiency and overload are generally regarded as causes of diseases involving OS and lipid peroxidation[86]. Patients with iron deficiency anemia are more sensitive to agents that induce OS[87,88]. On the other hand, daily iron supplementation resulted in increased lipid peroxidation and abnormal iron accumulation; although intermittent supplementation (once every 3 d) alleviated these effects[89]. It is thought that iron overload, mediated by mobilization of peripheral fat to the liver and development of hyperinsulinemia, promotes insulin resistance. Therefore, the syndrome of "insulin resistance-associated iron overload" was hypothesized in the presence of unexplained hepatic iron overload in patients with insulin resistance[90].

Increased iron storage has been linked with more advanced stages of NAFLD, *via* increased inflammation and oxidative stress[91].

Increased iron accumulation in NAFLD might be the results of decreased serum iron export protein levels, ferroportin, induced by the decrease of the iron regulatory peptide, and hepcidin. Generally, synthesis of hepcidin is upregulated by phlogosis and increased iron stores. Hepcidin in turn leads to the degradation of ferroportin and iron release[92]. In patients with NAFLD, increased expression of hepcidin and lower expression of ferroportin could favor iron accumulation and, consequently, OS and inflammation[93]. Iron overload is also very common in many types of non-biliary cirrhosis, and in end stage liver disease, including hemochromatosis. When liver iron overload is excessive, OS, involving production of iron catalyzed oxygen radicals, represents the main mechanism of liver injury, DNA alterations, and higher risk of cancer in patients affected by hemochromatosis[94].

Although the degree of necro-inflammation did not differ, iron stores were reported to be also elevated in patients with chronic hepatitis C compared to those with chronic hepatitis B[95]. HCV infection is probably associated with increased hepatic iron concentration and deposition (Kupffer cells and portal macrophages), higher serum transferrin saturation, and serum ferritin levels. Additionally, serum iron values were reported to be correlated with progression of liver disease and degree of hepatocyte necrosis[96]. Moreover, iron overload can activate hepatic stellate cells and promote the synthesis of collagen, contributing to hepatic fibrogenesis[97].

Probiotics

Probiotics, also known as "good bacteria" or "helpful bacteria," are live microorganisms (*e.g.*, bacteria), which are beneficial to health and are either the same as or similar to microorganisms found naturally in the human body (Lactobacillus or Bifidobacterium)[98].

Probiotics play a pivotal role in NAFLD and non-alcoholic steatohepatitis (NASH), obesity-related hepatocarcinogenesis, alcohol-related disorders, portal hypertension and obstructive jaundice[6,99,100].

Patients with hepatic diseases showed an impaired gut-liver axis, which contributes to increase blood levels of endotoxemia (lipopolysaccharides LPS) and chronic low-grade inflammation. Generally, LPS disseminates into the systemic circulation in two different ways: *via* a portal vein or through the lymphatic system. Underlying liver disease caused patients to report an increased gut permeability which promotes bacterial overgrowth and translocation, and increased expression of pro-inflammatory molecules (iNOS, ROS), which in turn promote major gut and sinusoidal permeability, increased pro-inflammatory cytokines and cells (*e.g.*, neutrophil), and mitochondrial damage[7,99-101].

The use of probiotics to manage liver injury is attributed to a variety of their health benefits. Probiotics, which increase cellular permeability and compete with pathogens for binding, improve colonization resistance to gut pathogens by reinforcing the mucosal barrier and restoring normal gut micro-ecology[102,103]. Probiotics can activate and modulate the immune system, and reinforce gut defense by immune exclusion, elimination and regulation[104,105]. The link between gut microbiota, liver inflammation, and immune system involves Toll-Like Receptors (TLRs), which are important mediators between the environment and the immunological response[106] and endogenous substances, such as short-chain fatty acids and HMGB1. TLRs involved in the pathogenesis of NASH are TLR2 (for lipoproteins and glycolipids in bacteria adhering to myeloid dendritic cells, mast cells or monocytes), TLR4 (for palmitic- stearic and lauric- acid, and LPS of B cells myeloid dendritic cells, mast cells, monocytes and intestinal epithelium) and TLR9 (for unmethylated CpG DNA-bacterial particles)[100,107].

Additionally, probiotics reduce hepatic triglyceride contents, ameliorate adipose tissue inflammation[108], and induce anti-oxidative enzymes that prevent the progression of NASH to hepatocellular carcinoma[58]. In animal models with portal hypertension, by reducing bacterial translocation, probiotics decreased the OS and/or increase vasodilator factors leading to improved endothelial dysfunction in the mesenteric artery[109].

Moreover, an experimental study investigated the role of probiotics in obstructive jaundice. The authors reported that probiotics (*Lactobacillus plantarum*), by activating the protein kinase C (PKC) pathway, could decrease intestinal epithelial cell apoptosis, reduce OS, and prevent tight junction disruption in biliary obstruction[101].

Although, Cochrane meta-analysis[110] did not approve or refute the use of probiotics as a therapeutic option for patients with NAFLD/NASH, several recent studies showed encouraging preliminary results[111,112]. Compared with controls, patients with liver diseases had initially decreased Bifidobacterium and Lactobacillus levels and their serum ALT, AST and GGT values were elevated significantly. After treatment, the group who received probiotics had significantly increased Bifidobacterium and Lactobacillus levels and decreased serum liver enzyme levels compared with patients receiving the placebo[113]. This evidence confirmed both gut-liver axis malfunction and the possible useful role of probiotics in the treatment of liver diseases.

TPN AND HEPATIC OXIDATIVE STRESS

TPN is life saving in patients with clinical problems that preclude enteral diet for a long period. However, long-term TPN-related complications, especially liver dysfunction, have been reported and confirmed by a biological significant increase of cytolysis[114,115]. Several possible mechanisms of TPN-induced liver dysfunction have been hypothesized. Firstly, TPN promotes alteration of some trace elements in hepatocytes. Depletion in the hepatic copper concentration might cause a decrease in the activity of antioxidant and detoxifying enzymes. A parallel depletion of zinc, a cofactor of tissue matrix metalloproteinase that degrades collagen, could induce the accumulation of the extracellular matrix, finally leading to the development of hepatic fibrosis and cirrhosis[116,117].

Secondly, TPN administration favors hepatic lipid accumulation, especially in children[118]. In addition to increased lipid synthesis, accelerated mobilization of fat deposits, impaired fatty acids oxidation and lipid accumulation leads to steatosis, mitochondrial and ER damage, activation of caspases, and consequent Fas ligand/TNF-α-mediated apoptosis. TPN also causes the depletion of carnitine, a compound necessary for the transfer of free fatty acids from the hepatic cytoplasm into the mitochondria. The cytosolic concentration of choline, a nutrient for lipoprotein release, also decreases, promoting lipid storage in hepatic cells[119,120]. Moreover, TPN favors lipid peroxidation by providing PUFAs and perpetuating lipid peroxidation[121].

Thirdly, TPN might lead to impairment of the gastro-intestinal immune system and the development of infections. The factors facilitating this process include: (1) abnormal proliferation and translocation of bacteria[122]; (2) decreased neutrophilic opsonic activity[123]; (3) atrophy of intestinal mucosa and related reduction of serum IgA levels; and (4) reduction of T-helper and IL 2 producing cells[124].

Finally, light exposure to nutrient mixtures affects hepatobiliary responses and histological changes. When TPN was administered intravenously, no damage was noted. Additionally, the severity of TPN-liver damage could be correlated with the duration of TPN administration[125].

In contrast to these data, an observational study assessed that, although the TPN-group showed some signs of increased OS, there were no signs for oxidative damage, compared with control-group. Moreover, the activity of the underlying disease was not correlated to increased OS[126].Other authors confirmed that an increase in OS bio-markers are not necessarily related to the route of pharmaconutrition (TPN); however, it might occur independently[127].

In the light of these data, to reduce the risk of liver disease related to TPN, several management strategies have been proposed recently, including reformulation of standardized parental nutrition. It has also been proposed that an optimal dose and type of parental lipid should be provided to minimize hepatic injury[128].

CONCLUSION

Although it is very difficult to correlate the biochemistry of a dietary intake with the pathophysiology of hepatic disease, diet significantly attenuates the relationship between OS and liver inflammation. In fact, dietary interventions may reduce the impact of hepatic diseases and could be useful in the treatment and prevention of progression to more severe disease. However, although the anti-oxidant properties of the diet are known, investigations into the relationship between the diet and OS are still limited, and most studies were conducted on a single diet element. We believe that the evaluation of combined and parallel roles of nutrients on inflammation and OS might be more helpful. Additionally, the potential correlation between diet nutrients and serological, histopathological, and molecular markers should be investigated.

Finally, the knowledge of enzymatic and non-enzymatic oxidative defense mechanisms will serve as a guiding principle for establishing the most effective nutrition intake to ensure adequate biological support, especially in patients affected by liver diseases. Investigations into the relationship between the dietary intake and OS mediators, which are enhance the inflammatory response directly and/or indirectly, are needed.

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