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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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Abstract

Background—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.

Aim and 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.

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

Keywords

Non-alcoholic Fatty Liver Disease; NASH; NASH CRN

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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 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 is 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.

Methods

This study was conducted on the available liver biopsies of adult patients (age ≥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 ≥ 5% hepatic parenchyma on liver biopsy with no significant alcohol consumption or other co-existing etiologies (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 two 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 10x and usually at 4x) 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.

Statistical Methods

We examined the relationship between steatosis grade and zonal location and other histological features, namely lobular inflammation (grade ≥ 2 vs. < 2), ballooning (few/many vs. none), Mallory bodies (rare/absent vs. many), zone 3 fibrosis (mild or moderate zone 3 perisinusoidal 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.

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 ≥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 was 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 was 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 predominant steatosis and so those results were not analyzed further. A zone 3 predominant distribution of steatosis was the most common pattern, being present in 37.2% of biopsies and this was used as our baseline for comparison. Moderate to severe steatosis was more likely to be pan-acinar and less likely to be azonal in distribution than mild steatosis. Pan-acinar steatosis was more likely to have ballooning hepatocellular injury, Mallory bodies, advanced fibrosis, and a diagnosis of definite

steatohepatitis than zone 3 steatosis. Steatosis in an azonal distribution was significantly more likely to be associated with ballooning injury, Mallory bodies and advanced fibrosis. Isolated periportal fibrosis was seen equally often with the different distributions of steatosis.

Discussion

In this study we found a statistically significant relationship between severity of steatosis and lobular inflammation, zone 3 fibrosis, and the diagnosis of definite steatohepatitis. This is a clinically relevant observation because imaging tests (ultrasound, CT, and MRI) often report the severity of steatosis, and until now the significance of severity of steatosis has not been systematically investigated. As it was recently demonstrated that degree of steatosis quantified by imaging correlates significantly with histological grading of steatosis (5,6), we propose that radiologically-evident severe steatosis should be explored as another variable increasing the risk for the presence of NASH and zone 3 fibrosis in patients with NAFLD. Previous studies have shown that diabetes, older age, and morbid obesity increase the likelihood of NASH in patients with NAFLD (7,8). Future studies should evaluate the role of steatosis severity (as assessed by imaging) in non-invasive prediction of NASH in patients with NAFLD.

Although moderate and severe degrees of steatosis were more often associated with definite steatohepatitis, there was no clear association between the degree of steatosis and the more prominent degree of ballooning injury or with Mallory bodies, both of which are characteristic parts of the pattern of injury of steatohepatitis (9). This may partly reflect the way that we chose to analyze the data, combining the mild degree of ballooning injury (NASH-CRN score of 1) with the absence of ballooning. A mild degree of ballooning would be sufficient in the presence of other features to make a definite diagnosis of steatohepatitis.

The zonal distribution of steatosis has not, to our knowledge, been systematically studied in NAFLD. We categorized the steatosis pattern into one of four categories: zone 3 predominant, zone 1 predominant, pan-acinar and azonal. The zone 1 pattern was very rare in this cohort of adults, although it is more common in our pediatric biopsies (10). Of the remaining three patterns, the zone 3 predominant was the most common. Operationally this was defined as a pattern of steatosis that spared zone 1, since many biopsies would show ballooning injury in zone 3 surrounded by a cuff of steatosis that was more prominent in zone 2 than zone 3. Pan-acinar distribution was used when the steatosis seemed to involve all zones of the liver equally, with generally equal involvement from one part of the biopsy to another. Azonal distribution was used when the pattern of steatosis could not be put into one of the other categories or when the architecture of the liver was so distorted by fibrosis and regeneration that a clear zonal distribution could not be defined. This latter bias was demonstrated by the 17 fold likelihood of observing advanced fibrosis when the steatosis was azonal. Biopsies with pan-acinar steatosis were more likely to have ballooning injury, Mallory bodies, and advance fibrosis than biopsies with zone 3 steatosis. The azonal pattern of steatosis was also more likely to show ballooning injury and Mallory bodies than zone 3 steatosis, but there was no increased likelihood for the early degree of fibrosis, either periportal or in zone 3.

The two-hit hypothesis of steatohepatitis suggests that the development of steatosis is a necessary precursor to the development of steatohepatitis. Since most pathologists would be reluctant to diagnose steatohepatitis in non-alcoholics in the complete absence of steatosis, it is difficult to challenge the necessity of this feature. This study would suggest that there is some relationship between the severity and location of steatosis and other features of steatohepatitis. In particular, peri-sinusoidal zone 3 fibrosis, which is the earliest degree of fibrosis, is highly associated with the severity of steatosis. The diagnosis of definite steatohepatitis is observed about 1.6–1.7 times more often in biopsies with moderate to severe degrees of steatosis. These effects are modest but do suggest that when there is more “substrate”

for the second hit to act upon that there may be increased likelihood of progression to steatohepatitis and fibrosis.

Isolated periportal fibrosis has been identified in a cohort of bariatric surgery patients as a feature of fibrosis progression in NAFLD (11). The incidence of this feature in our cohort is very low, only 5% of all the biopsies evaluated. Unlike isolated zone 3 perisinusoidal fibrosis, it seemed to be unrelated to steatosis severity or zonation. Our data would suggest that isolated periportal fibrosis may be related less to fatty liver disease itself than other findings that may be peculiar to bariatric surgery patients.

As this is a cross-sectional study, it is unable to address if patients with severe steatosis have a faster rate of progression to full blown steatohepatitis than those with milder steatosis. However, this may not be relevant because previous studies have shown that patients with simple steatosis rarely progresses to more advanced forms of NAFLD such as cirrhosis (1,2). It is also unknown whether the degree of steatosis affects progression within the context of established steatohepatitis. The issues of how the severity of individual features such as inflammation, steatosis, and balloon might affect the rate of progression will require large scale longitudinal studies.

If other studies confirm significant correlation between (a) steatosis severity by imaging and steatosis grade by histology (5,6) and (b) steatosis grade by histology and prevalence of steatohepatitis, then one potentially could consider the degree of hepatic steatosis (as quantified by imaging) as a surrogate therapeutic endpoint in pilot studies treating NASH as well as a surrogate safety endpoint in drug development. Many pharmaceutical companies developing compounds to treat metabolic conditions such as diabetes, obesity, and hyperlipidemia are routinely performing MR spectroscopy of the liver to monitor hepatic steatosis.

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Abbreviations

NAFLD
: Non-alcoholic Fatty Liver Disease

NASH
: Non-alcoholic Steatohepatitis

NASH CRN
: NASH Clinical Research Network

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Appendix: Members of the Non-alcoholic Steatohepatitis Clinical Research Network

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Table 1

Baseline patient characteristics and selected histological features of study liver biopsies (N=545)

Patient characteristics	
Age at biopsy, years, mean±SD	47.7 ± 11.5
Female, N (%)	339 (62%)
Race, N (%) Caucasian	433 (80%)
BMI (kg/m^2), mean±SD	34.3 ± 6.4
Diabetic, N (%)	163 (30%)
Histologic features, N (%)	
Steatosis Severity	
Mild	239 (44%)
Moderate	170 (31%)
Severe	136 (25%)
Steatosis Location	
Zone 3 (Central)	203 (38%)
Zone 1 (periportal)	3 (<1%)
Azonal	154 (28%)
Pan-acinar	185 (34%)
Lobular Inflammation	
Grade < 2	266 (49%)
Grade ≥ 2	279 (51%)
Ballooning	
Present	365 (67%)
Absent	180 (33%)
Mallory Bodies	
None/rare	379 (70%)
Many	166 (30%)
Sinusoidal Fibrosis	228 (42%)
Isolated Portal Fibrosis	26 (5%)
Bridging fibrosis or cirrhosis (%)	160 (29%)
Definite NASH (%)	319 (59%)

Table 2

Relationship between degree of hepatic steatosis and other histological features that define or accompany NASH

Histology feature	Steatosis Severity			P-value for trend
	Mild (N=239) N (%)	Moderate (N=170) N (%)	Severe (N=136) N (%)	
Lobular Inflammation				
Grade ≥2	95 (39.8%)	94 (55.3%)	90 (66.2%)	
Grade <2	144 (60.3%)	76 (44.7%)	46 (33.8%)	
Odds ratio (95% CI)	1.0	1.9 (1.2–2.8)	3.0 (1.9–4.7)	<0.0001
Ballooning				
Many	150 (62.8%)	121 (71.2%)	94 (69.1%)	
None/Few	89 (37.2%)	49 (28.8%)	42 (30.9%)	
Odds ratio (95% CI)	1.0	1.5 (0.9–2.3)	1.3 (0.8–2.1)	0.14
Mallory Bodies				
Many	83 (34.7%)	44 (25.9%)	39 (28.7%)	
Rare/absent	156 (65.3%)	126 (74.1%)	97 (71.3%)	
Odds ratio (95% CI)	1.0	0.66 (0.4–1.0)	0.76 (0.5–1.2)	0.15
Zone 3 Fibrosis				
Present	69 (53.1%)	77 (67.5%)	82 (75.2%)	
No fibrosis	61 (46.9%)	37 (32.5%)	27 (24.8%)	
Odds ratio (95% CI)	1.0	1.8 (1.1–3.2)	2.7 (1.5–4.9)	<0.001
Isolated Portal Fibrosis				
Present	14 (18.7%)	10 (21.3%)	2 (6.9%)	
No fibrosis	61 (81.3%)	37 (78.7%)	27 (93.1%)	
Odds ratio (95% CI)	1.0	1.2 (0.4–3.2)	0.3 (0.03–1.6)	0.25
Bridging fibrosis or cirrhosis				
Present	91 (59.9%)	44 (54.3%)	25 (48.1%)	
No fibrosis	61 (40.1%)	37 (45.7%)	27 (51.9%)	
Odds ratio (95% CI)	1.0	0.80 (0.5–1.4)	0.62 (0.3–1.2)	0.13
Definite NASH diagnosis				
Yes	124 (51.9%)	109 (64.1%)	86 (63.2%)	
No	115 (48.1%)	61 (35.9%)	50 (36.8%)	
Odds ratio (95% CI)	1.0	1.7 (1.1–2.5)	1.6 (1.0–2.5)	0.02

Table 3

Relationship between steatosis location and other histological features that define or accompany NASH*

Histology feature	Steatosis Location†			P-value: Azonal vs Zone 3	P-value: Panacinar vs. Zone 3
	Zone 3 - Central (N=203) N (%)	Azonal (N=154) N (%)	Panacinar (N=185) N (%)		
Lobular Inflammation					
Grade ≥2	100 (49.3%)	61 (39.6%)	117 (63.2%)		
Grade <2	103 (50.7%)	93 (60.4%)	68 (36.8%)		
Odds ratio (95% CI)	1.0	0.9 (0.6–1.2)	1.2 (0.9–1.7)	0.48	0.20
Ballooning					
Many	119 (58.6%)	115 (74.7%)	130 (70.3%)		
None/Few	84 (41.4%)	39 (25.3%)	55 (29.7%)		
Odds ratio (95% CI)	1.0	1.8 (1.4–2.4)	1.4 (1.1–1.8)	<0.0001	0.006
Mallory Bodies					
Many	43 (21.2%)	61 (39.6%)	62 (33.5%)		
Rare/absent	160 (78.8%)	93 (60.4%)	123 (66.5%)		
Odds ratio (95% CI)	1.0	2.1 (1.3–3.5)	2.4 (1.9–3.2)	0.003	0.009
Zone 3 Fibrosis					
Present	95 (56.2%)	36 (67.9%)	97 (74.6%)		
No fibrosis	74 (43.8%)	17 (32.1%)	33 (25.4%)		
Odds ratio (95% CI)	1.0	2.0 (1.0–3.3)	1.7 (1.0–2.9)	0.05	0.05
Isolated Portal Fibrosis					
Present	10 (11.9%)	7 (29.2%)	7 (17.5%)		
No fibrosis	74 (88.1%)	17 (70.8%)	33 (82.5%)		
Odds ratio (95% CI)	1.0	3.0 (1.0–9.2)	1.7 (0.6–5.0)	0.05	0.32
Bridging fibrosis or cirrhosis					
Present	22 (22.9%)	92 (84.4%)	46 (58.2%)		
No fibrosis	74 (77.1%)	17 (15.6%)	33 (41.8%)		
Odds ratio (95% CI)	1.0	16.7 (8.2–34.0)	4.4 (2.2–8.9)	<0.0001	<0.0001
Definite NASH diagnosis					
Yes	105 (51.7%)	99 (64.3%)	115 (62.2%)		
No	98 (48.3%)	55 (35.7%)	70 (37.8%)		
Odds ratio (95% CI)	1.0	2.2 (1.4–3.5)	2.4 (0.8–2.0)	0.001	0.24

* Odds ratios and p-values adjusted for steatosis severity.

† The 3 patients with Zone 1 (periportal) distribution of steatosis were dropped from the analysis.