Journal of Gastroenterology and Hepatology (2006) **21,** 169–173 DOI: 10.1111/j.1440-1746.2005.04221.x

HEPATOLOGY

Long-term prognosis of nonalcoholic fatty liver disease: Is pharmacological therapy actually necessary?

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Abstract

Background and Aim: Nonalcoholic fatty liver disease (NAFLD) comprises a wide spectrum of liver injury, ranging from steatosis and steatohepatitis to cirrhosis. Reasons for the different natural course in individuals with NAFLD are still unclear. The aim of this study was to describe the natural course of disease in individuals with NAFLD who did not receive pharmacological therapy.

Methods: A total of 27 individuals with NAFLD (male/female ratio: 10/17, mean age 49.7 years) were prospectively enrolled. Management after diagnosis consisted of establishment of an appropriate diet and exercise (walking and jogging) program, treatment of associated metabolic conditions such as diabetes and dyslipidemia, and discontinuation of potentially hepatotoxic drugs if the patient was taking these. Liver tests were performed at diagnosis and at 3-month intervals during the follow-up period. Mean follow-up period was 43.3 months (range 36–49 months).

Results: From baseline to the end of the follow-up period, although there was no significant difference observed in terms of the mean body mass index, serum aminotransferase levels significantly improved (48.8 ± 29.9 U/L to 31.6 ± 16.0 U/L for aspartate aminotransferase [AST] and 66.3 ± 38.3 U/L to 39.6 ± 22.9 U/L for alanine aminotransferase [ALT]; $P < 0.05$). No significant differences in platelet counts, serum albumin level or prothrombin time were observed ($P > 0.05$). No patient developed signs of advanced liver disease during the follow-up period.

Conclusion: A treatment strategy comprising diet, exercise and management of associated metabolic conditions is associated with improvement in aminotransferases among patients with NAFLD. Further investigation is needed to examine the long-term efficacy of this approach on liver histology and clinical outcomes.

Key words: liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, treatment.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a clinicopathological condition that comprises a wide spectrum of liver injury, ranging from only steatosis and steatohepatitis to fibrosis and cirrhosis.[1,2] NAFLD is a common histological finding in liver biopsy samples and affects 10–24% of the general population in different countries.[1] In the USA, the prevalence of NAFLD is up to 31%.[3] The prevalence of NAFLD is higher in individuals with obesity (range 60–75%), type 2 diabetes mellitus (range 28–55%) and hyperlipidemia (range 20–92%).[1–5] However, many individuals with NAFLD are non-obese, non-diabetic and have normal serum lipid levels and no liver test abnormalities.[6] Previous studies have shown that truncal obesity seems to be a significant risk factor for NAFLD, even in individuals with a normal body mass index (BMI).[1,7]

Although the clinical implications of NAFLD are derived mostly from its potential to progress to fibrosis and cirrhosis, simple steatosis also follows a relatively benign natural course in most individuals with NAFLD.[1,2,8] While the reasons for the different natural course in individuals with NAFLD apparently suffering from the same condition are still unclear, obesity, diabetes and age may promote progressive liver disease as

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Accepted for publication 24 June 2005.

they are associated with the presence of advanced liver fibrosis.[6]

Currently, therapeutic management for NAFLD is limited. Pharmacological therapy directed specifically at the liver damage has been evaluated recently.[1,2,9–12] Unfortunately, a lack of randomized placebo controlled trials with definitive histological endpoints limits the ability to make pharmacological treatment recommendations. The aim of this study was to examine the natural course of disease in individuals with NAFLD who did not receive pharmacological therapy.

METHOD

Patients

This was a prospective, longitudinal single center study. A total of 27 individuals with NAFLD (male/female ratio: 10/17, mean age 49.7 years) who were consecutively seen at Ankara University School of Medicine, Department of Gastroenterology, Liver Diseases Outpatient Clinic between January 2001 and March 2002 were enrolled. Criteria for inclusion were: (i) age >18 years; (ii) diagnosis of NAFLD; (iii) convincing evidence of absent or minimal alcohol consumption (<20 g alcohol/day for women and <30 g alcohol/day for men); (iv) absence of confounding disease including acute (hepatitis A, B or C) and/or chronic viral hepatitis; and (v) exclusion of other forms of liver disease including autoimmune, drug-induced and metabolic liver disease. Characteristics and demographics of the patients are shown in Table 1. All 27 individuals with NAFLD in this study signed an informed consent form before each procedure.

Liver injury and function tests

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin levels and complete blood cell counts were measured by our central laboratory on a 24-channel automated chemical analyzer using standard reagents. These liver tests were determined at diagnosis and at 3-month intervals during the follow-up period. For exclusion of other forms of liver disease, serum iron, ferritin, copper and ceruloplasmin levels were measured, and serological studies for antinuclear antibody, antismooth muscle antibody and antimitochondrial antibodies were performed.

Histological assessments

Liver biopsy was performed in 13 individuals (48.2%) with NAFLD. All liver biopsy specimens were fixed in 10% buffered formalin and embedded in paraffin. Paraffin sections (4 μm thick) were stained with hematoxylin and eosin (HE) and Masson's trichrome stain (used to characterize the fibrosis). Histological features of samples were interpreted as outlined by Brunt *et al.*[13] No repeat liver biopsy was performed to describe the natural history of NAFLD at the end of the follow-up.

Definition

Diagnosis of NAFLD was based on biochemical, radiological and histological criteria, requiring the presence of abnormal serum aminotransferases levels (ALT, AST), the presence of an abnormal ECHO pattern on sonography consistent with fatty infiltration,[14] and a liver biopsy documenting steatosis, necroinflammatory activity, Mallory's hyalin, lobular distribution, fibrosis or cirrhosis, and on exclusion of other forms of acute and chronic liver diseases.[13]

Diet and exercise

After diagnosis of NAFLD was confirmed, management was focused in the following areas: establishment of an appropriate diet and exercise (walking and jogging) program; improvement in associated conditions such as diabetes mellitus or moderate/severe hyperlipidemia; and discontinuation of potentially hepatotoxic drugs.

Individuals with NAFLD were ordered a conventional diet of 25 Cal/kg × ideal bodyweight (kg).[15] Three meals per day containing 60% carbohydrates, 15% protein and 25% fat were provided for each individual. All patients with NAFLD were seen by a dietician at the beginning of the study in order to organize dietary instruction. Exercise included walking and jogging for 20 min twice a day.[15,16] None of the patients received pharmacological therapy for NAFLD.

Obesity was defined as an excessive amount of body fat and was classified in accordance with World Health Organization (WHO)[17] and the National Institute of Health[18] guidelines. Obesity was determined in 37% (10/27) (BMI > 30 kg/m^2) and overweight in 44.4% (12/27) of patients (for males: BMI 26–30 kg/m^2; for females: BMI 24–30 kg/m^2).

Statistical analyses

All patients were included in the data analysis. The paired *t*-test and chi-squared test were used. A *P*-value of less than 0.05 was considered to be significant.

RESULTS

Characteristics of the 27 individuals with NAFLD are shown in Table 1. Mean follow-up period was 43.3 months (range 36–49 months) and there were no dropouts. Among the patients, 14.8% had diabetes mellitus (4/27), 40.7% (11/27) had hyperlipidemia and 22.2% (6/27) had hypertension. Four diabetics were using oral antidiabetic agents (three sulfonylurea, 60–90 mg/day and one acarbose), and their blood sugar levels were under control. During the follow-up period,

there were no new cases of diabetes detected. Six individuals with hyperlipidemia were on a lipid-reduced diet. All serological studies for HBs-Ag, anti-HBc IgM, anti-HCV, anti-HAV IgM, anti-CMV IgM and anti-EBV IgM were negative. Other possible etiological factors, including those which may have caused abnormal liver tests, were also ruled out. There was no past medical history of any drug use or abdominal surgery (small bowel resection, jejuno-ileal bypass) in any case. In liver biopsy specimens, 15.4% of samples had only steatosis, 46.2% had steatosis with inflammation and the remaining 38.4% had steatosis with inflammation plus fibrosis (Table 2).

Table 1 Initial characteristics of the 27 individuals with nonalcoholic fatty liver disease (NAFLD) enrolled in the present study

Characteristic	Mean ± SD
Age (years)	49.7 ± 11.6
Sex (male/female)	10/17
Body mass index (kg/m^2)	28.8 ± 4.3
Fasting glucose (N: 75–115 mg/dL)	102.0 ± 21.5
Cholesterol (N: 120–200 mg/dL)	205.4 ± 34.9
Triglyceride (40–200 mg/dL)	161.0 ± 57.1
ALT (U/L) (N: 10–31 U/L) (N: 10–37 U/L)	66.3 ± 38.3
AST (U/L) (N: 10–37 U/L)	48.8 ± 29.9
Baseline GGT (U/L) (N: 0–55 U/L)	67.4 ± 65.3
ALP (U/L) (N: 135–175 U/L)	126.5 ± 85.5
Albumin (g/dL) (N; 3.5–5.2 g/dL)	4.7 ± 0.3
Bilirubin (mg/dL) (N: 0.3–1.2 mg/dL)	0.8 ± 0.4
PT (seconds) (N: 10.5–14 s)	12.5 ± 1.1
PLT count (× 10^3/μL) (N: 202–386 × 10^3/μL)	282.0 ± 61.0

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transpeptidase; PLT, platelet; PT, prothrombin time.

There was no significant difference observed in terms of the mean BMI between baseline value and third year value (28.8 ± 4.3 kg/m^2 – 29.2 ± 4.9 kg/m^2; $P > 0.05$).

Aminotransferase levels in 15 of the 27 patients (55.6%) decreased to normal values at the third year of the follow-up period. A significant decrease in the serum aminotransferase levels from baseline to the end of the follow-up period was observed ($P < 0.05$). Mean baseline value for the serum AST level was 48.8 ± 29.9 U/L and for serum ALT it was 66.3 ± 38.3 U/L. At the third year of the follow-up period values were 31.6 ± 16.0 U/L for AST ($P = 0.014$) and 39.6 ± 22.9 U/L for ALT ($P = 0.001$) (Table 3).

The mean percentage decrease in the serum AST level at 12 and 36 months relative to the baseline level was 67.9% and 64.6%, respectively. The mean percentage decrease in serum ALT levels at 12 and 36 months compared to the baseline level was 70.4% and 59.7%, respectively (Table 4).

Table 2 Histological features of 13 individuals with nonalcoholic fatty liver disease (NAFLD)

Case	Steatosis	Inflammation	Fibrosis
1	++	++	+
2	++	+	+
3	++	+	+
4	+	–	–
5	+	+	–
6	+++	+	–
7	++	+	–
8	+++	+	–
9	+++	++	–
10	+++	+	–
11	++	+	+
12	++	–	–
13	++	+	+

Table 3 Mean values of laboratory data obtained at baseline and during the follow-up period of individuals with nonalcoholic fatty liver disease (NAFLD)

	Baseline	3 months	6 months	12 months	24 months	36 months
ALT (U/L) (N: 10–31 U/L)† (N: 10–37 U/L)	66.3 ± 38.3	41.3 ± 21.8	36.8 ± 18.5	46.7 ± 23.5	40.4 ± 21.6	39.6 ± 22.9
AST (U/L) (N: 10–37 U/L)	48.8 ± 29.9	29.7 ± 11.7	28.2 ± 9.0	33.2 ± 9.6	31.2 ± 10.4	31.6 ± 16.0
PLT count (10^3/μL) (N: 202–386 × 10^3/μL)	282.0 ± 61.0	275.40 ± 33.79	280.8 ± 53.2	288.0 ± 56.9	253.1 ± 36.2	268.8 ± 44.8

†Normal alanine aminotransferase (ALT) value for females. AST, aspartate aminotransferase; PLT, platelet.

Table 4 Percentage change in aminotransferase values of the 27 individuals with nonalcoholic fatty liver disease (NAFLD) compared to baseline

	0–12 months	0–36 months
ALT (IU/L) (N: 10–31 U/L)† (N: 10–37 U/L)	70.4	59.7
AST (IU/L) (N: 10–37 U/L)	67.9	64.6

†Normal alanine aminotransferase (ALT) value for females. AST, aspartate aminotransferase.

From baseline to the end of the follow-up period, no significant differences in terms of platelet count ($282.0 \pm 61.0 \times 10^3/\mu L$ to $268.8 \pm 44.8 \times 10^3/\mu L$), serum albumin level ($4.7 \pm 0.3$ g/dL to 4.6 ± 0.2 g/dL), and prothrombin time (12.5 ± 1.2 s to 12.0 ± 0.8 s) were observed ($P > 0.05$). No patient had developed signs of advanced liver disease during the follow-up period.

DISCUSSION

In the present study, with the establishment of an appropriate diet and exercise (walking and jogging) program and improvement in associated conditions, a significant improvement in serum aminotransferase levels was observed in individuals with NAFLD at the end of the first year and also during the third year of the follow-up period. This result is comparable with that observed by several investigators[8,19,20] who have suggested that, in contrast to alcohol-induced fatty liver disease, NAFLD seems to have a benign clinical disease course and minimal risk of progression to end-stage liver disease. Based on these results, it is reasonable to suggest that individuals with NAFLD who adhere to an appropriate diet and exercise (walking and jogging) program and whose associated conditions are effectively managed will demonstrate an improvement in liver test abnormalities.

In this study, the mean percentage decrease in serum AST level at 12 and 36 months relative to the baseline level was 68% and 65%, respectively, and for ALT it was 70% and 60%, respectively. However, improvement in serum aminotransferases does not correlate with histopathological improvement.

In the literature, several explanations are offered for the discrepancy in the findings of the natural course of NAFLD. First, NAFLD can progress to end-stage liver disease. The problem arises primarily because of the evolving definitions of NAFLD. In recent studies of nonalcoholic steatohepatitis, disease progression was estimated to range from 37 to 43% by follow-up biopsies.[8,21] Conversely, in a study of individuals with steatosis, only one developed fibrosis (1/40) and none developed cirrhosis.[4] Moreover, the type of NAFLD influences disease progression. Second, obesity, insulin resistance and hyperlipidemia are well-known factors that predispose to NAFLD. In the present study, obesity and diabetes mellitus were observed in only 37% and 15% of individuals with NAFLD, respectively. These numbers are slightly lower than those observed in previous studies. This discrepancy can be explained by other factors such as dietary habits and genetic, environmental or other unknown factors which might also influence the natural history of NAFLD.

There are several liver fibrosis markers indicated in the literature, but none has been proven to be superior to the others. Platelet count is a non-invasive indicator to the clinician of liver fibrosis. Although liver biopsy is a strong predictor of liver fibrosis, sampling error may lead to erroneous grading and staging in individuals with liver disease. In fact, liver biopsy is not routinely performed for diagnosis of NAFLD due to the current lack of effective medical therapy.[1] Patient non-compliance prevented us from performing sequential liver biopsies, which is a limitation of the present study. Nevertheless, from baseline to the end of the third year of the follow-up period, there was no significant change in either platelet count or albumin level.

In conclusion, based on the results of the present study, it is reasonable to suggest that an appropriate diet and exercise (walking and jogging) program and management of associated conditions will improve the liver test abnormalities of individuals with NAFLD who receive no pharmacological therapy. However, large prospective longitudinal follow-up studies are needed to gain more information on the natural history of NAFLD and to identify subgroups of NAFLD at risk of progressing to end-stage liver disease and potentially in need of effective treatment.

ACKNOWLEDGMENTS

Ramazan Idilman has been supported by the Turkish Academy of Sciences in the framework of the Young Scientist Award Program (EA-TUBA-GEBIP/2001-1-1, 2004-1-1). The authors thank Kenan S Kose from the Ankara University School of Medicine, Department of Bio-Statistics, for his statistical assistance.

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