FATTY LIVER

A POTENTIALLY SERIOUS PROBLEM

INTERNAL MEDICINE GRAND ROUNDS

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June 13, 1991

The presence of excess fat in hepatocytes is referred to as fatty liver. This is appreciated in histologic sections as droplets of non-staining material in formalin-fixed, paraffin-embedded, hematoxylin and eosin-stained tissue from which lipid has been extracted during the preparative process. When fresh tissue is frozen, the droplets take up lipid stains. The droplets vary in size from small to large. When large droplets predominate, the nucleus of the cell is pressed to the periphery of the hepatocyte, and the fat is referred to as macrovesicular. When small droplets are predominant, the nucleus is located centrally, cells have a foamy appearance and the fat is described as being microvesicular.

Microvesicular fat appears to characterize rapidly evolving fat accumulation in liver. Macrovesicular fat is dominant in more chronic forms of the condition. Large and small droplets coexist frequently. The mechanisms regulating size, other than rapidity of turnover, are not well understood. Fat may be concentrated zonally within the hepatic lobules (i.e. pericentral, midlobular, periportal), or distributed diffusely or focally without a clear-cut zonal appearance.

A pathological classification of fatty liver is contained in the following table.

Table 1. *Pathologic Differential Diagnosis of Fatty Liver*

Large-Droplet (Macrovesicular) Fat
Alcohol
Adult-onset diabetes
Obesity
Kwashiorkor*
Protein-calorie malnutrition
Systemic illness (e.g. tuberculosis, ulcerative colitis)
Jejunoileal bypass
Gastroplasty
Hyperalimentation*
Drugs
Methotrexate*
Phosphorus poisoning*
Cortoicosteroids
Estrogens (high dose)
Amiodarone
Perhexilene maleate
Small-Droplet (Microvesicular) Fat
Reye's syndrome
Acute fatty liver of pregnancy
Tetracycline toxicity
Valproic acid toxicity
Alcoholic foamy degeneration
Non-A, non-B hepatitis**

* Periportal hepatocytes preferentially affected in early stages
** May be admixed with macrovesicular fat

From Clain et al, Gastroenterology Clinics of North America 16:239, 1987 (24)

Large amounts of fat in liver may exist in a clinically non-detectable state - i.e. lack of symptoms, of physical findings (hepatomegaly), and with normal results of conventionally used liver blood tests implying persistence of critical cell function. Histology may reveal only fat without any coexistent cell necrosis, lobular inflammation or fibrosis. Under these conditions, fat may be considered to be benign although reflecting alterations in the balance of fat formation and removal from the hepatocyte. When these bounds are violated, however, we become more concerned with the pathologic implications of the fatty liver.

Chronic alcoholism is the condition in which fatty liver is noted frequently. When fatty liver is combined with cell necrosis, inflammation and fibrosis, progression to states of impaired hepatocellular function and cirrhosis develop with high frequency. The high morbidity accompanying these lesions termed alcoholic steatonecrosis is well known; although the mechanisms responsible for the findings other than for prolonged intake of large amounts of alcohol are poorly understood.

The thrust of the present discussion centers on the observations that lesions indistinguishable from those of alcoholic steatonecrosis are found in non-alcoholic patients with other conditions and that these lesions may progress to cirrhosis. Thus, nonalcoholic steatonecrosis is now recognized as occurring in patients who are obese or diabetic. The lesions appear with greater frequency in obese patients who have undergone surgery such as jejunoileal bypass to induce weight loss. They have been induced by medicines such as amiodarone and penhexiline maleate that induce a characteristic phospholipidosis in addition to the histologic findings of steatonecrosis.

Table 2

Classification of steatonecrosis

Group	Associated condition
Alcoholic	heavy, chronic alcohol consumption
Nonalcohlic	
Primary	diabetes mellitus
	obesity
	other
Secondary	jejunoileal bypass
	drugs
	perhexiline maleate
	amiodarone
	other

From Baker, Survey of Digestive Diseases 3:154, 1985 (35)

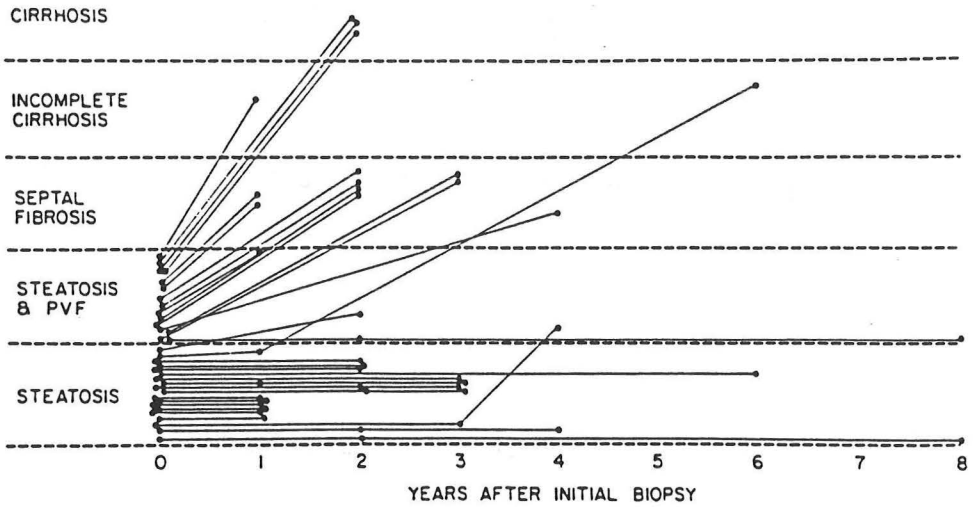
ALCOHOLIC LIVER DISEASE

This encompasses a spectrum of histologic and chemical presentations.

Table 3

Histologic Diagnosis in Alcoholic Liver Disease

1. Simple fatty liver - (alcoholic steatosis)
   Lipogranulomas
2. Alcoholic foamy degeneration
3. Alcohol-induced cholestasis
4. Perivenular fibrosis and sclerosis
   Pericellular (perisinusoidal) fibrosis
5. Alcoholic hepatitis
   Ballooning degeneration
   Liver cell necrosis
   Mallory bodies
   Inflammatory cell infiltrate
   Fibrosis
6. Alcohol-induced chronic active hepatitis
7. Alcoholic cirrhosis



Follow-up biopsy study on alcoholic patients whose initial biopsy showed simple fatty liver (steatosis) with or without perivenular fibrosis (PVF).

From Worner et al, JAMA 254:627, 1985 (4)

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OBESITY

In an extensive review of the literature of morbidly obese patients, Anderson and Gluud (16) reported that fatty liver was present in 1149 of 1429 liver biopsies (80 percent). Most were obtained prior to treatment with a surgical procedure. The degree of fatty change recorded in four large studies using similar screening systems is shown in the following table. Fat was predominantly macrovesicular and was either centrilobular or diffuse.

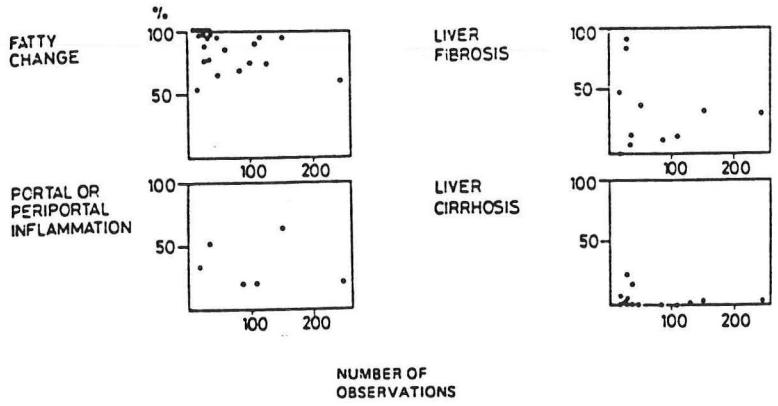
Table 4

Degree of fatty change (percentage) as stated in four large studies

Hepatocytes showing fatty change (%)	*Kern et al.*[28] *(n = 151)* (%)	*Halloran et al.*[23] *(n = 107)* (%)	*Salmon & Reedyk*[47] *(n = 47)* (%)	*Marubbio et al.*[32] *(n = 82)* (%)	*Total (n = 387)* (%)
0	6	11	36	32	17
< 25	40	30	17	23	31
25–50	20	25	11	20	20
50–75	17	19	28	25	33
> 75	17	15	9		

From Anderson et al, International Journal of Obesity 8:97, 1984 (16).

Inflammation, usually portal and lymphocytic, was detected on average in one-third of the biopsies. Fibrosis, when looked for, was demonstrated in 228 of 785 biopsies (29 percent). Cirrhosis was described in 27 of 977 patients. The prevalence of these findings varied from one report to another.



Prevalence of 4 pathological changes related to number of biopsies. Each dot represents data from one publication.

From Anderson et al, International Journal of Obesity 8:97, 1984 (16).

Emphasis on the presence of inflammation and cirrhosis in the fatty liver of obese patients was provided by the publication of Adler and Schaffner (12). Liver biopsy and liver tests were assessed in a selected group of 29 overweight patients referred for work-up of hepatomegaly and/or abnormal liver tests. A tabulation of clinical data is provided in Table 5, and of laboratory tests in Table 6.

Table 5

Clinical Data in 29 Obese Patients

Case No.	Age (yr) and Sex	Height (in)	Weight (lb)	Diabetes	Lipoprotein Class
		Group I.	**Fatty Liver**		
1	57, M	67	179	−	II
2	50, F	61	180	−	N
3	27, F	62	270	+	IV
4	69, F	62	252	+	N
5	23, M	70	210	−	IV
6	44, F	66	175	+	N
7	30, M	68	224	+	IV
		Group II.	**Fatty Hepatitis**		
8	60, F	61	171	+	IV
9	38, F	67	245	−	N
10	65, F	62	174	−	IV
11	52, F	63	180	−	IIB
12	54, F	66	281	+	N
13	37, F	65	230	+	IV
14	45, F	62	254	+	IV
15	37, M	69	198	+	IV
		Group III.	**Fatty Fibrosis**		
16	34, M	71	295	−	N
17	65, F	64	270	+	N
18	55, F	66	168	−	II
19	54, F	62	163	+	N
20	43, F	60	182	+	IV
21	25, F	64	194	+	N
22	50, F	62	213	+	N
		Group IV.	**Fatty Cirrhosis**		
23	18, F	66	197	+	N
24	39, F	65	250	+	IV
25	48, F	65	297	−	IV
26	32, M	66	370	−	N
27	66, M	60	198	+	N
28	58, F	62	182	+	N
29	56, F	64	173	−	N

From Adler et al, American Journal of Medicine 67:811, 1979 (12)

Table 6

Correlation Between Laboratory and Pathologic Data in 29 Obese Patients

SGOT		SGPT		Alkaline Phosphatase		Lipoprotein Pattern	Diabetes
Mean (U)	Abnormal (%)	Mean (U)	Abnormal (%)	Mean (U)	Abnormal (%)	(no. abnormal)	(no.)
			Group I. Fatty Liver (7 patients)				
95	71.5	115	85.8	99	39.0	4	4
			Group II. Fatty Hepatitis (8 patients)				
100	25	100	75	144	100	6	5
			Group III. Fatty Fibrosis (7 patients)				
110	33.4	185	50.0	117	33.4	2	5
			Group IV. Fatty Cirrhosis (7 patients)				
90	43.0	85	42.9	180	57.2	2	4

From Adler et al, American Journal of Medicine 67:811, 1979 (12)

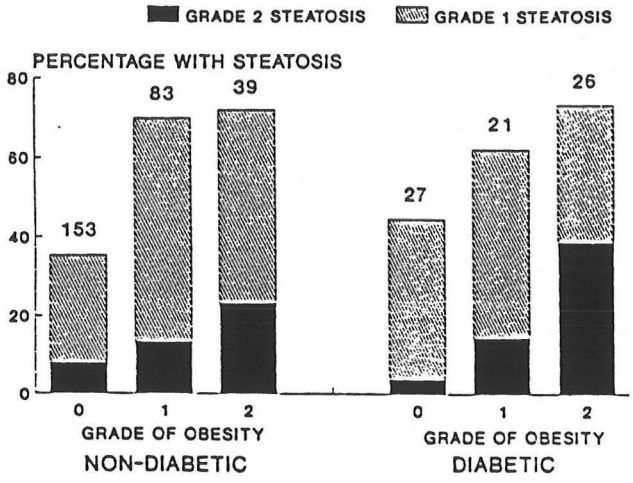
A broader assessment of fatty liver hepatitis and obesity is provided in the recent autopsy study of 351 nonalcoholic patients (26). The incidence of steatosis and steatohepatitis correlated with the degree of obesity. Adult onset diabetes was an additional risk factor. Diabetes was also prevalent in the patients of Adler and Schaffner described above in Table 5.

In the following figures from the publication of Wanless et al (26), grades of obesity are described as follows:

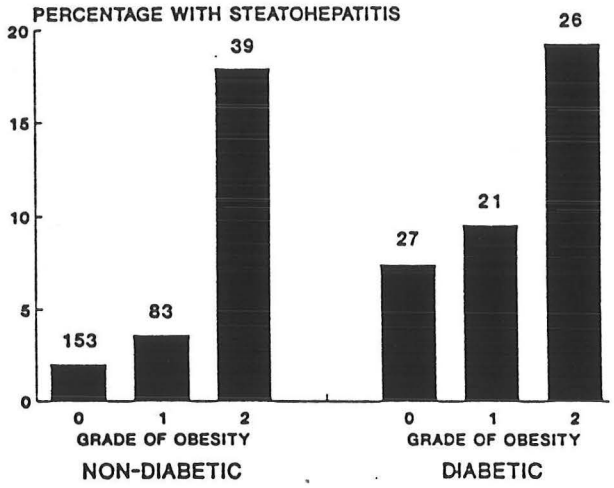
0 = <10% above ideal weight
1 = 10-39% above ideal weight or moderately obese
2 = at least 40% above ideal weight or described as massively or grossly obese

and grades of steatosis as follows:

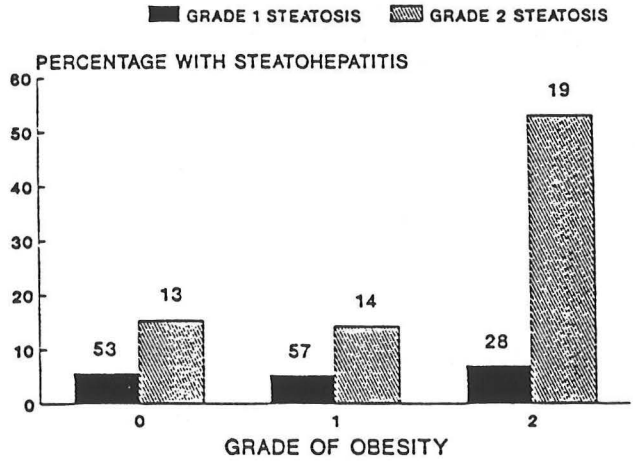
0 = <5% of cells contain fat
1 = 5-25%
2 = ≥25%



Effect of obesity and type II diabetes mellitus on steatosis.



Prevalence of steatohepatitis was proportional to the grade of obesity in type II diabetic patients and nondiabetic patients.



Prevalence of steatohepatitis was proportional to the severity of steatosis.

From Wanless et al, Hepatology 12:1106, 1990 (26)

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DIABETES

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NONALCOHOLIC FATTY LIVER DISEASE

By now, alcoholic liver disease in nonalcoholics was becoming more readily acceptable as an entity. A comparison of a series of 39 nonalcoholic with 68 alcoholic liver disease patients was provided by Diehl et al (37). The identifying feature was the presence of a biopsy with features usually associated with alcoholic liver disease.

Table 7

Clinical Features of Alcoholic and Nonalcoholic Patients With Alcohollike Liver Injury

Parameter	Nonalcoholic	Alcoholic	p
Sex (% female)	81	42	<0.001
Age (mean, yr)	52	50	NS
Diabetes (%)	55	38	NS
Obesity (%)	71	29	<0.001
Drugs (%)			
Diuretics	33	14	<0.05
Hypoglycemics	33	7	<0.001
Cardiac/HBP	39	3	<0.001
Estrogens	13	1	<0.001
Thyroid	15	0	<0.001
Transfusion (%)	8	10	NS
Asymptomatic (%)	77	12	<0.001
Fever, RUQ pain, emesis, or weight loss (%)	8	54	<0.001
Complications of portal hypertension (%)	10	26	<0.001
Liver-related death (%)	3	9	NS

HBP, high blood pressure; NS, not significant; RUQ, right upper quadrant.

Table 8

Biochemical Parameters in Alcoholic and Nonalcoholic Patients With Alcohollike Liver Injury

Parameter	Nonalcoholic (%)	Alcoholic (%)	p
AST, ALT >3 × normal	30	32	NS
AST/ALT >3	32	86	<0.001
Bilirubin >2 mg/dl	17	55	<0.005
Albumin <3.5 g/dl	0	65	<0.001
Prothrombin time >2 s prolonged	0	10	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NS, not significant.

Table 9

Histologic Parameters in Alcoholic and Nonalcoholic Patients With Alcohollike Liver Injury

Parameter	Nonalcoholic (n = 39)	Alcoholic (n = 68)	p
Microvesicular fat			
0	16 (41%)	34 (50%)	
1+	4 (10%)	20 (29%)	<0.05
2+	12 (31%)	10 (15%)	
3+	7 (18%)	4 (6%)	
Macrovesicular fat			
0	0 (0%)	5 (7%)	
1+	6 (15%)	24 (35%)	<0.05
2+	22 (56%)	28 (41%)	
3+	11 (28%)	11 (16%)	
Lobular inflammation			
0	1 (3%)	0 (0%)	
1+	17 (44%)	10 (15%)	<0.005
2+	18 (46%)	48 (71%)	
3+	3 (8%)	10 (15%)	
Portal inflammation			
0	4 (10%)	3 (4%)	
1+	19 (49%)	39 (57%)	NS
2+	15 (38%)	23 (34%)	
3+	1 (3%)	3 (5%)	
Mallory bodies			
0	4 (10%)	6 (9%)	
1+	19 (49%)	21 (31%)	NS
2+	15 (38%)	30 (44%)	
3+	1 (3%)	11 (16%)	
Fibrosis/cirrhosis			
0	1 (3%)	0 (0%)	
1+	13 (32%)	10 (15%)	<0.05
2+	10 (26%)	15 (10%)	
3+	5 (13%)	26 (38%)	
4+	10 (26%)	17 (25%)	

NS, not significant. Scale: 0, none; 1+, minimal, mild, or few; 2+, moderate; 3+, severe, marked, or many.

From Diehl et al, Gastroenterology 95:1056, 1988 (37)

Little is known about the natural history of nonalcoholic steatohepatitis. A recent follow-up study of forty-two patients for up to 21 years was published by Powell et al (39). Except for 2 patients with lipodystrophy, all were obese; 35 of 42 were women; 26 of 32 were hyperlipidemic, 15 were hyperglycemic. Serial liver biopsies in 13 patients showed slow progression in some of the cases. The disorder may ultimately result in cirrhosis. Liver test abnormalities were modest in degree. Complications of liver disease were not common.

Table 10

Summary of histological features

Histological finding	No. of patients
On initial biopsy (42 patients)	
Fatty liver	42
Lobular inflammation	42
Fibrosis (without cirrhosis)	18
Cirrhosis or marked fibrosis	3
Mallory's hyaline	4
Serial biopsies (13 patients)	
Unchanged	6
Active cirrhosis or marked fibrosis → Inactive cirrhosis or marked fibrosis	2
Fibrosis → cirrhosis	1
Fatty inflammation → fibrosis	3
Loss of inflammation and fibrosis	1

From Powell et al, Hepatology 11:74, 1990 (39)

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FATTY LIVER IN ASYMPTOMATIC PATIENTS WITH ELEVATED VALUES OF SERUM AMINOTRANSFERASES

Elevated values of serum aminotransferases are being detected with increased frequency in asymptomatic persons who volunteer as blood donors, or who undergo routine blood testing for periodic check-ups or have insurance physicals. Fatty liver is detected with significant frequency in needle biopsies of such patients.

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