Review

Current Knowledge about the Effect of Nutritional Status, Supplemented Nutrition Diet, and Gut Microbiota on Hepatic Ischemia-Reperfusion and Regeneration in Liver Surgery

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Abstract: Ischemia-reperfusion (I/R) injury is an unresolved problem in liver resection and transplantation. The preexisting nutritional status related to the gut microbial profile might contribute to primary non-function after surgery. Clinical studies evaluating artificial nutrition in liver resection are limited. The optimal nutritional regimen to support regeneration has not yet been exactly defined. However, overnutrition and specific diet factors are crucial for the nonalcoholic or nonalcoholic steatohepatitis liver diseases. Gut-derived microbial products and the activation of innate immunity system and inflammatory response, leading to exacerbation of I/R injury or impaired regeneration after resection. This review summarizes the role of starvation, supplemented nutrition diet, nutritional status, and alterations in microbiota on hepatic I/R and regeneration. We discuss the most updated effects of nutritional interventions, their ability to alter microbiota, some of the controversies, and the suitability of these interventions as potential therapeutic strategies in hepatic resection and transplantation, overall highlighting the relevance of considering the extended criteria liver grafts in the translational liver surgery.

Keywords: ischemia-reperfusion injury; nutritional status; supplemented nutrition; gut microbiota; partial hepatectomy; liver transplantation

1. Introduction

An ischemic period is commonly required during hepatectomy or transplantation to avoid possible bleeding or blood transfusions. However, reduction of blood flow damages the liver and impairs liver regeneration [1]. Although ischemia-reperfusion (I/R) injury is commonly associated with poor post-operative results after liver surgery [2], no effective strategies are currently available to resolve this clinical problem. The mechanisms responsible for I/R injury are extremely complex, different
depending on the liver type (steatotic versus non-steatotic), and involve a wide range of different cells and pro-inflammatory mediators [1–6]. Warm ischemia is associated with hepatic resections, and warm and cold ischemia is associated with liver transplantation (LT). The type of ischemia must be distinguished due to existing debate about the specific pathophysiological mechanisms of each surgical procedure. Other factors to be characterized in I/R injury are the percentage and duration of hepatic ischemia applied and the presence of regeneration (associated with hepatic resections) [7,8]. Steatotic livers have been demonstrated to be less tolerant of I/R injury than non-steatotic livers; therefore, the presence of fatty infiltration in the liver is associated with poor outcome following surgery [9–12]. Steatotic LT shows increased rates of graft failure compared with the post-operative outcomes of non-steatotic LT [9,13,14]. Similarly, complication rates following resection are two–three-fold higher in patients with hepatic steatosis [10,15]. Given the increasing prevalence of steatosis, and consequently the increase in the number of steatotic livers subjected to surgical conditions [16], the development of protective strategies in liver surgery are required.

Recent advances suggest new concerns about the pathophysiology of hepatic I/R injury. Preexisting nutritional status might affect the post-operative metabolism, liver function, inflammation, and regenerative capacity [17,18]. Starvation exacerbates warm ischemic injury due to the amount of glycogen stored in the liver [19–22]. Adenosine-5′-triphosphate (ATP) depletion during ischemia induces an acceleration of glycolysis [23]. Although glycolysis is essential for cell survival, its effects may also be detrimental due to lactate accumulation [23]. Overnutrition and specific diet factors are crucial for the pathogenesis and progression of nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis [24]. Although there have been a wide variety of experimental studies on factors and nutritional substrates supporting or inhibiting liver regeneration after resection, a limited number of clinical studies have been addressed [25]. The intestinal microbiota is important to regulate liver functions [26,27] and is crucial in the pathogenesis of NAFLD [28–30]. Dietary components, host-intrinsic factors of the gastrointestinal tract affect microbial composition [27,31]. The activation of innate immunity and inflammation caused by gut-derived microbial compounds can exacerbate I/R injury or impair regeneration after liver resections.

The aim of the present review was to summarize the current knowledge from 2014 to 2019 about the effect of starvation, nutritional interventions, and gut microbiota alterations on morbidity and mortality in both experimental and clinical studies of liver surgery. A clear distinction between warm and cold I/R injury (associated with liver resections and LT, respectively) is discussed. The complicated differentiation on experimental models using steatotic and non-steatotic livers is addressed to elucidate the mechanisms responsible of liver I/R injury and for the establishment of new targets and protective strategies. The different results regarding the potential benefits of starvation, nutritional diets, and gut microbiota alterations in different studies (experimental, translational, and clinical studies) in hepatic surgery are discussed. All of this might be useful for the design of appropriate experimental models and treatments in clinical liver surgery.

2. Starvation Effects on I/R Injury Associated with Liver Surgery

Experimental studies have shown that liver I/R injury is influenced by different nutrients. For instance, protein restriction improved hepatic I/R injury by up-regulating hydrogen sulfide [32]. The supplementation of vitamins C and E in the diet protected against hepatic I/R injury. This effect was exerted by the up-regulation of antioxidant enzymes as well as the down-regulation of cell adhesion molecules [33]. However, although these experimental studies have demonstrated some beneficial effects of pre-operative diet restriction/fasting in liver I/R injury, the underlying mechanisms remain to be clarified. Other findings are contradictory [34–36]. Experimental studies have shown that fasting exacerbates normothermic ischemic injury [19–22]. Therefore, to support the clinical translation of starvation, the mechanisms behind the fasting-induced protection against I/R injury need to be elucidated [37]. Nil per os (NPO) status in patients undergoing hepatectomy to avoid potential problems, potentially associated with the general anesthesia, may be associated
with immunomodulation risks to patients [38,39]. The NPO-associated fasting induces inflammatory responses in surgery [40]. The fasting state results in hyperglycemia, post-surgical infections, and increased length of stay [41–44]. Similarly, in clinical transplantation, donor starvation because the prolonged hospitalization or lack of an appropriate nutritional support would favor hepatic damage and primary nonfunction [45].

2.1. Studies of Short-Term Starvation (12–24 h)

The most recent preclinical studies investigating the effects of short-term starvation (12–24 h) on experimental models of normothermic I/R injury are summarized in Table 1. Twelve hours’ fasting protected against apoptosis and necrosis associated with I/R injury [46]. Higher levels of serum β-hydroxybutyric acid (BHB) and, consequently, forkhead box protein O1 (FOXO1) over-expression were detected following the 12 h fast, thereby increasing antioxidant mechanisms including heme oxygenase 1 (HO-1) and autophagy activity. BHB inhibited the nucleotide oligomerization domain-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome activity, the high-mobility group box 1 (HMGB1) release, and nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) activation [46]. In an ex vivo perfused rat liver model based on 60 min of ischemia and 60 min of reperfusion, the authors reported that starvation for 18 h fails to provide protection against liver I/R injury. The benefits of feeding were explained, at least partially, by increased energy metabolism (availability of energetic substrates) such as glycogen and high ATP levels [47]. These contradictory results [46,47] could be explained by the use of different experimental models of I/R (in vivo and ex vivo, respectively).

| Starvation Time   | Model             | Specie | Main Therapeutic Effects                                      |
|-------------------|-------------------|--------|--------------------------------------------------------------|
| Short-term: 12 h  | Ischemia          | Mice   | ↓ Liver injury, inflammation, apoptosis                      |
|                   | WIT: 60 min       |        | ↑ BHB, FOXO1 and HO-1                                        |
|                   | RT: 6, 1, 3, 6, 12 h |        |                                                              |
| Short-term: 18 h  | Ex vivo ischemia  | Rats   | ↑ Liver injury, inflammation, apoptosis                      |
|                   | WIT: 60 min       |        | ↓ Energetic substrates (ATP, glycogen)                       |
|                   | RT: 60 min        |        |                                                              |
| Short-term: 24 h  | Ischemia          | Mice   | ↓ Liver injury, inflammation, HMGB1                          |
|                   | WIT: 60 min       |        | ↑ Sirt1 activity, autophagy                                  |
|                   | RT: 6 h [37]      |        |                                                              |
|                   | Ischemia          | Mice   | ↓ Liver injury, inflammation, caspase-3                      |
|                   | WIT: 90 min       |        | ↑ Sirt1 activity, autophagy, anti-apoptotic proteins          |
|                   | RT: 6 h [48]      |        |                                                              |
| Long-term: 2–3 days | Ischemia         | Humans | ↓ Liver injury, inflammation, oxidative stress              |
|                   | WIT: 60 min       |        | ↑ Nrf2, HO-1 and Nqo1                                        |
|                   | RT: 6 h [37]      |        |                                                              |
| Long-term: 3–7 days | Ischemia         | Mice   | ↑ Liver injury, inflammation, HMGB1                          |
|                   | WIT: 60 min       |        |                                                              |
|                   | RT: 6 h [49]      |        |                                                              |
|                   | Ischemia          | Mice   | ↑ Liver injury, inflammation, caspase-3                      |
|                   | WIT: 90 min       |        | ↑ Sirt1 activity, autophagy, anti-apoptotic proteins          |
|                   | RT: 6 h [48]      |        |                                                              |
| Note: ATP, adenosine triphosphate; BHB, β-hydroxybutyric acid; FOXO1, forkhead box protein O1; h, hour; HMGB1, high-mobility group box 1; HO-1, heme oxygenase 1; min, minute; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Nqo1, NAD(P)H quinone dehydrogenase 1; Nrf2, nuclear factor erythroid-derived 2-related factor 2; RT, reperfusion time; Sirt1, sirtuin 1; and WIT, warm ischemia time.

Short-term fasting for 24 h protected against hepatic I/R injury by regulating the response of innate immune cells [37]. Authors have shown that such benefits might be explained by the reduction in the circulating HMGB1 levels, which induces changes in sirtuin 1 (Sirt1) and autophagy, resulting in the
nutrients regulation of short-term fasting [37]. In contrast with the results obtained in the ex vivo perfused rat liver model after 18 h fasting [47], the authors failed to find a correlation between the energy parameters, such as hepatic glycogen stores and fasting-induced protection. Altogether this suggests the relevance of using in vivo I/R models that simulate the clinical conditions as much as possible.

Qin et al. showed that starvation for 24 h inhibited hepatic I/R damage [48]. The authors suggested that starvation had anti-apoptotic effects in I/R by increasing the expression of anti-apoptotic protein such as B-cell lymphoma (BCL)-2/BCL-xl/phospho-protein kinase B (P-Akt) and decreased caspase-3 activity [48]. Similar to Rickenbacher et al. [37], the authors also concluded that starvation induced autophagy in the liver via the Sirt1 pathway [48]. Therefore, the results obtained in preclinical studies of fasting for 24 h suggest that starvation reduces cell death during hepatic I/R. Fasting-activated Sirt1 induced autophagy and promoted anti-apoptosis [48].

In the clinical context, liver resection is usually carried out under vascular occlusion to regulate bleeding [51]. Regeneration affects the mechanisms responsible of I/R injury, and I/R negatively affects liver regeneration. Thus, the beneficial effects of starvation reported to date might not be extrapolated to surgical conditions requiring partial hepatectomy (PH) under I/R.

To the best of our knowledge, only Zhan et al. [49] recently analyzed the effects of short-term fasting on PH under I/R in humans (Table 1). Thus, in a prospective, single-blinded, randomized study of 30 patients per group, 24 h fasting reduced damage, inflammation, and oxidative stress through regulation of nuclear factor erythroid-derived 2-related factor 2 (Nrf2), HO-1, and NAD(P)H quinone dehydrogenase 1 (Nqo1) signaling pathways [49]. However, postsurgical complications of control and fasting groups were similar [49]. Further clinical studies are required to confirm the benefits of 24 h of fasting in PH.

2.2. Studies of Long-Term Starvation (Two to Seven Days)

In addition to the investigations on the effects of short-term fasting for 24 h, Rickenbacher et al. [37] and Qin et al. [48] studied the effects of long-term starvation for two and three days (Table 1). Rickenbacher et al. showed that fasting for 24 h, but not two or three days, can reduce I/R injury via the Sirt1-mediated down-regulation of HMGB1 in circulation [37]. However, Qin et al. [48] found even more protective effects against I/R injury at two and three days of fasting than 24 h of fasting in mice. The reasons for these different findings may be related to the different experimental model used, such as duration of ischemia (60 min versus 90 min of ischemia). Three days of fasting or one week of preoperative protein/energy restriction decreased transaminases and hemorrhagic necrosis after 30 min of ischemia [50].

Further experimental investigations and clinical trials are needed to determine the effects of starvation and the exact fasting duration (one, two, or three days) to produce the greatest advantages in patients. Long-term diet restriction (more than 24 h) may be difficult to apply for human preoperative management. Experimental models that reproduce the clinical conditions might be useful for the implementation of protective treatments in clinical conditions in the short-term [52]. The studies mentioned above have been reported in non-steatotic livers. The prevalence of obesity ranges from 24% to 45% of the population; therefore, increases in the number of steatotic livers subjected to liver surgery are expected. Steatotic livers show poor regenerative response and increased vulnerability to I/R injury, and the mechanisms involved in the I/R pathology and protective strategies are different depending on the type of the liver (presence or absence of steatosis) submitted to surgery. Thus, future research in experimental models of PH with I/R and LT are required to understand the underlying mechanisms of starvation, especially in sub-optimal livers in order to ameliorate the viability of livers subjected to surgery and reduce consequently the post-operative problems.
3. Nutritional Support by Nutraceuticals and Functional Foods on Liver Surgery under Hepatic Ischemia-Reperfusion

The preoperative nutritional state considerably affects postoperative metabolism, organ function, and inflammatory responses [17], and nutritional status affects the liver regenerative capacity [18]. Therefore, the basal alimentary condition of the patient plays an important role in predicting postoperative complications. Patients with end-stage liver diseases who undergo LT usually present with malnutrition, which directly impacts the deterioration of the patient’s clinical condition, affecting post-transplantation survival [24]. The post-transplantation survival is even more relevant in the case of liver steatosis (the main feature of NAFLD) as these organs show high vulnerability to I/R injury and regenerative failure in comparison with non-steatotic livers [53].

As mentioned above, coinciding with the progressive adoption of the Western lifestyle and changes in nutritional habits, many studies have evidenced the increased incidence and prevalence of NAFLD and other related disorders [54]. Also, malnutrition induces dysbiosis with translocation of bacteria- and/or pathogen-derived components from the gut to the liver [55]. Conversely, several dietary components significantly benefit health [56], presenting antioxidant or anti-inflammatory properties as well as contributing to modifying the gut microbiome [18]. As a result, the re-establishment and maintenance of the correct nutritional status by these nutraceuticals and functional foods before, during, and/or after surgery could lead to improvements in complications related to I/R injury, representing a potential approach alone or in combination with other therapies to improve patient outcomes. Eventually, strategies based on nutrition support could become a major adjunct to the conventional management of I/R injury.

Combination of different nutrition tools like anthropometry, and body composition analysis, have been reported to formulate a composite score for malnutrition assessment [57]. The goals of nutritional therapy are mainly focused on improving protein malnutrition and regulate nutrient deficiencies. Studies to address I/R injury complications by dietary supplementation and functional foods in liver surgery covering 2014 to 2019 are summarized in Table 2.

3.1. Plant-Derived Supplements and Other Food Additives

Three studies focusing on nutrition support based on plant-derived supplements and other food additives were reported from 2014 to 2019 [58–60]. All of them targeted oxidative stress and inflammatory responses related to I/R injury in murine models. The more remarkable findings were strengths of the antioxidant defense systems and anti-inflammatory properties after the intervention. For instance, ankaflavin, a traditional food additive used in Eastern Asia and China, significantly decreased the proliferation of Kupffer cells and the protein expression of inflammatory cytokines (tumor necrosis factor α (TNF-α), interleukin (IL)-6, and IL-1β) and reduced apoptosis and liver steatosis in high-fat-diet-fed mice [58].

A similar plant-derived strategy tested the potential benefits of apocynin (4-hydroxy-3-methoxyacetophenone) in rats under I/R injury. In this case, a single dose of apocynin 30 min before surgery induced the production of superoxide dismutase (SOD), reduced lipid peroxidation, and decreased glutathione (GSH) limiting the cellular stress triggered by ischemia [59]. Also, Korean red ginseng extract, which contains ginsenosides, phenolic compounds, polysaccharides, and polyacetylenes, showed a chemopreventive effect through antioxidant, apoptotic, and anti-cell proliferation in various cancers. In concordance with these findings, a study conducted in rats in which hepatic cancer had previously been induced, supplementation starting two weeks before surgery and eight weeks after PH revealed chemopreventive effects by prevention of oxidative stress and regulation of redox-enzymes [60]. The potential limitation of all these studies is related to the limited specificity of the different plant-derived supplements and additives. The relevance of the changes on oxidative stress, TNF-α, IL-6, and/or IL-1β induced by such treatment requires further investigation. Studies aimed at evaluating if such benefits can be extrapolated in steatotic liver undergoing surgery might
be of clinical and scientific relevance. The potential toxicity and side effects of these components, dependent on the concentrations, required to confer protection should be investigated.

Table 2. Studies to address hepatic I/R injury by dietary supplementation and functional foods.

| Drug | Administration | Model | Specie | Main Therapeutic Effects |
|------|----------------|-------|--------|--------------------------|
| Anakaline (food additive) [59] | Gavage (orally) 0.624 mg/kg daily for 1 week | Ischemia, fatty liver | Mice | ↓ Liver injury, steatosis, oxidative stress, apoptosis, inflammatory cytokines (TNF-α, IL-6, IL-1β) |
| Apocynin (organic compound related to vanillin) [59] | Intraperitonally 20 mg/kg, 30 min before surgery | Ischemia | Rats | ↑ Oxidative stress (MPO) ↓ Antioxidant levels (SOD) |
| Korean red ginseng extract [60] | Orally 0.5%, 1%, or 2% for 10 weeks | PH | Rats | ↓ Lipid peroxidation, cytochrome P450 signaling pathway ↓ Antioxidant levels (GSH, GST, GPs) |
| Antioxidative nutrient-rich enteral diet (Polyphenole, Vitamin C and E) [13] | Orally ad libitum for 7 days | Ischemia | Mice | ↓ Liver injury, necrosis, inflammatory cytokines (IL-6, CCL5), MDA, cell adhesion molecules, neutrophils and macrophage infiltration ↑ Antioxidant levels (SOD, GSH) |
| Desophenol (analogue of probvamicin B5) [61] | Intraperitonally 500 mg/kg during the ischemic period | Ischemia | Rats | ↓ Oxidative stress (MPO), histologic tissue damage ↑ Antioxidant levels (SOD, GSH) |
| Vitamin C [62] | Intravenous 50-200 mg/kg after surgery | Ischemia | Swine | WIT: 15 min pringle maneuver with 5 min between occlusion RT: 4 h |
| Rosa mosqueta oil [63] | Orally 0.4 mL/g/day for 21 days | Ischemia | Rats | ↓ Liver injury, inflammation, oxidative stress ↓ α-linolenic acid, EPA and DHA fatty acids levels |
| Tilapia fish oil [17] | Gavage (orally) 0.4% body weight for 3 weeks | Ischemia | Mice | ↓ Liver injury, antioxidant levels (CAT, SOD, GPx), tissue TBARS, histologic tissue damage |
| Fish oil [64] | Gavage (orally) 12 mL/kg daily | PH | Rats | ↓ Liver injury, total bilirubin ↓ Proliferation, AMPK activation, liver-to-body weight ratio, tight junction, and BSEP protein expression |
| L-arginine [65] | Gavage (orally) 10% in 1 mL/100g of solution 15 min before surgery and 24 h until date of death | PH | Rats | WIT: 24 h, 72 h, and 7 days |
| L-glutamine [66] | Gavage (orally) 1 mL/100g body weight 6 h and 15 min before surgery | PH | Rats | WIT: 24 h, 72 h, and 7 days |
| Omega-3 fatty acids [67] | Orally 10 mg/kg/day for 28 days | PH | Rats | WIT: 24 h, 72 h, and 7 days |
| Omega-3 fatty acids [29] | Gavage (orally) 1 mL/100g (10% v/v) 15 min and 24 h before surgery | PH | Rats | ↓ GGT No effect in regeneration |
| Immunonutrients (EPA, arginine, and nucleotides) [68] | Orally 1000 kcal/day for 5 days before surgery | PH | Humans | ↓ Inflammatory response (IL-6), infection, severe complications |
| Immunonutrients (EPA, arginine, and nucleotides) [69] | Orally 3 x 257 mL/100 kcal, 54 g proteins, 12.6 g arginine, 1.3 g nucleotides, 3.3 g EPA/day x 5 days before surgery | PH | Humans | No benefits |
| Immunomodulating diet enriched with HWP [70] | Intravenous 20 mL/h 24 h after surgery | LDLT | Humans | ↓ Incidence of bacteremia |
| Hydrolyzed whey peptide (HWP) [71] | Orally 4 mL, every 6 h after reperfusion | Ischemia, steatotic liver | Rats | ↓ Liver injury, inflammatory cytokines (TNF-α, IL-6), NOx oxidative stress (UCP-2), necrosis ↓ Survival |
| Lipid emulsion [72] | Intravenous 5 mL/h after surgery | PH + ER, steatotic liver | Rats | ↓ Regeneration (HGF, cyclin A and E), IL-6, ATP, phospholipid levels |
| BCAA [73] | Orally 1000 mg valine, 2000 mg leucine, 1000 mg isoleucine in 200 mL until 2 h before surgery | PH | Humans | ↓ Lactate levels No effect in morbidity rates |
| BCAA [74] | Orally 4 g BCAA granules with 952 mg L-isoleucine, 1994 mg L-leucine, 1144 mg L-valine twice daily for 6 months | PH | Humans | ↑ Functional regeneration No effect in infections, nutritional and immunologic status |

Note: AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; BCAA, branched chain amino acids; BSEP, bile salt export pump; CAT, catalase; CXCL1, chemokine ligand 1; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GGT, gamma glutamyltransferase; GPx, glutathione peroxidase; GST, glutathione s-transferases; HGF, hepatic growth factor; HWP, hydrolyzed whey peptide; I/R, ischemia reperfusion; IL-6, interleukin; iNOS, nitric oxide synthase; LDLT, living donor liver transplantation; mg, milligram; min, minutes; MPO, myeloperoxidase; PH, partial hepatectomy; PAI-1, plasminogen activation inhibitor-1; RT, reperfusion time; S1P, sphingosine-1-phosphate; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; TGF-β, tumor growth factor β; GSH, total glutathione; TNF-α, tumor necrosis factor α; UCP2, uncoupling protein 2; and WIT, warm ischemia time.
3.2. Vitamins

Various vitamins deficiencies have been reported in receptors submitted to LT. Folate deficiency is caused by a decreased intake and absorption, dysregulation in renal excretion and limited hepatic storage. Folate and B12 supplementation is crucial to protect liver against alcoholic hepatitis [75]. Hypovitaminosis A is associated with impairment in immune function and increased risk of fibrosis, which are risk factors in liver surgery [76]. An anti-oxidative nutrient-rich enteral ordinary diet enhanced with vitamins C and E and supplemented with polyphenols (a combination of catechin and proanthocyanidin) for seven days before ischemic insult in mice was able to mitigate liver I/R injury, improving antioxidant and inflammatory parameters that reduced hepatocellular damage [33].

Dexpanthenol, also known as pro-vitamin B5, is oxidized to pantothenic acid (PA), which increases GSH content, coenzyme A (Co A), and ATP synthesis, thus playing a crucial role against oxidative stress and inflammation. In an experimental model of hepatic I/R in rats, a single dose of dexpanthenol before I/R induced the suppression of oxidative stress and increased antioxidant levels [61]. In a swine model of multiple injuries including I/R injury and hemorrhage, the authors observed a moderate improvement in coagulation dysfunction after intravenous provision of high-dose vitamin C and a reduction in proinflammatory/procoagulant response [62].

All these studies indicate the potential importance of vitamins in reducing the inflammation and damage in surgical conditions of I/R. The usefulness of vitamins in the presence of steatosis and in surgical conditions requiring ischemia and regeneration, such as liver resection or liver-related LT, remains to be elucidated.

3.3. Fish and Rosa Mosqueta Oils

Based on the well-established protective components of rosa mosqueta oil (i.e., \(\alpha\)-linolenic acid (ALA) and tocopherols), Dossi et al. reported that rosa mosqueta oil supplementation before the induction of I/R in rats increased liver ALA and its derived eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) fatty acid contents, with increases in \(\alpha\)-and \(\gamma\)-tocopherols, normalized liver oxidative stress parameters, and ameliorated liver and serum inflammation indexes [63].

Fish-oil-supplemented diets have been shown to reduce I/R injury. In this sense, a study conducted to identify the effect of tilapia fish oil, which is rich in unsaturated fatty acids, administered to rats by gavage during three weeks before I/R revealed that after ischemia and 1, 12, and 24 h of reperfusion, antioxidant enzyme activities of catalase (CAT), SOD, and glutathione peroxidase (GPx) decreased in the intervention group. Lipid peroxidation and liver damage decreased in this group [17]. Similarly, daily oral supplementation for 12 days with fish oil, comprising 40% DHA and 40% EPA, induced AMP-activated protein kinase (AMPK) activation and promoted the recovery of liver function during PH [64]. The role of each component included in either rosa-mosqueta- or fish-oil-supplemented diets on the mechanisms responsible for hepatic I/R remains unknown. The main mechanism involved in the effects of such treatments on I/R damage remain to be elucidated. This is a potential problem due to difficulties for the establishment of target signaling pathways in liver surgery. The effect of rosa mosqueta and fish oil supplementation in steatotic liver undergoing PH under vascular occlusion as well as in LT should be investigated.

3.4. Fatty Acids, Arginine, and Nucleotides

Polyunsaturated fatty acids (PUFAs) are fatty acids with two or more double bonds in their carbon chain. PUFAs can be further categorized according to the location of the first double bond relative to the terminal methyl group: Omega-3 and omega-6 and are characterized by the presence of a double bond three and six atoms away from the methyl terminus, respectively [77]. Long-chain PUFAs (LC-PUFAs), particularly omega-3 LC-PUFAs EPA and DHA, are associated with beneficial health effects [78].
In experimental and clinical studies performed in animals and humans, fatty acids, arginine, and nucleotides have shown the ability to modulate immune and inflammatory responses [18,69]. These nutrients, among others, have been labeled as pharmaconutrients [18].

Supplementation with amino acids, such as arginine, affects urea genesis, gluconeogenesis, and protein synthesis. Diets enriched with these amino acids increases the hepatic catabolism functions [79]. Enteral immunonutrition with arginine reduces the risk of infections in patients submitted to major operations [80]. The supplementation with L-arginine diet in rats hepatectomized was unable to confirm benefits in liver regeneration [65]. Conversely, a similar study using supplementation of L-glutamine in the diet of rats after PH revealed an increase in the amount of albumin and beneficial effects for liver regeneration [66]. Glutamine favors liver regeneration [66].

Omega-3 fatty acids affect the production of pro-inflammatory mediators, such as growth factors, chemokines, and matrix proteases, showing anti-inflammatory and immunomodulatory effects due to their rapid incorporation into cell membranes [67,68]. However, their effect on regeneration in livers undergoing resection has not been widely reported. Two studies evaluated whether omega-3 fatty acids protect against regeneration failure in PH in rats. Neither long-term supplementation before surgery [67] nor a preoperative supplementation plus the same dose every 24 h during the seven days post-surgery [18] showed any influence on the liver regeneration.

Concerning EPA, a study conducted in patients who underwent major hepatobiliary resection reported that preoperative immunonutrition decreased inflammation and protected against post-surgery infections and complications [68]. However, these benefits cannot be exclusively attributed to EPA because the oral supplementation was also enriched with arginine and nucleotides. A similar approach but with controversial results was conducted by Russell et al. Indeed, any benefit of preoperative immunonutrition was reported with arginine and n-3 fatty acids [69]. In a retrospective study reported by Kamo et al., liver recipients suffering from infection after LT were submitted to enteral immunonutrition enriched with nucleotides, arginine and omega-3 fatty acids, and hydrolyzed whey peptide (HWP) (an immunonutritional liquid). The main finding was a lower incidence of bacteremia in the intervention group compared with the control group [70].

For steatotic livers, Nii et al. tested the effects of HWP on hepatic I/R injury in rats with steatotic livers administered immediately after reperfusion and every six hours thereafter. This treatment ameliorated liver damage, improving function, histology, and survival following I/R [71]. In conditions of PH under I/R, a lipid emulsion comprising 52% linoleic acid, 22% oleic acid, 3% palmitic acid, 8% linolenic acid, 4% stearic acid, 1% other fatty acids, 8.184 g/L egg phospholipids, and 15 g/L glycerine infused in rats immediately after surgery for four hours protected against damage and regenerative failure [72].

3.5. Branched-Chain Amino Acid

A branched-chain amino acid (BCAA) is an amino acid with an aliphatic side-chain with a branch. BCAAs promote protein synthesis and glucose metabolism and are involved in fatty acid oxidation [81]. BCAAs favor liver regeneration, nutrition status, and hepatic encephalopathy. BCAAs have the ability to reduce oxidative stress and liver inflammation as well as lactate production [73].

A randomized controlled trial conducted in patients submitted to hepatectomy showed that supplementation with BCAAs administered two times a day for six months after surgery improved liver functionality and regenerative capacity [74]. Similarly, in patients submitted to liver resection, the preoperative BCAA supplementation decreased blood lactate, which is exacerbated by surgical stress patients [73].

3.6. Probiotics

Probiotics are cultures of single or multiple microbes that can regulate the properties of the existing gut microbiota. Probiotics can promote anti-inflammatory effects in gut, thereby preventing bacterial translocation and endotoxin generation [82] and are involved in the synthesis of antimicrobial agents that inhibit the invasion of pathogenic bacteria [83]. Probiotics might regulate the immune system,
inhibiting the release of cytokines like TNF-\(\alpha\) \[84\] and inducing the release of anti-inflammatory cytokines like IL-10 and tumor growth factor \(\beta\) (TGF-\(\beta\)) \[85\].

Current evidence has indicated the advantages resulting from the use of probiotics to prevent the infections after LT, as well as to improve the circulatory diseases associated with cirrhosis, hepatic encephalopathy, and Child–Pugh class \[86,87\]. The improvement in the neutrophil phagocytic capacity induced by probiotics regulated the infections, preventing bacterial translocation. These effects resulted in the restoration of the immune system \[88–90\].

In addition to the different types of nutritional support, the routes of administration should be considered. Oral intake is the first line therapy used to treat malnutrition and decrease the complications (hepatic encephalopathy, infections, and ascites among others) in liver diseases. However, the impact on survival remain to be elucidated \[91,92\]. It has been described that an increased dietary intake by oral nutrition improved liver function and lowered mortality compared with the enteral and parenteral nutrition \[93,94\]. Hasse et al. \[95\] demonstrated early enteral feeding beneficial effects like improved nitrogen balance and fewer viral infections associated with LT. Parenteral nutrition might be used as a second line approach in those who cannot be fed adequately by the oral or enteral route for instance in patients with unprotected airways and advanced hepatic encephalopathy \[96,97\]. All these data are not conclusive for selecting the most appropriate administration route of nutritional support. In a comparison between parenteral and early enteral nutrition, both strategies were equally effective to the maintenance of nutritional state \[97\]. The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines for organ transplantation recommend enteral nutrition or oral nutritional supplementation to improve nutritional status and liver function \[93,98–101\]. Enteral nutrition reduces the incidence of viral and bacterial infections. For enteral nutrition, the ESPEN guidelines recommend the use of more concentrated high-energy formulas in patients with ascites and BCAA-enriched formulas in hepatic encephalopathy patients \[95\].

4. Gut Microbiota and Hepatic Ischemia Reperfusion in Liver Surgery

The gut microbiota is crucial to the effects of diet, drugs, and disease \[102\]. The microorganisms that exist within the gastrointestinal ecosystem are termed gut microbiota, playing an essential role in the stimulation of immune response \[103\], the maintenance of intestinal barrier integrity \[104\], modulation of host–cell proliferation and vascularization \[105,106\], and regulation of neurological \[107\] and endocrine \[108\] functions. The human gut microbiota provides an energy source \[109\], is involved in the synthesis of vitamins and neurotransmitters \[110\], metabolizes bile salts \[111\], and eliminates toxins \[112\].

Disequilibrium in the microbiota composition, commonly referred to as dysbiosis, may lead to several diseases \[113,114\]. The gut and liver (the gut–liver axis) (Figure 1) communicate bidirectionally through the biliary tract, the portal vein, and the systemic circulation \[115\]. The translocation of bacterial products from the intestine to the liver induces inflammation in different cell types, such as Kupffer cells and a fibrotic response in hepatic stellate cells, resulting in deleterious effects on hepatocytes \[116\]. Bacterial translocation and fungal cell wall components are increased in experimental models of ethanol-induced liver disease \[117\].

Alterations in gut microbiota are important for determining the occurrence and progression of alcoholic liver disease (ALD) \[118–120\], NAFLD \[121,122\], nonalcoholic steatohepatitis (NASH) \[123,124\], cirrhosis \[125,126\], and hepatocellular carcinoma (HCC) \[127\]. Fecal microbiota transplantation could induce hepatitis B virus e-antigen (HBeAg) clearance in patients with persistent positive HBeAg, even after long-term antiviral treatment \[128\]. Ferrere et al. \[129\] observed that ALD in mice were reduced by fecal transplantation from alcohol-fed mice resistant to ALD or with prebiotics.

Evidence points to the involvement of the gut microbiota in the pathogenesis of NAFLD \[130,131\]. Cogger et al. showed that liver sinusoidal endothelial cells (LSECs) fenestrae are inversely and positively correlated with the gut abundance of Bacteroidetes and Firmicutes, respectively \[132\]. The gut microbiota also has an emerging role in NASH as a source of inflammatory stimuli \[130,133\].
Increased intestinal permeability and elevated plasma lipopolysaccharide (LPS) [134, 135] observed in NASH may also contribute to LSECs’ pro-inflammatory function [136].

Gut microbiota shifts the influence of hepatic metabolism through regulation of hepatic gene expression without direct contact with the liver [137, 138]. As a result, ischemia produced during liver surgery (i.e., LT or liver resection) is expected to alter the microbiota profile, potentially affecting inflammation, the immune response, and even regeneration. The gut–liver axis is widely implicated in the pathogenesis of liver diseases such as NAFLD, NASH, HCC, and acute liver failure [139]. The gut microbiota may also contribute to the generation of memory alloreactive T cells. T cells were reported to be important in transplant rejection and many experimental and clinical studies have shown that the intestinal microbiota is altered after allogeneic transplantation [140].

In the context of I/R injury, hepatic steatosis is a key factor to consider due to negative influences on patients’ outcomes [141]. Gut microbiota fundamentally influences processes such as lipogenesis, which is affected by the absorption of monosaccharides in the intestinal lumen by the microbiota [142], and bile acids, since they are able to de-conjugate them and turning them into secondary bile acids, which are capable of interacting with a nuclear receptor of the farnesoid receptor X [143]. Changes in gut microbiota promote the development of NAFLD since affect inflammation, insulin resistance, bile acids, and choline metabolism. The Western diet is associated with intestinal microbial dysbiosis [144] and the development and prevalence of NAFLD [145]. I/R injury is a common cause of rejection when grafts are sourced from NAFLD donors; the prevalence of the problem is increasing [141].

The gut microbiota alterations in NAFLD patients remain to be characterized [114]. Several reviews have highlighted studies focused on strategies to prevent and target gut microbiota (probiotics, prebiotics, diet or fecal microbiota transplantation, among others) in NAFLD [114, 115, 140, 146]. Others have addressed the management of nutrition in patients with end-stage liver disease undergoing...

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**Figure 1.** Gut microbiota and hepatic I/R. The dotted box summarizes the mechanisms involved in hepatic I/R injury and how some of these have been altered in the gut microbiota. ALD, alcoholic liver disease; ATP, adenosine triphosphate; Cyt c, cytochrome c; EC, endothelial cell; ET, endothelin; HCC, hepatocellular carcinoma; ICAM, intracellular cell adhesion molecule; IL, interleukin; INF, interferon; KC, Kupffer cell; LTB4, leucotriene B4; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NO, nitric oxide; PAF, platelet activating factor; ROS, reactive oxygen species; SC, stellate cell; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; and X/XOD, xanthine/xanthine oxidase.
Clostridiales. NKT cells was reduced after partial hepatectomy (PH) [154]. NKT cells and activated Kupffer cells produced high levels of interferon-γ (IFN-γ) and IL-12. Thus, antibiotic administration after PH could negatively affect regenerative response [154]. It has been reported that PH resulted in an upregulation of more than 6000 bacterial genes, some of them involved in regeneration and was also accompanied by hepatic I/R injury being caused by regulation of the intestinal microbiota remain to be clarified. None of these studies aimed to improve damage induced by I/R in steatotic livers.

Intestinal microbial characterization and alteration in early phase and subsequent intestinal barrier dysfunction during acute rejection after LT have been reported [148–153]. Due to the high sensitivity of microbial changes during acute rejection after LT, intestinal microbial variation has been suggested as predictive injury biomarkers in LT [153].

Gut microbiota might affect immune mediators such as IL-6 and regulate liver regeneration. Following the administration of antibiotics (Table 3), the number of CD1d-dependent natural killer T (NKT) cells was reduced after partial hepatectomy (PH) [154]. NKT cells and activated Kupffer cells produced high levels of interferon-γ (IFN-γ) and IL-12. Thus, antibiotic administration after PH could negatively affect regenerative response [154].

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Table 3. Therapeutic strategies in modulation of gut microbiota in liver surgery from 2014 to 2019.

| Drug                  | Administration | Model | Specie | Main Therapeutic Effects                                      |
|-----------------------|----------------|-------|--------|----------------------------------------------------------------|
| Ampicillin, neomycin  | Orally         | PH    | Mice   | ↓ Liver regeneration  |
| Vancomycin sulfate,   | 1 g/L, ampicillin, neomycin-sulfate, metronidazole, and 500 mg/L vancomycin for 4 weeks |        |        | ↓ Liver regeneration  |
| Metronidazole, and    |                |       |        | ↑ IFN-γ, IL-12                                 |
| Gentamicin [157]      | Gavage         | LT    | Rats   | ↓ Liver injury, necrosis, inflammation                      |
|                      | 2 mL. daily for 3 weeks |       |        |                                                                 |
| Rifaximin [158]       | Orally         | CIT: Not indicated | Humans | ↓ Liver injury, inflammation, early allograft dysfunction |
|                      | 550 mg twice daily for 28 days |       |        |                                                                 |
| Amoxicillin [159]     | Gavage         | LT    | Mice   | ↓ Liver injury, inflammation, early allograft dysfunction |
|                      | 50 mg/mL for 10 days before LT |       |        | ↑ PGE2, EP4, autophagy                                     |
| Neomycin, erythromycin| Orally         | LT    | Humans | ↓ Liver injury, inflammation, early allograft dysfunction |
| and ampicillin-sulbactum  | 1 g neomycin, erythromycin 4x and 3 g ampicillin-sulbactum before or on day of LT |       |        | ↑ PGE2, EP4, autophagy                                     |
| Cyclosporine A [160]  | Intragastrically | LT    | Rats   | ↓ Liver injury, inflammation                                |
|                      | 2 mg/kg twice daily for 28 days after LT |       |        |                                                                 |
| Tacrolimus [161]      | Subcutaneously, | LT    | Rats   | ↓ Liver injury                                                |
|                      | 1.0, 0.5, or 0.1 mg/kg every 12 h for 7 days and intragastrically once daily for 8–29 days after LT |       |        |                                                                 |
| Retinoid acid [162]   | Gavage         | PH    | Mice   | ↑ Liver regeneration, FGF21                                     |
|                      | 25 µg/g body weight 48 h before surgery |       |        |                                                                 |
| Prebiotics [163]      | Orally         | PH    | Humans | ↓ Infectious complications, septicemia, plasma endotoxin, serum zonulin concentration |
|                      | 2 g/day LP, LA-11, and BL-88, total of 2.6 × 10^14 CFU daily for 6 days before surgery and 10 days after surgery |       |        | ↓ Liver injury                                                |
| Time-restricted feeding [164] | Food restriction: 8–10 h/day, 12 weeks before surgery | Ischemia | Mice | ↓ Liver injury, inflammation, oxidative stress, apoptosis |
|                      |                | WIT: 60 min RT: 6, 12, 24 h |        |                                                                 |

Note: BL-88, Bifido-bacterium longum 88; CFU, colony forming units; CHOP, CCAAT/enhancer-binding protein homologous protein; CIT, cold ischemia time; EP, prostaglandin E2 receptor; FGF21, fibroblast growth factor 21; IFNy, interferon-gamma; IL, interleukin; LA-11, Lactobacillus acidophilus 11; LC3B, Light Chain 3 isoform B; LP, Lactobacillus plantarum; LT, liver transplantation; mTORC1, mammalian target of rapamycin complex 1; PGE2, prostaglandin E2; PH, partial hepatectomy; RT, reperfusion time; and WIT, warm ischemia time.

The administration of antibiotics reduces hepatic injury in rats submitted to LT with acute rejection, but the microvilli of the ileum epithelial cells were destroyed, inducing alterations in
Further studies are required for a more understanding of the immunity interactions between gut microbiota and the rejection after LT [157]. Two retrospective studies support the notion that antibiotics (rifaximin, neomycin, erythromycin, and ampicillin-sulbactam) administration prior to LT reduce infections associated with LT, thus reducing the liver injury, inflammation, and early allograft dysfunction [158,159]. However, further randomized controlled clinical trials are required to elucidate the exact mechanisms of action of such antibiotics, their target signaling pathways, and the optimal duration of treatment. Further experiments in animal LT models will be required to elucidate the specific molecular signaling pathways through which antibiotics may exert their actions, as well as to investigate whether the protection on hepatic damage induced by the treatment with antibiotics is exerted throughout changes in the gut microbiome.

Survival outcomes after LT have constantly improved using upgraded immunosuppressive agents [165]. However, the inadequate or excessive immunosuppression is associated with a higher risk of rejection, higher incidence of infection, drug toxicity, and increased mortality [166–170]. Experimental studies in rats have investigated the effect of immunosuppressive agents on the intestinal microbiota in LT. The results showed that cyclosporine A ameliorated hepatic injury and partially restore the intestinal microbiota after LT [160]. An optimal dosage of tacrolimus (FK506) induced normal graft function, and stable gut microbiota after LT in rats. This resulted in increased probiotics, including Faecalibacterium prausnitzii and Bifidobacterium spp. and decreased pathogenic endotoxin-producing bacteria, such as the Bacteroides–Prevotella group and Enterobacteriaceae. Thus, the use of the gut microbiota might be a novel strategy for the assessment of the dosage of immunosuppressive medications and its effects in receptors submitted to LT [161].

Retinoic acid, naturally present in the gastrointestinal tract, has a relevant effect in regulating lipid homeostasis [171,172] and can facilitate PH-induced liver regeneration [173,174]. Given the intimate relationship between gut-derived signaling and liver regeneration, authors hypothesized that retinoic acid may regulate gut microbiota thereby promoting liver regeneration [162]. Retinoic-acid-accelerated liver regeneration was associated with a reduction in the ratio of Firmicutes to Bacteroidetes. Retinoic acid had benefits on lipid circulation and regulated the FGF21-LKB1-AMPK pathway, which promoted energy metabolism and consequently the regenerative process in the liver [162]. Further studies will be required to elucidate the interaction between the modulation of microbiota and the improvement in proliferation induced by the retinoic acid. This will allow the development of clinical therapeutic strategies to promote liver regeneration.

In line with the results described above, the evidence suggests that probiotics play an important role in the stability of the intestinal microbiological environment and regulate intestinal microbiota. A double-center and double-blind randomized clinical trial conducted in colorectal liver metastases patients showed that the incidence of infectious complications after preoperative and postoperative supplementation with probiotics decreased blood Escherichia coli, Staphylococcus aureus, and Aeruginosin populations, improved intestinal barrier function, and reduced postoperative infection rate [163].

As time-restricted feeding (TRF) is a promising intervention against the worldwide trend of obesity and other metabolic diseases [175], a study conducted in mice investigated whether alteration in gut microbiota caused by TRF could alleviate hepatic I/R injury [164]. The results confirmed the adverse effect of I/R on the gut microbial population. However, TRF prior to surgery reduced the damage, oxidative stress, and inflammatory biomarkers associated with I/R, likely due to intestinal increases in Firmicutes phylum, Clostridia and Bacilli classes, Clostridiales and Lactobacillales orders, and Lachnospiraceae and Ruminococcaceae families, which could be hallmarks of a healthy gut [164].

5. Future Perspectives and Conclusions

The temporary occlusion of hepatic inflow is commonly used during liver resection or LT, creating an unsolved problem in clinical practice associated with post-operative morbidity and mortality.
Experimental studies have shown that liver I/R injury is influenced by various nutrients, suggesting the importance of dietary control for preventing I/R injury.

Today, starvation is not a feasible strategy in clinical practice. Future clinical and preclinical studies on PH with I/R and LT are required to understand the underlying mechanisms of starvation to increase the quality of livers subjected to surgery and reduce the post-operative disorders. Controversial results have been reported in experimental models of starvation under I/R conditions [37,48], which might be explained by the use of different times of ischemia (60 or 90 min). The literature draws upon research data that support the duration of ischemia differentially affects hepatic I/R injury [176–178]. This is of clinical interest since, in clinical practice, the timing of ischemia dependent on the complications associated with surgery cannot be predicted, whereas the effects resulting from starvation are dependent on the duration of ischemia and the duration of starvation. In clinical practice, long-term diet restriction of more than 24 h is difficult to apply for preoperative management in LT. Liver donors are often kept in the intensive care unit for periods no longer than six hours after diagnosis of brain death. The time frame between the declaration of brain death and organ procurement provides a shorter window for the starvation intervention. The effects of starvation on steatotic livers undergoing surgery should be evaluated since the mechanisms responsible for I/R and consequently the useful therapeutic strategies in clinical practice might be different in steatotic and non-steatotic livers submitted to surgery. The number of steatotic livers submitted to surgery is expected to increase, though steatotic livers show regenerative failure responses and reduced tolerance to I/R injury compared with non-steatotic livers. Therefore, research in experimental models of PH with I/R and LT that closely reproduce the clinical conditions is required to understand the underlying mechanisms of starvation, especially in sub-optimal livers.

To summarize, several nutrients and dietary supplements have antioxidant or anti-inflammatory properties and contribute to modifying the gut microbiome. These properties might warrant investigations using them as potential strategies to counteract I/R injury complications and promote regeneration from a nutritional point of view. The diagnosis of nutritional status and its re-establishment and maintenance, as well as providing adequate nutritional support during all phases of the surgery, could be considered the first step to formulating adequate I/R injury therapy. From our view, studies using this approach are insufficient, with only 20 studies from 2014 to 2019, with considerable variability in models, time, and administration. This suggests that the effects of such approaches on hepatic I/R injury are specific for each surgical procedure (for instance, warm ischemia associated with hepatic resections versus LT, times of ischemia, and type of treatment: Short or prolonged fasting).

Most studies based on nutrients and dietary supplements reported benefits on liver function and oxidative stress parameters, but we did not find many studies aimed to improve liver regeneration (six of 20) and only three reported improvements in this parameter. As steatotic grafts show increased vulnerability to I/R when they are transplanted and pre-existing steatosis is related with impairment of liver regeneration following PH [53,141], more than the only three studies performed in steatotic liver seems to be warranted. We only found one study reporting the use of probiotics as a strategy. As a dysbiotic microbiota induces the translocation of several bacterial components into the portal vein and favors the activation of innate immunity and inflammation [114], modulation of gut microbiota from a nutritional point of view is mandatory for evaluating and modifying alterations associated with I/R injury and, in consequence, further studies in this area are needed.

In our view, a strategy more appropriate for clinical practice is the re-establishment and maintenance of the correct nutrient deficiencies using nutraceuticals and functional foods before, during, and/or after surgery, dependent on the patient’s requirements. In hepatic resections, this strategy is suitable for the treatment of patients before during or after surgery, whereas in the case of LT, this strategy was only possible after LT with considerable difficulties during liver surgery.

For us, the use of plant-derived supplements, fish, and rosa mosqueta oils show limitations and are inadvisable due their limited specificity and the potential toxicity and side effects of these components. Vitamins, branched-chain amino acid, fatty acids, arginine, and nucleotides can be
administered in clinical practice only if deficiencies exist in the patients. Thus, exhaustive studies in patients are required since, for instance, hypervitaminosis is associated with toxic effects. Given the limited studies on the effect of administering vitamins in surgery, conclusions about their efficacy cannot be drawn. Before the administration of fatty acid, the deficiencies in specific types of fatty acid in the patient must be determined. In some cases, for instance EPA supplementation, benefits have been reported but whether the potential benefits are exclusively attributed to EPA is unknown because oral supplementation was also enriched with arginine and nucleotides. Only through exhaustive studies of the patient’s deficiencies can we select the most effective treatment for the patient. Unfortunately, these studies are not performed routinely in clinical practice since, in many cases, surgery is performed an emergency situation but the techniques that evaluate such components are complex, time consuming, and expensive.

Although I/R is known to have detrimental effects on the gut microbial population, studies reporting interventions targeting gut microbiota in the I/R setting are limited. A more accurate characterization of the gut microbiome and host responses using different liver surgery models, stages of liver disease, and larger cohorts of patients is required. A comprehensive understanding of the intestine microbiota’s role during hepatic surgery is lacking. Maintaining the stability and/or restauration of the intestinal microbiological environment could be a safe and sustainable tool for mitigating I/R injury, which could even effect regeneration. Although regulation of the gut microbiota has been primarily achieved through the use of probiotics, as well as through dietary intervention, studies recently reported using mainly antibiotics and mostly focused on avoiding graft rejection and infectious complications post-surgery [148,158,159,163]. Further investigations are required to elucidate whether personalized and precision medicine approaches based on gut microbiota are necessary dependent on the type of surgical procedure. Dose, frequency, and route of modulation of gut microbiota should be addressed.

Probiotics supplementation requires special consideration. This is associated with the regulation of infections by altering gut microbiota and improvements in inflammation and immunological problems associated with liver surgery. Of clinical interest, gut microbial profiles have been suggested as predictive injury biomarkers in LT. However, before the application of probiotics, an exhaustive examination of the alterations in the intestinal microbiota must be performed for the administration of specific probiotics that counteract such deficiencies in the patients. An alternative to the use of probiotics would be the administration of antibiotics. However, the specificity and the appropriate dose must be determined to prevent harmful effects to ileum epithelial cells and the mucosal barrier. Rapid techniques that routinely evaluate intestinal microflora would be necessary if the aim is to establish probiotics as a useful strategy in clinical of liver surgery, especially in LT. Consequently, nutritional support must be personalized based on the patient’s deficiencies. To date, I/R injury is a common complication for patients undergoing liver surgery and its relationship with changes in the gut microbiota is not totally understood. The understanding of such changes and mechanisms involved could help with restoring unhealthy microbial diversity and the richness of species, providing a potential therapeutic tool for treating I/R damage.

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Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| AKT          | Protein kinase B |
| ALA          | α-linolenic acid |
| ALD          | Alcoholic liver disease |
| AMPK         | AMP-activated protein kinase |
| ATP          | Adenosine triphosphate |
| BCAA         | Branched-chain amino acid |
| BCL          | B-cell lymphoma |
| BHB          | β-hydroxybutyric acid |
| CAT          | Catalase |
| Co A         | Coenzyme A |
| DHA          | Docosahexaenoic acid |
| EPA          | Eicosapentaenoic acid |
| ESPEN        | European Society for Parenteral and Enteral Nutrition |
| FOXO1        | Forkhead box protein O1 |
| GSH          | Glutathione |
| HBeAg        | Hepatitis B virus e-antigen |
| HCC          | Hepatocellular carcinoma |
| HMGB1        | High mobility group box 1 |
| HO-1         | Heme oxygenase 1 |
| HWP          | Hydrolyzed whey peptide |
| I/R          | Ischemia-reperfusion |
| IFNγ         | Interferon-gamma |
| IL           | Interleukin |
| LC-PUFAs     | Long-chain PUFAs |
| LSEC         | Liver sinusoidal endothelial cells |
| LT           | Liver transplantation |
| NAFLD        | Nonalcoholic fatty liver disease |
| NASH         | Nonalcoholic steatohepatitis |
| NF-κB        | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| NKT          | Natural killer T |
| NLRP3        | Nucleotide oligomerization domain-like receptor family, pyrin domain containing protein 3 |
| NPO          | Nil per os |
| Nqo1         | NAD(P)H quinone dehydrogenase 1 |
| Nrf2         | Nuclear factor erythroid-derived 2-related factor 2 |
| PA           | Pantothenic acid |
| PH           | Partial hepatectomy |
| PUFAs        | Polyunsaturated fatty acids |
| Sirt1        | Sirtuin 1 |
| SOD          | Superoxide dismutase |
| TGF-β        | Tumor growth factor beta |
| TNF-α        | Tumor necrosis factor alpha |
| TRF          | Time restricted feeding |

References

1. Peralta, C.; Jiménez-Castro, M.B.; Gracia-Sancho, J. Hepatic ischemia and reperfusion injury: Effects on the liver sinusoidal milieu. *J. Hepatol.* 2013, 59, 1094–1106. [CrossRef]
2. Fu, P.; Li, W. Nitric oxide in liver ischemia-reperfusion injury. In *Liver Pathophysiology*; Muriel, P., Ed.; Elsevier Inc.: London, UK, 2017; Volume 8, pp. 125–127.
3. Selzner, N.; Rudiger, H.; Graf, R.; Clavien, P. Protective strategies against ischemic injury of the liver. *Gastroenterology* 2003, 125, 917–936. [CrossRef]
4. Jaeschke, H. Molecular mechanisms of hepatic ischemia-reperfusion injury and preconditioning. *Am. J. Physiol. Gastrointest. Liver Physiol.* 2003, 284, G15–G26. [CrossRef]
5. Montalvo-Jave, E.E.; Escalante-Tattersfield, T.; Ortega-Salgado, J.A.; Piña, E.; Geller, D.A. Factors in the pathophysiology of the liver ischemia-reperfusion injury. *J. Surg. Res.* **2008**, *147*, 153–159. [CrossRef] [PubMed]

6. Gracia-Sancho, J.; Villarreal, G., Jr.; Zhang, Y.; Yu, J.X.; Liu, Y.; Tullius, S.G.; Garcia-Cardena, G. Flow cessation triggers endothelial dysfunction during organ cold storage conditions: Strategies for pharmacologic intervention. *Transplantation* **2010**, *90*, 142–149. [CrossRef] [PubMed]

7. Gracia-Sancho, J.; Casillas-Ramirez, A.; Peralta, C. Molecular pathways in protecting the liver from ischaemia/reperfusion injury: A 2015 update. *Clin. Sci.* **2015**, *129*, 345–362. [CrossRef] [PubMed]

8. Ramalho, F.; Alfany-Fernandez, I.; Casillas-Ramirez, A.; Massip-Salcedo, M.; Serafin, A.; Rimola, A.; Arroyo, V.; Rodes, J.; Rosello-Catafau, J.; Peralta, C. Are angiotensin II receptor antagonists useful strategies in steatotic and nonsteatotic livers in conditions of partial hepatectomy under ischemia-reperfusion? *J. Pharmacol. Exp. Ther.* **2009**, *329*, 130–140. [CrossRef]

9. Ploeg, R.J.; D’Alessandro, A.M.; Knechtle, S.J.; Stegall, M.D.; Pirsch, J.D.; Hoffmann, R.M.; Sasaki, T.; Sollinger, H.W.; Belzer, F.O.; Kalayoglu, M. Risk factors for primary dysfunction after liver transplantation—A multivariate analysis. *Transplantation* **1993**, *55*, 807–813. [CrossRef]

10. Behrns, K.E.; Tsiotos, G.G.; DeSouza, N.F.; Krishna, M.K.; Ludwig, J.; Nagorney, D.M. Hepatic steatosis as a potential risk factor for major hepatic resection. *J. Gastrointest. Surg.* **1998**, *2*, 292–298. [CrossRef]

11. Selzner, M.; Clavien, P.A. Fatty liver in liver transplantation and surgery. *Semin. Liver Dis.* **2001**, *21*, 105–113. [CrossRef]

12. D’Alessandro, A.M.; Kalayoglu, M.; Sollinger, H.W.; Hoffmann, R.M.; Reed, A.; Knechtle, S.J.; Pirsch, J.D.; Hafez, G.R.; Lorenzten, D.; Belzer, F.O. The predictive value of donor liver biopsies for the development of primary nonfunction after orthotopic liver transplantation. *Transplantation* **1991**, *51*, 157–163. [CrossRef] [PubMed]

13. Adam, R.; Reynes, M.; Johann, M.; Morino, M.; Astarcigolu, I.; Kafetzis, I.; Castaing, D.; Bismuth, H. The outcome of steatotic grafts in liver transplantation. *Transplant Proc.* **1991**, *23*, 1538–1540. [PubMed]

14. Todo, S.; Demetris, A.J.; Makowka, L.; Teperman, L.; Podesta, L.; Shaver, T.; Tzakis, A.; Starzl, T.E. Primary nonfunction of hepatic allografts with preexisting fatty infiltration. *Transplantation* **1989**, *47*, 903–905. [CrossRef] [PubMed]

15. Belghiti, J.; Hiramatsu, K.; Benoist, S.; Massault, P.; Sauvanet, A.; Farges, O. Seven hundred forty-seven hepatectomies in the 1990s: An update to evaluate the actual risk of liver resection. *J. Am. Coll. Surg.* **2000**, *191*, 38–46. [CrossRef]

16. Safwan, M.; Collins, K.M.; Abouljoud, M.S.; Salgia, R. Outcome of liver transplantation in patients with prior bariatric surgery. *Liver Transplant.* **2017**, *23*, 1415–1421. [CrossRef] [PubMed]

17. Saádi, S.A.; Abdelkafi, S.; Jbahi, S.; Van Pelt, J.; El-Feki, A. Temporal changes in hepatic antioxidant enzyme activities after ischemia and reperfusion in a rat liver ischemia model: Effect of dietary fish oil. *Hum. Exp. Toxicol.* **2015**, *34*, 249–259. [CrossRef]

18. Silva, R.M.; Malafaia, O.; Torres, O.J.; Czeckzo, N.G.; Marinho Junior, C.H.; Kozlowski, R.K. Evaluation of liver regeneration diet supplemented with omega-3 fatty acids: Experimental study in rats. *Rev. Col. Bras. Cir.* **2015**, *42*, 393–397. [CrossRef]

19. Caraceni, P.; Nardo, B.; Dondivalli, M.; Turi, P.; Vici, M.; Simoncini, M.; De Maria, N.; Trevisani, F.; Van Thiel, D.H.; Derenzini, M.; et al. Ischemia-reperfusion injury in rat fatty liver: Role of nutritional status. *Hepatology* **1999**, *29*, 1139–1146. [CrossRef] [PubMed]

20. Gasbarrini, A.; Borle, A.B.; Farghali, H.; Caraceni, P.; Van Thiel, D. Fasting enhances the effects of anoxia on ATP, Ca(2+), and cell injury in isolated rat hepatocytes. *Biochim. Biophys. Acta* **1993**, *1178*, 9–19. [CrossRef]

21. Bradford, B.U.; Marotto, M.; Lemasters, J.J.; Thurman, R.G. New, simple models to evaluate zone-specific damage due to hypoxia in the perfused rat liver: Time course and effect of nutritional state. *J. Pharmacol. Exp. Ther.* **1986**, *236*, 263–268. [CrossRef]

22. Tanigawa, K.; Kim, Y.M.; Lancaster, J.R., Jr.; Zar, H.A. Fasting augments lipid peroxidation during reperfusion after ischemia in the perfused rat liver. *Crit. Care Med.* **1999**, *27*, 401–406. [CrossRef] [PubMed]

23. Jimenez-Castro, M.B.; Casillas-Ramirez, A.; Massip-Salcedo, M.; Elias-Miro, M.; Serafin, A.; Rimola, A.; Rodes, J.; Peralta, C. Cyclic adenosine 3′,5′-monophosphate in rat steatotic liver transplantation. *Liver Transplant.* **2011**, *17*, 1099–1110.
24. Hammad, A.; Kaido, T.; Uemoto, S. Perioperative nutritional therapy in liver transplantation. *Surg. Today* 2015, 45, 271–283. [CrossRef] [PubMed]

25. Chiarla, C.; Giovannini, I.; Giuliano, F.; Ardito, F.; Vellone, M.; De Rose, A.M.; Nuzzo, G. Parenteral nutrition in liver resection. *J. Nutr. Metab.* 2012, 2012, 508103. [CrossRef] [PubMed]

26. Sonnenburg, J.L.; Bäckhed, F. Diet-microbiota interactions as moderators of human metabolism. *Nature* 2016, 535, 56–64. [CrossRef] [PubMed]

27. Wahlström, A.; Sayin, S.I.; Marschall, H.U.; Bäckhed, F. Intestinal Crosstalk between Bile Acids and Microbiota and Its Impact on Host Metabolism. *Cell Metab.* 2016, 24, 41–50. [CrossRef]

28. Moschen, A.R.; Kaser, S.; Tilg, H. Non-alcoholic steatohepatitis: A microbiota-driven disease. *Trends Endocrinol. Metab.* 2013, 24, 537–545. [CrossRef]

29. Acharya, C.; Sahingur, S.E.; Bajaj, J.S. Microbiota, cirrhosis, and the emerging oral-gut-liver axis. *JCI Insight* 2017, 2, 94416. [CrossRef]

30. Abu-Shanab, A.; Quigley, E.M. The role of the gut microbiota in nonalcoholic fatty liver disease. *Nat. Rev. Gastroenterol. Hepatol.* 2010, 7, 691–701. [CrossRef]

31. Ahuja, M.; Schwartz, D.M.; Tandon, M.; Son, A.; Zeng, M.; Swaim, W.; Eckhaus, M.; Hoffman, V.; Cui, Y.; Xiao, B.; et al. Oral1-Mediated Antimicrobial Secretion from Pancreatic Acini Shapes the Gut Microbiome and Regulates Gut Innate Immunity. *Cell Metab.* 2017, 25, 635–646. [CrossRef]

32. Hine, C.; Harputlugil, E.; Zhang, Y.; Ruckenstuhl, C.; Lee, B.C.; Brace, L.; Longchamp, A.; Treviño-Villareal, J.H.; Mejia, P.; Ozaki, C.K.; et al. Endogenous hydrogen sulfide production is essential for dietary restriction benefits. *Cell* 2015, 160, 132–144. [CrossRef] [PubMed]

33. Miyaochi, T.; Uchida, Y.; Kadono, K.; Hirao, H.; Kawasoe, J.; Watanabe, T.; Ueda, S.; Jobara, K.; Kaido, T.; Okajima, H.; et al. Preventive Effect of Antioxidative Nutrient-Rich Enteral Diet Against Liver Ischemia and Reperfusion Injury. *JPN J. Parenter. Enteral Nutr.* 2019, 43, 133–144. [CrossRef] [PubMed]

34. Mitchell, J.R.; Verweij, M.; Brand, K.; van de Ven, M.; Goemaere, N.; van den Engel, S.; Chu, T.; Forrer, F.; Müller, C.; de Jong, M.; et al. Short-term dietary restriction and fasting precondition against ischemia reperfusion injury in mice. *Aging Cell* 2010, 9, 40–53. [CrossRef] [PubMed]

35. Domenicali, M.; Caraceni, P.; Tandon, M.; Son, A.; Zeng, M.; Swaim, W.; Eckhaus, M.; Hoffman, V.; Cui, Y.; Xiao, B.; et al. Oral1-Mediated Antimicrobial Secretion from Pancreatic Acini Shapes the Gut Microbiome and Regulates Gut Innate Immunity. *Cell Metab.* 2017, 25, 635–646. [CrossRef]

36. Van Ginhoven, T.M.; Mitchell, J.R.; Verweij, M.; Hoeijmakers, J.H.; Ijzermans, J.N.; de Bruin, R.W. The use of preoperative nutritional interventions to protect against hepatic ischemia-reperfusion injury. *Liver Transplant.* 2009, 15, 1183–1191. [CrossRef]

37. Rickenbacher, A.; Jang, J.H.; Limani, P.; Ungethüm, U.; Lehmann, K.; Oberkofer, C.E.; Weber, A.; Graf, R.; Humar, B.; Clavien, P.A. Fasting protects liver from ischemic injury through Sirt1-mediated downregulation of circulating HMGB1 in mice. *J. Hepatol.* 2014, 61, 301–308. [CrossRef]

38. Awad, S.; Varadhan, K.K.; Ljungqvist, O.; Lobo, D.N. A meta-analysis of randomized controlled trials on preoperative oral carbohydrate treatment in elective surgery. *Clin. Nutr.* 2013, 32, 34–44. [CrossRef]

39. Maltby, J.R.; Sutherland, A.D.; Sale, J.P.; Shaffer, E.A. Preoperative oral fluids: Is a five-hour fast justified prior to elective surgery? *Anesth. Analg.* 1986, 65, 1112–1116. [CrossRef]

40. Page, A.J.; Ejaz, A.; Spolverato, G.; Zavadsky, T.; Grant, M.C.; Galante, D.J.; Wick, E.C.; Weiss, M.; Makary, M.A.; Wu, C.L.; et al. Enhanced recovery after surgery protocols for open hepatectomy—Physiology, immunomodulation, and implementation. *J. Gastrointest. Surg.* 2015, 19, 387–399. [CrossRef]

41. Ljungqvist, O.; Nygren, J.; Thorell, A. Modulation of post-operative insulin resistance by pre-operative carbohydrate loading. *Proc. Nutr. Soc.* 2002, 61, 329–336. [CrossRef]

42. Soop, M.; Nygren, J.; Myrenfors, P.; Thorell, A.; Ljungqvist, O. Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance. *Am. J. Physiol. Endocrinol. Metab.* 2001, 280, E576–E583. [CrossRef] [PubMed]

43. Hausel, J.; Nygren, J.; Lagerkranser, M.; Hellström, P.M.; Hammarqvist, F.; Almström, C.; Lindh, A.; Thorell, A.; Ljungqvist, O. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. *Anesth. Analg.* 2001, 93, 1344–1350. [CrossRef] [PubMed]

44. Eshuis, W.J.; Hermanides, J.; van Dalen, J.W.; van Samkar, G.; Busch, O.R.; van Gulik, T.M.; DeVries, J.H.; Hoekstra, J.B.; Gouma, D.J. Early postoperative hyperglycemia is associated with postoperative complications after pancreatoduodenectomy. *Ann. Surg.* 2011, 253, 739–744. [CrossRef] [PubMed]
45. Pruim, J.; van Woerden, W.F.; Knol, E.; Klompmaker, I.J.; de Bruijn, K.M.; Persijn, G.G.; Slooff, M.J. Donor data in liver grafts with primary non-function—a preliminary analysis by the European Liver Registry. Transplant Proc. 1989, 21, 2383–2384. [PubMed]

46. Miyauchi, T.; Uchida, Y.; Kadono, K.; Hirao, H.; Kawasoe, J.; Watanabe, T.; Ueda, S.; Okajima, H.; Terajima, H.; Uemoto, S. Up-regulation of FOXO1 and reduced inflammation by β-hydroxybutyric acid are essential diet restriction benefits against liver injury. Proc. Natl. Acad. Sci. USA 2019, 116, 13533–13542. [CrossRef]

47. Papegay, B.; Stadler, M.; Nuyens, V.; Kruys, V.; Boogaerts, J.G.; Vamecq, J. Short fasting does not protect perfused ex vivo rat liver against ischemia-reperfusion. On the importance of a minimal cell energy charge. Nutrition 2017, 35, 21–27. [CrossRef]

48. Qin, J.; Zhou, J.; Dai, X.; Zhou, H.; Pan, X.; Wang, X.; Zhang, F.; Rao, J.; Lu, L. Short-term starvation attenuates liver ischemia-reperfusion injury (IRI) by Sirt1-autophagy signaling in mice. Am. J. Transl. Res. 2016, 8, 3364–3375.

49. Zhan, C.; Dai, X.; Shen, G.; Lu, X.; Wang, X.; Lu, L.; Qian, X.; Rao, J. Preoperative short-term fasting protects liver injury in patients undergoing hepatectomy. Am. J. Transl. Med. 2018, 6, 449. [CrossRef]

50. Mauro, C.R.; Tao, M.; Yu, P.; Treviño-Villereal, J.H.; Longchamp, A.; Kristal, B.S.; Okajima, H.; Terajima, H.; Uemoto, S. Up-regulation of FOXO1 and reduced inflammation by β-hydroxybutyric acid are essential diet restriction benefits against liver injury. Proc. Natl. Acad. Sci. USA 2019, 116, 13533–13542. [CrossRef]

51. De Meijer, V.E.; Kalish, B.T.; Puder, M.; Ijzermans, J.N. Systematic review and meta-analysis of steatosis as a risk factor in major hepatic resection. Br. J. Surg. 2010, 97, 1331–1339. [CrossRef]

52. Bachellier, P.; Rosso, E.; Pessaux, P.; Ouissoultzoglou, E.; Nobili, C.; Panaro, F.; Jaeck, D. Risk factors for liver failure and mortality after hepatectomy associated with portal vein resection. Ann. Surg. 2011, 253, 173–179. [PubMed]

53. Álvarez-Mercado, A.I.; Bujaldon, E.; Gracia-Sancho, J.; Peralta, C. The Role of Adipokines in Surgical Procedures Requiring Both Liver Regeneration and Vascular Occlusion. Int. J. Mol. Sci. 2018, 19, 3395. [CrossRef]

54. López-Velázquez, J.A.; Silva-Vidal, K.V.; Ponciano-Rodriguez, G.; Chávez-Tapia, N.C.; Arrese, M.; Uribe, M.; Méndez-Sánchez, N. The prevalence of nonalcoholic fatty liver disease in the Americas. Ann. Hepatol. 2014, 13, 166–178. [CrossRef]

55. Vasco, M.; Paoliello, R.; Schiano, C.; Sommese, L.; Cuomo, O.; Napoli, C. Compromised nutritional status in patients with end-stage liver disease: Role of gut microbiota. Hepatobiliary Pancreat. Dis. Int. 2015, 14, 290–300. [CrossRef] [PubMed]

56. Chandrasekara, A.; Josheph Kumar, T. Roots and Tuber Crops as Functional Foods: A Review on Phytochemical Constituents and Their Potential Health Benefits. Int. J. Food Sci. 2016, 2016, 3631647. [CrossRef] [PubMed]

57. Bakshi, N.; Singh, K. Nutrition assessment in patients undergoing liver transplant. Indian J. Crit. Care Med. 2014, 18, 672–681. [CrossRef]

58. Yang, H.J.; Tang, L.M.; Zhou, X.J.; Qian, J.; Zhu, J.; Lu, L.; Wang, X.H. Ankaflavin ameliorates steatotic liver ischemia-reperfusion injury in mice. Hepatobiliary Pancreat. Dis. Int. 2015, 14, 619–625. [CrossRef]

59. Yücel, A.; Aydogan, M.S.; Ucar, M.; Sarici, K.B.; Karaaslan, M.G. Effects of Apocynin on Liver Ischemia-Reperfusion Injury in Rats. Transplant Proc. 2019, 51, 1180–1183. [CrossRef]

60. Kim, H.; Hong, M.K.; Choi, H.; Moon, H.S.; Lee, H.J. Chemopreventive effects of korean red ginseng extract on rat hepatocarcinogenesis. J. Cancer 2015, 6, 1–8. [CrossRef]

61. Ucar, M.; Aydogan, M.S.; Vardi, N.; Parlakpınar, H. Protective Effect of Dexpanthenol on Ischemia-Reperfusion-Induced Liver Injury. Transplant Proc. 2018, 50, 3135–3143. [CrossRef]

62. Reynolds, P.S.; Fisher, B.J.; McCarter, J.; Sweeney, C.; Martin, E.J.; Middleton, P.; Ellenberg, M.; Fowler, E.; Brophy, D.F.; Fowler, A.A., 3rd; et al. Interventional vitamin C: A strategy for attenuation of coagulopathy and inflammation in a swine multiple injuries model. J. Trauma Acute Care Surg. 2018, 85, S57–S67. [CrossRef] [PubMed]

63. Dossi, C.G.; González-Mañán, D.; Romero, N.; Silva, D.; Videla, L.A.; Tapia, G.S. Anti-oxidative and anti-inflammatory effects of Rosa Mosqueta oil supplementation in rat liver ischemia-reperfusion. Food Funct. 2018, 9, 4847–4857. [CrossRef] [PubMed]
64. Yao, H.; Fu, X.; Zi, X.; Jia, W.; Qiu, Y. Perioperative oral supplementation with fish oil promotes liver regeneration following partial hepatectomy in mice via AMPK activation. **Mol. Med. Rep.** 2018, 17, 3905–3911. [CrossRef] [PubMed]

65. Montenegro, W.S.; Malafaia, O.; Nassif, P.A.; Moreira, L.B.; Prestes, M.A.; Kume, M.H.; Jurkons, L.B.; Cella, I.F. Evaluation of liver regeneration with use of diet supplemented with L-arginine. **Acta Cir. Bras.** 2014, 29, 603–607. [CrossRef] [PubMed]

66. Magalhães, C.R.; Malafaia, O.; Torres, O.J.; Moreira, L.B.; Tefil, S.C.; Pinheiro Mda, R.; Harada, B.A. Liver regeneration with l-glutamine supplemented diet: Experimental study in rats. **Rev. Col. Bras. Cir.** 2014, 41, 117–121. [CrossRef]

67. Akbari, M.; Celik, S.U.; Kocaay, A.F.; Cetinkaya, O.A.; Demirer, S. Omega-3 fatty acid supplementation does not influence liver regeneration in rats after partial hepatectomy. **Clin. Exp. Hepatol.** 2018, 4, 253–259. [CrossRef]

68. Uno, H.; Furukawa, K.; Suzuki, D.; Shimizu, H.; Ohtsuka, M.; Kato, A.; Yoshitomi, H.; Miyazaki, M. Immunonutrition suppresses acute inflammatory responses through modulation of resolvin E1 in patients undergoing major hepatobiliary resection. **Surgery** 2016, 160, 228–236. [CrossRef]

69. Russell, K.; Zhang, H.G.; Gillanders, L.K.; Bartlett, A.S.; Fisk, H.L.; Calder, P.C.; Swan, P.J.; Plank, L.D. Preoperative immunonutrition in patients undergoing liver resection: A prospective randomized trial. **World J. Hepatol.** 2019, 11, 305–317. [CrossRef]

70. Kamo, N.; Kaido, T.; Hamaguchi, Y.; Uozumi, R.; Okumura, S.; Kobayashi, A.; Shirai, H.; Yagi, S.; Okajima, H.; Uemoto, S. Impact of Enteral Nutrition with an Immunomodulating Diet Enriched with Hydrolyzed Whey Peptide on Infection After Liver Transplantation. **World J. Surg.** 2018, 42, 3715–3725. [CrossRef]

71. Nii, A.; Utsunomiya, T.; Shimada, M.; Ikegami, T.; Ishibashi, H.; Imura, S.; Morine, Y.; Ikemoto, T.; Sasaki, H.; Kawashima, A. Hydrolyzed whey peptide-based diet ameliorates hepatic ischemia-reperfusion injury in the rat nonalcoholic fatty liver. **Surg. Today** 2014, 44, 2354–2360. [CrossRef]

72. Mendes-Braz, M.; Elias-Mir, M.; Kleuser, B.; Fayyaz, S.; Jiménez-Castro, M.B.; Massip-Salcedo, M.; Gracia-Sancho, J.; Ramalho, F.S.; Rodes, J.; Peralta, C. The effects of glucose and lipids in steatotic and non-steatotic livers in conditions of partial hepatectomy under ischaemia-reperfusion. **Liver Int.** 2014, 34, e271–e289. [CrossRef]

73. Nanno, Y.; Toyama, H.; Terai, S.; Mizumoto, T.; Tanaka, M.; Kido, M.; Ajiki, T.; Fukumoto, T. Preoperative Oral Branched-Chain Amino Acid Supplementation Suppresses Intraoperative and Postoperative Blood Lactate Levels in Patients Undergoing Major Hepatectomy. **JPEN J. Parenter. Enteral Nutr.** 2019, 43, 220–225. [CrossRef]

74. Beppu, T.; Nitta, H.; Hayashi, H.; Imai, K.; Okabe, H.; Nakagawa, S.; Hashimoto, D.; Chikamoto, A.; Ishiko, T.; Yoshida, M.; et al. Effect of branched-chain amino acid supplementation on functional liver regeneration in patients undergoing portal vein embolization and sequential hepatectomy: A randomized controlled trial. **J. Gastroenterol.** 2015, 50, 1197–1205. [CrossRef] [PubMed]

75. Müller, M.J. Malnutrition in cirrhosis. **J. Hepatol.** 1995, 23 (Suppl. S1), 31–35.

76. Riggio, O.; Ariosto, F.; Merli, M.; Caschera, M.; Zullo, A.; Balducci, G.; Ziparo, V.; Pedretti, G.; Fiaccadori, F.; Bottari, E.; et al. Short-term oral zinc supplementation does not improve chronic hepatic encephalopathy. Results of a double-blind crossover trial. **Dig. Dis. Sci.** 1991, 36, 1204–1208. [CrossRef]

77. Gorelick, P.B.; Counts, S.E.; Nyenhuis, D. Vascular cognitive impairment and dementia. **Biochim. Biophys. Acta** 2016, 1862, 860–868. [CrossRef]

78. Gempenerlein, K.; Dietrich, D.; Kohlstedt, M.; Zipf, G.; Bernauer, H.S.; Wittmann, C.; Wenzel, S.C.; Müller, R. Polysaturated fatty acid production by Yarrowia lipolytica employing designed myxobacterial PUFA synthases. **Nat. Commun.** 2019, 10, 4055. [CrossRef]

79. Senkal, M.; Mumne, A.; Eickhoff, U.; Geier, B.; Späth, G.; Wulfert, D.; Joosten, U.; Frei, A.; Kemen, M. Early postoperative enteral immunonutrition: Clinical outcome and cost-comparison analysis in surgical patients. **Crit. Care Med.** 1997, 25, 1489–1496. [CrossRef]

80. Barbul, A.; Fishel, R.S.; Shimazu, S.; Wasserkug, H.L.; Yoshimura, N.N.; Tao, R.C.; Efron, G. Intravenous hyperalimentation with high arginine levels improves wound healing and immune function. **J. Surg. Res.** 1985, 38, 328–334. [CrossRef]

81. Bifari, F.; Nisoli, E. Branched-chain amino acids differently modulate catabolic and anabolic states in mammals: A pharmacological point of view. **Br. J. Pharmacol.** 2017, 174, 1366–1377. [CrossRef]
82. Malaguarnera, G.; Giordano, M.; Nunnari, G.; Bertino, G.; Malaguarnera, M. Gut microbiota in alcoholic liver disease: Pathogenetic role and therapeutic perspectives. World J. Gastroenterol. 2014, 20, 16639–16648. [CrossRef] [PubMed]
83. Jones, S.E.; Versalovic, J. Probiotic Lactobacillus reuteri biofilms produce antimicrobial and anti-inflammatory factors. BMC Microbiol. 2009, 9, 35. [CrossRef] [PubMed]
84. Borruel, N.; Carol, M.; Casellas, F.; Antolín, M.; de Lara, F.; Espín, E.; Naval, J.; Guarner, F.; Malagelada, J.R. Increased mucosal tumour necrosis factor alpha production in Crohn’s disease can be downregulated ex vivo by probiotic bacteria. Gut 2002, 51, 659–664. [CrossRef] [PubMed]
85. McCarthy, J.; O’Mahony, L.; O’Callaghan, L.; Sheil, B.; Vaughan, E.E.; Fitzsimons, N.; Fitzgibbon, J.; O’Sullivan, G.C.; Kielty, B.; Collins, J.K.; et al. Double blind, placebo controlled trial of two probiotic strains in interleukin 10 knockout mice and mechanistic link with cytokine balance. Gut 2003, 52, 975–980. [CrossRef] [PubMed]
86. Sheth, A.A.; Garcia-Tsao, G. Probiotics and liver disease. J. Clin. Gastroenterol. 2008, 42 (Suppl. S2), S80–S84. [CrossRef] [PubMed]
87. Rayes, N.; Seehofer, D.; Theruvath, T.; Schiller, R.A.; Langrehr, J.M.; Jonas, S.; Bengmark, S.; Neuhaus, P. Supply of pre- and probiotics reduces bacterial infection rates after liver transplantation—A randomized, double-blind trial. Am. J. Transplant 2005, 5, 125–130. [CrossRef]
88. Stadlbauer, V.; Mookerjee, R.P.; Hodges, S.; Wright, G.A.; Davies, N.A.; Jalan, R. Effect of probiotic treatment on deranged neutrophil function and cytokine responses in patients with compensated alcoholic cirrhosis. J. Hepatol. 2008, 48, 945–951. [CrossRef]
89. Sharma, P.; Sharma, B.C.; Furi, V.; Sarin, S.K. An open-label randomized controlled trial of lactobacillus and probiotics in the treatment of minimal hepatic encephalopathy. Eur. J. Gastroenterol. Hepatol. 2008, 20, 506–511. [CrossRef]
90. Bajaj, J.S.; Saieian, K.; Christensen, K.M.; Hafeezullah, M.; Varma, R.R.; Franco, J.; Pleuss, J.A.; Krakower, G.; Hoffmann, R.G.; Binion, D.G. Probiotic yogurt for the treatment of minimal hepatic encephalopathy. Am. J. Gastroenterol. 2008, 103, 1707–1715. [CrossRef]
91. Stickel, F.; Hoehn, B.; Schuppan, D.; Seitz, H.K. Review article: Nutritional therapy in alcoholic liver disease. Aliment. Pharmacol. Ther. 2003, 18, 357–373. [CrossRef]
92. Halsted, C.H. Nutrition and alcoholic liver disease. Semin. Liver Dis. 2004, 24, 289–304. [CrossRef] [PubMed]
93. Elwyn, D.H.; Kinney, J.M.; Askanazi, J. Energy expenditure in surgical patients. Surg. Clin. N. Am. 1981, 61, 545–556. [CrossRef]
94. Cabré, E.; Periago, J.L.; Abad-Lacruz, A.; González-Huix, F.; González, J.; Esteve-Comas, M.; Fernández-Bañares, F.; Planas, R.; Gil, A.; Sánchez-Medina, F.; et al. Plasma fatty acid profile in advanced cirrhosis: Unsaturation deficit of lipid fractions. Am. J. Gastroenterol. 1990, 85, 1597–1604. [CrossRef]
95. Hassé, J.M.; Blue, L.S.; Liepa, G.U.; Goldstein, R.M.; Jennings, L.W.; Mor, E.; Husberg, B.S.; Levy, M.F.; Gonwa, T.A.; Klintmalm, G.B. Early enteral nutrition support in patients undergoing liver transplantation. JPEN J. Parenter. Enteral Nutr. 1995, 19, 437–443. [CrossRef] [PubMed]
96. Lochs, H.; Plauth, M. Liver cirrhosis: Rationale and modalities for nutritional support—The European Society of Parenteral and Enteral Nutrition consensus and beyond. Curr. Opin. Clin. Nutr. Metab. Care 1999, 2, 345–349. [CrossRef]
97. Fan, S.T.; Lo, C.M.; Lai, E.C.; Chu, K.M.; Liu, C.L.; Wong, J. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. N. Engl. J. Med. 1994, 331, 1547–1552. [CrossRef]
98. Morgan, M.Y.; Madden, A.M.; Jennings, G.; Elia, M.; Fuller, N.J. Two-component models are of limited value for the assessment of body composition in patients with cirrhosis. Am. J. Clin. Nutr. 2006, 84, 1151–1162. [CrossRef]
99. Plauth, M.; Cabré, E.; Riggio, O.; Assis-Camilo, M.; Pirlich, M.; Kondrup, J.; Ferenci, P.; Holm, E.; Vom Dahl, S.; DGEM (German Society for Nutritional Medicine); et al. ESPEN Guidelines on Enteral Nutrition: Liver disease. Clin. Nutr. 2006, 25, 285–294. [CrossRef]
100. DiCecco, S.R.; Francisco-Ziller, N. Nutrition in alcoholic liver disease. Nutr. Clin. Pract. 2006, 21, 245–254. [CrossRef]
101. Weismann, A.; Braga, M.; Harsanyi, L.; Laviano, A.; Ljungqvist, O.; Soeters, P.; Jauch, K.W.; Kemen, M.; Hiesmayr, J.M.; DGEM (German Society for Nutritional Medicine); et al. ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. Clin. Nutr. 2006, 25, 224–244. [CrossRef]
102. Sarin, S.K.; Pande, A.; Schnabl, B. Microbiome as a therapeutic target in alcohol-related liver disease. *J. Hepatol.* 2019, 70, 260–272. [CrossRef] [PubMed]

103. Fulde, M.; Hornef, M.W. Maturation of the enteric mucosal innate immune system during the postnatal period. *Immunol. Rev.* 2014, 260, 21–34. [CrossRef] [PubMed]

104. Kamada, N.; Chen, G.Y.; Inohara, N.; Núñez, G. Control of pathogens and pathobionts by the gut microbiota. *Nat. Immunol.* 2013, 14, 685–690. [CrossRef] [PubMed]

105. Ijssennagger, N.; Belzer, C.; Hooveld, G.J.; Dekker, J.; van Mil, S.W.; Müller, M.; Kleerebezem, M.; van der Meer, R. Gut microbiota facilitates dietary heme-induced epithelial hyperproliferation by opening the mucus barrier in colon. *Proc. Natl. Acad. Sci. USA* 2015, 112, 10038–10043. [CrossRef]

106. Reinhardt, C.; Bergentall, M.; Greiner, T.U.; Schaffner, F.; Ostergren-Lundén, G.; Petersen, L.C.; Ruf, W.; Bäckhed, F. Tissue factor and PAR1 promote microbiota-induced intestinal vascular remodelling. *Nature* 2012, 483, 627–631. [CrossRef]

107. Yano, J.M.; Yu, K.; Donaldson, G.P.; Shastri, G.G.; Ann, P.; Ma, L.; Nagler, C.R.; Ismagilov, R.F.; Mazmanian, S.K.; Hsiao, E.Y. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell* 2015, 161, 264–276. [CrossRef]

108. Neuman, H.; Debelius, J.W.; Knight, R.; Koren, O. Microbial endocrinology: The interplay between the microbiota and the endocrine system. *FEMS Microbiol. Rev.* 2015, 39, 509–521. [CrossRef]

109. Canfora, E.E.; Jocken, J.W.; Blaak, E.E. Short-chain fatty acids in control of body weight and insulin sensitivity. *Nat. Rev. Endocrinol.* 2015, 11, 577–591. [CrossRef]

110. Neuman, H.; Debelius, J.W.; Knight, R.; Koren, O. Microbial endocrinology: The interplay between the microbiota and the endocrine system. *FEMS Microbiol. Rev.* 2015, 39, 509–521. [CrossRef]

111. Devlin, A.S.; Fischbach, M.A. A biosynthetic pathway for a prominent class of microbiota-derived bile acids. *Science* 2013, 341, 295–298. [CrossRef]

112. Plaza-Díaz, J.; Álvarez-Mercado, A.I.; Ruiz-Marín, C.M.; Reina-Pérez, I.; Pérez-Alonso, A.J.; Sánchez-Andujar, M.B.; Torné, P.; Gallart-Aragón, T.; Sánchez-Barrón, M.T.; Reyes Lartategui, S.; et al. Association of breast and gut microbiota dysbiosis and the risk of breast cancer: A case-control clinical study. *BMC Cancer* 2019, 19, 495. [CrossRef] [PubMed]

113. Álvarez-Mercado, A.I.; Navarro-Oliveros, M.; Robles-Sánchez, C.; Plaza-Díaz, J.; Saéz-Lara, M.J.; Muñoz-Quezada, S.; Fontana, L.; Abadia-Molina, F. Microbial Population Changes and Their Relationship with Human Health and Disease. *Microorganisms* 2019, 7, 68. [CrossRef] [PubMed]

114. Tripathi, A.; Debelius, J.; Brenner, D.A.; Karin, M.; Loomba, R.; Schnabl, B.; Knight, R. The gut-liver axis and the intersection with the microbiome. *Nat. Rev. Gastroenterol. Hepatol.* 2018, 15, 397–411. [CrossRef] [PubMed]

115. Chen, P.; Schnabl, B. Host-microbiome interactions in alcoholic liver disease. *Gut Liver* 2014, 8, 237–241. [CrossRef] [PubMed]

116. Yang, A.M.; Inamine, T.; Hochrath, K.; Chen, P.; Wang, L.; Llorente, C.; Bluemel, S.; Hartmann, P.; Xu, J.; Koyama, Y.; et al. Intestinal fungi contribute to the development of alcoholic liver disease. *J. Clin. Investig.* 2017, 127, 2829–2841. [CrossRef] [PubMed]

117. Gubbard, S.L.; Lacy, B.E.; Levine, G.M.; Crowell, M.D. The impact of alcohol consumption and cholecystectomy on small intestinal bacterial overgrowth. *Dig. Dis. Sci.* 2014, 59, 638–644. [CrossRef]

118. Kirpich, I.A.; Solovieva, N.V.; Leikhter, S.N.; Shidakova, N.A.; Lebedeva, O.V.; Sidorov, P.I.; Bazhukova, T.A.; Soloviev, A.G.; Barve, S.S.; McClain, C.J.; et al. Probiotics restore bowel flora and improve liver enzymes in human alcohol-induced liver injury: A pilot study. *Alcohol* 2008, 42, 675–682. [CrossRef]

119. Casafont Morencos, F.; de las Heras Castaño, G.; Martín Ramos, L.; López Arias, M.J.; Ledeasma, F.; Pons Romero, F. Small bowel bacterial overgrowth in patients with alcoholic cirrhosis. *Dig. Dis. Sci.* 1996, 41, 552–556. [CrossRef]

120. Michail, S.; Lin, M.; Frey, M.R.; Fanter, R.; Palij, O.; Hilbush, B.; Reo, N.V. Altered gut microbial energy and metabolism in children with non-alcoholic fatty liver disease. *FEMS Microbiol. Ecol.* 2015, 91, 1–9. [CrossRef]
122. Raman, M.; Ahmed, I.; Gilleve, P.M.; Probert, C.S.; Ratcliffe, N.M.; Smith, S.; Greenwood, R.; Sikaroodi, M.; Lam, V.; Crotty, P.; et al. Fecal microbiome and volatile organic compound metabolome in obese humans with nonalcoholic fatty liver disease. Clin. Gastroenterol. Hepatol. 2013, 11, 868–875. [CrossRef] [PubMed]

123. Boursier, J.; Mueller, O.; Barret, M.; Machado, M.; Fizanne, L.; Araujo-Perez, F.; Guy, C.D.; Seed, P.C.; Rawls, J.F.; David, L.A.; et al. The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota. Hepatology 2016, 63, 764–775. [CrossRef] [PubMed]

124. Del Chierico, F.; Nobili, V.; Vernocchi, P.; Russo, A.; De Stefanis, C.; Gnani, D.; Furlanello, C.; Zandonà, A.; Paci, P.; Capuani, G.; et al. Gut microbiota profiling of pediatric nonalcoholic fatty liver disease and obese patients unveiled by an integrated meta-omics-based approach. Hepatology 2017, 65, 451–464. [CrossRef] [PubMed]

125. Qin, N.; Yang, F.; Li, A.; Prifti, E.; Chen, Y.; Shao, L.; Guo, J.; Le Chatelier, E.; Yao, J.; Wu, L.; et al. Alterations of the human gut microbiome in liver cirrhosis. Nature 2014, 513, 59–64. [CrossRef]

126. Chen, Y.; Ji, F.; Guo, J.; Shi, D.; Fang, D.; Li, L. Dysbiosis of small intestinal microbiota in liver cirrhosis and its association with etiology. Sci. Rep. 2016, 6, 34055. [CrossRef]

127. Yu, L.X.; Schwabe, R.F. The gut microbiome and liver cancer: Mechanisms and clinical translation. Nat. Rev. Gastroenterol. Hepatol. 2017, 14, 527–539. [CrossRef]

128. Ren, Y.D.; Ye, Z.S.; Yang, L.Z.; Jin, L.X.; Wei, W.J.; Deng, Y.Y.; Chen, X.X.; Xiao, C.X.; Yu, X.F.; Xu, H.Z.; et al. Fecal microbiota transplantation induces hepatitis B virus e-antigen (HBsAg) clearance in patients with positive HBsAg after long-term antiviral therapy. Hepatology 2017, 65, 1765–1768. [CrossRef]

129. Ferrere, G.; Wrzosek, L.; Cailleux, F.; Turpin, W.; Puchois, V.; Spatz, M.; Ciocan, D.; Rainteau, D.; Humbert, L.; Hugot, C.; et al. Fecal microbiota manipulation prevents dysbiosis and alcohol-induced liver injury in mice. J. Hepatol. 2017, 66, 806–815. [CrossRef]

130. Marra, F.; Svegliati-Baroni, G. Lipotoxicity and the gut-liver axis in NASH pathogenesis. J. Hepatol. 2018, 68, 280–295. [CrossRef]

131. Soderborg, T.K.; Clark, S.E.; Mulligan, C.E.; Janssen, R.C.; Babcock, L.; Ir, D.; Young, B.; Krebs, N.; Lemas, D.J.; Johnson, L.K.; et al. The gut microbiota in infants of obese mothers increases inflammation and susceptibility to NAFLD. Nat. Commun. 2018, 9, 4462. [CrossRef]

132. Cogger, V.C.; Mohamad, M.; Solon-Biet, S.M.; Senior, A.M.; Warren, A.; O’Reilly, J.N.; Tung, B.T.; Svistounov, D.; McMahon, A.C.; Fraser, R.; et al. Dietary macronutrients and the aging liver sinusoidal endothelial cell. Am. J. Physiol. Heart Circ. Physiol. 2016, 310, H1064–H1070. [CrossRef] [PubMed]

133. Friedman, S.L.; Neuschwander-Tetri, B.A.; Rinella, M.; Sanyal, A.J. Mechanisms of NAFLD development and therapeutic strategies. Nat. Med. 2018, 24, 908–922. [CrossRef] [PubMed]

134. Harte, A.L.; da Silva, N.F.; Creely, S.J.; McGee, K.C.; Billyard, T.; Youssef-Elabd, E.M.; Tripathi, G.; Ashour, E.; Abdalla, M.S.; Sharada, H.M.; et al. Elevated endotoxin levels in non-alcoholic fatty liver disease. Nutr. Biochem. 2010, 7, 15. [CrossRef] [PubMed]

135. Cogger, V.C.; Sullivan, D.; Senior, A.M.; Warren, A.; O’Reilly, J.N.; Tung, B.T.; Svistounov, D.; McMahon, A.C.; Fraser, R.; et al. Dietary macronutrients and the aging liver sinusoidal endothelial cell. Am. J. Physiol. Heart Circ. Physiol. 2016, 310, H1064–H1070. [CrossRef] [PubMed]

136. Hudson, A.L.; et al. Toll-like receptor-induced innate immune responses in non-parenchymal liver cells are cell type-specific. J. Infect. Immun. 2010, 82, 363–374. [CrossRef]

137. Björkholm, B.; Bok, C.M.; Lundin, A.; Raifer, J.; Hibberd, M.L.; Pettersson, S. Intestinal microbiota regulate xenobiotic metabolism in the liver. PLoS ONE 2009, 4, e9958. [CrossRef]

138. Chuang, P.; Huang, Y.L.; Chiu, C.C.; Liao, C.D.; Hsu, F.L.; Huang, C.C.; Hou, C.C. Metabolomics characterization of energy metabolism reveals glycogen accumulation in gut-microbiota-lacking mice. J. Nutr. Biochem. 2012, 23, 752–758. [CrossRef]

139. Wiest, R.; Albillos, A.; Trauner, M.; Bajaj, J.S.; Jalan, R. Targeting the gut-liver axis in liver disease. J. Hepatol. 2017, 67, 1084–1103. [CrossRef]

140. Wang, W.; Xu, S.; Ren, Z.; Jiang, J.; Zheng, S. Gut microbiota and allogeneic transplantation. J. Transl. Med. 2015, 13, 275. [CrossRef]

141. Álvarez-Mercado, A.I.; Gulfo, J.; Romero Gómez, M.; Jiménez-Castro, M.B.; Gracia-Sancho, J.; Peralta, C. Use of Steatotic Grafts in Liver Transplantation: Current Status. Liver Transplant. 2019, 25, 771–786. [CrossRef]
142. Bäckhed, F.; Ding, H.; Wang, T.; Hooper, L.V.; Koh, G.Y.; Nagy, A.; Semenkovich, C.F.; Gordon, J.I. The gut microbiota as an environmental factor that regulates fat storage. *Proc. Natl. Acad. Sci. USA* 2004, 101, 15718–15723. [CrossRef] [PubMed]

143. Schnabl, B.; Brenner, D.A. Interactions between the intestinal microbiome and liver diseases. *Gastroenterology* 2014, 146, 1513–1524. [CrossRef] [PubMed]

144. Martinez, K.B.; Leone, V.; Chang, E.B. Western diets, gut dysbiosis, and metabolic diseases: Are they linked? *Gut Microbes* 2017, 8, 130–142. [CrossRef]

145. Fan, J.G.; Kim, S.U.; Wong, V.W. New trends on obesity and NAFLD in Asia. *J. Hepatol.* 2017, 67, 862–873. [CrossRef] [PubMed]

146. Hammad, A.; Kaido, T.; Aliyev, V.; Mandato, C.; Uemoto, S. Nutritional Therapy in Liver Transplantation. *Nutrients* 2017, 9, 1126. [CrossRef]

147. Zhang, Q.K.; Wang, M.L. The management of perioperative nutrition in patients with end stage liver disease undergoing liver transplantation. *Hepatobiliary Surg. Nutr.* 2015, 4, 336–344.

148. Ren, Z.; Jiang, J.; Lu, H.; Chen, X.; He, Y.; Zhang, H.; Xie, H.; Wang, W.; Zheng, S.; Zhou, L. Intestinal microbial variation may predict early acute rejection after liver transplantation in rats. *Transplantation* 2014, 98, 844–852. [CrossRef]

149. Grąt, M.; Hołówko, W.; Wronka, K.M.; Grąt, K.; Lewandowski, Z.; Kosińska, I.; Krasnodebski, M.; Wasilewicz, M.; Gałecka, M.; Szachta, P.; et al. The relevance of intestinal dysbiosis in liver transplant candidates. *Transpl. Infect. Dis.* 2015, 17, 174–184. [CrossRef]

150. Bajaj, J.S.; Fagan, A.; Sikaroodi, M.; White, M.B.; Sterling, R.K.; Gilles, H.; Heuman, D.; Stravitz, R.T.; Matherly, S.C.; Siddiqui, M.S.; et al. Liver transplant modulates gut microbiobial dysbiosis and cognitive function in cirrhosis. *Liver Transplant.* 2017, 23, 907–914. [CrossRef]

151. Sun, L.Y.; Yang, Y.S.; Qu, W.; Zhu, Z.J.; Wei, L.; Ye, Z.S.; Zhang, J.R.; Sun, X.Y.; Zeng, Z.G. Gut microbiota of liver transplantation recipients. *Sci. Rep.* 2017, 7, 3762. [CrossRef]

152. Bajaj, J.S.; Kakiyama, G.; Cox, I.J.; Nittomo, H.; Takei, H.; White, M.; Fagan, A.; Gavis, E.A.; Heuman, D.M.; Gilles, H.C.; et al. Alterations in gut microbial function following liver transplant. *Liver Transplant.* 2018, 24, 752–761. [CrossRef] [PubMed]

153. Tian, X.; Yang, Z.; Luo, F.; Zheng, S. Gut microbial balance and liver transplantation: Alteration, management, and prediction. *Front. Med.* 2018, 12, 123–129. [CrossRef] [PubMed]

154. Wu, X.; Sun, R.; Chen, Y.; Zheng, X.; Bai, L.; Lian, Z.; Wei, H.; Tian, Z. Oral ampicillin inhibits liver regeneration by breaking hepatic innate immune tolerance normally maintained by gut commensal bacteria. *Hepatology* 2015, 62, 253–264. [CrossRef] [PubMed]

155. Liu, H.X.; Rocha, C.S.; Dandekar, S.; Wan, Y.J. Functional analysis of the relationship between intestinal microbiota and the expression of hepatic genes and pathways during the course of liver regeneration. *J. Hepatol.* 2016, 64, 641–650. [CrossRef] [PubMed]

156. Adolph, T.E.; Graner, C.; Moschen, A.R.; Tiig, H. Liver-Microbiome Axis in Health and Disease. *Trends Immunol.* 2018, 39, 712–723. [CrossRef] [PubMed]

157. Xie, Y.; Chen, H.; Zhu, B.; Qin, N.; Chen, Y.; Li, Z.; Deng, M.; Jiang, H.; Xu, X.; Yang, J.; et al. Effect of intestinal microbiota alteration on hepatic damage in rats with acute rejection after liver transplantation. *Microb. Ecol.* 2014, 68, 871–880. [CrossRef]

158. Ito, T.; Nakamura, K.; Kageyama, S.; Korayem, I.M.; Hirao, H.; Kadono, K.; Aziz, J.; Younan, S.; DiNocia, J.; 3rd; Agopian, V.G.; et al. Impact of Rifaximin Therapy on Ischemia/Reperfusion Injury in Liver Transplantation: A Propensity Score-Matched Analysis. *Liver Transplant.* 2019, in press. [CrossRef]

159. Nakamura, K.; Kageyama, S.; Ito, T.; Hirao, H.; Kadono, K.; Aziz, A.; Dery, K.J.; Everly, M.J.; Taura, K.; Uemoto, S.; et al. Antibiotic pretreatment alleviates liver transplant damage in mice and humans. *J. Clin. Investig.* 2019, 129, 3420–3434. [CrossRef]

160. Jia, J.; Tian, X.; Jiang, J.; Ren, Z.; Lu, H.; He, N.; Xie, H.; Zhou, L.; Zheng, S. Structural shifts in the intestinal microbiota of rats treated with cyclosporine A after orthotopic liver transplantation. *Front. Med.* 2019, 13, 451–460. [CrossRef]

161. Jiang, J.W.; Ren, Z.G.; Lu, H.F.; Zhang, H.; Li, A.; Cui, G.Y.; Jia, J.J.; Xie, H.Y.; Chen, X.H.; He, Y.; et al. Optimal immunosuppressor induces stable gut microbiota after liver transplantation. *World J. Gastroenterol.* 2018, 24, 3871–3883. [CrossRef]
162. Liu, H.X.; Hu, Y.; Wan, Y.J. Microbiota and bile acid profiles in retinoic acid-primed mice that exhibit accelerated liver regeneration. *Oncotarget* 2016, 7, 1096–1106. [CrossRef]

163. Liu, Z.; Li, C.; Huang, M.; Tong, C.; Zhang, X.; Wang, L.; Peng, H.; Lan, P.; Zhang, P.; Huang, N.; et al. Positive regulatory effects of perioperative probiotic treatment on postoperative liver complications after colorectal liver metastases surgery: A double-center and double-blind randomized clinical trial. *BMC Gastroenterol.* 2019, 23, 1714–1722. [CrossRef][PubMed]

164. Ren, J.; Hu, D.; Mao, Y.; Yang, H.; Liao, W.; Xu, W.; Ge, P.; Zhang, H.; Sang, X.; Lu, X.; et al. Alteration in gut microbiota caused by time-restricted feeding alleviates hepatic ischemia reperfusion injury in mice. *J. Cell. Mol. Med.* 2019, 23, 1714–1722. [CrossRef][PubMed]

165. Cheng, E.Y.; Everly, M.J. Trends of Immunosuppression and Outcomes Following Liver Transplantation: An Analysis of the United Network for Organ Sharing Registry. In *Clinical Transplants 2014*; Everly, M.J., Terasaki, P.I., Eds.; UCLA Immunogenetics Center: Los Angeles, CA, USA, 2015; Volume 2, pp. 13–26.

166. Ravaioli, M.; Neri, F.; Lazzarotto, T.; Bertuzzo, V.R.; Di Gioia, P.; Stacchini, G.; Morelli, M.C.; Ercolani, G.; Cescon, M.; Chiaregghin, A.; et al. Immunosuppression Modifications Based on an Immune Response Assay: Results of a Randomized, Controlled Trial. *Transplantation* 2015, 99, 1625–1632. [CrossRef][PubMed]

167. Jiang, J.W.; Ren, Z.G.; Cui, G.Y.; Zhang, Z.; Xie, H.Y.; Zhou, L. Chronic bile duct hyperplasia is a chronic graft dysfunction following liver transplantation. *World J. Gastroenterol.* 2012, 18, 1038–1047. [CrossRef]

168. Zhang, W.; Fung, J. Limitations of current liver transplant immunosuppressive regimens: Renal considerations. *Hepatobiliary Pancreat. Dis. Int.* 2017, 16, 27–32. [CrossRef]

169. Humar, A.; Michaels, M.; AST ID Working Group on Infectious Disease Monitoring. American Society of Transplantation recommendations for screening, monitoring and reporting of infectious complications in immunosuppression trials in recipients of organ transplantation. *Am. J. Transplant.* 2006, 6, 262–274. [CrossRef]

170. Jia, J.J.; Lin, B.Y.; He, J.J.; Geng, L.; Kadel, D.; Wang, L.; Yu, D.D.; Shen, T.; Yang, Z.; Ye, Y.F.; et al. “Minimizing tacrolimus” strategy and long-term survival after liver transplantation. *World J. Gastroenterol.* 2014, 20, 11363–11369. [CrossRef]

171. He, Y.Q.; Gong, L.; Fang, Y.P.; Zhan, Q.; Liu, H.X.; Lu, Y.L.; Guo, G.L.; Lehman-McKeeman, L.; Fang, J.W.; Wan, Y.J. The role of retinoic acid in hepatic lipid homeostasis defined by genomic binding and transcriptome profiling. *BMC Genom.* 2013, 14, 575. [CrossRef]

172. Yang, F.; He, Y.Q.; Liu, H.X.; Tsuei, J.; Jiang, X.Y.; Yang, L.; Wang, Z.T.; Wan, Y.J. All-trans retinoic acid regulates hepatic bile acid homeostasis. *Biochem. Pharmacol.* 2014, 91, 483–489. [CrossRef]

173. Huang, W.D.; Ma, K.; Zhang, J.; Qatanani, M.; Cuvillier, J.; Liu, J.; Dong, B.N.; Huang, X.F.; Moore, D.D. Nuclear receptor-dependent bile acid signaling is required for normal liver regeneration. *Science* 2006, 312, 233–236. [CrossRef][PubMed]

174. Liu, H.X.; Ly, I.; Hu, Y.; Wan, Y.J. Retinoic acid regulates cell cycle genes and accelerates normal mouse liver regeneration. *Biochem. Pharmacol.* 2014, 91, 256–265. [CrossRef][PubMed]

175. Melkani, G.C.; Panda, S. Time-restricted feeding for prevention and treatment of cardiometabolic disorders. *J. Physiol.* 2017, 595, 3691–3700. [CrossRef][PubMed]

176. Gonzalez-Flecha, B.; Cutrin, J.; Boveris, A. Time course and mechanism of oxidative stress and tissue damage in rat liver subjected to in vivo ischemia-reperfusion. *J. Clin. Investig.* 1993, 91, 456–464. [CrossRef][PubMed]

177. Kawachi, S.; Hines, L.N.; Laroux, F.S.; Hoffman, J.; Bharwani, S.; Gray, L.; Leffer, D.; Grisham, M.B. Nitric oxide synthase and postischemic liver injury. *Biochem. Biophys. Res. Commun.* 2000, 276, 851–854. [CrossRef]

178. Kuboki, S.; Shin, T.; Huber, N.; Eismann, T.; Galloway, E.; Schuster, R.; Blanchard, J.; Edwards, M.J.; Lentsch, A.B. Hepatocyte signaling through CXC chemokine receptor-2 is detrimental to liver recovery after ischemia/reperfusion in mice. *Hepatology* 2008, 48, 1213–1223. [CrossRef][PubMed]