Metabolic complications of parenteral nutrition in adults, part 2

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Purpose. Common metabolic complications associated with parenteral nutrition (PN) are reviewed, and the consequences of overfeeding and variables for patient monitoring are discussed.

Summary. Although PN is a lifesaving therapy in patients with gastrointestinal failure, its use may be associated with metabolic, infectious, and technical complications. The metabolic complications associated with PN in adult patients include hyperglycemia, hypoglycemia, hyperlipidemia, hypercapnia, refeeding syndrome, acid–base disturbances, liver complications, manganese toxicity, and metabolic bone disease. These complications may occur in the acute care or chronic care patient. The frequency and severity of these complications depend on patient- and PN-specific factors. Proper assessment of the patient’s nutritional status; tailoring the macronutrient, micronutrient, fluid, and electrolyte requirements on the basis of the patient’s underlying diseases, clinical status, and drug therapy; and monitoring the patient’s tolerance of and response to nutritional support are essential in avoiding these complications. Early recognition of the signs and symptoms of complications and knowledge of the available pharmacologic and nonpharmacologic therapies are essential to proper management. PN should be used for the shortest period possible, and oral or enteral feeding should be initiated as soon as is clinically feasible. The gastrointestinal route remains the most physiologically appropriate and cost-effective way of providing nutritional support.

Conclusion. PN can lead to serious complications, many of which are associated with overfeeding. Close management is necessary to recognize and manage these complications.

Index terms: Electrolytes; Manganese; Minerals; Nutrition; Toxicity

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Acid–base disturbances
Most acid–base disturbances in patients receiving PN therapy are related to the patients’ underlying conditions rather than to the PN components. However, excessive chloride salts in PN solutions may cause metabolic acidosis, and excessive acetate salts may cause metabolic alkalosis. The management of acid–base disorders relies mainly on correcting the underlying problem. Altering the chloride-to-acetate ratio in PN solutions may help to correct minor acid–base abnormalities. For example, because acetate is converted to bicarbonate at a 1:1 molar ratio, high acetate levels in PN help correct the bicarbonate deficit accompanied by losses from diarrhea and fistulas. Conversely, increasing the chloride content of PN may help correct metabolic alkalosis, such as occurs in patients with gastric fluid losses or undergoing diuretic therapy.

Liver complications
The overall frequency of PN-associated liver complications ranges from 7.4% to 84%. Some 15–40% of adult patients receiving long-term PN therapy may develop end-stage liver disease. The wide variation in the reported frequency is the result of heterogeneity in the population studied, the duration and composition of PN, and the liver complications reported in the studies. Mild to moderate elevation of liver enzymes is commonly seen within two weeks after starting PN, but liver enzymes return to normal after PN is
discontinued. With long-term PN, severe liver complications may occur, such as steatosis, steatohepatitis, cholestasis, and cholelithiasis. Although PN-associated cholestasis and hepatic steatosis can coexist, steatosis is more common in adults, while cholestasis is more common in children. Distinctive histopathological findings have been described in patients with PN-associated liver dysfunction. These include perportal inflammation, bile duct proliferation, portal bridging, canalicular and intralobular cholestasis, pigmented Kupffer cells, pseudocinacinar formation, portal–portal bridging, fatty droplets, pericellular and portal fibrosis, and cirrhosis.

**Hepatic steatosis and steatohepatitis.** The administration of excessive carbohydrate calories can cause hepatic steatosis and steatohepatitis. Hepatic steatosis describes fat accumulation in the hepatocytes, essentially in the form of triglycerides and cholesterol esters. Steatohepatitis is an advanced liver disease that is marked by severe hepatic inflammation that may rapidly progress to liver fibrosis and cirrhosis. Fat accumulation in the liver is the result of an imbalance between liver fat synthesis and secretion. Although hepatic steatosis is primarily the result of excessive dextrose infusion, other factors may also contribute, including lipid overfeeding and deficiencies in specific nutrients, such as carnitine, choline, and essential fatty acids. Patients with hepatic steatosis are mostly asymptomatic. However, steatosis should be suspected when hepatomegaly, malaise, and abdominal discomfort occur.

Dextrose and lipid balance. Glucose conversion to fat or de novo lipogenesis is presumably the result of an increased insulin:glucagon ratio in response to dextrose overfeeding. Excess calories and an imbalance in the carbohydrate:lipid ratio can both cause hepatic steatosis in PN patients. Hepatic steatosis occurred in 53% of patients who received only dextrose infusions, compared with 17% of patients who received mixed lipid and dextrose solutions (30% and 70% of nonprotein calories, respectively). Accumulation of fat in the liver was also reported in patients who received amino acid and carbohydrate mixtures, but not in patients whose PN also included lipid emulsions. In isolated case reports, patients who received lipid-free PN developed hepatic steatosis, possibly as a result of essential fatty acid deficiency. Hepatic steatosis resolved following lipid supplementation. However, the role of fatty acid deficiency in the development of steatosis remains uncertain, since fatty liver occurs even with adequate lipid supplementation. Nonetheless, excessive lipid infusion should be avoided, as it may also cause hepatic steatosis. Fat overload syndrome characterized by hypertriglyceridemia, fever, hepatosplenomegaly, coagulopathy, and multiorgan dysfunction occurred with lipid emulsion dosages of >4 g/kg/day.

These dosages, however, exceeded the maximum recommended lipid dosages of 1 g/kg/day in adults and 3 g/kg/day in children.

Carnitine deficiency. The role of carnitine deficiency in the pathogenesis of hepatic steatosis is less clear. Carnitine is an amine that transports LCTs across the mitochondrial membrane for oxidation. The improvement in fat metabolism with carnitine supplementation has led to the suggestion that carnitine plays a role in mobilizing hepatic lipid stores and thus could prevent steatosis. In animal studies, carnitine supplementation reduced liver fat accumulation. In humans, carnitine deficiency is mostly described in premature neonates because of their limited carnitine stores and their reduced ability to synthesize carnitine from methionine and lysine. Carnitine deficiency is rare in adults, but because carnitine is ubiquitous in the diet. One severely cachectic patient developed carnitine deficiency that was associated with elevated liver enzymes, hepatomegaly, and steatosis; the problems responded to carnitine supplementation. Carnitine supplementation has also been reported to prevent alcohol-induced hepatic steatosis. Carnitine is not routinely included in PN formulations. Carnitine supplementation in PN has been shown to enhance ketogenesis and fat metabolism in infants. Reduce hepatocyte fatty infiltration, and reverse hyperbilirubinemia. However, the effects of carnitine in preventing PN-associated liver toxicity have not been replicated in other studies. Although carnitine supplementation for one month normalized plasma and liver carnitine levels in patients receiving PN, it did not improve hepatic steatosis.

Choline deficiency. The role of choline deficiency in the pathogenesis of hepatic steatosis is also inconclusive. Choline, a quaternary amine that is ubiquitous in the diet and is derived in vivo from methionine metabolism, is essential in the synthesis of phospholipids and other components of cell membranes. Phosphatidylcholine is a byproduct of choline and is a substrate in lipoprotein synthesis. It has been proposed that reduced phosphatidylcholine synthesis as a result of choline deficiency leads to abnormal lipoprotein production and promotes triglyceride accumulation in the liver, causing hepatocyte distortion. Because choline is present in most foods, choline deficiency is rare. Although the methionine precursor is supplied in the amino acid mix in PN, choline deficiency has been reported in patients receiving long-term PN therapy. This is possibly due to methionine being metabolized differently when given intravenously rather than enteral. So far, limited data on the effects of choline supplementation in reversing steatosis in PN recipients...
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are available.\textsuperscript{168,186} A pilot study of 15 adult patients with hepatic steatosis receiving PN at home found that intravenous choline chloride supplementation at 2 g/day for up to 24 weeks was safe and effective in reducing the degree of hepatic steatosis.\textsuperscript{187} More research is still needed to clarify the role of choline in liver disease and to support any recommendation for routine choline supplementation in PN. Studies are under way to test the role of choline supplementation in preventing and treating PN-associated liver disease in adults.\textsuperscript{185} Hepatic steatosis and steatohepatitis. Hepatic steatosis can be reversed if a portion of the carbohydrates is replaced by lipid calories.\textsuperscript{188,189} In one study, replacing one third of carbohydrate calories in PN with lipid calories resulted in a 50% reduction in insulin secretion and improved glucose control.\textsuperscript{190} Avoiding carbohydrate overfeeding lowers insulin levels and minimizes the extent of carbohydrate conversion to fat in the liver.\textsuperscript{188} Monitoring liver function during PN is recommended. However, liver enzymes may not be sensitive indicators of hepatic steatosis, since they correlate poorly with the degree of fatty infiltration.\textsuperscript{191} Avoiding overfeeding and providing a balanced PN regimen are essential in preventing hepatic steatosis. A balanced PN regimen should provide 20–30% of total calories from lipids, 50–60% from dextrose, and the remaining 10–20% from amino acids.

Cholelithiasis. PN-associated cholelithiasis is the result of decreased gallbladder contractility during fasting. In the absence of oral intake or enteral stimulation, there is decreased secretion of cholecystokinin (CCK), a peptide hormone secreted in the duodenum in response to meals that induces gallbladder contractility. A distended gallbladder and an absence of gallbladder contractions were reported in patients receiving PN during prolonged fasting, but not in enterally fed patients.\textsuperscript{192} Bile accumulation in the biliary tract facilitates cholesterol gallstone formation\textsuperscript{193} and calcium bilirubinate precipitation in a form of sludge.\textsuperscript{194} Biliary sludge, gallstones, and hyperviscous and tenacious bile were found during surgical procedures to relieve refractory cholelithiasis in PN-dependent patients.\textsuperscript{195,196}

Patients with short-bowel syndrome are at increased risk of cholelithiasis and biliary sludge.\textsuperscript{197} This is due to several factors, including impaired bile flow during fasting, disrupted enterohepatic cycling with ileal resection, and canicular accumulation of toxic bile components, such as lithocholic acid.\textsuperscript{198,199} Twenty-three percent of patients who received PN for a mean of 13.5 months developed cholecystitis and gallstones.\textsuperscript{200} Gallbladder complications were significantly more frequent among PN recipients with ileal disease (Crohn’s disease or conditions requiring ileal resection) (40%) than among patients without ileal disease (25%). Among the patients with ileal disease, acalculous and calculous cholecystitis occurred in 32% of PN recipients, compared with 6% of a series of similarly defined patients who did not receive PN. Prolonged fasting, ileal disease and resection, and the use of narcotics and anticholinergics were correlated with an increased risk of gallbladder complications. The duration of PN therapy was not, however, correlated with the occurrence of gallbladder disease.

The best approach to preventing cholelithiasis is early initiation of oral or enteral feeding, even in small amounts, to stimulate CCK secretion, bowel motility, and gallbladder emptying. Cholecystectomy may be indicated in patients with cholecystitis. Injections of cholecystokinin octapeptide (CCK-OP) to induce gallbladder contractions and reduce biliary sludge have yielded mixed results and caused gastrointestinal intolerance in some patients.\textsuperscript{201,202} Treatment or prophylaxis with CCK-OP is uncommon and requires further evaluation.

Cholestasis. PN-associated cholestasis (PNAC) is less common in adults than in children. Factors predisposing patients to PNAC include a long duration of PN, overfeeding,\textsuperscript{161,203} short-bowel syndrome,\textsuperscript{204,205} bowel rest, bacterial translocation,\textsuperscript{203,206} and frequent sepsis.\textsuperscript{207} Limited data have also implicated excess methionine,\textsuperscript{208} phytosterols in lipid emulsions,\textsuperscript{209} and taurophilic deficiency (in children)\textsuperscript{210} in causing liver injury, but their effects remain uncertain.

Patients with PNAC may show increased serum liver aminotransferase, alkaline phosphatase, bilirubin, and \(\gamma\)-glutamyltransferase levels.\textsuperscript{211,212} An elevated alkaline phosphatase concentration is common in patients with PNAC and indicates biliary-tract damage. However, alkaline phosphatase may also be elevated in bone disease and is not a sensitive or specific marker of liver disease. Although elevated serum bilirubin is uncommon early in PN in adult patients, long-term PN may be associated with increased bilirubin when cholestasis occurs. A serum conjugated bilirubin concentration of \(\geq 2\) mg/dL is considered the most sensitive marker of cholestasis. Jaundice may also occur, depending on the severity of the clinical presentation.\textsuperscript{213}

PNAC is reversible if PN is discontinued before irreversible liver damage occurs. The underlying disorder requiring bowel rest and resulting in a lack of gut stimulation that made PN a necessity is a major predisposing factor for cholestasis. Bowel rest leads to increased intestinal permeability,\textsuperscript{214} alteration in gut hormone secretion,\textsuperscript{215} reduction in bile flow, decreased excretion of bile salts, bacterial overgrowth, bacterial and endotoxin translocation from the gut, and impaired intestinal immunologic mechanisms.\textsuperscript{216,217} Because of the detrimental effects of...
bowel rest, early initiation of enteral or oral feedings and weaning the patient from PN seem best to prevent PNAC.204 Other methods of preventing PNAC include avoiding overfeeding,79 using balanced sources of calories,218 cyclic PN infusion,219 and avoiding or treating sepsis.207

Pharmacologic measures can also be undertaken to prevent PNAC, improve bile flow, provide symptomatic relief of cholestasis, and reduce the toxic insult to the liver. Ursodiol has been shown to improve bile flow and reduce the clinical signs and symptoms of cholestasis.220 However, at 6–15 mg/kg/day, ursodiol yielded mixed and limited results. Ursodiol is available only in an oral dosage form, and its absorption may be limited in patients with intestinal resection. Also, the beneficial effects of ursodiol at usual dosages may be less than adequate to displace the toxic bile acids that are believed to accumulate and cause liver injury. CCK-OP has been used experimentally in infants to induce gallbladder contraction and improve bile flow.221,222 This approach reduced serum bilirubin levels and improved the clinical signs of cholestasis. However, experience with CCK-OP therapy in adults is limited, and its long-term effects on the liver are unknown.

Oral antibiotics, such as metronidazole, gentamicin, and neomycin, have been used to reduce intestinal bacterial overgrowth during prolonged bowel rest and in short-bowel-syndrome patients. Treating bacterial overgrowth reduces the population of bacteria translocating across the intestinal wall and the production of hepatotoxic endotoxins.223 Patients with short-bowel syndrome and end-stage liver disease may benefit from combined liver and bowel transplantation. Early referral of short-bowel-syndrome patients at high risk of liver complications for bowel transplantation may be an option before irreversible liver damage occurs.224

### Manganese toxicity

Manganese is a trace element that serves as a coenzyme in multiple chain reactions and is required for mucopolysaccharide production and cartilage, bone, and connective tissue formation. The recommended dosage of manganese supplementation has ranged from 0.08 to 0.5 mg/day. Typically, manganese is supplied in the PN solution at a daily dose of 0.5 mg as part of a multiple-trace-element additive. Since manganese is primarily eliminated via biliary excretion, patients with biliary obstruction or cholestasis may accumulate manganese to potentially toxic levels.225,226 Manganese accumulation has been mainly reported to cause neurotoxicity, especially in cholestatic patients receiving PN.225,227,228 A possible association between manganese accumulation and liver toxicity has also been suggested.229

Neurotoxicity is the most commonly reported toxicity of manganese accumulation in patients receiving PN. Magnetic resonance imaging (MRI) revealed deposition of manganese in the basal ganglia of PN-dependent patients.230 Patients who showed neurologic abnormalities with high blood manganese levels had brain abnormalities on MRI imaging.231 Reported neurologic symptoms related to manganese toxicity included parkinsonian symptoms, including muscle rigidity, tremor, gait, and mask-like facies,232 as well as neuropsychiatric disorders, such as headache,233 confusion, somnolence, and weakness.234 The neurologic signs and symptoms were reversed after manganese was removed from the PN solution.233,235

The effects of manganese on the liver are less clear. It has been postulated that manganese may cause hepatotocicity by affecting the biliary canalicular membrane.236,237 Although a correlation was found between elevated blood manganese concentrations and increased liver enzymes, there is no firm evidence that hypermagnesemia causes cholestasis.238,239 In one study of children who received PN for more than two weeks, a significant correlation was found between whole-blood manganese concentrations and elevated plasma aspartate aminotransferase and bilirubin levels.229 Manganese and bilirubin levels decreased after reduction or discontinuation of manganese supplementation. On the other hand, another study showed no significant difference in the frequency of cholestasis between two groups of infants who received either large or small amounts of manganese in PN.240 However, blood manganese concentrations were not measured in all infants in the study.

Patients with hypermagnesemia may or may not exhibit signs and symptoms of manganese toxicity. Abnormally elevated serum manganese levels have been reported in patients receiving long-term home PN without noticeable symptoms of toxicity.241 Since hypermagnesemia may occur even in the absence of cholestasis, it is possible that the current practice of manganese supplementation in PN at 0.5 mg/day may exceed the daily requirement or that PN additives may be a possible source of manganese contamination.242,243 To date, no clear relationship has been established between blood manganese levels and neurologic or liver abnormalities. Also, whole-blood or serum manganese levels may not necessarily reflect tissue stores.226 Nonetheless, periodic measurements of blood manganese concentrations provide a safety tool for monitoring manganese status. Restricting manganese in cholestatic patients receiving PN is warranted to prevent its accumulation.

### Metabolic bone disease

Metabolic bone disease, including osteomalacia, osteopenia, and osteoporosis, has been reported in patients receiving long-term PN.244,245 The actual frequency of metabolic...
bone disease in PN patients is unknown, but reports suggest that 40-100% of patients receiving long-term PN may have some degree of bone demineralization. Many patients with metabolic bone disease are asymptomatic, and the diagnosis is at times incidental. Symptomatic patients have bone pain, back pain, and fractures. Radiologic techniques commonly used in diagnosing bone disease include bone mineral density testing and qualitative computed tomography. Biochemical markers of metabolic bone disease may include increased serum alkaline phosphatase levels, low to normal plasma parathyroid hormone (PTH) levels, hypercalcemia, hypocalcemia, hypercalciuria, normal serum 25-hydroxyvitamin D levels, and low serum 1,25-dihydroxyvitamin D levels.

PN-related factors that predispose patients to metabolic bone disease include deficiencies of calcium, phosphorus, and vitamin D; vitamin D toxicity; aluminum toxicity; amino acid and hypertonic dextrose infusions. Other non-PN-related factors, such as corticosteroid therapy and metabolic acidosis, may contribute to bone loss. Corticosteroids inhibit bone formation and cause osteoporosis by reducing osteoblast proliferation and type I collagen synthesis, increasing renal calcium excretion, and inhibiting vitamin D-dependent calcium absorption. Chronic metabolic acidosis may cause bone demineralization by affecting the bone buffering systems or impairing vitamin D metabolism.

Calcium deficiency. Calcium deficiency in PN recipients is a major cause of metabolic bone disease. Hypocalcemia occurs as a result of decreased calcium intake or increased urinary calcium excretion or both. Solubility problems with calcium and phosphate limit the amounts of calcium and phosphorus that can be supplemented with PN and still avoid calcium and phosphate precipitation. Factors that cause hypercalcuria include excessive calcium and inadequate phosphorus supplementation; amino acids in PN solutions; cyclic PN infusion; and chronic metabolic acidosis.

Several studies have correlated amino acid intake with urinary calcium excretion. In one study, mean ± S.D. urinary calcium elimination increased from 287 ± 46 mg/day to 455 ± 58 mg/day when amino acids were increased from 1 to 2 g/kg/day. Although the exact mechanism of protein-induced hypercalcuria is unknown, it could be related to an increased glomerular filtration rate or increased excretion of sulfates, ammonia, and urinary titratable acidity that decreases renal calcium reabsorption. Alternatively, acidosis may contribute to bone loss. In renally impaired patients who developed osteomalacia with chronic hyperchloremic metabolic acidosis, treatment with oral bicarbonate resulted in improvement in the signs and symptoms of bone disease. Adequate amounts of acetate and chloride should be provided in PN solutions to maintain a normal acid-base balance. Patients with short-bowel syndrome who have significantly elevated lactic acid levels also developed osteomalacia, bone pain, and bone fractures, which led to the conclusion that lactic acidosis in these patients could have contributed to metabolic bone disease.

Cyclic PN infusion has also been shown to increase urinary calcium losses. In one study, urinary calcium excretion increased by 18% and 28% when PN was infused over 18 or 12 hours, respectively, compared with 24-hour PN infusion. About 80% of urinary calcium loss occurred during PN cycling that resulted in a negative calcium balance. However, another study showed that, although urinary calcium excretion increased during cyclic PN infusion, total mean daily urinary calcium excretion was not significantly affected.

Aluminum toxicity. Aluminum toxicity causes osteomalacia in patients receiving long-term PN therapy. Excess aluminum is mainly found as a contaminant of multivitamin, trace-element, and calcium and phosphate salt products. Because the kidneys are the main route of aluminum elimination, premature infants with inefficient kidney function and patients with renal failure are at higher risk of aluminum toxicity. Aluminum may exert toxic effects on the bones by impairing calcium bone fixation, reducing PTH secretion, or inhibiting the conversion of 25-hydroxyvitamin D to the active 1,25-dihydroxyvitamin D.

FDA has been investigating the aluminum contamination problem of intravenous products since 1986. In 2000, FDA issued a rule specifying acceptable aluminum concentrations in large-volume intravenous products. The rule states that for large-volume intravenous products used in PN, the package insert section under “precautions” should indicate that the product contains aluminum at a concentration no higher than 25 µg/L. Because the toxic effects of aluminum occur at the microgram level, FDA has defined a possible safe upper limit for parenteral aluminum intake as <4–5 µg/kg/day. Adhering to these limits requires an extensive effort by manufacturers to reduce aluminum contamination in the intravenous products used in the making of PN solutions.

Vitamin D toxicity. Typical vitamin D supplementation in adult PN solutions is 200 IU/day. It has been suggested that vitamin D in the multivitamin mix added to the PN solution may be toxic to the bones. The withdrawal of vitamin D from PN was associated with improvement in the clinical and biochemical indices of bone demineralization in PN-dependent patients. Also, positive calcium balance, subsidence of bone pain, fracture healing, and decreased calciuria and phosphaturia.
occurred after vitamin D removal. A two-year follow-up examination of patients for whom vitamin D was withheld from PN formulations showed normal bone histomorphometry despite a reduction in serum 25-hydroxyvitamin D concentrations.\(^{268}\) Withdrawal of vitamin D from PN for 4.5 years also resulted in improvement in mineral content in the lumbar vertebrae and normalization of serum PTH and 1,25-dihydroxyvitamin D concentrations.\(^{269}\) Although vitamin D toxicity has been suggested as a cause of metabolic bone disease, vitamin D deficiency also results in bone loss. To date, data on vitamin D excess and bone disease remain controversial. It has been suggested that a trial course of vitamin D omission from PN solutions may be warranted in PN recipients who show reduced serum 1,25-dihydroxyvitamin D and PTH concentrations and normal serum 25-
hydroxyvitamin D concentrations.\(^{267}\)

**Prevention and treatment.** To prevent metabolic bone disease in patients receiving PN, it is essential to provide sufficient calcium and phosphorus to improve bone mineralization.\(^{268,269}\) Although removal of vitamin D from PN solutions has been suggested for selected patients, the role of vitamin D in causing bone disease at the current dosage of 200 IU/day is inconclusive. Also, it is impractical for compounding pharmacies to remove vitamin D from the intravenous multivitamin mix. Routine monitoring of serum vitamin D, calcium, and phosphorus levels is recommended. However, insofar as aluminum is concerned, pharmacy policies should be established to regularly monitor aluminum levels in PN solutions. PN recipients with suspected metabolic bone disease should have their serum aluminum concentrations measured to rule out aluminum toxicity.

Theoretically, the use of bisphosphonates is a potential but unproven therapy for metabolic bone disease, although they are used to decrease bone resorption in postmenopausal osteoporosis. Patients undergoing long-term PN therapy should be encouraged to perform regular low-intensity exercises that may help increase lumbar spine bone density. Patients receiving home PN therapy should receive bone-density measurements yearly and whenever metabolic bone disease is suspected.\(^{266}\)

**Conclusion**

PN can lead to serious metabolic complications, many of which are associated with overfeeding. Close monitoring is necessary to recognize and manage these complications.

**References**

175. Kollef M H, McCormack M T, Caras WE
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221. Rintala RJ, Lindahl H, Pohjavuori M. Total parental nutrition-associated cholestasis in surgical neonates may be reversed by intravenous cholecystokinin.