NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

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OBJECTIVES

- To understand the pathophysiology of nonalcoholic fatty liver disease (NAFLD)
  - The link between NAFLD and insulin R
  - The relationship of insulin R to steatosis
  - The “second hit” theory of steatosis to NASH

- To learn about adipocytokines and HSCs, implicated in the development of hepatic inflammation and fibrosis in patients with NAFLD

- To understand the key items for diagnosis and management of NAFLD in children
# OBESITY

## BASIC FACTS

- **Epidemic of obesity, probably the most common health issue of children**

## DEFINITION

- **Because BMI norms for children vary with age and gender, BMI %tiles rather than absolute BMI’s are determined**

- **% of children 6-11 yrs of age with BMI >95\(^{th}\) more than doubled from 6.5 to 15.3 % betw late 70’s and 2000**

- **Cut off values to define the heaviest children are the 85\(^{th}\) and 95\(^{th}\) %tiles (BMI’s of 25 and 30, respectively, as maturity is approached in adolescence)**

- **Above #’s double if one includes children with BMI > 85\(^{th}\) %tile**

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**National Center for Health Stats, 2003**

**Strauss RS. JAMA 2001; 286:2845**
Medical Conditions Associated With Childhood Obesity

- Hypertension
- Hyperlipidemia
- Impaired Glucose Tolerance/ Diabetes
- Gallbladder Disease/ Gallstones
- Nonalcoholic Fatty Liver Disease (NAFLD)
  - Elevated Liver Transaminases Common
  - Severe Fibrosis and Cirrhosis Also Occur

Intra-abdominal fat is the main adipose depot associated with insulin resistance.

Visceral adipocytes are more metabolically active than subcutaneous adipocytes.

FFAs from visceral adipose tissue drain directly to liver via the portal vein.

Thus, potentially exerting > influence on hepatic glucose metabolism and fatty acid oxidation, ultimately contributing to the development of hepatic steatosis and steatohepatitis in the setting of insulin resistance.

NAFLD
Historical Facts

- Klatskin: In 1979, he presented findings of a landmark histologic study about nonalcoholic liver disease which mimicked alcohol induced hepatitis and cirrhosis

- Ludwig: In 1980, he coined the term “non-alcoholic steatohepatitis” in patients whose liver histology mimicked alcoholic hepatitis

Spectrum of NAFLD
BASIC FACTS

- NAFLD is a broad term -- Encompasses steatosis, steatosis w inflammation, NASH, and cirrhosis. NAFLD is now recogn’ as the most common cause of liver disease in pediatrics.

- The terms NAFLD and NASH are not interchangeable.

- NASH may be the most common cause of cryptogenic cirrhosis; it may lead to end stage liver disease and is a serious complication of childhood obesity.

- The link between NAFLD, insulin resistance and metabolic syndrome is not completely understood.
PATHOPHYSIOLOGY of NAFLD

INSULIN RESISTANCE

- Diabetes
- Obesity

STEATOSIS

- “BENIGN” STEATOSIS
- NASH

McCullough AJ. Jour Clin Gastro 2002;34:255
INSULIN RESISTANCE
Effect on Fat Metabolism

- Insulin (I) resistance enhances TG lipolysis & inhibits esterification of FFA within adipose tissue
- Liver TG syn is driven by FFAs and by I upreg’ PPARgamma & SREBP
- TG export via VLDL may be inhibited by dec syn of apolipoprotein B
## NAFLD
**Adipocytokines/ Hepatic Stellate Cells**

<table>
<thead>
<tr>
<th>Cytokines/Stellate C</th>
<th>Effects</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBESITY → Inc LEPTIN</td>
<td>1) Inc Exp of TNFα and TGF-B1&lt;br&gt;2) Deposition of Type I Collagen</td>
<td>Inc Liver Fibrosis</td>
</tr>
<tr>
<td>OBESITY → Dec ADIPONECTIN</td>
<td>1) Dec Exp of TNFα mRNA&lt;br&gt;2) Down Regulation of TGF-B1</td>
<td>Dec Liver Fibrosis</td>
</tr>
<tr>
<td>TNFα → Dec ADIPONECTIN&lt;br&gt;Inc INSULIN RESIST</td>
<td>Dec Gene Expression and Secretion of Adiponectin</td>
<td>Dec Liver Fibrosis</td>
</tr>
<tr>
<td>ADIPONECTIN</td>
<td>Suppresses HSC Proliferation and Migration</td>
<td>Dec Liver Fibrosis</td>
</tr>
<tr>
<td>HSC → MYOFIBROBLAST</td>
<td>Produces TGF-B1 and Extracellular Matrix Protein</td>
<td>Inc Liver Fibrosis</td>
</tr>
</tbody>
</table>

Pathogenesis of NAFLD

**INSULIN RESISTANCE** → **METABOLIC SYNDROME**

- **Altered Adipocytokines**
  - Inc Leptin
  - Dec Adiponectin
  - Inc TNFα

- **Impaired INSULIN Mediated Suppression Of Lipolysis**

- **ΔFAs**

- **Hepatic Stellate Cells**

**OBESITY**

- Increase in Liver Triglycerides

**STEATOSIS**

- Increase FA Uptake By Liver Inc’s Hep Glucose Outp

**Increased INSULIN Output**
Mitochondrial and peroxisomal oxidation of FFAs in liver

Free radicals (Reactive O2 species)

Lipid peroxidation of membranes

Hepatocyte membrane damage

Inflammation

Fibrosis

Progression of NAFLD

STEATOSIS → 10% → NASH → 24% → FIBROSIS (35%) → CIRRHOSIS (15%) → LIVER FAILURE → HEPATOCELLULAR CARCINOMA

Caldwell SH. Hepatol 2003;37: 1202
CHRONIC LIVER DISEASE

Prevalence in the U.S.

- Nonalcoholic Fatty Liver Disease ~20%
- Nonalcoholic Steatohepatitis ~3%
- Chronic Hepatitis C ~2%
- Alcoholic Liver Disease 0.7%
- Chronic Hepatitis B 0.4%
NAFLD: Epidemiology

- Overlooked or underestimated in the past, and not well known at present
- Highest prevalence is in adults aged 40-60 yrs, but NAFLD occurs in children & adolescents
- High prevalence in industrialized countries
- Females > Males, but controversial
- NASH appears to be overtaking chronic hepatitis C as the next “epidemic” in liver disease
NAFLD in CHILDREN  
Toronto Study

- 36 Children, Mean Age 12 yrs (4-16 yrs)  
  - 30 Obese; 2 Diabetic; 18 Abn Lipid Profiles  
  - 24 Liver Biopsied: Fat/Inflam, 88%  
    Fibrosis, 75%

- Evaluated Because of Transaminemia
- Tests for Other Diseases were Negative
- Conclusion: NAFLD Occurs in Children and may not be Benign

NAFLD in CHILDREN
San Diego Study

- 43 Children: Mean Age 12.4 yrs (3.3)
  - 38 Obese; 6 Diabetic
  - 43 Liver Biopsied: Steatosis, 30%; Portal Inflammation, 58%; Fibrosis, 63%

- Steatosis: Insulin “Sensitivity”, Age, Ethnicity
- Portal Inflam: ALT, Fasting Insulin
- Portal Fibrosis: RUQ Pain, Insulin Resistance

# Clinical Features of NASH

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>PHY EXAM</th>
<th>LABS</th>
<th>U/SOUND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Hepatomegal</td>
<td>ALT, AST 2-3X normal</td>
<td>Large liver w increased echogenicity</td>
</tr>
<tr>
<td>(majority)</td>
<td>(common)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Splenomegal</td>
<td>GGT (mild elevation)</td>
<td></td>
</tr>
<tr>
<td>(25%)</td>
<td></td>
<td>PT(INR) abn</td>
<td></td>
</tr>
<tr>
<td>RUQ Pain</td>
<td></td>
<td>w cirrhosis</td>
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</table>
NASH: Association with other Medical Problems

- **Non-Obesity Nutritional Abnormalities**
  - Central Hyperalimentation
  - Rapid Weight Loss

- **Metabolic Diseases (Other Than Obesity)**
  - Hypertriglyceridemia
  - Abetalipoproteinemia

- **Drugs**
  - Steroids, Methotrexate, Estrogens

- **Toxins (Environmental and Occupational)** eg., Hydrocarbons

- **Gastropexy** (Much Less Common Than *Jejunoileal Bypass*)
DIAGNOSIS of NASH

- Incidental discovery of abnormal liver function
- No specific lab studies suggest the diagnosis
- Steatosis vs NASH cannot be made reliably on clinical grounds, or with imaging studies
- Histologic inflammation does NOT always correlate with elevated AST & ALT ie., pt’s with steatosis (alone) may have inc’ AST & ALT
- Liver histology yields dx of NASH w certainty
### Histologic Features of NAFLD

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>STEATOSIS</strong></td>
<td>Macrovesicular; mild to severe; primarily zone 3</td>
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<tr>
<td><strong>STEATOHEPATITIS</strong></td>
<td>Inflammation, lobular, and mixed (mono/poly); ballooning, Mallory body, fibrosis</td>
</tr>
<tr>
<td><strong>FIBROSIS</strong></td>
<td>Initially pericellular, then bridging</td>
</tr>
<tr>
<td><strong>CIRRHOSIS</strong></td>
<td>Occurs in up to 15% over 10 years</td>
</tr>
</tbody>
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Histologic Features of NASH

- Macrovesicular steatosis and fibrosis

- Early fibrosis is pericellular and perisinusoidal (note the “chickenwire” appearance)

- Trichrome stain, X200

- Injured ballooned cells (B) and a mild neutrophilic infiltrate

- Aggregations of Mallory’s hyalin (MH) comprised of eosinophilic cytoskeleton filaments

- H&E stain, X400
<table>
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<th>HAIR SCORE</th>
<th>BAAT SCORE</th>
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<tbody>
<tr>
<td>Hypertension</td>
<td>BMI 28 Kg/m2</td>
</tr>
<tr>
<td>ALT &gt; 40 U/L</td>
<td>Age &gt; 50 years</td>
</tr>
<tr>
<td>Insulin Resistance Index &gt;5</td>
<td>ALT &gt; 2X normal</td>
</tr>
<tr>
<td>Triglycerides 1.7 mmol/L</td>
<td></td>
</tr>
</tbody>
</table>

Ratziu V. Gastroenterol 2000; 118, 1117.
## Role of Liver Biopsy in NAFLD

<table>
<thead>
<tr>
<th>ARGUMENTS +</th>
<th>ARGUMENTS -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclude Other Causes of Liver Disease</td>
<td>Generally, NAFLD has a Good Prognosis</td>
</tr>
<tr>
<td>Distinguish Steatosis versus NASH</td>
<td>Lack of Effective Therapy</td>
</tr>
<tr>
<td>Progress Based on Degree of Fibrosis</td>
<td>Risks and Cost Associated with Biopsy</td>
</tr>
</tbody>
</table>
Treatment of NAFLD/NASH

Current Approach

- Gradual, Sustained Weight Loss
  - Re-establish the “Family Table”
  - Promote Better Nutrition in Schools
- Exercise Program
  - Put High Priority on Family Fitness
  - Expand Green Spaces for Exercise
- Treat Diabetes
- Treat Lipid Disorder
- Treat Hypertension
Treatment of NAFLD/NASH

Experimental Therapies

- Insulin Sensitizing Drugs: Thioglitazones
  - Troglitazone
  - Pioglitazone
  - Rosiglitazone

- Antioxidants: Vitamin E

- Ursodiol
- Betaine
- Metformin

Charlton M. Clin Gastro Hepatol 2004;2: 1048
“Leave gourmandising....” King Henry V advises Falstaff,...”know the grave doth gape for thee thrice wider than for other men”

Shakespeare, 1564-1616