Non-alcoholic fatty liver disease

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This article reviews the nomenclature, clinical and histological basis for a diagnosis of non-alcoholic fatty liver disease or non-alcoholic steatohepatitis, its natural history, pathophysiology and an approach to clinical management.

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Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of disorders ranging from simple hepatic steatosis to 'complicated' NAFLD, comprising non-alcoholic steatohepatitis (NASH), fibrosing steatohepatitis and cirrhosis (Ludwig et al, 1980; Chitturi and Farrell, 2001). NASH, the most severe form of NAFLD, is emerging as a common, clinically important chronic liver disease in industrialized nations. The prevalence rates for NAFLD and NASH are estimated to be ~10–20% and ~2–3% respectively (Younossi et al, 2002). Such high prevalence rates are the result of the continuing epidemic of obesity and diabetes, which has been attributed to a combination of lifestyle changes and genetic susceptibility. NAFLD is increasingly recognized as a major cause of liver-related morbidity and mortality, and includes reports of hepatocellular carcinoma in persons with cryptogenic cirrhosis (Bugianesi et al, 2002).

TABLE 1.
Other forms of liver disease that need to be excluded in persons with probable non-alcoholic fatty liver disease

Disease entity	Clues
Alcohol-related liver disease	History, AST/ALT > 1, elevated mean corpuscular volume, high gamma-glutamyl transferase
Autoimmune hepatitis	Young women, anti-nuclear antibody, anti-smooth muscle antibody and/or antibody to liver-kidney microsome (LKM) positivity
Chronic hepatitis C	Risk factors, anti-HCV positive, HCV polymerase chain reaction positive
Chronic hepatitis B	Risk factors, hepatitis B surface antigen positive
Drug-induced hepatitis	Medication history and temporal relationship
Haemochromatosis	Family history, iron studies, haematochromatosis gene test
Primary biliary cirrhosis	Anti-mitochondrial antibody positivity
Sclerosing cholangitis	Association with inflammatory bowel disease, p-anti-neutrophil cytoplasmic antibody positivity
Wilson's disease	Family history, Kayser–Fleischer rings, raised serum copper and low serum ceruloplasmin
Alpha 1 anti-trypsin deficiency	Family history, lung disease (emphysema) low levels of alpha1 anti-trypsin; protease inhibitor genotype

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCV = hepatitis C virus.

DEFINITION

In 1980, Ludwig et al first introduced the term 'non-alcoholic steatohepatitis' to describe a form of liver pathology that was morphologically indistinguishable from alcoholic liver disease but which occurred in patients who did not consume alcohol. There is currently no universally accepted definition of what constitutes 'idiopathic' NASH. However, it is clear that NASH is a clinicopathological diagnosis. The clinical component includes:

- Confirmation of the presence of insulin resistance (IR)
- Exclusion of other forms of liver disease (*Table 1*) and secondary causes of steatohepatitis (*Table 2*).

The exclusion of alcoholic liver disease is important. What constitutes 'significant' alcohol consumption is a matter of controversy. All experts concur that consumption of <40 g/week of alcohol in the appropriate clinical context would be consistent with a diagnosis of NAFLD. Many investigators also include persons with metabolic liver disease associated with <20 g/day of alcohol as being consistent with NAFLD, while some have set limits of up to 40 g of alcohol perday. In practice, the lower the alcohol consumption, the more likely that the liver disease is solely the result of host metabolic factors. Confirmation of IR is based on the results of history, physical examination and laboratory findings (*Table 3*). Several histological classifications have been proposed for NAFLD. In general, the histological definition comprises steatosis, liver cell injury (ballooning degeneration and necrosis), lobular inflammation (mixed) and variable hepatic fibrosis. The classification

proposed by Matteoni and colleagues (1999) is the only one that has linked histology to clinical outcomes (*Table 4*).

EPIDEMIOLOGY

NASH is reported in all age groups including, but is typically recognized in the 4–5th decade of life (Harrison et al, 2002). Despite earlier data, NASH is now recognized as being equally prevalent in men and women. However, females appear to be over-represented in those with more advanced disease. NASH is reported in all ethnic groups, but African-Americans appear to have a higher risk for developing this condition (Clark et al, 2002). As mentioned, the prevalence rates for NAFLD and NASH are estimated to be ~10–20% and ~2–3% respectively (Younossi et al, 2002).

NATURAL HISTORY OF NAFLD OR NASH

The natural history of NAFLD varies according to the histological type. Simple steatosis is reported to have a benign clinical course, although progression to fibrosis and cirrhosis can occur in ~3% of patients (Matteoni et al, 1999). It seems probable that most cases of steatosis with lobular inflammation but without hepatocyte injury or fibrosis behave in the same way, with very low rates of fibrotic progression (Teli et al, 1995). However, ~20–25% of cases with NASH (NAFLD types 3 and 4) may progress to cirrhosis (Matteoni et al, 1999).

Once cirrhosis has developed, 40% of these patients may succumb to liver-related death over a 10-year period, the mortality rate being similar to or worse than cirrhosis associated with hepatitis C (Hui et al, 2003). NASH is currently considered to be the major cause of cryptogenic cirrhosis accounting for up to two thirds of cases (Bugianesi et al, 2002). NASH-associated cirrhosis can also decompensate into subacute liver failure, progress to liver cancer and recur post-transplantation (Caldwell and Hespenheide, 2002; Contos et al, 2001). If this progressive course is confirmed in larger prospective studies, NASH will cause a formidable disease burden in the decades to come.

DIAGNOSIS

Clinical history and physical examination

A detailed history and physical examination may provide important clues to the diagnosis of NAFLD or NASH (*Table 5*). The alcohol history must be carefully evaluated, and ideally, be corroborated from the GP and close family members. Drug-induced liver disease must be excluded.

Most patients with NAFLD or NASH are asymptomatic. When symptoms occur, they are usually non-specific. Fatigue and vague discomfort over the liver with hepatomegaly are common. Significant hepatic pain and tenderness is rare. There are no pathognomonic signs of NASH on physical examination. The majority of patients have central obesity which, it is important to note, is classified according to ethnicity (*Table 6*) (International Diabetes Institute, 2000; World Health Organization, 2000). Clinical stigmata of chronic liver disease such as muscle wasting,

TABLE 2.
Some causes of secondary steatohepatitis

Alcohol
Drugs (tamoxifen, amiodarone, methotrexate)
Copper toxicity (Wilson's disease, Indian childhood cirrhosis)
Jejuno-ileal bypass
Rapid profound weight loss (massive intestinal resection, gastroplasty, cachexia, bulimia and starvation)
Hypernutrition in adults (parenteral nutrition, intravenous glucose)
Disorders of lipid metabolism (abetalipoproteinaemia, hypobetalipoproteinaemia)
Jejunal diverticulosis (contaminated bowel syndrome)
Insulin resistance syndromes (familial and acquired lipodystrophies, Mauriac's syndrome, polycystic ovary syndrome)

TABLE 3.
Metabolic associations in persons with non-alcoholic fatty liver disease

Type 2 diabetes mellitus
Family history of type 2 diabetes
Insulin resistance*, with or without glucose intolerance †
Central obesity
Hypertriglyceridaemia, low high-density lipoprotein cholesterol
Rapid and massive weight loss in overweight subjects

* Insulin resistance. Homeostasis Model Assessment for insulin resistance (HOMA IR) = fasting insulin (mU/ml) x fasting glucose (mmol/litre)/22.5 (a level of >3 is usually consistent with insulin resistance) (Matthews et al, 1985). † Impaired glucose tolerance and impaired fasting glucose. Fasting plasma glucose (FPG) levels ≥ 100 mg/dl (5.6 mmol/litre) but <126 mg/dl (7.0 mmol/litre) or 2-hour values in oral glucose tolerance test (OGTT) of ≥ 140 mg/dl (7.8 mmol/litre) but <200 mg/dl (11.1 mmol/litre) (American Diabetes Association, 1997)

TABLE 4.
Categories of non-alcoholic fatty liver disease

Category	Pathology	Clinicopathological correlation
Type 1	Simple steatosis	Considered non-progressive
Type 2	Steatosis plus lobular inflammation	Probably benign (not regarded as NASH)
Type 3	Steatosis, lobular inflammation and ballooning degeneration	NASH without fibrosis
Type 4	Steatosis, ballooning degeneration, Mallory bodies, failure	NASH with fibrosis – may progress to cirrhosis and liver failure

NASH = non-alcoholic steatohepatitis. From Matteoni et al (1999)

gynaecomastia, spider telangiectasias and caput medusae are rare, appearing only when the disease progresses to an advanced stage.

Laboratory data

Elevated gamma-glutamyl transferase (GGT) is the commonest liver test abnormality in NAFLD, but this finding is non-specific. The alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are usually elevated, but are typically less than four times the upper limit of normal. Usually, the ALT/AST ratio is >1, but may approach or be <1 in those persons with cirrhosis. Patients with NASH may have normal liver enzymes, but on biopsy display the full spectrum of histological changes in NAFLD from simple steatosis to cirrhosis (Mofrad et al, 2003).

The correlation between liver enzyme abnormalities and the severity of histological changes is poor and hence any liver test abnormality needs to be fully assessed and investigated (Brunt et al, 1999; Garcia-Monzon et al, 2000). The serum bilirubin, albumin and coagulation studies are usually normal except in cases of advanced disease. A fully automated biochemical profile may reveal other features of the IR syndrome including hyperuricaemia, hypertriglyceridaemia and a low high-density lipoprotein cholesterol. A 2-hour oral glucose tolerance test, fasting insulin and C peptide can be used to confirm IR (*Table 3*) (Matthews et al, 1985). In 40% of patients, the serum ferritin is increased as an acute phase response, but the transferrin saturation is typically normal (Chitturi et al, 2002).

TABLE 5.
Pointers to non-alcoholic steatohepatitis or non-alcoholic fatty liver disease in clinical practice

Unexplained elevations of alanine aminotransferase and gamma glutamyl transferase, typically minor, in a person with metabolic risk factors (type 2 diabetes, obesity, dyslipidaemia, arterial hypertension, ischaemic heart disease and vascular disease)
Unexplained hepatomegaly
Recent weight gain and expanding waistline
Life-style or medication changes favouring weight gain
Family history of type 2 diabetes, non-alcoholic fatty liver disease, vascular disorders or hyperlipidaemia
Raised serum ferritin with normal transferrin saturation not attributable to iron storage disorder or alcohol
Abnormalities of hepatic imaging – diffuse increased echogenicity on ultrasound, radiolucency on computed tomography
Patients with chronic hepatitis C virus infection and diabetes and/or obesity
Patient with chronic hepatitis B virus infection, raised alanine aminotransferase but non-detectable hepatitis B virus DNA in the presence of metabolic risk factors

TABLE 6.
Ethnic-specific anthropometric criteria for the diagnosis of overweight and obesity

Category			Anthropometric criteria
Overweight		White Caucasian	BMI ≥ 25 kg/m^2
		Asian	BMI ≥ 23 kg/m^2
		Pacific Islander	BMI ≥ 26 kg/m^2
Obese		White Caucasian	BMI ≥ 30 kg/m^2
		Asian	BMI ≥ 25 kg/m^2
		Pacific Islander	BMI ≥ 32 kg/m^2
Central obesity	Waist* circumference	White Caucasian	WC ≥102 cm (men)
			WC ≥ 88 cm (women)
		Asian	WC ≥ 90 cm (men)
			WC ≥ 80 cm (women)
		Pacific Islander	Not determined
	Waist:hip ratio†		W/H ≥ 0.90 (men)
			W/H ≥ 0.85 (women)

From International Diabetes Institute (2000), World Health Organization (2000). BMI = body mass index. *Measurements taken anteriorly at a point midway between the lower border of the last rib above and the upper border of iliac crest below. †Hip measurements are taken at the point of maximal protrusion of buttocks

Hepatic imaging

Hepatic imaging may provide clues to the presence of steatosis, cirrhosis and/or hepatic space-occupying lesions. On ultrasound, the fatty liver appears diffusely 'bright' because of increased echogenicity of the liver parenchyma, particularly when extensive steatosis (involving at least 33% of hepatocytes) is present. On computerized tomography, steatosis gives the appearance of diffuse or localized areas of low density. Despite its utility, it should be noted that current imaging modalities cannot distinguish simple steatosis from NASH nor from other forms of liver disease.

The role of liver biopsy

Liver biopsy plays a critical role in the diagnosis of NAFLD or NASH. The biopsy can confirm or exclude a diagnosis of NAFLD or NASH, and reliably determine the severity of necrosis, inflammation and fibrosis. At present, clinical guidelines for liver biopsy in patients with suspected NAFLD are not standardized. The decision to perform a liver biopsy must be made on an individual basis. Clearly, it is not feasible to undertake biopsy in all obese persons with abnormal liver function tests. The authors' approach is not to recommend biopsy at first referral, but to institute life-style intervention strategies for 3–6 months. If liver function tests fail to normalize, a biopsy can be undertaken (*Figure 1*). A biopsy should also be seriously considered in all individuals who have a high likelihood of advanced hepatic fibrosis in order to better

define management strategies and provide prognostic information. Studies suggest that risk factors for advanced hepatic fibrosis include persons with a combination of obesity, type 2 diabetes mellitus and age >45–50 years (Angulo et al, 1999; Ratziu et al, 2000; Dixon et al, 2001).

PATHOPHYSIOLOGY

The development of NAFLD or NASH involves the interplay of multiple metabolic mechanisms and inflammatory pathways that link obesity, hepatic steatosis, hepatic inflammation and fibrosis. IR is the pathophysiological hallmark of NAFLD. In the absence of IR, a diagnosis of NAFLD is highly unlikely. IR may contribute both to hepatic steatosis and to hepatic necroinflammation. IR favours peripheral lipolysis resulting in increased free fatty acid release into the circulation, hepatic uptake of free fatty acids and their subsequent re-esterification and storage as triglycerides within the liver. Impaired lipid excretion in the form of very low-density lipoprotein has also been identified in persons with NASH (Charlton et al, 2002). Hepatic lipid storage predisposes the liver to injury, which can be initiated by free fatty acids (a consequence of IR), products of lipid peroxidation and pro-inflammatory cytokines such as tumour necrosis factor (TNF), interleukin (IL)-6, IL-8, leptin and low levels of adiponectin. Oxidative stress is common in animal and human models of NASH probably arising as a consequence of fatty acid oxidation. Products of oxidative stress can initiate a further cycle of hepatocyte injury and secondarily recruit pro-inflammatory mediators.

Liver fibrosis is the ultimate consequence of hepatic necroinflammation in NASH. Hyperinsulinaemia and hyperglycaemia, both consequences of IR, may contribute directly to the development of fibrosis. These conditions can induce and activate transforming growth factor (TGF)-β, which plays a key role in activating hepatic stellate cells to elaborate extracellular matrix as part of the wound-healing response. Leptin from adipose tissue likewise promotes fibrogenesis by stimulating hepatic stellate cells indirectly via increasing the production of TGFβ from sinusoidal endothelial cells and Kupffer cells. Hyperleptinaemia may in part explain the association between obesity and the risk of hepatic fibrosis in NASH (Day, 2002).

Finally, it is important to note that susceptibility to NASH is likely to be influenced by genetic factors that modulate host metabolic and inflammatory pathways involved in the pathogenesis of NASH (Day, 2002).

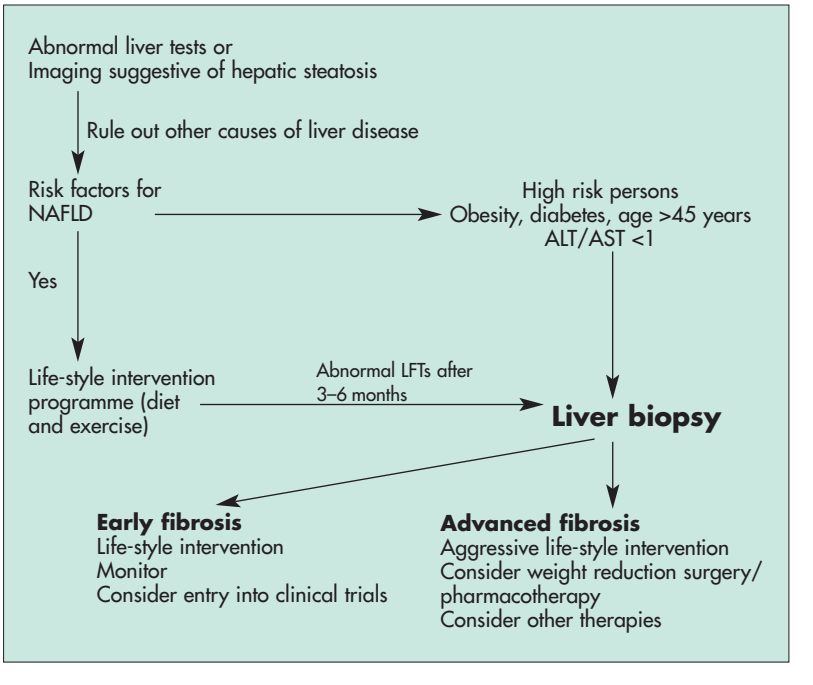
APPROACH TO MANAGEMENT

At present, there are no consensus guidelines for the management of patients with NAFLD or NASH. Therapeutic strategies have been largely empirical and are directed towards correction of risk factors including diabetes mellitus and hyperlipidaemia. Specific therapeutic options include weight reduction, weight reduction surgery, lipid-lowering agents, insulin-sensitizing agents, antioxidant, and hepatoprotective agents (*Table 7*).

Life-style intervention

The initial approach to the management of NAFLD or NASH is to institute a life-style intervention programme comprising strategies that enable weight reduction and enhance physical activity. Studies have shown that weight loss reduces IR with subsequent improvement of liver function tests and histology in patients with NAFLD or NASH (Wang et al, 2003). At present, there are no randomized controlled trials of weight reduction as a treatment for NAFLD or NASH. Based on the National Institute of Diabetes, Digestive and Kidney Diseases expert panel guidelines, the initial target of weight loss should be 10% of baseline weight within 6 months (0.5–1 kg/week) (Anonymous, 1998). However, rapid weight loss, in excess of 1 kg/week, should be avoided as this may exacerbate hepatic inflammation. In order to achieve these goals, a multidisciplinary approach is recommended.

Figure 1. A practical approach to the diagnosis and management of non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis. ALT = alanine aminotransferase; AST = aspartate aminotransferase; LFTs = liver function tests.



Based on the Diabetes Prevention Program guidelines, physical activity of moderate intensity (brisk walking at least 5 days a week, 30 minutes at a time, 150 minutes a week) and a low-energy, low-fat diet (<30% of energy intake) is recommended (Diabetes Prevention Program Research Group, 2002). It is also prudent to decrease saturated fats, increase polyunsaturated fats and antioxidants (vitamin C) and to add complex carbohydrates rich in fibre (15 g/day), fruits and vegetables.

Surgical therapies for weight reduction

Malabsorptive or restrictive (gastric banding) procedures are being increasingly used as therapy for weight reduction. Jejuno-ileal bypass is contraindicated in patients with NAFLD or NASH as it may lead to worsening of liver disease and hepatic decompensation. A recent report indicates that weight loss after gastric banding for morbid obesity results in a sigificant improvement or resolution of hepatic histological changes including fibrosis in persons with NAFLD (Dixon et al, 2004).

Pharmacotherapy of NAFLD or NASH

A variety of pharmacological therapies have been attempted in persons with NAFLD or NASH. Most trials are small, open-label, non-randomized studies for less than a year. Few have evaluated the effect of treatment on liver histology and clinical outcomes. Phentermine, sibutramine and orlistat are drugs currently approved for weight reduction. These agents can be considered in select groups of patients with NASH after diet and exercise (Harrison et al, 2003; Sabuncu et al, 2003).

TABLE 7.
Treatment options for non-alcoholic fatty liver disease

Therapy		Examples
Life-style intervention		Diet and exercise
Drugs for weight reduction		Orlistat, phentermine, sibutramine
Surgical therapies for weight reduction		Gastric banding
Lipid-lowering agents	Triglyceride-lowering agents	Gemfibrozil, clofibrate, probucol
	HMG CoA reductase inhibitors	Atorvastatin, simvastatin, pravastatin
Insulin-sensitizing medications	Biguanides	Metformin
	PPARγ agonists	Rosiglitazone, pioglitazone
	PPARα/γ agonists	Raraglitazone
	PPARα agonists	Clofibrate
Antioxidants		Vitamin E, vitamin C, betaine, N-acetylcysteine
Other hepatoprotective drugs		Ursodeoxycholic acid

HMG CoA = hydroxymethylglutaryl coenzyme A; PPAR = peroxisome proliterator-activated receptor

Hypertriglyceridaemia and/or hypercholesterolaemia is common in NASH. The usefulness of lipid-lowering agents for the treatment of NASH is inconclusive, but these conditions should be treated for cardioprotection.

The use of insulin-sensitizing agents holds the most promise since IR is universal in persons with NAFLD or NASH. Metformin, a biguanide insulin-sensitizing agent in clinical use for adults >30 years, has been used for the treatment of NAFLD. Its use is associated with significant improvements in liver tests, glucose disposal and a reduction in body mass index (BMI) (Marchesini et al, 2001; Promrat et al, 2004). Thiazolinediones (rosiglitazone, pioglitazone, raraglitazone) are a new class of oral hypoglycaemic agents that act as peroxisome proliferator-activated receptor (PPAR) γ agonists by selectively enhancing or partially mimicking certain actions of insulin with a resultant reduction in circulating levels of insulin, triglycerides and non-esterified free fatty acids. Reports demonstrate that use of these agents may have beneficial effects on liver function tests and necroinflammatory activity (Caldwell et al, 2001; Neuschwander-Tetri et al, 2003; Promrat et al, 2004). However, adverse effects were reported, and include elevations in serum alanine aminotransferase (ALT), weight gain (~4%) and occasional hepatotoxicity. While these medications are not standard pharmacotherapy for NASH, they may be useful particularly in patients with type 2 diabetes mellitus.

While IR appears essential for the development of NAFLD, oxidative stress has been demonstrated in animal and human models of NASH. It represents either the cause or the consequence of liver injury in NAFLD and may be an important determinant of disease progression and inflammatory recruitment. Antioxidants (vitamin E, vitamin C, betaine and N-acetylcysteine) and hepatoprotective agents (ursodeoxycholic acid) have been studied for the treatment of NASH but have not been shown to be unequivocally efficacious. Their utility in NAFLD or NASH awaits further evaluation in large well-controlled clinical trials with extended follow-up and clinically relevant end-points, particularly fibrosis progression.

CONCLUSIONS

NAFLD and NASH are common chronic liver diseases with the potential for progression to cirrhosis and liver-related death. They are frequently associated with obesity and IR. Once a diagnosis of NAFLD or NASH has been entertained on clinical and laboratory grounds, life-

style intervention through diet and exercise should be instituted for 3–6 months. Liver biopsy should be reserved for those with warning signs of advanced liver disease or if the liver tests fail to normalize despite life-style intervention. In those with advanced fibrosis, pharmacotherapy can be considered, ideally in the context of clinical trials. At present, there is no established therapy for NAFLD or NASH and treatment is largely empirical. The role of pharmacotherapy in NAFLD or NASH remains to be defined, and more work is needed to define patient subgroups that are most likely to benefit. **HM**

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KEY POINTS

- Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver disorders ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis.
- NASH is a clinicopathological diagnosis that requires confirmation of the presence of insulin resistance, exclusion of other forms of liver disease and appropriate liver histology.
- The alcohol history must be carefully evaluated to determine its contribution to liver injury.
- The natural history of NAFLD varies according to the histological type. Simple steatosis generally has a benign clinical course, whereas 20–25% of cases with NAFLD types 3 and 4 may progress to cirrhosis.
- Insulin resistance is the pathophysiological hallmark of NAFLD. In the absence of insulin resistance, a diagnosis of NAFLD is highly unlikely.
- The decision to perform a liver biopsy must be individualized.
- Risk factors for advanced hepatic fibrosis in NASH include persons with a combination of obesity, type 2 diabetes mellitus and age >45–50 years, together typically with an alanine aminotransferase/aspartate aminotransferase <1.
- Life-style intervention programmes comprising diet and exercise are the cornerstone of management in NAFLD or NASH.
- Pharmacotherapy, particularly with insulin-sensitizing agents, shows great promise but at present their use should be limited to clinical trials.