

Clinical Features and Natural History of Nonalcoholic Steatosis Syndromes

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ABSTRACT

Nonalcoholic steatohepatitis, along with other forms of nonalcoholic fatty liver disease, is a chronic liver disease that is attracting increasing significance. It is a clinicopathologic syndrome that was originally described in obese, diabetic females who denied alcohol use but in whom the hepatic histology was consistent with alcoholic hepatitis. This typical patient profile has been expanded and is now recognized to occur even in normal weight males without overt abnormalities in carbohydrate metabolism. Although originally believed to be a benign clinical entity, nonalcoholic steatohepatitis is now recognized as a cause of progressive fibrotic liver disease with adverse clinical sequelae. It is important to emphasize that nonalcoholic steatohepatitis is best considered one type of a larger spectrum of nonalcoholic fatty liver disease that is a consequence of insulin resistance and ranges from fat alone to fat plus inflammation, fat plus ballooning degeneration, and nonalcoholic steatohepatitis, the latter being the most serious form. As with any disease, the clinical importance of nonalcoholic steatohepatitis is related to its prevalence and natural history. Recent studies using different methodologies indicate that in the general population the prevalence of fatty liver and nonalcoholic steatohepatitis is approximately 20% and 3%, respectively. These prevalence rates are increased in certain subpopulations such as obesity and type 11 diabetes. Of greater concern is the recognition that cirrhosis and liver-related deaths occur in approximately 20% and 8% of these patients, respectively, over a 10-year period. Risk factors for these adverse clinical symptoms include patients older than the age of 45, the presence of diabetes or obesity, an aspartate aminotransferase/alanine aminotransferase ratio >1 and hepatic histology. However, a number of important unresolved issues must be clarified before the true natural history of this disease can be fully understood.

KEYWORDS: Nonalcoholic fatty-liver liver disease, nonalcoholic steatohepatitis, natural history, cirrhosis, obesity

Objectives: Upon completion of this article, the reader will be able to 1) discuss the prevalence of nonalcoholic steatohepatitis, and 2) comprehend that this liver disease may progress to cirrhosis and cause liver-related death.

In 1980, Ludwig and colleagues¹ gave the name nonalcoholic steatohepatitis (NASH) to a formerly recognized clinicopathologic syndrome^{2,3} that occurred in obese, diabetic females who denied alcohol use but in whom the hepatic histology was consistent with alcoholic hepatitis. In these typical patients from the original description,¹ hepatomegaly and mild abnormalities of liver function tests were common clinical findings. The liver biopsy specimens were characterized by the presence of striking macrovesicular fatty changes and evidence of focal necrosis with mixed inflammatory infiltrates and Mallory bodies. Fibrosis was present in most specimens, with 15% of the patients having cirrhosis. These authors¹ concluded that the cause of NASH was unknown and no effective therapy currently existed. To a large extent, these conclusions remain valid today. However, progress has been made in our understanding of NASH in a number of different areas, perhaps no more importantly than in the recognition that NASH is not a benign clinical entity but rather a common disease with serious clinical sequelae.^{4,7}

However the histologic criteria required for inclusion in NASH studies have varied. Some studies required only the presence of macrovesicular steatosis with parenchymal inflammation. Although such findings meet the literal definition of steatohepatitis, such a definition would include cases with benign steatosis and nonspecific reactive inflammation and could encompass other diseases such as Wilson's disease, steroid treatment, autoimmune liver disease, and many of the secondary causes of fatty liver shown in Table 1. More important, these milder histologic forms bear no similarity to alcoholic hepatitis, which must include fibrosis, neutrophilic inflammation, and hepatocyte damage (ballooning degeneration) with or without Mallory hyaline. In addition, as discussed in the following, these milder forms of nonalcoholic fatty liver disease have a benign clinical course as compared with cases that resemble alcoholic hepatitis which may progress to cirrhosis and cause liver-related deaths.⁷ We believe (and in agreement with other authors⁴) that the term

NASH should be restricted to cases that meet the histologic criteria for the diagnosis of alcoholic hepatitis.

Therefore, NASH should be considered as a type (albeit the most severe form) of a larger spectrum of nonalcoholic fatty liver disease (NAFLD) that is a consequence of insulin resistance with histological findings ranging from (1) fat alone to (2) fat plus inflammation to (3) fat plus ballooning degeneration to (4) fat plus alcoholic hepatitis-like lesions (sinusoidal fibrosis and polymorphonuclear infiltrates, with or without Mallory hyalin). Only types 3 and 4 should be considered as NASH.

Macrovesicular fatty liver (or steatosis) is a common finding that has been observed in a wide range of clinical conditions.^{8,9} Table 1 displays a proposed classification of NAFL into two types: the primary type, which is caused by the conditions associated with insulin resistance,¹⁰ and the secondary type, which is caused by drugs, surgical procedures, and a variety of miscellaneous disorders. An adequate review of all the causes of NAFL listed in Table 1 is beyond the scope and intent of this article. Therefore, this discussion will be focused on the clinical characteristics and the natural history of primary NAFL.

PREVALENCE

NAFL is an increasingly common problem worldwide and has been reported in Japan,^{29,30} Australia,⁵ North America,^{4,6,7} South America,³¹ northern Europe,³² southern Europe,³³ and the Middle East.¹⁴ However, the true prevalence of primary NAFL remains to be established. Table 2 provides estimates of the prevalence of NAFL using different methodologies. In patients undergoing liver biopsy, the prevalence of NAFL ranges between 15 and 39%.^{30,32,35} This wide range in the prevalence of NAFL is probably related to differences in study design. In the study by Propst et al.,³⁵ biopsies were done for patients found to have NAFL on ultrasonography,³⁵ while Hultcrantz et al.³² performed biopsies only for patients with chronically elevated transaminases. The prevalence of NASH

Table 1 Proposed Classification for NAFL*

Primary	Secondary†		
	<i>Drugs</i>	<i>Surgical procedures</i>	<i>Miscellaneous</i>
Conditions associated with an insulin resistance syndrome	Corticosteroids ¹¹	Gastroplexy ¹⁶	Abeta/hypobeta lipoproteinemia ^{20,21}
Diabetes mellitus (type II)	Synthetic estrogens ¹²	Jejunioileal bypass ¹⁷	Weber-Christian disease ²²
Obesity	Amiodarone ¹³	Extensive small bowel resection ¹⁸	TPN with glucose ²³
Hyperlipidemia	Perhexiline ¹⁴	Biliopancreatic diversion ¹⁹	Environmental toxins ²⁴
	Nifedipine ¹⁵		S. bowel diverticulosis ²⁵

* This classification refers to conditions and diseases associated only with macro or mixed macro/microvesicular steatosis. Conditions associated with predominantly microvesicular steatosis are excluded but can be reviewed by the reader elsewhere (references 26, 27, 28).

† Numbers are the reference numbers for the specified items.

ranged between 1.2 and 4.8%. Because patients undergoing liver biopsy are highly selected, these data do not reflect the true prevalence of NAFL in the general population.

Table 2 Prevalence of NAFL

Study Populations*	Prevalence (%)
1. Patients undergoing:	
a. Liver biopsy	
Nonomura ^{30*}	[1.2]
Propst ³⁵	15 [4.8]
Hultcrantz ³²	39
b. CT scan	
El-Hassan ³⁴	9.7
2. Postmortem analysis	
Random deaths	
Hilden ³⁶	24 [2.4]
Ground ³⁷	15.6 [2.1]
3. General population screening with ultrasound	
Nomura ²⁹	23
Lonardo ³³	21.5
Bellentani ³⁸	16.4

* Numbers are the reference numbers for the specific studies cited.

† Numbers in bracket indicate the percentage of patients with hepatic histology consistent with alcoholic hepatitis.

More accurate estimates can be obtained from studies investigating patients who had random deaths^{36,37} and from studies performing general population screening.^{29,33,38} Analyses of Evers from individuals who died randomly from auto³⁶ or plane³⁷ crashes showed prevalence rates for NAFL of 24 and 16%, respectively, while the prevalence of NASH was 2.4 and 2.1%. Because the plane crash study³⁷ included only crew members, it was presumed by those authors that significant alcohol use could be excluded as a cause of NAFL in these patients. Finally, in studies that performed hepatic ultrasonography prospectively in general populations in Japan and Italy,^{21,33,11} NAFL disease was observed

in 23%, 21%, and 16.4%, respectively.

Therefore, current best estimates make the prevalence of NAFL approximately 20% and of NASH 2-3% in the general population. However, as discussed subsequently, the prevalence of NAFL is higher in certain patient groups such as individuals with type II diabetes and obesity. It should be emphasized that the prospective population studies,^{29,33,38} while providing the prevalence of NAFL, cannot delineate the different histologic forms of NAFL.

CLINICAL CHARACTERISTICS

Patient Demographics (Table 3)

Most cases of NAFL occur in the fifth and sixth decades of life,^{1,4-6,30,39,40,41} although of considerable concern is the increase in occurrence of NAFL in children.⁴²⁻⁴⁵ Cases occur more frequently in females (65-83%),^{1,4,5,39,41} and there is a high prevalence in both type II diabetes mellitus (28-55%) and obesity (60-95%).^{1,3-5,39,41,46-48} The prevalence in patients with hyperlipidemic disorders is highly variable, being between 20 and 92%. One report⁶ suggests that this typical patient profile may need to be expanded because NAFL also occurs in normal weight males without diabetes or hyperlipidemia. In fact, such male patients existed in the other studies listed in Table 3 but were not the majority.

Clinical and Laboratory Findings

Most patients (45-100%) are asymptomatic,^{1,4,6,7} but there is always a percentage of patients,⁴⁻⁷ especially children,⁴²⁻⁴⁵ who have a variety of symptoms including right upper quadrant pain, abdominal discomfort, fatigue, or malaise.⁴⁶ Typically, NAFL patients present because of a wide variety of other conditions^{1,4,5,7,39,46-48} and are incidentally found to have abnormal liver function tests or hepatomegaly,^{1,4,6,7} the latter occurring in 12-75%.^{1,7,41,47} The prevalence of hepatomegaly may increase to 95% when assessed by ultrasonography.⁵

Table 3 Demographics

Author*	n	Age (Years)	Female (%)	Diabetes (%)	Obesity (%)	Hyperlipidemia (%)
Ludwig ¹	20	54	65	50	90	67
Diehl ³⁹	39	52	81	55	71	20
Lee ⁴	49	53	78	51	69	W
Powell ⁵	42	49	83	36	95	81
Bacon ⁶	33	47	42	21	39	21
Matteoni ⁷	132	53	53	33	70	92
Angulo ⁴¹	144	51	67	28	60	27

*Numbers are to the reference numbers for the specified studies.

†NR, not reported.

The most common abnormality in liver function tests is a two- to fivefold elevation in alanine aminotransferase (ALT) and aspartate aminotransferase (AST)^{1,5-7,41,47,49} with occasional reports of 10- to 15-fold elevations.⁴¹ Distinguishing it from alcohol-related injury, the AST/ALT ratio is reported to be <1 in 65-90% of NAFL patients.^{7,39-41,46-51} When the AST/ALT ratio is >1, it suggests that there is an advanced form of NAFL.^{7,41} Alkaline phosphatase and gammaglutamyltransferase (GGT) may be elevated two- to threefold in <50% of cases.^{1,6,7,41,46,48} As recently reviewed,^{46,48} serum bilirubin and albumin levels are rarely abnormal.^{1,5-7,41}

Two studies^{6,41} have reported elevated ferritin in approximately 50% of NAFL patients and increased transferrin saturation in 6-14% of patients. Despite these abnormalities in serum iron values, these studies and additional studies^{1,7} found no evidence of an increased hepatic iron concentration and the hepatic iron index has almost always been <1.9. Of interest, are two studies^{52,53} which suggest that heterozygosity for the HFE gene is increased in NAFL and may be associated with progressive injury.

Exclusion of Other Diseases

Hepatic fat may account for up to 5% of the weight of normal liver^{34,54} and is often increased in other liver diseases,^{46,55} including Wilson's disease, autoimmune liver disease, galactosemia, hepatitis C virus (HCV) infection, and alcoholic liver disease. Therefore, these diseases as well as the secondary causes of NAFL listed in Table 1 must be excluded before a diagnosis of primary NAFL can be made reliably. However, the exclusion of HCV and alcoholic liver disease is particularly important because of the high prevalence of these two hepatotoxic agents.

HEPATITIS C

The histopathology of HCV includes steatosis,⁵¹ and evidence suggests that HCV itself (through its core protein) may cause hepatic steatosis.^{57,58} This information, is important because many of the NAFL studies listed in Table 3^{1,4,5,39} were unable to exclude HCV in their patients. Although HCV may cause histologic changes that are similar to those observed in NAFL,^{46,58-60} studies have shown that NAFL is not associated with HCV^{7,41} and HCV is unlikely to be the cause of NAFL.⁵⁹⁻⁶¹ Although both HCV and NASH may involve fat, a number of findings make the histologic differentiation fairly straightforward. HCV more often has apoptotic bodies, portal lymphoid follicles, periportal fibrosis, and inflammation, while NASH more often has Mallory bodies, perisinusoidal fibrosis, ballooning degeneration, and nuclear vacuolation. Nonetheless, it is important to exclude HCV with serologic tests

before the diagnosis of primary NAFL can be established.

ALCOHOL

By its very definition, the diagnosis of NAFL cannot be made in the setting of excessive alcohol consumption.⁴⁶ However, there is no consensus among investigators concerning what is an excessive amount of alcohol,^{12,61} especially in the setting of preexisting fatty liver. Table 4 displays the weekly amount of alcohol consumption that excluded patients from the published reports regarding NAFL.^{1,3,5-7,39,41,52,53,64} As can be seen, there is a wide range of alcohol consumption allowed in these studies of "nonalcoholic" fatty liver disease. Studies published before 1990 allowed no alcohol consumption, whereas those published subsequently allowed up to 2 10 g per week. This is an important issue for a number of reasons: First, it has been estimated that 20 g of alcohol daily can cause hepatic steatosis.⁶⁵ Second, the hepatotoxic dose of alcohol in the general population can be as low as 20-30 g daily in females and 40 g in males.^{66,67} Third, hepatic steatosis is a risk factor for alcohol-induced liver injury.^{68,61} Finally, the hepatic toxic dose of alcohol in the setting of preexisting concurrent hepatic steatosis is unknown.⁶⁰

Although future studies will be required to determine what is an actual hepatotoxic dose of alcohol in patients with hepatic steatosis, it remains important for the clinician to obtain the extent of alcohol used, if any, in patients with NAFL. History, physical examination, and information from family members and other supporting medical personnel are all important in separating the patient with alcoholic liver disease from the patient with NAFL.⁷⁰ Many patients who consume alcohol either deny or underestimate their degree of alcohol ingestion.^{71,72}

Table 4 Alcohol Consumption in NAFL Studies Exclusion Limit (g/wk)

0	40	140
Ludwig1	Powell50	Bacon6
Diehl39	Angulo41	Teli64†
Lee4		George52
		Bonkovsky53
		Metteoni7†

* Numbers are the reference numbers for the specific studies.

† In these studies, 210 g/wk was the exclusion limit for males.

In fact, several studies have emphasized the difficulty in separating NAFL from alcoholic liver disease.^{39,40,50,51} Table 5 compares many of the histologic, clinical, and laboratory features in severe NAFL and alcoholic hepatitis. As shown, NAFL patients clinically are more likely to be asymptomatic females who are obese and/or diabetic with normal

liver function tests and an ALT/AST ratio of > 1. Histologically, the NAFL patients are less likely to have Mallory bodies, ductular proliferation, fibrosis, and cirrhosis and more likely to have nuclear vacuolation.

Table5 Features of NASH versus ASH*

Features	NASH	ASH
<i>Histologic</i>		
Steatosis (severe)		
Macro	85	57
Micro	49	21
Lobular hepatitis	54	85
Mallory bodies	3	16†
Nuclear vacuolation	76	7†
Ductular proliferation	53	96†
Periportal fibrosis	0	33†
Fibrosis/cirrhosis	38	63†
<i>Clinical/Laboratory</i>		
Age (years)	52	50
% Female	81	42†
% Diabetes	75	23†
% Obesity	71	29†
% Symptomatic	23	88†
ALT/AST > 1	Common	Atypical
Bilirubin > 2 mg%	17	55†
GGT	55	69
MCV	79	73

*Data are presented as the percentage of patients with the clinical and histologic abnormality as aggregated from Refs. 39, 40, 50, and 51. NASH, nonalcoholic steatohepatitis; ASH, alcoholic steatohepatitis.

† Significantly different from NASH

Nonetheless, overlap exists in the histologic features, clinical characteristics, and laboratory abnormalities between these two patient populations. Consequently, markers of excessive alcohol consumption have been investigated and one of them was proposed to be beneficial in diagnosing alcohol use in NAFL patients.^{11,7} This study⁵¹ found that the ratio of desialylated transferrin to total transferrin⁷⁴

had high diagnostic accuracy in identifying ongoing alcohol consumption, with other standard markers being unhelpful. However, as shown in Table 6 and extensively reviewed elsewhere,^{63,75} many of these markers have high diagnostic accuracy for diagnosing alcohol dependence but have low sensitivity for diagnosing amounts of alcohol consumption that are characterized as hazardous drinking, the category in which 20-40 g of daily alcohol consumption would generally fall. Even carbohydrate deficient transferrin is most diagnostic in males who consume >40-60 g daily for a prolonged period of time.⁷⁵ Therefore, although every effort should be made to search for alcohol use in a patient presumed to have NAFL (including urinary alcohol levels), it is very unlikely that any single test or combination of tests can ascertain 20-40 g of daily, alcohol consumption in a patient who denies alcohol use.

NATURAL HISTORY

The natural history of NAFL varies according to its histologic type. Patients with hepatic steatosis appears to have a benign clinical course^{7,14} without histologic progression⁶⁴ when followed for up to 19 years. In contrast, patients with other histologic forms may have histologic progression associated with hepatic stellate cell activation¹⁶ and adverse clinical sequelae. The data that indicate disease progression in NAFL are limited. Table 7 displays the results of three studies⁴⁻⁶ that reported histologic changes in 26 patients followed for up to 9 years. As shown, 27% of these patients had progression of fibrosis and an additional 19% advanced to cirrhosis. Other studies⁷⁷⁻⁷¹ also suggest that NAFL may be the cause of cryptogenic cirrhosis. Of note, the degree of steatosis may decrease or the steatosis may even disappear completely as cirrhosis develops.^{5,11}

Although the natural history of NAFL is related to its histopathology (as described above), various histologic criteria have been used to define "NASH." In many studies,^{1,5,1,41,52,53} NASH was diagnosed by the presence of steatosis and lobular inflammation

Table6 Screening Tests for Alcohol Use

Test	Hazardous Consumption		Alcohol Dependence	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
AST	10-30	90	33-50	>90
ALT	10-20	>80	20-50	>80
GGT	20-50	55-100	60-90	55-100
MCV	20-30	64-100	40-50	64-100
CDT	26-62	>90	65-95	>90
Bound acetaldehyde	55	75-95	40-97	75-99
-Hexosaminidase	86	98	66-95	95

CDT, carbohydrate-deficient transferrin; GGT, gamma glutamyltranspeptidase; MCV, mean corpuscular volume.

Table 7 NAFL Patients with Sequential Biopsies

	Length of Follow-up (Years)	n/Total*	Subsequent Histology			
			Improved	No Change	Progressed to	
					Fibrosis	Cirrhosis
Lee† (1989)	1.2–6.9	12/38	0/12	7/12	3/12	2/12
Powell† (1990)	1–9	12/41	1/12	5/12	4/12	2/12
Bacon (1994)	4–7	2/33	0/2	1/2	0/2	1/2
		26/112	1/26 (4%)	13/26 (50%)	7/26 (27%)	5/26 (19%)

*Represents the number of patients out of the total group who had sequential biopsies.

†In both the studies of Lee and Powell, one of the 13 patients with follow-up histology available had cirrhosis at index biopsy. Therefore, only the 12 patients without cirrhosis at index biopsy are included in this analysis.

(hepatitis) only. The alcohol-like lesions of ballooning degeneration, pericellular fibrosis, and Mallory hyalin were not necessary. Other studies^{4,80} used a stricter definition for the histologic diagnosis of NASH; including the alcoholic-like lesions mentioned above, in addition to steatohepatitis.

Emphasizing the importance of this issue, an approach to the histologic interpretation has been proposed⁸¹ and the reliability of the histologic interpretation of NAFL confirmed.⁸² Currently, there is no consensus regarding nomenclature and histologic categorization of this disease. However, a review⁴⁶ with which the current authors agree states that in addition to steatosis and inflammation, ballooning degeneration and/or fibrosis are key features in diagnosing the type of NAFL referred to as NASH.

The importance of relating the natural history of NAFL to the different histologic forms has been reported.⁷ This retrospective study of 136 patients, 98 of whom had complete data available at 10-year follow-up, separated NAFL into four histologic types shown in Table 8. As displayed in Figure 1, cirrhosis developed predominantly in type 3 (fat + ballooning degeneration) and type 4 (fat + fibrosis) occurring in 21% and 28% of these histologic types, respectively. These results are very similar to the prevalence of cirrhosis reported in the three studies⁴⁻⁶ summarized in Table 7.

Although there was no significant difference in overall death rates among the four histologic types,

Table 8 Types of Nonalcoholic Fatty Liver* (Proposed Categories)

Type 1	Fat alone
Type 2	Fat + inflammation
Type 3	Fat + ballooning degeneration
Type 4	Fat + fibrosis and/or Mallory bodies

*Only types 3 and 4 have been definitively shown to progress to advanced liver disease as shown by Matteoni et al.⁷

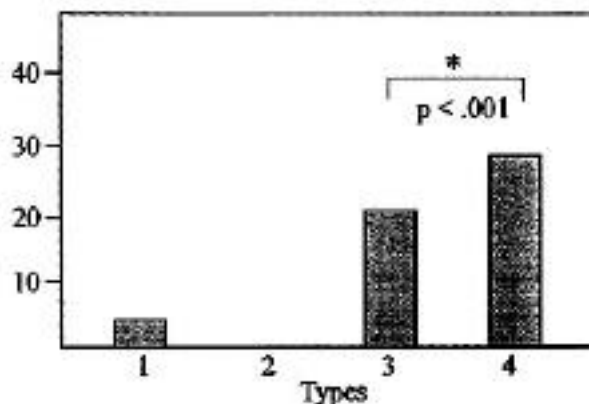


Figure 1 The percentage of patients with cirrhosis in the four different types of NAFL is displayed.

liver-related death was increased in NAFL patients with histologic necrosis (type 3 and 4). Over a 10-year period, there was an 11% death rate in the type 3 and 4 NAFL patients as compared with a crude adjusted death rate of 9.5 per 100,000 for the general population.⁸³ Furthermore, liver-related deaths were the second most common cause of death in NAFL with rates equaling those from coronary artery disease and trailing only cancer-related deaths. This study⁷ also confirmed the benign clinical course and histologic sequelae of type 1 NAFL (steatosis alone). Of particular importance is also the fact that this study⁷ excluded HCV and iron⁸⁴ as etiologic factors.

RISK FACTORS FOR PROGRESSIVE DISEASE

Table 9 displays results from the study of Angulo and colleagues,⁴¹ which identified age, the AST/ALT ratio, and the presence of either obesity or diabetes. Similar findings were also observed in the study by Matteoni and colleagues.⁷ As displayed, the risk for fibrotic liver disease increases if the patient with NAFL is older than age 45, has an AST/Aff ratio >1, and has either obesity or diabetes. Such information may be helpful in guiding the clinician in determining the need to

Table 9 Risk Factors for Fibrosis in NAFL*

		AST/ALT			
		<1	>1	<1	>1
Diabetes	+	4	50	47	66
and/or obesity	-	0	0	12	13
Age		<45		>45	

*Numbers represent the percentages of NAFL patients with significant fibrosis according to the numbers of risk factors present. Modified from Angulo et al.41

perform a liver biopsy by providing the likelihood of fibrotic disease in any individual patient.

Age and AST/ALT Ratio

A number of studies have found age to be a risk factor for cirrhosis.^{7,41,85} This probably reflects the duration of time that steatosis is at risk for a subsequent injury⁸¹ that initiates fibrosis. This is of particular concern in light of the increasing prevalence of obesity and hepatic steatosis among children.⁴²⁻⁴⁵ Therefore, it is uncertain whether or not the age of 45 will remain an accurate predictor of fibrosis or whether this age will decrease as the NAFL observed in children will cause a decrease in the age at risk or produce a cohort effect.

As with viral hepatitis, the AST/ALT ratio indicates a fibrotic stage of NAFL⁷ and, as mentioned previously, is also helpful in excluding an alcoholic etiology.⁸⁷

Obesity

Both early⁸⁸⁻⁹⁴ and more recent studies^{41,85} have established obesity as a risk factor for hepatic steatosis and fibrotic liver disease. It has been proposed that these lipid-laden hepatocytes act as a reservoir of hepatotoxic agents and are more susceptible to a second hit injury by compounds such as endotoxin and tumor necrosis factor.^{86,95} This leads to lipid peroxidation; a process that stimulates fibrogenesis.⁹⁶⁻⁹⁸ However, the distribution of fat may be more important than the total fat mass. Visceral fat, but not total fat mass, has been shown to be a predictor of hepatic steatosis⁹⁹⁻¹⁰¹; it also predicts hyperinsulinemia, decreased hepatic insulin extraction, and peripheral insulin resistance.¹⁰² Furthermore, lipolysis in visceral adipose tissue is somewhat resistant to insulin suppression,¹⁰³ thereby providing a source of potentially hepatotoxic fatty acids in hyperinsulinemic states such as liver disease. Decreasing visceral fat has also been shown to decrease hepatic insulin resistance.^{104,105}

Diabetes

Liver disease is common in patients with type 2 diabetes¹⁰⁶ and NAFL occurs in up to 75% of

diabetic patients.^{34,107-112} Although obesity is often a confounding variable in type 2 diabetes, a number of studies observed that the hepatic fibrosis that occurs in obese subjects was more prominent in obese patients with diabetes.^{7,92,113} In fact, a preliminary communication indicates that diabetes mellitus is an independent risk factor for liver-related deaths in NAFL patients.¹¹⁴

It is now recognized that insulin resistance is an important aspect of NAFL^{10,92} and is present even in NAFL patients who are of normal weight and have normal carbohydrate tolerance.¹⁰ In fact, hepatic steatosis has been proposed as a feature of the insulin resistance syndrome or syndrome X.^{115,116} In a recent cross-sectional study of 551 severely obese individuals,¹¹⁵ the risk of hepatic steatosis increased exponentially with each addition of the four components (type 2 diabetes, hyperlipidemia, visceral obesity and hypertension) of the insulin resistance syndrome.

SUMMARY

It is now clear that NAFL is a common chronic liver disease with the potential for progression to cirrhosis and to cause liver-related death. However, there are a number of unresolved issues pertinent to its natural history. First, a consensus must be reached regarding the minimal histologic criteria necessary for defining both NASH and the other histologic forms of NAFL. Second, once this is established, the natural history of the various histologic forms must be evaluated. Third, the minimal dose of alcohol in the setting of hepatic steatosis must be determined before a diagnosis of "nonalcoholic" fatty liver disease can be made confidently. Once these issues are resolved, the true natural history of NAFL can be established. This will allow its clinical management to be optimized and therapeutic interventions then may be tailor designed for the different forms.

ABBREVIATIONS

ALT alanine aminotransferase
 ASH ., alcoholic steatohepatitis
 AST aspartate aminotransferase
 CDT carbohydrate -deficient transferrin
 GGT gamma-glutamyltranspeptidase
 g/w grams/week
 HFE hemochromatosis gene
 HCV hepatitis C virus
 MCV mean corpuscular volume
 NAFL nonalcoholic fatty liver disease
 NASH nonalcoholic steatohepatitis

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