NASH- Risk factors and impact on CVD management

Karen Luken, MS, ARNP, FNP-C
Iowa Digestive Disease Center
Clive, Iowa
Objectives

• Identify risk factors for development of Nonalcoholic steatohepatitis (NASH) and hypertension

• Impact of NASH on cardiovascular disease (CVD) and other medical conditions
What is NASH?

• Nonalcoholic fatty liver disease (NAFLD) is an accumulation of fat, mainly triglycerides, in the hepatocyte resulting in insulin resistance
• NAFLD can be benign, or it can progress to nonalcoholic steatohepatitis (NASH) which can progress to cirrhosis
• Fat accumulation results in inflammation and potential scarring in the liver
• Need to identify from primary or secondary NAFLD
Causes of NAFLD

• Primary
  – Obesity
  – Type 2 DM
  – Hypertriglyceridemia
  – Glucose intolerance
  – Low HDL
  – Hypertension

• Secondary
  – Nutritional, drugs (Amiodarone, MTX, Tamoxifen), metabolic (pituitary, PCOS, estrogen), toxins, and infections (HCV genotype 3, HIV)
NAFLD Burden in the US

- 34% US population between 30-65 years old have steatosis
- 9.6% of population age 2-19 have steatosis
- Affects more than 55-88 million Americans
- Although the high prevalence of NAFLD a relatively small proportion progress to cirrhosis
Frequency of NASH as a Cause of Liver Transplantation (LT) in Adults

Charlton et al. Gastroenterology. 2011
Characteristics of NAFLD/NASH

• 50-90% are obese (BMI ≥30)
  – >40 inch waist in males; >35 inch waist female
• 55-65% have dyslipidemia
  – >150 trig; low HDL (<40 in men, <50 in women)
• 60-70% have hypertension
  – >130/85
• 30-60% Type 2 DM
• 50% of nondiabetic NAFLD patients have insulin resistance
  – Fasting glucose >100
  – About 75% of lean NAFLD patient (BMI <25) have at least 1 risk factor for metabolic syndrome
NAFLD Prevalence

- Adults
  - Overall: ~ 30%
  - Obese: ~ 50-70%
  - Severely Obese: 85%
  - DM2: ~ 65-75%

Schwimmer et al. Pediatrics 2006; 118: 1388-1393
Characteristics of NAFLD/NASH

- **Clinical features**
  - Asymptomatic, maybe mild fatigue

- **Biochemical features**
  - 78% of all NAFLD patients will have normal LFT’s
  - High fasting insulin levels
  - Dyslipidemia
  - Elevated ferritin

- **Histologic features**
  - Liver biopsy with steatosis, ballooning, or bridging fibrosis
  - Liver biopsy grade (inflammation) and stage (fibrosis)

- **Imaging**
  - Fatty infiltrate on imaging (US or CT)

- **Exclusion of other disease**
Exclusion of other disease

- Exclude liver disease from ETOH
  - <200gram/day in women (1-2 standard drinks) or <30gm/day men (2-3 standard drinks)
- Infectious hepatitis
  - Hepatitis A,B,C
- Autoimmune disease
  - Most common in women age 40-50
- Metabolic liver disease
  - Wilson, Hemochromatosis
- Toxins
  - Herbs, Tylenol, NSAID’s, cocaine, medications (Amiodarone, MTX, estrogen)
Diagnosis

• Diagnosis of exclusion
• Imaging
  – Sensitivity 80-95% when greater than 30% of liver has fatty infiltrate
  – MRE- MRI elastrography is being studied
• Labs
  – Fibrosure
  – APRI
  – PNPLA 3 genetic marker- research only for now
• Liver biopsy
  – Gold standard and only true way to diagnosis
  – If did a liver biopsy on everyone 55 MILLION + biopsies??!!
  – Sampling error can be 30%
• Fibroscan
  – 1 machine available in Des Moines, evaluate the stiffness of the liver
  – Can have failure rate 20-50%
<table>
<thead>
<tr>
<th></th>
<th>Transient Elastography (kPa)</th>
<th>MR Elastography (kPa)</th>
<th>ARFI (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutoff for F3-F4</strong></td>
<td>&gt; 10 kPa</td>
<td>4.15 kPa</td>
<td>1.48-2.06</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Can be performed in clinic with real-time results</td>
<td>- Accurate in obese patients and examines the entire liver</td>
<td>- Can be integrated into a conventional ultrasound</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Increased failure rate with obesity</td>
<td>- Expensive and time consuming</td>
<td>- Increased failure rate with obesity</td>
</tr>
<tr>
<td></td>
<td>- Expensive device</td>
<td>- Limited availability</td>
<td>- Cutoff values for advanced fibrosis vary significantly</td>
</tr>
<tr>
<td></td>
<td>- Cutoff values with XL probe need further validation</td>
<td>- Only a few published studies</td>
<td></td>
</tr>
</tbody>
</table>
2012 NAFLD Practice Guidelines

• Screening for NAFLD in primary care, diabetes or obesity clinics is **not advised** due to uncertainties surrounding Dx, Rx, and cost-effectiveness.

• Significant alcohol consumption: **> 21 drinks per week in men and > 14 drinks per week in women**

• Liver biopsy:
  - In patients at increased risk to have NASH and advanced fibrosis: **Metabolic syndrome, type 2 diabetes and ↑ NAFLD Fibrosis Score (NFS)**
  - When competing etiologies for hepatic steatosis and co-existing chronic liver diseases cannot be excluded

---

Cleveland Clinic

2012 NAFLD Practice Guidelines

- **Vitamin E and Pioglitazone** can be used in patients with biopsy-proven NASH. However, long term safety and efficacy is not established.

- It is **premature to consider bariatric surgery** as an established option to specifically treat NASH.
Treatment

• Control of blood sugars and cholesterol
• Try to change underlying problems if possible
  – change meds, limit etoh
• Weight loss
  – 10% initially and maintaining it off
• Motivation and maintaining it
• Multidisciplinary approach
• Follow up
  – difficult to determine who and how to follow
  – Slow change in decrease of fibrosis
# NASH Therapies in Development

<table>
<thead>
<tr>
<th>Category</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPAR agonist</td>
<td>Aramchol, ASK-1 inhibitors, ACC inhibitors, Anti-CB1, MetAP2 inhibitors others</td>
</tr>
<tr>
<td>DPP-4-i</td>
<td>PPAR agonist, SGLT2-i, FGF-19, FGF-21, ISIS-ANGPTL3 others</td>
</tr>
<tr>
<td>OCA</td>
<td>FXR agonist, ASBT-I, FGF-19, FGF-21 others</td>
</tr>
<tr>
<td>PPAR agonist</td>
<td>CVC, Anti-JNK, Anti-Ask, DHA, Anti-CB1 others</td>
</tr>
<tr>
<td>OCA</td>
<td>Anti-JNK-1, Anti-ASK, PPAR agonist, Nox inhibitors, Others</td>
</tr>
<tr>
<td>Simtuzumab</td>
<td>Anti-gal 3, Anti-CTGF, Angiotensin-receptors-blockers, Pentraxin-2, Anti-IL-17, Anti-TGF-beta</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acid synthesis</td>
<td>Insulin sensitivity</td>
</tr>
<tr>
<td>Bile acid synthesis</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Anti-fibrotic Early stage</td>
<td>Anti-fibrotic Late stage</td>
</tr>
<tr>
<td>Steatosis, ballooning, and inflammation</td>
<td>Stage 1-3 fibrosis</td>
</tr>
<tr>
<td>Stage 3-4 fibrosis</td>
<td>Resolution of NASH</td>
</tr>
<tr>
<td>Reduce the rate of progression of fibrosis or Improvement in fibrosis</td>
<td>Reversal of advanced fibrosis or Improvement in fibrosis</td>
</tr>
</tbody>
</table>

---

Rohit Loomba. Liver Learning. AASLD 2015
Prevention

• Achieve and maintaining an appropriate weight, blood sugar, cholesterol
• Target populations: childhood obesity, genetic predisposition
• If cirrhosis is present need surveillance for HCC
  – Screening for varcies
  – Consideration for liver transplant
Framingham Steatosis index

- Study of 1181 subjects and measured AST/ALT ratio, CT scan, sex, BMI, trig level, hypertension, and DM
- For each parameter given a score
- These parameters were more predictive than AST/ALT ratio alone
- Further study ongoing to determine if cost effective
  - Long term use of CT?
    - Long et al, Clinical Gastroenterology and Hepatology, 2016; Vol 14: 1172-1180
Gestational DM and NAFLD

- CARDIA study, age 18-30 in 4 US cities (Birmingham, Chicago, Minneapolis, Oakland)
- Assessed steatosis by CT scan and biochemical markers
- Longitudinal study initially had 5000+ but data was on 1115 women
- Gestational diabetes is a risk factor for NAFLD, and progression on to DM after pregnancy is also a risk factor for advanced disease
Novel Association low Vit D and NAFLD

- In 190 patients with biopsy proven NAFLD Vit D deficiency was present in 55% of the patients
- Possible proinflammatory pathway associated with low Vit D and NAFLD
- Study done with many genetic markers

Meta Analysis of NAFLD and CVD

• 16 unique observational studies with 34,043 subjects
• NAFLD was associated with increased risk of fatal and non fatal CVD events, however not able to draw definitive causal inferences
• Data to suggest NAFLD by itself is associated with increased CV death and events is unclear
• Unclear if simple steatosis is also a risk factor for CVD events
  • Targher et al, Journal of Hepatology, 2016; Vol 65, 589-600
Association of NAFLD with visceral adiposity and CV calcification scores in Elderly

- Prospective study 250 subjects median age 67 in southern California
- Compared visceral adipose tissue, liver spleen ratio, and coronary artery calcium (CAC) scores
- No association between NAFLD and CAC, but visceral adiposity is a potential CVD risk factor
  - Jacobs et al, Clinical Gastroenterology and Hepatology, 2016;14: 1337-1344
Young Finn Study

• 39 year study looking at childhood obesity
• 45,000 Swedish men
• Being overweight in late adolescence is a significant predictor of severe liver disease later in life, independent of ETOH
• Also recognized that these subjects had higher levels of PNPLA3 and TM6SF2 genes
Conclusion

• NAFLD/NASH is epidemic problem in US
• In future may just be some basic genetic testing to identify risks early in order to prevent disease
• Multidisciplinary approach to control risk factors
• Many studies and medication management is being studied, but so far control of weight, Blood sugars, cholesterol, increased activity and weight loss is here to stay for a long time
Thank You

Questions?