REVIEW

Non-alcoholic Fatty Liver Disease

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) comprises a disease spectrum ranging from benign hepatic steatosis to non-alcoholic steatohepatitis with inflammation (NASH) and liver cirrhosis. NAFLD is now recognised as the hepatic manifestation of the metabolic syndrome. Simple steatosis is benign, whereas NASH can progress to cirrhosis with its resultant complications. Liver biopsy remains the gold standard in the diagnosis of NAFLD/NASH. Lifestyle and dietary modifications to achieve sustained weight loss is the cornerstone of NAFLD/NASH treatment.

Keywords: cirrhosis, fibroscan, metabolic syndrome, steatosis, steatohepatitis

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is an increasingly common cause of chronic liver disease world-wide. It comprises a disease spectrum ranging from benign hepatic steatosis to non-alcoholic steatohepatitis with inflammation (NASH) and liver cirrhosis (Fig. 1). Although simple steatosis appears to be benign, NASH can progress to cirrhosis with its resultant complications, including hepatocellular carcinoma (HCC)[1]. It is increasingly recognised that NASH accounts for a significant proportion of "cryptogenic" or "idiopathic" cirrhosis. Primary NAFLD often co-exists with at least 1 feature of the metabolic syndrome (impaired glucose tolerance, central obesity, hypertension, hypertriglyceridaemia, low high-density lipoprotein [HDL] cholesterol). Its prevalence increases with the severity and number of metabolic syndrome features[2]. Insulin resistance appears to play a central role in the pathogenesis of primary NAFLD, which is now recognised as the hepatic manifestation of the metabolic syndrome[3]. Secondary causes of NAFLD include drugs, toxin exposure, parenteral nutrition, hypothyroidism, jejunoileal bypass surgery, etc (Table 1). This review is focused on the clinical aspects of primary NAFLD.

NATURAL HISTORY

There has been much interest with regards to the actual natural history of NAFLD. Current literature lack good longitudinal studies, some include non-standard definitions and diagnostic methods for NAFLD and often lack controls. The long-term clinical outcome of NAFLD is still controversial; although it has been described that prognosis varies with the degree of histologic injury.

Despite the limitations with sampling variability, liver biopsy remains the gold standard in NAFLD studies. Histology at time of diagnosis has been found to be the best predictor of disease progression. Benign steatosis without inflammation has a low likelihood of progression, whereas the presence of inflammation predicts progression to advanced fibrosis. Even in patients with fibrosis without inflammation, the risk of progression to advanced fibrosis is less. Patients with any inflammation in the setting of steatosis, have 2.5 times the likelihood of developing advanced fibrosis[4]. Several studies with paired liver biopsies have shown similar results with regards to fibrosis progression[5–14]. Patients with histological evidence of NASH or fibrosis tended to be female (61%), obese (63%), insulin-resistant and in the fifth

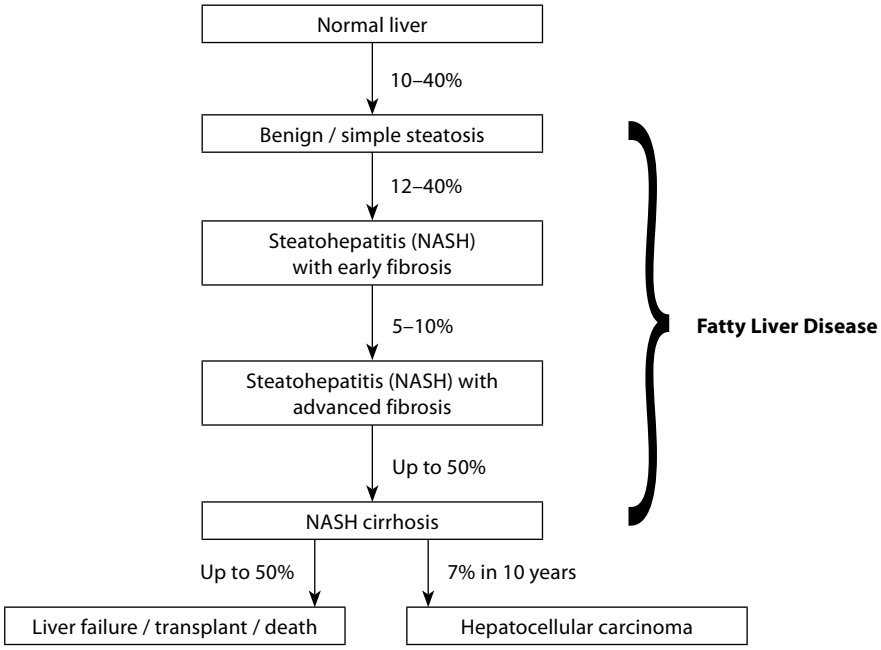

Fig. 1. Spectrum of non-alcoholic fatty liver disease.

Table 1. Causes of NAFLDw/NASH.

Primary NAFLD/NASH
▪ Associated with the Metabolic Syndrome
Secondary NAFLD/NASH
▪ Toxin exposure
▪ Drugs (e.g. Tamoxifen, amiodarone, oestrogens, glucocorticoids, HAART therapy)
▪ Gastroplasty / bowel resection / bowel bypass surgery
▪ Rapid weight loss / starvation
▪ Parenteral nutrition
▪ Hypothyroidism
▪ Bacterial overgrowth
▪ Wilson's disease
▪ Weber-Christian disease
▪ Abetalipoproteinemia

decade of life (mean age 47 years). One-third of these patients developed advanced fibrosis over a mean follow-up of 5.3 years.

About 7% of NASH patients with compensated cirrhosis will develop HCC within 10 years, while 50% will require a transplant or die from liver related causes[15,16]. Recently, some authors have described HCC in the non-cirrhotic fatty liver[17–19]. How this might impact on disease management or surveillance is not yet known. NASH patients have a risk of increased overall mortality (compared to the general population) and increased liver-related mortality (compared to patients with benign steatosis alone)[1,13,16,20,21]. Some studies have demonstrated an increased risk of cardiovascular mortality as compared to the general population[13]. Type 2 diabetic patients with NAFLD also have been described to have higher cardiovascular morbidity than type 2 diabetics without NAFLD[22].

EPIDEMIOLOGY

The true incidence and prevalence of NAFLD is difficult to determine due to variations in disease definition and a lack of standardised diagnostic tools. Population-based studies have primarily used imaging modalities such as ultrasound to diagnose NAFLD. These studies are therefore unable to provide prevalence data on NASH, which requires a liver biopsy for diagnosis.

In the United States, NAFLD is the most common cause of chronic liver disease, with an estimated prevalence of 20–30% and an estimated prevalence of 3.5–5% for NASH[23–25]. Suspected NAFLD represents one of the most common reasons why patients visit gastroenterologists in the ambulatory setting in the United States. Despite earlier reports which suggested a predominance of NAFLD in females, recent larger population studies have established that NAFLD occurs in both genders, all ethnicities and in all age groups, including children[26–28].

The prevalence of NAFLD and NASH increases with body weight. NAFLD has been documented in 10–15% normal individuals and up to 70–80% of obese individuals. Correspondingly, approximately 3% of non-obese individuals have underlying NASH as compared to 15–20% of morbidly obese individuals[29,30]. Obesity (BMI [body mass index] >30kg/m^2) is thus clearly associated with NASH, with an increased likelihood of developing NASH with increasing BMI. However, it is well-documented that the mean BMI (<27.5kg/m^2) in most Asian studies of fatty liver disease tends to be lower than that reported outside of Asia, where the mean BMI levels often exceed 32kg/m^2 [31]. Numerous studies have also clearly documented resolution of fatty liver following gradual weight loss[32–35]. Patients with truncal obesity are at higher risk of developing diabetes, hypertension and fatty liver.

Although obesity and diabetes are frequently clustered within families, a clear-cut pattern of inheritance of risk for NAFLD has not been identified. Several instances of NAFLD affecting multiple members of the same family have been reported in patients with rare familial disorders such as hypobetalipoproteinemia[36].

Diabetes mellitus is a major component of the metabolic syndrome and is associated with obesity and NAFLD. Diabetes may be a risk factor for the development of fibrosis. NAFLD has also been associated with disorders of lipid metabolism and syndromes associated with severe insulin resistance (e.g. lipoatrophic diabetes and Mauriac syndrome).

More advanced stages of NAFLD are associated with older age, higher body mass index, diabetes, hypertension, high triglycerides, and/or insulin resistance. An AST/ALT (aspartate aminotranferease/ alanine aminotransferase) ratio greater >1 may also indicate more severe disease.

In Asian countries, epidemiological data regarding NAFLD remains scarce. Prevalence rates of NAFLD in Asian populations range from 12.2% in the Philippines to 17.2% in Southern China, with a higher prevalence (up to 42%) amongst Asians with diabetes and metabolic syndrome[37]. In Singapore, significant NAFLD was found even in non-diabetic, pre-obese individuals[38] . With the rising incidence of diabetes mellitus and metabolic syndrome in Asian countries, we can expect an increased burden of disease from NAFLD in the present and future decades.

DIAGNOSIS

NAFLD is a clinical diagnosis based on the presence of transaminitis and fatty liver changes on ultrasound. The exclusion of other liver diseases, specifically alcohol-related liver disease, is a requisite criteria for diagnosis of primary NAFLD.

However, NAFLD can co-exist with other liver diseases such as chronic hepatitis C and hepatitis B. The proposed criteria for the diagnosis of NASH include (1) a histologic picture of steatohepatitis; (2) convincing evidence of minimal or no alcohol consumption; and (3) absence of serological evidence of viral hepatitis[39].

Evaluation of Suspected NAFLD

Most patients with NAFLD are asymptomatic and are diagnosed incidentally on routine blood tests and/or via ultrasound of the liver. In most patients, elevated ALT levels are discovered when transaminases are monitored in the setting of treatment of dyslipidemia with statins. Ultrasonographic fatty liver is sometimes diagnosed during evaluation for suspected gallstone disease.

Symptoms

There is limited data on symptomatology of NAFLD from longitudinal studies. Symptoms of fatty liver disease are unreliable, non-specific and do not correlate with the histological severity of the disease. When symptoms do occur in this condition, they are often non-specific and may not be brought to the attention of the physician. Fatigue has been reported to be the most common symptom. Some patients complain of right upper quadrant discomfort, which is typically a vague and nondescript ache. The development of ascites, jaundice and variceal haemorrhage indicate decompensated cirrhosis and are not specific for NASH-related cirrhosis.

Laboratory Abnormalities

Most patients with NAFLD have abnormal aminotransferases with elevated ALT and AST. The degree of transaminitis is often mild and is usually within 1–4 times the upper limit of normal, with ALT higher than AST. However, degree of ALT elevation does not correlate with histological severity of steatosis or fibrosis. A large proportion of NAFLD patients have normal liver enzymes, and a fraction of these patients may have significant NASH-related fibrosis despite normal ALT levels. Alkaline phosphatase (ALP) levels may also be mildly raised in NAFLD, up to twice the upper limit of normal. Similarly gamma glutamyltransferase (GGT) levels may be raised, although there is little data on the frequency and significance of GGT elevation in NAFLD. Bilirubin, albumin and prothrombin time are usually not affected in fatty liver disease until cirrhosis and liver failure develop.

In patients without prior known type 2 diabetes mellitus, the presence of glucose intolerance and insulin resistance should be evaluated with fasting blood glucose, insulin levels and HbA1c. Thirty to 50% of patients with NASH are likely to have either diabetes or glucose intolerance. Fasting lipid profiles shows the presence of co-existing hypertriglyceridemia and/or elevated low-density lipoprotein (LDL) levels in 20–80% of NAFLD patients.

Elevated serum auto-antibodies are elevated in 10–25% of patients with NAFLD. Low titre (<1:160) antinuclear antibody (ANA) positivity has been documented in up to 33% of NAFLD patients[40]. The significance of this association remains unclear. Liver biopsy is recommended in patients with suspected NAFLD with concomitant ANA titres >1:160 or anti smooth muscle titre >1:40 to exclude autoimmune hepatitis.

Exclusion of Other Causes of Transaminitis

The diagnosis of NAFLD requires the exclusion of alcoholic liver disease. It is thus important to obtain an accurate history of alcohol intake, including the daily quantity of alcohol consumption. There is no consensus agreement regarding the precise definition of significant alcohol consumption. However, the generally accepted cut-off for purposes of diagnosis of NAFLD is <10g of alcohol per day for females and <20g/day for males or no more than 1 drink per day for women and no more than 2 drinks per day in men. It is noteworthy that in individuals with metabolic risk factors such as obesity and diabetes, lower quantities of alcohol may contribute to significant liver disease, thus making the distinction even more challenging.

Chronic viral hepatitis should be excluded by the relevant serological screening tests for hepatitis B and C. Wilson disease should similarly be excluded by screening for caeruloplasmin levels. The presence of low titres of ANA positivity is common in NAFLD, however persistently high titres should be evaluated with a liver biopsy to exclude autoimmune hepatitis. A thorough drug history should be taken in order to exclude drug-related causes of transaminitis. In the local context, this should include a detailed enquiry into the use of traditional medications.

Diagnosis of NASH

NASH is a histological diagnosis, and is characterised by the demonstration of macrovesicular stetaosis, lobular inflammation, balloon degeneration of hepatocytes and pericellular fibrosis.

Liver biopsy is the current gold standard for the diagnosis of NASH. However there are practical limitations and controversies surrounding the use of liver biopsy as a regular diagnostic tool for suspected NASH in NAFLD patients. Liver biopsy is invasive and is associated with small risk of morbidity such as haemorrhage, biliary peritonitis and bowel perforation. In addition, liver biopsy is associated with a small (0.1%) risk of mortality[41]. As such, liver biopsy is poorly accepted by patients, especially for repeated assessment to determine disease resolution or deterioration. This limits its use as a practical diagnostic tool for NASH in the large volume of fatty liver patients encountered in day-to-day clincial practice. There are also technical limitations to the accuracy of liver biopsy, in particular sampling variability and interobserver variation. The precise histological definition of NASH is also controversial, with the existence of multiple scoring systems. In 2005, Kleiner *et al* described the NAFLD Activity Score in an attempt to introduce some form of standardisation for histological scoring in NAFLD trials, but its generalisability and clinical utility remain undetermined[42].

As a result of the invasive nature and poor acceptance of liver biopsy, much effort has been undertaken to identify non-invasive means of evaluating NASH. Over the past decade, several serum panels and diagnostic tools have shown promising results in the non-invasive estimation of fibrosis in NASH. However, to date, there has been very limited success in the ability to predict the degree of steatohepatitis in a non-invasive manner.

There have been numerous studies which have described the use of non-invasive prediction models for NASH using serum markers. Most of these studies were of small sample size and lacked external validation. Some recently described models with relatively large sample size and some degree of external validation are discussed here. The NAFLD fibrosis score consists of 6 variables (age, BMI, AST/ALT ratio, hyperglycemia, platelet count and albumin) was reported to reliably predict advanced fibrosis in NAFLD patients[43]. Other similar scoring systems which have shown promise as non-invasive indicators of NASH fibrosis include the European Liver Fibrosis panel, BARD score and Fibrotest[44–46]. However, these models require extensive external validation before they can be recommended for widespread clinical use.

Measurement of liver stiffness by transient elastography (Fibroscan) is a novel diagnostic tool that has been shown to be useful for the non-invasive diagnosis of fibrosis in NAFLD patients[47]. In a recent study, Wong *et al* reported that the performance of transient elastography was superior to serum markers (APRI, NAFLD fibrosis score and BARD score)[48].

Apart from fibrosis, assessment of hepatic steatosis is also important in NAFLD. The presence of fat in the liver can be detected using various imaging modalities, including ultrasound, computer tomography (CT) and magnetic resonance imaging (MRI). In a study comparing ultrasound and CT, ultrasonography was found to be more sensitive in detecting fatty change[49]. However, when fatty change is patchy or focal, CT and MRI are superior to ultrasound. In addition, MRI and CT offer the ability to provide semi-quantitative estimation of degree of steatosis.

MANAGEMENT (see TABLE 2)

Lifestyle Modification

The overall goal in lifestyle modifications for the treatment of NAFLD is to achieve gradual and sustained weight loss among obese patients through increased physical activity and dietary modifications. The major contributors of increased flux of fatty acids through the liver of NASH patients has been identified to be inappropriate adipose tissue lipolysis and hepatic de novo lipogenesis from excessive carbohydrates[50]. Insulin resistance is a major contributing factor to inadequate postprandial suppression of adipocyte lipolysis. Hyperinsulinaemia with impaired peripheral glucose metabolism promotes de novo lipogenesis in the liver.

Diet

Dietary modifications involve reducing the intake of foods which promote insulin resistance or hepatic lipotoxicity. For example, foods with high fat content increase circulating free fatty acids that are liberated by lipoprotein lipase. Moderate weight loss (approximately 6%) via caloric restriction

Table 2. Treatment options for NAFLD/NASH.

Non-Pharmacological	Pharmacological
Lifestyle modification	Weight-loss agents
▪ Dietary modifications	▪ Orlistat
▪ Exercise	▪ Sibutramine
▪ Combined diet & exercise	Insulin-sensitizers
Surgery	▪ Thiazoladinediones
▪ Restrictive bariatric surgery	▪ Metformin
▪ Malabsorptive bariatric surgery	Anti-fibrotic / hepatoprotective agents
▪ Combination restrictive-malabsorptive surgery	▪ Anti-oxidants
▪ Liver transplantation	▪ Ursodeoxycholic acid
	▪ Others

improves insulin resistance and intrahepatic lipid content[51].

a. Fructose

High fructose consumption is associated with the development of insulin resistance and NAFLD in epidemiologic studies[52–54]. Large amounts of fructose depletes hepatic energy because of rapid first-pass by the liver and phosphorylation by phosphofructokinase[55,56]. Fructose also impairs satiety mechanisms[57,58], further aggravating the problem of excessive caloric consumption.

b. Polyunsaturated fats

Several human observational[59–62] and animal studies[63,64] have demonstrated an improvement in liver triglyceride content and serum ALT levels with diets rich in polyunsaturated fats rather than monounsaturated fats.

c. Trans-fats

Double bonds in unsaturated fatty acids exist in *cis* configuration. During hydrogenation of unsaturated fats to saturated fats, some double bonds are isomerised to the *trans* configuration instead of being reduced to single bonds. Epidemiologic studies have identified trans-fats as a risk for cardiovascular disease[65]. However, data is scarce on the effects of trans-fats in the liver. In mice, trans-fat feeding resulted in severe steatohepatitis[66]. Trans-fat content in adipose tissue of NAFLD patients has also been observed to be higher than in control patients[67]. Not more than 2g/day of trans-fats should be consumed in the adult diet[68].

Exercise

Observational studies have shown an inverse correlation between fitness levels and NAFLD/NASH[69–71]. However, the long-term effects of improved fitness through regular aerobic exercise in NAFLD/NASH have not been established.

There is limited data on the effects of exercise alone in the management of NASH, as it is difficult to eliminate confounders such as weight loss and dietary changes. Some studies also question the role of exercise alone. A small study of diet and exercise for 2 weeks showed that caloric restriction reduced liver fat, but 2 weeks of exercise did not provide any additive benefit[72]. Another small study found that countering weight loss with a high-carbohydrate diet negated the beneficial effects of exercise on insulin resistance in overweight adults[73].

Combination Dietary Modifications and Exercise

Lifestyle modification combining exercise and weight loss effectively improves insulin sensitivity and prevents diabetes[74–77]. Several studies have demonstrated that even small amounts of weight loss (5% to 10%) results in significant improvements in NAFLD and NASH[78–80]. A large population study found that exercise and caloric restriction improved liver fat content after 9 months, despite only a 3.2% decrease in BMI[81]. Few studies include biopsies at the end of treatment and large, well-controlled

trials have not been published. For example, 10 studies consisting of 626 total patients have been published evaluating the effect of combination calorie restriction with exercise, but liver histology was the primary end point in only 4 of them (123 patients)[82]. Weight loss is difficult to sustain, hence, most studies are focused on changes which occur over a relatively short period of time.

Attaining ideal BMI is not a requisite for improvement in aminotransferases. In fact, rapid weight loss (>1.6 kg/week) should be avoided as it may exacerbate steatohepatitis or liver disease. Ideal lifestyle modification should aim for 90 to 140 minutes of aerobic forms of exercise per week with moderate caloric restriction (25 kcal/kg/day)[83], to achieve a 7% to 10% weight loss over a 6 to 12 month period[84,85].

Pharmacological Therapy

Although mild to moderate weight loss has been demonstrated to benefit NAFLD/NASH, this is difficult to sustain by diet and exercise alone. As a high level of motivation is required, poor compliance is often an issue[86–89]. Furthermore, the existence of other co-morbidities associated with or as a consequence of the metabolic syndrome (e.g. cardiovascular disease, osteoarthritis) often preclude the ability to achieve the target level of physical activity[90]. Hence the interest to develop effective pharmacotherapy to either achieve sustainable weight loss or improve the effects of NAFLD/NASH via other pathways. However, there are several unresolved issues with pharmacotherapy in NAFLD. Firstly, there are no clear recommendations when or in whom pharmacotherapy is indicated. It is believed that bland steatosis may worsen insulin resistance, whereas steatohepatitis may worsen liver disease and progress to frank cirrhosis. Although lifestyle modifications should be encouraged in all NAFLD patients, some authors suggest that only NASH patients should be offered pharmacotherapy[91]. However, a recent report suggests that steatosis alone may not be entirely benign[20]. In which case, perhaps pharmacotherapy should be offered to NAFLD patients who fail lifestyle modifications, or be offered concurrently with lifestyle modifications? Secondly, regardless the mechanism of action of drug employed and improved histologic changes demonstrated, studies have unanimously reported a regression of liver histology upon drug cessation. Thirdly, study design makes for difficult comparisons across studies. Variability ranges from inclusion/exclusion criteria, treatment/follow-up duration, the lack of histology at diagnosis, the lack of paired biopsies, to some studies including more than two treatment arms. Most studies have been small- to moderately-sized and few well-controlled trials have been reported. Fourth, as most drugs target a specific pathway in the development of NASH, no specific pharmacologic intervention has been found ideal because the pathogenesis of this disease is complex, involving the interaction of multiple pathways. Nevertheless, drug therapy in NAFLD can be classified according to those which promote weight loss, improve insulin resistance or prevent fibrosis.

Weight Loss Agents

Orlistat reduces the absorption of dietary triglycerides by 30% via the inhibition of gastric and pancreatic lipases. This results in a modest weight loss[92] with improvement of insulin sensitivity[92–95]. Small studies have reported improvements in liver enzymes[96,97] and NASH histology[98]. Two randomised prospective trials have been published which do not demonstrate the benefit of orlistat in NASH beyond that of weight loss[80,99]. There have also been recent concerns regarding the safety of orlistat in view of recent reports of hepatic failure occurring in some patients[100]. However, causality is not conclusively proven.

Sibutramine, a serotonin and noradrenaline re-uptake inhibitor, used as a weight loss agent has reported improved insulin resistance, biochemical and radiologic paramenters[101]. However, concerns regarding its safety have resulted in the US Food and Drug Administration advising against its use in patients with cardiovascular risk[102].

Insulin Sensitizers

Insulin resistance plays a key role in the pathogenesis of NASH. As such, it is hoped that improving insulin sensitivity would reverse NAFLD/NASH. However, some studies have shown that this alone may not be enough to improve liver injury[103].

a. Thiazoladinediones

   Glitazones are peroxisome proliferator-activated receptor-gamma (PPARγ) agonists which improve insulin sensitivity by increasing the uptake of fatty acids in adipose tissue, reducing hepatic glucose production and

increasing glucose uptake by peripheral muscles. Various drugs have been used, including rosiglitazone and pioglitazone. Four randomised trials involving 213 subjects[103–106] and 2 open-label studies[107,108] with paired histology have been published. Studies using the glitazones have consistently demonstrated reductions in transaminase levels and improved hepatic steatosis sustained throughout the treatment period. Some studies have even reported a normalisation of liver enzymes while on therapy. Improvements in transaminase levels have correlated with improved insulin sensitivity and loss of liver fat[103,104]. Improvement in hepatic fibrosis is less consistent[103,106–108]. There is concern over increased cardiovascular risk with the use of glitazones, including heart failure and myocardial infarction[109] and a black-box warning is issued for these adverse effects. Weight gain is a frequent adverse effect, due to the expansion of peripheral adipose tissue, and is not reversible despite treatment cessation[110]. This weight gain is not associated with increased cardio-metabolic risk.

b. Metformin

Initial studies using metformin for short periods could demonstrate substantial improvements in serum transaminases[111–113]. A Cochrane meta-analysis showed that metformin leads to normalisation of serum aminotransferases compared with dietary modification and improved steatosis by imaging[114]. However, open-label studies with longer treatment durations cast doubts over whether this effect is sustained beyond 6 months of therapy[115,116]. The benefits of metformin on liver histology are not consistently demonstrated[112,113,117].

Anti-fibrotic/Hepatoprotective Agents

a. Anti-oxidants

The use of anti-oxidants as a potential means to treat NASH is based on the hypothesis that oxidative stress is a key player in the pathogenesis of steatohepatitis and fibrosis development. Several drugs have been tried, including vitamin E, vitamin C, combination vitamin E and C[118], probucol[119,120], N-acetylcysteine[121,122]. Studies have also been conducted combining anti-oxidants with other therapies (e.g. with insulin-sensitisers). However, none of the anti-oxidants nor their combinations have shown consistent results in terms of biochemical nor histological benefits in NASH. To date, there is insufficient data to recommend the use of anti-oxidants as a treatment for NASH.

b. Ursodeoxycholic acid

Urseodeoxycholic acid is used as a hepatoprotective agent[123,124] which initially showed promise as a treatment for NASH. However, subsequent larger randomised control studies failed to demonstrate benefit in NASH histology, except for an improvement in steatosis[125,126]. A French study using high-dose ursodeoxycholic acid reported significant reductions in serum ALT levels and Fibrotest fibrosis marker[46,127].

Other Options

Other drugs which have shown some promise in animal studies of NASH include angiotensin-recepter blockers[128–130], betaine[131], pentoxifylline[132–136], nataglinide[137], rimonabant[138,139], probiotic VSL#3[140,141], synthetic adiponectin[142], leptin infusion[143,144]. Only a few studies have been performed in a small number of humans. Some of these studies with favourable outcomes for insulin resistance or obesity do not report specifically on liver outcomes. In late 2008, Sanofi-Aventis and Pfizer terminated their studies with rimonabant because of safety concerns. None of these drugs can yet be recommended as NASH therapy.

Bariatric Surgery

Local guidelines suggest a BMI >37.5 kg/m^2 without risk factors or BMI >32.5 kg/m^2 with risk factors or co-morbidities to be indications to consider bariatric surgery[145]. Bariatric surgery can be classified by their mechanisms of inducing weight loss: restrictive, malabsorptive or combination procedures.

Restrictive-type bariatric surgery reduces the capacity of the gastric reservoir, leading to early satiety and reduced food and caloric intake. Current options include adjustable gastric banding and sleeve gastrectomy. These laparoscopic surgical options are preferred in the high-risk surgical patient as they are less invasive and easier to perform than malabsorptive surgeries.

Table 3. Approach to the NAFLD/NASH patient in the clinical setting.

1. Confirm the diagnosis of NAFLD/NASH
   - Involves history-taking to exclude significant alcohol/drug intake or toxin-exposure
   - Involves the exclusion of other possible causes of abnormal liver tests or liver imaging
   - Consider liver biopsy for diagnostic and prognostic purposes
2. Screen and treat risk factors of the Metabolic Syndrome
   - i.e. insulin resistance, hypertension, central obesity, hyperlipidaemia
3. Advise lifestyle modifications
   - including exercise (30–45minutes thrice weekly) and dietary modifications
   - reduce sedentary lifestyle
   - avoid too rapid weight loss (>1.6kg/week)
4. Consider pharmacologic therapy as part of clinical trial or to control metabolic risk factors
   - e.g. the use of metformin in a diabetic patient
5. Consider surgical therapy
   - Bariatric surgery for patients with BMI >32.5kg/m^2 with co-morbidities or BMI >37.5 kg/m^2 without co-morbidities
   - Liver transplantation in a patient with decompensated NASH cirrhosis with / without hepatocellular carcinoma

Malabsorptive surgeries create a "short gut" by bypassing variable lengths of the small bowel to reduce intestinal absorption. The original jejunoileal bypass which achieved remarkable weight loss by bypassing >90% of the small intestine is no longer performed in view of its numerous resultant complications, including electrolyte losses and bacterial overgrowth[146,147].

Roux-en-Y gastric bypass and biliopancreatic diversion surgeries employ a combination of both restrictive and malabsorptive techniques. The gastric bypass can also be performed laparoscopically, reducing operative morbidity[148]. The Biliopancreatic diversion was initially developed to avoid the stasis associated with intestinal bypass by maintaining a flow of bile and pancreatic juice through the biliopancreatic limb[149].

Large case-cohort and meta-analysis studies of morbidly obese patients have demonstrated the benefits of bariatric surgery on survival and in improving their co-morbidities (e.g. diabetes, cardiovascular disease)[146,150,151]. There have been reports of improved liver steatosis, inflammatory scores and fibrosis with both restrictive and combination type surgeries[152–160]. Some of these studies have even reported complete resolution of NAFLD/NASH[155,157]. Although improvements in hepatic steatosis and inflammation have been fairly consistent across several studies, the effects on fibrosis have been less uniform. A small study of 7 obese patients also demonstrated an improvement in hepatic gene expression of several profibrogenic cytokines as a result of gastric bypass surgery, despite a lack of improvement of hepatic inflammation and fibrosis scores[161].

Caution must be exercised to avoid surgery which results in too drastic weight loss, which has been reported to lead to acute steatohepatitis, cholestasis, hepatic decompensation and even death in some patients[162]. Patients with significant pre-existing liver disease prior to bariatric surgery are less likely to tolerate surgeries with large malabsorptive components.

Liver Transplantation

NASH cirrhosis is an increasingly common indication for liver transplantation. According to the North American United Network for Organ Sharing (UNOS) data, NASH cirrhosis accounted for 0.1% of liver transplantations in 1996, compared to 3.5% of transplantations in 2005[163]. The reported one and three year patient survival is approximately 93% and 81% respectively, which is comparable to survival rates for liver transplantation performed for other indications[164,165].

NAFLD and NASH recurrence post-transplantation is common. Furthermore, the prevalence and severity of obesity and the metabolic syndrome also increase after liver transplantation[166,167]. Approximately 25% of patients develop steatosis within the first year after transplantation, and nearly 50% by 4 years, Up to 50% of patients with recurrent steatosis fulfill histologic criteria for NASH[168–173]. NAFLD/NASH recurrence may also run a more aggressive course post-transplantation; some studies have reported significant fibrosis occurring in the graft as early as 1 year after transplantation[164]. Post-transplantation survival is compromised in patients with recurrent NASH[171].

Risk factors for recurrent or de novo NAFLD identified in cross-sectional, post-transplantation studies include pre- and post-transplantation obesity, weight gain, diabetes mellitus/insulin resistance, decreased HDL cholesterol, and elevated total cholesterol and hypertension[163,168]. The use of corticosteroids and calcineurin inhibitor-based immunosuppression may contribute to the prevalence of these risk factors in the transplant recipient.

CONCLUSION

NAFLD is an increasingly common cause of chronic liver disease worldwide with potential for substantial impact on healthcare costs from its morbidity and mortality. A better understanding of the natural history and epidemiology of the disease has emerged, although ideal pharmacologic therapy is still lacking. Lifestyle modification via a multidisciplinary approach is required to both treat NAFLD and to reduce the morbidity and mortality from other features of the metabolic syndrome (Table 3).

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