Non-Alcoholic Fatty Liver Disease
An Update

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Non-Alcoholic Fatty Liver Disease

First described in 1980

- Ludwig et al. Non-alcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980; 55(7):434-438.

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
(Ong 2008, Ratziu 2010, Vernon 2011, Chalasani 2012)

- 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

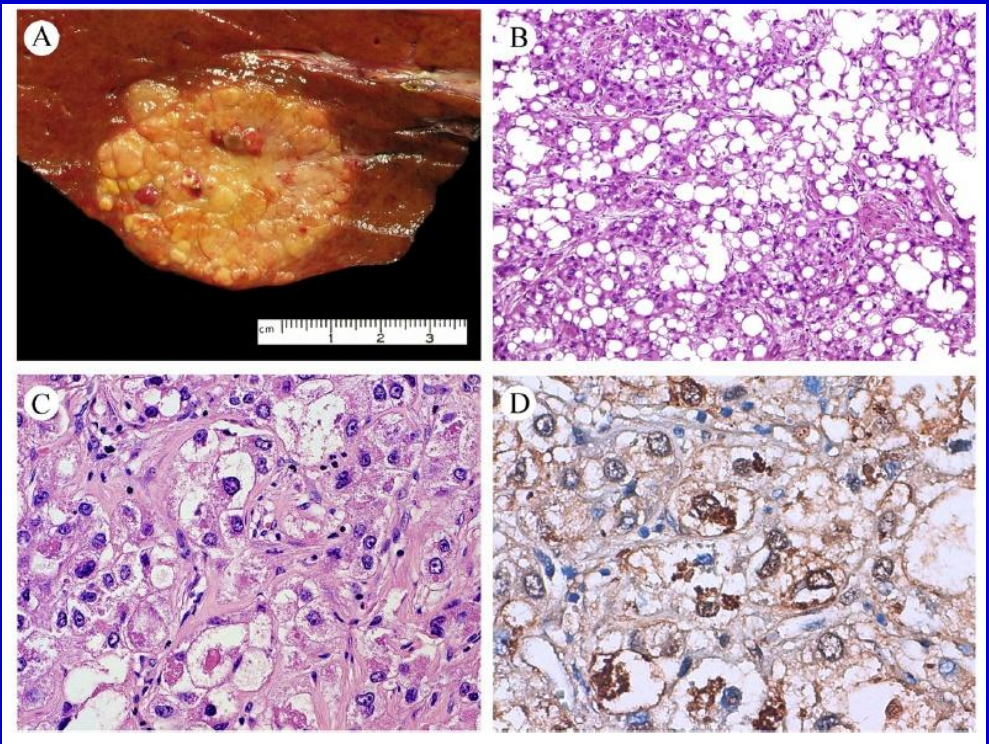
- Increasing numbers of cases reported
  - 40-65% of HCC complicating NAFLD occurred in non-cirrhotic liver (Paradis 2009, Yasui 2011, Duan 2012)

→ 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)

HCC Arising in NAFLD – Different Histological Features

"Steatohepatitic HCC" (Salomao 2010, Jain 2012, Salomao 2012)



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.

Current Role of Liver Biopsy

(from Chalasani, Gastroenterology 2012; 142: 1592-1609)

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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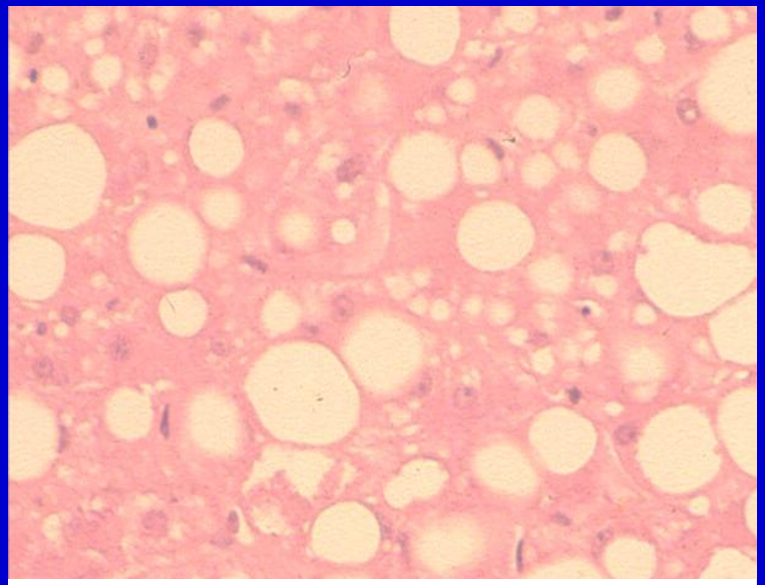
Histological Definition of Fatty Liver Disease

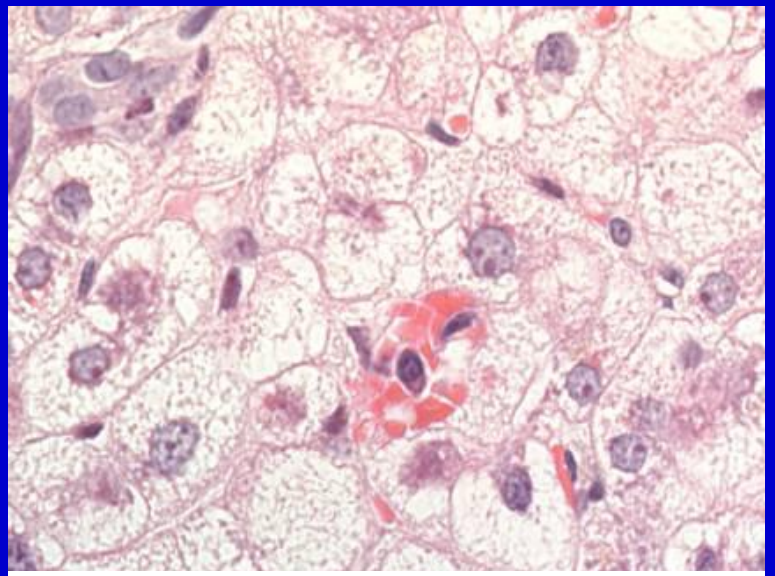
- Fatty change involving > 5% of hepatocytes (or parenchymal area)
- Mainly macrovesicular
- Predominantly perivenular

Hepatic Steatosis - Classification According to Droplet Size



Macrovesicular

Single large droplet, nucleus displaced to one side



Microvesicular

Numerous small droplets, nucleus remains central

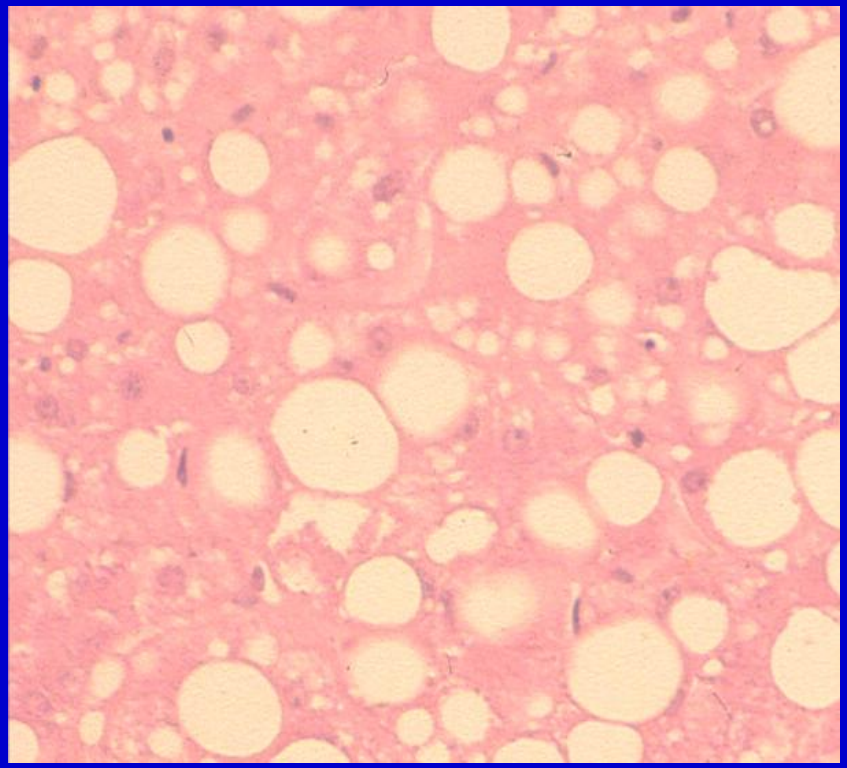
Fatty liver disease (alcoholic and non-alcoholic) mainly macrovesicular

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)

Hepatic Steatosis - Classification According to Droplet Size



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)

% involvement	Severity	Grade
<5	None	0
5-33	Mild	1
33-66	Moderate	2
>66	Severe	3

- 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)

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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

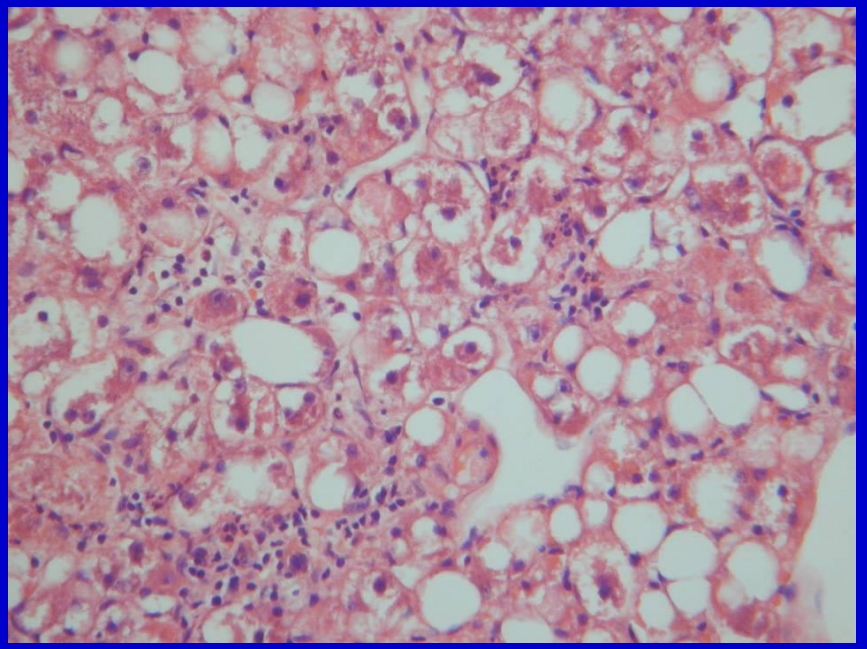
- fatty change
- ballooning
- Mallory-Denk bodies
- apoptosis/necrosis

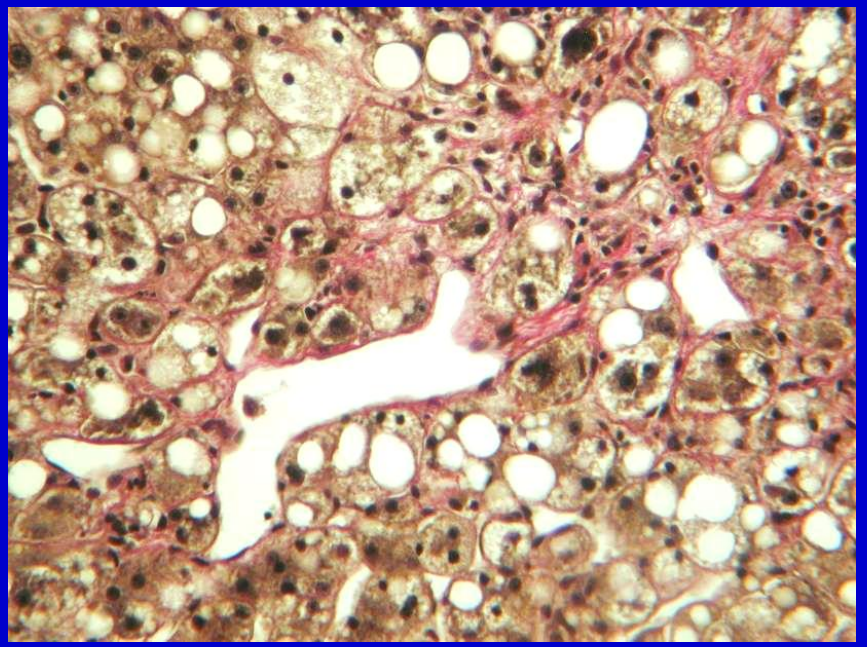
Inflammation

- 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 McCullough[8]

(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

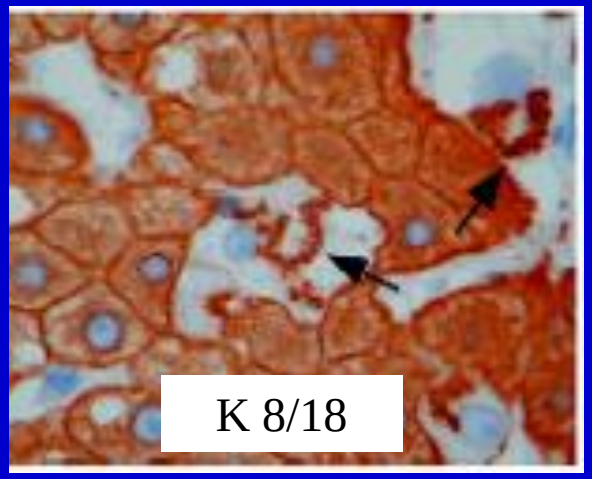
→ Enlarged Kupffer cells (PAS-D+, CD 68+) may be useful (but non-specific) marker of previous inflammatory damage

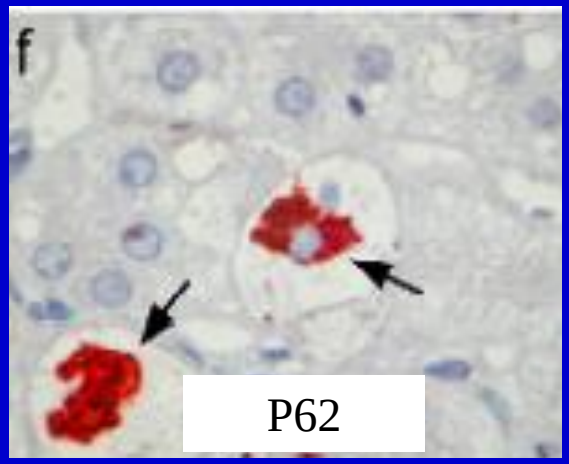
2. **Ballooning**
   - What defines a ballooned hepatocyte - size, shape, cytoplasmic "clarification"? (poor observer reproducibility)

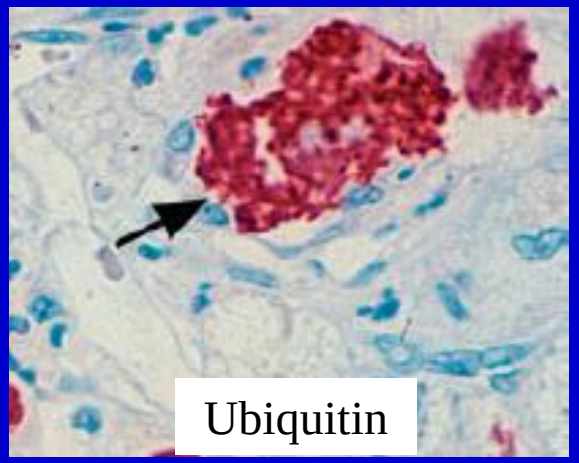
→ Use of immunostains to demonstrate small amounts of Mallory's hyaline

→ Use of connective tissue stains (HVG, Trichrome) to demonstrate foci of pericellular/perisinusoidal fibrosis

Mallory-Denk Bodies - Immunhistochemical 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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   - NAFLD vs Other Causes of FLD (mainly alcohol)
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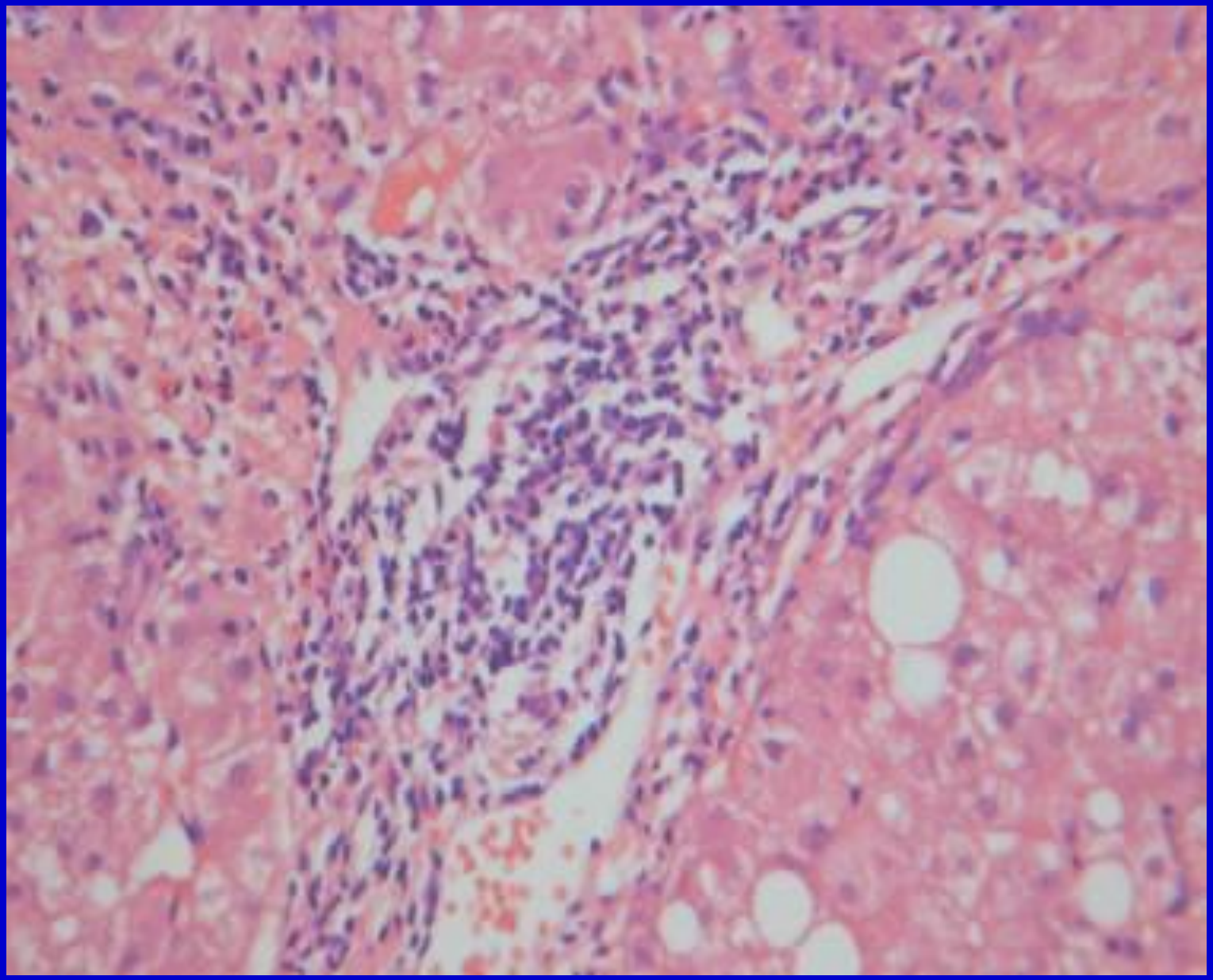
Portal/Periportal Changes in Fatty Liver Disease

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)

	None	Mild	More than Mild
Brunt 2009 (n= 728)	16%	60%	23%
Rakha 2010 (n= 214)	37%	33%	30%

2. Associated Features

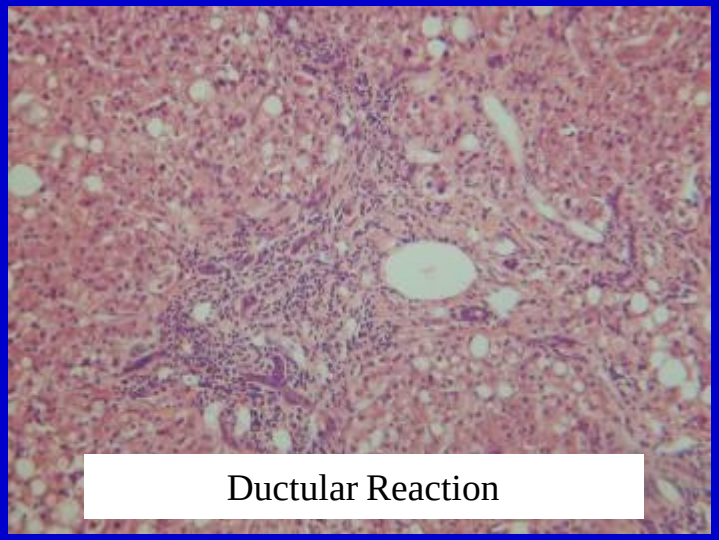
- Associated with steatosis severity, ballooning, advanced fibrosis and with periportal fibrosis (in children)

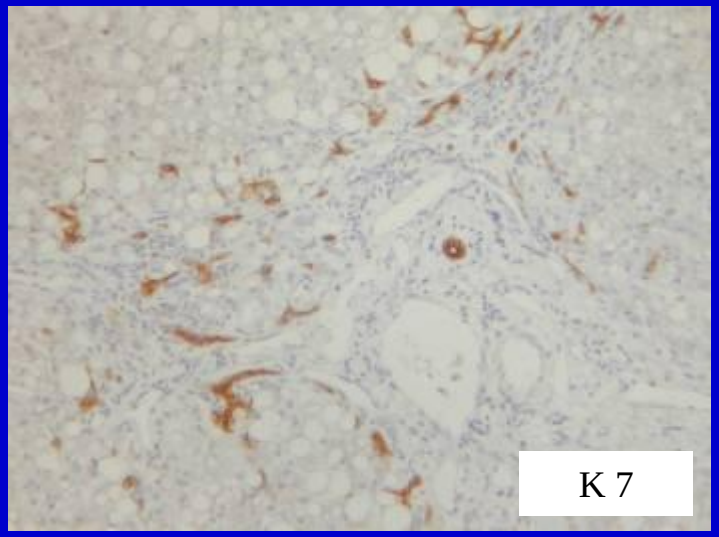
  (May also be a feature of treated / regressed NASH)

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

(Clouston 2005, Richardson 2007, Chiba 2011, Lieuw 2012)

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

(Schwimmer 2005 & 2006 , Nobili 2006, Roberts 2007, Nobili 2010, Della Corte 2012)

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

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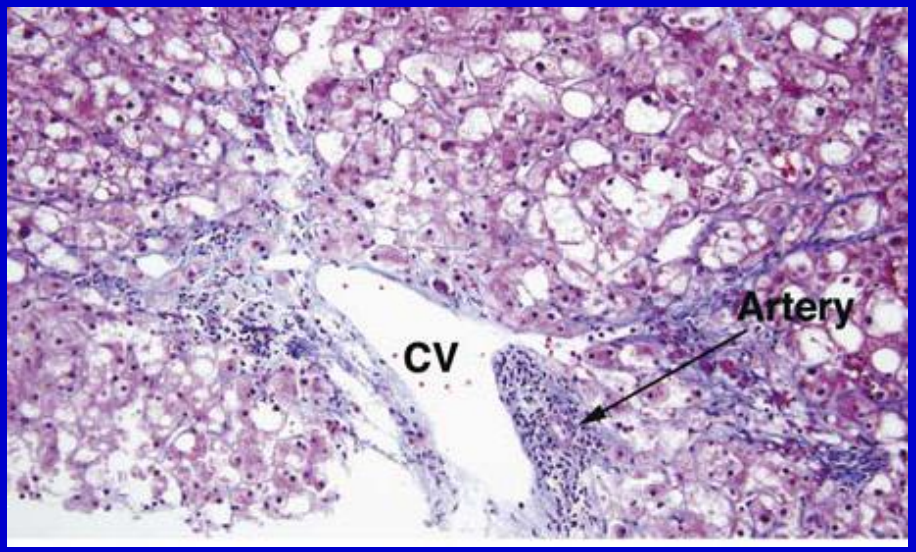
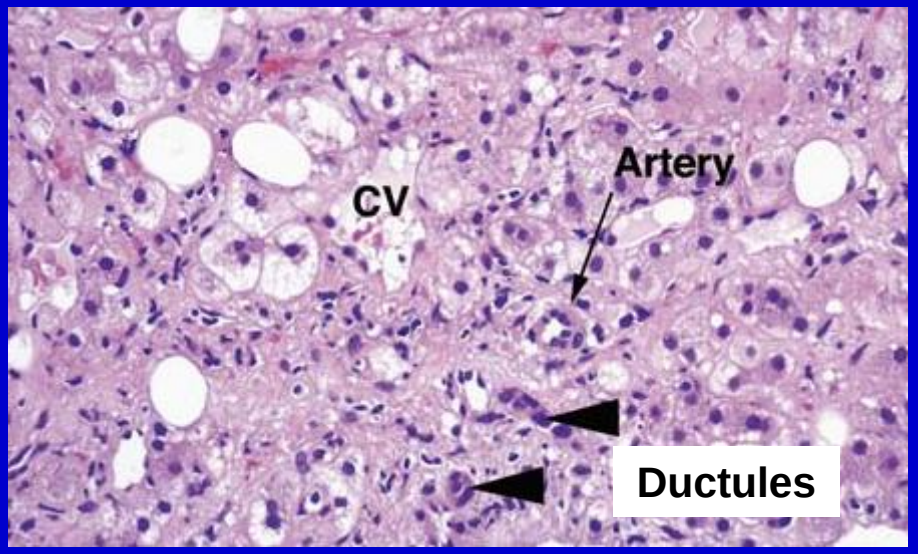
   - Portal tract changes in NAFLD
   - Centrizonal "arterialisation"
   - Grading & Staging

3. Aetiological Considerations
   - NAFLD vs Other Causes of FLD (mainly alcohol)
   - Interaction with other diseases

Centrizonal Arteries and Microvessels in Non-alcoholic Steatohepatitis

(Gill, Am J Surg Pathol 2011)





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)

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Grading & Staging of NAFLD

1. **Which scoring system do you use when assessing NAFLD biopsies ?**
    i. Brunt (1999)
    ii. Kleiner (2005)
    iii. Other
    iv. None

2. **Do you use histological scoring to establish a <u>diagnosis</u> of NASH (versus simple steatosis)?**

NIDDK NASH Clinical Research Network - NAFLD Scoring System

(Kleiner et al. Hepatology 2005; 41: 1313-1321)

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

Observer variability	Reproducibility good for fat & fibrosis Reproducibility less good for inflammation & ballooning
Sampling variability	Fat - reasonably uniform distribution Inflammation & fibrosis more variable
Uncertain significance of individual NAS Features or overall NAS Score	Importance of steatosis severity uncertain: • No longer regarded as "first hit" in pathogenesis of NASH • May be a protective mechanism (Neuschwander-Tetri 2010) Portal/periportal inflammation not included*

* Portal inflammation (0-2) incorporated into a recently proposed system for scoring paediatric NAFLD (Alkhouri 2012)

Endpoints and Clinical Trial Design for Nonalcoholic Steatohepatitis

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(HEPATOLOGY 2011;54:344-353)

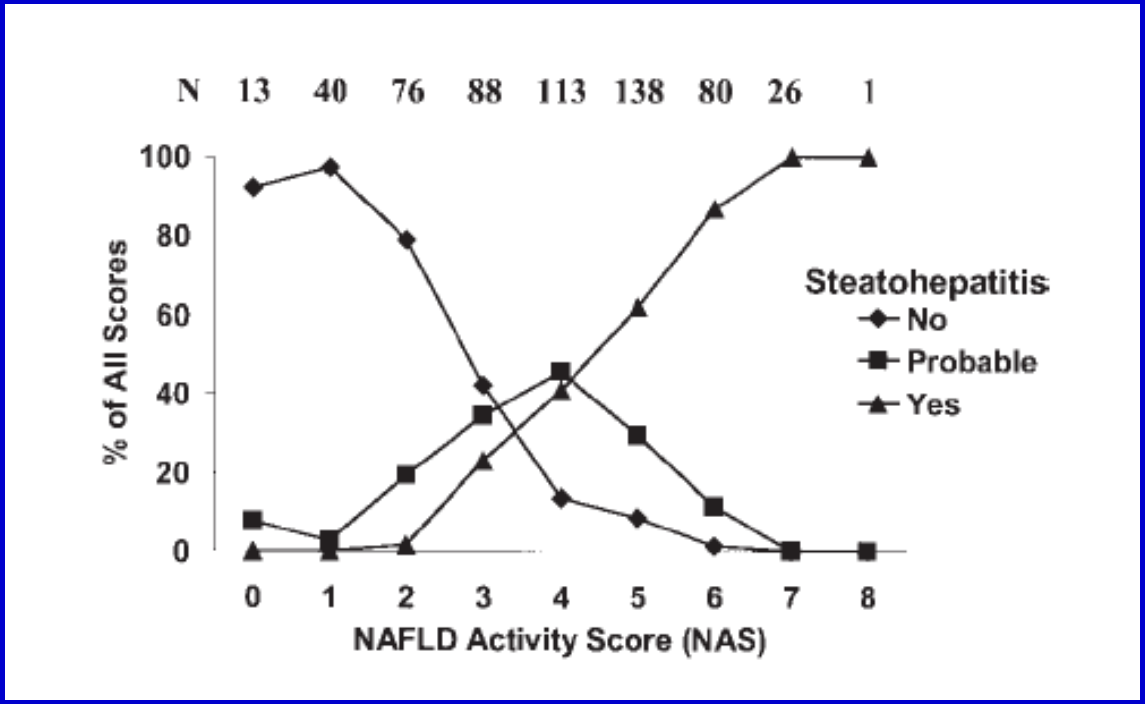
Disease Activity

- *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 $\geq$ 5 has subsequently been used to establish diagnosis of NASH, both in clinical trials and in routine practice

Nonalcoholic Fatty Liver Disease (NAFLD) Activity Score and the Histopathologic Diagnosis in NAFLD: Distinct Clinicopathologic Meanings

Elizabeth M. Brunt,[1] David E. Kleiner,[2] Laura A. Wilson,[3] Patricia Belt,[3] and Brent A. Neuschwander-Tetri[4]; for the NASH Clinical Research Network (CRN)

(HEPATOLOGY 2011;53:810-820)

Liver Biopsies from 976 adults in NASH Clinical Research Network studies

	Not Steatohepatitis (n = 204)	**Borderline Steatohepatitis** (n= 183)	**Definite Steatohepatitis** (n = 543)
NAS 0-4	194	131	136
NAS 5-8	14	52	407

NAS Score $\geq$ 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 Morbidly 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)

Ballooning	0 = none 1 = clusters of hepatocytes with rounded shape and pale cytoplasm 2 = same as grade 1 with enlarged hepatocytes (> 2x normal)
Inflammation	0 = none 1 = $\leq$ 2 foci per 20x field 2 = $\geq$ 2 foci per 20x field

Activity score $\geq$ 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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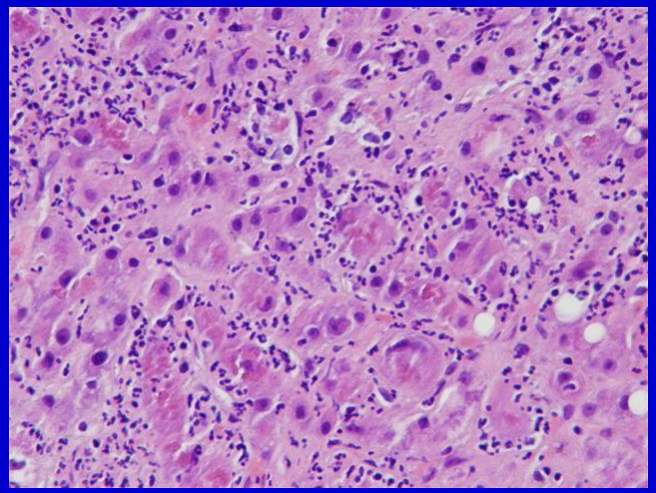
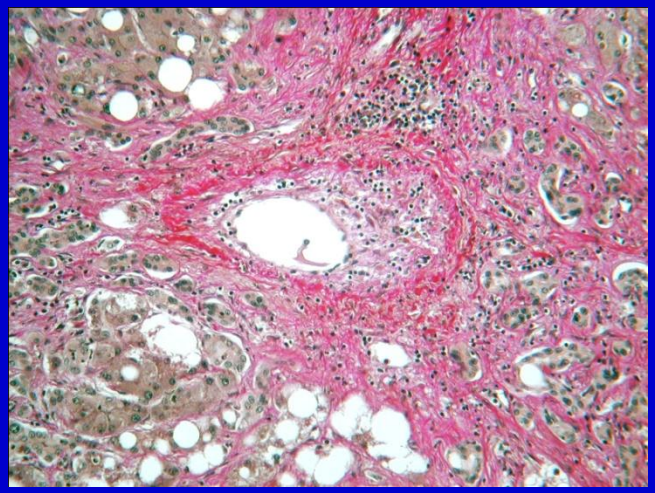
ALD vs NAFLD

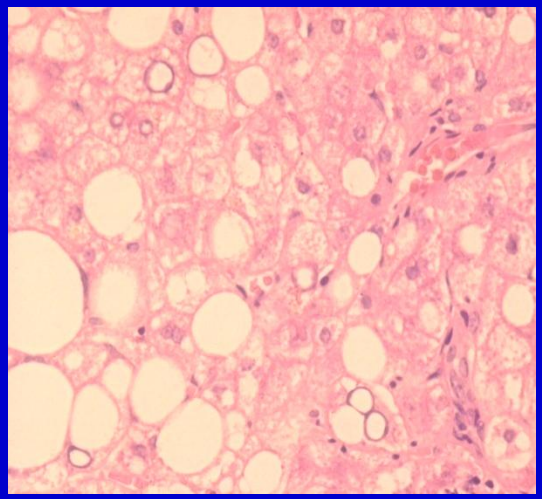
More common/prominent in ALD	More common/prominent in NAFLD
Ballooning	Steatosis
Mallory-Denk bodies	(esp in children and morbid obesity)
Lobular neutrophils	
Zone 3 fibrosis	Nuclear vacuolation of hepatocytes
	(70-80% of cases vs <10% in ALD)



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

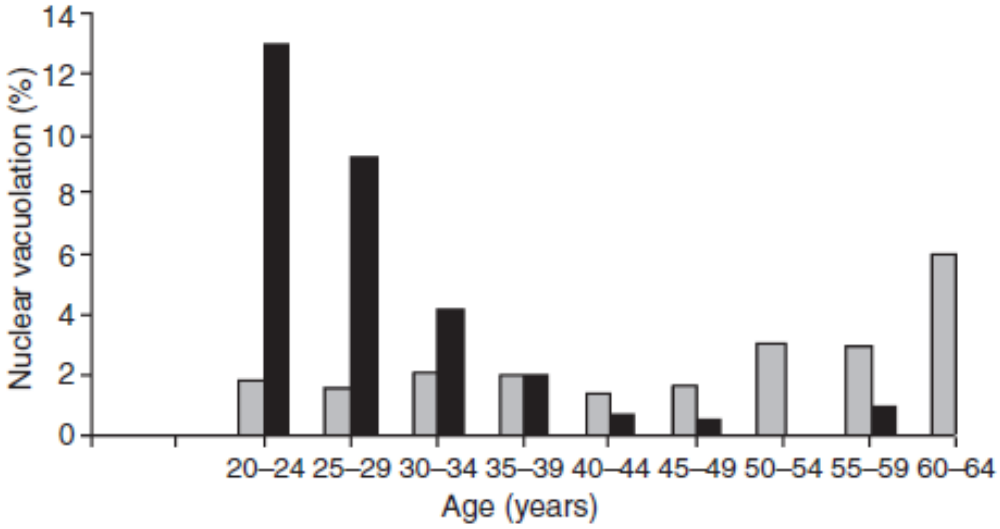


Figure 2. The incidence of nuclear vacuolation not associated with non-alcoholic fatty liver disease (NAFLD) (black) and associated with NAFLD (grey) in patients with chronic hepatitis B.

- 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)

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
     - 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

Interactions Between HCV and NAFLD
(Eslam 2011, Hubscher 2011, Bugianesi 2012)

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)

	Lifetime Non-Drinkers (n = 252)	Modest alcohol consumers (n = 331)
Steatohepatitis (definite)	70%	53%
Fibrosis stage 3-4	33%	21%

- 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
(Corradini 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…….

Saturday 17th November 2012

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?