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Relationship of steatosis grade and zonal location to histological features of steatohepatitis in adult patients with non-alcoholic fatty liver disease☆

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***Background/Aims*: The relationship between severity and zonal location of steatosis and the presence of steatohepatitis and various histological features that define NASH has not been formally studied.**

***Methods*: We conducted a study to examine the relationship of severity and zonal location of steatosis to the presence of NASH and to other histological features that define NASH in adult patients with NAFLD. Steatosis was graded as mild, moderate or severe. We examined the relationship between severity and zonal location of steatosis and the following: lobular inflammation, presence of ballooning, Mallory bodies, fibrosis score, and definite steatohepatitis.**

***Results*: Mild, moderate and severe steatosis was present in 44%, 31% and 25% of biopsies, respectively. Definite steatohepatitis was present in 59% and advanced fibrosis in 29% of liver biopsies. Increasing levels of steatosis severity were positively associated with lobular inflammation ($p < 0.0001$), zone 3 fibrosis ($p < 0.001$), and definite steatohepatitis ($p = 0.02$), but were unrelated to ballooning, Mallory bodies, or advanced fibrosis. As compared to zone 3 steatosis, pan-acinar steatosis was more often associated with ballooning, Mallory bodies, and advanced fibrosis.**

***Conclusions*: Patients with severe steatosis are more likely to have steatohepatitis. More studies are needed to confirm this observation and to explore its significance.**

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***Keywords*: Non-alcoholic fatty liver disease; NASH; NASH CRN; NAS; Steatosis**

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver disease with hepatic histology ranging from simple steatosis without significant necroinflammation to varying degrees of steatohepatitis and fibrosis [1]. Studies have shown that simple steatosis is largely benign whereas steatohepatitis can progress to cirrhosis and liver failure [1,2]. The pathogenesis of non-alcoholic steatohepatitis is not fully understood, but the working hypothesis suggests that a first hit leads to the development of steatosis and

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† A list of members of the Non-alcoholic Steatohepatitis Clinical Research Network is located in Appendix.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NASH CRN, NASH Clinical Research Network.

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is followed by a second hit that causes inflammation, ballooning, and fibrosis (steatohepatitis) [3]. Although hepatic steatosis is a key component of steatohepatitis, its precise relationship with other elements that define NASH (i.e., inflammation, ballooning, and fibrosis) and the presence of NASH are not clear. The histological definition of steatohepatitis does not require a particular amount or location of steatosis and we observed a wide range of steatosis in unequivocal cases of steatohepatitis. From a practical point of view, it is not known if patients with greater amounts of steatosis are more likely to have steatohepatitis than those with mild steatosis. Anecdotally, we have not observed a consistent relationship between the degree of hepatic steatosis and the presence of steatohepatitis, nor is steatosis a "required" element for alcoholic steatohepatitis. Therefore, we conducted a histology-based study to examine the relationships between the degree and zonal location of hepatic steatosis and various histological features that define and accompany NASH.

2. Methods

This study was conducted on the available liver biopsies of adult patients (age $\geqslant$ 18 years at time of biopsy) with definite NAFLD who were enrolled in the NAFLD Database Study conducted by the NASH Clinical Research Network (NASH CRN). The NAFLD Database Study is an observational study of patients with definite NAFLD, suspected NAFLD, and cryptogenic cirrhosis. Patients with steatosis involving $\geqslant$5% hepatic parenchyma on liver biopsy with no significant alcohol consumption or other coexisting aetiologies (e.g., autoimmune liver disease, hemochromatosis, PBC, etc.) were defined as having NAFLD. Significant alcohol consumption was defined as >14 drinks/week in men or >7 drinks/week in women on average within the preceding 2 years. The details of alcohol consumption were obtained by physician interviews and by administration of Skinner Lifetime Drinking History questionnaires. The Institutional Review Boards at each Clinical Center and the Data Coordinating Center reviewed and approved the NAFLD Database Study protocol and informed consents.

All liver biopsies were reviewed locally by the site pathologist and rescored centrally by the Pathology Committee according to the recently published NASH CRN scoring system [4]. The Pathology Committee consisted of a pathologist from each of the Clinical Centers and one pathologist from the National Institutes of Health. H&E, Masson's trichrome stains, and modified Perl's Prussian blue iron stains were evaluated for each case. Steatosis was graded as mild (5–33%), moderate (>33–66%), or severe (>66%) according to the amount of surface area of parenchyma visually determined to be involved by steatosis. The steatosis grading was one of the more reproducible aspects of the scoring system [4]. The assessment of steatosis grading was made at low magnification (at most 10× and usually at 4×) and it considered only the portion of the biopsy occupied by the hepatocytes (ignoring large bands of fibrosis, portal areas, vein profiles etc.). In many cases, the steatosis occupied contiguous areas of the biopsy in zonal distributions, rather than being scattered randomly on an individual cell basis. The zonal distribution of steatosis was categorized into four patterns: zone 3 predominant, zone 1 predominant, pan-acinar or azonal. The presence of definite steatohepatitis was determined by the consensus at central review by the study pathologists based on pattern recognition rather than aggregate of individual components of the NASH CRN scoring system.

2.1. Statistical methods

We examined the relationship between steatosis grade and zonal location and other histological features, namely lobular inflammation (grade $\geqslant$2 vs. <2), ballooning (few/many vs. none), Mallory bodies (rare/absent vs. many), zone 3 fibrosis (mild or moderate zone 3 peri-sinusoidal fibrosis, or zone 3 and periportal fibrosis vs. no fibrosis), bridging fibrosis or cirrhosis (presence vs. no fibrosis), isolated portal or periportal fibrosis (presence vs. no fibrosis), and definite steatohepatitis (presence vs. absence). Analyses of steatosis zonal location were adjusted for steatosis grade. Multiple logistic regression analyses were used to derive p-values presented in Tables 2 and 3. We included steatosis grade as a variable in the logistic regression models that assessed the relationship between zonality of steatosis and different histological variables (p-values presented in Table 3). Odds ratios, confidence intervals, and p-values for trends in proportion were calculated using Stata (release 9.1, Stata Corp, College Station, TX). p-values were determined by the Cochran–Armitage trend test, to test for change in histological features with increasing severity of steatosis, and a two-sided p-value < 0.05 was considered statistically significant.

3. Results

Seven hundred and seventy-five adults were enrolled in the NAFLD Database Study between October 2004 and December 2007. Our study group consisted of 545 adult patients with liver biopsies reviewed centrally by the Pathology Committee. The demographics of the patients were: mean age 48 ± 11.5 years, 62% females, 73% obese (defined as BMI $\geqslant$30), and 30% diabetic. Patient demographics and selected histological features of study liver biopsies are shown in Table 1.

There was a statistically significant relationship between the steatosis grade and lobular inflammation, zone 3 fibrosis, and the diagnosis of definite steatohepatitis (Table 2). Compared to liver biopsies with mild steatosis, lobular inflammation grade >2 was significantly more frequent in liver biopsies with moderate steatosis (OR = 1.9; 95% CI: 1.2–2.8) and even more frequent in liver biopsies with severe steatosis (OR = 3.0; 95% CI: 1.9–4.7) ($p < 0.0001$). The odds of zone 3 fibrosis were 1.8 times greater in liver biopsies with moderate steatosis (95% CI: 1.1–3.2) and 2.7 times greater in biopsies with severe steatosis (95% CI 1.5–4.9), compared to those with mild steatosis ($p < 0.001$). Similarly, compared to liver biopsies with mild steatosis, the odds of having definite steatohepatitis were 1.7 times greater among those with moderate steatosis (95% CI: 1.1–2.4), and 1.6 times greater among those with severe steatosis (95% CI: 1.0–2.5) ($p = 0.02$).

There existed no statistically significant relationship between the severity of steatosis and ballooning, portal fibrosis, or Mallory bodies (Table 2). Interestingly, there was a trend towards less steatosis at more advanced degrees of fibrosis, but this did not reach statistical significance ($p = 0.13$) (Table 2).

The general zonal location of the steatosis was also analyzed against the same set of histologic features (Table 3). Only 3 patients in this cohort had zone 1

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