Management of NAFLD

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Disclosures

- No conflict with Presentation

Ongoing Industry Contact
1. Abbott
2. Ocera
3. Gilead
4. Baxter
5. Genentech
6. Merck
7. GlaxoSmithKline
8. Axcan
9. Nestle
10. Celgene
11. Vertex
12. Denisco
Objectives

1. Introduction to obesity and metabolic endotoxemia
2. Gut barrier function, high fat/fructose diets and NAFLD
3. Case Presentations
4. Take Home Points

Classic Theory of Obesity

- Energy Intake
- High-calorie diet
- Energy Expenditure
- Sedentary lifestyle
- Genetics and Other factors
1. Obesity and metabolic endotoxemia

Dr. McClain, I eat like a bird and still gain weight

Alternative Approach

Gut Flora

- Obesity
  - ~2/3 overweight
  - ~1/3 obese

- NAFLD
  - #1 cause of liver enzymes
  - ~1/3 Americans

~1/3 overweight
~1/3 obese
~2/3 overweight
~1/3 obese
2. Gut Barrier function, high fat/fructose diets, and NAFLD

- Altered Gut Flora
- Increased gut permeability
- Increased LPS/Gut derived toxins
- Increased TLR4 activation
- Increased TNF production
- NAFLD
- Low grade systemic inflammation

Dietary Models of Obesity

- High Fat
  → NAFLD

- High Fructose
High-fat diet, gut flora, obesity, and NAFLD

Pivotal study – Germ-free mice less fat, but eat more!

Genetically obese mice have increased gut permeability and endotoxemia


Early bacterial translocation with high fat diet

Obese mice have altered gut flora, and transfer of gut flora induces weight gain

Ley, et al. PNAS 102(31):11070, 2005

Super Size

McDonald’s
3 meals per day
x 30 days
### HFD – Human Model

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>At 18 days</th>
<th>At 21 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP, mmHg</td>
<td>110/70</td>
<td>150/100</td>
<td>---</td>
</tr>
<tr>
<td>WT, lbs</td>
<td>165</td>
<td>225</td>
<td>230</td>
</tr>
<tr>
<td>TChol</td>
<td>60</td>
<td>120</td>
<td>240</td>
</tr>
<tr>
<td>TG</td>
<td>20</td>
<td>100</td>
<td>220</td>
</tr>
<tr>
<td>ALT</td>
<td>15</td>
<td>110</td>
<td>528</td>
</tr>
<tr>
<td>AST</td>
<td>21</td>
<td>130</td>
<td>187</td>
</tr>
</tbody>
</table>

### Fructose, Gut Flora and NASH

EFFECT OF SUGAR-SWEETENED BEVERAGES ON HEPATIC STEATOSIS IN MICE

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Artificial sweetener</th>
<th>Glucose</th>
<th>Sucrose</th>
<th>Fructose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic Fat</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
<td><img src="image5.png" alt="Graph" /></td>
</tr>
<tr>
<td>Hepatic TNFα</td>
<td><img src="image6.png" alt="Graph" /></td>
<td><img src="image7.png" alt="Graph" /></td>
<td><img src="image8.png" alt="Graph" /></td>
<td><img src="image9.png" alt="Graph" /></td>
<td><img src="image10.png" alt="Graph" /></td>
</tr>
</tbody>
</table>
Antibiotics Protect against high fructose diet-induced endotoxemia and NAFLD


Endogenous fructose BAD!
High Fructose and the metabolic syndrome
NAFLD

Sugar
HFCS
Fructose
Honey, Fruits

Brain
Liver
Vasculature
Muscle
Adipocyte

Activates taste centers
Addictive behaviors (dopaminergic and opioid receptors)
Leptin resistance
Neurostimulant

Fatty liver
Elevated triglycerides
ATP depletion
Inflammation
Uric acid generation

Inflammation
Endothelial dysfunction
Renal vasconstriction
Glomerular hypertension
Renal injury
Renal inflammation

Oxidative stress
Inflammation
Reduced adiponectin

Metabolic Syndrome
Insulin resistance
Elevated blood pressure
Abdominal obesity
Dyslipidemia
Fatty Liver
Inflammation
Oxidative stress
Endothelial dysfunction
Hyperuricemia

Diabetes

Johnson R J et al. Endocrine Reviews
2009;30:96-116

Innate Immune cells use TLRs to detect pathogen molecular patterns

Bacteria
Bacterial lipopolysaccharides
LPS
Flagellin
Unpathogenic bacteria
CpG DNA
Viruses
Poliomyelitis
Herpes simplex
HSV-1
F protein (SIV)
Env (MIV)

TLR2
TLR4
TLR9
TLR7
TLR3

CpG DNA
dsRNA
U-rich RNA

MylD88
MyD88
Ikk
Trx

O’Neill, Science 303:1481, 2004
TLR4 involved in all phases of Fatty Liver Disease

Fatty liver

Steatohepatitis

Cirrhosis

HCC

Profile, history & examination

Profile
Mrs LM
DOB: 6/18/62
Height: 5 ft. 3 in
Weight: 182 lbs, BMI 32.2
Presenting complaint:
NASH!

On examination:
No icterus
Few spiders over chest
Visceral adiposity
No ascites
No edema

History of presenting complaint:
Gallbladder symptoms for > 5 years
2 Recent attacks of RUQ pain with fever and chills prompted cholecystectomy and liver biopsy.
### Past medical history & drug history

**Past medical history**
- Weighed 116 lbs as senior in high school
- Gained weight after birth of 2 sons
- Drinks 4-6 mountain dews/day
- Type II DM ~ 15 yrs
- GB symptoms for >5 years with laparoscopic cholecystectomy and liver biopsy
- Increased cholesterol
- ? Hypertension
- Positive FH for DM, CAD

**Drug history**
- Metformin
- Statin –d/c’d
- prn Mirilax for constipation and bloating

### Test results

**Lab results**
- Liver biopsy – macrovesicular fat, neutrophil infiltration, hepatocyte necrosis, stage 2-3 fibrosis, 2+ iron, NASH vs ASH depending on history
  - H/H: 14/42
  - AST/ALT: 42/86
  - Alb: 4.2
  - Bili: 0.4

**Imaging results**
- RUQ – US
  - Coarsened echotexture of liver
  - Multiple gallstones in GB
  - CBD not dilated
  - No masses in liver
  - No ascites
Further Investigations
- Hep A B C Negative
- ANA 1:320
- Ceruloplasmin 21
- α1 antitrypsin normal
- Ferritin 720
- Serum iron 83
- AMA negative

Diagnosis
- NASH
- Obesity
- Increased cholesterol
- Diabetes
- S/P Cholecystectomy

Treatment decision

Selected treatment options:

Diet
- Stop pop/fructose
- Portion size

Exercise

Drugs - Options
- vitamin E
- Pentoxifylline
- Pioglitazone
- SAMe
- omega-3 fatty acids
- Probiotics
- Milk Thistle
• Monitor liver enzymes/tests
• Weight BMI
• Other?

Outcome-
• Started on pentoxifylline and probiotics


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Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

• 247 adults with NASH
  • 83 placebo
  • 80 pioglitazone 30mg
  • 84 Vitamin E 800 IU

Vitamin E ↓ Fat
Not Fibrosis

55 Patients Randomized

Pentoxifylline N=26
- Fibrosis
- NAS
- LFTs
- Oxidized fatty acids

Placebo N=29
- No change in fibrosis


66 NASH patients (biopsy documented)

Bifidobacterium longum + Fos (n=34)
- No patient withdrew

Placebo (n=32)
- No patient withdrew

Major Improvement
Some Improvement

ALT
CRP
TNF
Endotoxin
Liver Biopsy
- Fat
- Inflammation
- Fibrosis

### Progress evaluation & outcome

#### 2 month visit:
- ALT 86 → 61
- AST 42 → 36
- Weight 182 lbs → 174 lbs
- Vowed to d/c all sugared drinks
- Joined fitness program

#### 1 year follow-up:
- ALT 86 → 61 → 38
- AST 42 → 36 → 31
- Weight 182 → 174 → 161
- Research CK18 normal

### Case 1 questions

**Question # 1.**

This patient had a liver biopsy. With suspected NAFLD, who needs a liver biopsy, and are there non-invasive ways of monitoring liver injury and fibrosis? Should she have a follow-up liver biopsy?
Question # 2.

The patient had a positive ANA of 1:320.

• What are the implications of this related to autoimmune liver disease?
• Should she be treated for autoimmune hepatitis?

Question # 3.

The patient had an elevated ferritin of 720. Should she be screened for hemochromatosis and what are the implications of iron overload in NAFLD?

Question # 4.

The patient has a strong family history of coronary artery disease. Does NAFLD increase the risk factors for coronary artery disease and death due to this problem?


Question # 5.

Is it safe to treat the patient’s hyperlipidemia with a statin?

Case 1 questions

Question # 6.

The patient does not yet have cirrhosis. Should she undergo surveillance for HCC?


Case 1 questions

Question # 7.

Are there ethnic differences related to NAFLD?

Take Home Points

- NAFLD #1 cause of increased liver enzymes in U.S.
- Lifestyle modification including d/c sugared pop, weight loss, exercise of benefit
- Vitamin E decreases steatosis; does not decrease fibrosis
- Pentoxifylline may decrease fibrosis
- Factors that improve metabolic endotoxemia likely therapeutic targets
- Major cause of death CAD