June 2007(II): S57–S63

Obesity and Nonalcoholic Fatty Liver Disease

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With the increasing prevalence of obesity and type 2 diabetes mellitus in the general population, nonalcoholic fatty liver disease (NAFLD) has become a common diagnosis in clinical practice. Insulin resistance and oxidative stress play an important role in NAFLD development and progression. NAFLD affects one in three adults and one in 10 children/adolescents in the United States. Mortality in patients with NAFLD is significantly higher than in the general population of same age and gender with liver-related complications. Lifestyle intervention may improve NAFLD, but medications that increase insulin sensitivity and the antioxidant defenses in the liver deserve evaluation in carefully controlled trials.

Key words: diabetes, dyslipidemia, insulin resistance, nonalcoholic fatty liver disease (NAFLD), obesity

doi: 10.1301/nr.2007.jun.S57–S63

INTRODUCTION

Key Points

- Nonalcoholic fatty liver disease (NAFLD) comprises a spectrum of liver pathology including bland steatosis, steatohepatitis, cirrhosis, and hepatocellular carcinoma.
- NAFLD affects a substantial proportion of the general population from several countries.
- The prevalence and incidence of NAFLD is expected to increase worldwide as the global obesity epidemic spreads and the trend in developing countries toward the Western lifestyle continues.
- Insulin resistance is almost a universal finding in patients with NAFLD, and NAFLD is considered the hepatic manifestation of the metabolic syndrome, which includes central obesity, hyperglycemia, low high-density lipoprotein (HDL)-cholesterol, hypertension, and hypertriglyceridemia.
- Improvement of insulin resistance with lifestyle intervention constitutes an essential step in both the treatment and prevention of NAFLD. Medications that increase insulin sensitivity and the antioxidant defenses in the liver hold promise for the treatment of NAFLD.

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DISEASE DEFINITION

NAFLD refers to the accumulation of fat, mainly triglycerides, in hepatocytes that exceeds 5% of the liver weight. NAFLD primarily results from insulin resistance, and thus frequently occurs as part of the metabolic changes that accompany obesity, type 2 diabetes, and dyslipidemia. However, it is important to exclude secondary causes of steatosis (Table 1). The histological damage in NAFLD is very similar to that seen in patients with alcoholic liver disease, but NAFLD is by definition not alcohol induced. Alcohol abuse, hepatotoxic medications, and other liver conditions should be ruled out. However, given the high prevalence of obesity, diabetes, and dyslipidemia in the general population, NAFLD often coexists with liver diseases of other etiology.[1-3]

CLINICAL PRESENTATION

Patients may complaint of fatigue or malaise and a sensation of fullness or discomfort in the right upper abdomen. Health-related quality of life is significantly diminished due to insulin resistance-associated comorbidities. Hepatomegaly and acanthosis nigricans in children are common physical findings. Patients with "cryptogenic" cirrhosis share many clinical features of patients with NAFLD, suggesting that their symptoms are in fact the cirrhotic stage of unrecognized NAFLD. Insulin resistance and oxidative stress play a key role in the development and progression of NAFLD. Mild to moderate elevation of serum aminotransferases is the most common and often the only laboratory abnormality

Table 1. Causes of Nonalcoholic Fatty Liver Disease	
Primary	Obesity, glucose intolerance, type 2 diabetes, hypertriglyceridemia, low HDL cholesterol, hypertension
Nutritional	Protein-calorie malnutrition, rapid weight loss, gastrointestinal bypass surgery, total parental nutrition
Drugs	Glucocorticoids, estrogens, tamoxifen, amiodarone, methotrexate, diltiazem, zidovudine, valproate, aspirin, tetracycline, cocaine
Metabolic	Lipodystrophy, hypopituitarism, dysbetalipoproteinemia, Weber-Christian disease
Toxins	*Amanita phalloides* mushroom, phosphorus poisoning, petrochemicals, *Bacillus cereus* toxin
Infections	Human immunodeficiency virus, hepatitis C, small bowel diverticulosis with bacterial overgrowth

found in patients with NAFLD. The AST/ALT ratio is usually less than one, but this ratio increases as fibrosis advances. Imaging studies, including ultrasonography, computerized tomography (CT) scan, and magnetic resonance imaging (MRI), are sensitive in detecting steatosis, but the grade and stage of disease can be determined only with a liver biopsy.

Histological features include steatosis alone or in combination with mixed inflammatory cell infiltration, hepatocyte ballooning and necrosis, Mallory's hyaline, and fibrosis. These histological features are mostly seen in acinar zone 3, although portal-based injury is commonly seen in children. The diagnosis of NAFLD requires the exclusion of alcohol abuse and other etiologies as the cause of the liver disease. Treatment of patients with NAFLD should focus on the management of associated conditions including obesity and glucose and lipid abnormalities (Figure 1). Lifestyle intervention with diet and increased physical activity are the cornerstone in the management of NAFLD. Medications including insulin sensitizers and antioxidants are being evaluated in placebo-controlled trials. Patients with NAFLD with simple steatosis seem to follow a relatively benign course, whereas in others, NAFLD progresses to advanced fibrosis and cirrhosis with its consequent complications of portal hypertension and liver failure. Cirrhotic-stage NAFLD constitutes a common indication for liver transplantation. As in other types of cirrhosis, cirrhotic-stage NAFLD may be complicated by hepatocellular carcinoma (HCC).[1-3]

INCIDENCE AND PREVALENCE

Because no prospective studies have been conducted, the true prevalence of NAFLD and its different stages remains incompletely defined; the reported prevalence of NAFLD varies based on the information available in a given population and the diagnostic criteria used. Table 2 summarizes the results of several studies on the prevalence of NAFLD. Population-based studies provide more accurate figures, but only a few have been published to date. Using proton magnetic resonance spectroscopy, the Dallas Heart Study (a population-based cohort study performed in an ethically diverse community in the United States) reported that one in three adult Americans have steatosis,[4] which means that over 70 million adult Americans suffer from NAFLD. In that study,[4] 79% of patients with NAFLD had normal aminotransferase levels, so studies using liver enzymes as a surrogate for NAFLD underestimate the prevalence of NAFLD. A high prevalence rate of NAFLD has been reported from other countries. Using liver ultrasonography, a recent population-based cohort study performed in Italy found that one in four or five adults in that country suffer from NAFLD.[5] NAFLD also has reached epidemic proportions among populations typically considered at "low-risk" for this condition, with a prevalence in China and Japan of 15% and 14%, respectively, among adults. The clinical implications of this alarming prevalence of NAFLD are derived from the fact that it may progress to end-stage liver disease and liver cancer.[6,7]

Population-based studies provide better estimates of the prevalence of NAFLD in the general population than autopsy studies, hospital series, or studies performed exclusively in obese populations (Table 2). The prevalence of NAFLD among children is unknown, but some data indicate that 2.6% to 9.6% of children have NAFLD, increasing up to 38% to 53% among obese children (Table 2).

RISK FACTORS

NAFLD may affect any age and ethnic group. The prevalence of NAFLD in adults in the United States seems to be different among different ethnic groups, affecting 45% of Hispanics, 33% of whites, and 24% of blacks. The prevalence is significantly higher in white men (42%) than in white women (24%). There is no gender difference in prevalence among Hispanic or black populations.[4] In children and teens, the prevalence of

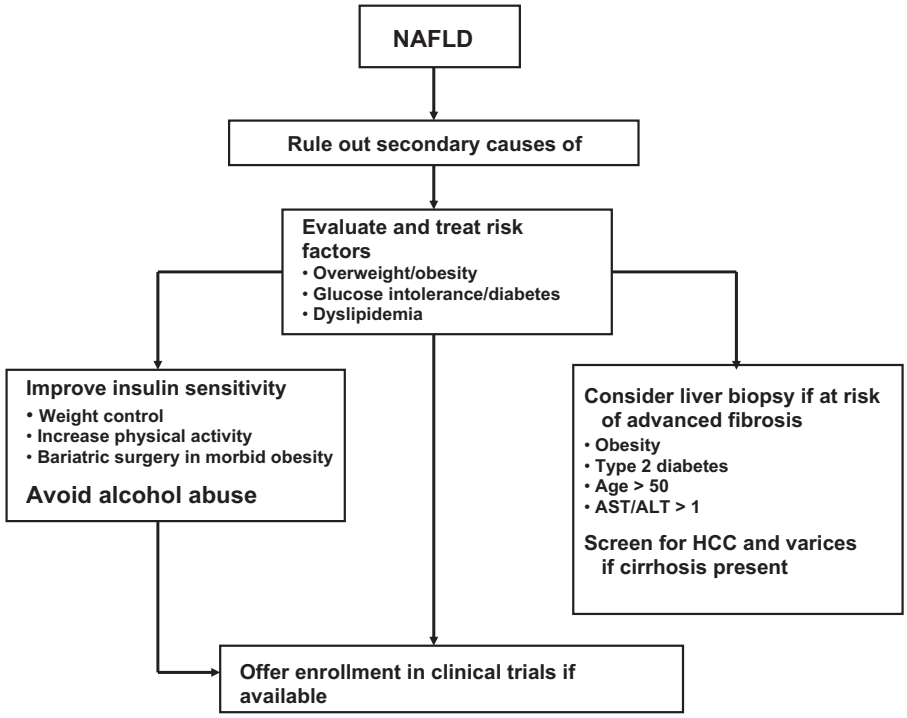

Figure 1. Diagnosis and treatment algorithm for nonalcoholic fatty liver disease (NAFLD).

NAFLD seems to be different among the different ethnic groups as well, with the highest prevalence among Hispanic and the lowest among black children.[8] Differences in body fat distribution and body composition among the different ethnic groups may partially explain the racial differences in prevalence. For example, Hispanics have a higher proportion of body fat and higher waist-to-hip ratio than their taller counterparts.[9] Similarly, Asians have a higher proportion of visceral fat and a lower proportion of lean body mass than white subjects with the same body mass index (BMI).[10]

The central (or upper body) obesity phenotype is associated with increased intraabdominal (or visceral) fat. Visceral adipose tissue has greater lipolytic potential than subcutaneous adipose tissue, and the release of free fatty acids (FFA) from visceral fat directly into the portal circulation creates a "first-pass" effect.[11] Increased FFA concentrations, in turn, are considered a major mediator of insulin resistance. In contrast, FFA flux and concentrations in individuals with predominantly lower body obesity tend to be normal, regardless of BMI.[11] Therefore, patients with central obesity are characteristically insulin resistant, and more commonly present with NAFLD than patients with lower-body obesity.[12]

In addition to central obesity, type 2 diabetes, dyslipidemia, and hypertension are risk factors for the development of NAFLD. However, NAFLD can also precede the development of these other comorbidities.[6] Environmental factors and a lifestyle promoting less physical activity and high-fat diets are well-known influences for the development of insulin resistance-associated comorbidities and NAFLD. The genetic predisposition for the development of central obesity and type 2 diabetes undoubtedly plays a role in the development of NAFLD, although family studies and studies specifically addressing the genetic susceptibility for NAFLD development are lacking.

NATURAL HISTORY AND PROGNOSIS

Changes in fibrosis stage have been specifically evaluated in four independent studies (Table 3). Overall, fibrosis progresses over time, but remains stable for a number of years in many cases, and may actually improve spontaneously in some.[7,13-15] Higher BMI and more insulin resistance or the presence of type 2 diabetes are risk factors for a higher rate of fibrosis progression.[7,15] As fibrosis develops and progresses over time, other features of NAFLD including steatosis, inflammation, and ballooning of hepatocytes significantly improve or disappear,[15] and thus liver biopsy features other than fibrosis severity may not be useful in predicting the long-term prognosis in an individual patient with NAFLD. Further, the histological features of NAFLD that create the basis for the histological diagnosis of nonalcoholic steatohepatitis (NASH), inflammation and hepatocyte ballooning, are unequally distributed throughout the liver parenchyma, with liver biopsy resulting in misdiagnosis in some patients.[16] When ele-

Table 2. Selected Studies on Prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

Author (year)	Study	Diagnostic Method	Country	N	Prevalence of NAFLD (%)	Prevalence of NASH (%)
Browning (2004)	Population-based	MR spectroscopy	United States	2287	31	ND
Bedogni (2005)	Population-based	Ultrasonography	Italy	598	23	ND
Fan (2005)	Population-based	Ultrasonography	China	3175	15	ND
Nomura (1988)	Population-based	Ultrasonography	Japan	2574	14	ND
Clark (2003)	Population-based	Aminotransferases	United States	15676	5.4	ND
Ruhl (2003)	Population-based	Aminotransferases	United States	5724	2.8	ND
Jimba (2005)	Health evaluation	Ultrasonography	Japan	1950	29	ND
Hamaguchi (2005)	Health evaluation	Ultrasonography	Japan	4401	18	ND
Park (2006)	Health evaluation	Ultrasonography	South Korea	6648	16	ND
Hultcrantz (1986)	Hospital series	Liver biopsy	Sweden	149	39	ND
Lee (1989)	Hospital series	Liver biopsy	United States	543	ND	9
Nonomura (1992)	Hospital series	Liver biopsy	Japan	561	ND	1
Byron (1996)	Hospital series	Liver biopsy	United States	1226	ND	11
Daniel (1999)	Hospital series	Liver biopsy	United States	81	51	32
Berasain (2000)	Hospital series	Liver biopsy	Spain	1075	ND	16
Hilden (1977)	Autopsy series	Liver biopsy	Sweden	503	24	ND
Ground (1982)	Autopsy series	Liver biopsy	United States	423	16	ND
Wanless (1990)	Autopsy series	Liver biopsy	Canada	207	29	6
El-Hassan (1992)	Outpatients	Ultrasonography, CT	Saudi Arabia	1425	10	ND
Lonardo (1997)	Outpatients	Ultrasonography	Italy	363	20	ND
Araujo (1998)	Outpatients	Ultrasonography	Brazil	217	33.5	ND
Omagari (2002)	Outpatients	Ultrasonography	Japan	3432	9	ND
Luyckx (1998)	Bariatric surgery	Liver biopsy	Belgium	528	74	ND
Silverman (1990)	Bariatric surgery	Liver biopsy	United States	100	86	36
Dixon (2001)	Bariatric surgery	Liver biopsy	Australia	105	71	25
Beymer (2003)	Bariatric surgery	Liver biopsy	United States	48	85	33
Spaulding (2003)	Bariatric surgery	Liver biopsy	United States	48	88	56
Mathurin (2006)	Bariatric surgery	Liver biopsy	France	167	ND	14.4
Franzese (1997)*†	Outpatients	Ultrasonography	Italy	72	53	ND
Tominaga (1995)*	Health evaluation	Ultrasonography	Japan	810	3	ND
Schwimmer (2006)*	Autopsy series	Liver biopsy	United States	742	9.6‡	3

* Pediatric series; † Obese children; ‡ 38 among obese; ND, not determined.

Table 3. Changes in Fibrosis Stage Evaluated in Studies with Sequential Liver Biopsy in Nonalcoholic Fatty Liver Disease

Author (year)	N	Average Time Between Biopsies	Progressed	Stable	Improved
		years (range)		*N (%)*	
Harrison (2003)	22	5.7 (1.4–15.7)	7 (32)	11 (50)	4 (18)
Fassio (2004)	22	4.3 (3–14.3)	7 (32)	11 (50)	4 (18)
Adams (2005)	103	3.2 (0.7–21.3)	38 (37)	35 (34)	30 (29)
Ekstedt (2006)	70	13.8 (10.3–16.3)	29 (41)	30 (43)	11 (16)

vated, aminotransferases improve or normalize spontaneously over time despite fibrosis progression.[15]

Studies evaluating the long-term prognosis of patients with NAFLD are summarized in Table 4. Overall, the disease progresses slowly over many years or decades, but the prognosis is different across the different stages of NAFLD. Patients with simple, bland steatosis appear to have a more benign prognosis. For example, a Danish study of a cohort of 109 predominantly morbidly obese subjects followed for nearly 17 years found the incidence of cirrhosis to be less than 1%.[17] During follow-up, a fourth of the patients died, but the survival curve of the general population fell within the 95% confidence interval of the survival curve of patients with bland steatosis. In that study, the patient who developed cirrhosis was the only one who died from liver-related causes. Conversely, patients with cirrhotic stage NASH have a worse prognosis, as was demonstrated in three recent studies.[18-20] In these studies, 9% to 26% of patients died within 4 to 10 years of follow-up, with most causes of death related to end-stage liver disease.

Overall, a diagnosis of NAFLD is associated with a shorter than expected survival than that for the general population of the same age and gender, as was recently demonstrated in two independent studies.[6,7] A community-based study performed in the United States included 420 patients with NAFLD and found liver-related complications to be the third most common cause of death among NAFLD patients; it is the thirteenth most common cause of death in the general population.[6] This indicates that complications of end-stage liver disease contribute greatly to mortality in patients with NAFLD. Patients dying from liver-related causes were those with more advanced NAFLD,[6] confirming observations of smaller studies.[17-20] Impaired fasting glucose or diabetes, older age, and presence of cirrhosis are risk factors independently associated with a higher mortality in NAFLD.[6]

A recent Swedish study of 129 patients presenting with abnormal liver enzymes found a significantly higher mortality among patients with NAFLD compared with the general population of the same age and gender after

Table 4. Studies on Long-Term Prognosis of Nonalcoholic Fatty Liver Disease (NAFLD)*

Author (year)	Diagnosis	N	Cirrhosis Prevalence†	Liver-Related Deaths	Overall Deaths	Average Time to Follow-up
				N (%)		*years*
Teli (1995)	Bland steatosis	40	0%	0	14 (35)	9.6
Dam-Larsen (2004)	Bland steatosis	109	1%	1 (0.9)	27 (24.8)	16.7
Matteoni (1999)	NAFLD	98	20%	9 (9)	48 (49)	8.3
Adams (2005)	NAFLD	420	5%	7 (1.7)	53 (12.6)	7.6
Ekstedt (2006)	NAFLD	129	7.8%	2 (1.6)	26 (20.2)	13.7
Lee (1989)	NASH	39	16.3%	1 (3)	10 (26)	3.8
Powell (1990)	NASH	42	7%	1 (2)	2 (5)	4.5
Evans (2002)	NASH	26	4%	0	4 (15)	8.7
Hui (2004)	Cirrhotic-stage NASH	23	100%	5 (21)	6 (26)	5.0
Hashimoto (2005)	NASH with septal fibrosis or cirrhosis	89	48%	6 (6.7)	8 (9)	3.7
Sanyal (2006)	Cirrhotic-stage NASH	152	100%	22 (14.5)	29 (19.1)	10

* NAFLD denotes the inclusion of both patients with simple steatosis and patients with NASH (Nonalcoholic steatohepatitis).

† Cirrhosis prevalence includes all patients diagnosed with cirrhosis at both baseline and during follow-up.

almost 14 years of follow-up.[7] Again, liver-related complications were the third most common cause of death among NAFLD patients, with cardiovascular disease and extrahepatic malignancy being the first and second most common causes of death, respectively.

The potential for NAFLD to result in end-stage liver disease is further highlighted by some data suggesting that NAFLD underlies a substantial proportion of cases of cryptogenic cirrhosis.[21] Half to 73% of patients with cryptogenic cirrhosis have a BMI in the obese category or suffer from diabetes. The prevalence of NAFLD as an unrecognized cause of cryptogenic cirrhosis is most likely underestimated, because some non-diabetic, non-obese (BMI $<$ 30) patients may suffer from central obesity and/or dyslipidemia, which may be the only risk factors for NAFLD and have not been consistently measured in series of cryptogenic cirrhosis. Further, the presence of NAFLD increases disease severity and progression in other liver diseases, including chronic hepatitis C infection, alcoholic liver disease, and hemochromatosis.[3]

QUALITY OF LIFE

The impact of NAFLD on health-related quality of life is currently being evaluated. Several studies have found a significant detrimental impact due to several comorbidities that are associated with the metabolic syndrome, such as obesity and type 2 diabetes, which often cluster with NAFLD.

PREVENTION

There have been no studies aimed at preventing NAFLD development. However, preventing the development of insulin resistance and its clinical manifestations (i.e., the metabolic syndrome) is expected to prevent NAFLD development. Weight gain and obesity resulting from increasingly sedentary lifestyles and high-fat diets seem to be a key factor in the development of insulin resistance and NAFLD.[1] Thus, achieving and maintaining appropriate weight control would be expected to prevent the development of NAFLD, as would the treatment of glucose and lipid abnormalities. This is further supported by data from the diabetes prevention program in the United States[22] demonstrating that both lifestyle intervention and the insulin-sensitizing drug metformin significantly reduce the development of the metabolic syndrome, which would prevent the development of NAFLD.

ISSUES IN EPIDEMIOLOGY KNOWLEDGE

There is a relative scarcity of NAFLD prevalence data available from population-based studies, no data on the changes in prevalence of NAFLD within a population over time, and no data on the incidence of NAFLD. The lack of a test or combination of tests that can diagnose NAFLD with 100% accuracy precludes drawing firm conclusions on incidence and prevalence and on different stages in the general population. Liver enzymes are insensitive and nonspecific for chronic liver disease. Imaging techniques such as ultrasonography and CT scan may provide false negative rates. More sensitive techniques such as MRI and spectroscopy are hindered by expense and lack of feasibility in large populations. Liver biopsy has been considered as the gold standard, but is limited by sampling and interpretation error, and by its cost and impractical applicability in population-based studies. Further, unless uniform data become available, estimates of the prevalence and incidence of NAFLD over time will most likely be affected by increased awareness of the disease.

RECOMMENDATIONS FOR FUTURE STUDIES

Further population-based studies are necessary to determine the true prevalence of NAFLD and its impact on health-related quality of life. Prospective studies with long-term follow-up will better define the natural history of NAFLD and its incidence in specific populations. Genetic studies are necessary to determine to what extent a genetic background predisposes to NAFLD development and progression to advanced liver disease. Carefully controlled clinical trials will better define the impact of lifestyle intervention and pharmacotherapy on NAFLD.[23]

CONCLUSIONS

With the increasing prevalence of obesity, type 2 diabetes, and the metabolic syndrome in the general population, NAFLD has become a common diagnosis in clinical practice. Bland steatosis remains stable for a number of years and will probably never progress in many cases, with most liver-related morbidity and mortality observed in those patients whose disease had progressed to advanced fibrosis and cirrhosis. Further studies are necessary to determine the impact of NAFLD on health-related quality of life, as well as the extent to which preventing the development of the metabolic syndrome will prevent NAFLD development and reduce liver-related morbidity and mortality.

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