Total parenteral nutrition (TPN), a lifesaving therapy, involves providing nutrition by bypassing the gut. Unfortunately it is associated with significant complications including gut atrophy and parenteral nutrition associated liver disease (PNALD). PNALD includes steatosis, cholestasis, disrupted glucose metabolism, disrupted lipid metabolism, cirrhosis, and liver failure. The etiopathogenesis remains poorly defined; however, an altered enterohepatic circulation, disrupting nuclear receptor signaling, is emerging as a promising mechanism. Rodent models and our piglet TPN model have shown that, during regular feeding, bile acids activate farnesoid X receptor (FXR) in the gut and enhance fibroblast growth factor 19 (FGF19) level. FGF19 regulates bile acid, lipid, and glucose metabolism. We noted reduced FGF19 with TPN use and substantial improvement in FGF19, bile acid, lipid, and glucose metabolism. We noted reduced FGF19 with TPN use and substantial improvement in FGF19, bile acid, lipid, and glucose metabolism. We noted reduced FGF19 with TPN use and substantial improvement in FGF19, bile acid, lipid, and glucose metabolism. Metabolic profiles with the FXR agonist chenodeoxycholic acid (CDCA). Additionally, CDCA caused gut growth and enhanced expression of glucagon like peptides (GLPs). GLPs regulate gut trophic effects, insulin, glucose homeostasis, and hepatic steatosis. GLP secretion is regulated by the CDCA activated receptor TGR5. This leads to an important conclusion that, in addition to a disrupted FXR-FGF19 axis, a disrupted TGR5-GLP axis may contribute to TPN related pathologies. Thus modulators of FXR-FGF19 and the TGR5-GLP axis could help bring forward novel treatment strategies.

1. Introduction

Parenteral nutrition has been in use since the 1960s [1, 2]. Total parenteral nutrition (TPN) involves providing all of patient's nutritional needs intravenously and is lifesaving in clinical settings in which adequate enteral based delivery of such nutrition is not possible. It has been one of the most promising modalities of nutrition in neonates, older pediatric patients, and adults with lost or impaired gut function. TPN infusion therapy has grown enormously over the last few decades. There are tens of thousands of patients worldwide permanently dependent on parenteral nutrition (PN) for survival [3]. In addition, there are several fold higher numbers of patients requiring PN for varying duration during hospital stay or home care. Unfortunately, it is also associated with important complications and significant morbidity and mortality, including the well-recognized parenteral nutrition associated liver disease (PNALD) which includes steatosis, cholestasis, disrupted glucose metabolism, disrupted lipid metabolism, cirrhosis, development of portal hypertension, and ultimately liver failure [4, 5]. The mechanisms of such injury remain poorly defined.

Despite multiple theories being advanced, the etiology and pathophysiology of PNALD remain elusive. Among the various possible mechanisms, a lack of enteral feeding resulting in gut atrophy and the disruption of enterohepatic circulation has been proposed as a contributor to PNALD [6, 7].
Using a piglet animal TPN model, we have documented TPN-induced liver and gut pathologies. We have also described the role of an altered enterohepatic circulation and disrupted signaling of bile acids contributing to such injury. This shall be the focus of this review.

1.1. Lack of Enteral Feeding. It is commonly believed that once cholestasis sets in, its reversal occurs only when a patient is receiving all or a major portion of the calories enterally. In fact, enteral nutrition helps to protect against the development of PNALD and cholestasis as noted in several studies [8–10]. In TPN model systems we have shown significantly elevated bilirubin and PNALD in animals on TPN versus those getting enteral feeds [8]. As reported in the literature, we have also noted significant hepatocellular dysfunction, elevated hepatic triglycerides, and steatosis with TPN use [11–13].

Numerous studies including results from our model have shown that TPN use also induces gut mucosal atrophy, which has been attributed possibly to the absence of trophic signals released in response to luminal nutrients, during regular feeding [14, 15]. However, the physiologic nature and relative importance of these trophic signals have yet to be established [16]. We noted significant gut atrophy within 2 weeks of TPN infusion [8]. However, recent evidence suggests that gut atrophy might be occurring much sooner. In a study using an animal TPN model, mucosal atrophy was found to occur as early as 24 hours in the jejunum as evident by a reduction in villous height and protein synthesis [17]. Given this evidence, it is believed that the underlying adaptation to TPN might occur much earlier, due to the high metabolic rate and rapid turnover of intestinal epithelial cells.

Thus it is possible that a lack of enteral feeding, which is known to disrupt normal enterohepatic circulation, may be a contributor to TPN-associated pathologies as documented in our previously published data [8].

Normal enterohepatic circulation depends on normal synthesis, conjugation, secretion, and recirculation of bile acids. This brings to attention an important question whether there is a homeostatic equilibrium of certain signaling molecules between the gut and the liver, a disruption of which leads to PNALD. This has taken special importance after the establishment of the existence of the nuclear receptor farnesoid X receptor (FXR) [18]. Several studies have shown that bile acids are physiological ligands for FXR. FXR is abundant in liver and gut tissue [19]. It is also well established that activation of FXR is noted with the primary bile acid chenodeoxycholic acid (CDCA), a potent FXR agonist. Bile acids have also been known to have a trophic effect on gut growth and integrity [20, 21]. We have shown significant gut growth and amelioration of atrophy with enteral bile acid treatment [8].

1.2. Bile Acid Mediated FXR Induction of Fibroblast Growth Factor 19 (FGF19)

1.2.1. FGF19 Production. During normal enterohepatic circulation, bile acid absorption in the ileum is associated with activation of FXR which has been shown to exert several important regulatory effects on lipid and carbohydrate metabolism.

In fact, recent insights from cell culture and animal models show that enteral bile acids robustly activate FXR in intestinal epithelial cells [8, 22, 23]. Such activation stimulates production of a growth factor, fibroblast growth factor 15 (FGF15) and its human orthologue fibroblast growth factor 19 (FGF19) which is delivered via the portal circulation to the liver [24]. We have assayed FGF19 in TPN versus enteral fed animals and found robust upregulation of FGF19 upon enteral bile acid treatment, with significant reduction upon TPN infusion [8].

1.2.2. Hepatic Bile Acids and Cholesterol 7 Alpha Hydroxylase (CYP7A1). In the liver, CYP7A1, which is a rate-limiting step for hepatic bile acid synthesis, is suppressed via the short heterodimer partner- (SHP-) liver receptor homologue 1 (LRH1) cascade [25, 26] and by mechanisms independent of SHP gene induction [27, 28]. Rodent studies and recently our work in a TPN piglet model have indicated that intestinal FGF19 may function as a secretory signal to the liver that contributes to intestinal FXR-dependent repression of CYP7A1 [29]. In order to determine whether fasting serum levels of FGF19 were changed with bile acid regulated enterohepatic circulation, Lundásen et al. assayed FGF19 levels in serum samples from subjects treated with the bile acid resin cholestyramine (which sequesters BAs preventing their absorption) and subjects treated with CDCA. Bile acid synthesis was determined by the serum levels of 7-alpha-hydroxy-4-cholestene-3-one (C4), a marker for CYP7A1 enzymatic activity. Treatment with cholestyramine led to an 18-fold increase in serum C4 and a reduction in FGF19 levels by 87%. In the CDCA treatment group, FGF19 levels increased by 250% while serum C4 levels decreased by 26% [30].

Importantly, FGF19 is expressed in the small intestine [31] but not in the liver [32, 33]. In a study by Kim et al., tissue-specific roles of FXR were examined. Tissue-specific FXR null mouse models for liver (FxrL) and intestine (FxrIE) were used. Bile acid pool size was increased with FXR deficiency in either liver FxrL or intestine FxrIE. Treatment of these mice with GW4064 a FXR-selective agonist significantly repressed CYP7A1 in FxrL mice but not in FxrIE mice. This demonstrated that the repression of CYP7A1 was mediated primarily by FXR activation in the intestine and not in the liver [34].

1.2.3. Glucose and Lipid Metabolism. Fu et al. have shown that, in obese mice resulting from leptin deficiency or genetic ablation of brown adipose tissue, treatment with human fibroblast growth factor 19 prevented or reversed diabetes and improved glycemic control. They also showed that there was a reduction in triglyceride levels in the FGF19 treated mice. Liver expression of leptin receptor and expression of acetyl coenzyme A carboxylase were acutely decreased with FGF19 [35]. We have also previously shown that TPN infusion, in addition to decreasing FGF19 levels, results in insulin resistance. Additionally hypertriglyceridemia was noted with
TPN infusion [8]. FGF receptor 4 (FGFR4) which is abundant in the liver is a receptor for FGF19 and FGF15 [36]. Mice lacking FGFR4 have an increased bile acid pool [36, 37]. An increased white adipose tissue mass, glucose intolerance, insulin resistance, hyperlipidemia, and hypercholesterolemia were seen by Huang et al. in FGFR4 deficient mice that were fed a normal diet, indicating an important role of FGFR4 in glucose and lipid metabolic regulation [38].

Ursodeoxycholic acid (UDCA) has been used in patients with TPN cholestasis with inconsistent results. Heubi et al. in their study in 22 infants on TPN, who received oral tauroursodeoxycholic acid (TUDCA) against controls, documented no difference in peak serum conjugated bilirubin, alanine aminotransferase, alkaline phosphatase, or bile acid levels [39]. Reihner et al. in their study on 61 human subjects noted significant suppression of CYP7A1 on treatment with CDCA at 15 mg/kg/day. No change in CYP7A1 levels was noted in the UDCA treated patients [40]. It is particularly important to know that the commonly used bile acids UDCA and TUDCA have minimal activity for FXR. Park et al. showed that while CDCA was a strong agonist for FXR, no activation of FXR was seen with UDCA [41]. Similar results were reported by Makishima et al. in 1999 [20]. We have also shown significant improvement in PNALD with CDCA infusion [8]. This pathway for the FXR-FGF19 axis during TPN infusion is schematically depicted in Figure 1.

The above seem to be some of the direct effects of an altered enterohepatic circulation leading to altered nuclear receptor signaling. We believe that the disrupted enterohepatic circulation also leads to several other nuclear receptor dependent pathways to become abnormal which contribute to TPN pathologies.

1.3. Bacterial Overgrowth, Endotoxin, and Inflammation. Intestinal hypomotility as a consequence of starvation promotes bacterial overgrowth in the small intestine [42]. On morphometric analysis we have shown severe villous blunting and significant reduction in the villous/crypt ratios with TPN infusion. This was most prominent in the proximal small bowel. In fact grossly the small bowel was thin and friable in TPN versus enteral feeding [8]. Such atrophy has been reported in other studies and it is possible that the atrophic gut contributes to increased permeability [16, 17].

Bacterial permeation across the gut wall increases with TPN use, likely worsened by bacterial overgrowth. This results in endotoxin associated downregulation of bile acid transport [43]. Neonates with short-bowel syndrome are particularly susceptible to both bacterial translocation and parenteral nutrition induced hepatic injury and thus occurrence of small-bowel bacterial overgrowth is concerning [44]. Lichtman et al. created small-bowel bacterial overgrowth in a rat model using jejunal self-filling blind loops. The animals developed weight loss, hepatomegaly, and hepatic inflammation as early as 4 weeks after the creation of the self-filling bowel loops. Subsequently they reported evidence of biliary tract injury in these rats with decreased bile flow rates, dilatation of bile ducts, and beaded appearance of the bile ducts on cholangiogram [45].

Multiple investigators have reported a decrease in inflammation induced liver injury in rats after antibiotic initiation of oral tetracycline and/or metronidazole, which indirectly suggests a role of bacteria in the development or exacerbation of PNALD [46]. Whiting et al. illustrated the role of endotoxin and tumor necrosis factor (TNF) in sepsis mediated cholestasis [47]. Other inflammatory or sepsis-related conditions like inflammatory bowel disease have been shown to contribute to the development of cholestasis [48, 49]. Both clinical and animal studies have demonstrated the role of cytokines in the development of PNALD. In rat studies, Zheng et al. found significantly higher levels of TNF and interleukin-6 (IL-6) in rats that received parenteral nutrition (PN) than in a control group receiving normal chow plus saline infusion. The PN group also had significantly higher levels of endotoxin in their portal blood [50]. Elevated cytokine levels were postulated to occur in response to bacterial translocation. Though treatment directed against cytokines helps in decreasing cholestasis, given the above evidence we believe that further studies are needed to definitively establish the role of these mediators in the development of PNALD. In one study, treatment with anti-TNF antibody resulted in improvement in a patient with PNALD [51].

1.4. Role of Nuclear Receptors in Bacterial Growth and Responses. Tumor necrosis factor and interleukin 1β (IL-1β), which are proinflammatory cytokines, have been shown to downregulate transcription of bile acid transporter, sodium-taurocholate cotransporting polypeptide (NTCP), via inhibition of the nuclear retinoic acid and retinoid X receptor heterodimer (RXR:RAR) in rats [52]. A downregulation of hepatic bile acid transporters, bile salt export pump (BSEP) and multidrug resistance protein 2 (MRP2), was noted by Hojo et al. after intravenous administration of lipopolysaccharide [53]. Studies in mice using intraperitoneal lipopolysaccharide administration showed reduced expression of the mRNAs of bile acid transporters, including NTCP and BSEP [54]. FXR has been shown to induce genes involved in gut protection and inhibit bacterial overgrowth and mucosal injury in ileum by Inagaki et al. Mice lacking FXR were shown to have increased ileal levels of bacteria and a compromised epithelial barrier [55]. In addition, FXR regulates endothelial nitric oxide synthase (eNOS), carbonic anhydrase 12 (CAR12), and angiogenin (ANG1) involved in gut inflammation, bacterial growth inhibition, and mucosal injury. Mice lacking FXR have compromised gut permeability on fluorescein isothiocyanate- (FITC-) conjugated dextran assay [56]. We have noted significant improvement in gut morphology with bile acid infusion in TPN infused animals [8]. Since bile acids are physiological ligands for FXR, there appears to be a central role for FXR in protecting the small intestine from bacterial invasion. It was also suggested that FXR agonists may prevent epithelial deterioration and bacterial translocation in patients with impaired bile flow. Our recent studies have shown a striking and robust gut growth with CDCA in a TPN piglet model [8]. Glucagon-like peptides (GLPs) which are thought to regulate gut trophic effects (GLP-2), insulin, and glucose metabolism (GLP-1)
FGF19 binds to FGFR4

CYP7A1: rate limiting step of bile acid synthesis is downregulated, resulting in decreased bile acid synthesis

CYP7A1

FGF19

FGFR4

Liver

Bile acids

Gut

Improves lipid profile and glycemic control

Figure 1: Schematic representation. (1) Bile acids (BA) secreted into bile. (2) BA reach terminal ileum. (3) BA cause secretion of FGF19 upon FXR stimulation. (4) FGF19 travels through the portal circulation to liver, binding to its receptor FGFR4. (5) Hepatic effects include suppression of CYP7A1, improvement in lipid profile, and glycemic control. FGFR4: fibroblast growth factor receptor 4; CYP7A1: cholesterol 7 alpha hydroxylase; FXR: farnesoid X receptor; FGF19: fibroblast growth factor 19.

were upregulated with CDCA in our TPN animal model [8]. GLP-1 has also been shown to modulate hepatic steatosis. As the GLPs are modulated via the CDCA activated G-protein coupled receptor TGR5, we postulate that at least partial improvement in PNALD could result from a direct effect of CDCA on TGR5 activation [16].

1.5. Role of Lipids in PNALD. There has been recent interest in fish oil based fat emulsions to improve TPN related pathologies. Though outside the purview of this review, we shall briefly discuss such an approach. Intralipid (Fresenius-Kabi) is the standard lipid emulsion for intravenous use in the US for TPN nutrition. Intralipid, which is produced from soybean oil, contains a high ratio (7:1) of n-6 to n-3 polyunsaturated fatty acids (PUFA). Phytosterols present in soy derived lipid emulsions are known FXR antagonists [57]. Recently Omegaven which has a very low ratio (1:8) of n-6 to n-3 PUFAs and is derived from fish oil has shown promise in several clinical studies. It has been shown that n-3 fatty acid solutions decrease de novo lipogenesis and prevent or attenuate PN-associated steatosis and cholestasis [58, 59]. Two n-3 fatty acids present in Omegaven are docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Peroxisome proliferator-activated receptor (PPAR) and liver X receptor (LXR) are nuclear receptors involved in bile and fat metabolism, which are known to be modulated by DHA [60]. Additionally, lipogenesis is inhibited by DHA and EPA via inhibition of the lipogenesis transcription factor, sterol regulatory element binding protein-(SREBP-)1c [61–63]. Bile salt transporters like BSEP are modulated via FXR and LXR which in turn are under regulatory control by n-3 PUFA. It is thus predicted that n-3 PUFA rich fat emulsions may alter the course of PNALD [64–66].

2. Conclusion

We conclude from rodent studies and our recent results from a TPN model that an altered enterohepatic circulation during TPN infusion contributes to TPN pathologies. This is the result of an alteration of the FXR-FGF19 axis and likely the TGR5-GLP axis. CDCA which is a physiological ligand for FXR exerts beneficial effects as noted in our TPN animal model. Such improvement is through activation of FGF19 upon FXR stimulation. Additionally, there is increased GLP secretion with activation of the CDCA activated G protein-coupled receptor TGR5. New literature is presenting very promising data on the role of bile acids and their regulation of hepatic steatosis, lipid, and glucose metabolism. In fact both FXR agonist and TGR5 agonists are being used in clinical studies for hepatic disorders. It is quite intuitive that further research evaluating such agonists in clinical human studies may bring a paradigm change in our approach to treating TPN related pathologies.
Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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