Abnormal Liver Tests and Fatty Liver Disease

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Conflict of interest: I sadly have nothing to declare 😞

• I have no conflicts of interests.
• I will not discuss off label investigational use of Medications.
Outline

• Abnormal LFts: Definition Patterns Epidemiology and Approach
• Relative contribution of NAFLD NASH to abn LFts
• Pattern of liver test abnormalities in ASH vs NASH and the alcohol –non alcoholic Fatty Liver Index
• NAFLD:
  – Definition
  – Epidemiology
  – Diagnosis
  – Natural History
  – Progression and Prognosis
    • Risk of death
    • Risk of cancer
  – Who to Biopsy and when
    • Role of non-invasive testing
    • NAFLD activity score
  – Management:
    • Modifiable and non-modifiable risk factors
    • Medications Vit E, Pioglitazone)
    • Bariatric surgery
Abnormal Liver Tests

• Occur in 1-9% asymptomatic population.
• Testing all: expensive; risk (including of invasive testing)
• However, do not miss treatable cause
• General approach:
  – Evaluate risk factors: History and physical
  – Confirm mildly elevated tests are not just transient. (retest, wait up to 6 m)
  – Use opportunity to screen high risk individuals (alcohol, HCV, HBV, Fatty liver)
Prevalence NAFLD in CLD

Prevalence in population: 1994 vs 2008 (NHANES)

Etiology of CLD: 2008 (NHANES)

NASH 6%
ALD 11%
CH-B 2%
Iron 9%
HCV 9%
CH-C 6%
NAFLD 57%

Approach to Chronically Elevated LFTS: “Pattern Recognition” and “Statistical”

• **Statistical approach:**
  – Viral Hepatitis blood transfusion < 1991, high risk work, age cohort
  – **NASH:** obese, diabetic
  – **ALD:** alcohol
  – Genetic/iron: Family history

• **Pattern:**
  – AST/ALT = hepatocellular injury
  – ALP (GGT) = cholestasis

IVDA, Incarceration, tattoos, MSM, Hep B: Immigrants
NAFLD 57%

NASH 6%

ALD 11%

HCV 9%

CH-B 2%

Iron 9%

CH-C 6%

Injection drug use

Transfusion prior to 1991

MSM

Birth cohort (1950-1964)

Obesity
Visceral obesity
Insulin resistance
POC
Type 2 DM
Caucasian /Hispanic
Hypertension
Dyslipidemia

Alcohol use

Immigrant (High prevalence Hepatitis B)

Iron : Non-specific
Any Liver dz

Injection drug use

Transfusion prior to 1991

MSM

Birth cohort (1950-1964)
Abnormal AST and ALT “Hepatocellular Injury Pattern”

• Common
  – Nonalcoholic fatty liver disease
  – Chronic viral hepatitis B and C (Care with IgM studies)
  – Alcoholic liver disease
  – Medication toxicity
  – Autoimmune hepatitis

• Less common
  – Wilson disease
  – Alpha-1-antitrypsin deficiency
  – Genetic hemochromatosis
ALP “cholestatic pattern” (use GGT to confirm liver origin of ALP)

• Common
  – Primary biliary cirrhosis
  – Primary sclerosing cholangitis
  – Neoplasm
  – Biliary obstruction (gallstones, etc)
  – Drug Induced cholestasis

• Less common
  – Autoimmune cholangiopathy
  – Sarcoidosis
Chronically elevated LFTS, hepatitis, fatty liver: “Statistical approach”: what is the addiction? Full evaluation in everyone if answer is not clear.
What is Steatohepatitis? (Gk *steato-* "fat", *hepatos-* "liver" + *itis-* "inflammation")
Fatty Liver: Is it NAFLD or Alcohol?

• Audience Response: Both alcohol and Obesity cause fatty liver. The following characteristics are diagnostic of alcoholic steatohepatitis (ASH) over NASH (non-alcoholic steatohepatitis):

• 1. AST > 100 with normal ALT
• 2. Mallory’s Hyaline on Liver biopsy
• 3. Ballooning degeneration on biopsy
• 4. Extensive pericellular and pericentral fibrosis
• 5. All of the above
NASH and ASH are indistinguishable histologically and by most clinical parameters

- AST > ALT: good for alcohol but also seen in severe NASH
- Obesity: and drinking go together

Pericellular fibrosis: equally likely in ASH and NASH

Mallory’s Hyaline: equally likely in ASH and NASH
How to Distinguish Alcoholic from Non-alcoholic Steatohepatitis: the ANI

http://www.mayoclinic.org/gi-rst/mayomodel10.html

Nooo Doc, I don’t drink....Never.... (well maybe just a little)

Ht 5.8 Wt 190lbs
AST 67 ALT 17
MCV109

ANI: Alcohol-non-alcoholic fatty liver index

Dunn: Diagnosis of Fatty Liver: Alcohol vs NASH: GASTROENTEROLOGY 2006;131:1057–1063
AST: 67 IU/l
ALT: 17 IU/l
MCV: 108 fl
Weight: 190 kg
Height: 68 cm
Gender: Male

Calculate ANI

ANI score: 13.417

Probability of Alcoholic Liver Disease: 100 %

Reset form
If we can’t believe our patients, what can we do?

Urine Ethyl glucuronide detects alcohol use up to 96 hrs

- 100-200ug/L detect consumption
- Detectable 40-100hrs after (dose dependent)
- “False” Pos: mouth wash, hand cleansers
- False Neg: Bacteria in urine
- Commercially avail
- Hair assays
Sensitivity/Specificity of Available Tests for Alcohol Detection

Urine Ethylene Glucuronide has highest positive and negative predictive value
What is NASH NAFLD: Summary

- Non-alcoholic fatty liver disease (NAFLD) refers to fat accumulation in hepatocytes not due to excess alcohol.
- It is the most common liver condition in the world (30%).
- Histologically: spectrum from mild hepatic steatosis, NASH- hepatocellular injury and inflammation, to cirrhosis.
- Pathogenesis is related to insulin resistance:
  - Central obesity or diabetes.
  - Increased lipid influx into the liver and increased de novo hepatic lipogenesis.
NAFLD summary

- NAFLD is commonly asymptomatic detected incidentally.
- Subjects with NAFLD have a higher mortality rate: are at increased risk cardiovascular disease, diabetes, cancer and kidney disease.
- Treatment
  - treat metabolic risk factors;
  - improve insulin resistance through weight loss and exercise. I
  - Insulin sensitizing agents such as pioglitazone and
  - antioxidant agents such as vitamin E.
Nonalcoholic Fatty Liver Disease
Spectrum of Disease

- Steatosis
- Steatohepatitis (NASH)
- Cirrhosis
- End-stage Liver Disease; Hepatocellular Carcinoma
Steatohepatitis

US: Hyper-echoic

Biopsy: Macro-vesicular fat

Pericellular and Central Fibrosis

Balloon Mallory’s Hyaline
Non-Alcoholic Liver Disease Scoring System (NAS)

• NAS is the unweighted sum of steatosis, lobular inflammation, and hepatocellular ballooning scores.

• Used to grade severity of NAFLD.

Kleiner, DE: Design and Validation of a Histological Scoring System for Nonalcoholic Fatty Liver Disease  HEPATOLOGY 2005;41:1313-1321
NAFLD Prevalence in Adults

G. Vernon et al Alim Pharm & Therap, 2011; 34:274-285
Obesity Trends 5 years

County-level Estimates of Obesity among Adults aged ≥ 20 years:
States 2004

County-level Estimates of Obesity among Adults aged ≥ 20 years:
States 2009

www.cdc.gov/diabetes
The severity of NAFLD is associated with the severity of the metabolic syndrome

Dixon et al, Gastroenterology, 2001; 121:91-100
Epidemiology: Key points

• NAFLD affects a third of the general population; NASH affects about 4-5%.
• NAFLD worsens the risk of getting diabetes.
• It is an independent risk factor for coronary artery disease and cardiovascular events.
• Diabetes is associated with more advanced liver disease.
Causes of NAFLD

- Metabolic syndrome-related
- Starvation
- TPN
- Drugs: amiodarone, diltiazem, tamoxifen, protease inhibitors
- Infections: HIV infection
- Celiac disease
- Jejuno-ileal bypass
- Genetic disorders of lipid metabolism: Abetalipoproteinemia
Key points re etiology-pathology

- NAFLD = spectrum of disease (fatty liver to steatohepatitis)
- Steatohepatitis: minimum criteria include fat, inflammation and ballooning
- Activity measured by NAFLD activity score
- Stage determined by fibrosis stage
- Histology similar to that with alcoholic steatohepatitis-more cholestasis, ballooning, Mallory-Denk bodies, central vein lesions in ETOH-hepatitis
- There are several causes of NAFLD
Who to evaluate?

- Persistently abnormal AST, ALT or Alk Phos
- Persistent unexplained hepatomegaly
- Abnormal hepatic imaging suggestive of NAFLD
Natural history of the disease
Subjects with NAFLD have a greater than expected mortality compared to matched controls.

- Risk factors for mortality:
  - Age ($p < 0.001$)
  - Diabetes ($p < 0.005$)
  - Cirrhosis ($p < 0.02$)

- Increased mortality:*
  - cardiovascular disease
  - liver disease

Adams et al, Gastroenterology, 2005, 129:113-121
NAFLD May Increase CVD Risk

- NAFLD associated with
  - Carotid plaques
  - Endothelial dysfunction
  - Framingham risk score

- CVD is leading cause of death in people with NAFLD
  - True for all U.S. adults
  - Especially true for those with HTN, DM, and high cholesterol (i.e. those at risk for NAFLD)
Outcomes of NASH-related cirrhosis: Child Pugh class A

Sanyal et al, Hepatology 2006, 43:682-689
Development of hepatocellular cancer in cirrhosis due to NASH vs HCV

Sanyal et al, Hepatology 2006, 43:682-689
NAFLD increases the risks of liver-related death

<table>
<thead>
<tr>
<th>Author</th>
<th>Odds ratio</th>
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<tbody>
<tr>
<td>Ekstedt</td>
<td>No controls had liver death</td>
</tr>
<tr>
<td>Dunn</td>
<td>4.4 (overall)</td>
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<tr>
<td>Rafiq</td>
<td>9.2</td>
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<tr>
<td>Ong</td>
<td>9.3</td>
</tr>
<tr>
<td>Feldstein</td>
<td>13.6 (overall)</td>
</tr>
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Natural history of NAFLD: Key points

- Changes in fibrosis are bi-directional
- Subjects with fatty liver may progress to steatohepatitis and cirrhosis but the risk is low (~5% over 5-15 yrs)
- Fibrosis stage progresses in 30-40% of subjects within a 3-5 yr time frame.
- Increasing age, diabetes and BMI are risk factors for progression
- It is a risk factor for HCC
- Disease recurs after transplant
What is the treatment?
Risk factors for disease progression

• Non-modifiable:
  – age
  – race
  – genetic background
  – baseline histology

• Modifiable:
  – weight gain
  – insulin resistance
  – diabetes
Diet
NHLBI guidelines (1998)

- Ideally, should be individualized to achieve energy deficit of 500-1000 Kcal/day
- Decrease saturated fats and keep total fats < 30% of total energy intake
- Decrease refined sugars
- (Avoid high fructose corn syrup enriched foods)
- Increase soluble fiber intake
Effect of weight loss on NAFLD

Effect of weight loss on NAFLD

Rationale for therapeutics for NASH

Insulin sensitizers → Insulin resistance → FFA + insulin + cytokines → Steatosis + metabolic dysregulation → ER stress, Oxidative stress, Mitochondrial injury → Inflammatory signaling, Apoptosis, Cell death → Stellate cell activation → Fibrosis → Anti oxidants
Pioglitazone or Vitamin E vs placebo for NASH: vitamin E was superior

Sanyal for NASH CRN, NEJM, 2010, April 28 EPub
Change in body weight

WEIGHT

Change (kg)

0 2.5 5

-2.5

0 24 48 72 96

Weeks

Placebo  Vitamin E  Pioglitazone

Sanyal for NASH CRN, NEJM, 2010, April 28 Epub
Treatment Summary

• Lifestyle Changes
  – Weight reducing diet
  – Increased Exercise

• Drug Treatment
  – Vitamin E is first Line
  – Pioglitazone works but associated with weight gain

• Bariatric surgery:
  – Promise for BMI>35+Diabetes Or BMI > 40
  – No RCTs
Conclusions

• Abnormal Liver tests assessed in context
• Fatty liver is common: NAFLD >> alcohol (use ANI to distinguish and Ethylene Glucuronide to detect recent alcohol use
• NASH/NAFLD characterized by fatty change, fibrosis pattern (pericellular) Mallory hyaline and Ballooning hepatocytes
• Associated with increased mortality (Mostly cardiovascular and cancer, but also liver disease).
• Treatment with weight reduction and exercise, Vit E and bariatric surgery in selected cases.
Comments or Questions?