Total parenteral nutrition-induced liver dysfunction: evidence and pathogenesis

Xiao-Gang Hui, Yutaka Hayashi

Tianjin, China and Sendai, Japan

Background: **Total parenteral nutrition (TPN) is known to be life-saving in patients with intestinal failure. But long-term TPN-related complications especially liver dysfunction have been the focus of studies. In this article, we address the evidence of TPN-induced liver lesions and the pathogenesis of these lesions.**

Data sources: **The articles about the relationship between TPN and liver function were retrieved from PubMed database.**

Results: **Varied injuries to the liver are induced clinically and experimentally by progressive deterioration after a longer period of TPN infusion. The mechanisms of cholestasis and fibrosis in pathological changes include alteration of trace elements in hepatocytes, metabolic disturbance of fatty acid, calorie overload, lithocholate effect, sepsis, etc. The administration route of TPN is excluded from the pathogenesis of liver disease, and light infusion should be avoided.**

Conclusions: **TPN may lead to liver dysfunction, but the causes are multifactorial. The authentic factor is unknown although progresses have been made in this field. Since conspicuous lesions are confined in the mesenchyma, further studies should concentrate on the relationship between Ito cells and TPN administration. The significant step toward the gene expression profiling of TPN-supplied liver is to elucidate the real etiologies.**

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Key words: **total parenteral nutrition; liver dysfunction; pathogenesis**

Author Affiliations: Department of Pediatric Surgery, Tianjin Children's Hospital, China (Hui XG); Department of Pediatric Surgery, Tohoku University School of Medicine, 1-1 Seiryomachi, Aobaku, Sendai, 980-8574, Japan (Hayashi Y)

Corresponding Author: Xiao-Gang Hui, MD, Department of Pediatric Surgery, Tianjin Children's Hospital, China (the present address: Department of Pediatric Surgery of Tohoku University Affiliated Hospital in Sendai, Japan; Email: barberahuizhai@yahoo.com.cn).

Introduction

In the late 1960s, total parenteral nutrition (TPN) was life-saving for children with chronic bowel obstruction, fistulae, loss of mucosal body surfaces, short bowel syndrome (SBS), and other clinical problems that precluded enteral diet by mouth or tube feeding for a long period of time. TPN as an essential fluid to meet nutritional needs and to avoid progressive starvation-induced malnutrition changed the outcome of patients from dying.[1] Since then, TPN has been an indispensable treatment in clinical practice and a panacea for infants and children who are unable to eat or absorb enteral nutrition.[1-4] As a result, the prognosis for patients with SBS has changed markedly, and the management of infants with congenital gastrointestinal anomalies and gut failure has improved significantly.[5,6] With the superiority of TPN administration in their mind, doctors have recognized the doctrine "a lager volume of intake, a better treatment for condition" until its safety and complications are investigated, especially in patients with SBS who are dependent on a longer duration of TPN support, and have progressive liver dysfunction, even end-stage liver fibrosis.

TPN-associated liver dysfunction

Loff et al[7] analyzed clinical, biochemical and histological data of 10 infants with TPN-induced liver dysfunction, who had been given TPN for at least 8 weeks. They were diagnosed as having necrotizing enterocolitis, gastroschisis, and intrauterine volvulus. Biopsy specimens were taken from each infant at different periods of TPN administration for histological examination of fibrosis, proliferative and inflammatory changes in five portal tracts (Pt) and for evaluation of degenerative changes in hepatocytes. Inflammation was determined by counting inflammatory cells infiltrating the Pt and classifying the cells as neutrophils, eosinophils and monocytes. Proliferative changes were judged by counting bile duct per Pt, and fibrosis was classified into mild proliferation limited to the Pt, moderate fibrosis with enlargement of the Pt, and severe fibrosis with bridging of portal areas. Degenerative changes

were differentiated into fatty changes and hydropic degeneration. Biochemically, the levels of bilirubin and aminotransferase increased intermittently and peaked after a minimum of 5 weeks. After 1 and 3 months, TPN induced slight periportal fibrosis, bile duct proliferation, and infiltration. Pronounced intracellular and canalicular cholestasis was observed in addition to extramedullary erythropoiesis and hydropic degeneration. A biopsy after 18 months showed alterations in the intracellular histoarchitecture, mild canalicular cholestasis, and hydropic degeneration. Biopsy specimen taken after 24 months revealed a precirrhotic liver with severe cholestasis and fibrosis with porto-portal bridging and single-cell necrosis.

In an experimental study, 31 rabbits were divided into three groups: 11 were given continuous TPN for 4 weeks, 9 received 20% reduced TPN and had free access to laboratory chow, and 11 enterally-fed animals as controls underwent the same surgical procedure except TPN. The formula of TPN and the indicators to be investigated were identical. In the 3 groups, mild to moderate periportal inflammation and single-cell necrosis occurred to some extent. Cholestasis was not observed in any group. In the rabbits that received infusions of TPN and partial parenteral nutrition (PPN), there was a marked increase in fibrosis and bile duct proliferation between 7 and 28 days shown by biopsy. Severe hydropic degeneration was shown in 90% of animals by the first biopsy after 7 days of TPN administration (Table). An increased level of bilirubin was observed after 4 weeks in the TPN group. Decreased levels of alkaline phosphatase and albumin and a slightly increased level of aminotransferases were noted in all groups. The different biochemical parameters of the 3 groups were not statistically significant. In conclusion, this study revealed that liver damage was caused by TPN solution itself in infants and rabbits. Mok[8] and others successfully produced animal models of TPN-associated liver complications. It has been accepted that TPN can lead to progressive liver dysfunction.

Possible mechanisms of TPN-induced liver dysfunction

Alteration of some trace elements in hepatocytes

Since copper is a cofactor for multiple liver enzymes, it is possible to hypothesize the possible role of copper in liver homeostasis in patients on TPN. In other functions, copper serves as a cofactor of antioxidant and free radical, detoxifying enzymes such as superoxide dismutase.[9] A depletion in liver copper concentration may cause a decrease in the activity of enzyme, making hepatocytes more susceptible to oxidative stress and damage. In addition, the lack of copper in hepatocytes of patients with severe liver damage may also be a surrogate marker for a decrease or absence of such trace elements as zinc in patients on TPN. Thus the concentration of zinc in the liver measured by atomic absorption spectrometry is significantly decreased after 10-12 days of TPN administration, which is in parallel with the liver copper concentration in patients supplied with zinc and copper.[10] Zinc is a cofactor of the enzyme known as tissue matrix metalloproteinase (TMMP), which degrades collagen, laminin, enzymatic activity of TMMP secondary to zinc depletion, leading to the accumulation of collagen and extracellular matrix (ECM) in the liver and finally the development of hepatic fibrosis and cirrhosis.[11]

TPN-induced hepatic steatosis and susceptible apoptosis of hepatocytes

In pathological changes of the liver induced by TPN, hepatic steatosis appears to be the earliest and frequent alteration. Two studies[12,13] found that triglyceride accumulation in the liver may occur within a few days after TPN administration in adults, particularly in children. In TPN-fed newborn piglets,[14] hepatic steatosis occurred 1 week after administration of

Table. Histological scoring of liver biopsies[7]

Group	Time (*n*)	Inflammation	Necrotic foci	Bile-duct proliferation	Portal fibrosis	Hydropic degeneration
G0	t1 (11)	1.2	0.8	1.2	1.3	0.0
G0	t2 (11)	1.2	0.9	1.6	1.7	0.1
G0	t3 (4)	1.3	0.8	1.5	1.7	0.2
G1	t1 (11)	0.9	0.7	1.0	1.2	2.5
G1	t2 (11)	1.3	1.2	2.2	2.5	2.2
G1	t3 (4)	1.3	0.8	2.2	2.4	2.5
G2	t1 (9)	1.2	0.3	1.2	1.3	2.2
G2	t2 (6)	1.5	0.2	1.5	1.3	2.1
G2	t3 (4)	1.5	0.0	1.8	2.0	2.0

Histological grading: 0: absent, 1: mild, 2: moderate, 3: severe; G0: control group, G1: TPN group, G2: PPN group; t1: first liver biopsy on day 7, t2: second liver biopsy on day 21, t3: third liver biopsy on day 28.

TPN. Thus the affected lipid metabolism such as increased mobilization of depot fat, increased synthesis, impaired transport, and decreased oxidation of fatty acids synergistically resulted in vesicular steatosis of the liver.[15] To assess the effect of steatosis and low viability of hepatocytes in piglets on TPN, markers of apoptosis were investigated in liver tissues. DNA fragmentation and activation of caspase-3 and -7 were seen exclusively in livers of the TPN piglets. Caspase-3 and -7 are recognized as the key executioners of apoptosis and both are partially or totally responsible for the proteolytic cleavage of many key proteins such as nuclear enzyme poly ADP ribose polymerase (PARP).[16] Experimentally, association of steatosis with apoptosis was also confirmed by increased lipid peroxidation and apoptosis of hepatocytes after TPN administration.[17] There are three major pathways, including activation of death receptors (Fas ligand, TNF-α), mitochondrial damage, and stress of the endoplasmic reticulum (ER) that culminate in activation of effector caspases, destruction of chromatin, and subsequent death by apoptosis.[18] Increased release of cytochrome C from mitochondria and cleavage of caspase-9 were observed in livers of TPN piglets compared with enteral nutrition (EN) pigs. Caspase-9 mediates apoptotic signals in response to mitochondrial damage and activation of caspase-9 requires cytochrome C.[19] The Bcl-2 family proteins mediate the major mitochondrial-associated apoptotic-signaling pathway. In this family, Bcl-2 is an antiapoptotic member and Bax is one of the proapoptotic members.[20] Proapoptotic proteins of the Bcl-2 family act on mitochondria and facilitate the release of cytochrome C.[21] In this study, downregulation of Bcl-2 and overexpression of Bax took place in TPN livers compared with EN ones. In addition, apoptosis is an active process that requires ATP for its execution and ATP level is a determinant marker of cell apoptosis.[22] In this animal model the adenosine triphosphate (ATP) concentration in livers of TPN piglets was lower than that in EN piglets. Recent studies suggested that TPN could induce apoptosis through the Fas pathway. Fas, a transmembrane receptor protein of the TNF receptor family, contains a death domain that signals via the apoptotic pathway. Caspase-8 is one of the initiator caspases associated with apoptosis involving death receptors. Increased levels of Fas expression and activation of caspase-8 in TPN liver tissues[14] indicated that TPN may cause hepatic apoptosis via both the mitochondrial and death receptor pathways. The death program may be initiated at the cell surface with activation of Fas or TNFR1 (usually involving in receptor trimerization) by their respective ligands, Fas ligand and TNF-α, or may result from a primary disturbance of mitochondrial function. In a recent study,[23] the evidence that apoptotic bodies are phagocytosed by stellate cells has suggested the existence of apoptosis in TPN-induced liver dysfunction.

Pathological changes in hepatocytes caused by TPN-associated sepsis and bacterial translocation

In many studies on TPN-induced hepatic dysfunction, inflammatory cell infiltration was regarded as an essential factor in the multifactorial pathogenesis. The impairment of host defence mechanism by TPN solution has been recognized as an important factor in the development of TPN-associated infection. Several studies have revealed an association between TPN and impairment of immune function in both animals and humans.[24-28]

In animal experiments or clinical investigations, liver biopsy specimens harvested after long-term TPN administration showed inflammatory infiltration of different degree at early stage. TPN induced or aggravated sepsis was demonstrated by empirical or clinical studies.[29] TPN-induced hyperglycemia was thought to contribute to dysfunction of neutrophils.[30] Glucose concentrations above 220 mg/dl have been shown to glycosylated immunoglobulins, causing a significant reduction of opsonic activity, which adversely affects immunity. In addition, the mucous membrane of the digestive tract is an important barrier to systemic invasion of bacteria into the blood stream and body tissues. However, bacteria that normally reside within the intestinal tract are able to invade the barrier and associated mesenteric lymphnodes under certain conditions, in a process of "bacterial translocation".[31] The factors facilitating this process include abnormal proliferation of bacteria, attenuation of host immunity, and physical insult to the mucous membrane barrier of the intestinal tract.[32,33] Studying TPN-induced impairment of local immunity of the digestive tract,[34-36] investigators compared the rats on standard TPN and those on free feeding, and found that TPN treatment caused atrophy of intestinal mucosa, a decreased number of Peyer's patches, and a reduction of S-IgA in bile and portal venous blood in addition to hypotrophy and degeneration of the mucous membrane of the digestive tract and a decrease in the number of S-IgA producing plasma cells of the small intestine. The atrophy of Peyer's patches caused a decrease in the number of T-helper and IL-2 producing cells, leading to a suppression of systemic immunity. Besides, the total count of bacteria was significantly higher in the TPN group than in the control group. Translocated bacteria served as pathogens intruding into the liver through the portal vein or bile duct to induce inflammatory changes

or other inflammation-related liver injuries via release of cytokines or their endotoxins. The pro-inflammatory cytokine or tumor necrosis factor (TNF) plays a key role in inflammation, proliferation and programmed cell death of hepatocytes. TNF binding to TNF receptor 1 (TNF-R1) leads to the recruitment of TNF-R associated death domain (TRADD), TNF-R associated factor 2 (TRAF2), and receptor interacting protein 1 (R1P1), thus forming complex I.[37] Signaling from the complex I leads to nuclear factor-κB (NF-κB) activation via activation of the inhibitor of κB kinase (IkK) complex. The IkKβ catalytic subunit of the IkK complex phosphorylates the NF-κB-bound IkBα, leading to its ubiquitination and subsequent proteasomal degradation. This makes NF-κB translocate to the nucleus, where the transcription of genes is induced with an NF-κB consensus site in their promoter region. In addition, signaling from the complex I activates the p38 and c-Jun activating (JNK) mitogen-activated protein (MAP) kinase.[38] Recruitment of Fas-associated death domain (FADD) and procaspase-8 results in the formation of the cytosolic complex II, where caspase-8 is activated. Caspase-8 initiates the mitochondrial pathway by cleaving Bid to tBid, which induces mitochondrial permeabilization that results in the release of cytochrome C. Thus an amplification loop results in full-blown caspase activity and subsequent apoptosis.

Effects of oxygen-derived free radical induced lipid peroxidation on hepatic tissues

Oxygen-derived free radicals are highly reactive short-lived chemical species with an unpaired electron. They are produced normally as a result of a number of physiological processes. In the mitochodrial electron transport chain, oxygen is reduced to water via a series of free radical intermediates.[39] Oxidative stress occurs when there is an imbalance between free radical production and antioxidant activity.[40] The double bonds of polyunsaturated fatty acids are particularly vulnerable to oxygen-derived free radical attack, resulting in the process of lipid peroxidation.[41] TPN may result in increased free radical activity by providing (1) substrates (polyunsatured fatty acids), (2) initiators for free radical reactions (carbon centered radicals derived from fatty acids), and (3) catalysts (transition metal ions) for free radical production. These reactive oxygen species (ROSs) can initiate lipid peroxidation by interacting mostly with cellular membrane of hepatocytes having the highest content of polyunsaturated fatty acids in their membranes.[42] The release of ROSs by inflammatory cells and the onset of lipid peroxidation contribute to perpetuation of liver necrosis.[43-45] Previous studies suggested a possible association between lipid peroxidation and liver fibrosis, involving chronic exposure to ethanol,[46] carbon tetrachloride,[47] or iron overload.[48]

Moreover, the concentration of 4-hydroxynonenal (HNE) is able to strongly stimulate the synthesis of procollagen type I by either cultured human[49] or rat liver fat storing cells (FSCs).[50] A similar but less pronounced profibrogenic effect of malondialdehyde (MDA) has been described on rat liver FSC[51] (MDA formed from the breakdown of lipid peroxides and HNE are both sensitive and specific for monitoring oxidative damage). FSCs are recognized as the main source of collagen and other ECM proteins in fibrotic livers.[52] Some study found that lipid peroxidation in the bile duct ligation rat model may stimulate collagen synthesis by proliferation of FSCs.[53] Although the role of lipid peroxidation in TPN-induced liver damage has not been elucidated, the relationship between oxygen-derived free radical induced lipid peroxidation and pathological alterations of the liver may be possible.

Other interpretations for the mechanisms

Bhatia et al[53] noticed that TPN solution is continually exposed to light and that hepatic dysfunction is the most common metabolic aberration associated with TPN. To explore whether light exposure to nutrient mixtures has effect on hepatobiliary responses, they conducted studies to compare the effects of TPN that had been exposed to light (+L) or protected from light (-L) on hepatobiliary function of rats. The results showed that +L rats lost more weight and had lower bile flow, higher taurocholate output in bile, higher biliary osmolarity, and higher inorganic phosphate in bile. Hepatic histology demonstrated scattered foci of necrosis in all +L rats and only one of eight -L rats. These data demonstrated that protection of TPN solutions from light minimizes TPN-associated alterations in hepatobiliary function and histology. They also observed that histological changes in the +L rats were contrary to TPN-induced histological changes reported previously, suggesting a different mechanism.

Moss et al[54] investigated whether TPN administration route is involved in the progressive cholestasis of prepubescent rabbits. No significant structural and functional changes took place in the liver whether TPN was given intravenously or enterally.

To elucidate the mechanism of liver fibrosis caused by hyperalimentation, a typical cell known as Ito cell, has been studied. Ito cell is one of the perisinusoidal-constituent cells that play multiple roles in liver pathophysiology. The function of the cell is to expand from a fat-storing site to a center of extracellular matrix metabolism and mediator production in the liver. The

cell can be detected in the perisinusoidal area of the normal livers of human and mammals.[55-58] Ito cell is confirmed primarily to be responsible for the production of liver fibrogenesis in different animal models including extrahepatic bile duct ligation in broiler chickens[59] and congestive liver in rats.[60] The activation, proliferation and transformation of myofibroblastic features of Ito cell are considered to be critical factors involving liver fibrogenesis. Although this mechanism in other animal model with liver injuries has not been duplicated in TPN-induced liver lesion, this investigation would become a hot topic. Since macroarray analysis has been employed to examine the unknown etiologies for some diseases such as biliary atresia,[61] it would be applicable to this unsolved problem.

In conclusion, for patients with SBS or other conditions involved in gut failure, parenteral nutrition support is very important during the whole period of therapy including transplantation. However, total parenteral nutrition-associated liver dysfunction requires for cessation of TPN and restoration of early enteral feeding. The solution to this dilemma seems to become a compulsive duty and a breakthrough in the treatment of these patients. The present multifactorial viewpoint appears to make this problem more complicated, which requires elucidation of the predominant mechanism in subsequent studies.

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