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  - Current reported reference labs are outdated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

Common conditions with established association	Other conditions
Obesity (most common risk factor)	Hypothyroidism
T2DM (one to two third of patients)	Obstructive Sleep Apnea
Dyslipidemia	Hypopituitarism
Metabolic Syndrome	Hypogonadism
Polycystic Ovary Syndrome	Pancreatoduodenal resection
	Psoriasis

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

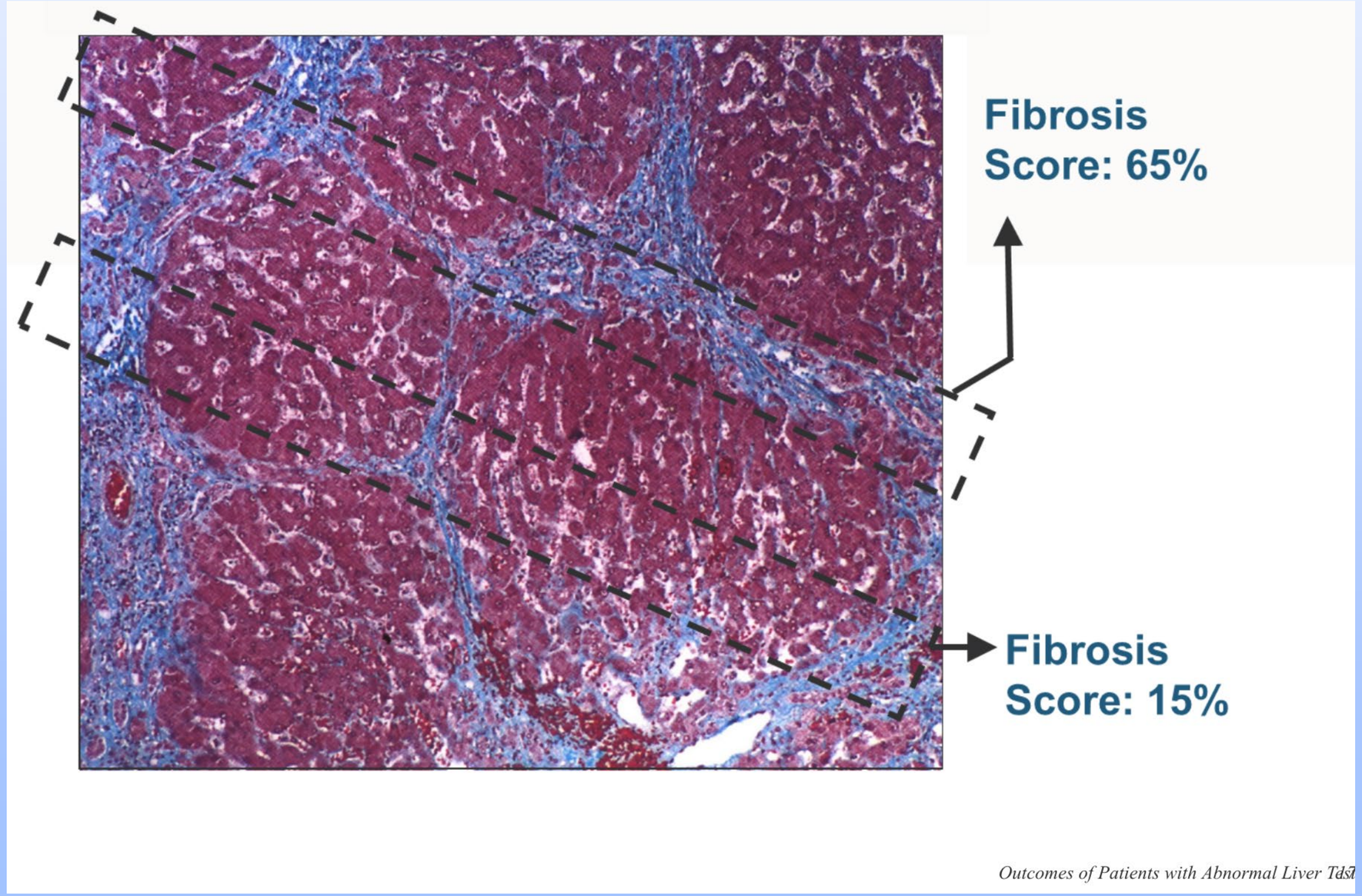
Noninvasive prediction of steatohepatitis and advanced fibrosis

- Metabolic syndrome is strong predictor of steatohepatitis.
- Clinical decision aids
  - NFS http://gihep.com/calculators/hepatology/nafld-fibrosis-score/
  - FIB-4 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



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

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