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Novel strategies to prevent total parenteral nutrition-induced gut and liver inflammation, and adverse metabolic outcomes

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Novel strategies to prevent total parenteral nutrition-induced gut and liver inflammation, and adverse metabolic outcomes

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Abbreviations

AMPK, AMP-activated protein kinase; AA, arachidonic acid; ABCG5, ATP-binding cassette sub-family G member 5; ABCG8, ATP-binding cassette sub-family G member 8; ALA, α -linolenic acid; BA, bile acids; BSEP, bile salt export pump; CCK, cholecystokinin; COX, cyclooxygenase; CYP7A1, cholesterol 7-hydroxylase; DHA, docosahexaenoic acid; DDP-4, dipeptidyl-peptidase-4; EGF, epidermal growth factor; EPA, eicosapentaenoic acid; FGF15/19, fibroblast growth factor 15 (mouse)/fibroblast growth factor 19 (human); FGFR4, fibroblast growth factor receptor 4; FXR, farnesoid X receptor; GIP, glucose-dependent insulintropic polypeptide (gastric inhibitory polypeptide); GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; GUDCA, glyoursodeoxycholic acid; IL-1 β , interleukin-1 β ; INF- γ , interferon gamma; LA, linoleic acid; LOX, lipoxygenase; LPL, lipoprotein lipase; LPS, lipopolysaccharide; LXR, liver X receptor; MLCK1, myosin light chain kinase 1; MyD88, myeloid differential primary response gene 88; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain containing 3; P450, cytochrome P450 monooxygenase; IFALD, intestinal failure-associated liver disease; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acids; SDA, stearidonic acid; TFN- α , tumor necrosis factor alpha; TGR5, Takeda G protein-coupled receptor (G protein-coupled bile acid-activated receptor); TLR4, Toll-like receptor 4; TPN, total parenteral nutrition; VLDL, very-low-density lipoproteins

Keywords

parenteral nutrition; lipid emulsion; intestinal failure-associated liver disease, n-3 fatty acids, bile acids

Abstract

Total parenteral nutrition (TPN) is a life-saving therapy administered to millions of patients. However, it is associated with significant side effects, namely liver injury, risk of infections, and metabolic derangements. In this review, we first identify the underlying causes of TPN-associated side effects, specifically gut atrophy, dysbiosis of the intestinal microbiome, leakage of the epithelial barrier with bacterial invasion and inflammation. We analyze the role of the bile acid receptors FXR and TGR5, of pleiotropic hormones and growth factors, and further scrutinize the mechanisms of insulin resistance, namely the lack of insulinotropic and insulinomimetic signaling of gut-originating incretins as well as the administration of potentially toxic phytosterols and pro-inflammatory fatty acids mainly released from soybean oil-based lipid emulsions used for TPN. Finally, we propose novel approaches in the design of next generation lipid delivery systems by modifying the physicochemical properties of lipid emulsions, the use of lipid emulsions generated from sustainable oils containing high amounts of anti-inflammatory n-3 fatty acids, beneficial adjuncts to TPN, and concomitant pharmacotherapies to mitigate TPN-associated side-effects.

1. Total parenteral nutrition, a life-saving therapy

Total parenteral nutrition (TPN) is a life-saving nutritional therapy under conditions where enteral feeding is contraindicated or insufficient. TPN is provided to millions of patients who are unable to orally ingest or digest and absorb the necessary daily amount of food (partial or total parenteral nutrition). While parenteral nutrition is in many cases transient, lasting from days to weeks, thousands of patients every year in the US alone require home-based long-term (>3 months) parenteral nutrition.^[1] In addition, in the US half a million infants, including premature and low-birth-weight infants, depend on TPN.^[2] Indications for total or partial parenteral nutrition encompass a wide range of clinical conditions such as critically ill patients (trauma, surgery, sepsis, shock), patients on home parenteral nutrition because of chronic intestinal failure, cachectic cancer patients, patients with inflammatory bowel disease (Crohn's disease, ulcerative colitis), patients with gastrointestinal obstruction, high-output enterocutaneous fistula, or short-bowel syndrome, (mostly) geriatric patients with acute or chronic debilitating diseases who cannot meet nutritional requirements, and patients with intractable nausea and vomiting (hyperemesis gravidarum). Moreover, malnutrition (calories- and/or protein-related) is a common health care issue with a high prevalence among hospitalized patients (20-50%) and is clearly linked to higher health care costs because of increased complications, longer hospital stays, and higher use of home health care services.^[3,4] In critically ill patients, supplementary parenteral nutrition to enteral nutrition aiming to satisfy the increased caloric needs under stress is also thought to decrease complication rates and associated health care costs.^[5] However, some of these indications have been challenged recently^[6] and current guidelines^[7] predominantly

emphasize the role of TPN as the last resort nutritional therapy when enteral feeding is impossible or contraindicated.

2. Complex problems associated with current TPN formulations

The problems caused by TPN are mainly due to its non-circadian, often continuous around-the-clock administration, necessary to allow the provision of sufficient daily calories, in conjunction with its artificial intravenous, as opposed to enteral, route of calorie-dense nutrient supply, which bypasses the natural metabolic gatekeepers, namely the gut and the liver.^[8] In addition, while lipid emulsions represent an essential part of TPN (10-20 vol.-% of a parenteral infusion are lipids) because of their density of calories and the provision of essential fatty acids, they have been also identified as a cause of serious TPN-associated side effects (**Table 1**).^[9,10] TPN-related complications that have been reproduced in animal models include gut atrophy,^[11-15] epithelial leakage with invasion of pathogens,^[12,16-21] dysbiosis of the gut microbiome,^[22-25] liver dysfunction,^[26-29] and finally liver injury/steatosis.^[30-35] Intestinal failure-associated liver disease (IFALD), a type of nonalcoholic steatohepatitis, previously also called TPN-associated liver disease, occurs in 60% of infants and children with TPN^[36,37] and in 15% of adults with long-term TPN.^[38] TPN also elicits profound metabolic derangements.^[31,39,40] Insulin resistance and hyperglycemia increase morbidity and mortality due to infections, cardiac decompensation, and renal and respiratory failure.^[41-43] Beside prematurity, which is of significance in newborns and infants, the following mechanisms, specifically operative in adults, are thought to be causally involved in TPN-associated adverse effects and will be discussed in detail below:

- i. Disruption of bile acid sensing and signaling from the gut to the liver in the absence of luminal contents
- ii. Disruption of insulin signaling pathways
- iii. Dysbiosis and gut epithelial barrier leakage
- iv. Altered immune responses, changes in blood coagulation, presence of environmental toxins

2.1 Disruption of bile acid sensing and signaling from the gut to the liver in the absence of luminal contents

The entrance of food into the stomach triggers a myriad of signals that initiate the process of digestion, such as production of gastrin to stimulate acid production to lower the pH in the stomach. Stimulated by luminal contents and gut bacteria (intestinal microbiome), specialized chemosensitive cells scattered throughout the intestinal epithelium produce hormones and growth factors that are acting locally in the gut, but are also transported via the portal vein to the liver (enterohepatic circulation), pancreas, and other organs (**Figure 1**). Enteroendocrine cells sense and transduce nutrient signals from lipids, proteins, and carbohydrates by activating G protein-coupled receptors and solute carrier transporters,^[44] and constitute the largest endocrine organ of the human body, producing many hormones such as gastrin (G-cells), ghrelin (P- or X-cells), somatostatin (D-cells), cholecystokinin (CCK; I-cells), glucose-dependent insulinotropic peptide (GIP; K-cells), glucagon-like peptide-1 and -2 (GLP-1 and GLP-2) and peptide YY (pYY) (L-cells). For instance, cholecystokinin (CCK) liberated from I-cells in the proximal small intestine, stimulates digestive enzyme secretion from the exocrine pancreas and enhances bile discharge from the gallbladder. In the healthy

state, the cycle of gallbladder filling and emptying dictates the flow of the bile into the intestine, establishing the enterohepatic circulation of bile acids (BA; **Figure 1**). Lack of CCK release and subsequently decreased emptying of the gallbladder leads to bile stasis and disruption of the enterohepatic circulation. Absence of enteral food intake with lack of luminal contents results in gut atrophy and epithelial leakage as early as 24 hours after TPN initiation, tissue invasion of potentially pathogenic bacteria, and IFALD.^[45] The fact that IFALD, which is characterized by cholestasis progressing to fibrosis and cirrhosis, can be prevented by the introduction of enteral nutrition or the preservation of only a small part of the daily nutrition via the enteral pathway (trophic feeding or minimal enteral feeding ~15% of the energy requirements),^[46] clearly testifies to the importance of the integrity of the gut-liver axis. In addition, the composition of lipid emulsions used in TPN, in particular the use of soybean oil-based Intralipid® rich in n-6 polyunsaturated fatty acids (PUFA), is also thought to be involved in the pathogenesis of IFALD and that liver injury could be prevented by the use of alternative lipid emulsions.^[35,47] In particular, it was postulated that phytosterols present in plant-derived oils, as opposed to fish oil, may be toxic to the liver^[48,49] and that the higher amount of antioxidants in newer generation lipid emulsions would protect the liver from oxidative damage, but this was later refuted.^[33] Newer studies point to the importance of an intact gut-liver axis in maintaining liver homeostasis.^[45,50]

BA do not just function as detergents to facilitate digestion and absorption of lipids in the small intestine, but also regulate cholesterol homeostasis and act as key metabolic signaling molecules.^[51] BA control the release of gut hormones from a diverse population of enteroendocrine cells predominantly located in the distal small intestine

and the colon and this process involves two major signaling axes contributing to the gut-liver crosstalk (**Figure 1**).^[51,52]

2.1.1. Farnesoid X receptor (FXR) signaling

Farnesoid X receptor (FXR), also called bile acid receptor, is a ligand-activated transcription factor, which is highly expressed in the terminal ileum and is activated by primary BAs, increases fibroblast growth factor 19 (FGF19, FGF15 in mice; subsequently referred to as FGF15/19) secretion into the portal circulation.^[37] FXR is also found in liver, entire intestine, kidney, adrenal glands, fat tissue, heart, and even the lungs.^[53] In hepatocytes, FGF15/19 acts via FGFR4 (in conjunction with hepatic FXR^[54]) to repress BA synthesis by reducing the expression of CYP7A1, the enzyme responsible for the rate-limiting step of BA synthesis.^[55] FGF15/19 also stimulates gallbladder filling.^[56] Hepatic FXR upregulates genes involved in the uptake (Na⁺-taurocholate cotransporter polypeptide and organic anion-transporting peptide 2/8), and export of BAs (bile acid export pumps, including multidrug resistance proteins). As such, FXR signaling controls the response of the liver during the fasting-refeeding transition.^[51] Interestingly, lipopolysaccharide from gram-negative bacteria reduces the expression of FXR,^[57] ultimately contributing to cholestasis. FXR knockout mice show hepatotoxicity, elevated plasma lipids and insulin resistance, reminiscent to TPN-associated metabolic side effects.^[58,59] In mice, dysregulation of BA homeostasis typically occurs after only a few days of infusing TPN solutions containing soybean oil-based lipid emulsion,^[60] and disruption of the enterohepatic circulation of BAs reduces FGF15/19 production. Likewise, hepatic FXR and CYP7A1 gene expression were suppressed in preterm piglets when receiving TPN, irrespective of the lipid component

provided (Intralipid®, Omegaven®, or SMOFlipid®).^[35] Interestingly, FXR gene expression in the ileum was significantly increased and the portal venous plasma concentrations of FGF19 were exclusively decrease in the group receiving Intralipid®-based TPN.^[35] Studies with tissue-specific FXR knockout mice emphasize the importance of gut as opposed to hepatic FXRs in the gut-liver crosstalk,^[61] also explaining as to why FXR agonist treatment in the presence of a short, dysfunctional or diseased bowel is unable to elicit trophic effects in the liver. Obviously, protective effects through FGF15/19 signaling in the liver depend on the healthy gut.^[50]

Beside regulation of BA homeostasis, FXR also controls glucose homeostasis by repressing hepatic gluconeogenesis and stimulating hepatic glycogen synthesis.^[62,63] Likewise, FGF15/19 is known to stimulate hepatic protein and glycogen synthesis by binding to a receptor complex including fibroblast growth factor receptor 4 (FGFR4) in hepatocytes.^[64] It is also known to suppress gluconeogenesis by reducing cAMP response element-binding protein (CREB) and FoxO1 signaling,^[65] to enhance energy expenditure,^[66] and to reduce “glucose effectiveness”, a brain-mediated insulin-independent glucose lowering mechanism causing increased lactate production.^[67] Finally, FGF15/19 also reduces hepatic lipogenesis.^[68] Oddly enough, mice with FoxO1/3/4 deficiency in hepatocytes show increased susceptibility to diet-induced hepatic lipid overload,^[69] but patients with nonalcoholic fatty liver disease, a condition similar to IFALD, show increased FoxO1 signaling.^[70]

2.1.2. G protein-coupled bile acid-activated receptor signaling

It is well known that in response to dietary carbohydrates, L-cells secrete GLP-1 and GLP-2, while K-cells secrete GIP.^[44] Secretion of glucagon-like peptides from L-cells is

regulated by neighboring somatostatin-producing D-cells^[71] as well as lipids.^[72] In the early nineties, BAs were also shown to modulate the production of pYY and proglucagon,^[73] from which both GLP-1 and GLP-2 are formed by the action of coexpressed prohormone convertase 1/3 in intestinal enteroendocrine L-cells.^[74] The bile acid-triggered proglucagon synthesis was later found to be dependent on the activation of G protein-coupled bile acid-activated receptor (GP-BAR1), also called Takeda G protein-coupled receptor (TGR5).^[52] TGR5 is mainly expressed in gut mucosal crypts but also other tissues (gallbladder, smooth muscle, neural cells, brown adipose tissue, as well as immune cells including dendritic cells and macrophages). BAs also control the expression of prohormone convertase 1/3, again via TGR5.^[75] While GLP-1 is predominantly insulinotropic (“incretin effect”, see next paragraph), the action of GLP-2 is transduced by GLP-2 receptor, expressed predominantly within the gastrointestinal tract.^[76] GLP-2 promotes expansion of the mucosal epithelium, enhances barrier function, and increases intestinal blood flow.^[76] In the piglet model, TPN causes a rapid reduction in intestinal blood flow that precedes the onset of gut atrophy.^[13] GLP-2 co-infusion increases blood flow, albeit only to the proximal small intestine^[77] and dose-dependently fosters epithelial cell survival.^[78] However, addition of GLP-2 to TPN does not fully reproduce the intestinal trophic effects observed with enteral nutrition.^[78] Epidermal growth factor (EGF) is also trophic to the intestine^[79] and both hormones are important for optimal protection against gut mucosal atrophy in TPN.^[80-82] In addition, it has been recently also discovered that TPN upregulates bone morphogenetic protein signaling, which inhibits the Wnt- β -catenin pathway essential for intestinal epithelial cell growth.^[83] Also, activation of the CELF1 (Elav-like family

member-1, an RNA binding protein acting as a regulator of alternative splicing, translation and mRNA degradation)/p53 axis has been shown to mediate sustained anti-proliferative pro-apoptotic signaling with G2 cell arrest causing villus atrophy in a TPN rat model.^[84] Interestingly, CELF1 is equally activated in fish-, soybean- and olive oil treated Caco-2 cells, but only olive oil-induced apoptosis can be fully reversed by CELF1 silencing,^[85] implying the involvement of different pro-apoptotic mechanisms in response to specific fatty acids potentially released from TPN.

2.2 Disruption of insulin signaling pathways

TPN causes insulin resistance, hyperglycemia as well as iatrogenic counter-regulatory hypoglycemia, which adversely affect clinical outcome.^[43,86,87] Metabolic dysfunction with insulin resistance results from the following three major issues, namely:

2.2.1. Loss of the physiological incretin effect

TPN exacerbates risk of hyperglycemia due to direct intravenous infusion of glucose, bypassing the gut and thus decreasing the release of the incretin hormones GLP-1 and GIP (**Figure 1**).^[88] Moreover, gut atrophy caused by TPN -often compounded by an already dysfunctional or short bowel (in humans defined as <50 cm long) is accompanied by a reduced production of incretins.^[39] GLP-1 and GIP are secretory potentiators of insulin biosynthesis and release in a glucose-dependent manner, an effect estimated to account for approximately 50-70% of the total insulin secretion in response to oral glucose administration. Consequently, they facilitate the uptake of glucose by muscle tissue and the liver, while simultaneously suppressing glucagon secretion by the pancreatic α -cells, leading to reduced endogenous glucose production from the liver (insulinotropic action).^[88,89]

2.2.2. Loss of the insulinomimetic action of gut-derived peptides

Intact GLP-1 and GIP are rapidly cleaved to their inactive metabolites GLP-1 (9-36) and GIP (3-42) by the enzyme dipeptidyl-peptidase-4 (CD26/DDP-4), which is expressed not only in the enterocyte brush border but also in the endothelial cells lining the capillaries of the lamina propria,^[90] and thus lose their potent insulinotropic action. It was recently discovered that GLP-1 is also cleaved and inactivated by DDP-4 secreted by specialized β 7-integrin-dependent gut-residing T-cells, establishing an immune-incretin axis to control the availability of insulinotropic GLP-1.^[91] GLP-1(9-36) suppresses hepatic glucose production, promotes the translocation of the glucose transporter GLUT4 in skeletal muscle, exerts cardioprotective actions, and reduces oxidative stress in vascular tissues (“insulinomimetic” action).^[92,93] Previous studies have further demonstrated anti-inflammatory and epithelial barrier enforcing effects of GLP-1(9-36) in gut intraepithelial T-cells.^[94]

2.2.3. Lipid-induced insulin resistance

Lipid emulsions are added to TPN solutions to supply essential fatty acids and to provide calorie-dense fuel for the cellular energy metabolism (9 kcal/g, i.e. double the amount of proteins and sugars ~4 kcal/g). Lipids are recommended to supply 15% up to a maximum of 30% of the total daily required calories. Previous reports have shown that both high plasma level of free fatty acids (FFA) and amino acids can acutely reduce the ability of insulin to promote glucose utilization in humans.^[95] In addition, the continuous provision of lipids leads to cellular overload of insulin-sensitive tissues with lipid intermediates (diacylglycerols, ceramides), which interfere with insulin signaling pathways and impair glucose disposal.^[96-99] Formation of reactive oxygen species in mitochondria and the

endoplasmic reticulum due to lipid overload exacerbates insulin resistance.^[100,101] It is thus no surprise that in the heart, which is specifically sensitive to reactive oxygen species and mitochondrial dysfunction due to its high energy demand, fatty acid overload causes contractile dysfunction^[102,103] and/or arrhythmia.^[104] In healthy rats, TPN containing predominately long-chain n-6 PUFA markedly increased cardiac lipoprotein lipase (LPL) activity necessary for lipid disposal and enhanced lipid deposition in hepatic Kupffer cells.^[105] Conversely, the use of a lipid emulsion with 50% medium-chain and 50% long-chain fatty acids did not results in increased cardiac LPL activity or lipid deposition in Kupffer cells.^[105] Accordingly, lipomatous hypertrophy of the cardiac interatrial septum has been reported previously after long-term TPN in adults with Intralipid® as part of their TPN regimen.^[106]

All these factors contribute to the compensatory elevated insulin levels, typically observed in TPN.^[8,31,39,40,107] However, hyperinsulinemia itself further worsens insulin resistance by serine hyper-phosphorylation^[99] and/or tyrosine de-phosphorylation^[108] of key insulin signaling players.

2.3 Dysbiosis and gut epithelial barrier leakage

In vitro studies using cell lines have revealed that cytokines, such as tumor necrosis factor-alpha (TNF- α) or interferon-gamma (INF- γ), can impair epithelial barrier function by disrupting tight junctions.^[109-111] Multiple elements of the gut epithelial barrier, a single layer of constantly renewing epithelial cells, are compromised simultaneously with up-regulation of pro-inflammatory signaling as soon as luminal contents decrease.^[17,112] Myeloid differential primary response gene 88 (MyD88) upregulation appears essential as MyD88 knockout mice subjected to TPN exhibit reduced pro-

inflammatory signaling and do not develop epithelial barrier dysfunction.^[25] In addition, the mucosal lymphoid cell populations, responsible for secretory immunoglobulin A,^[113] significantly change with TPN leading to increased production of INF- γ and a decline in the anti-inflammatory interleukin-10 (IL-10) expression.^[19] Intestinal inflammation with breakdown of cytoskeletal proteins forming tight junctions -such as occludin, junctional adhesion molecule-A, zonula occludens-1, and claudins- is ultimately responsible for the loss of epithelial barrier integrity.^[19,114,115] Changes in the microbiome composition, i.e., loss of diversity and increased abundance of enterobacteriaceae and proteobacteria combined with reduced abundance of lactobacilli,^[18,116] enhance the susceptibility to bacterial invasion by compromising mucins secreted by goblet cells^[117] and anti-microbial lysozyme and defensins.^[118] In fact, tissue invasion with translocation of bacteria to mesenteric lymph nodes is a frequent finding (~60% in the rat model).^[16] Conversely, certain bacteria enhance the expression of cytoskeletal proteins improving epithelial integrity (“beneficial microbial or luminal signaling”).^[119] Hepatic Toll-like receptor 4 (TLR4)-mediated inflammation and steatosis, ultimately also resulting in severe systemic inflammation, was early identified as a hallmark of TPN.^[120,121] It is associated with mitochondrial dysfunction^[122,123] and increased production of reactive oxygen species, and causes cell death via inflammasome activation. Accordingly, infliximab, an anti-TNF- α monoclonal antibody, is able to alleviate IFALD in mice.^[124] The assembly of the NLR family pyrin domain containing 3 (NLRP3) inflammasome, which plays a key role in early host defense and the innate and adaptive immune system,^[125] results in activation of caspase-1, which finally causes the cleavage of pro-IL-1 and pro-IL-18 to active IL-1 β and IL-18.^[125,126] NLRP3 inflammasome activation

disrupts intestinal epithelial barrier function.^[127,128] Importantly, BAs influence the gut microbiota composition by shaping the host's intestinal immunity and, in turn, alterations in the composition of the microbiota affect BA synthesis and uptake.^[129] For instance, BAs inhibit the inflammasome in macrophages by PKA-mediated ubiquitination via TGR5 activation,^[130] and increase CD95 death receptor phosphorylation, preventing CD95-mediated apoptosis in hepatocytes.^[131] However, hepatic inflammation as observed in IFALD with enhanced NF κ B signaling inhibits FXR-mediated upregulation of canalicular BA transporters in hepatocytes, while the lack of FGF15/19 greatly enhances BA production leading to cholestasis (**Figure 2**).^[132] Novel discoveries also demonstrate that not only the lack of enteral nutrition but phytosterols found in soybean oil-based lipid emulsions affect gut microbiota and thus directly impact intestinal inflammation and activate hepatic Kupffer cells, triggering IFALD.^[22] Similar observations were recently also confirmed in a piglet model.^[24] Phytosterols interfere with FXR and potentially disrupt BA homeostasis and impair the pleiotropic signaling from the gut.^[133] However, if phytosterols are combined with fish oil devoid of phytosterols, they “lose” their toxicity nearly completely, raising questions as to which degree phytosterols are indeed involved in the pathogenesis of IFALD.^[35] Irrespective of their role to affect the microbiome, phytosterols do appear to boost the inflammatory response to endotoxin in Kupffer cells.^[134] Finally, since lipophagy as part of the larger autophagy machinery is essential in removing excess cellular lipids,^[135] it is possible that inflammation-associated impaired autophagy, as described in a TPN model of critically ill rabbits,^[136] is causally involved in some TPN-associated side-effects, specifically IFALD.

2.4 Altered immune responses, changes in blood coagulation, presence of environmental toxins

A large number of studies in intensive care patients linked TPN with soybean-based lipid emulsion to higher infection and mortality rates, suggesting detrimental effects on the immune system and prompting the European Society for Parenteral and Enteral Nutrition (ESPEN) to recommend “that the use of intravenous fat emulsions based solely on a soybean oil rich in 18 carbon n-6 PUFA should be avoided due to their likely pro-inflammatory effects”.^[7] TPN-induced alterations in the gut, including changes in the microbiome, potentially activate vagal neurons with marked impact on B- and T-lymphocytes, neutrophil granulocytes, and macrophages as well as cytokine production (for review see^[137,138]). In addition, immune-modulation also occurs from the use of specific fatty acids in TPN affecting membrane properties (cell membrane fluidity, lipid rafts), increasing the production of bioactive lipid mediators, directly interfering with cellular signaling (e.g. TLR4), and activating transcription factors such as peroxisome proliferator-activated receptors (PPARs).^[139] Triglycerides containing long-chain n-6 PUFA, the precursors of arachidonic acid and many prostanoids and leukotrienes (**Figure 3**), are known to promote inflammation and cell adhesion.^[140-142] Immunosuppression was suggested from clinical studies in TPN-treated patients after bone marrow transplantation showing a lower incidence of graft-versus-host disease,^[143] which is likely caused by the dysfunction of the reticuloendothelial system and phagocytosis,^[144] and impairment of the lipopolysaccharide (LPS)-induced generation of reactive oxygen species in neutrophils.^[145] Activation of a pro-inflammatory pro-coagulant state with TPN has been also reported specifically with

soybean-based lipid emulsions bearing a high risk of pulmonary embolism in children with TPN (up to 35%).^[146] In this context it is interesting to know that soybean oil-based lipid emulsions have been shown to induce inflammation of pulmonary vessels in pigs causing pulmonary hypertension and formation of granulomas,^[147] and to deteriorate gas exchange in patients with acute respiratory distress syndrome.^[148] Conversely, the use of n-3 PUFA may increase the risk of bleeding and atrial fibrillation.^[149] Plant sterol esters (plant equivalents of cholesterol) have been also reported to reduce T-cell based immune activity in the gut of volunteers^[150] and may be causally involved in TPN-induced dysbiosis^[22,23] and IFALD.^[151] They possibly act as antagonists of BA receptors.^[49] Fish oil devoid of phytosterols appears to prevent IFALD, while this benefit is lost when stigmasterol is added.^[133] However, treating pediatric patients with fish oil emulsions completely devoid of phytosterols may still cause liver injury,^[152] suggesting that the mechanisms are more complex. In fact, a rare genetic disease, sitosterolemia, in which phytosterols accumulate in the liver, does not exhibit liver injury and cholestasis, dismissing a primary role of phytosterols in IFALD. A scientific opinion on the safety of plant sterols from the European Food and Safety Authority (EFSA) panel on food additives concluded that there is no evidence showing chronic toxicity, carcinogenicity or developmental toxicity with phytosterols or their esters.^[153] Heparin is another potentially toxic substance used in many TPN protocols. Heparin has been shown to compete with insulin for insulin receptor binding^[154] and to induce cholestasis.^[155] To avoid these complications, ethanol locks for central venous lines in patients with long-term TPN have been recommended.

Although there is growing evidence that TPN supplemented with fish oil as opposed to soybean oil has a better safety profile, and improves clinical outcomes,^[156-160] there are multiple sustainability issues surrounding fish oil sources.^[161] It is nowadays clear that fish oil cannot meet future high market demands for n-3 PUFA. Overfishing challenges species survivability, reduces species diversity, and disrupts ecosystems. Moreover, aquatic sources of n-3 PUFA pose an increasing health risk to patients because of significant accumulation of “persistent organic pollutants” (POPs) in the food chain that are considered a substantial risk to human health and are subject to the Stockholm Convention (<http://www.pops.int/TheConvention/ThePOPs/AllPOPs/tabid/2509/Default.aspx>; accessed June 30, 2019).

3. Urgent need for novel products for safe and sustainable intravenous nutrition

The above list of problems associated with current TPN clearly testifies to the urgent need for novel products and therapies. Given that many problems associated with current TPN are linked to the administered lipids, novel approaches aim at creating lipid delivery systems with different physicochemical properties and fatty acid compositions. This could be combined with pharmacological means targeting specific side effects. Regulatory bodies such as the US Food and Drug Administration (FDA) have already approved alternative lipid emulsions (**Table 1**) based on olive oil (n-9 monounsaturated fatty acids) or containing marine n-3 PUFA (SMOFlipid®, Omegaven®) Intralipid® remains the most prevalently used intravenous lipid emulsion in medicine to date.^[156] Indeed, there is insufficient scientific information on the biological actions and on potential clinical complications of newer intravenous lipid emulsions for nutritional

support, specifically the fish oil-based lipid emulsion Omegaven®. Therefore, the American Society for Parenteral and Enteral Nutrition (ASPEN) states in a recent landmark paper on urgent research priorities^[3] that *“Future research should include basic science-oriented investigations aimed at improving understanding of the science of nutrient regulation in different disease states, as well as clinical and translational research to determine how the practice of nutrition support can continue to be refined”* and further identifies *“the development of alternate products, or methods of delivery of nutrients that are safe and effective”* as one of the research topics in greatest need for immediate attention. This has been reinforced in the update research agenda 2018 stipulating that “laboratory-based studies should be continued to promote the safety of parenteral nutrition” and emphasizes that “mechanistic insights from preclinical studies will help to inform and plan future clinical studies.”^[162]

4. Strategies to prevent TPN-associated side-effects

4.1 Targeting the physicochemical properties of lipid emulsions and designing next generation parenteral lipid delivery vehicles

Although parenteral lipid emulsions are isosmotic with pH of ~7.5, TPN formulations are hypertonic and acidic (pH~6) and are therefore administered through a larger central vein. The average droplet diameter of lipid emulsions is 250-350 nm to simulate chylomicrons (<500 nm). In the circulation, the artificial lipid droplets of the emulsions rapidly acquire apoprotein C and E and are degraded by tightly regulated lipoprotein-lipase-mediated hydrolysis at the endothelium.^[163,164] N-6 triglyceride rich particles tend to depend on proteoglycan-mediated cell anchoring, while n-3 triglyceride rich particles depend more on LDL receptors,^[165] and droplet size is an important determinant of lipoprotein lipase-

mediated hydrolysis.^[166] Remnants are removed from the circulation by the liver and finally degraded by hepatic lipases.

Nanotechnology has opened new avenues in the design of lipid emulsions with unique pharmacokinetic and pharmacodynamic features.^[167,168] While we appreciate the physicochemical definition and distinction between microemulsions (thermodynamically stable) versus nanoemulsions (thermodynamically unstable) and the terminology controversies around the two technical terms, in practice a definite distinction between microemulsion versus nanoemulsion is often impossible.^[169] Hence, we will use the term nanoemulsion subsequently in this review. Although some experimental studies on lipid nanoemulsions with smaller droplets (diameter <200 nm; termed artificial lipoprotein-like particles) have been published previously,^[170] demonstrating technical feasibility, none of these studies thoroughly explored their biological actions, because these emulsions are primarily used as drug-delivery carriers. In fact, they show markedly distinct pharmacokinetics and pharmacodynamics, namely a slower cellular uptake and a reduced hepatic uptake: 80% of a single injection of artificial lipoprotein-like particles with a droplet size of ~50 nm can be recovered after a single *in situ* pass through the rat liver as opposed to only 30% with the standard Intralipid® with a droplet size of ~250 nm.^[170] Accordingly, hepatic accumulation is markedly lower, potentially causing less inflammation and metabolic derangements.^[170,171] It appears that tissue uptake and distribution are distinct from conventional emulsions for parenteral nutrition and also less dependent on lipoprotein receptors and lipoprotein lipase.^[172-174] Moreover, intracellular partitioning between fatty acid oxidation *versus* lipid storage, i.e., the biological fate of supplied lipids, may depend on the droplet size.^[175] For example, the majority of fatty acids utilized by the heart are

derived from chylomicrons, with only a minor portion originating from very-low-density lipoproteins (VLDL).^[176,177] Fatty acids released from chylomicrons preferentially undergo β -oxidation, whereas fatty acids released from VLDL are equally distributed between β -oxidation and lipid storage.^[176,177] Interestingly, addition of apoprotein E to lipid emulsions was also shown to decrease accumulation of lipids in tissues.^[178] Differences in uptake and metabolic fate may lead to reduced metabolic, cardiac, hepatic, and intestinal derangements by reducing lipotoxicity of the administered lipids. Nanoemulsions with smaller droplets may also display easier tissue penetration in the presence of inflammation.^[170] Despite these promising observations, there remain some caveats, as the smaller droplet size may require a higher amount of emulsifier, which interferes with lipoprotein lipase activity. Beside egg yolk, which mainly contains phosphatidylcholine, the standard emulsifier found in commercial parenteral lipid emulsions, it should be determined whether small doses of alternative emulsifiers, such as cholesterol, sphingomyelins, or polyethylene glycol, could be safely used as “co-emulsifiers”. For example, addition of polyethylene glycol has the distinctive advantage of reducing lipid uptake by the mononuclear phagocyte system.^[179] In any case, the lowest possible amount of emulsifiers to achieve stable conditions of lipid emulsions should be used and these next generation lipid vehicles should meet all the requirements as outlined in Chapter 729 of the United States Pharmacopeia.^[180]

4.2 The use of sustainable oils in parenteral lipid delivery vehicles

Besides representing a dense source of energy, the desirable properties of lipid emulsions for TPN use are (a) provision of essential fatty acids in order to avoid deficiencies (a major concern in pediatric patients) (b) provision of “equilibrated”

amounts of saturated, monounsaturated, and polyunsaturated fatty acids, and (c) supply of fatty acids with beneficial biological activities from sustainable potentially less risky oils, specifically devoid of toxins accumulated in the food chain. Although the term “equilibrated amount” is not clearly defined, dietary requirements for essential fatty acids are known and recommendations on the required daily intake of n-6 PUFA and n-3 PUFA do exist. The predominant n-3 PUFA in the diet are the 18-carbon n-3 α -linolenic acid (ALA with 3 double bonds), the 20-carbon n-3 eicosapentaenoic acid (EPA with 5 double bonds), and the 22-carbon n-3 docosahexaenoic acid (DHA with 6 double bonds). Fish is a uniquely rich source of EPA and DHA, but other natural sources of long n-3 fatty acids exist such as marine algae, and krill. The European Food Safety Authority (EFSA) recommends intakes of EPA and DHA of 250 mg/day (1 to 2 fatty fish meals per week) in all age groups with additional 100-200 mg of DHA during pregnancy and lactation (<https://efsa.onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2017.e15121>; accessed July 2019).

The infusion of lipid emulsions with the release of n-6 PUFA results in dose-dependent acute lipid-induced insulin resistance^[98] and alterations in insulin signaling.^[96,97,99] However, changes in insulin sensitivity upon infusion of fish oil-based lipid emulsions are less pronounced or even absent.^[181,182] This may be related to the fact that clearance of fish oil-base lipid emulsions is less dependent on lipoprotein lipase activity and shows preferred peripheral tissue uptake.^[164,175] Of note, in those studies, the authors added triDHA (3 DHA molecules bound to the glycerol moiety) to a standard lipid emulsion and showed accelerated blood clearance, an observation, which may be solely due to the use of the artificial fish oil analog triDHA.^[164,175] In any case, lipoprotein

lipase activity is inhibited by EPA and DHA implying that the slower release of fatty acids impairs their cellular uptake.^[183] Additional mechanisms underlying n-3 PUFA-induced insulin-sensitizing actions have been reported, including inhibition of serine/threonine protein phosphatase activity, a short-term effect,^[184-186] changes in membrane fluidity via the so-called Lands cycle^[187] and lipid remodeling^[188] with altered insulin binding, a medium-term effect,^[189] and changes in gene expression through repression of transcription factors,^[190,191] a long-term effect. Most clinical data show that the use of fish oil-based lipid emulsions can improve clinical outcomes, specifically in the critically ill patients.^[141,156,192] This is consistent with numerous experimental and translational studies showing that n-3 PUFA counteract the negative effects of saturated fatty acids on insulin sensitivity, inflammation, and immunosuppression.^[181,182,193-196] A recent study also showed strong anti-inflammatory effects of n-3 endocannabinoids derived from DHA and EPA acting through endogenous cannabinoid receptors.^[197] In addition, n-3 PUFA possess inflammation-resolving “pleiotropic” and “anti-sarcopenic” anabolic activities as they compete with arachidonic acid metabolism for the formation of resolvins, protectins, and maresins (**Figure 3**).^[198-201] Finally, n-3 PUFA beneficially affect gut microbiota and help preserve epithelial barrier function.^[22,24] In contrast, n-9 monounsaturated fatty acids found in olive oil appear neutral with regard to inflammation and immune response,^[139,142,202] while the n-6 PUFA linoleic acid, although essential, supports arachidonic acid metabolism and hence is pro-inflammatory, atherogenic, prothrombotic, and immunosuppressive because of potential dysfunction of the reticuloendothelial system.^[141] Hence the use of lipid emulsions in TPN that release DHA and EPA appears to be beneficial and some evidence suggests that a ratio of n-

6:n-3 PUFA of 1 (or even lower) is most favorable.^[203] Medium-chain fatty acids (C8-12), as present in SMOFlipid®, are a valuable supplement to lipid emulsions with long n-3 PUFA as they are readily oxidized in a carnitine palmitoyl-transferase-independent manner, potentially further reducing liver injury and cardiac toxicity.^[196] Because of their protein-sparing effects, medium-chain fatty acids also improve nitrogen balance.^[141] Unfortunately, they are sourced from coconut oil, again raising questions with regard to sustainability (monoculture farming, overuse of fertilizers).

Given that the demand for fish as a source of n-3 PUFA will soon outpace supply,^[161] it is tempting to turn to oilseed crops, including genetically engineered species, producing large amounts of n-3 PUFA. In this regard, oil from flaxseed (*linum usitatissimum*) contains >50% n-3 PUFA in the form of ALA (**Table 2**).^[204] ALA is only partially converted by desaturase and elongase to DHA in mammals (5-25%) (**Figure 4**). Although ALA insignificantly affects tissue EPA and DHA contents, but some evidence suggests beneficial anti-inflammatory effects of ALA similar to DHA in humans.^[204] Interestingly, the conversion of ALA to DHA is dependent on the formulation of the flaxseed-based emulsion, at least for the enteral application.^[205,206] Although flaxseed oil contains phytosterols (but with a distinct profile compared with soybean oil and at lower concentrations),^[207] it also contains additional potentially beneficial compounds such as polyphenols and antioxidant squalenes, which correlate with favorable biological actions.^[208,209] Similarly to DHA, stearidonic acid (SDA), an n-3 PUFA found in hemp (a strain of *cannabis sativa*), inhibits LPS-induced production of NO via inactivation of NF- κ B and mitogen-activated protein kinase signaling in macrophages.^[210] In addition, γ -linolenic acid, although it is an n-6 PUFA, has distinct

anti-inflammatory actions (paradox of γ -linolenic acid).^[211] In the past, the use of structured triglycerides for lipid emulsions with random esterification of long- and medium-chain fatty acids to the glycerol moiety, has been also proposed to reduce TPN-induced side-effects,^[212] but because of the significant costs associated with their fabrication and the limited biological benefits, this approach has not been a real breakthrough. Collectively, generation of novel lipid emulsions with promising plant oils appears feasible and allows for the production of more sustainable lipid emulsions.

4.3 Pharmacotherapies to mitigate TPN-associated side-effects

The limitation of maximum glucose (14 mg/kg/min) and fat (0.1 g/kg/min) infusion rates and the use of TPN cycles with 2-6 hours off can help to reduce TPN-associated side-effects.^[39] Recent studies have shown that the use of closed-loop insulin delivery systems in patients receiving TPN can help to significantly ameliorate metabolic dysregulation.^[213] However, this appears, as elegant it may be, only a short-term fix for a much more complex problem. Hence, the use of concomitant exogenous drugs and adjuncts to TPN formulations has been suggested to counteract adverse effects, specifically metabolic derangements, hepatic inflammation, and infections and sepsis. It is noteworthy that a reduction in side effects can be efficaciously achieved by administering some of the daily calories through the enteral pathway as a supplement to TPN (minimal enteral feeding), but this is only possible when partial enteral nutrition is allowed and no bowel dehiscence present. In fact, Lidder et al. showed that combining parenteral with enteral nutrition in patients undergoing esophagectomy requiring postoperative TPN is beneficial with regard to glucose metabolism and incretin GIP secretion.^[214]

4.3.1 Targeting the gut-liver axis and the intestinal microbiome

To prevent gut atrophy, oral EGF with topical effects on the gut epithelium was successful in increasing jejunal weight and enhancing digestive enzymes such as intestinal alkaline phosphatase in a piglet model.^[215] An elegant way to stimulate the gut epithelium, while simultaneously fostering the growth of “good” gut bacteria, involves the administration of genetically-engineered EGF-expressing *Lactobacillus lactis*.^[216] This could be used in combination with novel GLP-2 analogues with low systemic clearance such as apraglutide.^[217] Based on the key role of BA signaling in the gut-liver axis, the use of BAs or analogs such as the hydrophilic ursodeoxycholic acid, as supplements to TPN, could be of potential interest.^[218] Ursodeoxycholic acid is a naturally occurring BA (~5% of the total human BA pool) and is used in the treatment of primary biliary cirrhosis and cholestatic hepatitis. Clinical studies show that this medication can prevent or significantly delay liver-associated complications, but optimal timing, dosing, and duration of treatment is largely unknown.^[219,220] Multiple agonists of BA receptors such as obeticholic acid have been already developed aiming at treating nonalcoholic steatohepatitis, which has many features of IFALD.^[218] Understanding the BA toxicity structure-activity relationship may help to create more efficacious less toxic drugs of this class in the future.^[221] Interestingly, Yangonin, a naturally occurring FXR agonist from the tropical crop Kava, was shown to attenuate lipid accumulation and to decrease gluconeogenesis in a mouse model of nonalcoholic fatty liver disease.^[222] Activation of other nuclear receptors than BA receptors such as androstane, pregnane X and liver X receptors appear to have less beneficial effects in IFALD despite their documented protective hepatic actions.^[223,224] Recently, it has been shown that the actions of the

anti-diabetic drug metformin are mediated by mechanisms related to the microbiome and BA signaling.^[225] According to these studies, metformin reduces the abundance of *bacteroides fragilis* in the gut, which produces the secondary BA glyoursodeoxycholic acid (GUDCA) via its bile salt hydrolase. Since GUDCA is an FXR antagonist, which reduces the formation of FGF15/19 in the gut and thus increases hepatic BA production, metformin may ultimately improve hepatic insulin sensitivity in TPN-receiving patients.^[64,226] Changing the microbiome with antibiotics such as metronidazole,^[227] rifampicin (which reduces CYP7A1 expression but unfortunately also enhances lipogenesis), or supplements such as anthocyanins might successfully mitigate TPN-associated side-effects in patients with long-term TPN. Anthocyanins are plant-based flavonoid-type polyphenols found in berries and colored vegetables with anti-inflammatory, anti-oxidant,^[228] and gut microbiota-modifying properties.^[229] Recent studies show beneficial effects with regard to the metabolism^[230,231] and liver protection against fibrosis.^[232] Similar to fatty acids and primary BAs, which are metabolized by gut microbiota to short-chain fatty acids and secondary BAs, respectively, anthocyanins are metabolized to biologically active drugs such as isovanillic acid 3-O-sulfate, which is a well-known insulin sensitizer.^[233] Supplementation of TPN with short-chain fatty acids was shown to increase GLP-2 expression and to prevent gut atrophy.^[234] Recent research has also highlighted the importance of intestinal alkaline phosphatase, which is nearly lost in TPN due to gut atrophy, in maintaining intestinal microbial balance.^[235] In fact, mice with knockout of the intestinal alkaline phosphatase show accelerated fat absorption and, when exposed to high-fat diet, develop obesity and insulin resistance because of changes in their intestinal microbiome.^[236] Importantly, oral supplementation

of intestinal alkaline phosphatase prevents adverse metabolic effects.^[237] Since the intestinal mucus layer and barrier function is impaired in TPN, the use of mucus protectors may be an alternate option to prevent the threat of infection and sepsis. In this regard, genetically engineered bacteria secreting protease inhibitors such as SPINK,^[238,239] alpha1-antitrypsin,^[240] or glycosidase inhibitors^[241] may be promising. An exciting approach of preventing or treating epithelial leakage has been recently reported by Graham and collaborators.^[242] The investigators developed a novel drug named divertin, which prevents the trafficking of myosin light chain kinase 1 (MLCK1) to the actomyosin ring of tight junctions in epithelial cells. Since MLCK1 is recruited to tight junctions upon TNF- α stimulation and weakening tight junctions by phosphorylation of the actomyosin ring, diversion (but notably not inhibition, which would cause major side-effects) of MLCK1 prevents epithelial leakage and protects from flux of food antigens and microbiota or components thereof such as endotoxin into the sterile bowel wall. Daily injections of divertin in mouse models of inflammatory bowel disease drastically reduced inflammation in the bowel and decreased mortality. It is tempting to speculate that addition of divertin to TPN formulations might also reduce the risk of infection and sepsis. Because of its pleiotropic effects, FGF15/19 administration has been also suggested as a potential candidate to treat hepatic and metabolic side effects, but concerns related to its tumorigenic actions mediated through FGFR4 have been a major barrier for its use until recently, when FGF15/19 variants without carcinogenic potential have been created.^[243]

4.3.2. Targeting hepatic and whole body metabolism

Pharmacological approaches, which have been initially suggested for nonalcoholic fatty liver disease may also work in mitigating IFALD such as PPAR γ and PPAR α/δ agonists.^[244] Thyroid hormone mimetics such as glucagon-T3 (in this drug the glucagon only serves as peptidase-resistant vehicle safeguarding T3 to the liver) specifically target the liver and improve glucose tolerance and reduce the body fat via FGF21.^[245] Synergistic combinations of AMP-activated protein kinase (AMPK) activators have been tested in the treatment of nonalcoholic fatty liver disease and may be helpful in IFALD.^[246] AMPK inhibits lipogenesis in the liver by restricting SREBP1c, increasing hepatic fatty acid oxidation via phosphorylation of acetyl-CoA carboxylase, and further by upregulation of autophagy.^[247] An innovative approach to combat multiple TPN-associated side effects including IFALD with a single drug may be the co-administration of designer monomeric peptides combining the effects of two or three metabolic hormones such as GLP-1, glucagon, oxyntomodulin (which is co-secreted with GLP-1 from L-cells in the small intestine and acts as agonist of GLP-1 and glucagon receptors), GIP, and peptide YY (also co-secreted with GLP-1 from L-cells binding to neuropeptide Y2 and Y5 receptors) during TPN.^[248] In fact, a multi-agonist drug acting at three key metabolic hormone receptors including GLP-1, GIP, and glucagon receptors, successfully reduced body weight, improved glycemic control and reversed hepatic steatosis in rodent models of high-fat feeding.^[249,250] Therefore, the concomitant use of DPP4 inhibitors, GLP-1 agonists, or smart combinations of metabolic hormones have a great potential to offset multiple side-effects, but no clinical studies have been conducted so far.^[88] Recently, an important hepatocyte-macrophage acetoacetate shuttle has been discovered, which protects the liver against fibrosis.^[251] Acetoacetate,

a ketone body, produced in hepatocytes is shuttled to macrophages, where it is processed via succinyl-CoA oxoacid transferase (which is not expressed in the liver) to acetyl-CoA. The generated carbon bodies are subsequently used to form glycoproteins/proteoglycans, which inhibit hepatic stellate cells to produce extracellular matrix. Most interestingly, increasing nutritional supply of acetoacetate elicits the same anti-fibrotic actions in rodent models of dietary hepatic fibrosis implying that acetoacetate as supplement to TPN formulations may provide anti-fibrotic protection in the liver. Inhibition of $\text{TNF}\alpha$ signaling by infliximab has been also suggested previously, but this seems unsafe in the presence of potential bacterial invasion, specifically in critically ill patients.^[124] However, the surprisingly strong anti-inflammatory actions of digoxin, a cardiac glycoside, were recently reported in a mouse model of steatohepatitis, notably at lower doses than required for inotropic therapy in the heart.^[252] According to these studies, digoxin binds in the liver to pyruvate kinase M2 attenuating the interaction between PKM2 and histones and thus downregulating HIF-1 α transcription and inflammation. This observation suggests that sterile inflammation due to hypoxia may play a role in nonalcoholic steatohepatitis and possibly also in IFALD. With few exceptions, lipid emulsions used in current TPN take advantage of different types of vitamin E analogs as antioxidants, mainly γ -tocopherol in soybean oil and α -tocopherol in other lipid emulsions such as fish oil.^[253] A large clinical study in patients with nonalcoholic fatty liver disease showed marked improvement in steatosis and inflammation, when treated with vitamin E.^[254] It has been suggested that vitamin E may also activate hepatoprotective “xenobiotic” nuclear receptors such as pregnane X and androstane receptors.^[255] Disappointingly, supplementation of vitamin E to TPN,

was unable to successfully prevent IFALD.^[33] However, the combination of vitamin E with other synergistic anti-oxidant drugs could help to reduce metabolic, hepatic, and microbiome-related problems. Hydroxytyrosol is a simple small, water and fat soluble, phenolic compound found in olive oil. It has been shown to effectively protect low density lipoproteins against oxidation.^[256] Recent research with hydroxytyrosol also shows that it reduces inflammation in the liver by potentiating formation of resolvins from n-3 fatty acids.^[257] Interestingly, hydroxytyrosol also prevents the depletion of PUFA in the liver under conditions of oxidative stress by upregulation of desaturase activity,^[258] reduces gut and liver inflammation by restoring intestinal barrier integrity in a rat model of high-fat feeding,^[259] and improves obesity and insulin resistance by modulating gut microbiota in high fat diet-fed mice.^[260] A clinical study in pediatric patients with nonalcoholic fatty liver caused by diverse hepatic disorders and treated with hydroxytyrosol over only four months showed reduced insulin resistance, oxidative stress markers, triglyceride levels, and hepatic steatosis.^[261] Finally, novel insulin sensitizers such as remogliflozin (a selective inhibitor of the renal sodium-dependent glucose transporter with additional anti-oxidant effects) and the dual PPAR α / δ agonist elafibranor, an experimental medication that showed promising results in nonalcoholic fatty liver disease, may also prove to be beneficial in IFALD.^[262]

5. Conclusions

Current TPN is associated with complex potentially life-threatening side effects. The use of fish oil-based lipid emulsions in TPN is promising but unsustainable in the future and harbors significant environmental and human health risks. In recent years, many of the underlying mechanisms of TPN-associated side effects have been unraveled, showing

the fascinating intricate interplay between nutrition, microbiota, gut, and whole-body metabolism. This opens the possibility of exploring novel approaches to mitigate TPN-associated side effects and making TPN safer for patients and the environment.

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Conflict of Interest

The authors declare no conflict of interest.

Table 1. Common lipid emulsions used for total parenteral nutrition

	Intralipid® 20%	Omegaven® 10%	SMOFlipid® 20%	Clinoleic® 20%	Lipofundin® 20%
Soybean oil	20 g (100%)	0 g	6 g (30%)	4 g (20%)	10 g (50%)
Olive oil	0 g	0 g	5 g (25%)	16 g (80%)	0 g
Coconut oil	0 g	0 g	6 g (30%)	0 g	10 g (50%)
Fish oil	0 g	10 g (100%)	3 g (15%)	0 g	0 g
PUFA g%	60%	58%	29%	20%	30%
MUFA g%	24%	26%	30%	63%	12%
SFA g%	16%	16%	41%	17%	58%
n-6 FA g%	53%	~6-7%	20%	19%	26%
n-3 FA g%	7.8%	52%	8%	2%	4%
n-6 to n-3 ratio	7:1	1:8	~2.5:1	9:1	~7:1
Vitamin E (µg per mL)	165*	230 ⁺	205 ⁺	57 ⁺	222 ⁺

Numbers indicate grams per 100 mL. Emulsions are 20% with the exception of Omegaven®, which is only available as 10% emulsion. Quantities are given per 100 mL. All emulsions use egg yolk lecithin as emulsifier and glycerol to adjust for osmolarity. Intralipid® is manufactured by both Fresenius Kabi and by Baxter, SMOFlipid®, and Omegaven® are manufactured by Fresenius-Kabi; Lipofundin® by B. Braun; ClinOleic® by Baxter. SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids. *mainly γ -tocopherol, ⁺mainly α -tocopherol.

Table 2. Natural oils and their fatty acid composition

Fatty acid	Notation	SO	XO	CO	OO	FO*
Caproic acid	C6:0	0	0	0.5	0	0
Caprylic acid	C8:0	0	0	8	0	0
Capric acid	C10:0	0	0	6	0	0
Lauric acid	C12:0	0	0	48	0	0
Myristic acid	C14:0	0	0	18	0	7.7
Palmitic acid	C16:0	11	5.5	8.5	13	25.3
Palmitoleic acid	C16:1n7	0	0	0	0.5	6.7
Stearic acid	C18:0	4	3.5	2.5	1	3.1
Oleic acid	C18:1n9	23	17	7	70	14.5
Linoleic acid	C18:2n6	54	15	1.5	15	2.7
α -Linolenic acid	C18:3n3	7.5	58	0	0.5	1.3
γ -Linolenic acid	C18:3n6	0	0	0	0	3.2
Stearidonic acid	C18:4n3	0	0	0	0	0
Arachidonic acid	C20:4n6	0.4	1	0	0	0.6
Eicosapentaenoic acid	C20:5n3	0	0	0	0	12.5
Docosapentaenoic acid	C22:5n3	0	0	0	0	2.1
Docosahexaenoic acid	C22:6n3	0	0	0	0	8.9
Others		0	0	0	0	11.4

Numbers represent percent of total fatty acids. SO, soybean oil; XO, flaxseed oil; CO, coconut oil; OO, olive oil; FO, fish oil (*from menhaden fish).

Figure 1 Gut-liver axis. Primary bile acids (BAs) are produced by the liver and are released into the duodenum via bile duct. This process is stimulated by enteral nutrition. In the small intestine, BAs are deconjugated and dehydroxylated into secondary BAs by intestinal microbiota. Approximately 95% of secondary BAs are re-absorbed in the terminal ileum and transported back to the liver through the portal vein (enterohepatic circulation), whereas the remaining 5% enter the colon. BAs that are released after meals suppress cholecystokinin (CCK) production in the duodenum, thus blocking further gallbladder contractions and reducing the stimulation of the exocrine pancreas to produce and secrete digestive enzymes. In the distal ileum, resident enterocytes that express the farnesoid X receptor (FXR), which is activated by bile acids, release fibroblast growth factor 15 (fibroblast growth factor 19 in humans; FGF15/19) into the portal vein. FGF15/19 activates fibroblast growth factor receptor 4 (FGFR4) in the liver and, in conjunction with BA-activated hepatic FXR, downregulates BA synthesis through inhibition of cholesterol 7 α -hydroxylase (CYP7A1), while upregulating transporters of BA uptake and secretion. FGF15/19 and FXR signaling also improve lipid and glucose homeostasis. Takeda G protein-coupled receptor 5 (TGR5) is another BA receptor expressed in gut mucosal crypts that induces the release of glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide-2 (GLP-2) from enteroendocrine cells. GLP-2 promotes local mucosa proliferation and

strengthens the epithelial barrier, while the incretins GLP-1 and GIP directly stimulate insulin secretion in the pancreas. GLP-1 is a primary incretin hormone released from the small intestine in response to nutrient ingestion. The majority of circulating “bioactive GLP-1” is in the form of GLP-1(7-36)amide, which stimulates glucose-dependent insulin secretion, while it inhibits glucagon release. Its half-life is extremely short (<2 min) and it is further degraded to GLP-1(9-36)amide, which does not affect insulin secretion, but has pleiotropic effects on different organs including the liver. This figure was created using Servier Medical Art templates (available at <https://smart.servier.com/>), which are licensed under a Creative Commons Attribution 3.0 License.

Figure 2 Dysbiosis of the intestinal microbiome, epithelial leakage, and TPN-induced liver injury. The shift in microbial diversity in the gut (“microbiome”) to gram-negative proteobacteria promotes production of inflammatory cytokines such as tumor necrosis factor alpha ($\text{TNF}\alpha$). $\text{TNF}\alpha$ signaling leads to a breakdown of claudins, occludins and other cytoskeletal proteins acting as cell-to-cell adhesion molecules. Leakage of the epithelial barrier facilitates the absorption of endotoxin (LPS) and the invasion of bacteria. Gut-derived flushed-in LPS (via the mesenteric veins) activates Kupffer cells in the liver through Toll-like receptor 4 (TLR4) and causes a release of cytokines such as interleukin-1 β (IL-1 β) inhibiting farnesoid X receptor (FXR) signaling via $\text{NF}\kappa\text{B}$ activation. Reduced bile acid secretion because of reduced activity of bile salt export pump (BSEP)

and multidrug resistance-associated protein 2 (MRP2; also called canalicular multispecific organic anion transporter 1) ultimately causes cholestasis. NF κ B also inhibits liver X receptors and expression of hepatic sterol transporters (ABCG5, ABCG8), which causes accumulation of certain phytosterols specifically present in soybean oil-based lipid emulsions. Phytosterols can further aggravate inhibition of FXR signaling and enhance NF κ B signaling in Kupffer cells. This figure was created using Servier Medical Art templates (available at <https://smart.servier.com/>), which are licensed under a Creative Commons Attribution 3.0 License.

Figure 3 Synthesis of lipid mediators. Bioactive lipid mediators of inflammation are generated from polyunsaturated fatty acids by action of three enzyme families, namely cyclooxygenases (COX), lipoxygenases (LOX), and cytochrome P450 mono-oxygenases (P450). COX produces prostanoids, i.e., prostaglandins, prostacyclins, and thromboxanes, from either arachidonic acid (AA) (2-series prostanoids) or eicosapentaenoic acid (EPA) (3-series prostanoids). 5-LOX produces leukotrienes from either AA (4-series leukotrienes) or EPA (5-series leukotrienes). LOX-mediated oxygenation of EPA and docosahexaenoic acid (DHA) produces a series of specialized mediators of the resolution phase of inflammation (resolvins, protectins, and maresins). Lipoxins (or lipoxygenase interaction products) such as lipoxin A4 are also pro-resolving mediators synthesized via two sequential oxygenation reactions of AA catalyzed by 15-LOX and

5-LOX. Protectins (not shown) are generated from EPA by 15-LOX followed by enzymatic epoxidation and hydrolysis.

Figure 4 Metabolism of polyunsaturated fatty acids. Humans can synthesize longer n-6 and n-3 fatty acids from the essential fatty acids linoleic acid (LA) and α -linolenic acid (ALA), respectively, through a series of desaturation and elongation reactions. LA and ALA compete for the same desaturase and elongase enzymes - namely Δ -6 desaturase, Δ -5 desaturase, and the enzyme elongation-of-very-long-chain-fatty-acids protein-2 (ELOVL2) - in the synthesis of longer polyunsaturated fatty acids, such as arachidonic acid (AA) and eicosapentaenoic acid (EPA). ALA is considered an essential n-3 fatty acid because it cannot be synthesized by humans. Its conversion to EPA and docosahexaenoic acid (DHA) is limited, suggesting that EPA and DHA are “conditionally essential nutrients”.

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FIGURE 1

FIGURE 2

FIGURE 3

FIGURE 4