Hepatobiliary, renal and bone complications of intestinal failure

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Abnormal liver function tests in patients with intestinal failure (IF) may be due to the underlying disease, IF or the treatments given (including parenteral nutrition (PN)). PN-related liver disease in children usually relates to intrahepatic cholestasis and in adults to steatosis. Steatosis may be consequent upon an excess of carbohydrate, lipid or protein, or upon a deficiency of a specific molecule. Pigment-type gallstones are common in adults and children with IF; these develop from biliary sludge that forms during periods of gallbladder stasis. Ileal disease/resection, parenteral nutrition, surgery, rapid weight loss and drugs all increase the risk of developing gallstones. Gallstone formation may be prevented by reducing gallbladder stasis (oral/enteral feeding or prokinetic agents), altering bile composition, or by means of a prophylactic cholecystectomy. Calcium oxalate renal stones are common in patients with a short bowel and retained functioning colon and are consequent upon increased absorption of dietary oxalate; they are prevented by a low-oxalate diet. An osteopathy may occur with long-term parenteral nutrition.

Key words: intestinal failure; short bowel; parenteral nutrition; liver disease; gallstones; renal stones; osteopathy.

Intestinal failure (IF) occurs when there is reduced intestinal absorption so that macronutrient and/or water and electrolyte supplements are needed to maintain health and/or growth. Without such treatment or compensatory mechanisms undernutrition and/or dehydration will result. This definition allows the severity of intestinal failure to be graded according to the type of nutritional support needed (severe: parenteral nutrition (PN), moderate: enteral nutrition, mild: oral supplements) and a wide range of underlying diagnoses are included. Acute (or temporary) intestinal failure is potentially reversible and is most commonly encountered; over 90% of patients with severe IF are seen in the peri-operative period. Chronic intestinal failure is less common, and most patients in this category have a short bowel.

The aims in managing a patient with IF are:
1. to provide the nutrition/water and electrolytes necessary to maintain health/growth;
2. to reduce the severity of intestinal failure (convert severe to moderate or mild intestinal failure);
3. to prevent and treat complications;
4. to achieve a good quality of life.

This chapter relates to the prevention and treatment of hepatobiliary, renal and bone complications. In general the complications can relate to the underlying disease, to IF, or to the treatments given.

HEPATOBILIARY COMPLICATIONS

Hepatobiliary problems associated with IF give rise to parenchymal (steatosis or ‘fatty’ liver) or cholestatic liver disease, or to gallstones. In adults the predominant abnormality is steatosis and gallstones, while in children (most data from neonates and infants) it is intrahepatic cholestasis and gallstones. The difference between hepatobiliary complications in adults and children may reflect the immaturity of the neonatal biliary excretion system, which may be more sensitive to hypoxia than that of an adult.

Steatosis occurs early (within 2 weeks of starting PN), is usually asymptomatic (although it can cause painful hepatomegally), is reversible and may rarely progress to steatohepatitis (or intrahepatic cholestasis) and to cirrhosis. Steatosis is due to accumulation of mainly triglyceride within the cytoplasm of hepatocytes (macrovesicular steatosis) and is most prominent around the portal tracts, a distribution also found with some hepatotoxins (e.g. phosphorus). Steatosis is often detected on ultrasound, CT or MRI scans or found on a liver biopsy, but may not be suspected as the liver function tests (LFTs) may be of a cholestatic nature. Steatosis can theoretically occur by many possible mechanisms: excess lipid reaching the liver (from infusion or tissues), increased hepatic lipid uptake, increased lipid synthesis, failure of fatty acids to enter mitochondria, decreased β-oxidation, failure of lipoprotein (very low density lipoprotein, VLDL) synthesis or secretion. Excessive carbohydrate and an impairment of hepatic triglyceride secretion may be most important. Insulin resistance (or deficiency of insulin) is the most reproducible factor in the development of non-alcoholic fatty liver disease.

Intrahepatic cholestasis is associated with an inflammatory infiltrate (mainly lymphocytes), occurs late (after 3 weeks PN), is slow to resolve (LFTs return to normal 5 months after PN is stopped) and commonly gives rise to cirrhosis and hepatic failure. It may follow from steatosis.

In patients with acute IF and receiving PN, abdominal sepsis, renal failure, pre-existing liver disease and blood transfusions correlate better with abnormal liver histology than PN. Alcoholism, obesity, non-insulin-dependent diabetes mellitus and hyperlipidaemia are all associated with steatosis, and may be important contributing factors to abnormal LFTs. A patient with abnormal LFTs while receiving PN should be screened for sepsis and renal impairment: their past and current medications (including alcohol/steroids) and blood product transfusions are examined. In addition, screening tests for general causes of acute and chronic liver disease (e.g. viral hepatitis (A, B or C), autoimmune hepatitis, primary biliary cirrhosis, alpha 1 antitrypsin deficiency, haemachromatosis and Wilson’s disease) are usually performed. Mechanical obstruction of the biliary tree is excluded with an abdominal ultrasound or magnetic resonance cholangio-pancreatography (MRCP).

If liver abnormalities are due to IF, they may relate to the underlying disease, intestinal failure or to the treatments (nutrition/drugs) given (Table 1). As the causes of
liver abnormalities are usually multiple, it may be difficult to identify the key contributing factor(s). The abnormal LFTs are rarely associated with permanent liver damage.

Underlying disease

Inflammatory bowel disease (IBD) may be associated with sclerosing cholangitis (usually men with ulcerative colitis) or choledolithiasis (Crohn’s disease). Many patients (up to 53%) with IBD have histological abnormalities (steatosis and pericholangitis) on liver biopsy, even though their LFTs are normal.\textsuperscript{10,11} Patients who have had a bowel resection for mesenteric vascular disease may have associated diabetes or hyperlipidaemia.

Shock, surgery, malignancy (especially haematological) and sepsis may all cause abnormal LFTs independently of the PN, and this may be mediated by tumour necrosis factor.\textsuperscript{12}

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<th>Table 1. Causes of liver disease in intestinal failure (IF).</th>
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<td>Other factors that may contribute to steatosis/abnormal liver function tests include alcohol, diabetes, obesity and many drugs (e.g. steroids, anaesthetic agents and opiates).</td>
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Intestinal failure

Undernutrition

If unrecognized or inadequately treated, malabsorption of nutrients may result in undernutrition. Protein-calorie malnutrition (kwashiorkor not marasmus), and rapid weight loss are all associated with macrovesicular steatosis. In kwashiorkor, in which there is severely limited protein intake, the steatosis may be due to insulin resistance, reduced lipoprotein synthesis, or to essential fatty acid or carnitine deficiency. The liver damage of kwashiorkor does not lead to cirrhosis following successful nutritional treatment.

Bacterial endotoxin/overgrowth

If any bowel is defunctioned, blind ending, immotile or dilated, the intestinal mucosa may become damaged and bacterial endotoxins may cross the mucosa. A similar situation occurs with bowel inflammation, alcohol ingestion, hypoperfusion or hypoxia. The endotoxin may cause hepatic injury, leading to hepatic steatosis by cytokine release (especially tumour necrosis factor).

Metronidazole prevents steatosis after jejunoileal bypass, and has prevented a rise in LFTs in patients given PN.

Short bowel

Abnormal LFTs are most common in those with a very short small bowel (less than 100 cm) remaining, and death from liver failure is most likely to be in those with the shortest remaining lengths of bowel. Experimentally, LFTs return to normal after small bowel transplantation.

In patients with less than 200 cm small bowel remaining, an alkaline phosphatase and γ-glutamyltransferase level above the normal range is common (49% and 34% respectively); an elevated bilirubin occurred in 10% and an elevated AST in 7%.

Treatment related

Parenteral nutrition

The abnormal LFTs with PN start with a rise in the AST, and the peak abnormality occurs at about 2 weeks, with a range of 1–4 weeks. The frequency of LFT abnormalities in patients receiving PN varies from 25 to 100%. Hyperbilirubinaemia occurs in 0–46% of patients given PN. Clinicians often attribute abnormal LFTs or liver disease in patients with IF to PN; however, PN is rarely the main cause.

Chronic cholestasis, as defined by two of three tests (γ-glutamyltransferase, alkaline phosphatase or conjugated bilirubin) being more than 1.5 times the upper limit of normal for more than 6 months, occurred in 65% of patients receiving long-term home parenteral nutrition (HPN). Of patients fed for more than 2 years, 26% at 2 and 50% at 6 years had severe liver complications (65% chronic cholestasis). Some 15% of adult patients receiving HPN in the USA developed end-stage liver disease, and this was most common in those with a very short bowel and chronic inflammation. Liver disease is the cause of death of 0–14% adult patients receiving HPN. 22% of all deaths of patients on HPN were due to liver disease.

Liver function problems most commonly occur with PN in neonates if they are premature, have low birth weight, sepsis, no oral intake and having gastrointestinal
surgery (usually leading to a short bowel), and in conditions associated with hypoxia (intracranial haemorrhage and patent ductus arteriosus). The greatest problems (cholestasis, fibrosis and high mortality) are in patients (often children) with the shortest length of remaining bowel who are dependent for all their nutritional needs upon the PN.

The liver-related problems of PN occur even if the PN is infused into the portal vein in animal experiments. The liver-related problems of PN occur even if the PN is infused into the portal vein in animal experiments.3,4,30

PN may cause liver function abnormalities if there is no oral intake, an excess or deficiency of a macro- or micronutrient.

No oral/enteral intake
No oral/enteral nutrition may cause problems due to a reduction in the circulating plasma levels of specific gastrointestinal hormones, bacterial overgrowth, mucosal atrophy, increased intestinal permeability, and impaired mucosal immunity. Upper gastrointestinal hormones that increase the release of insulin (gastric inhibitory peptide and glucagon-like peptide-1) are reduced if there is no oral/enteral intake, so higher serum glucose levels are likely to result. Lower gut gastrointestinal hormones that stimulate small intestinal growth (e.g. glucagon-like peptide-2) are reduced if no food enters the lower gut, and may contribute to small bowel mucosal atrophy.

Bacterial overgrowth enhances secondary bile acid production and may reduce bile flow22, thereby predisposing to both intrahepatic cholestasis and gallstones. Bacterial overgrowth, mucosal atrophy, increased intestinal permeability and impaired mucosal immunity could allow endotoxins and bacteria to cross the mucosa. However, in humans, poor nutritional status, parenteral nutrition and mucosal atrophy do not predispose to bacterial translocation33, but distal gut obstruction and IBD do.34

Excess nutrients
When parenteral nutrition was first used, large amounts of energy were given (more than 2000 kcal daily, more than 5 g/kg/day glucose (which is the maximum glucose oxidation rate in burns patients35), 2 g/kg/day lipid (maximum clearance in health is 3.8 g/kg/day) and 2 g/kg/day amino acids) and steatosis resulted. All the macro-nutrients in excess can cause steatosis with a chronic cholestatic picture in adults and children. A portion of the abnormality may be due to macronutrients increasing hepatic oxygen consumption, causing a relative hypoxia (especially in children) and thus leading to liver injury.

Excess glucose increases insulin secretion and stimulates the rate-limiting enzymes for fatty acid synthesis (acetyl CoA carboxylase and fatty acid synthetase), and so contributes to hepatic steatosis.38 Steatosis was less likely when 30% of the glucose energy was replaced by lipid39; the introduction of lipid also reduced insulin levels. In animal studies, parenteral glucagon, which causes hepatic fatty acid release while inhibiting synthesis, prevented PN-induced steatosis.40

In neonates and infants the excessive administration of parenteral amino acids can cause cholestatic jaundice.3,41,42

Excessive lipid may be expected to cause liver disease partly by increasing pro-inflammatory factors. The administration of more than 1 g/kg/day of lipid (as a 20% lipid emulsion rich in ω6 polyunsaturated fatty acids) can result in a severe progressive cholestatic jaundice.38,43

A mixture of long- and medium-chain triglycerides in a PN bag was protective against endotoxin-induced liver damage in rats44 and improved macrophage function. However
in humans, a mixture of long- and medium-chain triglycerides has only resulted in a lower serum bilirubin level.\textsuperscript{45,46} 

A fat overload syndrome (with the same characteristics as Silverstein’s syndrome) can occur when more than 4 g/kg/day lipid is given.\textsuperscript{47–49} In this, polyunsaturated fatty acids and phospholipids cannot be cleared from the reticuloendothelial cells and thus accumulate in the cytoplasm of macrophages in the liver (Kupffer cells), spleen and bone marrow and in circulating leukocytes. Fever, hepatosplenomegaly, coagulopathy (thrombocytopenia), pulmonary infiltrates and itching may occur.\textsuperscript{49} A cholestatic picture occurs in the LFTs, and a microvacuole steatosis (foamy macrophages) on liver biopsy is observed when specific stains (e.g. oil red O or Sudan Black) are used. If the bone marrow is examined, sea-blue histiocytes may be shown with Giemsa staining.\textsuperscript{50} This syndrome is most likely to occur when lipid has been given for a long time (median 5 years) and was common when cottonseed oil was used prior to the availability of soybean emulsions. When the intravenous lipid is stopped, the itching recedes over several months.\textsuperscript{50}

Other compounds or elements in excess have been associated with abnormal LFTs in patients receiving PN; these include vitamin A, aluminium, copper and toxic by-products (photosterols and tryptophan metabolites). Copper and manganese are excreted in bile, and should not be given if obstructive jaundice is present. Tryptophan in solutions containing sodium bisulphite (a preservative no longer used) reacts to produce a hepatotoxic product that causes cholestatic LFTs.\textsuperscript{51}

Lack of nutrients

Choline, a precursor for phospholipid biosynthesis, and thus lipid secretion as very low density lipoprotein (VLDL), can become deficient and cause reversible LFT abnormalities.\textsuperscript{52–54} Oral supplementation of the diet with lecithin, from which choline is manufactured, reduces hepatic fat content.\textsuperscript{54}

Taurine is the principle bile acid conjugate in neonates; it promotes bile flow and protects against lithocholate toxicity.\textsuperscript{36,55} Neonates may not be able to make taurine from methionine and cysteine\textsuperscript{55}, so they rely upon taking enough in the diet. Taurine plasma levels may be very low in neonates receiving PN, and are associated with severe cholestatic liver dysfunction.\textsuperscript{57} After an ileal or colonic resection, there is a reduced secretion of bile acids by the liver, especially of taurine conjugates, and there is increased secretion of secondary bile acids (especially lithocolic acid, which is the least soluble bile acid). Thus, it may be beneficial to supplement PN with taurine in neonates\textsuperscript{58} and this with early treatment of sepsis, PN cycling and some enteral feeding improved the outcome in children with a short bowel.\textsuperscript{59}

Carnitine is responsible for the transfer of long-chain fatty acids into the mitochondria for oxidation. It can be synthesized from the essential amino acids methionine and lysine (both present in PN), but under conditions of stress carnitine may not be manufactured in sufficient amounts. Low plasma levels of lysine and of carnitine have been observed in patients receiving HPN. These low levels are associated with a raised alkaline phosphatase, a low serum albumin and steatosis.\textsuperscript{60} Carnitine supplementation may minimize fatty infiltrates\textsuperscript{61}, but its addition to a PN regimen did not improve the abnormal LFTs of four HPN patients.\textsuperscript{62}

Glutamine is not given in conventional PN, although it may help the mucosal barrier integrity and it protects against steatosis in animals.\textsuperscript{72}

Essential fatty acid deficiency may develop within 2 weeks of glucose-based PN (no lipid); it causes steatosis\textsuperscript{63–65} by impairing hepatic lipoprotein transport. If no lipid is given in a PN regimen, care is needed to avoid essential fatty acid deficiency.
Low serum phosphate levels may be important and could worsen hepatic hypoxia and steatosis. The serum phosphate levels correlate inversely with serum AST levels. Molybdenum deficiency has been associated with cholestasis. Other anti-oxidants (e.g. vitamin E and selenium) may be important.

Cyclical PN
Continuous PN results in hyperinsulinism and high rates of lipogenesis. Cyclic PN, in which PN is stopped for at least 8 hours, resulted in lower insulin levels, less hepatomegally and improved LFTs. Cyclic PN permits a period of FFA mobilization from body stores during the non-infusion (low insulin) period.

Other factors
Patients with IBD who are receiving PN have increased concentrations of the secondary bile acid lithocholic acid in their bile (7–15% of bile acids compared with <1% normally), and this was associated with the development of abnormal LFTs.

Drugs
While many drugs (including antibiotics) can be hepatotoxic, codeine phosphate causes sphincter of Oddi dysfunction and octreotide predisposes to gallstones (see below).

Prevention/treatment
It may be difficult to determine how much/which hepatotoxic effects are due to PN and which are due to other factors. The methods of avoiding abnormal LFTs in patients on PN include avoiding/treating sepsis, some oral/enteral feeding, avoiding over-feeding (particularly carbohydrate and staying below the maximum glucose oxidation rate), while giving adequate macro- and micronutrients (consider choline/carnitine), vitamins and trace elements, and using cyclical PN. Cholestasis may be avoided/treated by giving taurine to infants, and ursodeoxycholic acid may have a role. If abnormal LFTs occur and infective, autoimmune, congenital, obstructive and drug causes are excluded, a trial of metronidazole may be helpful. Severe liver disease in a patient with a very short bowel is one of the most common reasons for performing a small bowel transplant (usually with a liver).

GALLSTONES
Gallstones are common in patients with acute and chronic intestinal failure. They occur in 45% of patients with a short bowel (with and without a colon), and are more common in men than in women. Supersaturation of bile, nucleation and crystallization, and reduced gall bladder contractility are traditionally the key factors that produce a ‘lithogenic bile’. In patients with IF, the stones are of the pigment type, composed of calcium bilirubinate. The stones probably develop in biliary sludge which has formed due to gallbladder stasis. Biliary sludge contains calcium bilirubinate or unconjugated bilirubin, cholesterol monohydrate crystals, and increased amounts of mucin glycoproteins. Biliary sludge may disappear spontaneously, but frequently evolves into gallstones. Sludge may persist or recur in 50% of cases, and gallstones may form in up to 14% of affected subjects over 3 years. Calcium bilirubinate crystals, within biliary sludge, are more commonly found in men than in women.
Gallstones in IF patients may occur owing to ileal disease/resection, fasting/PN, surgery, rapid weight loss or drug treatments (Figure 1). Bacterial overgrowth, as mentioned earlier, may have a role.32

**Ileal disease/resection**

There is an increased prevalence of gallstones (25%) in patients with Crohn's ileitis or ileo-colitis 78–80, and these occur with equal frequency in men and women.80,81 Men with a short bowel (with or without a retained colon) have a higher prevalence of gallstones than do women.73 These stones often appear calcified on a plain abdominal radiograph.79 Gallstones are more common in patients with ileitis than in those with ileo-colitis or colitis 82, and their likelihood may increase with the length of bowel resected81, the duration of disease, previous surgery, and the age of the patient.80,83

The disruption of the enterohepatic circulation and consequent loss of bile salts should lead to an increase in cholesterol saturation (relates to concentrations of cholesterol, bile salts and phospholipids); this was the case in some studies of patients with 'ileal dysfunction or resection'84,85 but not in others.84 A reduced amount of deoxycholic acid and an increased amount of ursodeoxycholic acid (UDCA) (which helps keep cholesterol soluble) are found in the bile of patients with ileal Crohn's disease.85,86 Bilirubin concentrations in bile are two- to threefold higher in patients with ileal disease as compared to those with no ileal disease85,86, while phosphatidylcholine levels are not different.85 The majority of patients (children and adults) who undergo ileal resection and require long-term total parenteral nutrition (TPN) develop pigment gallstones.87 In patients with Crohn's disease gallbladder contractility is reduced after a fatty meal88,89, which may contribute to the formation of biliary sludge.

**Fasting/total parenteral nutrition**

Long-term parenteral nutrition in both adults and children is commonly associated with gallstones (40%)90–96 which, in patients with a very short bowel, are often symptomatic.90 Acute cholecystitis may occur, but is less common.94,97 Gallstones are more common in men than in women.93 Some 23% of adults develop gallbladder
disease after starting TPN. In children, cholelithiasis may be associated with a massively dilated gallbladder. When parenteral nutrition is total (no oral intake), or in patients who fast, biliary stasis and hence biliary sludge rapidly form. There is a progressive increase in the incidence of biliary sludge from 6% after 3 weeks of TPN, to 50% between 4 and 6 weeks, reaching 100% after 6 weeks. The sludge gradually disappears when oral refeeding is begun. Gallstones will have started to become apparent by 4 months. Bile is not supersaturated consequent on TPN, but bile flow is impaired and gallbladder emptying during both continuous and cyclic infusions is reduced. A medium/long-chain triglyceride mixture in a PN regimen may be more likely to cause biliary sludge than long-chain triglycerides alone.

Surgery

Major abdominal surgery (not involving the biliary system), cardiac valve replacement surgery, and a period in an intensive care therapy all predispose to gallstone development, with an equal sex incidence. This is again likely to be due to bowel rest causing biliary stasis, biliary sludge and the formation of gallstones.

Rapid weight loss

Cholesterol gallstones are common (40%) in morbidly obese patients, and this figure increases with a diet causing rapid weight loss or after weight-reducing surgery. Some 38% of patients undergoing gastric by-pass surgery developed gallstones which formed during the time of maximal weight loss. Reduced gallbladder motility is likely to be the most important factor, but cholesterol saturation also increases. A significant increase in the gallbladder volume occurred in obese patients taking a low-energy, low-fat diet after 10 days, and could be secondary to minimal cholecystokinin (CCK) secretion or to excess secretion of pancreatic polypeptide or somatostatin (gallbladder wall relaxants).

Drug treatments

Octreotide, a long-acting somatostatin analogue used in the treatment of a high-output jejunostomy, increases the risk of cholelithiasis. It reduces post-prandial gallbladder contractility and slows intestinal transit; thus, more secondary (more lithogenic) bile acids are formed by intestinal bacteria. Opiate and anti-cholinergic drugs reduce gallbladder contractility, and may increase the probability of developing gallbladder disease.

PREVENTION OF SLUDGE AND GALLSTONES

Gallbladder stasis may be prevented by oral/enteral feeding, CCK injections, pulsed amino acid infusions, non-steroidal anti-inflammatory drugs (NSAIDs), sphincterotomy or prophylactic cholecystectomy. Bile may be made less lithogenic by reducing secondary bile acid formation (cisapride or metronidazole) or giving ursodeoxycholic acid (UDCA).
Oral/enteral feeding

Stimulation of gallbladder contraction by giving only a minimal oral intake of food (protein and long-chain triglycerides) causes sufficient release of CCK to prevent biliary sludge formation. Four weeks after stopping TPN and resuming an oral diet, TPN-induced biliary sludge disappeared.\textsuperscript{114}

Cholecystokinin

CCK given to adults and neonates receiving TPN stimulates gallbladder contraction, thereby preventing biliary stasis and subsequent sludge formation.\textsuperscript{115,116}

Pulsed amino acid infusions

Periodic rapid infusions of amino acids stimulate endogenous release of CCK and thus cause gallbladder contraction, preventing biliary stasis and sludge formation.\textsuperscript{117–119}

Non-steroidal anti-inflammatory drugs

Studies in the prairie dog (which predictably develops cholesterol gallstones when fed a high cholesterol diet) showed that high-dose aspirin prevented gallstone recurrence after dissolution therapy.\textsuperscript{120} Patients with gallstones given therapeutic doses of indomethacin have an increase in gallbladder emptying.\textsuperscript{121} Thus, indomethacin may have a prokinetic effect on a diseased gallbladder and may prevent gallstone formation.

Sphincterotomy

In the prairie dog, a sphincterotomy (sphincter of Oddi) prevented cholesterol gallstones forming, although the bile remained supersaturated.\textsuperscript{122} No such studies have been performed in humans.

Prophylactic cholecystectomy

As patients with a short bowel are at high risk of forming gallstones, prophylactic cholecystectomy has been proposed at the time of the last resection.\textsuperscript{123}

Cisapride/metronidazole

A slowing of intestinal transit will result in luminal bacteria manufacturing more secondary bile acids (e.g. lithocholic acid). Cisapride, which increases gastrointestinal transit, reduces the formation of secondary bile acids by intestinal bacteria, and thus reduces the lithogenicity of bile in patients with gallstones, while improving gallbladder emptying.\textsuperscript{124} Cisapride may have a future role in preventing gallstone formation. However, most therapies for patients with a short bowel aim to slow intestinal transit, so its use may be limited to patients with intestinal dysmotility.

Metronidazole suppresses anaerobic intestinal luminal organisms (thus the production of secondary bile acids) and reduced the PN associated rise in LFT's in patients with Crohn's disease.\textsuperscript{17} Metronidazole may have a role in preventing cholestasis.
Ursodeoxycholic acid (UDCA)

UDCA is a secondary bile acid that, unlike others, reduces cholesterol crystallization, by reducing the concentrations of promoting factors (e.g. aminopeptidase N, haptoglobin and some immunoglobulins). UDCA is an effective therapy in reducing PN-related cholestasis (see earlier) and may be an effective medical prophylaxis/treatment for cholestasis.

NEPHROLITHIASIS

Both uric acid and calcium oxalate renal stones are common in patients with an ileostomy, and may be related to many of these patients being chronically dehydrated. Calcium oxalate renal crystallization is predominantly a problem in patients with chronic intestinal failure due to a short bowel and retained colon. Calcium oxalate may form renal stones in the collecting system, or may be deposited in the renal parenchyma (nephrocalcinosis). Patients with a short bowel and retained colon have a 25% chance of developing symptomatic calcium oxalate renal stones, which occur at a median time of 30 months (range 2–67) after the surgery. These stones may cause attacks of renal colic, an obstructive uropathy (which may cause irreversible renal damage), and urinary tract infections (which, in the presence of obstruction, may cause a pyonephrosis). Nephrocalcinosis may be associated with an asymptomatic progressive impairment of renal function.

Oxalate is a metabolic end product that cannot be metabolized in man. Under normal circumstances, most urinary oxalate is derived from the metabolism of amino acids (mainly glycine) and of ascorbic acid. Less than 10% is derived from dietary oxalate. However, after an ileal resection, there is increased colonic absorption of dietary oxalate.

Renal stone formation has three phases: nucleation, growth, and aggregation. At all stages, supersaturation of urine with calcium and oxalate is needed. There are many potential factors that contribute to calcium oxalate renal stone formation (Figure 2).

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**Figure 2.** Mechanisms for oxalate renal stones.
Reduced luminal calcium. Colonic oxalate absorption (and ultimately renal excretion) is increased by factors that reduce the available intraluminal calcium, either by forming a complex with calcium or by increasing its absorption. As the dietary intake of lipid increases, so enteric hyperoxaluria increases. This occurs as unabsorbed fatty acids in the colon preferentially form insoluble calcium soaps, leaving oxalate unbound and readily available for absorption. Calcium absorption is increased by a low serum or low dietary calcium intake, hyperparathyroidism, and vitamin D administration, and as all reduce the colonic luminal calcium concentration, they all leave more oxalate to be absorbed.

Increased colonic permeability. Unabsorbed bile acids directly increase colonic permeability to oxalate, as demonstrated by an infusion of chenodeoxycholate into the colon, which increased oxalate absorption fivefold. In addition, cholestyramine (a bile-salt-binding drug) taken orally reduces oxalate absorption.

Reduced bacterial breakdown of oxalate. Oxalobacter formigenes, an anaerobic bacterium, found within the colon, degrades oxalate to carbon dioxide and formate. If its numbers are reduced, it could contribute to increased amounts of oxalate being available for absorption. It is cultured less frequently from the stools of patients with Crohn’s disease or steatorrhoea. Its growth is inhibited by low bile acid concentrations, as occur in patients with a short bowel and retained colon.

Vitamin deficiency. Pyridoxine deficiency may increase the metabolic formation of oxalate and/or the ileal absorption. Thiamine deficiency may increase oxalate production. In contrast, ascorbic acid deficiency decreases oxalate absorption.

Hypocitraturia. Citrate prevents nucleation, the first step in renal stone formation. Hypocitraturia is common in patients with malabsorption or jejunoileal bypass. Citrate excretion and urine pH are reduced by systemic acidosis, including that caused by gastrointestinal bicarbonate wastage, and by hypomagnesaemia. Hypocitraturia in patients with malabsorption can be corrected by oral citrate supplementation and magnesium injections.

Type of oxalate ingested. Sodium oxalate as found in tea is more readily absorbed than calcium oxalate in most foods.

Dehydration. Patients with a short bowel and diarrhoea, even with a functioning colon in continuity, are more prone to dehydration and a reduced urinary volume; this makes the urine more supersaturated and nucleation more likely to occur.

Prevention/treatment

To prevent calcium oxalate renal stone formation, patients with a short bowel and retained colon (or indeed any patient who has had an ileal resection) should avoid dehydration and take a diet low in oxalate. A low oxalate diet means avoiding foods such as spinach, rhubarb, beetroot, and excessive cups of tea (Table 2). Fat restriction is theoretically good, but may not be desirable for nutritional reasons. Substitution of medium-chain triglycerides may be effective in reducing oxalate absorption. Restriction of dietary oxalate and fat intake reduces urinary oxalate excretion.

Dietary calcium must be increased. Calcium salts reduce absorption of dietary oxalate in patients with ileal resection or jejunoileal bypass. Calcium-containing organic marine hydrocolloid decreases oxalate absorption without increasing calcium absorption.

Binding bile salts with cholestyramine has variable effects. It binds oxalate in vitro and some studies showed that it decreases urinary oxalate excretion. However,
other studies have shown no benefit\[145,152\] or even increased urinary oxalate excretion.\[161\]

Aluminium salts can bind oxalate in vitro.\[155\] There was a halving of urinary oxalate excretion after oral aluminium hydroxide had been given to four patients with enteric hyperoxaluria\[162\], but no such reduction was observed in another study.\[161\]

**OSTEOPATHY**

Osteopenia/osteoporosis is generally associated with increasing age, female gender, smoking, alcohol, reduced exercise, reduced sunlight exposure, and taking steroids, loop diuretics or heparin.\[163\] Patients with IF may have osteomalacia due to malabsorption and vitamin D deficiency, or an osteopathy due to corticosteroid use (e.g. for Crohn’s disease) or parenteral nutrition.

**PN osteopathy**

PN osteopathy is different from that caused by the other risk factors for osteoporosis. When HPN is begun, osteopenia and/or osteomalacia is found in about 50% of patients; this is due to immobility and chronic malabsorption causing negative calcium, magnesium and/or vitamin D balance.\[164\] Patients receiving HPN have increased bone resorption during the early phase of treatment, but this returns to normal by 6 months.\[165\]

Patients receiving HPN for more than 6 months may develop a progressive osteopathy of the lower limb long bones with associated joint pains, hypercalcuria and a low bone formation rate.\[165–170\] This is a restructuring osteopathy, in which the rate of trabecular bone resorption exceeds that of formation. Patients may also complain of

| Table 2. Oxalate content of food using enzymatic or gas chromatographic methods. |
|---------------------------------|-----|
| mg/100 g                         |
| Rhubarb                         | 537–860 |
| Spinach                         | 571–750 |
| Beetroot                        | 675   |
| Okra                            | 264   |
| Wheat bran                      | 240   |
| Peanuts                         | 116–185 |
| Bran flakes                      | 141   |
| Almonds                         | 131   |
| Rice bran                       | 123   |
| Chocolate                       | 117–366 |
| Parsley                         | 100   |
| Tea                             | 55–280a |

\[a\] mg/100 ml.

loose teeth or of teeth actually falling out soon after starting parenteral nutrition; this may relate to a loss of alveolar bone. A T-score (number of SD’s below mean bone mineral density of young subjects) of less than $-2.5$ occurred in 41% of 165 patients having PN for more than 6 months; 35% had bone pain and 10% had a bone fracture. Factors that may be responsible for PN osteopathy include acidosis, aluminium or vitamin D toxicity, loss of diurnal parathormone rhythm, amino acid infusions, hypomagnesaemia and cytokine effects.

**Acidosis**

In some patients there is an excessive excretion of calcium and phosphorus, which may reflect acidosis associated with a rapid nutrient infusion. There are reports of improvement in the calcium balance by increasing the amount of phosphorus given, and so increasing the renal tubular absorption of calcium.

**Aluminium toxicity**

In the past, aluminium contamination of feeds in adults caused pain in the long bones and weight-bearing joints, a decreased rate of bone formation and patchy osteomalacia on bone biopsy. Changing from a casein hydrolysate solution to a balanced crystalline amino acid solution reduced the aluminium infused and improved bone disease.

**Vitamin D toxicity**

Vitamin D administration has been associated with bone disease, and in those with depressed parathormone levels bone disease can be corrected by removing vitamin D from the PN. After the removal of vitamin D the serum levels of parathormone and 1,25-hydroxy-vitamin D increased towards normal. The effect of vitamin D in increasing intestinal calcium absorption is not likely to be relevant to patients dependent on parenteral feeding, while the effect of increasing bone re-absorption may be detrimental.

In some reports, serum vitamin 1,25-hydroxy-vitamin D levels have been reduced while 25-hydroxy-vitamin D levels are normal. In more recent reports they have both been within the normal range.

**Loss of diurnal rhythm of parathormone**

Reports of parathormone levels are variable (usually low) and the normal diurnal nocturnal rise of parathormone is prevented by PN.

**Amino acid infusions**

Intravenously infused amino acids increase and intravenous phosphate reduces urinary calcium loss. An amino acid infusion of more than 2 g/kg caused more calcium to be lost in the urine than was infused.
Hypomagnesaemia

Hypomagnesaemia, which is common in patients with a short bowel, reduces the secretion and function of parathormone, so that renal conservation of calcium is reduced and 1,25-hydroxy-vitamin D is not made in adequate amounts. Thus, calcium and magnesium are not adequately absorbed from the gut; this may further contribute to bone disease.\(^{182}\)

Cytokines

Cytokines (e.g. interleukins 1 and 6, and tumour necrosis factor alpha) can increase bone resorption.\(^{183}\)

Prevention/treatment

Patients with intestinal failure (especially if starting HPN) are advised to have a bone density measurement made initially and repeated every 2 years. If there is evidence of osteopenia or osteoporosis, the calcium and phosphorus intake should be assessed, and oral (or parenteral) calcium supplements and vitamin D given. Exercise and sunlight exposure are encouraged, while smoking should stop and alcohol consumption be kept low. Oestrogen therapy may be given to women who have ovarian failure. Consideration to withdrawing heparin treatment, its addition to a PN bag (if the units practice) or from flushes should be given but balanced against the risk of catheter-associated central vein thrombosis. A small amount of fluoride and/or biphosphonates (e.g. clodronate) may be used, depending upon regular bone density measurements.\(^{184,185}\) Calcitonin (10-day course) may be helpful in relieving pain from the osteopathy. Vitamin D may be stopped if the serum parathormone or 1,25-hydroxy-vitamin D levels fall.

**Practice points**

Abnormal liver function in patients with intestinal failure
- may be due to underlying disease, intestinal failure or the treatments given
- patients with a very short bowel have the most severe liver disease, and may need to be considered for a small bowel (and liver) transplant

Abnormal liver function associated with parenteral nutrition (PN)
- rarely due to PN alone; another cause (e.g. sepsis, drugs, pre-existing liver disease) should be sought
- neonates/infants develop intrahepatic cholestasis, and adults develop steatosis. Both can progress to cirrhosis
- may be due to macronutrient excess (especially carbohydrate), lack of a specific molecule (e.g. choline), no oral/enteral intake, non-cyclic PN, or drug treatments
- 22% of deaths of patients receiving PN are due to liver disease
Gallstones in intestinal failure
- pigment-type stones occur in 45% of patients with a short bowel (more commonly in men)
- result from periods of biliary stasis in which biliary sludge forms and coalesces to form pigment-type stones
- ileal disease/resection, fasting/PN, surgery, rapid weight loss, or drug treatments are all contributing factors
- may be prevented by oral/enteral feeding, CCK injections, pulsed amino acid infusions, NSAIDs, reducing the bacterial formation of secondary bile acids in the bowel, ursodeoxycholic acid, sphincterotomy or prophylactic cholecystectomy
- acalculous cholecystitis may rarely occur

Calcium oxalate renal disease in intestinal failure
- discrete renal stones or generalized nephrocalcinosis
- stones occur in 25% of patients with a short bowel and a retained colon
- a low oxalate diet is the most important preventative measure
- other measures that may prevent stone formation include oral calcium supplements, a low fat diet or cholestyramine

Osteopathy
- may occur with long-term parenteral nutrition
- acidosis, aluminium or vitamin D toxicity, loss of diurnal parathormone rhythm, amino acid infusions, hypomagnesaemia and cytokines may be responsible
- a bone density measurement is recommended as home parenteral nutrition (HPN) training begins, and may be repeated every 2 years
- exercise and sunlight exposure are encouraged. Smoking should stop and alcohol consumption should be kept low
- adequate calcium, phosphorus and vitamin D should be provided
- oestrogen therapy may be given to women who have ovarian failure
- a biphosphonate (e.g. clodronate) may be given

Research agenda
- the reasons patients with a very short bowel develop the most severe liver disease needs to be determined
- the progression of PN-induced liver disease needs to be clarified. Does steatosis progress to intrahepatic cholestasis and cirrhosis in adults and children?
- the simplest/most efficacious way of reducing gall bladder stasis needs to be determined
- controlled trials are needed to establish the most effective way of preventing calcium oxalate renal stone formation in patients with a short bowel and a retained functioning colon
- more research into the causes and treatment of PN-associated osteopathy is needed
REFERENCES


Hepatobiliary, renal and bone complications of intestinal failure


