Review Article

New insights into intestinal failure–associated liver disease in adults: A comprehensive review of the literature

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Abstract

Intestinal failure–associated liver disease (IFALD) remains one of the most common and serious complications of parenteral nutrition (PN), causing a wide spectrum of hepatic manifestations from steatosis and mild cholestasis to portal hypertension and end-stage liver failure. The prevalence of IFALD depends on the diagnostic criteria and ranges from 4.3% to 65%. Moreover, many factors are shown to contribute to its development, including nutrient deficiencies, toxicity of PN, infections, and alterations of bile acid metabolism and gut microbiota. Prevention and management of IFALD aim at ameliorating or eliminating the risk factors associated with IFALD. The use of PN formulations with a lower ratio omega-6-to-omega-3 polyunsaturated fatty acids, cycle PN, optimization of enteral stimulation and prevention and early treatment of infections constitute the main therapeutic targets. However, failure of improvement and severe IFALD with end-stage liver failure should be considered as the indications of intestinal transplantation. The aim of this review is to provide an update of the epidemiology, pathophysiology, and diagnosis of IFALD in the adult population as well as to present a clinical approach of the therapeutic strategies of IFALD and present novel therapeutic targets.

Keywords: Intestinal failure–associated liver disease, liver injury, parenteral nutrition, parenteral nutrition associated liver disease

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INTRODUCTION

The European Society for Clinical Nutrition and Metabolism (ESPEN) defines intestinal failure as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth."[1] It is classified into three types: acute, prolonged acute, and chronic [Table 1].[2] Parenteral nutrition (PN) is frequently used in clinical practice to prevent malnutrition and provide most of the necessary nutrients in patients with inadequate intestinal absorption or in patients where enteral nutrition is contraindicated.[3] PN contains protein, carbohydrates, fat, vitamins, water, and trace elements, whereas the solution and duration of PN depends on the underlying diseases and nutrition status of the patient.[4] Despite the various benefits, the administration of PN has been associated with many complications, including hyperglycemia,[5] refeeding

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Table 1: Classification of intestinal failure

Type I: acute, short-term, and usually self-limiting condition
Type II: prolonged acute condition, often in metabolically unstable patients, requiring complex multidisciplinary care and intravenous supplementation over periods of weeks or months.
Type III: chronic condition, in metabolically stable patients, requiring intravenous supplementation over months or years. It may be reversible or irreversible

syndrome in malnourished patients,[3] thromboembolic complications,[6] infections,[7] metabolic bone disease,[8] cholelithiasis,[9] and PN-associated liver disease (PNALD).[10]

Recently, the terminology "intestinal failure–associated liver diseases (IFALD)" has replaced the term PNALD.[11] In particular, ESPEN recommends that the term IFALD should refer to liver injury as a result of one or more factors relating to intestinal failure including, but not limited to, PN and occurring in the absence of other primary parenchymal liver pathology, other hepatotoxic factors, or biliary obstruction.[12] Particularly, IFALD has been commonly found in patients with PN, presenting with a wide spectrum of manifestations, including cholestasis, steatosis/steatohepatitis, and fibrosis. Progression to cirrhosis and development of end-stage liver failure occurs only in a minority of adults in comparison to infants.[13] The disease etiology seems to be multifactorial. The aim of this review is to present the epidemiology of the disease in the adult population and analyze the possible pathogenetic pathways. In addition, a great emphasis has been placed in the management of IFALD, including the prevention and treatment and the presentation of new therapeutic strategies.

LITERATURE SEARCH

A thorough review of the literature up to April 2020 was performed using PubMed to identify articles regarding IFALD in adults.

The search was performed using the search string: ("intestinal failure associated liver disease" OR "parenteral nutrition associated liver disease") AND ("etiology" OR "causes" OR "diagnosis" OR "prevalence" OR "epidemiology" OR "treatment" OR "prevention" "management" OR "novel therapy"). Only articles in English were reviewed.

DIAGNOSIS

The diagnosis of IFALD mainly requires the exclusion of other causes of liver injury and the temporal association between the administration of PN and elevation of liver function tests. IFALD usually causes mild elevation of liver enzymes, i.e., γ-GT >5 times the upper limit of normal (ULN), ALT >2–3 ULN, and the increase of total bilirubin 2–3 times than the pre-PN levels. The elevation of liver enzymes occurs between the first and third week after the initiation of PN.[14] In addition, alkaline phosphatase is predominantly elevated in the majority of patients with IFALD.[8] Usually, individuals, who receive PN, are critically ill or postoperative patients, being at a high risk of ischemic hepatitis, acalculous cholecystitis, reactivation of virus hepatitis, and drug-induced liver injury. Therefore, the aforementioned causes of liver injury should be ruled out. In all cases, abdominal ultrasound should be performed for the exclusion of biliary complications, such as acute cholecystitis or cholelithiasis or thrombosis of hepatic vessels. Exclusion of viral hepatitis is mandatory.

The pattern of liver enzyme elevation plays a critical role in the diagnostic approach. Consequently, ischemic hepatitis, acute viral hepatitis or exacerbation chronic viral hepatitis should be considered, if the aminotransaminases level is greater than 1,000 IU/L.[15] Notably, benign postoperative cholestasis may be confused with IFALD. In benign postoperative cholestasis, conjugated bilirubin progressively increases within the first 2 to 10 days of surgery and cholestasis due to hypoxemia, hypotension, administration of halogenated anesthetic agents, and when resorption of hematomas occur.[16]

The standard diagnostic criteria for IFALD have not been established. Consequently, the prevalence of IFALD depends on the diagnostic criteria used and ranges from 4.3% to 65% [Table 2].[17-23]

PATHOPHYSIOLOGY

The etiology of IFALD seems to be multifactorial and nutrient deficiencies, nutrient toxicity, intestinal microbiome dysbiosis, altered bile acid metabolism, and catheter-related factors may contribute to its development [Table 3].[24] In recent years, studies have mainly focused on the gut–lipid–liver axis, demonstrating the molecular alteration of bile acid metabolism, such as the role of fibroblast growth factor-19 (FGF-19), the impact of fecal microbiota, and the role of lipid emulsion.

Nutrient deficiencies

Nutrient deficiencies occur frequently in patients with PN and may contribute to liver injury.[25] Particularly, patients receiving PN are shown to have low levels of carnitine,[26] as low as 50% of the normal plasma carnitine level.[27] Carnitine is an essential co-factor of β-oxidation into mitochondria and seems to be involved in the

Table 2: Presentation of prevalence and outcomes of IFALD, depending on diagnostic criteria

Study	Number of patients	Mean duration of PN (months)	Diagnostic criteria of IFALD	Prevalence of IFALD	Outcomes of IFALD
Cavicchi *et al*.[17]	90	45	Presentation of chronic cholestasis and exclusion of other causes. Chronic cholestasis was defined as a value at least 1.5-fold the upper limit of normal on two of three liver function measures-levels of γ-GT, ALP, and TBIL-that persisted for at least 6 months.	65% (58/90)	Cirrhosis 5.5% (5/90) Extensive fibrosis 19% (17/90)
Lloyd *et al*.[18]	113	54	Presentation of chronic cholestasis and exclusion of other causes. Chronic cholestasis was defined as a value at least 1.5-fold the upper limit of normal on two of three liver function measures-levels of γ-GT, ALP, and TBIL-that persisted for at least 6 months.	24% (27/113)	Not available
Sasdelli *et al*.[20]	113	84.2	Exclusion criteria: presence of malignant disease, evident causes of liver injury or disease (viral infection, toxic drugs, autoimmune disease, chronic alcohol abuse). 9 diagnostic criteria for IFALD used. -IFALD-cholestasis Cavicchi criterion: a value >1.5 the upper limit of normal (ULN) on two of γ-GT, ALP, and serum conjugated bilirubin for >6 months. ConBil criterion: conjugated bilirubin >0.3 mg/dL for >6 months TotBil criterion: total bilirubin >1 mg/dL and conjugated bilirubin >0.3 mg/dL for >6 months IFALD-steatosis AAR index: AST/ALT ratio <1 when AST and ALT >ULN Ultrasound criterion: liver ultrasound echogenic appearance of steatosis IFALD-fibrosis APRI index: AST to platelets (PTL) ratio index = [(AST/ULN AST) x 100]/PLT (10^9/L)] >0.88 FIB-4 index: Fibrosise-4 index=Age (years) x AST)/[PLT (10^9/L) x $ALT^{1/2}$]; advanced fibrosis: >2.67: IFALD unclassified Luman *et al*. criterion: any deranged LFT >1.5 the ULN after >6 months of HPN starting Beath *et al*. criterion : ALP and γ-GT >1.5 the ULN and US signs of liver steatosis	Not available	IFALD-cholestasis Cavicchi criterion 8% ConBil criterion 15% TotBil criterion 5% IFALD-Steatosis AAR index 19% US criterion 43% IFALD-Fibrosis APRI index 11% FIB-4 index 22% IFALD-unclassified Luman criterion 40% Beath criterion 7%
Chan *et al*.[19]	42	80	End-stage liver disease. Exclusion criteria were a diagnosis of acquired immunodeficiency syndrome or the use of home TPN for less than 1 year.	14% (6/42)	All patients with end-stage liver disease have 100% mortality 10.8±7.1 months after the initial bilirubin elevation.
Luman *et al*.[21]	107	40	Any biochemical parameter of liver function test that is 1.5 times above the reference range when the test was performed at least 6 months after initiation of PN.	47.7% (51/107)	No decompensated or end-stage liver disease was noted for any of the patients in this study.
Salvino *et al*.[23]	162	25.7	All patients on home PN for at least 6 months. Patients were excluded if they had active malignancy, underlying liver disease, or exposure to a hepatotoxin. Severe liver dysfunction was defined as having all of the following criteria: total bilirubin 3 mg/dL; albumin <3.2 g/dL; and prothrombin time 3 sec prolonged.	4.3% (7/162)	Not available
Cazals-Hatem *et al*.[22]	32	Not available	Adults with intestinal failure treated with PN and who underwent liver biopsy. Indications for liver biopsy were the appearance of unexplained chronic liver blood test abnormalities, and/or an assessment before potential intestinal transplantation.	Not applicable	Significant hepatic fibrosis 56% (18/32) Minimal steatosis 12.5% (4/32) Sinusoidal dilation 18.75% (6/32) Phospholipidosis deposits 6.25% (2/32)

regulation of liver regeneration.[28] The administration of L-carnitine has been associated with suppression of skeletal muscle loss in cirrhotic patients[29] and prevention of non-alcoholic steatohepatitis progression in animal models.[30] In human studies, carnitine supplementation has been associated with the improvement of hepatic steatosis in patients with nonalcoholic fatty liver disease and diabetes.[31] However, intervention studies have not demonstrated the benefit of L-carnitine administration in home PN with abnormal liver tests and low plasma carnitine concentrations, suggesting that carnitine deficiency is not a major cause of IFALD.[32]

Table 3: Factors involved in the etiology of intestinal failure associated liver disease (IFALD)

Nutrient deficiencies
Carnitine deficiency
Taurine deficiency
Choline deficiency
Vitamin C deficiency
Vitamin E deficiency
Nutrient toxicity
Glucose overload
Large amount of phytosterols
Trace elements overload
Gut microbiota-related factors
Small intestine bacterial overgrowth
Increased intestinal barrier permeability
Suppression of Paneth cell bactericidal response
Decreased IgA secretion
Increased translocation of endotoxins and bacteria
Alteration of bile acid metabolism
Loss of gut hormone stimulation
Decrease of FGF19 levels
Catheter-related factors
Sepsis

Decreased plasma taurine levels have been reported in patients receiving long-term PN.[33] Taurine is a sulfur-containing amino acid and plays a role in the metabolism of bile acids, formatting tauro-conjugated bile acids.[34] Taurine supplementation in guinea pigs has been associated with increased bile flow and prevention of cholestasis induced by sulfated glycolithocholate.[35] In addition, taurine administration seems to offer a significant degree of protection against PN-associated cholestasis in neonatal patients.[36] On the other hand, in a phase IV prospective clinical study, the administration of PN with taurine in postsurgical adult patients in the short term (5–7 days) had no effect on the liver function parameters.[37]

Choline is essential for normal hepatic VLDL secretion and the regulation of lipoprotein homeostasis.[38] Low plasma-free choline has been detected in 80% of patients receiving long-term PN and has been associated with abnormalities of hepatic enzymes.[39] Choline deficiency may result in progressive hepatic disease, which ranges from liver steatosis to cirrhosis,[40] while choline-supplemented PN may contribute to the reversal of these abnormalities.[41,42] Moreover, a recent study has suggested that plasma-free choline levels are closely associated with the grade of liver steatosis and fibrosis in patients with nonalcoholic steatohepatitis.[43]

Detection of low serum levels of vitamins C and E have been reported in adult patients with short bowel syndrome receiving PN.[44] Vitamin C and E deficiencies have been associated with the development of liver steatosis,[45,46] while the administration of vitamin E seems to have a beneficial effect on nonalcoholic fatty liver disease.[47] Furthermore, in piglet models, the addition of vitamin E in intravenous lipid emulsion prevented serum and liver increases in biliary and lipidemic markers of IFALD.[48]

Nutrient toxicity

Glucose overload

Glucose stimulates insulin secretion and is a necessary energy source of the brain, renal medulla, and red blood cells.[49] However, increased dextrose concentrations in PN induce hepatic steatosis due to elevated portal venous insulin–glucagon molar ratio,[50] which could also be associated with the insulin-stimulated lipogenesis of liver.[51] In contrast, in patients with steatosis, the use of cyclic TPN was not associated with prolonged abnormal insulin levels and it did not result in further deterioration of liver function tests.[52] In addition, glucose infusion at rates 5> mg/kg/min seems to result in hepatic steatosis.[25] According to the American Society for Parenteral and Enteral Nutrition guidelines, the recommended glucose infusion rate is 4–5 mg/kg body weight/min in adults; however, the infusion rate should be adjusted to each patient in order to achieve normoglycemia.[53]

Lipids

Parenteral lipids are necessary for patients with intestinal failure. However, many lipid emulsions used for PN are based on vegetable oils that contain a large amount of phytosterols. Intravenous administration of phytosterols has been associated with the development of liver steatosis in patients receiving long-term PN.[54,55] Phytosterolemia may result in the accumulation of phytosterols in cell membranes and interferes with the function of transport proteins involved in the secretion of bile acids,[56] causing cholestasis.[57] Many studies have demonstrated higher phytosterol levels in patients on PN, although an association between phytosterol intake and development of IFALD has not been found in all studies,[57,58] suggesting that phytosterolemia alone may not cause IFALD and other factors are involved.[55]

Trace elements overload

PN contains trace elements, the increased levels of which may lead to liver injury. In detail, aluminum toxicity may rarely occur in adult patients receiving PN with predisposing factors, such as kidney failure,[59,60] and may cause cellular degeneration as well as necrosis of hepatocytes.[61] Increased levels of manganese have also been reported in patients on long-term PN receiving a multitrace element preparation.[62] 90% of manganese is excreted via the biliary system[63] and overload of manganese may induce cholestasis.[64,65]

Gut microbiota-related factors

The gut microbiome plays an essential role in the human homeostasis and alterations of intestinal microbiome may disrupt the gut–liver axis and contribute to liver injury.[66] In adult patients with short bowel syndrome, changes in the intestinal environment due to the overall adoption, which includes hyperphagia, mucosal remodeling of the remaining part of the intestine,[67] and lower intestinal pH,[68] results in the alteration of microbiota composition[69] that may result in altered bile acid metabolism and development of cholestasis.[70] Furthermore, many studies have demonstrated small intestine bacterial overgrowth (SIBO) in patients with intestinal failure on home PN.[71,72] SIBO may increase intestinal permeability, production of endotoxins, and release of proinflammatory cytokines in the liver, causing liver damage.[73] Moreover, many studies have suggested an association between SIBO and nonalcoholic fatty liver disease.[74,75]

In addition, PN and paucity of enteral feeding have been associated with the suppression of Paneth cell bactericidal response,[76] decreased IgA secretion,[77] and increased intestinal barrier permeability[78] due to low epithelial cell proliferation and increased apoptosis,[79] leading to increased translocation of endotoxins and bacteria to the portal circulation and the liver, thereby causing inflammation.[66]

Alterations of bile acid metabolism

The disruption of the enterohepatic circulation of bile salts may contribute to the development of IFALD.[80] FGF-19 is predominantly produced in the terminal ileum, activated by the farsneoid X receptor (FXR), and participates in the metabolism of bile acids. FGF19 induces gallbladder smooth muscle relaxation and gallbladder refilling and decreases the hepatic bile acid synthesis by the repression of cholesterol-7a-hydroxylase, in response to increased levels of bile acids on terminal ileum.[81,82] In a prospective study, serum FGF19 levels were measured in 52 patients with intestinal failure after 10 months on PN. FGF19 concentrations were lower compared to healthy matched controls. FGF19 levels were further decreased in patients without remaining ileum and were positively associated with the remaining ileum length. Furthermore, FGF19 correlated with portal inflammation and fibrosis, suggesting that FGF19 may contribute to the pathogenesis of IFALD.[83]

In addition, enteral feeding promotes the secretion of several gastrointestinal hormones, such as gastrin, cholecystokinin, peptide YY, and secretin, which stimulate the bile flow and the contraction of gallbladder. Consequently, the lack of enteral intake may cause a reduction of bile flow.[84]

Catheter-related factors

Sepsis seems to be a significant risk factor in the development of IFALD. A prospective study found that each septic episode increases the risk of IFALD development by 3.2-fold.[85] Placement and handling of the central venous catheter are major sources of bacteremia and catheter-related complications have been associated with sepsis development.[86]

MANAGEMENT

The management of IFALD is challenging, requiring early therapeutic interventions and elimination of predisposing risk factors [Figure 1], while a close collaboration between internists, hepatologists, dietitians, surgeons, and transplant centers is necessary.

Duration of nutrition

Cycle PN infusion (<24 hours, usually 8–12 hours) should be considered in patients with intestinal failure, especially

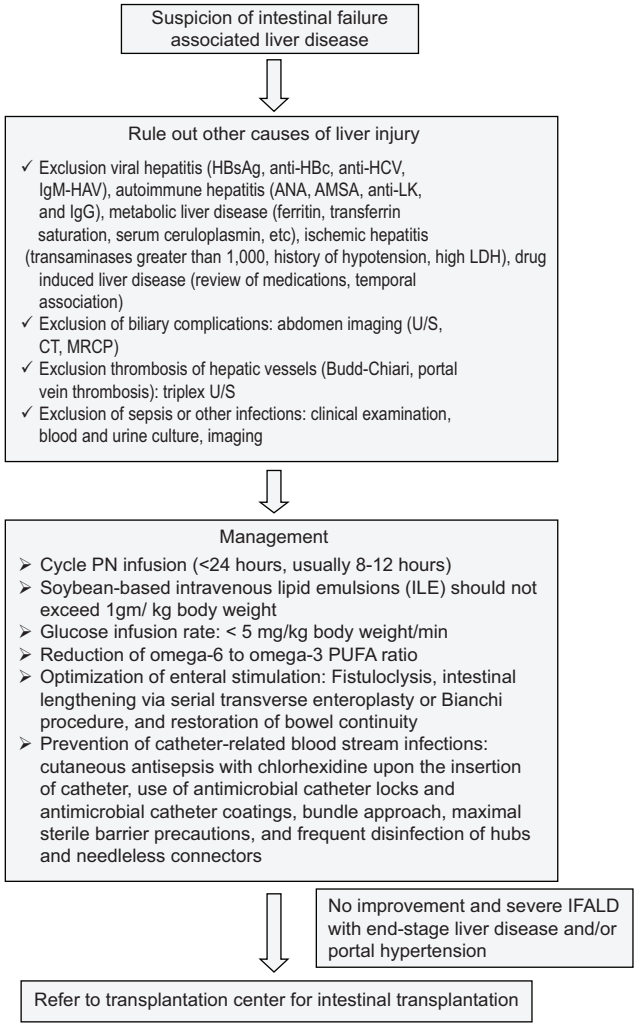

Figure 1: Algorithm of intestinal failure-associated liver disease management

in patients requiring long-term PN, because it has been associated with a lower risk of liver injury, compared to continuous PN infusion.[87] Also, patients with elevated liver function tests receiving continuous PN infusion may experience stabilization or improvement with a switch to cyclic PN infusion.[88]

Composition of nutrition

Appropriate regulation of components and PN dosage plays a critical role in the prevention and management of IFALD. According to ESPEN recommendations, the daily administration of soybean-based intravenous lipid emulsions (ILE) should not exceed 1 gm/kg body weight, because excessive administration may lead to hepatic steatosis and inflammation and has been associated with IFALD development.[89,90] In recent years, there are many available formulations of ILE, such as soybean oil-based ILE, fish oil-based ILE and several mixtures of soybean oil, coconut oil medium-chain triglycerides (MCT), and fish oil ILE.[91] Many studies have suggested that olive oil-based ILE presents better liver tolerability compared to soybean oil-based ILE, causing less frequent cholestasis and elevated hepatic enzymes.[92,93] Both fish oil- and olive oil-based ILE contain a large amount of omega-3 polyunsaturated fatty acids (PUFA), reducing omega-6 to omega-3 PUFA ratio.[94] Animal models have demonstrated that omega-6 PUFA may increase hepatic steatosis and inflammation compared to omega-3 PUFA.[95] Furthermore, a recent meta-analysis of randomized control trials suggests that omega-3 PUFA supplementation in patients with NAFLD may decrease hepatic steatosis and liver enzyme parameters.[96] In addition, several case reports and case series have documented that the use of omega-3 PUFA supplemented ILE or fish oil-based emulsion may reverse liver damage, improving liver function tests in patients with IFALD.[97-99] However, further studies are required. Based on this data, ESPEN recommends the reduction of omega-6 to omega-3 PUFA ratio wherever possible.[12]

Optimization of enteral stimulation

The improvement of enteral stimulation contributes to the reduction of PN calories and may ameliorate hepatic function in IFALD patients, as a result of the prevention of mucosal atrophy and of gut microbiota imbalance and improvement of gastrointestinal immunity.[100] Fistuloclysis in patients with high-output upper enteric fistula has been associated with the improvement of liver function tests.[101] In addition, intestinal lengthening via serial transverse enteroplasty or Bianchi procedure (longitudinal intestinal lengthening and tailoring) in adult patients with short small bowel seems to be an effective measure to increase intestinal capacity and weaning from PN[102] and may improve or prevent IFALD.[103] Furthermore, restoration of bowel continuity may reduce the risk of cholestasis. In a retrospective study of patients with a short bowel syndrome owing to mesenteric infarction, restoration of bowel continuity has been associated with the resolution of chronic cholestasis, probably because of the association with the discontinuation or reduction of PN.[104] Segmental reversals of the small bowel is another surgical procedure for the improvement of intestinal absorption and reduction of PN in adult patients with short bowel syndrome.[105] However, there are no data regarding the impact of this procedure on IFALD.

Sepsis

The prevention of catheter-related bloodstream infections (CRBSI) may include cutaneous antisepsis with chlorhexidine upon the insertion of catheter, use of antimicrobial catheter locks and antimicrobial catheter coatings, bundle approach, maximal sterile barrier precautions, and frequent disinfection of hubs and needleless connectors.[106] In addition, early diagnosis and treatment of these infections are essential to avoid severe complications. When a CRBSI is suspected, a catheter culture must be obtained and empirical antibiotic treatment should be started after appropriate cultures.[107]

Transplantation

Intestinal transplantation should be recommended as a life-saving procedure in patients with IFALD-induced life-threatening complications.[108] In adults with IFALD, intestinal transplantation may be classified into two types: a) isolated intestine transplant and b) combined liver and intestine transplant depending on the progress of IFALD.[109]

Isolated intestinal transplantation is recommended in IFALD patients with a mild or moderate liver disease without signs of portal hypertension and absence of cirrhosis (platelets count >150,000/μl, minimal hepatosplenomegaly, total plasma bilirubin <6 mg/dl, stage 1–2 fibrosis on biopsy).[110] In this subgroup of patients, main indications for intestinal transplantation include frequent episodes of severe dehydration, despite intravenous fluid supplement in addition to PN, frequent central line sepsis, thrombosis of two major central venous channels and high risk of death attributable to the underlying disease.[111]

Combined liver and intestinal transplantation should be considered in patients with severe IFALD and portal hypertension development and/or end-stage liver disease.[110] The liver and small intestine are implanted en

bloc in order to avoid hilar dissection and decrease the risk of vascular and biliary complications.[112]

NOVEL THERAPEUTIC STRATEGIES AND PERSPECTIVES

Several medications have been suggested to improve or prevent the progression of IFALD. Glucagon-like peptide-2 (GLP-2) is released by the L cell of the distal ileum and colon, resulting in the reduction of proximal intestine motility whereas it increases the mucosal surface area.[113] Several studies have reported the positive effect of GLP-2 analogues on the requirements of PN in patients with intestinal failure due to small bowel syndrome. However, their role on the management of IFALD remains largely unclear.[114] Many studies in animal models have suggested that the administration of GLP-2 may improve cholestasis and liver injury in IFALD.[115,116] A randomized phase 2 trial demonstrated that in patients with short bowel syndrome, glepaglutide administration, a novel long-acting GLP-2 analogue, may improve hepatic excretory function at the cost of enhanced liver macrophage activation and increased liver stiffness, which subsequently may result in unwanted liver damage. Thus, the benefit of GLP-2 in IFALD requires further investigation.[114,117]

Ursodeoxycholic acid (UDCA) has been suggested as an effective treatment of IFALD. Studies on pediatric patients and infants with IFALD have demonstrated that the use of UDCA (10–30 mg/kg/d) may induce the full or partial remission of IFALD cholestasis and shorter duration of cholestasis.[118,119] In adults, a small, nonrandomized study found that a one- or two-month course of UDCA (11 mg/kg/d) may induce the improvement of liver function tests.[120] However, further studies are needed.

Various studies have suggested that the use of probiotics may play a protective role against alcoholic hepatitis[121] and nonalcoholic fatty liver disease,[122] improving intestinal barrier function and preventing bacterial translocation.[123] A recent study investigated the use of probiotics to prevent SIBO in patients with intestinal failure and demonstrated a higher prevalence of IFALD in patients who did not use probiotics (54.4% vs 39.1%). Nevertheless, the multivariable analysis did not confirm a statistically significant difference (OR: 0.303–1.146, 95%CI: 0.303–1.146).[124] It is also worth noting that there are few data on the use of empirical antibiotic therapy to treat suspected SIBO or bacterial translocation and to improve IFALD. Specifically, a retrospective analysis demonstrated that the use of metronidazole during TPN was associated with a lower elevation of liver enzymes,[125] while another study documented that metronidazole use may reduce or stabilize cholestatic enzymes in adult patients receiving PN.[126] Nevertheless, the prophylactic use of antibiotics to prevent IAFLD is not recommended due to the risk of the side effects of antibiotics, the possible bacterial resistance development, and the limited data on long-term outcomes.[2]

Activation of bile acid receptors, such as FXR, leads to reduced hepatic bile salt load and has been associated with antiinflammatory effects. Because of these beneficial effects, bile acid signaling is an interesting therapeutic target for hepatic disease treatment.[127] In rat models of IFALD, the administration of FRX agonists (GW4064, INT-747) alleviated liver injury by regulating the bile acid metabolism.[128,129]

CONCLUSION

IFALD remains a major complication in adult patients requiring long-term PN, causing a wide range of manifestations. The pathophysiology of IFALD seems to be multifactorial, including nutrient-related factors and alteration of the gut–liver axis. The management requires a multidisciplinary approach, including alteration of PN preparations and surgical management to reduce or revert the progression of liver injury. Future research is essential to clarify the pathogenetic mechanisms of IFALD and the development of new therapeutic agents and procedures.

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Conflicts of interest
There are no conflicts of interest.

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