

Nonalcoholic fatty liver disease (NAFLD)

郝立智醫師

永康榮民醫院新陳代謝科

Reference: NEJM, Volume 346:1221-1231 April 18, 2002 Number 16

Outline

- Introduction
- Epidemiologic Features
 1. Risk Factors
 2. Prevalence
- Clinical Manifestations
 1. Clinical Features
 2. Laboratory Abnormalities
 3. Imaging Studies
 4. Histologic Findings
- Pathogenesis
- Diagnosis
 - Role of Liver Biopsy
- Natural History
- Management
 1. Associated Conditions
 2. Drug Therapy
 3. General Recommendations
- Conclusions

Introduction (1)

- NAFLD is an increasingly recognized condition that may progress to **end-stage liver disease**.
- Pathological picture resembles **alcohol-induced liver injury**, but it occurs in p'ts who do not abuse alcohol.
- A variety of terms describe this entity, including fatty-liver hepatitis, nonalcoholic Laënnec's disease, **DM hepatitis**, alcohol-like liver disease, and **nonalcoholic steatohepatitis (NASH)**.

Introduction (2)

- **NAFLD** is the preferred term, from simple steatosis to steatohepatitis, advanced fibrosis, and cirrhosis.
- Steatohepatitis (**NASH**) represents only a stage within the spectrum of NAFLD.
- Clinical implications of NAFLD are derived mostly from its common occurrence in the general population and its potential to progress to cirrhosis and liver failure.
- NAFLD should be differentiated from steatosis, with or without hepatitis, resulting from **secondary causes** (Table 1), have distinctly different pathogeneses and outcomes.

Epidemiologic Features- Risk Factors (1)

- **Obesity, type 2 DM, and hyperlipidemia** are coexisting conditions frequently associated with NAFLD.
- The reported prevalence of obesity in several series of NAFLD varied between **30 and 100 %**, the prevalence of type 2 DM varied between **10 and 75 %**, and the prevalence of hyperlipidemia varied between **20 and 92 %**. Some children with NAFLD have **type 1 DM**.
- The prevalence of NAFLD increases by a factor of **4.6** in obese people, defined as those with a BMI at least **30**.
- Regardless of BMI, the presence of **type 2 DM** significantly increases the risk and severity of NAFLD.

Epidemiologic Features- Risk Factors (2)

- **Truncal obesity** seems to be an important risk factor for NAFLD, even in normal BMI.
- About **half of hyperlipidemia** were found to have NAFLD on ultrasound examination in one study.
- **Hypertriglyceridemia** rather than hypercholesterolemia may increase the risk of NAFLD. A **family history** of steatohepatitis or cryptogenic cirrhosis has also been implicated as a risk factor for this disorder.
- NAFLD may affect **any age** and most racial groups.
- The typical NAFLD is a **middle-aged woman**, but some have found a higher prevalence of NAFLD in males than in females.

Epidemiologic Features- Prevalence (1)

- NAFLD affects 10 to 24 % of the general population in various countries. The prevalence increases to 57.5 % to 74 % in obese persons.
- NAFLD affects 2.6 % of children and 22.5 % to 52.8 % of obese children.
- NAFLD is a common explanation for abnormal liver-test results in blood donors, and the cause of asymptomatic elevation of aminotransferase levels in up to 90 % of cases once other causes of liver disease are excluded.
- **NAFLD** is the most common cause of abnormal liver-test results among adults in the United States.

Epidemiologic Features- Prevalence (2)

- Prevalence of NAFLD in USA is unknown.
- **Obesity** affects **22.5 %** of people 20 years of age or older.
- **Steatosis** is found in over two thirds of the obese population, regardless of diabetic status, and in more than 90 % of morbidly obese persons (those weighing more than 200 % of their IBW).
- **Steatohepatitis** affects about 3 % of the lean population (those weighing less than 110 % of their IBW), 19 % of the obese population, and almost half of morbidly obese people.
- On the basis of U.S. population in year 2000, **30.1 million** obese adults may have steatosis, and **8.6 million** may have steatohepatitis.

Epidemiologic Features- Prevalence (3)

- DM affects 7.8 % of the U.S. adult population, whereas about 50 % (range, 21 to 78 %) DM (7.8 million people) have NAFLD.
- DM and obesity may pose an added risk: among severely obese p'ts with DM, 100 % had at least mild steatosis, 50 % had steatohepatitis, and 19 % had cirrhosis.
- Prevalence of NAFLD in USA seems to be substantially greater than the 1.8 % prevalence of HCV infection.
- The figures may underestimate the real prevalence of NAFLD, since many p'ts are nonobese and nondiabetic, and the disease is increasingly diagnosed in children and adolescents.

Clinical Features

- Most NAFLD have **no S/S** of liver disease at diagnosis, although many p'ts report fatigue or malaise and a sensation of fullness or discomfort on RUQ abdomen.
- **Hepatomegaly** is the only physical finding in most p'ts.
- **Acanthosis nigricans** may be found in children with NAFLD.
- Findings of chronic liver disease and diminished numbers of platelets suggest advanced disease with cirrhosis.
- A high proportion of cryptogenic cirrhosis share many of the clinical and demographic features of NAFLD, suggesting **unrecognized NAFLD**.

Laboratory Abnormalities (1)

- Mildly to moderately elevated serum levels of GOT, GPT, or both are the most common and often the only laboratory abnormality found in NAFLD.
- The ratio of **GOT to GPT** is usually less than 1, but this **ratio increases as fibrosis advances**, leading to a loss of its diagnostic accuracy in cirrhotic NAFLD.
- Serum **ALP**, **γ -GT**, or both are above the normal range in many p'ts, although their degree of elevation is less than that seen in alcoholic hepatitis.

Laboratory Abnormalities (2)

- Other abnormalities, including **hypoalbuminemia**, a **prolonged PT**, and **hyperbilirubinemia**, may be found in cirrhotic-stage NAFLD.
- Elevated serum **ferritin** are found in half the p'ts, and increased **transferrin saturation** in 6 to 11 % of p'ts. **Hepatic iron index** and **hepatic iron level**, however, are usually in normal range.
- **Heterozygosity for the hemochromatosis (*HFE*) gene** may be increased in NAFLD and that hepatic iron overload may be associated with more severe liver disease.
- Clinical data from large numbers of p'ts, however, have shown that this is not always the case.

Imaging Studies (1)

- On **ultrasonography**, fatty infiltration of the liver produces a diffuse increase in echogenicity as compared with that of the kidneys.
- Regardless of the cause, **cirrhosis** has a similar appearance on ultrasonography.
- **Ultrasonography** has a sensitivity of 89 % and a specificity of 93 % in detecting **steatosis** and a sensitivity and specificity of 77 % and 89 %, respectively, in detecting **increased fibrosis**.

Imaging Studies (2)

- Fatty infiltration of the liver produces a low-density hepatic parenchyma on **CT scanning**. Steatosis is diffuse in most NAFLD, but occasionally, it is focal.
- Sono and CT scans may be misinterpreted as showing malignant liver masses.
- In such cases, **MRI** can distinguish space-occupying lesions from focal fatty infiltration (characterized by isolated areas of fat infiltration) or focal fatty sparing (characterized by isolated areas of normal liver).
- **Magnetic resonance spectroscopy** allows a quantitative assessment of fatty infiltration of the liver.

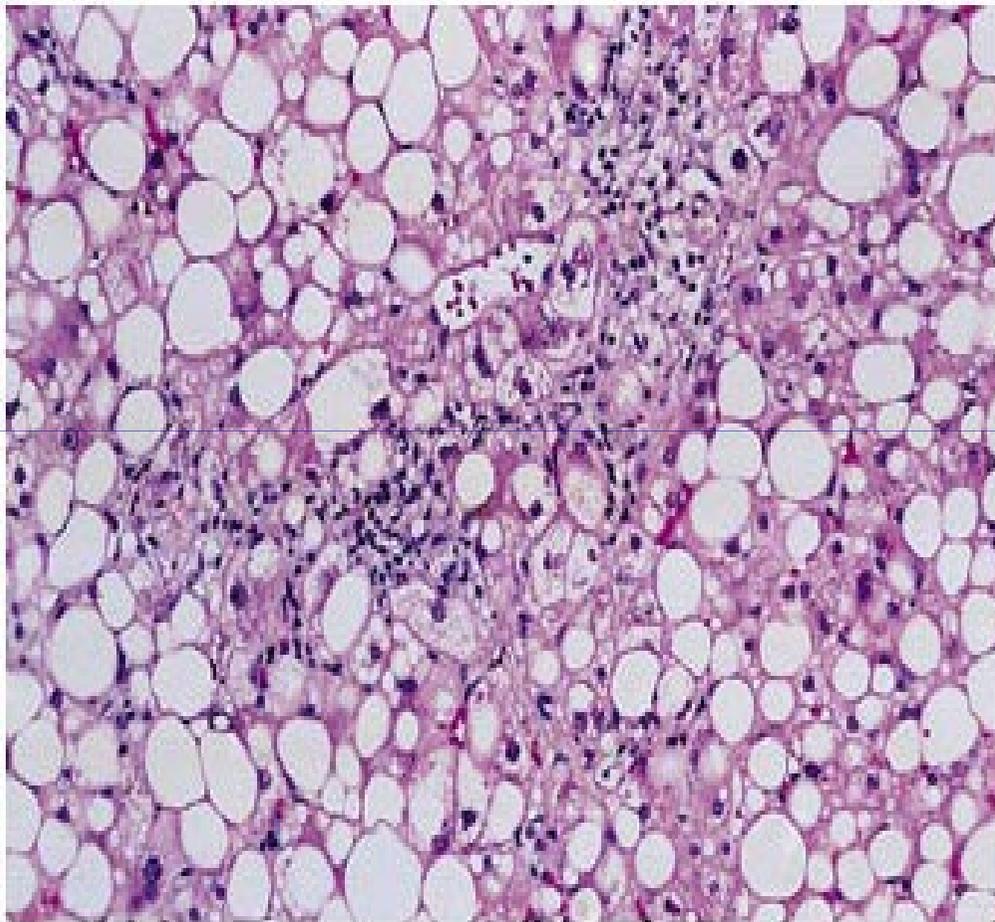
Histologic Findings (1)

- NAFLD is histologically indistinguishable from the liver damage resulting from alcohol abuse.
- **Liver-biopsy features** include steatosis, mixed inflammatory-cell infiltration, hepatocyte ballooning and necrosis, glycogen nuclei, Mallory's hyaline, and fibrosis ([Figure 1](#)).
- The presence of these features, alone or in combination, accounts for the wide spectrum of NAFLD.
- **Portal tracts** are relatively spared from inflammation, although **children** with NAFLD may show a predominance of portal inflammation as opposed to a lobular infiltrate.
- **Mallory's hyaline** is notably sparse or absent in children with NAFLD.

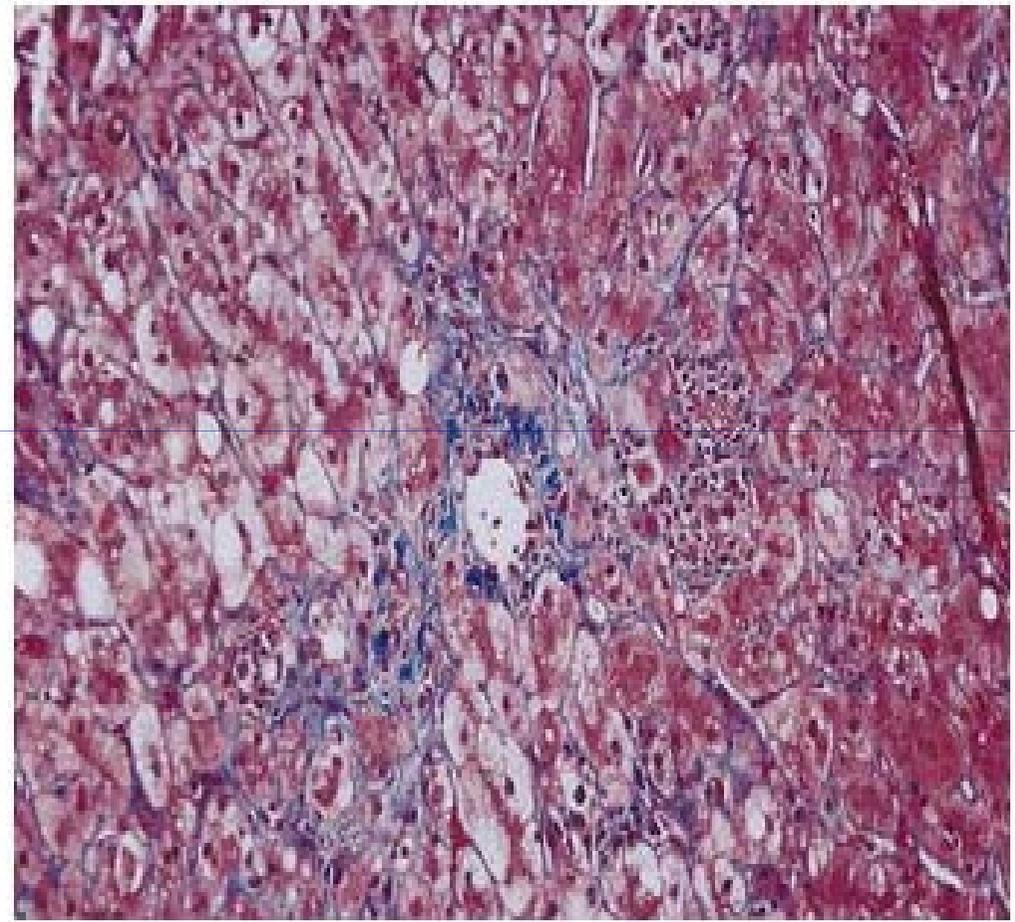
Histologic Findings (2)

- In some p'ts with cirrhosis, the features of steatosis and necroinflammatory activity may no longer be present.
- A finding of **fibrosis** in NAFLD suggests more advanced and severe liver injury.
- According to a number of cross-sectional studies including a total of 673 liver biopsies, some degree of **fibrosis** is found in up to 66 % of p'ts at diagnosis, whereas **severe fibrosis** (septal fibrosis or cirrhosis) is found in 25 % and well-established **cirrhosis** is found in 14 %.

Figure 1. Characteristic Findings of Nonalcoholic Fatty Liver Disease on Liver-Biopsy Specimens.



A



B

- **Panel A** shows steatosis (predominantly **macrovesicular**), an inflammatory infiltrate, Mallory's hyaline, and hepatocyte ballooning (hematoxylin and eosin, x200).
- **Steatosis** is predominantly as **macrovesicular fat**, although some hepatocytes may have an admixture of microvesicular steatosis.
- **Fatty infiltration**, when mild, is typically concentrated in acinar zone 3, whereas moderate-to-severe fatty infiltration has a more diffuse distribution.

- The **inflammatory infiltrate** usually consists of mixed neutrophils and lymphocytes and predominates in zone 3.
- **Ballooning degeneration of hepatocytes** results from the accumulation of intracellular fluid and is characterized by swollen cells, typically in zone 3 near the steatotic hepatocytes.
- **Mallory's hyaline** is found in about half of adult p'ts with NAFLD and is usually located in ballooned hepatocytes in zone 3, but it is neither unique nor specific to NAFLD.

- **Panel B** shows perivenular fibrosis as well as pericellular and perisinusoidal fibrosis in zone 3 (Masson's trichrome, x200).
- The pattern of fibrosis is one of the characteristic features of NAFLD. **Collagen** is first laid down in the pericellular space around the central vein and in the perisinusoidal region in zone 3.
- In some areas, the collagen invests single cells in a pattern referred to as "**chicken wire**" fibrosis, as described in alcohol-induced liver damage. This pattern of fibrosis helps to distinguish NAFLD and alcoholic liver disease from other forms of liver disease in which fibrosis shows an initial portal distribution.

Histologic Findings (3)

- The combination of steatosis, infiltration by mononuclear cells or PMN cells (or both), and hepatocyte ballooning and spotty necrosis is known as **NASH**.
- Most p'ts with this type of NAFLD have some degree of **fibrosis**, whereas **Mallory's hyaline** may or may not be present.
- The severity of steatosis can be graded on the basis of the extent of involved parenchyma ([Table 2](#)).
- A system that unifies the lesions of steatosis and necroinflammation into a "grade" and those of the types of fibrosis into a "stage" has been proposed ([Table 2](#)).

Pathogenesis (1)

- The pathogenesis of NAFLD has remained poorly understood since the earliest description of the disease.
- Much current thinking remains hypothetical, since the mechanism or mechanisms are still being worked out.
- It is not yet understood why simple steatosis develops in some p'ts, whereas steatohepatitis and progressive disease develop in others.
- Differences in **body-fat distribution** or **antioxidant systems**, possibly in the context of **a genetic predisposition**, may be among the explanations.

Pathogenesis (2)

- A net retention of lipids within hepatocytes, mostly in the form of TG, is a **prerequisite** for development of NAFLD.
- The primary metabolic abnormalities leading to lipid accumulation are not well understood, but they could consist of alterations in the pathways of uptake, synthesis, degradation, or secretion in hepatic lipid metabolism resulting from **I.R.** (Figure 2A).
- **I.R.** is the most reproducible factor in the development of NAFLD. The molecular pathogenesis of I.R. seems to be **multifactorial**, and **several molecular targets** involved in the inhibition of insulin action have been identified.

Pathogenesis (4)

- Clinically significant amounts of dicarboxylic acids, which are potentially cytotoxic, can be formed by **microsomal β -oxidation**. This pathway of fatty-acid metabolism is closely related to mitochondrial β -oxidation and peroxisomal β -oxidation (**Figure 2C**).
- Deficiency of the enzymes of **peroxisomal β -oxidation** has been recognized as an important cause of microvesicular steatosis and steatohepatitis.
- Deficiency of **acyl-coenzyme A oxidase** disrupts the oxidation of very-long-chain fatty acids and dicarboxylic acids, leading to extensive microvesicular steatosis and steatohepatitis.
- Loss of this enzyme also causes sustained hyperactivation of **PPAR- γ** , leading to transcriptional up-regulation of PPAR- γ – regulated genes.

Pathogenesis (3)

- These include **Rad** (ras associated with DM), which interferes with essential cell functions (growth, differentiation, vesicular transport, and signal transduction); **PC-1** (a membrane glycoprotein that has a role in I.R.), which reduces insulin-stimulated tyrosine kinase activity; **leptin**, which induces dephosphorylation of insulin-receptor substrate-1; **fatty acids**, which inhibit insulin-stimulated peripheral glucose uptake; and **TNF- α** , which down-regulates insulin-induced phosphorylation of insulin-receptor substrate-1 and reduces the expression of the insulin-dependent glucose-transport molecule **Glut4**.
- **I.R.** leads to fat accumulation in hepatocytes by two main mechanisms: **lipolysis and hyperinsulinemia** (Figure 2B).

Pathogenesis (5)

- **PPAR- γ** has been implicated in promoting hepatic synthesis of **uncoupling protein-2**, which is expressed in the liver of p'ts with NAFLD.
- Increased intrahepatic levels of fatty acids provide a source of oxidative stress, which may in large part be responsible for the progression from steatosis to steatohepatitis to cirrhosis.
- **Mitochondria** are the main cellular source of reactive oxygen species, which may trigger steatohepatitis and fibrosis by three main mechanisms: **lipid peroxidation**, **cytokine induction**, and **induction of Fas ligand** (Figure 2D).

Figure 2. Possible Mechanisms of Pathogenesis of NAFLD

- In **Panel A**, hepatic fatty acids are normally esterified into triglycerides, some of which are exported out of hepatocytes as VLDL.
- The increased level of lipids, mostly in the form of **triglycerides**, within hepatocytes in p'ts with NAFLD results from an imbalance between the enzyme systems that promote the uptake and synthesis of fatty acids and those that promote the oxidation and export of fatty acids.

- In **Panel B**, insulin resistance (owing to inhibition of TNF- α , Rad, PC-1, eptin, and fatty acids) leads to accumulation of fat in hepatocytes by two main mechanisms: **lipolysis** (increases circulating fatty acids) and **hyperinsulinemia**.
- Increased uptake of fatty acids by hepatocytes leads to **mitochondrial β -oxidation overload**, with the consequent accumulation of fatty acids within hepatocytes.
- Fatty acids are substrates and inducers of the microsomal lipxygenases cytochrome P-450 2E1 and 4A.
- **Cytochrome P-450 2E1** is invariably increased in the steatohepatitis and may result in the production of free oxygen radicals capable of inducing lipid peroxidation of hepatocyte membranes.

- Extensive lipid peroxidation is also observed in transgenic mice in which the cytochrome P-450 2E1 gene has been knocked out, suggesting that **cytochrome P-450 4A enzymes** may have the principal role.
- **Hyperinsulinemia** resulting from insulin resistance increases the synthesis of fatty acids in hepatocytes by **increasing glycolysis** and favors the accumulation of triglycerides within hepatocytes by decreasing hepatic production of **apolipoprotein B-100**.

- **Panel C** shows the relation between microsomal ω -oxidation, peroxisomal β -oxidation, and mitochondrial β -oxidation, as well as the regulatory role of PPAR- α ligand.
- **Microsomal ω -oxidation** of fatty acids generates dicarboxylic fatty acids, which are further degraded by peroxisomal β -oxidation.
- **Peroxisomal β -oxidation** generates chain-shortened acyl-coenzyme A.
- Very-long-chain fatty acids are converted to acyl-coenzyme A by the action of acyl-coenzyme A synthetase.

- **Acyl-coenzyme A** serves as a substrate for peroxisomal oxidation, but if left unmetabolized, it functions as a PPAR- α ligand.
- **PPAR- α** controls the induction of genes involved in microsomal, peroxisomal, and mitochondrial fatty-acid oxidation systems in liver, and it may also promote hepatic synthesis of **uncoupling protein-2**.
- The role of this protein in the pathogenesis of NAFLD remains uncertain. It may help **inhibit hepatocyte apoptosis**, but it may also increase the vulnerability of fatty hepatocytes to subsequent injury when exposed to secondary insults such as **endotoxin or TNF- α** .

- In **Panel D**, mitochondrial reactive oxygen species promote progression from steatosis to steatohepatitis and fibrosis by three main mechanisms: **lipid peroxidation, cytokine induction, and Fas ligand induction**.
- Reactive oxygen species trigger lipid peroxidation, which causes cell death and releases malondialdehyde (MDA) and 4-hydroxynonenal (HNE).
- **MDA and HNE** cause **cell death**; cross-link proteins, leading to the formation of Mallory's hyaline; and activate stellate cells, promoting collagen synthesis. HNE has chemotactic activity for neutrophils, promoting tissue inflammation.
- Reactive oxygen species also induce the formation of the cytokines **TNF- α , TGF- β , and IL-8**. TNF- α and TGF- β cause caspase activation and hepatocyte death.

- **TGF- β** activates collagen synthesis by stellate cells and activates tissue transglutaminase, which cross-links cytoskeletal proteins, promoting the formation of Mallory's hyaline.
- **IL-8** is a potent chemoattractant for human neutrophils.
- **TNF- α** induced by reactive oxygen species further impairs the flow of electrons along the respiratory chain in mitochondria.
- **Mitochondrial reactive oxygen** species can deplete hepatic antioxidants, allowing accumulation of more reactive oxygen species.
- **Mitochondrial reactive oxygen** species cause expression of the Fas ligand in hepatocytes, which normally express the membrane receptor Fas.
- **Fas ligand** on one hepatocyte can then interact with Fas on another hepatocyte, causing fractional killing.

Pathogenesis (6)

- P'ts with steatohepatitis have ultrastructural mitochondrial lesions, including **linear crystalline inclusions in megamitochondria**.
- This mitochondrial injury is absent in most p'ts with simple steatosis and in healthy subjects.
- P'ts with steatohepatitis slowly resynthesize ATP in vivo after a fructose challenge, which causes acute hepatic ATP depletion.
- This impaired ATP recovery may reflect the mitochondrial injury found in steatohepatitis.

Pathogenesis (7)

- Thus, although symptoms of liver disease rarely develop in p'ts with fatty liver who are obese, have DM, or have hyperlipidemia, the steatotic liver may be vulnerable to further injury when challenged by additional insults.
- This has led to the presumption that progression from simple steatosis to steatohepatitis and to advanced fibrosis results from **two distinct events**.
- First, **I.R.** leads to the accumulation of fat within hepatocytes, and second, **mitochondrial reactive oxygen** species cause lipid peroxidation, cytokine induction, and the induction of Fas ligand.

Diagnosis (1)

- Diagnosis is usually suspected in persons with **asymptomatic elevation of aminotransferase** levels, radiologic findings of **fatty liver**, or unexplained persistent **hepatomegaly**.
- The clinical diagnosis and liver tests have a **poor predictive value** with respect to histologic involvement.
- **Imaging studies**, although of help in determining the presence and amount of fatty infiltration of the liver, cannot be used to accurately determine the severity of liver damage.
- The clinical suspicion of NAFLD and its severity can only be confirmed with a **liver biopsy**.

Diagnosis (2)

- Requires the exclusion of **alcohol abuse** as the cause of liver disease; a daily intake as low as **20 g** in females and **30 g** in males may be sufficient to cause alcohol-induced liver disease in some p'ts (350 ml [12 oz] of beer, 120 ml [4 oz] of wine, and 45 ml [1.5 oz] of hard liquor each contain 10 g of alcohol).
- Other causes, such as **viruses, autoimmune responses, metabolic or hereditary factors, and drugs or toxins**, should be ruled out.
- The decision on how extensive the serologic workup should be must be individualized.
- Specific laboratory test results, along with a number of histologic findings on liver biopsy, make the diagnosis of liver diseases with these other causes straightforward in most cases.

Role of Liver Biopsy (1)

- **Liver biopsy** remains the best diagnostic tool for confirming NAFLD, as well as the most sensitive and specific means of providing important prognostic information.
- Liver biopsy is also useful to determine the effect of medical treatment, given the poor correlation between histologic damage and the results of liver tests or imaging studies.

Role of Liver Biopsy (2)

- An age of 45 years or more, the presence of obesity or type 2 DM, and a ratio of GOT to GPT of 1 or greater are noteworthy indicators of **advanced liver fibrosis** (Table 3).
- In the subgroup of overweight p'ts with a BMI over 25, older age, higher BMI, and higher levels of GPT and TG are also indicators of more advanced liver fibrosis.
- In severely obese p'ts with a BMI over 35, an index of I.R. of more than 5, systemic HTN, and an elevated GPT level correlate strongly with the presence of **steatohepatitis**, whereas HTN and raised levels of GPT and C-peptide suggest the presence of **advanced fibrosis**.

**TABLE 3. ADJUSTED ODDS RATIOS FOR SEVERE FIBROSIS
(SEPTAL FIBROSIS OR CIRRHOSIS). ***

| RISK FACTOR | ODDS RATIO (95% CI) |
|--|----------------------------|
| Age \geq 45 yr | 5.6 (1.5–21.7) |
| Obesity (body-mass index \geq 30) | 4.3 (1.4–13.8) |
| Aspartate aminotransferase:alanine aminotransferase ratio $>$ 1 | 4.3 (1.5–12) |
| Type 2 diabetes mellitus | 3.5 (1.2–9.8) |

*Adapted from Angulo et al.¹⁴ with the permission of the publisher. CI denotes confidence interval.

Natural History (1)

- Determined by the severity of histologic damage.
- In five series, 54 of 257 p'ts with NAFLD underwent liver biopsy during an follow-up of 3.5 to 11 years. 28 % had progression of liver damage, 59 % no change, and 13 % had improvement or resolution of liver injury.
- Progression from steatosis to steatohepatitis and to more advanced fibrosis or cirrhosis has been recognized in several cases. Some of the few deaths that occurred among the 257 p'ts were liver-related, including one from HCC.
- Many NAFLD have a relatively benign course, whereas in some others, the disease progresses to cirrhosis and its complications.

Natural History (2)

- P'ts found to have **pure steatosis** on liver biopsy seem to have the best prognosis, whereas steatohepatitis or more advanced fibrosis are associated with a worse prognosis.
- In one study, progression of liver fibrosis occurred only in p'ts with necrosis and inflammatory infiltration on liver biopsy. In another study, 36 % NAFLD died after a mean follow-up of 8.3 years; **liver-related diseases** were the second most common cause of death, exceeded only by **cancer**.
- There was a trend toward more liver-related deaths among steatohepatitis, which can be explained by the higher **HLJ** prevalence of cirrhosis among these p'ts.

Natural History (3)

- Some data suggest that the coexistence of steatosis with other liver diseases, such as **HCV infection**, could increase the risk of progression of the liver disease.
- The natural history of cirrhosis resulting from NAFLD has not been completely defined.
- In a recent study, **2.9 %** of 546 liver-transplantation procedures performed in a single center were for end-stage steatohepatitis.
- This suggests that although NAFLD is common, only a minority of p'ts will require liver transplantation.

Management-Associated Conditions

- In DM or hyperlipidemia, good metabolic control is always recommended, but not always effective in reversing NAFLD.
- Improvement in liver-test results is almost universal in obese adults and children after **weight reduction**.
- Fatty infiltration usually decreases with weight loss in most p'ts, although necroinflammation and fibrosis may worsen.
- Rate of weight loss is important and may have a critical role in determining histologic findings will improve or worsen.
- In p'ts with a high degree of fatty infiltration, **rapid weight loss may promote necroinflammation, portal fibrosis, and bile stasis**. A weight loss of about **500 g/wk in children** and **1600 g/wk in adults** has been advocated.

Management-Drug Therapy

- No medications proved to directly reduce or reverse liver damage **independently of weight loss**.
- Only small pilot studies lasting one year or less have been reported to date.
- **Gemfibrozil, vitamin E (α-tocopherol), and metformin** have been shown to improve liver-test results.
- **Ursodiol, betaine, vitamin E, and thiazolidinedione troglitazone** led to improvement in liver-test and histologic findings-- deserve further evaluation in controlled clinical trials that have sufficient statistical power and include clinically relevant end points.
- **Troglitazone** has been removed from the market because of its potential hepatotoxicity.

Management-General Recommendations (1)

- An attempt at **gradual weight loss** along with appropriate control of **serum glucose and lipid levels** is a useful first step.
- Perhaps these should be the only treatment recommendations for p'ts with NAFLD with **pure steatosis** and no evidence of necroinflammation or fibrosis.
- Since most p'ts who have problems from NAFLD have steatohepatitis, treatment is more likely to be aimed at those with **steatohepatitis**.

Management-General Recommendations (2)

- P'ts with steatohepatitis, particularly those with fibrosis on liver biopsy, should be monitored closely, with more careful metabolic control, and be offered enrollment in clinical trials.
- Many cirrhotic-stage NAFLD have coexisting conditions that reduce the usefulness of liver transplantation.
- For **decompensated cirrhosis**, liver transplantation is a potential therapeutic alternative.
- NAFLD may recur in the **allograft** or develop after liver transplantation for **cryptogenic cirrhosis**.

Metformin in non-alcoholic steatohepatitis (1)

- There is no established treatment for steatohepatitis in p'ts who are not alcoholics.
- This disease is a potentially progressive liver disease associated with hepatic insulin resistance.
- Only a weight-reducing diet in overweight p'ts has proved effective.
- We treated 20 p'ts who had steatohepatitis but were not alcoholics with metformin (**500 mg three times a day for 4 months**), an agent that improves hepatic insulin sensitivity.

Metformin in non-alcoholic steatohepatitis (2)

- When compared with the six individuals not complying with treatment, long-term metformin significantly **reduced mean transaminase concentrations**, which returned to normal in **50%** of actively-treated p'ts.
- Also, **insulin sensitivity improved** significantly and **liver volume decreased by 20%**.
- Similar data have been reported in insulin-resistant *ob/ob* mice with fatty liver.
- A randomised-controlled study is needed.

Conclusions (1)

- NAFLD affects a large proportion of the world's population. **I.R. and oxidative stress** have critical roles in the pathogenesis of NAFLD.
- **Liver biopsy** remains the most sensitive and specific means of providing important prognostic information.
- **Simple steatosis** may have the best prognosis within the spectrum of NAFLD, but it has the potential to progress to **steatohepatitis, fibrosis, and even cirrhosis**.
- **No effective medical therapy** is currently available for all NAFLD.
- **Weight reduction**, when achieved and sustained, may improve the liver disease.

Conclusions (2)

- Pharmacologic therapy aimed at the underlying liver disease holds promise.
- However, **questions** remain regarding the use of drug therapy and the effect of recommended dietary measures.
- **Liver transplantation** is a therapeutic alternative for some p'ts with decompensated, end-stage NAFLD, but NAFLD may recur after liver transplantation.