NASH, Cirrhosis, HCC
On the Rise:
How can primary care be better prepared?

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NAFLD and NASH: Background
- Nonalcoholic fatty liver disease (NAFLD) is a spectrum - mildest form is simple fatty liver.
- Nonalcoholic steatohepatitis (NASH) is a subtype of NAFLD - fatty liver with inflammation
- NAFLD affects 20-30% of US population, NASH affects 2-3% – on the rise with obesity
- Primary NAFLD considered the hepatic complication of the metabolic syndrome
- Can progress to cirrhosis, hepatocellular carcinoma, and liver failure in 10-15% of NASH pts

NAFLD Associations
- NAFLD is closely associated with
  - Metabolic syndrome
  - Obesity
  - Insulin resistance
- NAFLD rising alongside rise in obesity
Association with Obesity and Men
- Among morbidly obese going into bariatric surgery,
  - 91% NAFLD and 37% NASH
- NASH in morbidly obese men was almost twice as high as in morbidly obese women (60.3% vs 30.9%).
  - NASH more common in men may reflect higher prevalence of metabolic syndrome in men
- Less common in African-Americans (less metabolic syndrome in African-Americans)

Making the Diagnosis
- Most cases of NAFLD are clinically silent
- Most patients detected due to incidental finding of elevated aminotransferase levels or radiographic studies suggesting the liver is fatty

Evaluation of suspected NAFLD
- Exclude alcohol use
  - (not more 1–2 drink/ day)
- Exclude secondary causes of fatty liver:
  - Drugs (corticosteroids, amiodarone, MTX, CCB, tamoxifen)
  - Altered nutritional states (rapid wt loss, TPN, cachexia)
  - Metabolic or genetic (Wilson disease, lipodystrophy)
  - Miscellaneous (HIV, IBD, hepatotoxins)
- Imaging studies:
  - U/S - increased echogenicity
  - CT - low attenuation
  - Liver biopsy
- Exclude other liver dz:
  - Hepatitis B and C
  - Alpha-1 antitrypsin defic.
  - Hemochromatosis
  - Autoimmune hepatitis (anti-smooth muscle antibody, antinuclear antibody)
  - Wilson disease (ceruloplasmin)
CT – Fatty Liver

Limited Understanding of Natural History

- Rate of disease progression unclear
- Unclear which clinical, biochemical, or histologic factors predict progression
- In 1995 cohort with 11 yrs follow up, simple steatosis did not progress to NASH or cirrhosis.
- But once patients have developed NASH, 32% to 41% of patients have fibrosis progression over a median follow-up of 4.3 to 13.7 years.


Cohort Study

- 22 patients with NASH underwent repeat liver biopsy to measure fibrosis progression
  - At least 3 years following baseline biopsy
- Liver biopsy specimens examined in blind, unpaired manner
  - Scored for steatosis (fat) and fibrosis (scarring)
- Median follow-up 4.3 yrs


NASH

Disease progresses in 30%

- 31.8% had progressive fibrosis, none progressed to cirrhosis
- Significant predictors of progression:
  - Obesity: 86% progressors vs 27% nonprogressors (P = .01)
  - Median BMI: 33.2 progressors vs 29.0 nonprogressors (P = .024)
- No significant differences: Age, sex, diabetes, hyperlipidemia, ALT, AST:ALT ratio, Serum albumin, prothrombin time

Fibrosis can progress, without correlation to liver enzymes

- Fibrosis severity increased over time in NAFLD patients
  - Significant variability in histologic course
  - Fibrosis progression more common if diabetes, higher BMI, and lower fibrosis stage at initial biopsy

- Aminotransferases, steatosis, and liver inflammation improved over time
  - AST, ALT more indicative of steatosis and inflammation than fibrosis progression in NAFLD

Significant variability in histologic course

Fibrosis progression more common if diabetes, higher BMI, and lower fibrosis stage at initial biopsy

Aminotransferases, steatosis, and liver inflammation improved over time

AST, ALT more indicative of steatosis and inflammation than fibrosis progression in NAFLD


NASH: Treatment Strategies

- Treatment of NAFLD gaining increasing attention
- Weight loss and treating components of the metabolic syndrome
- Insulin sensitizers such as biguanides and glitazones, antioxidants such as vitamin E, and lipid-lowering agents
  - shown promise in small clinical trials, but the evidence remains preliminary

Treatment of NAFLD gaining increasing attention

Weight loss and treating components of the metabolic syndrome

Insulin sensitizers such as biguanides and glitazones, antioxidants such as vitamin E, and lipid-lowering agents
  - shown promise in small clinical trials, but the evidence remains preliminary

Treatment Studies in NASH

<table>
<thead>
<tr>
<th>Tx</th>
<th>N</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>52</td>
<td>Randomized, double-blind, placebo controlled trial, ALT declined by half in 48% in the orlistat group vs 26.4% in the placebo group, with mean weight loss of 6% to 8% of body weight in both groups</td>
</tr>
<tr>
<td>Diet</td>
<td>74</td>
<td>Retrospective review, high fat intake (48% of calories) was associated with lower odds of hepatic inflammation compared with 26% fat intake (odds ratio 0.13, ( P = .007 ))</td>
</tr>
<tr>
<td>Metfor</td>
<td>110</td>
<td>In an open-label, randomized trial, ALT levels normalized in 56% of the metformin group compared with 22% of controls taking vitamin E or following a prescriptive diet (( P = .0006 ))</td>
</tr>
</tbody>
</table>

Treatment Studies in NASH (2)

<table>
<thead>
<tr>
<th>Tx</th>
<th>N</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosiglitazone</td>
<td>30</td>
<td>Open-label, single-arm study, 10 (45%) of 22 patients had resolution of NAFLD on liver biopsy after treatment</td>
</tr>
<tr>
<td>Vitamin C, E</td>
<td>45</td>
<td>Randomized, double-blind, placebo-controlled trial, fibrosis scores on liver biopsies improved with vitamins C and E; no changes in ALT or incidence of hepatic inflammation or fibrosis</td>
</tr>
<tr>
<td>Ursodeoxy-cholic acid</td>
<td>166</td>
<td>Randomized, double-blind, placebo-controlled trial, no change was seen in steatosis, fibrosis, or enzyme levels</td>
</tr>
</tbody>
</table>
Metformin vs. Vitamin E vs. Diet

Randomization

Optional liver biopsy

Nondiabetic NAFLD patients (N = 110)

Metformin* 2 g/day (n = 55)

Vitamin E 800 IU/day (n = 28)

Prescriptive weight-reducing diet (n = 27)

*Metformin progressively increased from 250 mg twice daily to maximum dose over 4 weeks to minimize gastrointestinal side effects.


Metformin Superior to Vitamin E or Prescriptive Diet


Body Mass Index and ALT Normalization

- Body mass index (BMI) significantly decreased from baseline values within each group
- Multivariate analysis found % change in BMI and metformin treatment to significantly increase chance of ALT normalization
  - Odds ratio BMI, 1.22
    - 95% confidence interval (CI) = 1.10-1.37 (P = .0002)
  - Odds ratio metformin treatment, 5.98
    - 95% CI = 2.05-17.45 (P = .0011)


Preliminary support for Metformin

- Long-term metformin treatment significantly better than vitamin E or diet at achieving ALT normalization
  - In nondiabetic NAFLD patients who all received brief nutritional counseling
  - Metformin benefits not limited to reduced BMI
  - Significantly better control of metabolic syndrome parameters also observed with metformin
- Requires confirmation in double-blind trial and showing changes in liver histology


### NAFLD Outcomes According to Treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metformin (n = 55)</th>
<th>Vitamin E/Diet (n = 55)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT normalization (&lt; 40 U/L), %</td>
<td>56.3</td>
<td>21.8</td>
<td>.0006</td>
</tr>
<tr>
<td>Mean reduction in BMI, kg/m²</td>
<td>1.3</td>
<td>1.0</td>
<td>.113</td>
</tr>
<tr>
<td>Mean reduction in fasting glucose, g/dL</td>
<td>56.3</td>
<td>77</td>
<td>.125</td>
</tr>
<tr>
<td>Mean reduction in fasting insulin, µU/mL</td>
<td>82</td>
<td>86</td>
<td>.029</td>
</tr>
<tr>
<td>Maximum HOMA reduction, units</td>
<td>1.5</td>
<td>0.5</td>
<td>.0002</td>
</tr>
<tr>
<td>Metabolic syndrome, %</td>
<td>18</td>
<td>32.5</td>
<td>.001</td>
</tr>
</tbody>
</table>

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Multivariate analysis found % change in BMI and metformin treatment to significantly increase chance of ALT normalization

Requires confirmation in double-blind trial and showing changes in liver histology
Lipid-lowering agents

- A few small studies found that aminotransferase levels fell with both statins and gemfibrozil.
- Even if liver enzyme levels are abnormal, most experts believe that statins are relatively safe to use in patients with NAFLD who need cholesterol-lowering agents.


Cirrhosis

- Cirrhosis is the end stage of chronic hepatitis.

<table>
<thead>
<tr>
<th>Disease</th>
<th>History of alcohol abuse</th>
<th>AST/ALT ratio often &gt;2:1; AST and ALT both &lt;500 IU/mL (if no other processes)</th>
<th>GGT may be ↑</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic liver disease</td>
<td>HCV Ab +, HCV RNA +</td>
<td>AST, ALT may be ↑ or normal</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>HBsAg +, HBV DNA +</td>
<td>AST, ALT usually ↑; may be normal</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Antimitochondrial antibodies +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>History of inflammatory bowel disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>ANA often +, ASMA often +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>ANA often +, ASMA often +, Anti-LKM-1 often +</td>
<td></td>
<td>Hypergammaglobulinemia</td>
</tr>
<tr>
<td>NAFLD</td>
<td>History of obesity, dyslipidemia, DM</td>
<td>↑ AST and/or ALT Fatty infiltration of liver on imaging</td>
<td></td>
</tr>
</tbody>
</table>

Cirrhosis is the end stage of chronic hepatitis.

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Decompensated Cirrhosis

- Can remain compensated for many years before a decompensating event
- Decompensation marked by development of any of these complications: Jaundice, variceal bleed, ascites, encephalopathy
- Development of HCC can lead to decompensation

Management of Compensated Cirrhosis

1. Treatment of underlying liver disease
   - HBV and HCV (prior lecture)
   - Abstinence from alcohol
2. Prevention of portal hypertension complications
   - Screen all patients with EGD for varices
   - Primary prophylaxis for variceal bleed
3. Screening for HCC

Prevent Additional Insults

- Screening EGD in Cirrhosis
  - To detect the presence/size of varices to determine whether the patient should receive primary prophylaxis to prevent hemorrhage
  - Gastroesophageal varices are present in approximately 50% of cirrhotic patients
  - Patients with gastroesophageal varices develop variceal hemorrhage at a rate of around 12.5 to 15% per year.
  - Mortality following variceal hemorrhage is around 15-20%.
Primary prophylaxis
After detecting varices on screening EGD

The following interventions are recommended based on RCTs demonstrating delay in time to first variceal hemorrhage:

- Nonselective β-blockers (propranolol, nadolol)
- Endoscopic variceal ligation (EVL)

Management of decompensated cirrhosis

1. Acute variceal hemorrhage
2. Spontaneous bacterial peritonitis
3. Ascites
4. Hepatic encephalopathy

Secondary prophylaxis
Prevention of recurrence after acute bleed

The following interventions are recommended based on randomized clinical trials and meta-analyses:

- Nonselective β-blockers (propranolol, nadolol, timolol) plus endoscopic variceal ligation (not β-blockers alone)
- Recommended rescue therapies are TIPS or shunt surgery

Treatment of uncomplicated ascites

The following interventions are recommended based on controlled and uncontrolled studies as well as expert opinion:

- Salt restriction
- Spironolactone plus furosemide, but not furosemide alone
- Large-volume paracentesis plus albumin in hospitalized patients with tense ascites in whom other complications have been resolved
- Short-term (7-day) antibiotic prophylaxis in cirrhotic patients with (or without) ascites admitted with GI hemorrhage
Regularly Calculate the MELD

- Model for End-Stage Liver Disease (MELD) Score
  - The MELD score is a newer method for predicting 3-month survival. It is used for liver allocation (transplant) by the United Network for Organ Sharing (UNOS) and has been adopted for use in the nontransplant setting.
  - It is used to determine how urgently a patient needs a liver transplant within the coming 3 months.
  - MELD = 3.78\(\ln \text{serum bilirubin (mg/dL)}\) + 11.2\(\ln \text{INR}\) + 9.57\(\ln \text{serum creatinine (mg/dL)}\) + 6.43
  - A calculator for determining MELD scores is available on the web

Referral for Liver Transplant

- Local referral guidelines, usually based on MELD score
- Typically should refer for early transplant consideration if MELD >8

Hepatocellular Carcinoma (HCC)

A Growing Epidemic of HCC

- Worldwide –
  - 5th most common cancer
  - 3rd most common cancer death
- In US, Incidence rising rapidly, due to hep C
  - 1.4/100,000 (1976-80) → 5.8/100,000 (*)
- 82% of 530,000 cases caused by viral hepatitis
  - 316,000 with hepatitis B
  - 118,000 with hepatitis C
Overlapping Epidemiology
HBV, HCV, HIV and Hepatocellular Carcinoma

HIV
Hepatitis B
Hepatitis C
Hepatocellular Carcinoma

HCC has poor prognosis

- Aggressive tumor
- Median survival following diagnosis is approximately 6 to 20 months.
- Mainstay of therapy is surgical resection, but majority are not eligible due to tumor extent or liver function.

AFP

- Does not correlate well with extent of HCC
- Elevated AFP is seen in chronic liver disease without HCC
  - 23% of HCV patients had AFP >10 ng/mL
- Test characteristics depend on study population, cutoff level, and gold standard
  - Specificity 41-65%
  - Sensitivity 80-94%
- Newest recommendation for screening is to use ultrasound only, AASLD (2005) and not using AFP as a sole screening test.
- However, a rise in AFP should raise suspicion

Imaging used for HCC

Ultrasound
- Hard to distinguish small lesions
- Sensitivity 40-78%, specificity 90%
- Frequently requires confirmatory CT

CT
- Hard to distinguish tumor from cirrhotic nodules
- Sensitivity 68%, specificity 81%
- Higher sensitivity helical CT with arterial phase contrast

MRI
- Higher sensitivity and specificity in cirrhosis in differentiating benign regenerative nodules
Imaging of HCC

MRI of the liver in 73 yo man with alcohol and HCV

Criteria for Good Screening Tests

- Early detection reduces cancer death
- Acceptably low number of false positives

Best evidence for a good screening test:

- Randomized trials
- Well-done prospective case-control studies

Data to support the impact from HCC screening?

- One prospective randomized trial of screening for HCC in 18,000 hepatitis B patients in China
- No morbidity or mortality benefit has been demonstrated from screening
- Cohort studies and cost-efficiency modeling support screening
- Consensus recommendations, but not evidenced based - therefore not as widely accepted
- No prospective trial can realistically be expected randomizing to screening vs. no screening

Published HCC Guidelines

- VA Guidelines soon
Published HBV and HCV Guidelines on HCC Screening

- HBV guidelines by AASLD (2007) and others recommend screening based on demographics and clinical stage – but not only in cirrhosis
- HCV guidelines by NIH (2002), AASLD (2004), VA (2006) recommended screening every 6-12 months AFP and ultrasound only in patients with HCV cirrhosis or coinfection

Argument for HCC screening

- Definable population
- Early detection is necessary for treatment with surgical resection, ablation or transplant
- Prognosis for advanced disease is poor

Argument against HCC screening

- Methods for screening are limited
- High cost of testing
- High frequency needed to detect early
- Even with detection, available treatments of HCC are poor
- No prospective studies have demonstrated a mortality benefit

Why not screen all HCV and HBV?

- Not all HCV patients are appropriate
- In HCV, genotype and viral load not influence on HCC risk
- HBV natural history variable among groups
- HBV more oncogenic
- HBV genotypes vary in HCC risk
- HBV viral load vary with HCC risk
Rationale for HCC screening in chronic HBV

- In 70–90% of persons, tumor begins as a single lesion
- Doubling time variable: 1–12 months (mean, 6 months)
- Long asymptomatic stage
- Evidence-based: One case-historical control study; several case series studies
- Can develop in absence of cirrhosis

Lok & McMahon, Hepatology 2001; 34: 1225
Di Bisceglie, Gastroenterology 2004; 127(suppl. 1): 104

Which patients with HBV should be screened?

- Screening recommended in high risk patients with AFP and liver ultrasound every 6 months
  - male, mean age >45 years
  - with cirrhosis
  - family history of HCC
- HCC does occur in inactive carriers but screening is controversial
  - consider periodic testing for elevated AFP in individuals from endemic areas

Categorization of HCC Treatments

- Potentially curative therapy
  - resection, transplant, local ablation
- Palliative
  - trans-arterial chemoembolization (TACE), chemotherapy
- No therapy

Screening for HCC in HBV + Alaska natives

- 16-year population-based study of 1487 HBsAg-positive Alaska natives
- AFP levels measured 6-monthly – if elevated, followed by ultrasound examination
- Elevated AFP in 61 men, 39 non-pregnant women (6.7% of total study population)
- HCC diagnosed in 32
- Screening (semiannual AFP measurements) of HBsAg+ Alaskan natives effective in detecting HCC at resectable stage
  - 5- and 10-year survival rates significantly improved with screening

McMahon et al, Hepatology 2000; 32: 842

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Non-surgical HCC therapies
- Liver transplantation
- Radiofrequency ablation (RFA)
- Percutaneous ethanol or acetic acid ablation
- Transarterial chemoembolization (TACE)
- Cryoablation
- Radiation therapy
- Systemic chemotherapy

Sorafenib – oral systemic chemotherapy for advanced HCC

Individuals with advanced HCC, naive to systemic therapy, with well-preserved liver function
- Sorafenib 400 mg po twice daily (n = 299)
- Placebo (n = 303)


Sorafenib: Phase III trial
- Randomized placebo-controlled trial, international
- Assessments
  - Patients assessed every 3 weeks and at end of treatment
  - Tumor measurements performed every 6 weeks and at end of treatment by CT imaging or MRI
- Primary endpoints: overall survival and time to symptomatic progression
- Secondary endpoints: time to radiologic progression, disease-control rate, safety
- Intent-to-treat analysis
- Study prematurely terminated - 321 deaths had occurred at this time


Results
- Sorafenib associated with significantly longer overall survival vs placebo
  - 10.7 vs 7.9 months, respectively (P < .001)
  - 1-year survival: 44% vs 33%, respectively (P = .0009)
- Time to symptomatic progression not significantly different between sorafenib and placebo groups
  - 4.1 vs 4.9 months, respectively (P = .77)
- Time to radiologic progression significantly longer with sorafenib vs placebo
  - 5.5 vs 2.8 months, respectively (P < .001)
- No complete and few partial responses observed in both arms

Results continued

- Incidence of treatment-related AEs higher in sorafenib arm vs placebo arm
  - Most events grade 1/2 in severity - all-grade diarrhea, weight loss, hand-foot skin reaction, alopecia, anorexia, voice changes

- Overall incidence of serious AEs from any cause comparable between sorafenib and placebo arms (52% vs 54%, respectively)

- Similar proportion of patients discontinued treatment in each arm


Sorafenib summary

- The only FDA-approved chemotherapy agent for advanced HCC, based on demonstration of survival benefit