Non-Alcoholic Fatty Liver Disease
An Update

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Non-Alcoholic Fatty Liver Disease

First described in 1980


Subsequently recognition of metabolic syndrome as major risk factor

Until recently - increasingly common indication for liver biopsy

Strategies to avoid liver biopsy (non-invasive methods)

- Blood tests (single or in combination)
- Imaging studies (e.g. Ultrasound, MRI, transient elastography)
  - Assess various components of fatty liver disease e.g. steatosis, apoptosis, inflammation, fibrosis

Liver biopsy still regarded as “gold standard” for establishing diagnosis of NASH and assessing disease severity.
NAFLD – Rising Prevalence

• Overall prevalence in Europe & US estimated at 20-30%
  • Most cases in general population have simple steatosis
  • Prevalence of NASH estimated at 3-5%

• In tertiary care centres using liver biopsy 40-60% of cases of NAFLD have features of NASH

• Now the commonest cause (40%) of newly diagnosed chronic liver disease

• Predicted to be the commonest cause of cirrhosis (and liver-related mortality)

• Only 6% of deaths in patients with NAFLD are from liver disease (versus 25% from CVS disease and 24% from neoplasia)
NAFLD and HCC
(Baffy 2012)

HCC as a complication of NASH - associated cirrhosis
• Prevalence 0.35%-4.2%/year (lower than HCV-cirrhosis)

HCC arising in non-cirrhotic NAFLD
• Increasing numbers of cases reported
  — 40-65% of HCC complicating NAFLD occurred in non-cirrhotic liver
    (Paradis 2009, Yasui 2011, Duan 2012)
→ Metabolic syndrome as risk factor for malignancy

• Most have pre-cirrhotic fibrosis (with steatohepatitis)
• Some cases occur in patients with simple steatosis
• A few arise from adenomas (inflammatory type) - (Paradis 2009)
Steatohepatitic features (fat, ballooning, Mallory-Denk bodies, inflammation, fibrosis) involving at least 50% of tumour (Salamao 2012)

- Present in 10/21 (48%) NASH patients (vs 5/21 (24%) ALD & 1/76 (1.3%) other diseases)
- Associated with features of steatohepatitis in non-neoplastic liver
Current Role of Liver Biopsy

The Diagnosis and Management of Non-alcoholic Fatty Liver Disease: Practice Guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology

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GASTROENTEROLOGY 2012;142:1592–1609

When to Obtain a Liver Biopsy in Patients with NAFLD?

Liver biopsy remains the gold standard for characterizing liver histology in patients with NAFLD. However, it is expensive and carries some morbidity and very rare mortality risk. Thus, it should be performed in those who would benefit the most from diagnostic, therapeutic guidance, and prognostic perspectives.
Recommendations

13. Liver biopsy should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis. (Strength – 1, Evidence - B)

14. The presence of metabolic syndrome and the NAFLD Fibrosis Score may be used for identifying patients who are at risk for steatohepatitis and advanced fibrosis. (Strength – 1, Evidence - B)

15. Liver biopsy should be considered in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver diseases cannot be excluded without a liver biopsy. (Strength – 1, Evidence - B)
Indications for Liver Biopsy
(Birmingham Liver Unit)

1. Cases where non-invasive investigations (NAFLD Fibrosis Score, Fibroscan) have produced an “indeterminate score” for fibrosis (or an unexpected score)

2. Cases where there are concerns about an additional aetiology for liver disease
Histological Assessments in NAFLD

1. Establishing the Diagnosis

2. Assessing Disease Severity
   - “Simple” Steatosis vs Steatohepatitis
   - Portal tract changes in NAFLD
   - Grading & Staging

3. Aetiological Considerations
   - NAFLD vs Other Causes of FLD (mainly alcohol)
   - Interaction with other diseases
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Histological Definition of Fatty Liver Disease

- Fatty change involving > 5% of hepatocytes (or parenchymal area)
- Mainly macrovesicular
- Predominantly perivenular
Hepatic Steatosis - Classification According to Droplet Size

Fatty liver disease (alcoholic and non-alcoholic) mainly macrovesicular

Large droplets begin as small ones – mixed patterns of droplet size common

“Pure” microvesicular steatosis – different causes & consequences

• Disorders of mitochondrial beta -oxidation of fatty acids (“mitochondrial hepatopathies”)
• Serious metabolic disturbances, including acute liver failure (e.g. Reye’s syndrome, acute fatty liver of pregnancy, anti-retroviral drug toxicity)
Fat droplets that are neither large nor very small. How should these be classified?

- Probably best regarded as a variant of macrovesicular steatosis
- Macrovesicular steatosis can be sub-classified into small-, medium- or large droplet forms (“mediovesicular steatosis” – Brunt 2012)
Assessing Fat Droplet Size in Fatty Liver Disease - Clinical Relevance

**Alcoholic Liver Disease** (Teli 1995)
- In patients with “pure” alcoholic fatty liver, cases with mixed droplet size had higher risk of progression to cirrhosis than those with macrovesicular steatosis only (28% vs 3%)

**Recent studies in NAFLD** (Soderberg 2011, Tandra 2011)
- “True” microvesicular steatosis occurred in 102/1022 (10%) of biopsies from patients with NAFLD (NASH Clinical Research Study - Tandra 2011)
- Presence associated with more severe disease (more ballooning, & inflammation, higher NAS score, more severe fibrosis) and with presence of megamitochondria
- Functional significance in mediating disease progression uncertain
Methods for Assessing Presence and Severity of Steatosis

Standard Approach for H&E stained sections (Brunt 1999, Kleiner 2005)

<table>
<thead>
<tr>
<th>% involvement</th>
<th>Severity</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>5-33</td>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td>33-66</td>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td>&gt;66</td>
<td>Severe</td>
<td>3</td>
</tr>
</tbody>
</table>

- Good intra- and inter-observer reproducibility for overall grade
- Reproducibility less good for assessing finer scales of steatosis severity
- Poor correlation with fat content measured biochemically
Methods for Assessing Presence and Severity of Steatosis
Alternative Approaches

**Tissue – Based** (El Badry 2009, Levene & Goldin 2012)
- Digital image analysis (H&E or Oil Red O stained sections)
  - More accurate for quantifying steatosis
  - Correlates better with biochemical measurement of triglyceride

**Radiological - MRI & MRS** (Raptis 2012, Urdzik 2012)
- MRI assessment correlates better with chemical fat content than DIA or standard pathological assessment

**BUT**
- MRI-based assessment found to be inaccurate in another study (Levene 2012)
- DIA no predictive value over conventional histological grading (Turlin 2009)
Histological Assessments in NAFLD

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3. Aetiological Considerations
   - NAFLD vs Other Causes of FLD (mainly alcohol)
   - Interaction with other diseases
Steatohepatitis (versus simple fatty change)

1. **Presence of steatohepatitis indicates more severe disease**
   - less likely to be reversible
   - more likely to progress to fibrosis or cirrhosis

2. **Non-invasive techniques less reliable than liver biopsy in distinguishing simple steatosis from steatohepatitis**
Steatohepatitis - Histological Features
(mainly perivenular distribution)

Hepatocellular injury
- fatty change
- ballooning
- Mallory-Denk bodies
- apoptosis/necrosis

Inflammation
- neutrophil polymorphs
- other cells (e.g., T lymphocytes)

Fibrosis
- perisinusoidal
- pericellular
Endpoints and Clinical Trial Design for Nonalcoholic Steatohepatitis

Arun J. Sanyal,1 Elizabeth M. Brunt,2 David E. Kleiner,3 Kris V. Kowdley,4 Naga Chalasani,5 Joel E. Lavine,6 Vlad Ratziu,7 and Arthur McCullough8
(Hepatology 2011;54:344-353)

(Based on AASLD Research Workshop, 2009)

Steatohepatitis

The minimal criteria for the diagnosis of steatohepatitis include the presence of >5% macrovesicular steatosis, inflammation, and liver cell ballooning, typically with a predominantly centrilobular (acinar zone 3) distribution in adults.

Similar to criteria previously proposed by Brunt (1999) and Neuschwander-Tetri (2003)
Histopathological Diagnosis of NASH
(Brunt 1999, Neuschwander-Tetri 2003, Sanyal 2011)

- > 5% steatosis, mainly macrovesicular
- lobular inflammation (polymorphs as well as mononuclear cells)
- hepatocyte ballooning, most apparent near steatotic cells

Problems With Applying AASLD Diagnostic Criteria for NASH

1. Inflammation
   - May be minimal/absent
   - Neutrophils rarely prominent, may not be present
→ Enlarged Kupffer cells (PAS-D+, CD 68+) may be useful (but non-specific) marker of previous inflammatory damage

2. Ballooning
   - What defines a ballooned hepatocyte - size, shape, cytoplasmic “clarification”? (poor observer reproducibility)
→ Use of immunostains to demonstrate small amounts of Mallory’s hyaline
→ Use of connective tissue stains (HVG, Trichrome) to demonstrate foci of pericellular/perisinusoidal fibrosis
Mallory-Denk Bodies - Immunohistochemical Demonstration
(from Denk 2006, Zatloukal 2007)

Co-staining for keratins 8/18 & ubiquitin improves detection of hepatocyte injury in NAFLD
(Guy, Human Pathol 2012)

- Identifying normal-sized hepatocytes, not readily appreciated as “ballooned” in H&E sections
- Improved categorisation of cases classified as “suspicious” (borderline) for NASH

- Study using Oil Red O staining and electron microscopy has shown that ballooned hepatocytes contain fat droplets, possibly related to dilated endoplasmic reticulum (Caldwell 2010)
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Portal/Periportal Changes in Fatty Liver Disease

1. Portal inflammation +/- interface hepatitis (chronic hepatitis-like)

2. Biliary features (resembling low-grade biliary obstruction)

3. Isolated portal fibrosis (without features of steatohepatitis)
   - Adults with morbid obesity
   - Paediatric NAFLD
Portal Inflammation in NAFLD
Portal Inflammation in NAFLD – Prevalence & Associated Features
(Brunt 2009, Rakha 2010)

1. **Prevalence (in adults)**

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>More than Mild</th>
</tr>
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<tbody>
<tr>
<td>Brunt 2009 (n= 728)</td>
<td>16%</td>
<td>60%</td>
<td>23%</td>
</tr>
<tr>
<td>Rakha 2010 ( n= 214)</td>
<td>37%</td>
<td>33%</td>
<td>30%</td>
</tr>
</tbody>
</table>

2. **Associated Features**

- Associated with steatosis severity, ballooning, advanced fibrosis and with periportal fibrosis (in children)
  
  (May also be a feature of treated / regressed NASH)

3. **Pathogenesis & Clinical Significance**

- Mechanism uncertain
- **No** association with auto-antibodies
- Predicts fibrosis progression in serial biopsies (Argo 2009)
Portal Changes in NAFLD - Biliary Features

**Ductular Reaction in NAFLD**

- Steatosis impairs hepatocyte replication
  - Further hepatocyte injury triggers progenitor cell activation & ductular reaction
  - Ductular reaction promotes periportal fibrosis
    (also associated with portal inflammation – Chiba 2011)
NAFLD in Children - Differences Compared with NAFLD in Adults

**Steatosis**
- often more severe
- may have different distribution (panacinar or periportal)

**Other lobular changes less well developed**
- less ballooning/Mallory’s hyaline
- less perisinusoidal/pericellular fibrosis

**Portal/periportal changes more prominent**
- more portal inflammation
- more portal fibrosis

**Type 2 NAFLD** (Schwimmer 2005)
Steatosis, portal inflammation and portal fibrosis (without typical features of steatohepatitis)
- Present in 62% paediatric NASH biopsies, 19% Type 1 (adult pattern), 19% mixed (type 1 & 2)

Subsequent studies showed more frequent cases (50-80%) with mixed pattern
(Carter-Kent 2009, Takahashi 2011)
- “Type 2 pattern” still more common in children than adults
Histological Assessments in NAFLD

1. Establishing the Diagnosis

2. Assessing Disease Severity
   - “Simple” Steatosis vs Steatohepatitis
   - Portal tract changes in NAFLD
   - Centrizonal “arterialisation”
   - Grading & Staging

3. Aetiological Considerations
   - NAFLD vs Other Causes of FLD (mainly alcohol)
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Centrizonal arteries present in 40/100 (40%) randomly selected NASH biopsies

- Prevalence increases with fibrosis stage (62% stage 3-4 vs 21% stage 1-2)
- Microvessels (CD34)+ present in 100%
  → Possibly reflects neo-angiogenesis in response to local ischaemia

- Ductular reaction present in 55% (may be mistaken for portal tracts)
Histological Assessments in NAFLD

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Grading & Staging of NAFLD

1. Which scoring system do you use when assessing NAFLD biopsies?
   i. Brunt (1999)
   iii. Other
   iv. None

2. Do you use histological scoring to establish a diagnosis of NASH (versus simple steatosis)?
### Activity Score (0-8)

**Steatosis (0-3)**
- <5%; 5-33%; 33-66%; >66%

**Lobular Inflammation (0-3)**
- <2; 2-4; >4 foci/20x

**Ballooning (0-2)**
- None, few, many/prominent

### Fibrosis Score (0-4)

1a: Zone 3 perisinusoidal (mild)
1b: Zone 3 perisinusoidal (moderate)
1c: Portal/periportal only
2: Zone 3 & portal/periportal
3: Bridging
4: Cirrhosis

- Scoring system intended to assess disease severity, particularly in clinical trials (similar to Ishak system for HCV)
- NOT intended to establish or confirm a diagnosis of NASH
### Histological Grading & Staging of NASH (Kleiner System) Problems and Limitations

<table>
<thead>
<tr>
<th>Problem</th>
<th>Details/Issues</th>
</tr>
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<tbody>
<tr>
<td><strong>Observer variability</strong></td>
<td>Reproducibility good for fat &amp; fibrosis&lt;br&gt;Reproducibility less good for inflammation &amp; ballooning</td>
</tr>
<tr>
<td><strong>Sampling variability</strong></td>
<td>Fat - reasonably uniform distribution&lt;br&gt;Inflammation &amp; fibrosis more variable</td>
</tr>
<tr>
<td><strong>Uncertain significance of individual NAS Features or overall NAS Score</strong></td>
<td>Importance of steatosis severity uncertain:&lt;br&gt;• No longer regarded as “first hit” in pathogenesis of NASH&lt;br&gt;• May be a protective mechanism (Neuschwander-Tetri 2010)&lt;br&gt;Portal/periportal inflammation not included*</td>
</tr>
</tbody>
</table>

* Portal inflammation (0-2) incorporated into a recently proposed system for scoring paediatric NAFLD (Alkhouri 2012)
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(Hepatology 2011;54:344-353)

Disease Activity

- It is recommended that the NAFLD activity score (NAS) be used to define and quantify disease activity (Grade 1b).

Stage of Disease

- It is recommended that a validated method for the staging of NASH be used for assessment of changes in disease stage in clinical trials of NASH. The NASH CRN fibrosis staging system is one such system and is the most validated system currently available.
NAFLD Activity Scores in 512 Liver Biopsies from Adults with NAFLD
(Kleiner 2005)

- Cases with NAS 0-2 mostly diagnosed as “not NASH”
- Cases with NAS 5-8 mostly diagnosed as “NASH”

- NAS ≥ 5 has subsequently been used to establish diagnosis of NASH, both in clinical trials and in routine practice
Liver Biopsies from 976 adults in NASH Clinical Research Network studies

<table>
<thead>
<tr>
<th></th>
<th>Not Steatohepatitis (n = 204)</th>
<th>Borderline Steatohepatitis (n = 183)</th>
<th>Definite Steatohepatitis (n = 543)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAS 0-4</td>
<td>194</td>
<td>131</td>
<td>136</td>
</tr>
<tr>
<td>NAS 5-8</td>
<td>14</td>
<td>52</td>
<td>407</td>
</tr>
</tbody>
</table>

NAS Score ≥ 5 present in:
- 75% of biopsies with definite NASH
- 28% of biopsies with borderline NASH
- 7% of biopsies with not NASH

Conclusion: The diagnosis of definite SH or the absence of SH based on evaluation of patterns as well as individual lesions on liver biopsies does not always correlate with threshold values of the semiquantitative NAS. Clinical trials and observational studies should take these different performance characteristics into account.
Scoring System for Evaluation of Liver Lesions in Morbibly Obese Patients
(Bedossa Hepatology, November 2012)

679 liver biopsies obtained from obese patients undergoing bariatric surgery
- 230 (34%) – NASH
- 291 (43%) – NAFLD without NASH
- 158 (23%) – no NAFLD

Steatosis, Activity, Fibrosis (SAF) Score
- Steatosis (0-3), Fibrosis (0-4) scored as per NASH-CRN (Kleiner 2005)
- Activity Score (0-4) = combined score for ballooning (0-2) and inflammation (0-2)

<table>
<thead>
<tr>
<th>Ballooning</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>0 = none</td>
<td></td>
</tr>
<tr>
<td>1 = clusters of hepatocytes with rounded shape and pale cytoplasm</td>
<td></td>
</tr>
<tr>
<td>2 = same as grade 1 with enlarged hepatocytes (&gt; 2x normal)</td>
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<table>
<thead>
<tr>
<th>Inflammation</th>
<th>Score</th>
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<tbody>
<tr>
<td>0 = none</td>
<td></td>
</tr>
<tr>
<td>1 = ≤ 2 foci per 20x field</td>
<td></td>
</tr>
<tr>
<td>2 = ≥ 2 foci per 20x field</td>
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Activity score ≥ 2 closely correlated with original histological diagnosis of NASH
Very good intraobserver agreement (kappa - 0.82) interobserver agreement (kappa - 0.80) in validation series of patients with metabolic syndrome
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## ALD vs NAFLD

<table>
<thead>
<tr>
<th>More common/prominent in ALD</th>
<th>More common/prominent in NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ballooning</td>
<td>Steatosis</td>
</tr>
<tr>
<td>Mallory-Denk bodies</td>
<td>(esp in children and morbid obesity)</td>
</tr>
<tr>
<td>Lobular neutrophils</td>
<td>Nuclear vacuolation of hepatocytes</td>
</tr>
<tr>
<td>Zone 3 fibrosis</td>
<td>(70-80% of cases vs &lt;10% in ALD)</td>
</tr>
</tbody>
</table>

Severe alcoholic (steato)hepatitis  
ALD - central sclerosing hyaline necrosis/fibrosis  
NAFLD Nuclear vacuolation
Nuclear Vacuolation in HBV Infected Patients  
(Levene & Goldin, Histopathology 2010)

**Prevalence:**
- Nuclear vacuolation present in $40/872$ (4.6%) of patients (all > 20 years old)
  - “Physiological” vacuolation may persist in adults

Another recent study from Cambridge (Aravinthan J Clin Pathol 2011) suggested that nuclear vacuolation is a manifestation of hepatocellular senescence independent of age or disease aetiology (8 cases studied - 2 NAFLD, 2 ALD, 4 HBV/HCV)
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     - HCV, ALD, Iron overload
Interactions Between HCV and NAFLD
(Eslam 2011, Hubscher 2011, Bugianesi 2012)

Steatosis frequently present in biopsies from HCV+ patients (40-86%)

Two main pathways for HCV-induced steatosis:
1. Viral (genotype 3) - steatosis severity correlates with HCV RNA levels
2. Metabolic (other genotypes) - steatosis severity associated with insulin resistance
   (HCV infection promotes several mechanisms leading to insulin resistance – e.g. insulin signalling, glucose uptake, cytokine production)

Viral eradication results in improvement of steatosis (HCV-genotype 3) and insulin resistance (HCV-genotype 1)

Both pathways can lead to the development of steatohepatitis
Clinical Relevance of Steatosis and Insulin Resistance

1. **Prognosis**
   - Increased risk for fibrosis progression and development of HCC

2. **Treatment**
   - Predict poor response to treatment with interferon and ribavirin.
   - Recent data suggest that insulin resistance (rather than steatosis) is the main factor determining fibrogenesis, carcinogenesis and therapeutic responses.
Interaction between NAFLD and Alcoholic Liver Disease

• **Diagnosis of NAFLD requires absence of significant alcohol consumption (< 20g/day in women, < 30g/day in men)**

• **Modest alcohol consumption (< 20g/day) may reduce frequency of steatohepatitis and severity of fibrosis** (Dunn 2012)

<table>
<thead>
<tr>
<th></th>
<th>Lifetime Non-Drinkers (n = 252)</th>
<th>Modest alcohol consumers (n = 331)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatohepatitis (definite)</td>
<td>70%</td>
<td>53%</td>
</tr>
<tr>
<td>Fibrosis stage 3-4</td>
<td>33%</td>
<td>21%</td>
</tr>
</tbody>
</table>

• **Heavy alcohol consumption (including “binge drinking”) associated with increased risk of fibrosis progression** (Ekstedt 2009, Stepanova 2010)

• **“Until further data from rigorous prospective studies become available, people with NAFLD should avoid alcohol of any type or amount”**
  (Liangpunsakul & Chalasani, Am J Gastro 2012)
Interaction between NAFLD and Iron Overload  
(Corradiini 2012, Dongiovanni 2012)

Mild siderosis (hepatocellular and non-parenchymal) common in NAFLD  
- Insulin resistance important in pathogenesis (“dysmetabolic iron overload syndrome”)

Hepatic iron overload also promotes insulin resistance  
- Insulin resistance reversed by iron depletion

Siderosis in hepatocytes and reticulo-endothelial cells both associated with more severe fibrosis in NAFLD (Valenti 2010, Nelson 2011)

Siderosis also implicated in the pathogenesis of HCC in NAFLD (Sorrentino 2009)

In patients with haemochromatosis (C282Y homozygotes), steatosis and diabetes implicated in fibrosis progression (Powell 2005, Wood 2012)
And, finally.........
1. Name the player heading a goal
2. What was the final score?
3. Who was relieved of his managerial position a few days later?