Fatty Liver – What to do?

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Liver Enzymes

- Liver enzymes are not liver function tests!
- “True” liver function tests
  - Albumin
  - INR
  - Bilirubin
- The patient with elevated liver enzymes usually has normal liver function
- LAE’s (Liver Associated Enzymes)
What is a normal ALT?

We do not know!

- Normal values vary among laboratories and geographic regions
  - Normal range 31-72 U/L
- ALT levels correlate with BMI

Males < 30 U/L
Females < 19 U/L

Prevalence of Elevated Transaminases in the US

If defined as
- AST \(<37 \text{ or } ALT \(<40
- \text{No hepatitis C or alcohol use}

ALT elevated – 7.3%
AST elevated – 3.6%
Either elevated – 8.1%

Prevalence of elevated liver tests was 2x higher compared to NHANES 1988-1994

NHANES 1999-2002

Is ALT a Sensitive Marker of Liver Disease?

- **Hepatitis C viremia**
  - Historical normal values (up to 40 U/L)
    - Sensitivity 55%, specificity 97%
  - Updated normal values (males 30 U/L, females 19 U/L)
    - Sensitivity 76%, specificity 89%

- **Detection of fibrosis in NAFLD**
  - 43% of normal ALT patients had fibrosis
  - 38% of elevated ALT patients had fibrosis

Serum ALT in Perspective

- We don’t know what a normal level is
- It lacks sensitivity for common liver diseases
- Elevations may be seen in normal people
- Degree of elevation does not correlate with severity of liver disease
Case Presentation

- 49 y/o female comes to establish care after moving to your area
- Pertinent history
  - Hypertension
  - Obesity
  - Fibromyalgia
- ROS
  - Weight gain of 45 pounds over the last year
  - Diffuse arthralgias and myalgias
  - No history of liver disease, denies alcohol use
  - Prior physician had a “concern” about lupus
Case Presentation

Medications
- Gabapentin,
- duloxetine,
- lisinopril,
- acetaminophen/hydrocodone PRN

Exam
- BMI 39, BP 145/90
- No significant findings on exam
<table>
<thead>
<tr>
<th>Current Labs</th>
<th>One year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST – 75</td>
<td>AST 50</td>
</tr>
<tr>
<td>ALT – 105</td>
<td>ALT – 80</td>
</tr>
<tr>
<td>AP – 98</td>
<td>AP – 105</td>
</tr>
<tr>
<td>T. bilirubin – 0.4</td>
<td>T. bilirubin – 0.5</td>
</tr>
<tr>
<td>Albumin 4.2</td>
<td>Albumin 4.0</td>
</tr>
<tr>
<td>Total protein – 6.5</td>
<td>Total protein – 6.9</td>
</tr>
<tr>
<td>ANA (+) 1:160</td>
<td></td>
</tr>
</tbody>
</table>
## Initial Step

### Exclude common treatable liver diseases
- Chronic viral hepatitis
  - HBsAG, anti-HCV
- Hemochromatosis
  - Serum iron, TIBC and ferritin

### Our Patient’s Results
- HBsAg (-)
- Anti-HCV (-)
- Iron 59
- TIBC 350
- Transferin saturation 17%
- Ferritin 650 ng/ml
Our Patient’s Results

Iron 59
TIBC 350
Transferrin saturation 17%
Ferritin 650 ng/ml

Could this be Hemochromatosis?

- Common – 1/400 whites, penetrance of ~30%
- Presents with mild (<4x ULN) transaminase elevations
- End-organ damage in middle age
- Best screening test – transferrin saturation ≥45%
  - Elevated ferritin may indicate inflammation
- Genetic testing available to establish the diagnosis
  - C282Y homozygote
  - C282Y / H63D heterozygote

Adams PC, Barton JC. Lancet 2007;370:1855-60
Our Patient’s Results

- AST - 75
- ALT - 105
- AP - 98
- T. bilirubin - 0.4
- Albumin 4.2
- Total protein - 6.5
- ANA (+) 1:160
- IgG level - normal

Could this be Autoimmune Hepatitis?

- Treatable, fatal if untreated
- Typical presentation
  - Significant ALT elevation (>5x ULN)
  - Elevated total protein, gamma globulin, IgG levels
  - Increased bilirubin is common
- Autoimmune markers
  - ANA (+) in ~ 67%
  - F-actin Smooth Muscle antibody (+) in ~ 87%
- Liver biopsy with typical but not diagnostic findings

Krawitt EL. NEJM 2006;354-366
**Our Patient’s Results**

- AST – 75
- ALT – 105
- AP – 98
- Total bilirubin – 0.4
- Albumin 4.2
- Total protein – 6.5

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**Could this be alcoholic liver disease?**

- History unreliable
- Alcoholics usually do not develop liver disease
  - Don’t assume alcohol use is the cause of elevated transaminases
- Typical liver enzyme pattern
  - AST:ALT ratio > 2 or 3
  - Levels usually < 200 U/dl
- Diagnosis
  - Exclude other causes of liver disease

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### Our Patient’s Results

<table>
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<tr>
<th>Test</th>
<th>Value</th>
</tr>
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### What about Celiac Disease?

- Affects 1% of the US population
- Elevated liver enzymes
  - Most common hepatic presentation of celiac disease
  - 40% adults and 54% of children with Celiac disease
- Up to 9% of patients with unexplained elevated liver enzymes have celiac disease
- Diagnostic testing
  - TTG IgA antibodies

Common Liver Diseases to Always Exclude

- Chronic viral hepatitis
  - anti-HCV, HBsAg
- Hemochromatosis
  - iron, TIBC, ferritin
- Autoimmune hepatitis
  - typical presentation, elevated IgG, typical liver biopsy
- Non-alcoholic fatty liver disease (NAFLD)

Most common cause of elevated liver enzymes

Fatty liver disease (NAFLD)

The hepatic manifestation of the metabolic syndrome

Our Patient's Results

AST – 75
ALT – 105
AP – 98
T. bilirubin – 0.4
Albumin 4.2

Cholesterol - 295
LDL – 175
HDL – 32
Triglycerides – 350
FBS – 99 mg/dL

The Metabolic Syndrome

1. Abdominal obesity ✓
2. Hypertension ✓
3. Elevated triglycerides ✓
4. Low HDL ✓
5. Fasting BS >100 mg/dL

Driven by insulin resistance

HOMA: Glucose x insulin / 405 – if > 2
indicates insulin resistance

NAFLD

- Encompasses 2 diseases
  - Fatty liver – fat without inflammation
  - Steatohepatitis (NASH) – fat with inflammation

- Prevalence in the US
  - NAFLD – 46%
  - NASH – 12.2%

- Prevalence by race
  - Hispanics – 58.3%
  - Whites – 44.4%
  - African-Americans – 35.1%

## Risk Factors for NAFLD

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<th>Emerging Association</th>
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<tbody>
<tr>
<td>Obesity</td>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Obstructive Sleep apnea</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Hypopituitarism</td>
</tr>
<tr>
<td></td>
<td>Hypogonadism</td>
</tr>
</tbody>
</table>
Diagnosing NAFLD

- Exclude other causes of liver disease
  - EtOH < 20g / day

- Identify the typical phenotype
  - Metabolic syndrome criteria

- Be aware that ultrasound may lead to an incorrect diagnosis in 10% to 30% of cases
  - A “bright liver” may indicate fibrosis, not fat
  - A normal liver may have up to 30% fat

- Recognize common confounding variables
  - ANA is positive in up to 30%
  - Elevated ferritin is common in NAFLD

Liver Biopsy – Diagnostic Tool

- Only tool that confirms fat in the liver
- Differentiates NAFLD from NASH

Our Patient’s Results

Platelets: 325,000/mm³
AST: 75
ALT: 105
AST:ALT ratio: 0.6
HOMA score: 6
Direct Bilirubin: 0.1
MCV: 89
RUQ Ultrasound: consistent with steatosis

Selective Use of Liver Biopsy

- Identify patients likely to have advanced fibrosis
  - Platelet count < 150,000
  - AST:ALT ratio > 0.8
  - Elevated direct bilirubin
  - High levels of insulin resistance
  - Elevated MCV

- Non-invasive tools to detect NASH or fibrosis may soon be available.

Management of NAFLD

- **Weight loss and Exercise**
  - Diet low in simple sugars
  - Favor low glycemic foods
  - Not a “low fat diet”!

- **Recognize that NAFLD is a marker for premature cardiac death**

Carotid Artery Intimal Media Thickness

Increased risk for atherosclerosis

Can you prescribe a statin?

- **Yes!**

- **Dallas Heart Study¹**
  - Statin use:
    - No increased prevalence of elevated ALT
    - No worsening hepatic steatosis

- **Histopathological study²**
  - Statin use:
    - Significant reduction in liver fat
    - Reduced progression to advanced fibrosis

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¹ Browning JD. Hepatology 2006;44:466-471  
Fatty Liver Disease

Can I just take a pill?
Pioglitazone for NASH

Impaired glucose tolerance or type II DM

Biopsy confirmed NASH

All patients placed on weight reduction program

Pioglitazone 45mg/d

Belfort R et al. NEJM 2006;355:2297-307
Vitamin E for NASH

Non-diabetics with NASH

Pioglitazone 30mg/d or Vitamin E as d-tocopherol 800 IU/d

Histologic improvement:
vitamin E – 43%
pioglitazone – 19%

Sanval. NEJM 2010
Surgical Weight Loss?

- **Roux-y-gastric bypass**
  - 82-85% improvement in inflammation
  - 39-75% improvement in fibrosis

- Monitor for signs of liver dysfunction before and after surgery

Optimizing Metabolic Syndrome

- ACE inhibitor
  - Reduced Steatosis
  - Decreased inflammatory cytokines
  - Stable / Reduced fibrosis

- ARB

- Fish Oil
  - Improved histological steatosis
  - Improved insulin sensitivity

- Statins
  - SAFE!
  - Improved biochemistry
Management of NAFLD - Recommendations

- If diabetes present
  - Favor pioglitazone
    - **Pro:** reduces intrahepatic insulin resistance, clinical data shows benefit
    - **Con:** weight gain, other toxicity
  - Consider metformin
    - **Pro:** Weight loss
    - **Con:** No change in intrahepatic insulin resistance, clinical studies show limited to no benefit in NASH

- All patients
  - Weight loss counseling
  - Consider d-tocopherol, 800 IU/d
Fatty Liver Disease

summary
Approach to Elevated Liver Tests

Look for common treatable diseases
a) viral hepatitis, b) hemochromatosis c) alcohol abuse

Consider important treatable diseases
Celiac sprue
Autoimmune hepatitis
Medication hepatotoxicity

Features of the metabolic syndrome present?

yes
NAFLD likely, look for evidence of advanced fibrosis, consider biopsy

no
Referral for expert evaluation liver biopsy
What Will the Specialist Look For?

- Wilson’s disease
- Alpha-1 anti-trypsin deficiency
- Occult hepatitis B infection
- Seronegative autoimmune hepatitis
- NAFLD without metabolic syndrome
- Others
Take Home Points

1. Liver enzymes are important markers of liver dysfunction but are not
   - Liver function tests
   - Accurate markers of severity of liver disease

3. Every patient with elevated ALT deserves an evaluation to detect treatable conditions

4. Month to month variation is expected, minor changes in levels have no prognostic significance
Take Home Points

1. NAFLD is the most prevalent liver “disease” in the United States
3. Hard to predict development of NASH or cirrhosis
4. Treatment should focus on weight loss, optimal control of blood sugars and lipids
5. Vitamin E in non-diabetic first line therapy, +/- Pioglitazone as alternative