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Review

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Total Parenteral Nutrition in Patients with Kidney Disease

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ABSTRACT

Total parenteral nutrition (TPN) may lead to concerning kidney outcomes with long-term administration. This can be delayed and improved by daily monitoring of the serum concentrations of clinical markers that correlate with kidney function but only in conjunction with changing the parenteral nutrition formula to account for these concentration changes. The current evidence suggests that hyperglycemia, hypertriglyceridemia, and deranged fluid/electrolyte balance remain significant areas of concern with TPN in patients with acute kidney injury, chronic kidney disease, and patients undergoing kidney replacement therapy. Tight monitoring of calorie intake, protein intake, and micronutrients is required in patients with end-stage kidney disease due to the high occurrence of protein–energy wasting or those undergoing kidney replacement therapy due to loss of nutrients during dialysis. Given the complications, TPN should only be used when enteral feeding is completely contraindicated or cannot sufficiently address nutrient intake goals due to secondary issues such as anorexia. These findings are discussed with the clinical practice guidelines recommended by The American Society for Parenteral and Enteral Nutrition and the European Society for Clinical Nutrition and Metabolism. Mechanisms of TPN-induced kidney diseases are also discussed.

Keywords: Kidney, nutrition, parenteral, transplantation, dialysis

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INTRODUCTION

Parenteral nutrition (PN) is a life-sustaining intervention for patients with or at risk of malnutrition, intestinal failure, or recurrent gastrointestinal bleeding due to conditions such as peptic ulcer disease or esophageal varices.[1] Parenteral nutrition may be intravenously (IV) administered as the exclusive caloric source (total parenteral nutrition; TPN) if enteral nutrition (EN) is contraindicated or concomitantly with enteral nutrition (supplemental parenteral nutrition; SPN) when SPN alone fails to meet the caloric needs of the patient.[2,3] Total parenteral nutrition is a fundamental medical procedure,[1,4] on par with intravenous fluids, antibiotics, or blood transfusions, and non-adherence to safe practice guidelines can result in death.[5,6]

The American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) recommend total or supplemental PN as a second choice of nutrition support and only if the use of EN is deemed impractical after a thorough evaluation.[1,4]

COMPOSITION OF TOTAL PARENTERAL NUTRITION SOLUTIONS

Although clinicians individualize the composition of TPN to meet the needs of each patient, the 3 main macronutrients are dextrose, amino acids, and lipid emulsions. The highest glucose utilization rate for carbohydrates delivered through dextrose monohydrate—most frequently as 40%, 50%, and 70% concentration—ranges

from 5 to 7 mg/kg/min.[7] Hyperglycemia and hypertriglyceridemia can occur due to the combination of direct dextrose infusion into the bloodstream and a rise in stress hormones due to the underlying conditions.[8] Lipids are a source of calories and defend against fatty acid deficiencies. If fat-free TPN is used, essential fatty acid deficiency may appear after about 3 weeks.[7] The amount of protein is adjusted depending on the underlying condition. For example, patients in critical conditions require 1.5 g/kg/day of protein, 0.6 to 0.8 g/kg/day with chronic kidney disease (CKD), 1.2 to 1.3 g/kg/day with hemodialysis, and a temporary protein restriction with acute hepatic encephalopathy.[7] Other ingredients of TPN may include minerals, vitamins, electrolytes, trace elements, and non-nutritive medications, and the dosage of each can be adjusted depending on the patient's need.[6]

RISKS AND BENEFITS OF TOTAL PARENTERAL NUTRITION

The early life origin of the adult metabolic disturbances hypothesis stipulates that the metabolism is reprogrammed due to epigenetic changes brought on by a shift in the DNA expression pattern. Early TPN administration in guinea pigs inhibited DNA methyltransferase and prolonged DNA hypomethylation.[9] Wildhaber et al[10] reported alterations in the expression of the intraepithelial lymphocyte-related genes, which may play a significant role in the altered immune response induced by TPN and increased occurrence of sepsis following TPN administration. The administration of intravenous lipid emulsions (ILE), in particular, may also impact drug metabolism due to the altered expression of CYP450 enzymes.[11] In rodent studies, soybean oil-based (Intralipid®) and fish oil-based lipid emulsions (Omegaven®) decreased the expression of most drug metabolism genes, including Cyp2d9, Cyp2f2, and Cyp2b10.[11] Additionally, Intralipid® downregulated Cyp3a11,[11] which has also been shown to be downregulated in models sepsis-induced acute kidney injury (AKI).[12]

In line with these animal studies, clinical studies report several TPN-related complications such as hyperglycemia, hypertriglyceridemia, fluid and electrolyte imbalances (refeeding syndrome), parenteral nutrition-associated liver disease (liver enzyme abnormalities, steatosis, fibrosis or cirrhosis), parenteral nutrition-associated cholestasis, development of biliary sludge, gallstones, and catheter-related mechanical injuries and bloodstream infections.[6,13,14] In patients with acute pancreatitis, TPN may be associated with a longer length of hospitalization, higher mortality, and the risk of pancreatic infection, organ failure, and surgical intervention.[15,16]

In addition, the lack of enteral nutrient intake causes detrimental changes to the gut mucosa and microbiota.[17] For instance, studies in rodents have shown that lack of enteral stimulation during TPN induces intestinal atrophy with marked immune-system-related changes such as increased Paneth cell size, eosinophils infiltration in the gastric fundus and the colon, reduction in CD4+ cells in the lamina propria, downregulation of Th2 IgA stimulating cytokines (IL-4, IL-5, IL-6, IL-10, and IL-13), and upregulation of intercellular adhesion molecule 1 (ICAM-1).[13] Lack of enteral stimulation during PN has also been shown to induce changes in gut microbiota, such as a decrease in the population of Firmicutes, including Lactobacillaceae, leading to the overall dominance of Proteobacteria and Bacteroidetes in the microbiota.[18,19] These changes in gut microbiota have been implicated in PN-associated hyperglycemia, liver disease, sepsis, septicemia, and heightened immune response with possible additive effects from increased microbial toxin pool.[18,20,21] However, the evidence to support the findings of these animal studies in humans is weak at best.[13,17,22] A systematic review of 13 clinical trials indicated insufficient evidence for bacterial translocation, increased risk of sepsis, villous atrophy, impaired immune functions, or mortality in pediatric patients receiving TPN.[22]

Furthermore, TPN may also increase the risk of kidney disease. Studies have shown that TPN-induced kidney disease (TPN-KD) is a significant complication in patients receiving long-term TPN, with the incidence ranging from 14% to 43%.[23] Total parenteral nutrition-induced kidney disease can manifest in several ways, including AKI, CKD, and electrolyte imbalances. Several factors contribute to the development of TPN-KD, including the composition of the TPN solution, the duration of TPN administration, and the presence of other underlying comorbidities.[24,25] Total parenteral nutrition solutions containing high levels of glucose, amino acids, and electrolytes have been found to increase the risk of developing TPN-KD, which can lead to further complications such as electrolyte imbalances, metabolic acidosis, and kidney failure.

Some meta-analytic studies have shown comparable or lower mortality risk with TPN (versus standard of care usually comprising oral diet plus intravenous fluids or standard EN) with consistent evidence for improved nutritional status and lower complication rate in critically ill,[26-28] surgery patients,[29] 2 subpopulations of patients who are also likely to have underlying kidney disease. These findings indicate that the risks and benefits of TPN must be assessed based on the nature of the underlying condition. Therefore, the present review aims to provide evidence-based effects of TPN on patients with kidney diseases.

MAIN POINTS

- Total parenteral nutrition induced kidney disease (TPN-KD) is a significant complication in patients receiving long-term TPN with the incidence ranging from 14% to 43% and can manifest in several ways, including acute and chronic kidney disease and electrolyte imbalances.
- Whenever possible, enteral nutrition should be used as the primary form of nutrition therapy for patients with kidney failure.
- The prevention and management of TPN-KD involves careful monitoring of electrolyte imbalances and adjusting the composition of the TPN solution accordingly.

TOTAL PARENTERAL NUTRITION AND KIDNEY DISEASES

Effects of Total Parenteral Nutrition in Patients with AKI

In some patients who are unwell and severely catabolic, the salutary benefits of TPN may be considerably reduced. The evidence is significantly weaker for the assertion that TPN speeds up recovery from AKI (formerly acute kidney failure). Abel et al[30,31] were the first to propose that TPN expedited recovery of kidney function and enhanced survival in individuals with AKI. They compared a patient group that received a mixture of 50% glucose and 50% essential amino acids with a group that only received 50% glucose. Amino acid supplementation increased survival from 44 to 75%. However, these studies were critiqued for sampling bias, as only 53 of 150 TPN referrals were included.[32]

Moreover, early studies primarily focused on assessing the metabolic response to TPN in patients with preexisting AKI rather than patient outcomes and showed that hyperglycemia is a significant concern in this patient group.[33] More recent studies demonstrated that TPN is also independently associated with higher serum inflammatory biomarkers (sICAM-1), infection rate, and mortality than EN among ICU patients with AKI[34] and acute acalculous cholecystitis among surgical patients.[35] Additionally, incident AKI after TPN administration has been known for over 4 decades.[36] Total parenteral nutrition in the form of acute ILE administration has also been shown to induce AKI with a dose-response effect.[37]

The detrimental effects of TPN in AKI may be associated with its calorie content. High-calorie TPN (40 kcal/kg/day) was associated with higher adverse events (hyperglycemia, higher insulin and nutritional fluid requirements, and hypertriglyceridemia) compared to low-calorie TPN (30 kcal/kg/day) in critically ill patients with AKI with no differences in terms of estimated nitrogen balance, protein catabolic rate, or urea generation rate.[38] The amount of protein in TPN seems to play a minor role, if any, in TPN-induced AKI. No differences in kidney function or survival were observed with low (2.3 g of nitrogen per day) or high protein (11.3 g of nitrogen per day) content of TPN in patients with AKI.[39] However, adding amino acids to TPN reduces complications and mortality rates compared to amino acid-free TPN.[40]

Effects of Total Parenteral Nutrition in patients with Chronic Kidney Disease

Relatively fewer studies have reported the impact of TPN on patients with CKD not undergoing kidney replacement therapy (KRT). In a pediatric study, only 2 out of 25 patients (8%) undergoing long-term home PN for intestinal failure with normal estimated glomerular filtration rate (eGFR) at baseline had deteriorated eGFR <90 mL/min/1.73 m^2 at 3 years, although the study did not separately report data for TPN (48% of the study population or SPN (52% of the study population).[41] However, in another pediatric study where all participants (n = 13) received long-term TPN, all patients had below-normal true GFR (measured using DTPA labeled with indium 111) after 1-11 years, while eGFR using the Schwartz formula overestimated the true GFR.[42] Similarly, over 50% of adult patients receiving long-term nocturnal PN developed below-normal true GFR measured by inulin clearance, which was unrelated to the duration or composition of the PN solution.[43,44] Furthermore, 71% of patients with deteriorated GFR on long-term PN showed signs of chronic sodium depletion and dehydration, which strongly predicted decreased GFR.[44]

Notably, these findings are from observational studies in patients requiring PN for a short bowel, and the role of the underlying bowel condition in GFR deterioration cannot be eliminated. For instance, pediatric patients with intestinal failure had a higher occurrence of nephrocalcinosis, which led to longer PN duration.[45] However, Pironi et al[46] showed that the risk of developing CKD was substantially higher among adult intestinal transplant recipients (incidence rate = 45%) than those on TPN alone (incidence rate = 15%) with a 5-year probability of maintaining an eGFR ≥60 of 44% and 84%, respectively. It should be noted that the cause of kidney function decline in intestinal transplant recipients is not known,[46] and the role of the transplant procedure and immunosuppression therapy cannot be eliminated.

Effects of Total Parenteral Nutrition in Patients Undergoing Kidney Replacement Therapy

Malnutrition is one of the strongest predictors of morbidity and mortality in patients undergoing KRT. An estimated 20%-60% of patients undergoing maintenance hemodialysis are malnourished,[47] with a 42% global prevalence of protein–energy wasting (PEW) in this subpopulation of patients.[48] The survival rate of patients requiring concomitant treatment with hemodialysis and amino acid-free TPN is only 33%, with pneumonia, gastrointestinal bleeding, septicemia, shock, and respiratory distress as the primary complications.[49]

The high prevalence of malnutrition and PEW in patients undergoing KRT may be attributed to the prescription of low protein diet to delay disease progression, loss of appetite, and dialysis-induced nutrient losses resulting in a net protein catabolic state which may be compounded by dialysis-induced inflammation, efficacy of uremia and metabolic acidosis correction, and dialysis adequacy, frequency, and duration.[50] For instance, 6-16 g of plasma amino acids can be lost during hemodialysis, depending on the modality and dialysate rate.[51-54] Therefore, greater emphasis has been given to achieving amino acid and nitrogen balance during dialysis among patients with AKI receiving TPN.[55] A protein infusion of 2.5 g/kg/day was optimal for maintaining normal levels of plasma essential and non-essential amino acids in critically ill patients with AKI[56] and anuria.[57]

For patients with end-stage kidney disease (ESKD) presenting with mixed marasmus-kwashiorkor type of malnutrition with a decline in somatic and visceral protein mass and high mortality, SPN may be administered during dialysis (intradialytic parenteral nutrition; IDPN).[58] However, a systematic review by Sigrist et al[59] reported that the evidence for the beneficial (or

detrimental) effects of IDPN on body composition, serum albumin, or mortality rates was still controversial due to poor design or inconsistencies in the reported outcomes supporting earlier findings of Wong et al.[58]

Transplantation

Transplantation is the gold-standard treatment for ESKD patients. Kidney transplant recipients are typically able to tolerate an oral diet on the first postoperative day. Therefore, TPN is rarely required in these patients unless accompanied by intestinal dysfunction.[60] However, the protein catabolism rate is exceptionally high during the soon-after kidney transplant due to the severe breakdown of lean body mass equivalent to 50% body surface area full-thickness burn even with the intake of 1.2g of protein per kilograms of the ideal body.[61] Therefore, if TPN is indicated, it must be modified to meet the patients high protein requirements post-transplantation.

MECHANISMS OF TOTAL PARENTERAL NUTRITION-INDUCED KIDNEY DAMAGE

Although the mechanism of kidney injury due to TPN administration leading to incident kidney disease or the deterioration of kidney function in patients with preexisting kidney disease is not fully understood,[43] it is likely to be multifactorial, at least involving components of hyperglycemia, hypertriglyceridemia, immunological reaction, and fluid/electrolyte imbalance.

Hyperglycemia is the most common adverse effect of TPN[6] as well as the most common cause of kidney disease,[62] and the heightened risk of systematic inflammation, infections, and intracellular acidosis with hyperglycemia in critically ill patients is well documented.[63] TPN-induced hyperglycemia has been attributed to the infusate's high glucose or gluconeogenic substrate content, which can directly increase blood glucose concentration.[64] Hyperglycemia during TPN administration may be further compounded by the stress associated with trauma, illness, or surgery, which may induce peripheral insulin resistance and reduce glucose utilization by peripheral tissues.[64] Additionally, an increase in stress hormones such as cortisol during trauma, illness, or surgery may induce gluconeogenesis, leading to hyperglycemia in critically ill patients.[64]

Moreover, the infusate's high glucose or gluconeogenic substrate content can increase insulin secretion and induce hepatic lipogenesis and triglyceride synthesis but suppress hepatic triglyceride secretion, leading to steatosis.[13] Recently, hypertriglyceridemia has been shown to exacerbate the severity of diabetic CKD.[65] In addition, long-term PN in pediatric patients is associated with higher incident CKD, possibly due to an increase in tubular proteinuria, a well-known risk factor of CKD.[66]

However, TPN-associated acute kidney damage may be more significantly associated with changes in body fluid/electrolyte balance. There is overwhelming evidence to suggest the involvement of fluid overload and osmotic diuresis in the pathogenesis of AKI[67] and CKD.[68-70] TPN comprises large fluid volume and osmotic loads (from dextrose and amino acids), which acts as an osmotic diuretic leading to hyponatremia with high urine flow rate, osmolar clearance, urinary nonelectrolyte, nonurea solute excretion, and a net negative free water clearance as observed by Batuman et al.[71] Moreover, the high protein load of TPN can induce metabolic acidosis,[72] further contributing to hypertonic dehydration.[73] TPN-induced osmotic diuresis may also contribute to electrolyte imbalance in the forms of hypokalemia,[36] hypomagnesemia,[43] and hypophosphatemia,[71,72] which may be further compounded in the presence of diabetes.[73] Batuman et al[71] also demonstrated that much of the volume load shifts from intracellular to extracellular fluid, leading to hyperosmotic stress, which can trigger cellular dehydration, inflammatory response, and cell death.[74] Hyperosmotic stress has been implicated in the pathogenesis of eye diseases, diabetes, inflammatory bowel disease, and cardiovascular diseases.[74]

CONSIDERATIONS FOR FORMULATION AND DOSING OF TOTAL PARENTERAL NUTRITIONFOR PATIENTS WITH KIDNEY DISEASES

Whenever possible, EN should be used as the primary form of nutrition therapy for patients with kidney failure (see also enteral nutrition recommendations from the German Society of Nutrition (DGEM)).[32] However, enteral intake is usually limited in kidney failure patients, making it difficult to administer a quantitatively sufficient EN. Even patients with only somewhat impaired kidney function exhibit abnormal stomach and intestinal motility, which frequently limits the quantity of EN that can be tolerated. Despite the risks of TPN, it is indicated as a life-saving therapeutic modality in severely ill patients, especially among those with CKD or with AKI requiring KRT when EN is contraindicated or cannot sufficiently address nutrient intake goals due to secondary issues such as anorexia.[1,32,75,76] About 11%-56% of patients with CKD (stages 3-5) and 28%-80% of those undergoing maintenance dialysis exhibit cachexia or PEW.[77] Therefore, the primary nutritional goal of TPN in these patients must be to supply adequate calories while managing any underlying risk of hyperglycemia and protein. A minimal EN should be considered to improve intestinal integrity, even if PN is necessary.

Clinical professionals should modify protein intake in accordance with kidney function, catabolic rate, and loss of nutrients during dialysis to achieve a favorable nitrogen balance in AKI. In kidney failure patients, PN should also aim to reduce the hypercatabolic state, prevent or treat malnutrition, and address its related effects on inflammation, wound healing, immunology, and other bodily processes like antioxidative potential. Chronic dietary therapy aims to slow the progression of CKD through protein or phosphate restriction; however, short-term PN, which is often only used in emergency settings, does not help this purpose.[32]

Nutritional plans for AKI in the late 1980s and early 1990s were predominantly based on protein intakes of 1 g/kg/day, which

resulted in recommendations from reliable evaluations,[78] ratios of 150 : 1-600 : 1 of calories to nitrogen, and finally, up to 30-45 kcal/kg. Studies in the early 2000s recommended that the ideal nutritional plan for individuals with AKI should contain a higher protein intake (1.5-1.8 g/kg/day) and a relatively low-calorie content (25-35 kcal/kg/day) compared to the previous recommendations.[56] Fiaccadori et al[38] suggested that the risk of adverse effects is higher with 40 kcal/kg/day than with 30 kcal/kg/day. Regarding specific amino acids, patients with CKD receiving glutamine[79] and arginine-enriched[80] TPN exhibited better clinical outcomes.

Patients requiring KRT have higher protein requirements (2.5 g/kg/day) due to high amino acid loss in the dialysate.[56,57] Additional consideration must be given to this patient subpopulation to maintain adequate electrolyte intake due to the risk of hyponatremia, hypophosphatemia, hypokalemia, and hypomagnesemia. Due to elevated requirements in ESKD, critical illness, and significant effluent losses during KRT, trace elements such as selenium, zinc, and copper should be evaluated and supplemented.[78,81] Care must be taken while administering ascorbic acid and vitamin A to patients with kidney disease through TPN solution. Cases of nephrolithiasis and kidney insufficiency secondary to ascorbic acid-induced hyperoxaluria have been reported.[82,83] Similarly, cases of hypervitaminosis A have also been reported in patients with kidney failure receiving TPN.[84]

In critically ill patients, the severity of the underlying illness, the degree of malnutrition, and the accompanying catabolism are important considerations when determining whether to begin TPN.[85] If EN is contraindicated, PN must be commenced within 3-7 days.[1] Indirect calorimetry must be used to calculate energy usage to direct nutritional therapy and prevent under- or overfeeding in hospitalized patients with AKI or CKD.[1]

MAJOR PRACTICE GUIDELINES

Although ASPEN does not have recommendations specifically for patients with kidney diseases, it recommends PN osmolarity of up to 900 mOsm/L as safe for peripheral infusion.[86] ASPEN also recommends maintaining the final amino acid, monohydrated dextrose, and lipid emulsion concentrations at ≥4%, ≥10%, and ≥2%, respectively, in 3-in-1 admixtures for the stability of up to 9 days refrigerated (5°C) followed by 24 hours at room temperature.[86]

In contrast, ESPEN makes specific recommendations for patients with AKI, CKD, or kidney failure.[76,78] Per ESPEN guidelines, TPN for patients with AKI should be aimed at providing optimum energy (20-30 kcal/kg/day), protein (0.8-1.2 (maximum 1.5) g/kg/day), and micronutrients to prevent protein–energy malnutrition, loss of lean mass, further metabolic or immune derangements, and death, the same as any catabolic condition.[76,78] It also notes inadequate evidence for micronutrient requirements in patients with AKI. In cases of electrolyte derangements, ESPEN recommends electrolyte-free or custom 3-in-1 admixtures. Although PN is rarely used in conservatively treated CKD patients, if indicated, energy intake ≥30-35 kcal/kg/day and protein of 0.55-0.60 g/kg/day is recommended for better nitrogen balance in non-dialysis patients with CKD with similar clinical goals as those outlined for catabolic condition in the ICU setting above.[76]

For patients undergoing maintenance hemodialysis, ESPEN recommends macronutrients and micronutrients doses as follows: energy (35 kcal/kg/day), protein (1.2-1.5 g/kg/day), folic acid (1 mg/day), pyridoxine (10-20 mg/day), vitamin C (30-60 mg/day), vitamin D according to serum calcium, phosphorus and parathyroid hormone levels, phosphate (800-1000 mg/day), potassium (2000-2500 mg/g), sodium (1.8-2.5 g/day), fluid (1000 mL plus urine volume) and in patients with significant trace-element depletion zinc (15 mg/day) and selenium (50-70 mg/day).[76]

MONITORING KIDNEY HEALTH OF PATIENTS UNDER TOTAL PARENTERAL NUTRITION

The Kidney Disease: Improving Global Outcomes (KDIGO) defines AKI based on a 50% increase in serum creatinine (SCr) within 7 days, 0.3 mg/dL increase in SCr within 2 days, or oliguria for over 6 hours.[87] In contrast, CKD is defined as a gradual decline in kidney function over 3 months or more, with GFR < 60 mL/min per 1.73 m^2 as the diagnostic threshold.[87] Therefore, monitoring of SCr and GFR may be necessary with TPN administration in patients at risk or with AKI or CKD.

Amino acid-derived compounds like creatinine can be metabolized to release ATP to fulfill the high energy demand of tissues during stress, injury, or infection. Along with SCr, a marker of creatinine utilization, enzymes [glycine amidinotransferase and guanidinoacetate *N*-methyltransferase (GAMT)] and substrates (glycine, arginine, and methionine) involved in creatinine synthesis can also be monitored, especially for scientific reporting.[88] It should be noted that although TPN is frequently necessary after premature birth, pediatric PN products do not include creatinine. Given that all the necessary creatinine must be produced from scratch, arginine and methionine, 2 precursor amino acids, will be in great demand. Arginine is a conditionally required amino acid for infants, even though de novo arginine synthesis occurs in the small intestine mucosa during first-pass metabolism, predominantly from dietary proline.[89]

On the other hand, GFR serves as a barometer for kidney health. Since the kidney is a significant source of GAA and is the only precursor for creatinine production in the body, maintaining homeostatic creatinine levels requires healthy kidney function. Therefore, GFR correlates with the body's creatinine reserves.[90]

As evident from the preceding sections, the prevention and management of TPN-KD involves careful monitoring of electrolyte imbalances and adjusting the composition of the TPN

solution accordingly. Serum electrolytes such as sodium, bicarbonate, potassium, chloride, calcium, trace elements such as selenium, zinc, copper, and hormones such as insulin are related to kidney functions. It is critical to monitor these variables while administrating TPN to detect potential decline in kidney function. Monitoring these variables also allows the detection of refeeding syndrome and evidence-based modifications to TPN composition formulas to suit individual patients' needs.[1,90] In addition to daily serum sodium, calcium, potassium, chloride, bicarbonate, SCr, urea, and protein, Hamdan and Puckett[3] underscored the need to monitor 12-hour charts of intake and outflow, 8-hourly urine sugar, and daily liver function tests.

The standard monitoring recommendations ASPEN[1] and ESPEN[76,78] during TPN include energy and protein intakes, complete blood counts, glucose, triglycerides, electrolytes, liver enzymes (including total and direct bilirubin, gamma-glutamyl transferase [GGT], aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total albumin and protein), and kidney function tests (SCr and urea) up to 3 times daily after initiating TPN until stable.

TOTAL PARENTERAL NUTRITION AND KIDNEY HEALTH: FUTURE PERSPECTIVES

Total parenteral nutrition is an indispensable lifesaving therapeutic modality for pediatric and adult kidney disease patients. However, several gaps in our understanding remain unaddressed. The evidence used to inform the current practice guidelines for TPN use in patients with kidney disease is based mainly on observational data with small participant size and expert opinions.[91] Therefore, a robust evidence base for macro- and micronutrient requirements, formulation, and dosing for patients with different types of kidney disease requiring TPN is urgently required to manage the risk of secondary complications beyond just kidney disease. Hyperglycemia, hypertriglyceridemia, hepatobiliary diseases, and deranged fluid/electrolyte balance remain significant areas of concern with TPN.

Additionally, the current understanding of the impact of TPN on gut atrophy and microbiota is primarily based on animal studies, and future clinical trials must address this gap. Moreover, there is a dearth of controlled trials evaluating the effects of TPN with EN on patient outcomes; the few available trials have been underpowered and yielded inconclusive results.[1] Lastly, the current evidence indicates that reducing the duration of TPN administration and promoting enteral feeding whenever possible reduce TPN-KD incidence.[24] However, optimal TPN initiation timing and TPN duration for patients with kidney diseases are yet to be established.

There are also several other gaps in our understanding of the effect of TPN on patient outcomes that were not addressed in this review due to the scope. For instance, early infants' brain development and healthy liver function depend greatly on optimal feeding, and TPN's impact on these organ systems is under-researched. In comparison to patients receiving continuous PN, studies in newborns indicate that those on cyclic PN have delayed liver damage.[92] Also, the impact of TPN on nutrient-induced gut-derived hormones such as ghrelin and glucagon-like peptide 1 is not fully understood outside laboratory animal studies. In terms of formulation, the superiority of lipids derived from fish or soybean oil, mixed oils enriched in omega-3 fatty acids, or short-chain fatty acids is yet to be established.

In conclusion, despite the broad range of adverse effects from limited research, TPN continues to spark interest as a lifesaving therapeutic in patients with kidney disease. The prevention and management of TPN-KD involves careful monitoring of electrolyte imbalances and adjusting the composition of the TPN solution accordingly. Patients with underlying comorbidities such as diabetes and preexisting kidney disease are at higher risk of developing TPN-KD. Therefore, close monitoring of kidney function is essential in these patients to detect and manage TPN-related kidney dysfunction early. Acute kidney injury can be reversible with appropriate management, such as adjusting the composition and rate of TPN administration and correcting electrolyte imbalances. However, if left untreated, TPN-KD can progress to CKD and irreversible kidney failure.[93]

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