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# The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies☆

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***Background/Aims*: The histological course of nonalcoholic fatty liver disease (NAFLD) remains undescribed. Therefore, we examined the liver histology of NAFLD patients who had undergone sequential liver biopsies.**

***Methods*: Data on 103 patients who underwent serial liver biopsies in the absence of effective treatment were reviewed, and biopsies scored in a blind fashion.**

***Results*: Mean interval between biopsies was 3.2 ± 3.0 years (range 0.7–21.3). Fibrosis stage apparently progressed in 37%, remained stable in 34% and regressed in 29%. Severity of steatosis, inflammation, hepatocyte ballooning and Mallory's hyaline improved significantly. Aminotransferases decreased significantly between biopsies, paralleling improvement in steatosis and inflammatory features but not fibrosis stage. The rate of fibrosis change ranged from −2.05 to 1.7 stages/year. By multivariate analysis, diabetes ($P = 0.007$) and low initial fibrosis stage ($P < 0.001$) were associated with higher rate of fibrosis progression, as was higher body mass index ($P = 0.008$) when cirrhotics were excluded.**

***Conclusions*: Fibrosis in NAFLD progresses slowly over time with considerable variability in the rate of changes among patients. Changes of aminotransferases do not parallel changes in fibrosis stage. Diabetic patients with elevated BMI and low fibrosis stage are at risk for higher rates of fibrosis progression.**

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***Keywords*: Fibrosis; Biopsies; Progression; Cirrhosis; Diabetes; Obesity; Inflammation; Ballooning; Mallory's hyaline**

## 1. Introduction

Paralleling the rise in incidence of obesity and diabetes, nonalcoholic fatty liver disease (NAFLD) is emerging as one of the most common causes of chronic liver disease [1–3]. The disease is intimately related to insulin resistance and may progress to steatohepatitis (NASH) and cirrhosis with its complications [4–6]. However, it is uncertain what proportions of patients have progressive disease. In addition, the rate of disease progression or change in liver histological features over time is unknown. Thus, it remains unclear whether some factors predict higher rates of progression.

Fibrosis stage is recognized as the most objective indicator of liver damage and is the best prognostic marker for morbidity and mortality in liver disease of various etiologies. Few studies have investigated the natural history of NAFLD by examining fibrosis stage among patients with paired liver biopsies, with the largest series including only 22 patients [7–10] Due to small numbers, conclusions remain limited. We, therefore, sought to evaluate individuals with well-defined NAFLD who had undergone serial liver biopsies during follow-up.

Our aims were (1) to determine in a large number of patients, the *histological course* of NAFLD by analyzing

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*Abbreviations* BMI, body mass index; HDL, high density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SD, standard deviation.

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the change in liver histology over time; and (2) to examine whether routinely determined clinical, laboratory or histological features predicted fibrosis progression.

## 2. Methods

### 2.1. Patients

One hundred and three patients with NAFLD who had undergone more than one liver biopsy were identified from our master diagnostic index. These patients were seen at the Mayo Clinic Rochester between 1980 and 2003. The study was approved by the Mayo Institutional Review Board and all patients gave written informed consent for participation in medical research. The diagnosis of NAFLD was based upon: (1) steatosis involving at least 10% of hepatocytes on biopsy, (2) ethanol consumption of less than 140 g/week, (3) exclusion of patients with evidence of other liver disease using standard clinical, laboratory and histological criteria. Patients were also excluded if they had a secondary cause of NAFLD [1]. One patient had serial biopsies prior to 1990 without hepatitis C serology. He had no hepatitis C risk factors and his histology was not compatible with hepatitis C infection.

Patients underwent a complete medical history, physical examination and imaging study. Laboratory parameters included aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase, albumin, prothrombin time, platelet count, total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, glucose, iron studies (serum iron, ferritin, total iron binding capacity and transferrin saturation), hepatitis B and C serology, auto-antibodies, serum gamma globulins, ceruloplasmin, $\alpha$1-antitrypsin level and phenotype.

The homeostatic model assessment (HOMA) was calculated using the formula [11]: IR = (insulin × glucose)/22.5; and the quantitative insulin-sensitivity check index (QUICKI) using the formula [12]: QUICKI = 1/[log(insulin) + log(glucose)]. The metabolic syndrome was defined using the criteria proposed by the National Cholesterol Education Program (ATP III), i.e., when at least three of the five following features were present [13] hyperglycemia (fasting blood glucose $\geq$110 mg/dl, or known diabetes mellitus), hypertension (blood pressure $\geq$130/$\geq$85 or under treatment), hypertriglyceridemia ($\geq$150 mg/dl or under pharmacological treatment), low-HDL cholesterol ($<$40 mg/dl for males and $<$50 mg/dl for females), and obesity (BMI $\geq$30 kg/m$^2$). As waist circumference was not measured for most of our patients, we substituted a BMI $\geq$30 kg/m$^2$ to define obesity [14].

Of the 103 patients, a repeat liver biopsy was performed as part of their medical follow-up in 26 patients and as part of a clinical trial in 77. These 77 patients included 50 participants in a placebo-controlled trial (27 randomized to placebo and 23 to ursodiol) [15], and 27 participants in a pilot study of clofibrate or ursodiol [16]. Both liver enzymes and histology were unchanged after a year of treatment with clofibrate [16] whereas changes in liver enzymes and histological features were identical among patients treated with ursodiol or placebo for 2 years [15] In addition, patients who received pharmacotherapy as part of a clinical trial, had the same change in histological features and rate of disease progression as those who did not receive pharmacotherapy (Table 1). Hence, as neither clofibrate nor ursodiol affected the liver condition, patients were pooled together for the purpose of this study. The time elapsed from first to last biopsy was not significantly different ($P$ = 0.2) between the 77 participants in a clinical protocol and the 26 patients who had biopsies as part of the standard evaluation.

### 2.2. Liver histology

Liver biopsy specimens were read under coded identification by a single liver pathologist who was unaware of the patient details or biopsy sequence. Biopsies were routinely stained with hematoxylin–eosin, and Masson's trichrome. All biopsies were a minimum of 15 mm in length and had an appropriate number of portal tracts to make a confident evaluation of histological features and diagnosis [17]. Histological features were interpreted according to the schema outlined by Brunt et al. [18]. Briefly, steatosis was graded on a 3-point scale: grade 1 = steatosis involving $<$33% of hepatocytes, grade 2 = 33–66%, grade 3 $>$66%. Inflammation was graded on a 4-point scale: grade 0 = no or negligible inflammation, grade 1 = mild, grade 2 = moderate, grade 3 = severe. Fibrosis was staged on a 5-point scale: stage 0 = no fibrosis, stage 1 = zone 3 perisinusoidal/perivenular fibrosis, stage 2 = zone 3 and periportal fibrosis, stage 3 = septal/bridging fibrosis, stage 4 = cirrhosis. In addition, the following histological features were scored: hepatocellular ballooning (0 = absent, 1 = mild, 2 = marked); Mallory's hyaline (0 = absent, 1 = occasional, 2 = several); and hepatocellular iron (0–4 + as per Searle). Severity of lobular inflammation, hepatocellular necrosis, portal tract inflammation, pericellular fibrosis, portal fibrosis, and bridging fibrosis were also recorded and scored as described [18].

NASH was defined as either the presence of steatosis plus mixed lobular inflammation plus hepatocellular ballooning, as proposed during the AASLD single topic conference [19], or the presence of steatosis plus any stage of fibrosis. Steatosis plus either lobular inflammation or ballooning (but not both) was termed 'steatosis with nonspecific inflammation', whereas steatosis without lobular inflammation, ballooning or fibrosis was termed 'bland steatosis'.

### 2.3. Statistical analysis

Patients were divided into groups according to change in fibrosis stage between biopsies; either 'progressors' (increased in fibrosis stage), 'stable' (no change) and 'regressors' (decreased in fibrosis stage). Fibrosis rate was

**Table 1**
**Change in liver histology was not different between patients on drug treatment compared to untreated patients**

| | Treated (ursodiol/clofibrate) | Untreated (placebo/clinical biopsy) | $P$ value |
|---|---|---|---|
| $N$ | 50 | 53 | |
| Fibrosis stage | | | |
| Change between biopsies (mean ± SD) | 0.04 ± 1.23 | 0.34 ± 1.43 | 0.9 |
| Regressors/stable/progressors (%) | 30/36/34 | 28/32/40 | 0.8 |
| Steatosis grade | | | |
| Change between biopsies (mean ± SD) | −0.4 ± 0.8 | −0.4 ± 1.0 | 0.9 |
| Regressors/stable/progressors (%) | 50/38/12 | 46/42/12 | 0.9 |
| Inflammation grade | | | |
| Change between biopsies (mean ± SD) | −0.2 ± 0.7 | −0.1 ± 0.7 | 0.5 |
| Regressors/stable/progressors (%) | 28/60/12 | 23/62/15 | 0.8 |
| Ballooning grade | | | |
| Change between biopsies (mean ± SD) | −0.3 ± 0.6 | −0.1 ± 0.6 | 0.2 |
| Regressors/stable/progressors (%) | 33/63/4 | 25/61/14 | 0.2 |

The proportion of patients who regressed (42 vs. 35%, $P$ = 0.6), remained stable (23 vs. 38%, $P$ = 0.2), or progressed (35 vs. 27%, $P$ = 0.5) in fibrosis stage was not significantly different between patients biopsied for clinical reasons ($n$ = 26) and patients participating in clinical trials ($n$ = 77).

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