Fatty Liver Hepatitis (Steatohepatitis) and Obesity: An Autopsy Study with Analysis of Risk Factors

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Steatohepatitis (fatty liver hepatitis), histologically identical to alcoholic disease, occurs in some obese patients after jejunoileal bypass. A similar lesion occurs rarely in obese patients without bypass surgery, but the risk factors are poorly understood. Hepatic steatosis, steatohepatitis and fibrosis were sought in 351 apparently nonalcoholic patients at autopsy and various risk factors were evaluated. Incidence of steatosis and steatohepatitis correlated with the degree of obesity. Steatohepatitis was found in 18.5% of markedly obese patients and 2.7% of lean patients. Additional risk factors for steatohepatitis were type II diabetes, weight loss in the preterminal period shortly before death and intravenous glucose therapy in the last week of life. Severe fibrosis was found in 13.8% of markedly obese patients and in 6.6% of lean patients; this difference was largely explained by the higher prevalence of diabetes in obese groups.

The risk factors defined in this study are known to be associated with abnormalities of free fatty acid metabolism. Obesity, type II diabetes and intravenous glucose therapy are associated with hyperinsulinemia, which may inhibit fatty acid oxidation. Obesity and weight loss increase the presentation of fatty acids to the liver. Similar metabolic changes may occur in obese patients after jejunoileal bypass surgery. Thus this study supports the hypothesis that fatty acids have a role in the hepatocellular necrosis found in some obese individuals. (HEPATOLOGY 1990;12:1106-1110.)

It is well known that large-droplet fatty change (steatosis) of the liver is common in asymptomatic obese individuals. Recently it has become evident that some obese nonalcoholic individuals, especially women, have steatosis accompanied by significant hepatic necrosis with Mallory bodies (steatonecrosis or steatohepatitis) and progression to cirrhosis (1-6). Although it is known that this progressive disease is especially likely to develop in morbidly obese patients undergoing jejunoileal bypass surgery (7-10), the risk of significant obesity-related liver disease developing in the general population has not been adequately quantitated. The risk factors leading to steatohepatitis are not well understood. For example, it is not clear whether diabetes and obesity are independent risk factors. The role of weight loss is uncertain. It is also not clear whether the female predominance indicates a hormonal effect or whether this is related to the high prevalence of obesity in women.

The purpose of this study was to document the prevalence of hepatic steatosis, steatohepatitis and fibrosis and to examine possible risk factors for the development of these lesions among obese and nonobese patients who were apparently nonalcoholic. An autopsy population was studied because this provides a large sample of liver tissue, and patients can be selected without bias related to discovery of clinical liver disease and a nonobese control group can easily be obtained.

METHODS

The autopsy records of Toronto Western Hospital from 1960 to 1987 were reviewed to select 207 patients described as obese. An equal number of nonobese patients, matched for gender and age, were selected as controls (obesity grade 0). Obesity was quantitated by description or, when weight and height were available, as the percent over ideal body weight according to standard tables (11). Obesity was graded as 0 (< 10% above ideal weight), 1+ (10% to 39% above ideal weight or described as moderately obese or abdominal fat pad 1 to 3 cm thick) or 2+ (at least 40% above ideal weight or described as massively or grossly obese or fat pad > 3 cm thick).

The clinical records were reviewed without knowledge of the autopsy findings for height, weight, recent weight change, duration of the final hospitalization, blood sugar, cause of death and history of diabetes mellitus, specific liver diseases or alcohol abuse. Alcohol abuse was defined as recurrent physical or social impairment apparently resulting from alcohol use. Standard criteria for viral hepatitis and PBC were used. Therapy with insulin, heparin, steroids, amiodarone, perhexilene or anorexiants was recorded. Therapy with intravenous glucose infusions in the last week of life was also recorded.

Among the 414 patients a history of probable alcohol abuse was found in 63 patients. Thirty-eight were in the obese group and 25 were in the nonobese group. These 63 patients were removed and the remaining 351 cases became the subjects for the remainder of this study. A history of recent weight change could be estimated for 295 of these patients.

One slide of liver stained with hematoxylin and eosin was examined from each case in a blinded fashion. Various parameters were semiquantitated: large-droplet steatosis (0 to

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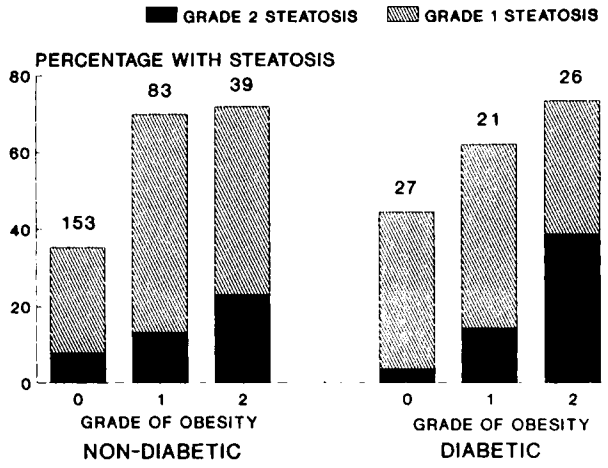

FIG. 1. Effect of obesity and type II diabetes mellitus on steatosis. The prevalence and severity of steatosis is proportional to the grade of obesity. There is no significant effect of diabetes on steatosis. $p < 0.001$ for obesity grade 0 vs. 1, steatosis grade 1, diabetes ignored. $p < 0.001$ for obesity grade 0 vs. 2, steatosis grade 2, diabetes ignored. $p < 0.001$ for obesity grade 0 vs. 1, steatosis grades 1 and 2, diabetes ignored. $p < 0.001$ for obesity grade 0 vs. 2, steatosis grades 1 and 2, diabetes ignored. $p < 0.05$ for obesity grade 1 vs. 2, steatosis grade 2, diabetes ignored. Two patients with type I diabetes were excluded from this analysis. Numbers over the bars are the number of patients in the group.

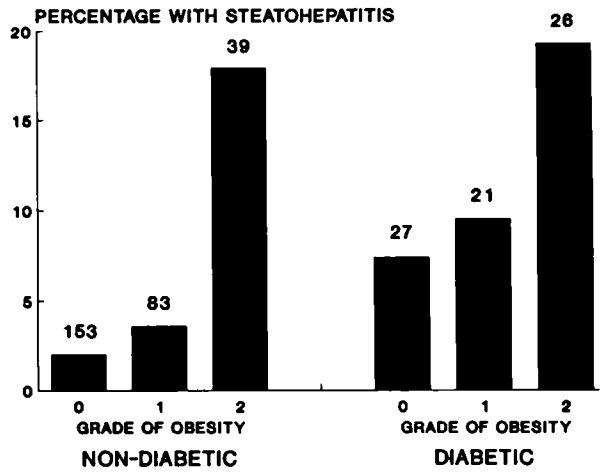

FIG. 2. Prevalence of steatohepatitis was proportional to the grade of obesity in type II diabetic patients and nondiabetic patients. Diabetic patients were more likely to have steatohepatitis than nondiabetic patients ($p < 0.05$). $p < 0.001$ for obesity grade 0 vs. 2, effect of diabetes ignored. $p < 0.01$ for obesity grade 1 vs. 2, effect of diabetes ignored. Numbers over the bars are the number of patients in the group.

2+, where 0 is <5% of cells, 1+ is 5% to 25% of cells and 2+ is ≥25% of cells), steatohepatitis (0 to 3+), Mallory's hyalin (0 to 3+) and fibrosis (0 to 3+, where 3 is cirrhosis). The minimum criterion for steatohepatitis was ballooning with clearing of the hepatocellular cytoplasm accompanied by large-droplet steatosis. Of the 22 patients considered to have steatohepatitis, 19 had neutrophilic infiltration, 18 had pyknotic nuclei and 17 had Mallory bodies. Mallory bodies were seen in three cases without obesity or steatosis. All three patients had cholestasis; one had PBC and shock, one had shock alone and one had sepsis. The patients with cirrhosis had a micronodular pattern. Zone III ischemic necrosis was ignored and viral hepatitis–like changes were not encountered. The χ^2 test was used for statistical evaluation when numbers were sufficient.

RESULTS

Steatosis. The prevalence and severity of steatosis was proportional to the grade of obesity (Fig. 1). For example, grade 2 steatosis increased from 7.1% in nonobese patients to 29.2% in patients with grade 2 obesity ($p < 0.001$). This effect was seen in patients with or without histories of type II diabetes. Among type II diabetic patients, the prevalence of steatosis was not significantly different in insulin-dependent compared with noninsulin-dependent patients (e.g., 20% vs. 18.4% for grade 2 steatosis). A history of preterminal weight loss did not affect the prevalence of steatosis (data not shown).

Steatohepatitis. Among the 351 patients there were 22 cases with steatohepatitis. The portion having steatohepatitis increased with the grade of obesity: from 2.7% without obesity to 18.5% with grade 2 obesity ($p < 0.001$) (Fig. 2). A history of type II diabetes mellitus was associated with a 2.6-fold increase in prevalence of steatohepatitis (12.2% vs. 4.7%, $p < 0.05$) (Fig. 2). We saw a trend toward increased prevalence of steatohepatitis among type II diabetic patients requiring insulin therapy compared with diabetic patients not receiving insulin (20.0% vs. 8.2%, not significant). A history of intravenous glucose therapy in the last week of life was associated with an increased prevalence of steatohepatitis (59% vs. 35%, $p < 0.05$). No patient with steatohepatitis received intravenous glucose in excess of 5 gm/dl concentration and none received estrogen therapy or intravenous hyperalimentation. There was no correlation between heparin or steroid therapy and steatohepatitis (data not shown).

Obese patients with weight loss in the last month of life were more likely to have steatohepatitis than those without weight loss (23.3% vs. 8.3%, $p < 0.05$) (Fig. 3). This effect was similar in men and women, but the numbers are too small for statistical analysis (data not shown). The exact amount of weight lost was documented in six patients with steatohepatitis; four of these had lost weight at a rate between 6 and 11 kg/mo.

The prevalence of steatohepatitis among obese patients was not influenced by the duration of the final hospital stay. The prevalence was 10%, 8.9% and 14.8% with durations of <1, 1 to 4 wk and longer than 4 wk, respectively.

For any given degree of obesity, the prevalence of steatohepatitis was proportional to the degree of steatosis (Fig. 4).

The risk factors for steatohepatitis (type II diabetes, weight loss and severe steatosis) appeared to be at least partially independent. Of the 22 patients with steatohepatitis, all but two had at least one of these factors.

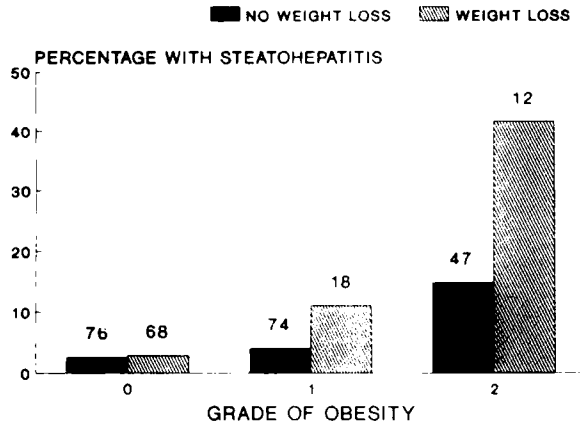

FIG. 3. Prevalence of steatohepatitis in obese patients was greater in those with a history of terminal weight loss. $p < 0.05$ for weight loss vs. no weight loss, obesity grades 1 and 2 combined.

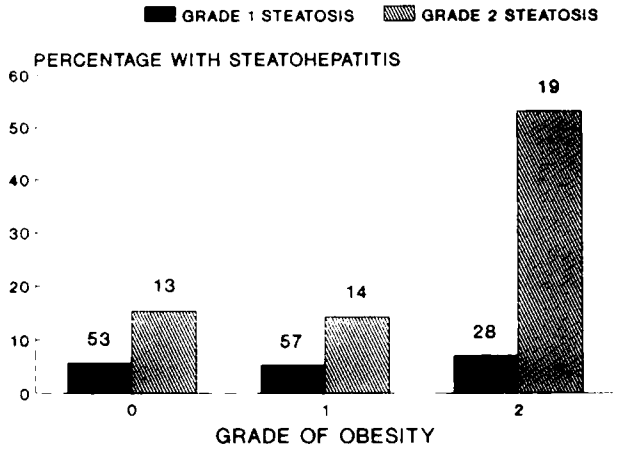

FIG. 4. Prevalence of steatohepatitis was proportional to the severity of steatosis. $p < 0.001$ for steatosis grade 1 vs. grade 2, all grades of obesity combined. $p < 0.01$ for steatosis grade 1 vs. grade 2, grade 2 obesity only.

The prevalence of steatohepatitis increased with the number of risk factors involved (Table 1).

The severity of steatohepatitis correlated with obesity, diabetes and hepatic fibrosis (Table 2). There was no apparent association of severity with gender, weight loss, presence of cirrhosis or blood sugar during the last hospital stay (data not shown).

Fibrosis. The prevalence of fibrosis was higher in the severely obese than in lean patients. This effect was entirely explained by the association of fibrosis with type II diabetes (Fig. 5). Fibrosis was more prevalent in patients with steatosis (Fig. 6). Fibrosis was as prevalent in patients with weight loss as in those without weight loss (8.2% vs. 7.1%).

Effect of Gender. Among the obese patients the women-to-men ratio was 2.1:1. Among severely obese patients (grade 2) this ratio was 4.4:1. However, for any degree of obesity, men and women were equally likely to have steatosis, steatohepatitis or diabetes (data not shown). Among patients with steatohepatitis the women-to-men ratio was 1.75:1(3.0:1 for obesity grade 2). Among patients with severe fibrosis (grade 2 or 3) the women-to-men ratio was 2.4:1(4.0:1 for obesity grade 2).

TABLE 1. Effect of weight loss, steatosis and type II diabetes mellitus on percentage of nonalcoholic patients with steatohepatitis

Weight loss	Steatosis grade	Diabetes mellitus: No	Diabetes mellitus: Yes
No	1	3 (67)[a]	5 (20)
Yes	1	11.1 (27)	14.3 (7)
No	2	23.5 (17)	38.5 (13)
Yes	2	33 (12)	100 (1)

[a]Number of patients at risk is in parentheses.

DISCUSSION

This study confirms that hepatic steatosis is associated with obesity and that the degree of steatosis correlates with the degree of obesity (12-14).

Steatohepatitis, characterized by large-droplet fatty change and ballooning of hepatocytes—usually with Mallory bodies and neutrophilic infiltration—is most commonly associated with alcohol abuse. However, identical lesions have been found in up to 26% of obese patients after jejunoileal bypass surgery (15). In the last decade it has become apparent that steatohepatitis occurs in a small percentage of obese individuals without previous bypass surgery. The pathogenesis of steatohepatitis is poorly understood in both alcoholic and nonalcoholic individuals, in part because the clinical risk factors for the development of the lesion have not been fully delineated.

This study indicates that steatohepatitis occurs in 18.5% of markedly obese individuals but in only 2.7% of lean individuals. This prevalence is higher than found in most reported biopsy studies. For example, the prevalence of steatohepatitis in biopsy from obese patients ranged from 1% to 9% (16, 17). When studies including persons drinking moderate amounts of alcohol are excluded, the prevalence is less than 1%. However, Mallory bodies were found in 24% to 74% of biopsy specimens from selected nonalcoholic obese patients with liver test abnormalities (1, 3). The high prevalence of steatohepatitis found in our study may be explained in part by the increased sensitivity when large amounts of tissue are examined at autopsy. In addition, most patients in our study had undergone catabolism before death that would be metabolically similar to the starvation associated with the postjejunoileal bypass state (see below). The possibility that alcohol abuse was present in some of our patients cannot be totally eliminated. However, alcohol abuse could be reasonably excluded in many cases because of long-term institutionalization or senility. Lack of correlation between prevalence of steatohepatitis and duration of the final hospitalization also does not favor a role for alcohol abuse in our study.

Investigation of possible risk factors disclosed that steatohepatitis correlated with grade of obesity, presence of type II diabetes, weight loss shortly before death

TABLE 2. Prevalence of various conditions (percentage) in patients with different degrees of steatohepatitis

Conditions	Severity of steatohepatitis			
	0	1	2	3
Obesity grade 2	16	43	60	60
Diabetes, type II	20	29	50	40
Weight loss	32	43	44	40
Steatosis grade 2	10	43	70	80
Fibrosis grade 2-3	6	14	40	60
Cirrhosis (fibrosis grade 3)	2	14	10	0
No. of patients	329	7	10	5

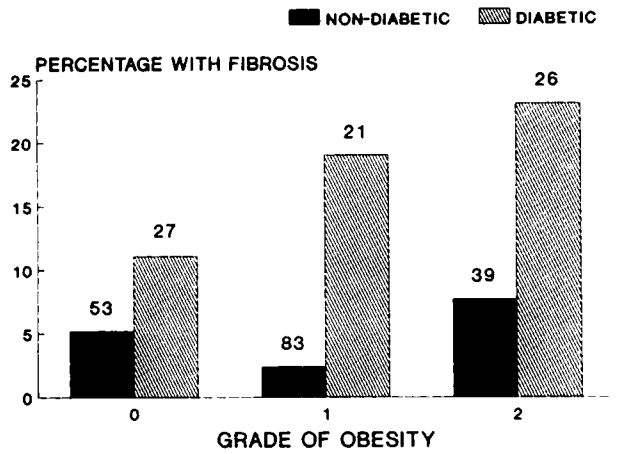

FIG. 5. Prevalence of fibrosis (grade 2 to 3) was greater in diabetic patients than in nondiabetic patients. The prevalence of fibrosis was greater in obese patients but this effect was entirely explained by the presence of diabetes. $p < 0.001$ for nondiabetic patients vs. diabetic patients, grade of obesity ignored. $p < 0.05$ for nondiabetic vs. diabetic patients, obesity grade 1. Numbers over the bars are the number of patients in the group.

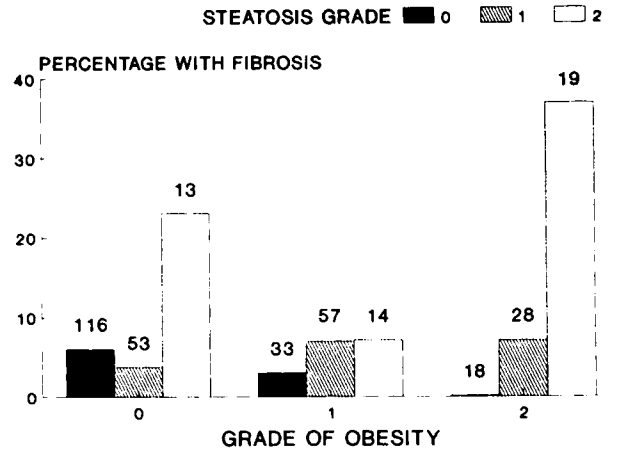

FIG. 6. Prevalence of fibrosis (grade 2 to 3) was greater when steatosis was severe (grade 2) than with lesser grades of steatosis. $p < 0.001$ for steatosis grade 0 vs. 2, grade of obesity ignored. $p < 0.01$ for steatosis grade 1 vs. 2, grade of obesity ignored. $p < 0.05$ for steatosis grade 0 vs. 2, obesity grade 2 only. $p < 0.05$ for steatosis grade 1 vs. 2, obesity grade 2 only.

and severity of hepatic steatosis and that these factors appeared to be additive. An additional association with intravenous infusion of glucose in the week before death may be explained by the fact that wasting individuals are likely to require such therapy. Another explanation of theoretical interest is that glucose infusions might predispose a patient to steatohepatitis (see below). Although most patients with steatohepatitis were women, this could be explained by the higher prevalence of obesity among women compared with men in our study population.

Possible factors suggested to explain the pathogenesis of steatohepatitis in postjejunoileal bypass patients have included the absorption of bacterial products or bile acids from the blind loop (7, 9, 18, 19), protein malnutrition (20), deficiency of essential fatty acids or vitamin E (9) and the mobilization of free fatty acids during weight loss (21). It has recently been suggested that insulin has a role in the development of obesity-related steatohepatitis (22). This hypothesis is based on the observation that steatosis and steatohepatitis occur in subcapsular liver of type I diabetic patients treated with intraperitoneal insulin during chronic peritoneal dialysis. It is known that insulin inhibits fatty acid oxidation (23) and this effect might lead to increased cellular levels of toxic free fatty acids.

This hypothesis may explain how the risk factors defined in this study lead to steatohepatitis. Each of these factors could augment the presentation of free fatty acids to the liver. The association with obesity may be related to the large source of fatty acids stored in adipose tissue and to insulin resistance. Obese individuals who are diabetic have greater insulin resistance and higher plasma free fatty acids than nondiabetic individuals (24-26). Obese individuals and type II diabetic patients usually have elevated or normal plasma insulin levels (27, 28), which may be sufficient to inhibit hepatic disposal of fatty acids, thus favoring accumulation of free fatty acids and triglycerides in hepatocytes. Indeed, free fatty acids have been found to be elevated in liver tissue of obese patients (29, 30).

The role of weight loss in the development of steatohepatitis in our series can be understood by comparing patient condition shortly before death with the postjejunoileal bypass state. Steatohepatitis after jejunoileal bypass occurs during the period of maximal weight loss; necrosis is most severe in those patients who lose the most weight (15). However, obese patients without bypass surgery who lose a comparable amount of weight by fasting have improved liver function and histological findings (9). The explanation for this paradox may lie in the diet. Weight loss is associated with a marked flux of

free fatty acids from adipose tissue to the liver (31). Obese patients have a drop in insulin levels during fasting, whereas postbypass patients continue to eat and stimulate pancreatic insulin secretion during the period of weight loss. In this study patients often lost weight in the period before death while caloric intake was supported by intravenous carbohydrate infusion. This carbohydrate load may stimulate insulin secretion in amounts sufficient to inhibit hepatic fatty acid oxidation but not sufficient to prevent mobilization of fatty acids from adipose tissue.

This hypothesis is supported by the marked ketonuria found in fasting obese patients and the absence of ketonuria in patients after jejunoileal bypass (20). This difference is likely a response to insulin-induced inhibition of the β-oxidation pathway in the latter group. The relevance of this hypothesis to the fatty liver of kwashiorkor is suggested by the absence of ketonuria in that condition also. Another observation of interest is the development of steatohepatitis and cirrhosis in a nonalcoholic woman who repeatedly induced vomiting shortly after eating (32). This practice probably would have led to wide swings of insulin concentration coupled with starvation and mobilization of free fatty acids.

The importance of obesity-related liver disease as a cause of cirrhosis is unknown. Although most patients with steatohepatitis in this study had mild or moderate histological activity, progressive and clinically significant disease had probably occurred because we also found a correlation of hepatic fibrosis with obesity, diabetes and severity of steatosis. In this series there were six obese and three nonobese patients with cirrhosis. From this data, and assuming a 16.7% prevalence of obesity (as found in our autopsy population), one can estimate that obesity-related cirrhosis is present in 0.3% of the general autopsy population, in 1.8% of obese patients at autopsy and in approximately 12% of all cirrhotic patients. The 1.8% prevalence among obese patients is comparable to the estimate of 3% (range 0% to 24%) found in biopsy series (14, 17).

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