Fibrosis Progression in Nonalcoholic Fatty Liver Versus Nonalcoholic Steatohepatitis: A Systematic Review and Meta-Analysis of Paired-Biopsy Studies

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BACKGROUND & AIMS: **Little is known about differences in rates of fibrosis progression between patients with nonalcoholic fatty liver (NAFL) vs nonalcoholic steatohepatitis (NASH). We conducted a systematic review and meta-analysis of all studies that assessed paired liver biopsy specimens to estimate the rates of fibrosis progression in patients with nonalcoholic fatty liver disease (NAFLD) including NAFL and NASH.**

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METHODS: **Through a systematic search of multiple databases and author contact, up to June 2013, we identified studies of adults with NAFLD that collected paired liver biopsy specimens at least 1 year apart. From these, we calculated a pooled-weighted annual fibrosis progression rate (number of stages changed between the 2 biopsy samples) with 95% confidence intervals (CIs), and identified clinical risk factors associated with progression.**

RESULTS: **We identified 11 cohort studies including 411 patients with biopsy-proven NAFLD (150 with NAFL and 261 with NASH). At baseline, the distribution of fibrosis for stages 0, 1, 2, 3, and 4 was 35.8%, 32.5%, 16.7%, 9.3%, and 5.7%, respectively. Over 2145.5 person-years of follow-up evaluation, 33.6% had fibrosis progression, 43.1% had stable fibrosis, and 22.3% had an improvement in fibrosis stage. The annual fibrosis progression rate in patients with NAFL who had stage 0 fibrosis at baseline was 0.07 stages (95% CI, 0.02–0.11 stages), compared with 0.14 stages in patients with NASH (95% CI, 0.07–0.21 stages). These findings correspond to 1 stage of progression over 14.3 years for patients with NAFL (95% CI, 9.1–50.0 y) and 7.1 years for patients with NASH (95% CI, 4.8–14.3 y).**

CONCLUSIONS: **Based on a meta-analysis of studies of paired liver biopsy studies, liver fibrosis progresses in patients with NAFL and NASH.**

Keywords: Fibrosis; Cirrhosis; Nonalcoholic Steatohepatitis; Fatty Liver; Natural History.

Q9 Q10 Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the United States.[1–6] It is defined as the presence of hepatic steatosis in at least 5% of hepatocytes on liver biopsy examination in individuals who consume little or no alcohol, after exclusion of other causes of liver disease.[2] NAFLD can be classified broadly into 2 subtypes: nonalcoholic fatty liver (NAFL), which generally is considered to be benign with negligible risk of progression to advanced fibrosis and liver-related mortality, and nonalcoholic steatohepatitis (NASH), which generally is considered to be progressive with a substantial risk of progression to advanced fibrosis and liver-related mortality.

Several longitudinal cohort studies have provided novel insight into the natural history of liver disease in patients with NAFLD.[5,7–10] Despite these advances, the fibrosis progression rate in NAFLD remains to be quantified and is poorly understood.[9] Observational studies with paired liver biopsy specimens in patients with NAFLD, although prone to ascertainment and selection bias, offer some of the best available natural history data on rate and risk factors associated with progressive

Abbreviations used in this paper: **ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; FPR, fibrosis progression rate; I^2, inconsistency index; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; RCT, randomized controlled trial.**

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fibrosis. Based on a pooled analysis of 10 studies including 221 patients with NASH alone, Argo et al[11] estimated that 37.6% of patients have progressive fibrosis over 5.3 years; the mean rate of progression for the entire cohort was 0.03 stages per year. However, in this study, patients with NAFL were excluded. Although previous studies have suggested that NAFL may be benign, and does not lead to progressive fibrosis,[12] emerging data suggest that fibrosis progression may be seen not only in NASH, but also in NAFL.[13]

There are limited data on the differences in the fibrosis progression rate in patients with NAFL vs NASH. Therefore, we aimed to perform a systematic review and meta-analysis of studies in patients with biopsy-proven NAFL and NASH who underwent paired liver biopsies at least 1 year apart and to quantify differences in fibrosis progression in patients with NAFL vs NASH.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, and the process followed an a priori established protocol.[14]

Selection Criteria

Studies included in the meta-analysis met the following inclusion criteria: (1) cohort studies and placebo-controlled randomized controlled trials (RCTs), (2) included adult patients (>18 y) with a histologic diagnosis of NAFLD at any stage of baseline fibrosis, (3) repeat liver biopsy was performed at least 1 year apart, and (4) contained sufficient information to allow estimation of the fibrosis progression rate (FPR) by each baseline fibrosis stage.

We excluded the following studies: (1) the diagnosis of NAFLD and/or degree of fibrosis (either baseline or during follow-up evaluation) was established using noninvasive means; (2) participants in the active arm of a clinical trial (ie, patients randomized to potentially disease-modifying active intervention for NAFLD); (3) cross-sectional studies; (4) studies in which the time difference between paired biopsies was fewer than 12 months; and (5) studies in which there were insufficient data to allow estimation of FPR (ie, insufficient data on person-years of follow-up evaluation, or mean/median duration of follow-up period/time between 2 biopsies, or only contained information on mean change in fibrosis stage for the entire cohort). In case of multiple studies from the same cohort, we included data from the most recent comprehensive report.

Search Strategy

We conducted a comprehensive search of multiple electronic databases from 1985 to June 2013 containing data on adults, with no language restrictions. The databases included Ovid Medline In-Process and Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Web of Science, and Scopus. The search strategy was designed and conducted by an experienced medical librarian (L.J.P.) with input from the study's investigators (S.S., R.L.), using controlled vocabulary supplemented with keywords, for cohort studies and placebo-controlled RCTs of NAFLD. The details of the search strategy are included in the Supplementary Table 1. The title and abstract of studies identified in the search were reviewed by 2 authors independently (S.S., A.M.A.) to exclude studies that did not address the research question of interest, based on prespecified inclusion and exclusion criteria (see earlier). The full text of the remaining articles was examined to determine whether it contained relevant information. Next, the bibliographies of the selected articles and review articles on the topic were searched manually for additional studies. Third, a manual search of conference proceedings of major gastroenterology and hepatology conferences (The Liver Meeting, organized by the American Association for the Study of the Liver; The International Liver Congress, organized by the European Association for the Study of the Liver; and Digestive Diseases Week, organized in conjunction with the American Gastroenterological Association) between 2008 and 2012 was conducted to identify additional studies published only in abstract form. Supplementary Figure 1 shows the schematic diagram of study selection.

Data Abstraction

Data on the following study- and patient-related characteristics, as well as histologic classification and risk factors associated with progressive fibrosis, were abstracted onto a standardized form: (1) study characteristics: primary author, time period of study/year of publication, and country of the population studied; (2) patient characteristics: total number of patients with NAFLD who underwent paired biopsies, demographic and clinical characteristics at time of first biopsy (age, sex, body mass index or obesity, presence of diabetes, hypertension, metabolic syndrome), baseline laboratory characteristics (aspartate aminotransferase [AST], alanine aminotransferase [ALT], AST/ALT ratio, platelet count, ferritin, and measure of insulin resistance, using the homeostasis model of assessment–insulin resistance), and treatment undertaken by participants, including lifestyle changes and potentially disease-modifying therapy (vitamin E, thiazolidinediones, metformin); (3) histologic characteristics: proportion of patients with NASH and NAFL separately, baseline and follow-up fibrosis stage for individual patients in the study, time interval between paired biopsies to allow calculation of FPR (person-years, mean or median follow-up period of cohort, time