Learning Objectives

1. Evaluate patients with fatty liver disease
2. Review the pathophysiology of NASH
3. Participate in multidisciplinary management of patients with NASH

NAFLD

“Nonalcohol related steatotic liver diseases”

Spectrum of NAFLD

- Fat
- Fat with Inflammation
- Cirrhosis
- NAFL (Nonalcoholic steatohepatitis)
- NASH/Lipotoxic Liver Disease
- HCC+ (Hepatocellular carcinoma)

NAFLD

- Most common liver disorder in the world
- Most common etiology of ↑ LFTs in US
- Prevalence: NAFLD 6.3% - 33%  NASH 5%

USA → NAFLD 46%  NASH 12.2%
**NAFLD**

- Between 4th and 6th decade
- Independent risk factor for CAD and cardiovascular events
- ↑ Risk for HCC
- Genetic predisposition → PNPLA 3 (rs738409) → Fibrosis → HCC

**Hepatic Steatosis Gender Disparities in Whites**

- Compared with the Hispanic population (45% for men and women) and the black population (24% for men and women), a gender disparity was found in the white population

<table>
<thead>
<tr>
<th>Gender</th>
<th>Fatty Liver in the white population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>42%</td>
</tr>
<tr>
<td>Women</td>
<td>24%</td>
</tr>
</tbody>
</table>

**Metabolic Syndrome**

- Insulin Resistance DM
- Hyperlipidemia
- Hypertension

**NAFLD Severity Associated with Metabolic Syndrome Severity**

NASH was found in...

- 7% of patients with neither DM nor HTN
- 31% of patients with HTN alone
- 62% of patients with DM alone
- 75% of patients with both HTN and DM

*Dixon et al., Gastroenterology 2001*
**Metabolic Syndrome**

- Energy supply > metabolic needs
- TG-derived metabolites
- Insulin resistance
- Inflammation
- Cellular dysfunction
- Apoptosis

**“Chronic Inflammatory State”**

- TNFα
- NF-κB
- AP-1
- IL1β
- IL-18
- LPS

→ Lipotoxic Liver Disease

→ Defective intestinal barrier function

**Biochemical Abnormalities of Insulin Resistance**

- Obesity, Genetics, Environment, Diet, Activity
  (Insulin sensitivity vs. resistance)

- Hyperinsulinemia
  - ↑ FFA
  - Met Clearance glucose
  - ↑ Hepatic glucose output
  - ↑ Glucose load

**Clinical and Laboratory Features of NAFLD**

<table>
<thead>
<tr>
<th>Signs</th>
<th>Laboratory Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Laboratory Features</td>
</tr>
<tr>
<td>Asymptomatic (48-100%)</td>
<td>2-4 fold elevation of ALT and AST</td>
</tr>
<tr>
<td>Fatigue, Malaise</td>
<td>AST/ALT &lt;1 in most cases,</td>
</tr>
<tr>
<td>Liveromegaly</td>
<td>Alkaline phosphatase elevated in 1/3</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Normal bilirubin, albumin and PT</td>
</tr>
<tr>
<td>Spider angiomata, Palmar erythema</td>
<td>Elevated serum ferritin (53-62%)</td>
</tr>
<tr>
<td>Ascites</td>
<td>Low titer (&lt;1/320), ANA</td>
</tr>
</tbody>
</table>

**“Two Hit” Hypothesis**

- Uncoupled oxidation and phosphorylation
- CYP-450 activation
- Peroxisomal fatty acid oxidation

→ oxidative stress within the hepatocytes

- TNF-α
- ↑ ROS - ↓ antioxidants

- NASH
**Diagnosis**

a) Presence of fatty infiltration of the liver

b) Establish the non-alcoholic nature of the disease

**Fatty Liver**

Ultrasound

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**Liver Biopsy**

NAFL  
NASH

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Liver Biopsy

“Patients with NAFLD at risk to have NASH and advanced fibrosis”

- Presence of the metabolic syndrome
- NAFLD fibrosis score >0.676
- To exclude competing etiologies for hepatic steatosis and coexisting liver diseases
- During bariatric surgery
- During cholecystectomy

Clinical and Laboratory Features of NAFLD

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Laboratory Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Asymptomatic (48-100%)</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td></td>
<td>2-4 fold elevation of ALT and AST</td>
<td>1/3 Normal bilirubin, albumin and PT</td>
</tr>
<tr>
<td></td>
<td>AST/ALT &lt;1 in most cases, Alkaline phosphatase elevated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>To exclude competing etiologies for hepatic steatosis and coexisting liver diseases</td>
<td>Elevated serum ferritin (53-62%)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Vague RUQ pain Fatigue Malaise</td>
<td>Splenomegaly Spider angioma Palmar erythema Ascites</td>
</tr>
<tr>
<td></td>
<td>Low titer (&lt;1/320), ANA Elevated transferrin saturation Cys282Tyr mutation of HFE gene</td>
<td></td>
</tr>
</tbody>
</table>

Diabetics have Double the Risk
NAFLD and HCC

Incidence Rate of CNLD per 10,000 Person Years

- Diabetics: 18.13
- No diabetes: 9.55

Incidence Rate of HCC per 10,000 Person Years

- Diabetics: 2.39
- No diabetes: 0.87

“Steatohepatitic Hepatocellular Carcinoma”

CNLD = chronic nonalcoholic liver disease
NAFLD

- Natural History
  - Histologic stability → 59%
  - Improvement → 13%
  - Progression to cirrhosis → 28%

Management

- All NAFLD → Treatment of metabolic syndrome (obesity, hyperlipidemia, insulin resistance and DM)
  - NAFL → No liver specific treatment
  - NASH → Treatments aimed at improving liver disease

Therapies for NASH

- Weight loss and lifestyle modification
- Weight loss → Orlistat, Rimonabant
- Insulin sensitizing agents → Metformin, Thiazolidinediones
- Antioxidants → Vitamin E, Betaine, N-acetylcysteine
- Lipid lowering agents → Clofibrate, Atorvastatin, Gemfibrozil, Omega-3 Fatty Acids
- Anti-TNF → Pentoxifylline (off-label use)
- Intestinal flora modifiers → Probiotics
- Chinese Herbal Medicines
- Bariatric surgery

Issues Related to the Treatment of NASH

- Studies did not follow basic design requirements for clinical trials
- Disappointing results have not led to a clear recommendation to treat patients with NASH
- Given the very slow progressive nature of NASH, only surrogate markers of clinical outcome can be used
**Weight Loss and Lifestyle Modifications**

- Promrat et al. RCT: Diet, exercise and behavior modifications vs structural education in 31 obese NASH patients for 48 weeks. Weight loss goal [>7%]. Biopsy at baseline and at 48 weeks.
- **Conclusions:** Significant improvements in steatosis, lobular inflammation, ballooning, NASH Activity Score (NAS) and weight reduction were achieved through lifestyle intervention.
- Eckardt et al. 56 participants with biopsy-proven NASH were randomly assigned to 1 of 4 lifestyle modification for 6 months. All subjects received a repeat 6-month biopsy.
  - standard care
  - low-fat diet and moderate exercise
  - moderate-fat/low-processed-carbohydrate diet and moderate exercise
  - moderate exercise only
- **Conclusions:** Regardless of intervention group, lifestyle modification improved liver histology ($p < 0.001$), with no difference detected between subgroups ($p > 0.31$).

**Caveats:**
- Larger group size studies needed
- Adherence to lifestyle interventions can be problematic
- Only 15% of the patients will achieve weight loss
- Fatigue was a common reason not to exercise
- Lack of confidence of performing exercise

“Weight loss, dietary changes and exercise should be recommended to all patients with NASH, primarily to modify their cardiovascular risks rather than liver-related risks.”

**Coffee Consumption in NAFLD Patients With Lower Insulin Resistance is Associated with Lower Risk of Severe Fibrosis**

- Bambha et al. 782 adults (≥18 years) in the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) from 2004 to 2008
- Diabetes was present in 24% (n = 189). NASH was present in 79% (n = 616), and 25% (n = 199) had advanced fibrosis.
- Coffee consumers with less IR, defined as HOMA-IR<4.3, had a lower odds of advanced fibrosis [OR = 0.64; 95% CI, (0.46-0.88), $p = 0.001$].
- The effect of coffee on fibrosis varied with degree of IR (interaction $p = 0.001$).
- **CONCLUSIONS:** Coffee intake is inversely associated with advanced fibrosis among NAFLD patients with lower HOMA-IR.

**Association of Coffee and Caffeine Consumption with Fatty Liver Disease, Nonalcoholic Steatohepatitis, and Degree of Hepatic Fibrosis**

- Molloy et al., Brooke Army Medical Center Hepatology clinic, 306 patients
  - Controls
  - Bland steatosis
  - NASH stage 0-1
  - NASH stage 2-4
  - **Bland steatosis vs. NASH stage 0-1**, there was a significant difference in CC (P = 0.005)
  - **NASH stage 0-1 vs. NASH stage 2-4**, there was a significant difference in CC (P = 0.016)
- **CONCLUSION:** Coffee CC is associated with a significant reduction in risk of fibrosis among NASH patients
  - “Drinking coffee has a protective effect in NASH through the reduction of hepatic inflammation and fibrosis.”
Prospective Clinical Trials of Thiazolidinediones

**Drug & Dosage**
- Pioglitazone 45 mg/day
- Pioglitazone 30 mg/day
- Pioglitazone 30 mg/day or vitamin E 800 IU/day
- Rosiglitazone 4-8 mg/day
- Rosiglitazone 8 mg/day or Metformin 850 mg 2x/day
- Pioglitazone 30 mg/day

**Duration**
- 6 mo
- 12 mo
- 95 weeks
- 12 mo
- 96 weeks
- 48 weeks
- 6 mo

**Diagnosis**
- NASH
- DM
- IFG or +DM
- NAFLD
- NASH
- Not specified
- No specific
- NASH
- -DM
- NASH

**Population**
- IFG or +DM
- -DM
- Placebo/diet
- Vitamin E 400 IU/day
- Placebo
- Placebo
- Placebo
- Placebo

**Comparator/Therapy**
- Placebo/diet
- Histologic improvement, not fibrosis
- Histologic improvement, ALT↑
- Histologic improvement with vitamin E
- Improved steatosis & ALT levels
- Vitamin E

**Results**
- Histologic improvement
- Safety of pioglitazone in non-diabetics with NASH not established (wt. gain, CHF, bone loss, bladder Ca)
- Histologic benefits may not be maintained after the first year of therapy
- Risks vs. benefits → diabetic patient with NASH

Prospective Clinical Trials of Metformin

**Drug & Dosage**
- Metformin 1000 mg/day
- Metformin 850 mg 2x/day
- Metformin 500-3000 mg/day
- Metformin 500-1000 mg/day extended release
- Metformin 2000 mg/day or Vitamin E 800 IU/day
- Metformin 1700 mg/day

**Duration**
- 6 mo
- 6 mo
- 6 mo
- 12 mo
- 12 mo
- 6 mo

**Diagnosis**
- NAFLD
- NASH
- NAFLD
- NASH
- NAFLD
- NAFLD

**Population**
- Overweight & -DM
- -DM
- IFG or +DM
- -DM & 1 of: BMI>27, IFG, PCOS, metabolic syndrome
- -DM
- Obese & +DM

**Comparator/Therapy**
- Hypocaloric diet
- Lipid-reducing medication
- Placebo/DASH diet, exercise
- Weight reducing drug
- Diet/exercise

**Results**
- Echogenic improvement in both groups
- No significant histologic improvement
- No histologic or ALT level differences
- No histologic or ALT level differences
- ALT↑
- No differences in steatosis or ALT levels

Prospective Clinical Trials of Metformin

- No significant effect on liver histology
- Can be used for diabetic patients with NASH
- Not recommended as a specific treatment for liver disease in adults with NASH
Vitamin E

- Trials → Varying criteria, different doses, unclear formulations, use of other drugs, limited histologic data

- PIVENS trial
- ↓ aminotransferases
- Improvement in steatosis, inflammation, ballooning and resolution of steatohepatitis
- No effect on hepatic fibrosis


Vitamin E

- Concern → ↑ overall mortality and ↑ risk for prostate CA

- AASLD
  - “Vitamin E improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first line pharmacotherapy for this patient population”

Gastroenterology 2012;142:1592-1609

Prospective Clinical Trials of HMG CoA Reductase Inhibitors (Statins)

<table>
<thead>
<tr>
<th>Drug &amp; Dosage</th>
<th>Duration</th>
<th>Diagnosis</th>
<th>Population</th>
<th>Comparator/Therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin 10 mg/day</td>
<td>8 mo</td>
<td>NASH + hyperlipidemic &amp; DM</td>
<td>cholesteryl lowering diet</td>
<td>ALT ↓</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin 10 mg/day</td>
<td>24 mo</td>
<td>NASH + hyperlipidemic &amp; male</td>
<td>diet</td>
<td>ALT, fibrosis ↓, no improvement in vitamin</td>
<td></td>
</tr>
<tr>
<td>Simvastatin 10 mg/day</td>
<td>12 mo</td>
<td>NASH + hyperlipidemic</td>
<td>placebo</td>
<td>No histologic or ALT level differences</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin 40 mg/day or 20 mg/day or pravastatin 40 mg/day or fluvastatin 80 mg/day</td>
<td>6 mo</td>
<td>NASH + hyperlipidemic, atorvastatin group</td>
<td>atorvastatin or pravastatin</td>
<td>No histologic improvement, ALT ↓, fibrosis ↓</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin 40 mg/day</td>
<td>36 mo</td>
<td>NAFLD + CAD</td>
<td>Coronary Artery Disease</td>
<td>Usual care</td>
<td>ALT ↓, Cardiovascular mortality ↓</td>
</tr>
</tbody>
</table>


Prospective Clinical Trials of HMG CoA Reductase Inhibitors (Statins)

- No RCT with histologic endpoints

- Statins significantly improve liver tests and cardiovascular outcomes in patients with elevated liver enzymes due to NASH

- Statins not recommended to treat patients with NASH but are safe to be used to treat hyperlipidemia

Gastroenterology 2012;142:1592-1609
Prospective Clinical Trials of Ursodiol

<table>
<thead>
<tr>
<th>Drug &amp; Dosage</th>
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<th>Population</th>
<th>Comparator/Therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ursodiol</td>
<td>3 mo</td>
<td>NAFLD</td>
<td>Overweight</td>
<td>Placebo</td>
<td>ALT ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No histologic changes</td>
</tr>
<tr>
<td>Ursodiol</td>
<td>6 weeks</td>
<td>NAFLD</td>
<td>Obese women</td>
<td>Placebo &amp; 1200 kcal/day diet</td>
<td>ALT ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Steatosis ↓</td>
</tr>
<tr>
<td>Ursodiol</td>
<td>6 mo</td>
<td>NAFLD</td>
<td>No specific, but 3 mo dietary run in</td>
<td>Placebo &amp; vitamin E &amp; vitamin C</td>
<td>ALT ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No echogenic changes</td>
</tr>
<tr>
<td>UDCA</td>
<td>12 mo</td>
<td>NASH</td>
<td>No specific</td>
<td>Placebo</td>
<td>ALT ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Serum fibrosis markers ↓</td>
</tr>
<tr>
<td>Ursodiol</td>
<td>18 mo</td>
<td>NASH</td>
<td>No specific</td>
<td>Placebo</td>
<td>GGT ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ursodiol</td>
<td>24 mo</td>
<td>NASH</td>
<td>No specific</td>
<td>Placebo</td>
<td>Same histology and ALT in both groups</td>
</tr>
</tbody>
</table>

• “No evidence of efficacy, not recommended for the treatment of NASH”

Pharmacotherapy 2013;33(2):233-242
Gastroenterology 2012;142:1592-1609

Prospective Clinical Trials of Orlistat

<table>
<thead>
<tr>
<th>Drug &amp; Dosage</th>
<th>Duration</th>
<th>Diagnosis</th>
<th>Population</th>
<th>Comparator/Therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>6 mo</td>
<td>NASH</td>
<td>Obese</td>
<td>Calorie restricted diet</td>
<td>↓ Fat</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ ALT &amp; AST</td>
</tr>
<tr>
<td>Orlistat</td>
<td>6 mo</td>
<td>NASH</td>
<td>No specific</td>
<td>Placebo/behavioral weight loss program</td>
<td>↓ Fat</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ ALT</td>
</tr>
<tr>
<td>Orlistat</td>
<td>36 weeks</td>
<td>NASH</td>
<td>Overweight</td>
<td>Calorie restricted diet &amp; vitamin E 800 IU/day</td>
<td>Biochemical and histologic improvement was no different</td>
</tr>
</tbody>
</table>

• No evidence supporting efficacy
• Not recommended as potential therapy for NASH

Pharmacotherapy 2013;33(2):233-242

Prospective Clinical Trials of Pentoxifylline

<table>
<thead>
<tr>
<th>Drug &amp; Dosage</th>
<th>Duration</th>
<th>Diagnosis</th>
<th>Population</th>
<th>Comparator/Therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentoxifylline</td>
<td>12 weeks</td>
<td>NASH</td>
<td>No specific</td>
<td>Placebo/ANA diet &amp; exercise</td>
<td>ALT ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>12 mo</td>
<td>NASH</td>
<td>No specific but NASH controlled</td>
<td>Placebo</td>
<td>no effect on fibrosis scores</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>12 mo</td>
<td>NASH</td>
<td>No specific</td>
<td>Placebo</td>
<td>ALT ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Steatosis ↓</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>6 mo</td>
<td>NAFLD</td>
<td>No specific</td>
<td>Placebo/ dietary advice</td>
<td>ALT ↓</td>
</tr>
</tbody>
</table>

• “No evidence of efficacy, not recommended for the treatment of NASH”

Pharmacotherapy 2013;33(2):233-242

Obeticholic Acid (OCA)

• FXR, VDR, PXR CAR family
• FXR → Gene regulators in the liver and gut
• Obeticholic acid → Potent FXR agonist
• NASH CRN FINT Trial, 8 centers, 283 patients
• 72 weeks, histologic and fibrosis improvement
• “Interim analysis showed significant improvement with OCA leading to early termination of treatment in the remaining patients”

<table>
<thead>
<tr>
<th>OCA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved histology</td>
<td>45%</td>
</tr>
<tr>
<td>AE: Pruritus, ↑LDL, ↓ HDL</td>
<td></td>
</tr>
</tbody>
</table>

Obeticholic Acid

- **REGENERATE Study:**
  
The primary efficacy analysis indicated that treatment with once-daily OCA 25 mg met the primary endpoint:
  
  - Fibrosis improvement (≥ 1 stage) with
  - No worsening of NASH after 18 months

### Compounds Currently Under investigation

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>MoA</th>
<th>Phase</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENFIT</td>
<td>GFT505</td>
<td>PPAR γ/δ agonist</td>
<td>2b</td>
<td>NASH</td>
</tr>
<tr>
<td>Intercept (NDDK)</td>
<td>OCA</td>
<td>FXR agonist (bile acid)</td>
<td>2b</td>
<td>NASH</td>
</tr>
<tr>
<td>CENTAUR</td>
<td>Cenicriviroc</td>
<td>Inhibitor of ligand binding to CCR2/CCR5</td>
<td>2a</td>
<td>Liver fibrosis/NASH</td>
</tr>
<tr>
<td>Gilead</td>
<td>Simtuzumab</td>
<td>Mab against LOXL2</td>
<td>Complete</td>
<td>Liver fibrosis/NASH</td>
</tr>
<tr>
<td>Immuron</td>
<td>Hyperimmune bovine colostrum</td>
<td>Induction of regulatory T cells</td>
<td>2a</td>
<td>NAFLD/NASH</td>
</tr>
<tr>
<td>Intercept (NDDK)</td>
<td>Emricasan</td>
<td>Caspase protease inhibitor</td>
<td>2a</td>
<td>NAFLD/NASH</td>
</tr>
<tr>
<td>GALMEDI</td>
<td>Anamchol</td>
<td>Synthetic Fatty Acid/ bile acid conjugate</td>
<td>2a(complete)</td>
<td>NAFLD/NASH</td>
</tr>
<tr>
<td>GALACTIN</td>
<td>GR-MD206</td>
<td>Galectin-3 inhibitor</td>
<td>2a</td>
<td>NASH with advanced cirrhosis</td>
</tr>
<tr>
<td>BMS</td>
<td>BMS986036</td>
<td>Recombinant FGF-21</td>
<td>2a</td>
<td>NASH</td>
</tr>
</tbody>
</table>

### Increased U.S. Demand for WLS

- From 16,000 (1992) to 100,000+ (2003) procedures per year
- 140,000 procedures are anticipated for 2004

### Restrictive Procedures

- A
- B
- C

Seminars in Liver Disease 24:1-371
**Laparoscopic Adjustable Gastric Banding**
- Weight loss
- Histologic improvement (91%)
- Improvement of the liver tests
- Improvement of the metabolic syndrome

**Roux-en-Y Gastric Bypass**
- ↓ BMI
- ↓ Metabolic syndrome
- ↓ LFTs
- Histologic improvement (89%)

**Bariatric Surgery for NAFLD**
- Mummadi et al. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis
  - 15 studies (766 paired liver biopsies)
  - % ↓ in mean body mass index after bariatric surgeries ranged from 19.11 to 41.76
    - Improvement or resolution in steatosis was 91.6% (95% confidence interval [CI], 82.4%-97.6%)
    - in steatohepatitis was 81.3% (95% CI, 61.9%-94.9%)
    - in fibrosis was 65.5% (95% CI, 38.2%-88.1%)
    - for complete resolution of nonalcoholic steatohepatitis was 69.5% (95% CI, 42.4%-90.8%).
- **CONCLUSIONS:** Steatosis, steatohepatitis, and fibrosis appear to improve or completely resolve in the majority of patients after bariatric surgery-induced weight loss.

Recommendations

1. Exercise regularly
2. Well-balanced diet
3. Weight control
4. Control of Diabetes Mellitus
5. Control of hyperlipidemia
6. Avoid alcohol
7. Coffee
8. ↓ fructose intake

Recommendations

9. Vitamin E 800 IU qd in non-diabetics with biopsy proven NASH → Benefits vs. Risks (prostate CA, ↑ overall mortality). Confirm therapeutic response with biopsy?
10. Pioglitazone 30 mg qd in diabetic patient with biopsy proven NASH → Benefits vs risks
11. Bariatric surgery:
   • BMI >40 kg/m2 who have failed diet and exercise (with or without drug therapy)
   • BMI >35 kg/m2 and obesity-related co-morbidities (hypertension, impaired glucose tolerance, diabetes mellitus, dyslipidemia, sleep apnea)
12. HCC surveillance in patients with cirrhosis

NAFLD

- Significant public health problem
- Related to the metabolic syndrome
- We need a better understanding of the pathophysiology of NASH
- Prospective, randomized, long term, controlled trials, with histologic follow up, to assess current and new therapies