Non-alcoholic Fatty Liver Disease

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Definition of NAFLD

- Evidence of hepatic steatosis by imaging or histology
- No causes for secondary hepatic fat accumulation
  - Significant alcohol consumption:
    - >21 drinks/wk in men and >14 drinks/wk in women
  - Steatogenic medications: amiodarone, MTX, corticosteroids, tamoxifen
  - Hereditary disorders: Wilson’s disease
  - Hepatitis C, genotype 3
  - Starvation, TPN
Definition of NAFLD

• Metabolic risk factors most common
  – Obesity, diabetes, dyslipidemia

• Further defined as NAFL or NASH
  – Simple steatosis (no fibrosis)
  – Steatosis with inflammation (no fibrosis)
  – Steatosis, inflammation and fibrosis (NASH)
  – Steatosis, inflammation, balloon cells, Mallory’s hyaline or fibrosis (NASH)
Risk Factors Associated with NAFLD

- Insulin resistance is the hepatic manifestation of metabolic syndrome (MS)
- MS defined by 3 or more of the following
  - Elevated triglycerides (>150 mg/dL)
  - HDL levels <40 in men and <50 in women
  - Elevated fasting glucose (>110 mg/dL)
  - HTN (>130/85 or antihypertensive meds)
  - Abdominal obesity
Prevalence of NAFLD

- Worldwide ranges from 6.3% to 33%
  - Median of 20% general population
- Patients undergoing bariatric surgery, >90%
- High prevalence in type II diabetes mellitus
  - US study of type II showed 69% prevalence
- High serum TG and low HDL very common
- Prevalence increases with age
- Hispanics and Asians higher risk, AA lower
Natural History

- Simple steatosis have very little progression
- NAFLD has increased overall mortality
  - Most common cause is cardiovascular death
- NASH patients have increased liver related mortality
- Patients at increased risk of hepatoma (HCC)
  - Lower decompensation and mortality compared to HCV
Incidental Fatty Liver

• Unsuspected NAFLD + signs/symptoms attributable to liver disease or abnormal liver tests, evaluate and work up (1, A)

• Unsuspected + no liver related signs/symptoms and normal liver tests, reasonable to assess for metabolic risk factors and alternate causes such as alcohol or medication (1, A)

• Unsuspected, asymptomatic and normal liver tests, liver biopsy cannot be recommended (1,B)
Initial Evaluation

• Newly suspected NAFLD, exclude other CLD
  – HH, AIH, viral, Wilson’s
  – Elevated ferritin common in NAFLD but elevated ferritin and iron saturation = further testing
    • Liver biopsy if high ferritin, high sat%, homozygote or heterozygote C282Y

• Up to 50%NAFLD can have nl ALT and AST
Noninvasive Assessment

• NAFLD Fibrosis Score:
  – Age, BMI, hyperglycemia, platelet ct, albumin, AST/ALT ratio

• Transient elastrography measures liver stiffness---limited by patients with high BMI

• Metabolic syndrome predicts presence of SH in NAFLD, can move towards a liver bx
When to order a liver biopsy?

- Increased risk for NASH: presence of MS and possibly NAFLD score
- Suspected NAFLD with competing etiologies of fatty liver and coexisting CLD cannot be excluded without liver bx
Elev ALT and/or AST and FL on imaging + Presence of co-existing CLD

**NO**
DM or MS?

**YES**
Work up CLD and ?bx

**NO**
Liver bx

? AST>ALT, low alb, low plt

**YES**
Liver bx

?>65yo, FHx DM, FHx cirrhosis

**YES**
Liver bx

Reassess q 6-12 m
Management: Lifestyle

• Weight loss
  – Randomize 31 obese with NASH to intense lifestyle change (diet, behavior mod., 200 minutes/wk of moderate physical activity x 48 wks) vs. basic education alone
    • Intense arm 9.3% weight loss vs. 0.2%
    • Had improved steatosis, necrosis and inflammation
      – No change in fibrosis
    • If >7% loss, significant improvement in bx
Management: Lifestyle

- Weight loss improves steatosis either by low calorie diet alone or in conjunction with increased physical activity (1,A)
- 3-5% lost body fat necessary to improve steatosis but greater weight loss up to 10%, may be needed to reduce necroinflammation (1,B)
- Exercise alone may reduce steatosis but ability to reduce other liver histology unk (1,B)
Management: Metformin

• n=110 NASH (AJG 2005)
  – metformin 2 gm/day, vit E 800 IU/day or dietary induced wt loss x 12 months
  – AST, ALT improved more with metformin
  – Only modest improvement in steatosis and inflammation with metformin

• n=26 open label trial of metformin
  – Only 30% with improved NASH activity
    • Confounded by significant weight loss
Management: Metformin

• Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adult patients with NASH (1,A)
Management: Thiazolidinediones

- RCT pioglitazone 45mg/d with impaired GT or DM II (Belfort, NEJM, 2006)
  - Significant weight gain in pioglitazone
  - Significantly improved liver tests, steatosis, ballooning and inflammation
- N=74 RCT lifestyle change with either pioglitazone 30 mg/d or placebo x 12 mo. (Gastro 2008)
  - Steatosis without signif change but fibrosis did improve
Management: Thiazolidinediones

- **PIVENS** study, multicenter RCT, x 2 yr (Sanyal, NEJM, 2010)
  - N=247 non diabetic patients with NASH
    - Pioglitazone 30mg/d, vit E 800 IU or placebo
  - Primary end point: >2pts NAS with further goals
  - 19% placebo vs. 34% pioglitazone vs. 43% vit E
  - Pioglitazone did not meet primary end point
  - Resolution of NASH, sec. end point, significantly higher in pioglitazone than placebo
  - 4.7 kg weight gain with pioglitazone
Management: Thiazolidinediones

• Meta-analysis 5 RCTs pioglitazone significantly improved steatosis and inflammation, not fibrosis
• Long term safety of TZDs
• Recent meta-analysis 19 trials 16,390 pts, signif. reduction death, MI or stroke but higher rate of CHF
• Pioglitazone can treat bx proven NASH
  – Majority were not DM, long term safety ? (1,B)
Management: Vitamin E

- Multiple studies but different doses, unclear formulations, use of other antioxidants, limited histology
  1. Vitamin E assoc with decreased LFT
  2. Vitamin E improved steatosis, inflammation, ballooning and resolution of SH
  3. Vitamin E has no effect on fibrosis
Management: Vitamin E

- **PIVENS** trial
  - Pure alpha tocopherol 800 IU/day x 2 years
    - Primary endpoint achieved in greater number with vitamin E compared to placebo, 42% vs. 19%

- Safety
  - Does vitamin E increase all-cause mortality
Management: Vitamin E

- Vitamin E 800 IU/d improves liver histology in non-DM patients with bx proven NASH and should be considered 1\textsuperscript{st} line therapy (1, B)

- Vitamin E is \textbf{not} recommended for NASH in DM, NAFLD without bx, NASH cirrhosis or cryptogenic cirrhosis
Management: Ursodeoxycholic acid (UDCA)

- Single large RCT showed no histological benefit over placebo and therefore not recommended for the treatment of NAFLD or NASH (1, B)
Currently no FDA approved pharmacotherapy for the treatment of NASH

There is no one specific dietary approach but lifestyle modification with diet and exercise has shown potential benefit
Management: Bariatric surgery

- Bariatric surgery is not contraindicated with NAFLD or NASH
- The type and safety in established NASH cirrhosis not established
- Premature to recommend bariatric surgery as established option to treat NASH (1,B)
Statin Use in NAFLD and NASH

- These patients are at increased risk for cardiovascular disease (CVD)
- *Serious liver injury from statins rarely seen*
- Statins are safe in patients with liver disease
- No evidence that patients with chronic liver disease including NAFLD are at increased risk for serious liver injury from statins
Questions?