LUDWIG INSTITUTE FOR CANCER RESEARCH

Imperial College London

Liver Pathology in the Obese

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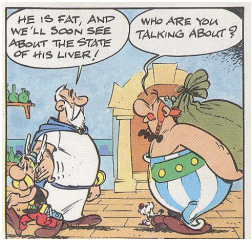
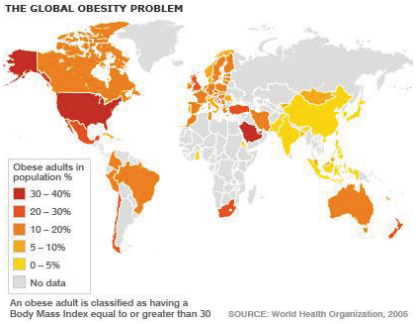


Ludwig et al. Non-alcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980; 55(7):434-438.



Liver Diseases Associated with Obesity

- Fatty change
- Fatty liver hepatitis (adult and paediatric patterns)
- Cirrhosis
- Isolated portal tract expansion.
- Hepatic adenoma
- Liver cell cancer
- Cofactor in other liver diseases

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Non-Alcoholic Fatty Liver Disease

Risk Factors Associated with NAFLD

Common Conditions With Established Association	Other Conditions Associated With NAFLD
Obesity	Hypothyroidism
T2DM	Obstructive sleep apnea
Dyslipidemia	Hypopituitarism
MetS*	Hypogonadism
Polycystic ovary syndrome	Pancreatoduodenal resection
	Psoriasis

Non-Alcoholic Fatty Liver Disease (NAFLD)

(1) evidence of fatty change, either by imaging or histology, and

(2) lack of secondary causes of hepatic fat accumulation such as **significant alcohol consumption,** drugs, or single gene disorders.

Significant alcohol intake:

> 21 standard drinks per week in men and

> 14 standard drinks per week in women.

Alcohol and NAFLD

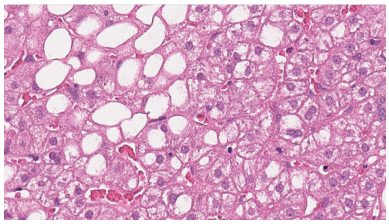
- Several cross sectional studies have suggested a beneficial effect of light alcohol consumption (on average, less than one drink per day) on the presence (defined either biochemically or by imaging) and severity of NAFLD.
- A recent metanalysis (of over 40,000 participants from 6 studies) raised the possibility of potential confounding variable caused by lower BMI among those who are moderate drinkers.

J Hepatol 2012;57:384

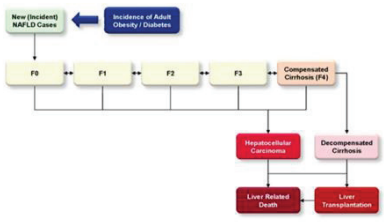
NAFLD: "NAFL" vs. "NASH"

- Non-alcoholic fatty liver (NAFL): more than 5% fatty change without evidence of hepatocellular injury in the form of hepatocyte ballooning.
- Non-alcoholic steatohepatitis (NASH): presence of 5% fatty change and **ballooning**, and inflammation, and with or without any fibrosis.

Fatty change



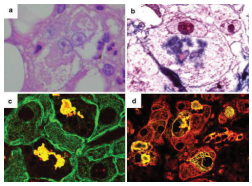
NAFLD Markov Model



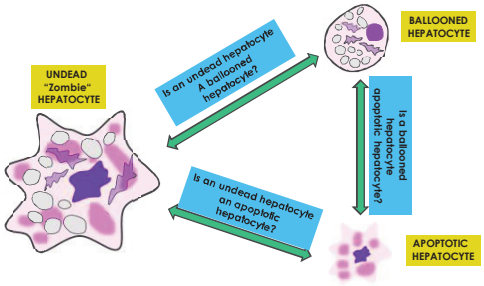
Histological features of NASH

- Large droplet fatty change
- Ballooning +/ - Mallory–Denk bodies
- Inflammation, lobular or portal
- Apoptotic hepatocytes
- Fibrosis

Ballooning and Mallory-Denk Bodies

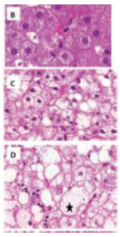


(**a**) Hematoxylin and eosin stained
(**b**) Chromotrope aniline blue staining
(**c**) Immunofluorescence using antibodies against K8/K18
(**d**) Immunofluorescence using antibodies against p62



Lucie Vištejnová

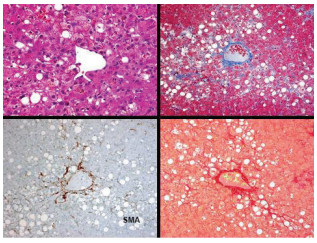
Types of ballooning



Ballooning and lobular inflammation grading.
B) Normal hepatocytes, ballooning, grade 0. Cytoplasm is pink and granular and liver cells have sharp angles.
(C) Ballooning, grade 1. Hepatocytes have rounded contours with clear reticular cytoplasm. Size is similar to that of normal hepatocytes,
(D) Ballooning, grade 2. Cells are rounded with clear cytoplasm and twice as large as normal hepatocytes (star)

Hepatology 2012;56:1751

Fibrosis in NASH: Zone 3 Pericellular fibrosis



Nuclear Vacuolation in NAFLD

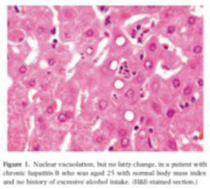
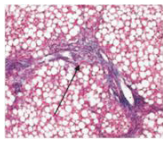


Figure 1. Nuclear vacuolation, but no fatty change, in a patient with chronic hepatitis B who was aged 25 with normal body mass index and no history of excessive alcohol intake. (H&E-stained section.)

Histopathology 2010;56:426.

Paediatric NASH

- Children with NAFLD are reported as early as years and with NASH-related cirrhosis as early as age 8 years.
- May show predominantly portal disease



	Type 1		Type 2
Ballooning degeneration	+	+	−
Perisinusoidal fibrosis	−	+	+
Steatosis	+		+
Portal inflammation	−	+	+
Portal fibrosis	−	−	+

Hepatology 2005;42:641

Liver Diseases Associated with Obesity

- Fatty change
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- Glycogenic hepatopathy
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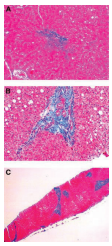
Isolated Portal Fibrosis



- Found 1/3 of morbidly obese patients
- Should be considered a spectrum of NAFLD that may precede NASH in morbid obesity.

Hepatology 2004;40:475

Recent Developments in NASH

- New histological features
- New ways of looking at biopsies

Centrilobular ductular reaction correlates with fibrosis stage and fibrosis progression in non-alcoholic steatohepatitis

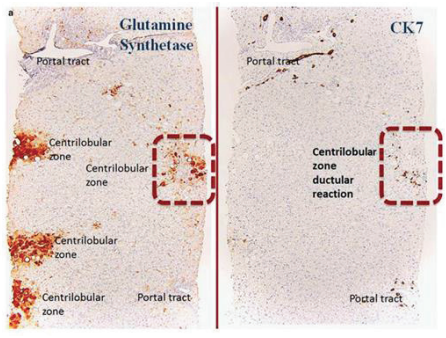
Modern Pathology 2018: 31; 150–159

Recent Developments in NASH

- New histological features

e.g. centrilobular ductular reaction

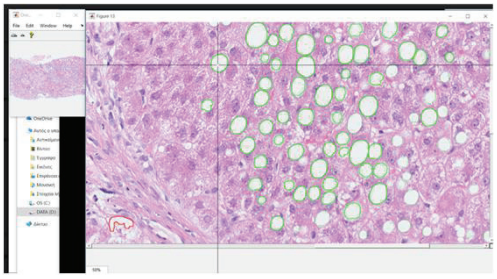
- New ways of looking at biopsies



Centrilobular Ductular Reaction

- Centrilobular ductular reaction was identified in 90% of patients and 38% of centrilobular zones.
- The prevalence of centrilobular ductular reaction increased as non-alcoholic steatohepatitis grade increased and also as stage of fibrosis increased in the cross-sectional study.
- In the *longitudinal study*, the frequency of centrilobular ductular reaction in the initial biopsies was significantly higher in the group of progressors and correlated with the rate of fibrosis progression.

Zoomed area with fat



Recent Developments in NASH

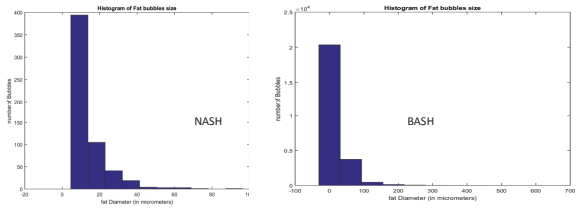
- New histological features

e.g. centrilobular ductular reaction

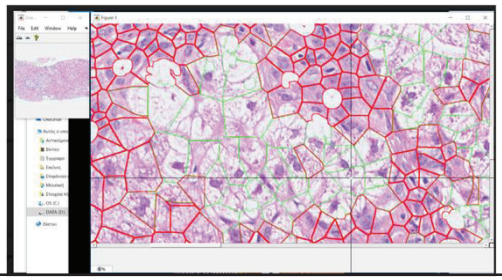
- New ways of looking at biopsies

e.g. image analysis

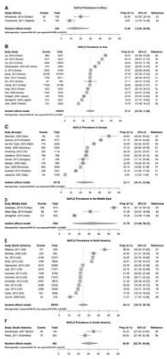
Size of fat droplets



Zoomed area with ballooning



Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes



Hepatology 2016;64:73

Prevalence of NAFLD

Global prevalence of NAFLD is 25% with highest prevalence in the Middle East and South America and lowest in Africa.

Hepatology 2016;64:73

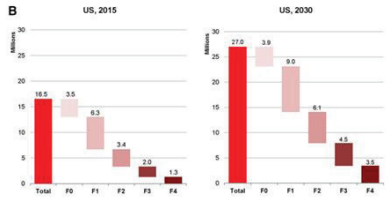
HEPATOLOGY

AASLD

HEPATOLOGY, VOL. 67, NO. 1, 2018

Modeling the Epidemic of Nonalcoholic Fatty Liver Disease Demonstrates an Exponential Increase in Burden of Disease

Chris Estes,[1] Homie Razavi,[1] Rohit Loomba,[2] Zobair Younossi,[3] and Arun J. Sanyal[4]



Distribution of the NASH population by fibrosis stage in the United States for 2015 and 2030.

NAFLD in Patients Undergoing Bariatric Surgery I

The liver biopsies form 1000 consecutive patients undergoing weight loss surgery were reviewed:

- 80% had NAFLD, of which
- 70% had fatty change and
- 14% with NASH and/or fibrosis.

There was no no significant difference in BMI or age between those with /without liver disease.

Surg Obes Relat Dis 2015;11:137-141.

Cryptogenic Cirrhosis

- Most patients with cryptogenic cirrhosis have what is considered "burned out" NAFLD.
- They have a disproportionately high prevalence of metabolic risk factors (including obesity) that resemble patients with NAFLD

Ann Hepatol 2009;8:346

NAFLD in Patients Undergoing Bariatric Surgery II

In a prospective study of 109 patients with NASH showed that at 1 year.

- NASH resolved in 85%
- Fibrosis improved in 33%

Gastroenterology 2015;149:379-388

A metanalysis showed:

- The majority improved/resolved fat, inflammation, and ballooning.
- Fibrosis decreased by 12%

Obes Surg 2015;25:2280-2289.

Liver biopsies in NAFLD

- Indications
- Scoring Systems

NAFLD Activity Score (NAS)

Steatosis grade	Lobular inflammation	Hepatocellular ballooning
0: <5%	0: None	0: None
1: 5-33%	1:<2 foci/20x field	1: Mild, few
2: 34-66%	2: 2-4 foci/20x field	2: Moderate – marked,
3: >66%	3: >4 foci/20x field	many
NAFLD activity score (NAS): 0-8		
Steatosis (0-3) **+**	Lobular Inflammation (0-3)	**+** Ballooning (0-2)

Kleiner Hepatology. 2011; 53(3): 810–820.

Indications for Liver Biopsy in NASH

- Liver biopsy should be considered in patients with NAFLD who are at increased risk of having steatohepatitis and/or advanced fibrosis as based on non-invasive studies.
- Liver biopsy should be considered in patients with suspected NAFLD in whom competing aetiologies for fatty change and the presence and/or severity of coexisting chronic liver diseases which cannot be excluded without a liver biopsy.

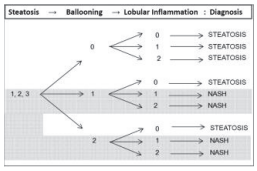
Hepatology 2018 ;67:328-357.

NASH CRN Fibrosis

Fibrosis:*
0: None
1a: Mild zone 3 perisinusoidal fibrosis
requires trichrome stain to identify
1b: Moderate zone 3 perisinusoidal fibrosis
may be appreciated on H&E
1c: Portal fibrosis only
2: Zone 3 perisinusoidal fibrosis and periportal fibrosis
3: Bridging fibrosis
4: Cirrhosis

*based on the use of Masson's trichrome stain

The Steatosis, Activity Fibrosis (SAF) score



Fibrosis as in Kleiner

Hepatology
Volume 59, Issue 2, pages 565-575, 26 JUN 2014 DOI: 10.1002/hep.27173
http://onlinelibrary.wiley.com/doi/10.1002/hep.27173/full#hep27173-fig-0001

"Although distinguishing NASH from NAFLD may still have relevance for clinical practice, we suggest that using this binary classification in clinical research is somewhat artificial."

Gastroenterology 2015 Nov;149(6).

Does the SAF predict natural history?

After adjustment for fibrosis, the SAF score was not associated with increased mortality in NAFLD.

SAF score and mortality in NAFLD after up to 41 years of follow-up.
Scand J Gastroenterol. 2016 Sep 10:1-5.

Natural History of NAFLD

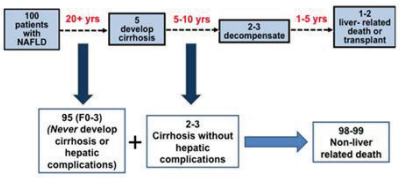
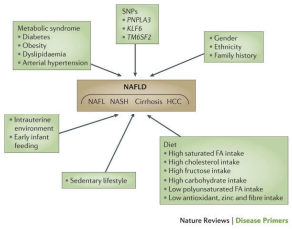


FIG. 2. The natural history of NAFLD is depicted, with the lifetime frequency of clinically relevant progression of fibrosis and development of liver-related and non-liver-related deaths.

Hepatology 2016:64;19-22

Factors associated with NAFLD development and progression



Nat. Rev. Dis. Primers
doi:10.1038/nrdp.2015.80

Factors determining the prognosis of NAFLD

"Patients with fibrosis, regardless of steatohepatitis or NAFLD activity score, had shorter survival times than patients without fibrosis."

Gastroenteroloy, 2015: 149;389–397

Progression of fibrosis in NAFLD

- A meta-analysis of studies of paired liver biopsy studies.
- The annual fibrosis progression rate in patients with NAFLD who had stage 0 fibrosis at baseline was 0.07 stages compared with 0.14 stages in patients with NASH.
- These findings correspond to 1 stage of progression in:
  - 14.3 years for patients with NAFLD and
  - 7.1 years for patients with NASH.

Clinical Gastroenterology and Hepatology 2015;13:643

Prognosis of NAFLD

The NAS was not able to predict overall mortality, whereas fibrosis stage predicted both overall and disease-specific mortality.

Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up.
Hepatology. 2015 May;61(5):1547-54.

Results of Liver Transplantation

- 1- and 3-year patient and graft survival rates that are comparable to other indications.
- Histological evidence of NAFLD is common:

  Steatosis ≥ grade 2 is observed in 60% by the end of the 2nd year

  NASH with bridging fibrosis or worse seen in only 5% of recipients by the 5th year.

  Am J Gastroenterol 2010;105:613-620.

A recent paper has suggested a more aggressive disease.

Transplantation 2017;101:1867-1874.

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- **Fatty change**
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- **Cirrhosis**
- Isolated portal tract expansion.
- Liver cell cancer
- Hepatic adenoma

NASH and cardiovascular disease

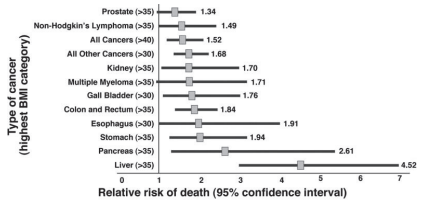
NAFLD is an independent risk factor for atherosclerosis and cardiovascular disease.

The most common cause of death in patients with NAFLD is cardiovascular disease, independent of other metabolic comorbidities

J Hepatol, 2016;65:95

Arterioscler Thromb Vasc Biol, 2015; 35:1284

Obesity and HCC



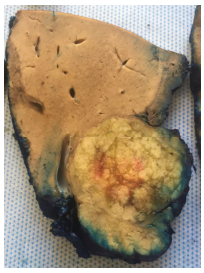
N Engl J Med 2003 ;348:1625

NAFLD and HCC

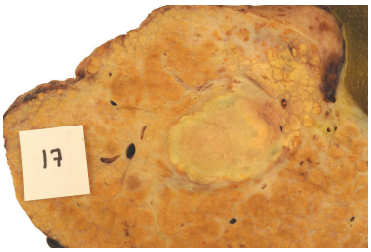
- NAFLD is now the 3rd commonest cause of HCC in the USA.
- The incidence of NAFLD-related HCC is increasing at 9% /year.
- Patients with NAFLD-related HCC are older.
- Around 13% of HCC reported from a US study did not have cirrhosis. - NAFLD was independently associated with HCC in the absence of cirrhosis.

Hepatology 2016;14:124

HCC in non-cirrhotic liver



HCC in cirrhotic liver



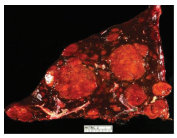
HCC and non-cirrhotic NAFLD

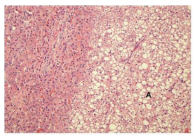
- More often detected at a later tumor stage
- After patient matching, it has a similar survival rate compared to HCV infection

Hepatology 2016;63:827

Liver adenomas and NAFLD

- Obesity and/or the metabolic syndrome is a risk factor for liver adenomas.
- Inflammatory HCA is associated with obesity and with steatosis in the nontumoral liver.
- Multiple adenomas are associated with maturity onset diabetes of the young type 3 (MODY3), a condition caused by germline mutations in HNF1A.





International Journal of Hepatology
Volume 2013, Article ID 604860

This is a common problem

"coexisting disease represented 5.5% of all hepatitis C biopsies and 4.0% of other forms of chronic liver disease"

Coexisting fatty change is a bad prognostic factor

Mod Pathol 2003;16:49

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- Fatty change
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- Cirrhosis
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- Cofactor in other liver diseases.

Conclusion

- Fatty liver disease is very common and is becoming commoner.
- It ranges from fatty change to liver cell cancer.
- We need to learn how to extract more information from liver biopsies.

@robdgol