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Other disease associations with non-alcoholic fatty liver disease (NAFLD)

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Non-alcoholic fatty liver disease (NAFLD) is usually seen in middle-aged women with obesity, non-insulin-dependent diabetes mellitus and/or hyperlipidaemia. NAFLD has also been associated with other conditions. Surgical procedures to treat obesity such as jejunoileal bypass and gastroplasty as well as massive small bowel resection have been associated with NAFLD. Mechanisms such as rapid weight loss, certain nutritional deficiencies and bacterial overgrowth have been proposed. Other nutritional conditions such as extreme malnutrition and total parenteral nutrition can also cause NASH. This can be due to abnormal glucose and fat metabolism, deficiencies like carnitine, essential fatty acid and choline or, in the case of parenteral nutrition, excess of calories, glucose or lipids. Several drugs have also been implicated as well as some inborn errors of metabolism and, more rarely, other diseases.

Key words: non-alcoholic steatohepatitis; jejunoileal bypass; obesity; parenteral nutrition; drugs; malnutrition.

INTRODUCTION

Non-alcoholic steatohepatitis (NASH) is a condition that is characterized by hepatomegaly due to liver steatosis, elevated serum aminotransferase levels and histology that is similar to alcoholic hepatitis in the absence of alcohol abuse. Most affected patients are asymptomatic. It is usually seen in middle-aged women with obesity, non-insulin-dependent diabetes mellitus and/or hyperlipidaemia.[1,2] NASH has also been associated with other conditions such as surgical procedures, parenteral nutrition, drugs, metabolic disorders and certain nutritional deficiencies (Table 1–3). This chapter will review some of these conditions.

SURGICAL PROCEDURES

Jejunoileal bypass, once a popular treatment for morbid obesity, was associated with a 40% incidence of liver function abnormalities post-operatively and with severe NASH and hepatocellular failure in up to 6% of patients.[3,4] This was not always resolved by surgical correction. In those patients who underwent liver transplantation, NASH could recur rapidly, particularly in patients who did not have the jejunoileal bypass reversed at

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Table 1. Disorders associated with steatosis and NASH.

A. Acquired	
Diabetes mellitus	Inflammatory bowel disease
Extreme malnutrition	Obesity
Serum lipid abnormalities	Total parenteral nutrition
Jejunoileal bypass	Biliopancreatic diversion
Extensive small bowel resection	Gastroplasty for morbid obesity
Partial lipodystrophy	Jejunal diverticulosis with bacterial overgrowth
B. Inborn errors of metabolism	
Abetalipoproteinaemia	Familial hepatosteatosis
Galactosaemia	Glycogen storage disease
Hereditary fructose intolerance	Homocystinuria
Systemic carnitine deficiency	Tyrosinaemia
Refsum's disease	Schwachman's syndrome
Weber–Christian syndrome	Wilson's disease

NASH, non-alcoholic steatohepatitis.

Table 2. Possible factors playing a role in TPN-induced liver disease.

A. **TPN related**
- Excess calories
- Excess lipids (> 1 g/kg per day)
- Riboflavin (vitamin oxidation)
- Continuous TPN (no cycling)

B. **Deficiencies**
- Choline
- Essential fatty acids
- L-carnitine
- Taurine (infants)

C. **Surgery related**
- Extreme short bowel
- Bacterial overgrowth/translocation
- Disruption of enterohepatic circulation
- (Toxic bile salts?)

D. **Underlying diseases**
- Coexistent liver diseases (e.g. hepatitis B and C)
- Sepsis
- Inflammation

TPN, total parenteral nutrition.

the time of transplantation.[5] NASH has also been described after biliopancreatic diversion,[6] extensive small bowel resection[7] and gastroplasty for morbid obesity.[8]

Rapid weight loss following these surgical procedures, as during profound fasting, may be one of the contributors to NASH. Protein–calorie malnutrition[9] and increased flux of free fatty acids into the liver, enhancing hepatic synthesis of triglycerides, may also play a role. In a study of 14 obese women who underwent jejunoileal bypass, a significant increase in plasma free fatty acids was noted.[10] Other causes such as decreased carnitine concentrations and essential fatty acid deficiency have also been reported.[11] However, carnitine supplementation had no benefit.[10]

Table 3. Drugs and toxins associated with steatosis or NASH.

A. **Cytotoxic/cytostatic drugs**	
L-asparaginase	Azacytidine
Azauridine	Methotrexate
B. **Antibiotics**	
Azaserine	Bleomycin
Puromycin	Tetracycline
C. **Other drugs**	
Amiodarone	Coumadin
Dichloroethylene	Ethionine
Ethyl bromide	Oestrogens
Flectol H	Glucocorticoids
Hydrazine	Hypoglycin
Orotate	Perhexilene maleate
Safrole	Tamoxifen
Isoniazid	Nifedipine
Diltiazem	Chloroquine
D. **Nucleoside analogues**	
Didanosine	Fialuridine
Stavudine	Zidovudine
E. **Chemicals**	
Industrial exposure to petrochemicals	
Organic solvents	

NASH, non-alcoholic steatohepatitis.

Another possible aetiological factor is bacterial overgrowth. This is supported by the fact that NASH may be prevented or reversed in some patients following jejunoileal bypass by the use of metronidazole.[12] NASH has also been reported in small intestinal diverticulosis with bacterial overgrowth.[2,13] Bacterial overgrowth may also increase intestinal permeability and absorption of endotoxins.[14,15] It is also associated with ethanol production.[16] Ethanol was detected in the blood of some morbidly obese patients post-jejunoileal bypass.[17] An increase in intestinal-derived ethanol might increase portal blood ethanol levels enough to induce hepatic steatosis. Ethanol and its metabolites may also alter intestinal permeability and enhance the systemic absorption of endotoxin.[18] Endotoxins can activate macrophages and stimulate production of cytokines such as tumour necrosis factor-alpha (TNF-α).[19] TNF-α is increased in patients with liver disease[20,21] and is required for ingested alcohol to produce hepatic steatosis.[22] In the study by Wigg et al,[23] bacterial overgrowth was present in 50% of patients with NASH and serum TNF-α levels were higher in patients with NASH compared with controls. However, intestinal permeability and serum endotoxin levels were similar in both groups.

TOTAL PARENTERAL NUTRITION

Several hepatic abnormalities have been observed with total parenteral nutrition (TPN)[24] but they are usually benign and transient. The benign changes occur generally within 4 weeks of starting TPN, whereas the more serious complications occur later, usually after 16 weeks of therapy. Hepatic complications associated with long-term parenteral nutrition occur more frequently and are more severe in infants than in adults. A small subset of patients develop progressive disease. In general, TPN

is associated with three well recognized hepatobiliary complications: fatty liver, cholestasis and gallbladder disease related to sludge formation.[25,26]. Fatty liver is the most common histological finding when patients receiving TPN have hepatic enzyme abnormalities.[27] However, there is a poor correlation between the degree of fatty change and liver enzyme levels.[28] Hepatic abnormalities include elevated serum aminotransferase and alkaline phosphatase values and histological alterations such as steatosis, steatohepatitis, lipidosis and phospholipidosis, cholestasis, fibrosis and cirrhosis. Steatosis is predominant in patients with elevated liver biochemistries.[25] Serial biopsies suggest that steatosis is an early event with cholestasis often supervening subsequently.[25] Histological changes described with cholestasis are bile duct proliferation, canalicular bile plugs, centrilobular cholestasis, bile pigment within hepatocytes and a mixed (granulocytic and lymphocytic) periportal infiltrate. Cholestasis may progress to fibrosis and chronic hepatic failure.[29]

The aetiology of changes in liver function is multifactorial and often obscure. Almost all the components of the TPN solution have been implicated as the cause of hepatic dysfunction (see Table 2). The rate of glucose infusion and the caloric excess are most frequently cited as causing hepatic fatty infiltration. There is a direct correlation between total calories from TPN and fatty infiltration with triglycerides.[30] Increasing the dextrose concentrations also correlates with increasing hepatic lipid accumulation.[31] In addition, there is a rise in blood insulin concentration with increasing caloric load during TPN[32] and, in some cases, plasma fatty acids and triglycerides can also become elevated due to insulin resistance.[27] This metabolic profile of hyperinsulinaemia, insulin resistance, hypertriglyceridaemia and high levels of plasma free fatty acids that can be seen during TPN is similar to that seen in type II diabetes mellitus. Lipogenesis in the liver is upregulated by absorption of large carbohydrate loads and by an elevated insulin/glucagon ratio.[33] The triglycerides synthesized in the liver are then transported in the form of very low density lipoproteins (VLDL), whose main protein constituent is apolipoprotein B-100.[34] Apolipoprotein B-100 is the limiting factor for VLDL synthesis.[33,34] The production of triglycerides probably increases more than that of apolipoprotein B-100, leading to lipid accumulation in the liver. This is supported by animal and human studies.[35,36]

It has also been reported that essential fatty acid deficiency may be another possible cause for hepatic dysfunction, since infusion of a fat emulsion corrects the serum abnormalities in some patients.[37,38] Essential fatty acids include the polyunsaturated fatty acid linoleic acid (18:2 omega 6) and its in vivo metabolites such as arachidonic acid (20:4 omega 6). Essential fatty acids are vital components of phospholipids and may perhaps contribute to the development of fatty liver by affecting the hepatic biosynthesis of lipoproteins, which require the phospholipid derivative, phosphatidylcholine.[39] Patients on fat-free TPN for prolonged periods develop alopecia and a scaling dermatitis due to essential fatty acid deficiency.[38] Conversely, the administration of fat calories in excess has also been reported to cause abnormalities in serum liver enzyme levels.[40]

Carnitine, which plays an important role in the oxidation of fatty acids, has also been shown to be decreased in long-term TPN.[41,42] Carnitine shuttles long-chain fatty acids into the mitochondria where the process of beta-oxidation can take place. Although improvements in liver biochemistries have been reported with carnitine supplementation during TPN, metabolic studies have not shown any beneficial effect of carnitine supplementation on the rates of fatty acid oxidation in humans.[43,44] One study showed no improvement in transaminase levels, plasma free fatty acid levels, plasma triglyceride levels or the grade of hepatic steatosis by histological examination.[45]

Choline, a precursor of phospholipid biosynthesis can be decreased in up to 80% of patients in long-term TPN.[46,47] Phosphotidylcholine, a necessary component for lipoprotein synthesis, is a choline phospholipid biosynthesized from choline and phospholipid.[48] In the face of phosphotidylcholine deficiency, hepatic triglyceride secretion may be compromised leading to hepatic triglyceride accumulation.[49,50] In a few human studies, choline supplementation with oral lecithine and intravenous choline was reported to reverse TPN-induced fatty liver changes.[46,47]

Other causes such as an amino acid imbalance,[51] photo-oxidized products of amino acid residues[52] and sources of infused lipids[53] have also been suggested to predispose to TPN-induced NASH. Recently, a study looked at the prevalence of liver disease and contributing factors in 90 patients receiving home TPN for permanent intestinal failure.[40] Of these, a surprisingly large proportion, 58 patients (65%), developed chronic cholestasis after a median of 6 months and 37 (41.5%) developed complicated home parenteral nutrition-related liver disease after a median of 17 months. Of these, 17 showed extensive fibrosis after 26 months and five had cirrhosis after 37 months. Six patients died of liver disease (22% of all deaths). The prevalence of complicated liver disease was 26 ($\pm$9)% at 2 years and 50 ($\pm$13)% at 6 years. Factors found to be significantly associated with chronic cholestasis were a TPN-independent risk for liver disease, a bowel remnant shorter than 50 cm in length and a parenteral lipid intake of 1 g/kg of body weight per day or more (omega-6-rich long-chain triglycerides). Among those with (46 patients) and those without (11 patients) chronic cholestasis, histological cholestasis was found in 35 (76%) and 3 (27%), portal inflammation in 40 (87%) and 10 (90%), macrosteatosis in 29 (63%) and 11 (100%), ductular proliferation in 27 (59%) and 8 (72%) and hepatocyte necrosis in 20 (43%) and 2 (18%), respectively. Phospholipidosis or microsteatosis (or both) was found in 36 (63%) of the 57 patients who underwent liver biopsy. Microvesicular steatosis with deposits of long-chain triglycerides and lipoprotein X (containing equimolar amounts of cholesterol and phospholipids)[54] has been reported after infusion of 20% Intralipid, which is high in omega-6 polyunsaturated fatty acids and low in omega-3 polyunsaturated fatty acids.[55,56] Induced liver phospholipidosis was also described in patients receiving long-term TPN.[57] The high prevalence (63%) of phospholipidosis and microvesicular steatosis during long-term TPN with 20% fat emulsions has also been confirmed.[54] Based on the study by Cavicchi et al,[40] the data suggest that induced phospholipidosis and microvesicular steatosis in both hepatocytes and Kupffer cells play a key role in home TPN-related liver disease pathogenesis. This is probably related to excess lipid infusion and might be related to the phospholipid emulsifier. However, in North America it is very unusual to administer lipid at a rate greater than 1 g/kg per day and this may explain why the prevalence of TPN-induced liver disease seems lower. In 1999, a Boston study[58] reported that among 42 patients receiving at least 1 year of TPN, 6 (14%) developed end-stage liver disease.

Thus, liver dysfunction is frequent with long-term TPN in those with permanent intestinal failure and liver disease is one of the main causes of death. Interventions that have been used (albeit largely unproven) to prevent or treat hepatic complications include providing a portion (20–40%) of calories as fat, cycling the infusion (stopping for at least 8–10 h/day), avoiding excessive calories and treating with metronidazole or ursodeoxycholic acid. However, acalculous cholecystitis, gallbladder sludge and cholelithiasis should be sought as alternative causes of liver dysfunction in patients treated with TPN. When cholestasis is present, copper and manganese supplementation should be eliminated or decreased to prevent dangerous accumulation in the liver and basal ganglia.

MALNUTRITION

In addition to obesity, fatty liver and NASH can also be seen at the other end of the nutritional spectrum in states of extreme malnutrition. While kwashiorkor, a form of severe protein–calorie malnutrition, is associated with fatty infiltration,[59] marasmus (deficiency in all nutrients) is almost never associated with fatty liver. In kwashiorkor, typically, there are high plasma levels of free fatty acids[59] and glucose intolerance.[60,61] This is associated with both impairment of insulin secretion and decreased insulin sensitivity.[60,61] In addition, although protein intake is deficient, carbohydrate intake is often adequate or even in excess of required calories,[59] stimulating hepatic lipogenesis.[35,62]

Deficiencies of nutrients such as carnitine and essential fatty acids may also be important contributors in the development of non-alcoholic fatty liver disease (NAFLD) in states of severe malnutrition. Beta-oxidation impairment due to carnitine deficiency may contribute to hepatic triglyceride accumulation by shifting the hepatic metabolism of fatty acids toward VLDL synthesis. In primary carnitine deficiency, fatty liver is a common clinical finding.[63] Secondary carnitine deficiency due to malnutrition, defects in intermediary metabolism, certain diseases and drug reactions may also lead to fatty liver.[64,65] Essential fatty acid deficiency can also occur in a state of malnutrition and may play a role in the pathogenesis of fatty liver.[66,67]

Thus, severe malnutrition may lead to fatty liver and possibly NASH due to a state of insulin resistance and an imbalanced diet with low calories and excess carbohydrates. In addition, certain deficiencies such as of carnitine and essential fatty acids may play a role.

DRUGS

HIV infection and the use of nucleoside analogues

Severe hepatic steatosis and lactic acidosis among patients infected with HIV-1 was first described in the early 1990s[68] and by early 1994 at least 40 cases had been reported in association with the use of nucleoside analogues.[69,70] Didanosine, stavudine, fialuridine and zidovudine have all been associated with fulminant liver failure, micro- and/or macrovesicular steatosis and lactic acidosis[71,72] and with causing mitochondrial toxicity in vitro.[73] Impaired replication of mitochondrial DNA was proposed as the mechanism resulting in mitochondrial injury.[74] Nucleoside analogues are prodrugs that are converted into their active, triphosphorylated form. Once incorporated into growing DNA chains, phosphorylated nucleoside analogues act as chain terminators. They inhibit mitochondrial DNA polymerase gamma and induce mitochondrial DNA depletion.[75] The earliest signs of mitochondrial dysfunction, which precede structural abnormalities, include reduction of cytochrome oxidase and impaired beta-oxidation of fatty acids leading to accumulation of fat droplets within cells. Microvesicular steatosis is usually found and is also the most typical liver abnormality observed in genetically-induced mitochondrial disorders.[76]

Initial symptoms may be mild and non-specific such as nausea and abdominal discomfort; this may lead to a delay in diagnosis until patients are severely ill. Of note, hepatic steatosis may be severe despite near-normal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and myopathy may be present with only modest elevations of creatine kinase.[68,70] Women seem to be disproportionately affected by nucleoside analogue-associated toxicity[68,77] and it is interesting to note that NASH is predominantly found in women. As anti-retroviral regimens have become more

complex, elevations in ALT and AST levels have become common, especially in patients with concomitant hepatitis B or C infection. Because this form of microvesicular hepatic steatosis may be life-threatening, it should always be considered as a possible cause of newly elevated ALT and AST levels in individuals taking nucleoside analogues. Newly elevated ALT and AST levels require closer monitoring; levels of serum lactate and pancreatic and muscle enzymes should be measured. Computed tomography or ultrasound may be indicated to identify fatty liver. Physicians should consider changing the nucleoside analogue component of anti-retroviral regimens if hepatic steatosis persists and therapy should be temporarily discontinued in patients with lactic acidosis and associated hepatic steatosis, myopathy or pancreatitis.

Other drugs and toxins

In addition, NAFLD has been associated with a number of other drugs (see Table 3) such as 4,4′-diethylaminoethoxyhexestrol,[78] amiodarone,[79] perhexiline-maleate,[80] tamoxifen,[81] isoniazid[82] and synthetic steroids.[83] The field is well reviewed by Farrell.[84]

Drugs such as amiodarone and perhexiline maleate are known to act as inhibitors of mitochondrial beta oxidation and are, therefore, more readily associated with microvesicular steatosis.[80,85] NAFLD caused by either perhexeline maleate or amiodarone can progress even after withdrawal of the drug because of its long half-life.[80] Amiodarone can cause asymptomatic elevation of liver enzymes, hepatic granulomas, acute liver failure, cholestatic hepatitis, phospholipidosis and steatohepatitis sometimes with cirrhosis.[79] Duration of use appears to be a major risk factor, with nearly all affected persons having taken amiodarone for more than 1 year.[80] Perhexiline was used in Europe to treat angina pectoris and caused hepatic side effects in up to one-third of cases. These reported cases of hepatotoxicity have included phospholipidosis, hepatocellular hyperplasia, granulomatous hepatitis, steatohepatitis and micronodular cirrhosis. In cases of steatohepatitis, Mallory bodies and pericellular fibrosis were prominent. NASH associated with perhexiline was often severe with complications such as portal hypertension leading to death in about 50% of cases.

Nifedipine, diltiazem, stilboestrol and tamoxifen have also been associated with NASH based on more or less well documented case reports. Tamoxifen, an oestrogen receptor ligand with both agonist and antagonist actions, is commonly used in the treatment of breast cancer. Reported cases have included cholestasis, peliosis hepatis, acute hepatitis and massive hepatic necrosis as well as steatosis.[86] Ogawa et al[87] found radiological evidence of hepatic steatosis in 24 out of 66 patients with breast cancer treated with tamoxifen for 3–5 years. Seven other women have been diagnosed with NASH after taking tamoxifen for 7–33 months, two with cirrhosis.[81] These patients had normal liver biochemistries before receiving tamoxifen and were reported to have no risk factors for NASH. However, a few were obese (body mass index >30 kg/m^2).[86]

Methotrexate can induce significant liver disease.[78] Other factors such as alcohol ingestion, obesity, type 2 diabetes, pre-existing liver disease and age greater than 50 years can predispose to methotrexate-induced liver abnormalities. Some authors have even suggested that NASH can lead to methotrexate-induced hepatic fibrosis.[88]

NAFLD has also been reported with long-term glucocorticoid therapy.[89] However, the paucity of these reports, considering the fact that steroids are frequently used, suggest that other risk factors may have contributed to NAFLD.

Recently, NASH was described as a consequence of chronic exposure to several volatile petrochemical substances in the workplace.[90] Cotrim et al[90] described a high occurrence of asymptomatic NASH (on liver biopsy) in workers chronically exposed

to high atmospheric concentrations of several petrochemicals. Liver enzymes and macrovesicular steatosis improved in those removed from the environment. Fatty liver but not NASH has also been reported in association with organic solvent exposure.[91]

Inborn errors of metabolism

NASH has also been associated with Weber–Christian Disease.[92] This disease is characterized by abnormal fat metabolism and enlargement of the liver has been found in more than 50% of the documented cases. Histologically fatty changes are present in almost all cases and portal fibrosis and cirrhosis in about 10%. Presence of Mallory bodies has also been reported.

Abetalipoproteinaemia is an autosomal recessive disorder of lipid metabolism characterized by low serum triglyceride and cholesterol levels as well as by gastrointestinal and neurological abnormalities.[93] Failure to secrete apolipoprotein B leads to retention of triglycerides in the small intestine and liver. Two cases of NASH have been reported, where micronodular cirrhosis developed after institution of a diet supplemented with medium-chain triglycerides.

Both hepatic steatosis and Mallory bodies can be found in the liver of individuals with Wilson's disease. It is important to distinguish NASH from Wilson's disease because the latter requires treatment with copper chelation to improve prognosis. Wilson's disease is caused by diverse mutations of a nuclear gene encoding a copper-transporting P-type adenosine-triphosphatase (ATPase).[94] Decreased biliary elimination of copper causes progressive accumulation within hepatocytes and mitochondria. Copper cycles between an oxidized and a reduced state and can generate hydroxyl radicals and other reactive oxygen species (ROS). Patients with Wilson's disease also exhibit a marked decrease in mitochondrial respiratory chain complexes. This may further increase the production of mitochondrial ROS.[95] These ROS are unstable molecules that can oxidize proteins and membrane lipids leading to lipid peroxidation and steatohepatitis.

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is also associated with hepatic steatosis.[96] MCAD is the most common hereditary disease of fatty acid oxidation and one of the most common inborn errors of metabolism (1 : 15 000). The mechanism of hepatic fat accumulation remains unclear but may involve disrupted mitochondrial fatty acid metabolism.

Others

The lipodystrophies may be associated with metabolic abnormalities including insulin resistance and hypertriglyceridaemia. They are broadly classified into generalized or partial forms, each one either congenital or acquired. Fatty liver and cirrhosis are common in congenital total lipodystrophy but not in partial lipodystrophy. NASH has been described in two cases of partial lipodystrophy in association with hyperinsulinaemia.[97] In one study, among 38 patients with rare insulin receptor mutations, lipodystrophy syndromes and the HAIR-AN syndrome (hyperandrogenism, insulin resistance, acanthosis nigricans), 10 had persistently elevated serum transaminase levels. Steatosis was present in the eight who underwent liver biopsy and four had Mallory bodies.[98]

There are also several case reports of coeliac disease and steatohepatitis with Mallory bodies. Hepatic steatosis was reversible on a gluten-free diet.[99] However, no difference in the frequency of endomysial antibodies (a marker for coeliac disease) between

patients with NASH and the general population was found. There have also been at least three cases reported of NASH associated with psoriasis.[100] However, in these cases, two had a body mass index > 30 kg/m^2 and one was taking 30 g of alcohol per day.

SUMMARY

Non-alcoholic fatty liver disease (NAFLD) is associated with several conditions other than the metabolic syndrome. Some of these conditions, such as total parenteral nutrition (TPN) and kwashiorkor, are associated with some features of the metabolic syndrome such as imbalances in caloric intake in favour of carbohydrates and states of hyperinsulinaemia and insulin resistance that can lead to increased delivery of free fatty acids to the liver. Other conditions include: (i) surgery that induces significant malabsorption and rapid weight loss, such as jejunoileal bypass and massive small bowel resection; (ii) bacterial overgrowth; (iii) nutritional deficiencies such as carnitine and essential fatty acids; (iv) drugs and (v) other conditions related to inborn errors of metabolism and certain diseases. Although in some of these conditions such as with drugs or genetic disorders, the mechanism inducing NASH is better understood, in other conditions such as in parenteral nutrition, jejunoileal bypass and extreme malnutrition, the pathogenesis is obscure and, most probably, several mechanisms play

Practice points

- surgical procedures such as jejunoileal bypass, gastroplasty and massive small bowel resection may induce NASH. Jejunoileal bypass has been abandoned because of severe liver complications
- profound weight loss and deficiency state need to be prevented following these surgeries
- if bacterial overgrowth is suspected, a trial with metronidazole or tetracycline can be helpful
- liver dysfunction related to parenteral nutrition is often due to excess calories, glucose or lipids
- acalculous cholecystitis, gallbladder sludge and cholelithiasis should be considered
- severe malnutrition can be associated with NAFLD including NASH
- NASH is usually reversible once the dietary imbalance and the deficiencies are corrected
- drug toxicity should be ruled out as a cause when evaluating a patient with NASH
- severe microvesicular steatosis and lactic acidosis can be associated with the use of nucleoside analogues

Research agenda

- the aetiopathogenesis of NASH following massive small bowel resection continues to elude clinicians. More studies are required
- the mechanisms underlying the severe liver complications related to long-term parenteral nutrition remain largely unknown and more studies are needed in this area

a role. In addition to increased free fatty acid delivery to the liver, endotoxin–cytokine injury, bacterial overgrowth, oxidative stress and mitochondrial injury are all the focus of intense research. Until these are well understood, no therapy for NASH will be really effective unless the triggering condition is removed.

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