Abnormal LFTs and Nonalcoholic Steatohepatitis: Assessing Severity and Optimizing Management

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Screening of NAFLD on high risk population

- Liver biochemistries might be normal in NAFLD
  - Current reported reference labs are outdated
- Cost-effectiveness of screening not proven yet
- No systematic screening on family member is recommended
- Ultrasound and transient elastography promising but not enough data to support
- High index of suspicious on high risk patients (T2D)
Prevalence of NAFLD

• Overall global prevalence is 25.24% (1)

• Estimate prevalence of NASH in the general population is 1.5%-6.45% (1)

• Ethnicity difference (2,3)
  • Hispanics > nonHispanic whites > nonHispanics blacks > Alaskan-natives and American-natives (2)

• Genetic variation of PNPLA-3 (5)
Diagnosis criteria for NAFLD

- Hepatic steatosis by image or histology
- No significant alcohol consumption
- Absence of other potential culprits that might cause hepatic steatosis
## High risk groups for NAFLD

<table>
<thead>
<tr>
<th>Common conditions with established association</th>
<th>Other conditions</th>
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<tbody>
<tr>
<td>Obesity (most common risk factor)</td>
<td>Hypothyroidism</td>
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<td>T2DM (one to two third of patients)</td>
<td>Obstructive Sleep Apnea</td>
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<tr>
<td>Dyslipidemia</td>
<td>Hypopituitarism</td>
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<tr>
<td>Metabolic Syndrome</td>
<td>Hypogonadism</td>
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<td>Polycystic Ovary Syndrome</td>
<td>Pancreatoduodenal resection</td>
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<td>Psoriasis</td>
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Natural history of NAFLD

- Increased mortality compared with matched-control population
- Leading cause of death is cardiovascular disease
- Cancer related mortality is among three top caused of death
- Third most common cause of HCC in USA (9% annual rate)
- 13% of NAFLD HCC patient do not have cirrhosis (6)
- Cryptogenic cirrhosis most probable burn out NAFLD
Important outcomes in NAFLD

- Fibrosis progression (best predictor of mortality)
- Development of HCC (0.44/ 1000 person-years)
Alcohol consumption and NAFDL

• Definition mutually exclusive of significant alcohol consumption

• Significant alcohol consumption is >21 drinks/week for men and >15 drinks/week for women

• Standard drink is 14 gm of pure alcohol
Incidental discovery of hepatic steatosis

- 11% patient incidental HS are at high risk of advanced hepatic fibrosis
- Incidental HS on image should be evaluated as NAFLD (chronic liver disease work-up)
- Patient with negative work-up needs metabolic risk factor assessment
Evaluation of inspected NAFLD

• Meet diagnostic criteria

• Medical history and exam considering risk factors (obesity, dyslipidemia, IR DM, hypothyroidism, PCOS, sleep apnea, etc.)

• Exclude co-existing etiologies of chronic liver disease

• Be aware of serological abnormalities that do not represent CLD (eg. ferritin, autoantibodies)

• Liver biopsy should be considered in significant elevations of ferritin (>1.5 ULN), or clinical features suspicious for AIH (>5 ULN aminotransferases, high globulins, high protein to albumin ratio, etc.)
Non-invasive assessment of steatohepatitis and fibrosis

- Liver biopsy gold-standard, however limited by cost, sampling errors and morbidities, mortalities
- Serum aminotransferases, CT, MR do not reliable assess liver histology
Non invasive quantification of hepatic steatosis

- MR spectroscopy and MR proton density fat fraction
- Transient elastography
Noninvasive prediction of steatohepatitis and advanced fibrosis

- Metabolic syndrome is strong predictor of steatohepatitis.

- Clinical decision aids
  - FIB-4 [http://gihep.com/calculators/hepatology/fibrosis-4-score](http://gihep.com/calculators/hepatology/fibrosis-4-score)

- Biomarkers
  - Enhanced Liver Fibrosis (panel, not available in USA)
  - Fibro Test, Hepascore, Fibrometer

- Imaging
  - TE (VCTE)
  - MRE
When to obtain a liver biopsy

• NAFLD patient at high risk of steatohepatitis and advanced fibrosis
  • MetS, NFS, FIB-4 liver stiffness by TE or MRE
• Suspected NAFLD with competing etiologies
When to obtain a liver biopsy

Outcomes of Patients with Abnormal Liver Test
Management of patient with NAFLD

• Whom to treat
  • Treat associated metabolic co-morbidities
  • Pharmacology treatment should be reserved to patient with biopsy-proven NASH
Management of patient with NAFLD

• Lifestyle interventions
  • Loss of >5% of body weight improves hepatic steatosis (9)
  • Loss of >7% of body weight improves NASH
  • Loss of >10% of body weight improvement in all features
  • Exercise have been associated with improvement on hepatic steatosis
  • Combination of hypo-caloric diet (deduction in 500-1000kcal/day) and moderate exercise probable will have the best outcomes
Management of patient with NAFLD

- Insulin sensitized
  - Metformin: no significant improvement on liver histology
- Thiazolidinediones: pioglitazone improves histology in T2D and no T2D with biopsy-proven NASH (Bladder CA, weight gain, cardiovascular events)
- GLP-1: Liraglutide associated with resolution of steatohepatitis and less fibrosis progression. More weight loss and GI side effects
- Vitamin E
  - Decrease in aminotransferases in NASH
  - Improvement in steatosis, inflammation, and balloting in non T2D
  - No effect on hepatic fibrosis
  - Meta-analysis showed increase in all-cause mortality
  - Increase in prostate cancer
Management of patient with NAFLD

• Bariatric surgery

  • Improves long-term survival and death from CVD and malignancy

  • Foregut bariatric surgery had demonstrated improvement in steatohepatitis and fibrosis

  • Most single-center or prospective cohorts studies

  • Foregut bariatric surgery might be considered on case-by case basis on compensated NASH or cryptogenic cirrhosis
Management of patient with NAFLD

• CVD and Dyslipidemia
  • NAFLD considered a risk factor for CVD
  • NAFLD frequently associated with proatherogenic liver profile
  • Use of statins seldom cause hepatotoxicity in patient with NAFLD irrespective of baseline liver enzymes elevation
NAFLD therapies in horizon

• Farnesoid X receptor agonist
  • Obeticholic acid
    • Ongoing phase 3 trial (REGENERATE, REVERSE)
    • Data expected late this year
  • Tropifexor
    • Ongoing phase 2 trial
    • Improvement on ALT, HFF and body weight
• Dual PPARa/d agonist
  • Elafibranor
    • Efficacy in NASH without fibrosis and cardiometabolic profile (phase 2)
  • Saroglitazar
    • Improvement on ALT, hepatic steatosis, IR, and dyslipidemia
References


