Association of Nonalcoholic Fatty Liver Disease with Insulin Resistance

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BACKGROUND AND PURPOSE: Nonalcoholic fatty liver disease is frequently associated with type 2 diabetes mellitus, obesity, and dyslipidemia, but some patients have normal glucose tolerance or normal weight. We tested the hypothesis that there is an association between nonalcoholic fatty liver disease and insulin resistance that is independent of diabetes and obesity.

SUBJECTS AND METHODS: We measured anthropometric and metabolic variables in 46 patients with chronically elevated serum aminotransferase levels, "bright liver" on ultrasound scan, and normal glucose tolerance. Indexes of insulin resistance and secretion were determined using the homeostasis model assessment method. They were compared with 92 normal subjects who were matched for age and sex.

RESULTS: Patients with nonalcoholic fatty liver disease were characterized by fasting and glucose-induced hyperinsulinemia, insulin resistance, postload hypoglycemia, and hypertriglyceridemia. Insulin resistance [odds ratio (OR) = 15 per percent increase, 95% confidence interval (CI): 3.0 to 70], fasting triglyceride level (OR = 3.1 per mmol/liter increase, 95% CI: 1.1 to 8.9), 180-minute blood glucose level (OR = 4.3 per mmol/liter decrease, 95% CI: 1.6 to 12), and average insulin concentration in response to oral glucose (OR = 3.0 per 100 pmol/liter increase, 95% CI: 1.5 to 6.2) were independently associated with nonalcoholic fatty liver disease. The exclusion of overweight and obese subjects did not change the results.

CONCLUSION: Nonalcoholic fatty liver disease is associated with insulin resistance and hyperinsulinemia even in lean subjects with normal glucose tolerance. Genetic factors that reduce insulin sensitivity and increase serum triglyceride levels may be responsible for its development. **Am J Med. 1999;107: 450–455.** ©1999 by Excerpta Medica, Inc.

Less than 20 years ago, Ludwig et al (1) coined the term "nonalcoholic steatohepatitis" to identify a syndrome characterized by fatty liver and lobular hepatitis in patients who had negligible alcohol intake. Patients have chronically elevated serum alanine aminotransferase levels that indicate ongoing liver injury that may progress to fibrosis, cirrhosis, and hepatocellular failure. The syndrome, recognized as a clinical entity since 1962 (2), is mainly associated with obesity (3,4), diabetes (3,5–7), and dyslipidemia (5–9). More recently, the spectrum of disease has been expanded to fatty liver with or without inflammation, and the term "nonalcoholic fatty liver disease" is used to include all patients with hepatic steatosis, whether or not there is active inflammation.

In earlier studies, fatty liver was considered to be an incidental pathologic finding that was without clinical significance. More recent studies have challenged this idea. Approximately half of the patients with nonalcoholic steatohepatitis develop liver fibrosis, 15% develop cirrhosis, and 3% may progress to liver failure or liver transplantation (10). In 15% to 50% of patients, liver fibrosis or cirrhosis may be diagnosed at presentation (11).

Although type 2 diabetes mellitus and fatty liver are associated, the prevalence of steatosis in patients with type 2 diabetes is unknown, because there has not been a systematic study that included liver biopsies. From 21% to 78% of diabetic patients have fatty liver seen with ultrasound examination (11,12), and serum alanine aminotransferase levels are frequently increased (13,14). However, attempts to link nonalcoholic fatty liver disease to altered glucose tolerance have been unsuccessful. The prevalence of type 2 diabetes varies from 2% to 55% in patients with nonalcoholic fatty liver disease (15), and the amount of steatosis is more closely related to the degree of obesity (3). In addition, some patients with nonalcoholic fatty liver disease are lean, have normal fasting glucose levels with normal glucose tolerance, and do not have increased plasma lipid levels (7).

Because type 2 diabetes, obesity, and dyslipidemia are all associated with decreased sensitivity to insulin, this study was designed to determine the association between nonalcoholic fatty liver disease and insulin resistance, while adjusting for the effects of diabetes and obesity. Insulin sensitivity and β-cell function were estimated by the homeostasis model assessment method (16), which

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correlates with direct, quantitative measurements of insulin sensitivity (17).

MATERIAL AND METHODS

Patients

Since September 1997, all outpatients who visited our Department of Liver and Metabolic Disease for chronically elevated serum aminotransferase levels were screened for hepatitis B, C, and Epstein-Barr virus infection, nonorgan-specific autoantibodies, and hereditary defects (α_1-antitrypsin deficiency and iron and copper storage diseases). Alcohol consumption was assessed by detailed history and laboratory markers (serum γ-glutamyl transpeptidase levels and mean corpuscular volume of red blood cells). All patients also received an ultrasound scan of the liver. In a cohort of more than 300 patients with liver disease, we found 76 patients who had a "bright" liver on ultrasound examination and no evidence of viral, autoimmune, or congenital defects that were responsible for their liver disease. After excluding patients who consumed even moderate alcohol amounts (more than 20 g/day), or who were suspected of surreptitious alcohol consumption, and those with fasting or glucose-stimulated hyperglycemia [fasting glucose level greater than 6.5 mM (115 mg/dL) or 120-minute blood glucose level after a 75 g glucose load greater than 8 mM (144 mg/dL)] (18), 46 patients remained. Age, height, weight, waist and hip circumferences, and fasting plasma glucose, insulin, total and high-density lipoprotein (HDL) cholesterol, triglyceride, uric acid, and glucose and insulin levels during an oral glucose tolerance test were recorded. No patient had ascites or other evidence of advanced liver disease; patients' prothrombin activity always exceeded 85% of normal, albumin levels were greater than 40 g/liter, and total bilirubin levels were less than 25 μM (1.5 mg/dL). The ultrasound examination did not show signs of portal hypertension.

Ninety-two control subjects (2 for each patient) were matched for sex and age ($\pm$3 years). They all had a normal ultrasound liver scan. After the selection, they underwent a routine biochemical evaluation, including serum

Table. Characteristics of Patients with Nonalcoholic Fatty Liver Disease and Control Subjects*

	Number (%) or Mean $\pm$ SD (range)		
	Nonalcoholic Fatty Liver Disease (n = 46)	Controls (n = 92)	*P* Value
Male sex (%)	30 (65%)	60 (65%)	>0.99
Age (years)	45 $\pm$ 13 (15–76)	43 $\pm$ 10 (23–72)	0.52
Weight (kg)	82 $\pm$ 16 (55–130)	70 $\pm$ 10 (49–90)	<0.001
Height (cm)	170 $\pm$ 9 (149–183)	170 $\pm$ 9 (146–188)	0.84
Body mass index (kg/m^2)	28.2 $\pm$ 4.0 (22.3–42.2)	24.2 $\pm$ 2.0 (19.7–28.5)	<0.001
Waist circumference (cm)	92 $\pm$ 13 (62–119)	80 $\pm$ 12 (55–108)	<0.001
Hip circumference (cm)	103 $\pm$ 10 (80–128)	96 $\pm$ 10 (78–122)	<0.001
Waist-to-hip ratio	0.89 $\pm$ 0.10 (0.72–1.18)	0.84 $\pm$ 0.06 (0.70–0.96)	<0.001
Serum alanine aminotransferase (mU/mL)†	87 $\pm$ 41 (41–233)	20 $\pm$ 6 (8–36)	<0.001
Serum cholesterol (mmol/L)	5.3 $\pm$ 0.9 (2.3–7.0)	5.2 $\pm$ 1.0 (2.9–8.6)	0.75
Serum HDL cholesterol (mmol/L)	1.2 $\pm$ 0.3 (0.6–2.1)	1.4 $\pm$ 0.5 (0.6–3.0)	<0.001
Serum uric acid (μmol/L)	324 $\pm$ 106 (155–583)	245 $\pm$ 60 (137–404)	0.14
Serum triglycerides (mmol/L)	2.4 $\pm$ 1.0 (0.9–4.9)	1.4 $\pm$ 0.6 (0.6–3.2)	<0.001
Fasting serum glucose (mmol/L)	5.2 $\pm$ 0.6 (3.9–6.2)	5.0 $\pm$ 0.6 (3.9–6.5)	0.04
120-min glucose (mmol/L)‡	5.7 $\pm$ 1.1 (3.3–8.0)	6.0 $\pm$ 1.1 (3.6–8.2)	0.11
180-min glucose (mmol/L)‡	4.2 $\pm$ 0.8 (2.6–6.3)	4.9 $\pm$ 0.8 (3.2–7.4)	<0.001
Fasting insulin (pmol/L)	103 $\pm$ 29 (65–201)	60 $\pm$ 19 (29–108)	<0.001
Mean insulin (pmol/L)‡	469 $\pm$ 247 (208–1,592)	247 $\pm$ 103 (60–646)	<0.001
Fasting C-peptide (pmol/L)	980 $\pm$ 263 (596–1,854)	547 $\pm$ 178 (132–1,264)	<0.001
C-peptide to insulin molar ratio	9.8 $\pm$ 2.5 (5.8–18.1)	9.7 $\pm$ 3.4 (2.7–19.4)	0.98
Insulin resistance (%)§	3.3 $\pm$ 1.0 (2.2–5.6)	1.8 $\pm$ 0.6 (0.9–2.4)	<0.001
β-cell function (%)§	197 $\pm$ 121 (77–810)	134 $\pm$ 82 (34–585)	<0.001

* To convert from SI units to traditional units, multiply cholesterol and HDL cholesterol levels in mmol/L by 38.7 mg/dL; multiply uric acid levels in μmol/L by 0.167 mg/dL; multiply triglyceride levels in mmol/L by 89 mg/dL; multiply glucose levels in mmol/L by 18 mg/dL; multiply insulin levels in pmol/L by 0.14 μU/mL; multiply C-peptide levels in pmol/L by 0.0036 ng/mL.

† Normal values <40 mU/mL.

‡ Measured during oral glucose tolerance test.

§ Measured by the Homeostasis Model Assessment.

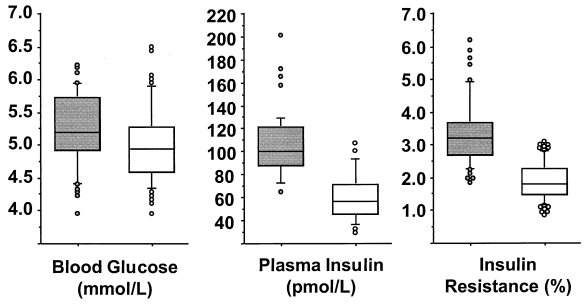

Figure 1. Box plot representation of fasting glucose and insulin levels, and insulin resistance in patients with nonalcoholic fatty liver disease (**gray boxes and circles**) and in control subjects (**open boxes and circles**). Each box comprises the values between the 25th and the 75th percentiles, and the **bold horizontal line** is the median value; the whiskers stretch from the 10th and to the 90th percentile. **Circles** represent individual outliers.

aminotransferase levels and an oral glucose tolerance test. Only subjects with normal serum aminotransferase and fasting serum glucose levels, as well as normal glucose tolerance tests, were considered. Fasting lipid levels were not considered as selection criteria.

No subject had evidence of any chronic disease, nor were any being treated with drugs known to affect glucose, lipid, or hepatic metabolism at the time of the study. Cigarette smoking was not considered. All subjects gave informed consent to take part in the study, which was approved by the senior staff committee of our department.

Methods

Plasma glucose levels, both in the fasting state and in response to a standard glucose load, were measured in duplicate with an automated analyzer. The coefficient of variation for any single determination was 1.5%. Insulin levels were measured by an immunoenzymometric assay (AIA-PACK IRI, AIA-1200 system; Tosoh Company, Tokyo, Japan) with inter- and intra-assay coefficients of variation for the quality control less than or equal to 7%. C-peptide was measured by radio-immunoassay (Lisophase; Tecnogenetics, Milan, Italy), with coefficients of variation less than or equal to13%. The average insulin level during the glucose tolerance test was calculated by means of the trapezoidal rule. Fasting serum cholesterol, HDL cholesterol, uric acid, and triglyceride levels were measured by routine laboratory techniques.

The index of insulin resistance was calculated on the basis of fasting values of plasma glucose and insulin, according to the homeostasis model assessment method (16), as insulin resistance (%) = (insulin)/22.5 $\times$ $e^{-\ln (\text{glucose})}$, where insulin is in μU/mL and glucose is in mmol/liter. Similarly, the index of insulin secretion was calculated as β-cell function (%) = (20 $\times$ insulin)/(glucose $-$ 3.5).

Ultrasound liver studies were carried out by an experienced operator who was blinded to laboratory values (viral and autoimmune markers, as well as to fasting and postload glucose levels). The diagnosis of "bright" liver was based on abnormally intense, high-level echoes arising from the hepatic parenchyma, with an amplitude similar to that of echoes arising from the diaphragm. (Normally, the amplitude of liver echoes is one-half to one-third that of the diaphragm.)

Statistical Analysis

Differences between mean values in control subjects and patients with nonalcoholic fatty liver disease were tested with Student's *t* test for unpaired data. Because several sets of variables were tested simultaneously, the limit of significance was calculated according to Duncan's multiple range (19) at $P = 0.005$. A stepwise logistic regression analysis was carried out to identify the independent predictors of having nonalcoholic fatty liver disease, testing the following variables that were significant in univariate analyses: weight, body mass index (weight/height^2), waist circumference, waist-to-hip ratio, fasting serum triglyceride and insulin levels, average insulin levels and 180-minute glucose levels during the oral glucose tolerance test, and insulin resistance. The analyses were repeated after exclusion of subjects with a body mass index exceeding 25 kg/m^2. All analyses were carried out on a personal computer and StatView II program (ABACUS Concepts, Inc, Berkeley, California) or SPSS/PC + 4.0 package (SPSS, Inc, Chicago, Illinois). Results are expressed as mean $\pm$ SD.

RESULTS

Among the 46 patients with nonalcoholic fatty liver disease (Table), 20 (43%) were overweight (body mass index from 25 to 30 kg/m^2) and 13 were frankly obese (body mass index greater than 30 kg/m^2). Of the 92 control subjects, 28 (30%) had a body mass index exceeding 25 kg/m^2, but none was obese. Fat was mainly distributed in the splanchnic area. Among the patients, the mean waist circumference was 95 $\pm$ 14 cm in men and 87 $\pm$ 11 cm in women, significantly greater than in the controls [men 84 $\pm$ 11 cm ($P < 0.001$), women 72 $\pm$ 10 cm ($P < 0.001$)]. The waist-to-hip ratio was greater than or equal to 1 in 6 of 30 men and greater than or equal to 0.9 in 2 of 16 women. In the control group, the waist-to-hip ratio was always normal (less than 0.9).

Serum cholesterol levels were mildly elevated, exceeding the recommended upper limit of 5.2 mM, in 24 (52%) of 46 patients with nonalcoholic fatty liver disease and in 41 (44%) of 92 controls. HDL cholesterol levels were significantly decreased in the patients, whereas uric acid levels were moderately increased (Table). Fasting triglyceride levels were increased (greater than 2 mM) in the ma-

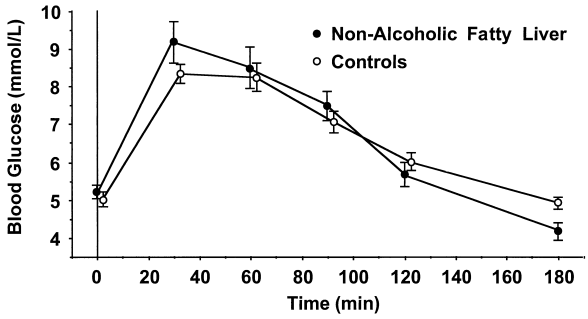

Figure 2. Time course of blood glucose levels during an oral glucose tolerance test in control subjects (**open circles**) and in patients with nonalcoholic fatty liver disease (**closed circles**). Data are presented as means with 95% confidence intervals. The difference in 180-minute values is statistically significant ($P < 0.005$).

jority (61%) of patients with fatty liver, and in only 12 control subjects (26%).

Fasting glucose levels were only 0.2 mM (4 mg/dL) greater in patients with nonalcoholic fatty liver disease than in controls (Figure 1). During the glucose tolerance test, no differences were observed between groups, except at 180 minutes, when patients with nonalcoholic fatty liver disease showed a trend toward late hypoglycemia (Figure 2).

Fasting insulin levels were nearly twice as great in patients with nonalcoholic fatty liver disease, as were the average insulin levels during the glucose tolerance test. Similarly, mean fasting C-peptide levels were 80% greater, whereas the C-peptide-to-insulin molar ratio was similar in the two groups. The index of insulin resistance was 100% greater in the patients (Figure 1), whereas the index of β-cell function was only mildly elevated. In control subjects, insulin resistance correlated with body mass index ($r = 0.38$, $P < 0.001$) and waist-to-hip ratio ($r = 0.35$, $P = 0.001$), whereas in patients with nonalcoholic fatty liver disease insulin resistance was not associated with either body mass index ($r = 0.09$, $P = 0.55$) or waist-to-hip ratio ($r = 0.08$, $P = 0.60$).

Insulin resistance was the strongest predictor of having nonalcoholic fatty liver disease, with an odds ratio (OR) of 15 [95% confidence interval (CI): 3.0 to 70] per percent increase in insulin resistance. In addition, serum triglyceride level [OR = 3.1 (95% CI: 1.1 to 8.9)] per mmol/liter increase, 180-minute plasma glucose level [OR = 4.3 (95% CI: 1.6 to 12)] per mmol/liter decrease, and average insulin level during the glucose tolerance test [OR = 3.0 (95% CI: 1.5 to 6.2)] per 100 pmol/liter increase were also independently associated with nonalcoholic fatty liver disease. When expressed in common US units, the corresponding odds ratios were 1.9 (95% CI: 1.1 to 3.4) per 50 mg/dL increase in triglyceride level, 2.3 (95% CI: 1.3 to 3.9) per 10 mg/dL decrease in 180-minute plasma glucose level, and 4.9 (95% CI: 1.8 to 14) per 20 μU/mL increase in average insulin levels.

In lean patients with fatty liver (body mass index less than or equal to 25 kg/m^2), serum triglyceride levels were greater when compared with overweight or obese subjects (2.9 ± 1.1 mM vs 2.2 ± 0.9 mM, corresponding to 258 ± 96 mg/dL and 197 ± 83 mg/dL, $P < 0.04$), whereas insulin resistance was similar ($2.9 \pm 1.0\%$ vs $3.5 \pm 1.0\%$). The exclusion of overweight and obese patients and control subjects did not change these results substantially. Nonalcoholic fatty liver disease was still associated with insulin resistance [OR = 11 (95% CI: 1.1 to 110) per percent increase], as were fasting triglyceride level [OR = 4.0 (95% CI: 1.0 to 16) per mmol/liter increase] and average insulin levels in response to oral glucose [OR = 2.3 (95% CI: 1.0 to 5.3) per 100 pmol/liter increase].

DISCUSSION

The present study demonstrates that insulin resistance, elevated serum triglyceride levels, hyperinsulinemia, and lower glucose levels after a glucose load are associated with nonalcoholic fatty liver disease, irrespective of body weight, body mass index, fat distribution, and glucose tolerance. The diagnosis of nonalcoholic fatty liver disease was based on exclusion of known etiologic factors responsible for liver disease (viral, genetic, autoimmune) and on ultrasound examinations, but was not confirmed by liver biopsy. Saverymuttu et al (20), in a prospective study comparing ultrasound scanning with histologic examination, showed that the ultrasound examinations can accurately identify steatosis with a sensitivity of 94% and a specificity of 84%. Quantitative data may be obtained by texture analysis of the digitized ultrasonographs (21), but a recent study showed that standard ultrasonography may also be used (22). In the present study, invasive procedures were not allowed by the ethics committee, and we could not determine the types of fatty liver disease in our patients.

Insulin resistance was measured by the homeostasis model assessment method, which has a relatively low reproducibility, reflecting day-to-day variability in fasting glucose and especially insulin levels, as well as analytical uncertainty. A change of 1 μU/mL in the insulin level in control subjects may cause a 20% change in insulin resistance. Despite this, the method correlates closely with quantitative, functional tests, such as the euglycemic glucose clamp (16). The low coefficient of variation of blood glucose levels in our laboratory, as well as the low inter- and intra-assay coefficients of variation of plasma insulin levels, increase the reliability of the measurement of insulin resistance by the homeostasis model that we used.

Nonalcoholic fatty liver disease was closely associated with insulin resistance, independent of body mass index

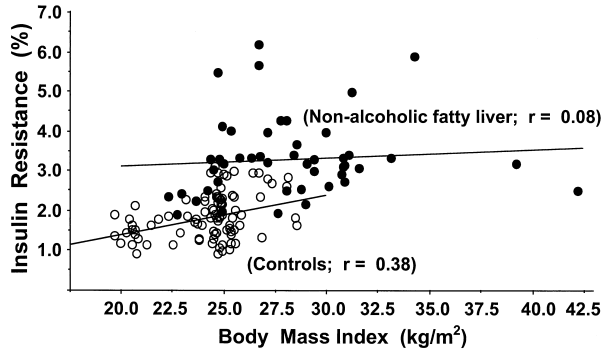

Figure 3. Correlation between insulin resistance, calculated by the homeostasis model assessment, and body mass index in patients with nonalcoholic fatty liver disease (**closed circles** n = 46, $P = 0.55$) and in control subjects (**open circles** n = 92, $P < 0.001$).

and fat distribution. Although most patients in our series were overweight or frankly obese, the exclusion of overweight or obese subjects did not change the results. Wanless and Lentz (3) found that the degree of steatosis in nonalcoholic fatty liver disease is proportional to the degree of obesity. Among overweight or obese subjects in our study, insulin resistance was moderately greater than that in lean patients. However, no correlation was observed between insulin resistance and body mass index in patients, in contrast to the strong correlation in control subjects (Figure 3). This suggests that in nonalcoholic fatty liver disease, insulin resistance may be a primary phenomenon, possibly in addition to obesity-associated insulin resistance, whereas in normal subjects sensitivity to insulin may depend primarily on obesity. Body mass index and waist-to-hip ratio were not independently associated with nonalcoholic fatty liver disease, suggesting that obesity and splanchnic fat distribution might also be effects of insulin resistance, rather than being directly involved in the etiology of fatty liver.

The insulin resistance in our patients may have been part of the usual association between hyperinsulinemia and liver disease. Patients with advanced liver disease are usually insulin resistant (23); hyperinsulinemia in these patient is related to both decreased hepatic insulin degradation and pancreatic hypersecretion (24,25). However, none of our patients had evidence of cirrhosis, all had normal laboratory values (apart from increased serum aminotransferase levels), and none had ultrasonographic signs of portal hypertension. In addition, fasting C-peptide levels were increased and the C-peptide to insulin molar ratio was normal. Therefore, their hyperinsulinemia reflects insulin hypersecretion, not decreased insulin degradation by a failing liver. Thus, the corresponding insulin resistance measured by the homeostasis method cannot be merely a result of liver disease. However, studies of insulin resistance and serum triglyceride levels in patients with mild liver disease of a different etiology, such as chronic viral hepatitis in the absence of fatty liver, are warranted.

Patients with diabetes or impaired glucose tolerance were excluded from the study, because the homeostasis model is not reliable with marked hyperglycemia. Several patients in our series had mild fasting hyperglycemia, whereas the mean 3-hour blood glucose level in patients was lower than in controls. Reactive hypoglycemia was never symptomatic and was related to glucose-stimulated hyperinsulinemia, which is frequently observed in early type 2 diabetes (26).

This suggests that patients with nonalcoholic fatty liver disease and normal or near normal glucose levels are part of a spectrum of a disease that includes obesity and type 2 diabetes (10), which are associated with fasting and postload hyperinsulinemia and insulin resistance. Such a conclusion is supported by the study of Lee et al (27), who found that fasting hyperinsulinemia and reduced glucose tolerance, compatible with insulin resistance, were equally common in both obese and normal-weight patients with nonalcoholic fatty liver disease. Lean patients with nonalcoholic fatty liver disease and normal glucose tolerance might represent an initial stage of the metabolic syndrome X (28), which may lead to type 2 diabetes and obesity. These patients frequently have increased serum triglyceride levels, hypertension (29), and splanchnic fat distribution (30) in the absence of overt obesity. Most of these features are shared by our patients, who had lower-than-normal serum HDL cholesterol levels, mildly increased serum uric acid levels, hyperinsulinemia, and reactive hypoglycemia in response to oral glucose. Liver pathology has been reported in severely obese patients with syndrome X (31).

The nature of the connection between insulin resistance, glucose-induced hyperinsulinemia, elevated serum triglyceride levels, and hepatic steatosis remains a matter of speculation. In individual patients, genetic conditions might be primarily responsible for increased serum triglyceride levels, causing peripheral insulin resistance at a receptor level. This was probably the case in our lean patients with fatty livers, who were characterized by less severe insulin resistance and more pronounced hypertriglyceridemia. In other patients, such as those who are overweight, obese, or who have type 2 diabetes, the primary abnormality may be genetically induced insulin resistance or obesity, which secondarily increases serum triglyceride levels via enhanced peripheral lipolysis. In both situations, the resulting hepatic supply of fatty acids and insulin might enhance triglyceride deposition in the liver, with lipids acting as first "hit" in progressive steatohepatitis (32). The second "hit," increased lipid peroxidation, might be related to hypertriglyceridemia and fatty acid deposition, increasing substrates as yet uncharacterized for oxidative stress. In the absence of potentially hep-

atotoxic drugs, genetic conditions such as hemochromatosis (33), dietary habits (34), as well as acquired deficiencies in antioxidant systems [mainly vitamins (35)] may be involved.

Our results have therapeutic implications that should be tested in clinical studies. A weight-reducing nutritional regimen in obese subjects or insulin-sensitizing drugs, such as metformin or thiazolidinediones, irrespective of body mass index, might break the link between hyperinsulinemia and insulin resistance with elevated serum triglyceride levels, which in turn may reduce progressive hepatic steatosis and liver disease.

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