Impact Of Total Parenteral Nutrition On Liver Function In Long-Term Patients

Ahmad Abdullah Alshamrani[1] , Doaa Omar Asraf[2] , Khalid Abdullah AlHarbi[3] , Areej Omar Basunaid[4] , Abdullah Mohammed Alshehri[5] , Abdulrahman YaanAllah Alfaeq[6] , Naif Suliman Almahyawi[7] , Mohammed ali alshamrani[8] , Lujainah Sami Basubrain[9] , Fawaz Salih Alzahrani[10] , Helal Ahmed Alomar[11] , Razan Khalid Rambo[12]

[1]Pharmacist I King abdulaziz Medical city in Jeddah.
[2]Super Visor Pharmacy Services King abdulaziz Medical city in Jeddah.
[3]Pharmacy supervisor King Abdulaziz Medical City- Jeddah
[4]Pharmacist King Abdulaziz Medical City- Jeddah.
[5]Pharmacist Li King Abdulaziz Medical City- Jeddah.
[6]Pharmacist II King abdulaziz Medical city in Jeddah.
[7]Pharmacy technician National guard hospital.
[8]Pharmacy technician III King abdulaziz Medical city in Jeddah.
[9]Pharmacist I King Abdulaziz Medical City - Specialized Poly Clinic - Jeddah.
[10]Pharmacy technician III King Abdulaziz Medical City, National Guard.
[11]Pharmacy technician III King Abdulaziz Medical City, National Guard.
[12]Pharmacist, King Abdulaziz medical city

Abstract

In the second half of the last century, total parenteral nutrition (TPN) achieved a major change in the management of potentially reversible, life-threatening malnutrition. It allowed patients either to regain adequate feeding for short or eventually longer recovery from multiple nonfunctioning organ systems or throughout long-lasting disease or other malabsorption, with the expectation that disorderly function would give way to a new balance of body functions and morphology without any need for organ replacement or to be held in good nutrition and metabolism status when they were in danger of long-lasting fasting during either acute illness without need for hospitalization or towards chronicity of otherwise highly treatable morbidities after recovery from life-threatening malnourishment. Therefore, this was the decade indexing the ethics of involuntary research trials, incidents secondary to

massive clinical use of illicit drugs, and transplant immunosuppression without rigorous careful dosing.

In one of the large-series studies, 31% of the chronic renal insufficiencies were mainly caused in using more TPN (0.5 g of protein/kg ibw/day alone; for 14 extra g of protein/d only about five-fifths extra intravenous amino acids were given, two in i.v. fat), but we are still lucky not to have heard of more series, a farley more incidences of potentially avoidable disease, substantial physical handicap, and usually demise. Norms count too: 8% to 10% of healthy energy metabolism/activity scale. The most comprehensive series of children uncared for but for TPN describe only occasional liver incidents, not otherwise preventable difficulties, when the child was too small for (partial) food intake.

1. Introduction

Nutritional support is an essential aspect of management in many patients with gastrointestinal disease. Enteral nutrition is usually employed and is well tolerated by many patients, but parenteral nutrition can be required when enteral nutrition is not practicable. Clinically, serious complications, such as liver disease, may be associated with parenteral nutrition. There are a number of different types of manufactured parenteral nutrition, including ones which contain the three main groups of nutrients in different combinations. However, it is not known whether there is a difference in the development of these serious complications, such as liver disease, between individuals provided with these different types of manufactured parenteral nutrition. This study therefore aims to observe and record the liver function of patients, stable on PN up to 20 years, and to see whether there are any differences exist between those patients on a high intake of manufactured PN and those on a lower intake of manufactured PN with more food.

The use of total parenteral nutrition (PN) is an established interventional method for the nutritional support of malnourished patients. The provision of a partially or fully synthetic manufactured solution (MS), compared with a solution with high food content, in the long-term provision of PN may have a detrimental effect on liver function. This retrospective cohort study aims to examine if there is a relationship between the long-term exposure to a high intake of manufactured parenteral nutrition (PN) and the abnormalities seen in liver function. Evaluated liver function tests include alkaline phosphatase, albumin, bilirubin, gamma-glutamyl transferase, alanine transaminase, prothrombin time, aspartate aminotransferase, and ammonia.

1.1. Background and Rationale

Parenteral nutrition is the administration of nutrients, including carbohydrates, amino acids, essential fatty acids, electrolytes, vitamins, minerals, and trace elements, intravenously. It is also called TPN - Total Parenteral Nutrition. There is a lot of work on analyzing the effect of parenteral nutrition on the liver, as it is a risk factor for alterations in many long-term patients. The age of TPN candidates tends to increase, and with age, the incidence of liver disease and surgery on the bowel also increases. In the past, parenteral nutrition caused a lot of liver-related complications among infants, but this occurs rarely today. However, the underlying mechanisms involved in the development of cholestasis are more complex in adults, involving a whole variety of factors and interactions between bile and lipid metabolism, glucose homeostasis, microsomal metabolic activity, and antioxidant defense, to mention only a few.

Because of the continuous infusion of nutrients, portal venous flow progressively ceases, and intrahepatic vasoconstriction occurs. The preferential utilization of lactate, glutamine, and ketones also suppresses gluconeogenesis. Thereafter, the excessive amount of calories and substrate occupy the liver's glycogen storage range. The decrease in liver flow and the disturbance of glucose metabolism play an important role in inducing liver injury. In studies, some researchers suggest that the high calorie content of parenteral nutrition can cause acute liver failure within 14 to 25

days. This kind of injury is dose-independent and not related to calorie intake. On the other hand, hepatic steatosis caused by a high calorie load can progress slowly to steatohepatitis and hepatic cirrhosis.

1.2. Research Aims and Objectives

The study's primary aim was to determine the effect of total parenteral nutrition on liver function, and in particular, whether it can produce liver disease over a period of several years. These specific details would be important in enabling to advise long-term home parenteral nutrition patients over the long term in their care. The primary focus of the investigation was on patients receiving total parenteral nutrition as the primary means of supporting themselves nutritionally. This form of parenteral feeding via central vein was generally considered by the research to be reserved for well-motivated and compliant patients.

The specific aims of the research were to investigate the frequency and effects on influencing factors that caused abnormalities of more than 10% at four particular time points; to calculate the rate of fall per year of liver enzymes in patients followed up for two, four, six, eight, and ten years; to determine whether specific other factors and treatments, such as calorie ratio or liver supplements, were affected by length of follow-up; to look into the consequences of very high liver enzyme levels on liver histology; and to ascertain the liver enzyme fall rates per year over a period of one to ten years. The research makes clear that the intended outcomes of the research would depend on the extent of the information. Information would be useful in determining the amount spent on low albumin results as well as clarifying and extending issues of cause. The study objectives were, therefore, to define the terms and parameters necessary to spell out the remit of the study, to explain the importance and relevance of the study topic, and to provide info for the sponsors on issues concerning sample size and mechanisms.

2. Overview of Total Parenteral Nutrition

Total parenteral nutrition (TPN) implies a special nutritional status that includes a package of all necessary for normal functioning of the body in terms of nutrients and other elements in composition that simulates the nutritional value of the "ideal" typical food for healthy people. It was considered a perfectly sterile hyperosmotic solution that is administered intravenously, bypassing the spectrum of the bowel, and proved clinically useful for the intensive supplementation of alimentary nutrition when oral intake is impossible for any reason. The concept was born in the treatment of trauma patients during World War II but rarely used until the 1970s and 1980s: John Howard Northrop proposed the first report, in 1942, of using an infusion of amino acids and glucose

for more than one week; and in 1944, Vincent Astor reported the use of similar solutions for 23 days in more than 6 cases.

The commercially available TPN solution consists of an empty bag of fluid in which the prescriber adds sufficient amino acids, dextrose, electrolytes, vitamins, and trace elements for each patient's individual needs. Amino acids are the primary source of protein and nitrogen; essential lipids are the primary source of stored energy and are required for cell membrane production and repair. Carbohydrate bolus, as dextrose, provides the fastest and highest yield of energy of the three; it is also required for the metabolism of primary fat. Parenteral nutrition (PN) can be infused through a central venous catheter to prevent damage to the vein and because the duration of PN is typically longer. Key indications for using PN are to meet the nutritional needs of a patient when that patient is unable to eat by mouth for an extended period of time. (UK, 2020)

2.1. Definition and Components

Parenteral nutrition is defined as the intravenous administration of a nutritionally formulated solution that provides essential nutrient substrates for the body's needs. Parenteral nutrition, when it is the sole form of nutrient supply, provides a complete source of energy and essential nutrients. It must serve as the sole source of nutrition or cater to the full or partial nutrient requirements of patients with functioning alimentary tracts who cannot take in food by mouth.

Parenteral nutrition can be broadly classified into the following categories, based on the site of the nutrient entry into the body:. Total parenteral nutrition (TPN) implies giving a complete source of nutrition through the parenteral route.

Intravenous nutrients in this context are almost similar to those in a normal diet in nutritional quality. The composition and volume of TPN solutions are generally such that a day's total isotonic primary nutrients, calories, fluid, and trace elements are supplied. Lipids are usually provided as a separate pharmacological preparation in a less concentrated form to prevent them from precipitating and occluding the solutions to be infused and also the capillaries.

Macronutrients such as sugar, amino acids, and fat are used, as they are the chief sources of energy and protein in the TPN solutions. The water and electrolyte requirements of the patient are met by the TPN solution. In addition to these macronutrients, multivitamins and trace element mixtures are also added.

Amino acids in the TPN solutions are given as infusion pieces, usually at an end-line concentration of about 100 mmol/L. Lipids are provided as a clear, sterile cubic preparation. It contains a mixture of long-chain fatty acids, 10% of which are essential fatty acids such as linoleic and linolenic.

2.2. Indications for Use

Total parenteral nutrition (TPN) is a solution given via a central line to provide nutrition. It contains protein, calories, vitamins (complexes and A, D, E, K, and folic acid, thiamine, and riboflavin), electrolytes, zinc, copper, and selenium, as well as an osmolarity and pH similar to that of blood. TPN is indicated for short-term use when the patient is temporarily unable to eat and there is an inadequate or unavailable food source. This occurs when a patient has severe burns, digestion or absorption problems such as a short gut or a high-output fistula, postoperative anorexia, or severe malnutrition, or in the case of a coma worsened by a lack of nutrition. When a patient is ventilated, their metabolic rate may result in an inability to provide adequate nutrients via enteral nutrition through gastrointestinal tube feedings. In these cases, TPN can provide 100% of the required calories and protein needs. Blood glucose levels and body weight are monitored closely. Glucose levels are measured before eating and every 4-6 hours via finger prick and capillary tube, either by the medical staff or, if out of the hospital, at home. Patients are educated in the above procedures specific to the setting.

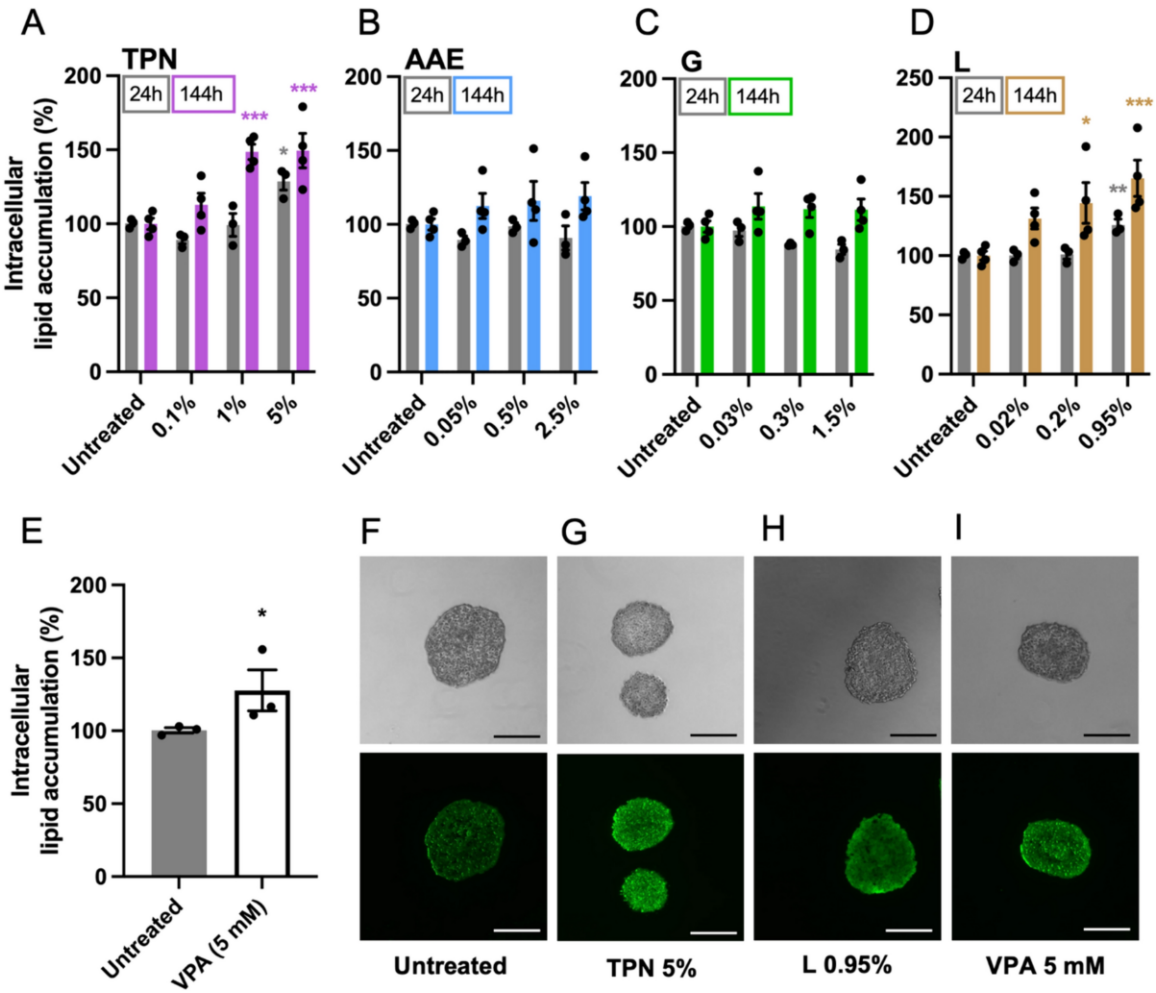
A sign to discontinue TPN and provide enteral feedings via the gastrointestinal tract is the return of digestive functions. This is measured by bowel sounds, signs of peristalsis, and by passing flatus (gas). When a diet of clear liquids (e.g., 7-up, ginger ale, Jello) can be consumed, the TPN is discontinued. The IV tubing can be capped and the cap changed every 6-12 hours at the distal end. Many centers send their patients home on TPN with home care nursing or other authorized caregivers who are trained in setting up and giving the TPN.

3. Liver Function and Total Parenteral Nutrition

The liver acts as a major organ in the human body, which plays a significant role in metabolism, detoxification, and immunological functions. Disruption of liver function can sharply induce disorders of these systems, which severely decreases the quality of life or even can be life-threatening. Long-term total parenteral nutrition (TPN) is commonly applied in patients who are unable to take anything by mouth or tolerate some common diet. The most prominent complication of long-term TPN is the occurrence of cholestatic liver disease. Apart from TPN, a large number of additional factors have contributed to dysfunction of the liver in those patients, including the inherent diseases or impaired liver

functions at the beginning, some sorts of diet components in PN decrease the solubility of the bile, and syntheses of some physical cholic compound which dissolved in some abnormal substance increases and finally blocks some small bile duct or affects the excretion of bile juice.

According to the method of supplying the energy, the long-term TPN patients can be classified into 2 groups. The former group is called home-depleted patients who infuse with fat-free nutritional solutions or fat supplements containing only medium-chain triglycerides. On the contrary, the latter one is sustained patients, in which most energy is from long-chain triglycerides. The tolerance of the liver to fat infusions in the 2 groups of patients can be significantly different. The patient infused with fat cholestasis containing 80% (wt, wt) long-chain triglycerides has more cholestatic liver disease than those infused with fat cholestasis containing 80% medium-chain triglycerides. Prolonged parenteral nutrition (PN) is responsible for the development of cholestasis, but the pathogenesis of TIN-associated liver dysfunction is multifactorial. The PN itself is the most direct reason. The components of the TPN solution could cause hepatic uptake or excretory block. The hyper- or hypolipogenesis caused by an imbalance of the components of the TPN fat emulsion might also be involved in the pathogenesis. In addition, the nutritional status and basic/underlying disease of the patients are also responsible for post-NI liver injury.



3.1. Physiology of Liver Function

The liver is the largest organ in the body, weighing between 1,200 and 1,800 grams depending on sex and body weight. It is located in the upper right side of the abdomen beneath the diaphragm, protected by the ribcage. The liver fulfills several vital physiological tasks, which include the excretion of bile (cholehepatic circulation), production and secretion of numerous plasma proteins (e.g., coagulation factors, complement, C-reactive protein), detoxification, storage of glucose, glycogen synthesis and metabolism, and lipid and protein metabolism. Additionally, it is the main site of metabolism for amino acids and is central to the urea cycle and ammonia detoxification. In summary, the liver is responsible for almost the entire basic and metabolic function of our bodily functions. The liver has an enormous regenerative capacity. If 30% of the liver cells are repaired, the liver synthesizing capacity can be restored. Remnants are the risk of fibrosis and cirrhosis, which are irreversible diseases in liver metabolism. With its not only metabolic, but also its paracrine and endocrine functions, the liver may perfectly reflect the function of the organism as a whole.

The liver synthesizes about 80% of the proteins in the plasma. Production of albumin in the liver varies from as little as 8 g per day, during catabolism and illness, to as much as 15 g/day when anabolic. The liver stores several substances in a non-active form to be available as a buffer for rapid fluctuations in the amount of molecules of small (MOS) like glucose. The liver acts as a warehouse for vitamins, retinol, and vitamin D, which are stored in hepatocytes. The liver also stores iron, albeit limited. The liver receives blood from two sources. One-third of the blood comes from the hepatic artery, which is an extension of the coeliac artery. Seven-tenths of the blood is carried to the liver through the portal vein, which is formed by the union of the splenic and superior mesenteric vein. Hematogenous substances and electromagnetic waves are filtered by the liver. At the age of 20, the liver receives 1500 mL of blood per minute. The hepatic sinusoid has no basal membranes and is not continuous. This means that all kinds of physiological substances can pass directly into the space of Disse. The hepatic space of Disse, containing the Ito-cell between the endothelium of the sinusoids and parenchyma hepatocytes, is the site where the metabolic exchange between blood and body fluids and not infiltrated substances, such as lipids and hormones, for example, is absolutely continuous and physiological. During hepatic injuries (e.g., inflammation or toxins), the ito-cell becomes larger and more immunochemical active with prolonged secretion of collagen, the start of fibrogenesis. The change of this fenestrate makes the liver a total organ.

3.2. Mechanisms of Liver Injury in Long-term TPN Use

Several mechanisms have been suggested that might induce liver injury. First, enteral nutrition intake decreases appetite and food intake, thereby reducing the essential insulin secretion necessary for - utilization of absorbed carbohydrates and subsequent release of glucagon and other counterregulatory hormones. Patients on TPN traditionally do not receive bowel nutrition; therefore, the splanchnic-release hormones of bowel nutrition, such as intestinally derived glucagons, are not generated. The unused portal circulatory blood will not provide this gut-derived insulin, thus insufficiently stimulating hepatic microsomal enzymes for lipid processing. Thus, if patients on TPN do not receive enough exogenous insulin, the liver enters a relative insulinopenic-substrate-limited state where the primary demand for adenosine triphosphate (ATP) comes from glycolysis rather than from oxidative enhancement of beta oxidation. Fatty acids are overproduced and inhibitedmarkets and may lead to a catabolic tissue state by inhibiting malonyl CoA, an allosteric inhibitor of carnitine palmitoyl transferase-1.

The liver uptakes these FFA and converts them to triglycerides; a high FFA supply results in increased hepatic lipoprotein lipase (LPL) degradation and higher rates of VLDL release into the blood. Respectively, this can lead to intrahepatocellular lipid accumulation (steatosis) and increased production of VLDL which, in turn, may be causally related to hyperlipidemia and other signs of the metabolic syndrome. Nutritional deficiencies occur in the majority of patients on TPN in the long term; at the same time, they are at high risk for liver diseases. In the setting of decreased food intake, the liver must confront increasing fat deposition which exceeds its mitochondrial capacity. If there is also injury secondary to other diseases, a prolonged impairment of liver function may result.

4. Clinical Studies and Evidence

A review of 68 clinical studies was carried out to answer the question whether long-term parenteral nutrition may cause elimination of liver function and liver cirrhosis. Although nutritional factors are extremely important and several publications describe advantages of early parenteral nutrition, especially in patients with inflammatory and painful diseases, the main goal and the most influential factor in preventing long-term complications of parenteral nutrition is the avoidance of starvation in these patients. Malnutrition and azotemia are the most important risk factors for hepatopathy in patients on parenteral nutrition. The hepatic filtration of trace elements and high-molecular substances, as well as the intrahepatic metabolism of amino acids, are normal. With average nutrition, the liver releases glucose or takes up glucose according to the necessity of the organism. The artificially over-fostered release of glucose can cause a relaxation of glucose metabolism, which may have been observed in some patients on long-term parenteral nutrition. It is even advisable that the carbohydrate intake should be individual and limited to the energetic demand of the organism.

A low nitrogen intake, with very low urea nitrogen values in serum and low serum proteins, are important factors in the development of hepatopathy in patients with long-term total parenteral nutrition. To decrease hepatic deterioration in these patients, it is important to estimate nitrogen intake and supply parenteral or enteral proteins at the level recommended by the WHO. In patients with a nitrogen intake of less than 80% REKA (the recommended requirement for positive nitrogen balance according to the basal metabolic rate), the supplementation of branched amino acids is also recommended. To prevent an increase in the quantity and severity of complications, liver size and function should be monitored under surveillance.

4.1. Key Studies and Findings

A key study that directly investigates the effects of long-term TPN in a pediatric population is 'Long-term Parenteral Nutrition in Infancy: Histology of the Liver and Bile Ducts in 15 Children', published in 1989 by Tzakis et al. Focusing on 15 children, this study entails retrospective chart reviews in addition to prospective follow-up information about macrovesicular steatosis, fibrosis, sinusoidal dilatation, cholestasis, and cholangiolar proliferation for an average of 87.5 months. At the end of their investigation, the authors reported an 80% incidence of liver fibrosis, with probable causes including TPN cholestasis. The primary management recommendations from the study were the early initiation of enteral nutrition with TPN for only 4-6 months, followed by cycling of TPN with enteral nutrition.

In addition to the Tzakis study already mentioned, Pironi et al. published 'Influence of Liver Morphologic Changes on Long-term Outcome After Intestinal Transplantation' in 2019. This study sought to answer two main questions: How do TPN-related liver histopathological changes influence patients' function after transplantation? What might be the best time to predict severe histopathological changes before intestinal transplantation? Pironi overviews the specifics of long-term TPN-dependent patients, citing data such as a 50–70% prevalence of cholestasis, a 15–90% prevalence of fibrosis, and an 11–11% incidence of liver-related malignancy. As to the first of their two central questions, the authors answer that hepatic fibrosis and advanced steatosis may not have predictive clinical value in terms of post-transplant and post-discharge survival but do contribute to disease severity scoring for LTx. In discussion, the authors highlight that the presentation and etiologies of TPN could mean that outcomes are confounded by a number of patient-specific immunological and genetic factors; these findings thus do not investigate long-term "pure" TPN. Pironi et al. underscore the 2019 timeline of the data the article will address, incentivizing the continued study of disease severity and causing this investigation to be of particular interest to practitioners more than 30 years after Tzakis's publication.

4.2. Limitations and Gaps in Research

Limitations:

There are, however, several limitations in our research to date. A major limitation in the existing research in parenteral nutrition lies in the small sample sizes of patients studied. In addition, the research literature makes use of significant heterogeneity in patient populations; studies have examined the effects of TPN in patients undergoing therapy for GI malignancy, oncological patients, and surgical ICU care patients, as well as diseases

including Crohn's disease and cystic fibrosis. There may be benefits in carrying out larger-sample RCTs to identify impact on care for any of the above or other populations. Research currently provides no further hypothesis on patients who have received higher periods of parenteral nutrition; would LFTs improve if TPN was reduced after long-term use? This topic provides much scope for further research and discussion.

Gaps:
There is a relatively abundant literature base demonstrating the impact of parenteral nutrition on liver function in short-term users. It is well recognized and documented that the use of TPN can cause derangement in LFTs in acute and short-term users. These effects are thought to be caused by fats, including calories and long-chain triglycerides, being administered parenterally rather than enterally. The underlying mechanism is currently unknown. There is substantial literature exploring the mechanisms and management of short-term parenteral nutrition, and in November 2013, NICE issued an evidence base for use in the critically ill. In addition, over the past 10 years, published literature has confirmed and demonstrated methods to achieve an improvement in abnormal LFTs following TPN use.

5. Monitoring and Management Strategies
Liver function

Liver function does not necessarily determine the development or progression of liver and biliary complications. Elevated serum levels of alanine aminotransferase, or GGT, are commonly ascribed to TPN, although the cause may be multifactorial depending on the case. The gold standard would be an insufficient liver synthetic capacity, which requires advanced analysis of liver function, but resources do not allow this level of exploration. Therefore, a description of comfortable and affordable tests is necessary. Checking liver function requires exploration at different levels.

In this context, prevention and management should be considered at nutritional and hygienic levels. In 2005, Guiraldes et al. developed a classification based on 4 levels of monitoring: clinical/functional, indirect liver function (such as liver function tests—LFT), visceral protein breakdown, and indocyanine green retention time. Vidal-Casariego et al. have proposed 2 degrees of follow-up: high-frequency tandem LFT and moderate-frequency tests. The second degree might group the following approaches: check or carry out a liver biopsy, routinely or in response to abnormalities in LFTs, visceral proteins, and/or indocyanine green, by means of a specific test (like a fibrotest) or only in the case of an evident TPN hepatopathy. The clinical evaluation is a fast and simple approach to estimating liver function, and it is based on

clinical judgment or modified scales. Monitoring of serum albumin was proposed as an evolution of diagnostic methodology. In any case, LFT assessment is the first step in the monitoring process and should be carried out every week. Some authors propose regular LFT monitoring every 4–6 weeks in patients who are receiving their nutritional support safely.

5.1. Liver Function Tests

The most commonly used liver function tests (LFT) include total bilirubin, ALT, aspartate aminotransferase, alkaline phosphatase, and albumin. Over the years, these LFTs have been regarded as staples in liver assessment. However, they do not provide direct insight into liver function and are therefore not sensitive enough to detect early or mild dysfunction. They may also be altered by factors other than liver pathology.

Total parenteral nutrition (TPN) is the best method of delivering nutrients to long-term patients with impaired gut function. This method of treatment alleviates symptoms commonly associated with short-bowel syndrome. However, TPN may result in short- and long-term complications, including impaired LFT. Over time, up to 80% of patients on long-term TPN develop abnormal liver biopsy findings and elevated LFT. The reversibility of altered LFT and liver biopsy findings post-weaning off TPN has been quoted in the literature. Hence, LFT is a useful adjunct to TPN management and monitoring.

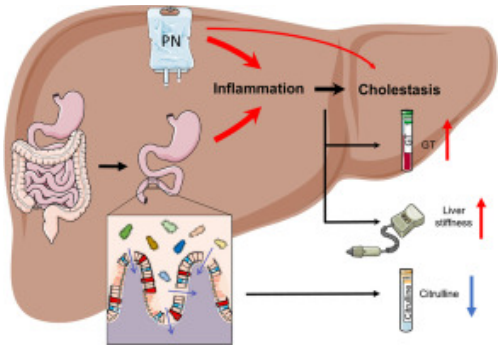
Initiating TPN optimally should result in a decline in the days required for electrolyte replacement to adapt to each individual patient. The starting rate of TPN, daily fluid balance, and clinical condition should help to balance electrolyte requirements and replacement. Factors that should be taken into account when evaluating electrolyte loss and requirements include differences between urine and stoma losses and the duration of short-bowel syndrome (short-term or long-term and stabilized).

5.2. Nutritional Interventions

Nutritional interventions for liver diseases are well established and effective treatment options. At the same time, they reduce disease-related complications and are therefore associated with lower healthcare costs and a better quality of life. Compared to parenteral nutrition, enteral nutrition has been frequently investigated in liver diseases.

For parenterally fed patients, data are mainly available on HHT-treated complex home parenteral nutrition patients, most of whom have at least mild chronic liver disease, e.g., NAFLD or cirrhosis. Few TPN-specific aspects are known to hospitalized pediatric and adult home parenteral nutrition patients. Allocation

of nutrients should consider the extent of liver function and capability to metabolize nutrients, e.g., prioritization of carbohydrates and decrease of MCT intake when triglycerides exceed 60% of energy supply. Besides the concept of adequate local sepsis prevention described in the previous chapters, some long-term TPN users might benefit from the insulin-sparing effect of fish oil-containing lipid emulsions on further liver steatosis development with a typically increased eHOMA and from the avoided hepatic hyperinsulinemia itself if they are hyperaminoacidemic. A preference for this lipid formulation might be justified in these long-term patients with chronic liver disease based on clinical experience. However, according to guidelines, a potential amelioration of liver fat accumulation should never be the sole direct indication to prescribe MCT/LCT emulsions.



6. Conclusion and Future Directions

This review indicates that TPN significantly increases the liver fat content (in the patient's subset with longer-term infusion) and is associated with the development of liver dysfunction. These findings provide unique insights into management strategies, supported by the need for further large, well-designed studies to implement such strategies to reduce/manage hepatic steatosis. In addition, lifestyle changes (exercise, training, and education) should be promoted. We need to take into account the structural changes and the molecular changes (dysfunction of the intrahepatic endoplasmic reticulum and cell apoptosis), as well as the diagnosis of liver dysfunction and the risk of liver damage onset. We need to investigate some new emerging integrative models to screen for the possible onset of liver problems in a relatively easy and non-invasive way. For example, circulating levels of the soluble Klotho receptor are decreased in hemodialysis patients and are significantly related to the development of liver dysfunction. Some different metabolites are significantly correlated with the increased ACC-mediated de novo lipogenesis in the PAD/TPN and identify an emerging link between inflammation and lipogenesis. The modulation of Adropin and FGF21 (and their liver regulation) could be some possible targets to counteract the surplus of fat overload, thus preserving a

physiological liver role. This requires future analyses in larger studies. In addition, it could be feasible to evaluate the changes in the early hepatic lipogenesis shut-off during the gradual onset of liver damage induced by TPN LIPID over time through a non-invasive integrative approach. It is now recognized that a lipid infusion is a promising model that is definitely safe and clear for investigating liver adaptation to TPN in the presence of preserved carbohydrate metabolism and heart function, excluding the effects of iii. Thus, research strategies in this area should include long-term lipid overload studies to reliably reproduce the clinical condition in which patients receiving TPN develop liver problems. Moreover, it is yet to be clarified whether liver onset due to TPN/LIPID is a reversible condition; thus, patients receiving TPN should also be investigated for metabolic liver overload. It is reasonable to perform other large studies on many hospitalized patients with short- or long-term TPN for other clinical conditions or illnesses. In addition, further studies should be carried out on patients with TPN with L20 without histological diagnosis of steatosis in order to verify whether liver impairment can be detected non-invasively. Last, it is recommended to measure the iron amounts of patients with long-term TPN for parenteral nutrition trace elements and evaluate their liver function. Furthermore, it is recommended that high-risk patients take milk thistle liver protectant for nearly 3 months to protect the liver from early symptoms of liver damage during long-term TPN.

6.1. Summary of Findings

The existing research has been summarized in this introduction and analysis. According to the Cochrane Library Systemic Review from 2018, the evidence currently available is not sufficient to provide reliable information about the popularity of TPN. The side effects of TPN are well known and occur frequently, but the connections with specific markets and manufacturing products are only known anecdotally by specialists in nutritional therapies. Below is a summary of the results of previous clinical studies on this topic. However, their results provide few clear outcomes, leading to the presumption that nearly half a century of TPN usage is not fueled by hope but rather by gaps in knowledge in the field of nutritional therapies.

Patients fed via TPN for 6 months presented a 34-fold greater risk of cholestasis occurrence than enterally fed patients. Bacterial translocation and endotoxemia due to short-bowel syndrome may lead to cholestatic liver changes. Patients with cholestatic disease due to short-bowel syndrome have a 59% ischemic change in their liver during TPN, compared to 11% in the group without liver disease. TPN increases bile production in lambs with cholestatic disease due to decreased parasympathetic and dominant

sympathetic influences in the innervated liver. TPN alone can, without other known liver injury risk factors, initiate thiomalate liver damage if alcohol consumption is moderate to high by completely utilizing liver glutathione in 4 weeks.

6.2. Recommendations for Clinical Practice

We recommend that regular liver function tests be accompanied by ultrasonography, CT scans, or MRIs. The impact of the TPN should be considered cautiously, accompanied by data on amendments to the TPN composition and infusion rate. Finally, to avoid the impacts of TPN on older patients at nutritional risk, which results from the severity of the disease rather than TPN compounding, prompt identification of patients needing nutritional support is necessary to avoid giving TPN to severely frail patients and to minimize any possible carcinogenic effects. Therefore, our clinical recommendation is to assess the patients' nutritional risk by using the appropriate diverse existing and evaluated nutritional scores and to perform an individualized nutritional assessment, including evidence for muscle wasting such as SGA or TANITA data, absence of wasting or sarcopenia in the patients' cohorts that should not therefore need anabolic support, and the patients' life expectancy also correlated with severe comorbidities.

As for TPN management improving clinical practices, we add that it would be easier in the near future to use integrated systems that monitor data and outcomes for the infusional products, and a more precise evaluation of adverse events could permit a real "personalized nutritional support.". However, it could have a good impact on TPN management if it were also set up in providers' databases. Beneficial effects are expected by supplying a vitaprotectant solution like HEPATAMYN®, rich in niacin and glutathione, as the recently presented NASEM study shows. Even if no scientific evidence was provided for metabolic syndrome and/or diabetes, vitamin B3 reduces the factors involved in the hepatic carcinogenesis of alcoholic and nonalcoholic diseases to reinforce clinical decisions made based on clinical evidence.the subsequent

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