Digestive and Hepatic Complications of Obesity

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The Medical Weigh
Obesity Complications

• Cholelithiasis
• GERD
• Fatty Liver disease (NAFLD)
• Gastrointestinal Cancers
Gallstones

- Incidence in Obesity
- Maclure et al NEJM 1989
  - “Nurses Health Study”
  - BMI >30 – 2x risk
  - BMI > 45 – 7x risk !!

- Data in Men less impressive
Gallstones

Cost?
- Difficult to estimate
- Suspected to be approximately $5 bil. Annually
- Includes surgery, visits etc
- Johns Hopkins 2009
Gallstones - Mechanism

- #1 Hyper secretion of Cholesterol into Bile
  - Obese with inc. LDL, VLDL levels
  - Crystal formation --- Stones
  - *Mabee Surgery 1976*
    - 9 obese patients vs controls
    - Consistently higher secretion of cholesterol into bile

The “4 F’s”
Gallstones - Mechanism

• #2 Decreased Gallbladder Contractility
  – Hyperinsulinemia
    • Known to interfere with CCK binding to receptor in gallbladder

• *Peroni, Alimentary Pharm. and Therapy 2002*
  – Larger Gallbladder Volume between meals
  – Hence, Increased stasis time leading to crystal formation
Gallstones Mechanism

• The Irony….
  – Weight loss can increase GS formation!
  – 25% form new GS on VLCD
  – 35% form new GS on low fat diets (1-3g)
  – Decreased CCK secretion with low fat meals
  – 4g fat in meal – min. GB contraction, 10g – Max!
Gallstones Treatment

- **Festi et al Int. J. Obesity Related Met. Dis. 1998**
  - Increasing the fat content of VLCD Prevented GS formation

- So what to do?
  - Diet should contain >800 kcal/day *and* 15-30 g fat/day
  - Ursodeoxycholic Acid – 600mg/day
  - Cholecystectomy for symptomatic stones
GERD

- **Incidence**
  - In obesity - up to 72%
  - *Nilsson, JAMA 2003*
    - \( \text{BMI} > 35 \) – 3x increase in men and 7x increase in women

- **Severity** – Increased in the obese
  - *El Serag, Scand. J. Gastro 2002*
    - \( \text{BMI} > 35 \) significantly increased risk of severe esophagitis vs nl weight
GERD

- Cost
  - Always difficult to estimate
  - ACG ~ 2 billion/week in lost US productivity
  - Medication costs - $$$
GERD – Mechanism in Obesity

• Development of Hiatal Hernia
  – Pandolfino, Gastroenterology 2006
    • 285 pt’s studied with Esophageal manometry
    • Obese patients more likely to have EGJ disruption and Increased GE pressure gradients

• Increased Intrabdominal pressures
  – Corley, GUT 2007
    • Association between Abdominal Diameter (independent of BMI!) and GERD symptoms!
GERD - Treatment

• Medications – PPI’s, H2RA’s antacids etc
• What about weight loss??
  – Jacobsen et al, NEJM 2006 – Nurses Health study
    • Strong correlation between BMI and GERD symptoms
  – Singh – abstract DDW 2010
    • 2/3 of pt’s in weight loss program reported resolution of GERD symptoms
NAFLD

• Definition
  – Non-Alcoholic Fatty Liver Disease
  – Includes NASH and IFL
  – Macrovesicular steatosis in > 5% of hepatocytes
  – NASH – Is “fatty liver” with inflammation (necroinflammatory changes)
    • 15-20% of NAFLD
NAFLD - Definition

NAFLD

Isolated fatty liver

1. None to very minimal progression to cirrhosis
2. No increased risk of death compared with the general population

NASH

1. Increased risk of death compared with general population. Causes of death, in order:
   a. Cardiovascular
   b. Malignancy
   c. Liver-related
2. NASH with fibrosis portends worse prognosis
   a. Fibrosis progression associated with DM, severe IR, BMI, weight gain >5kg, rising ALT, AST, cigarette smoking

HCC

~7% over 6.5 years

NASH Cirrhosis

~11% over 15 years, but significant variability

Decompensation

~31% over 8 years

NAFLD - Prevalence

• Occurs in > 66% in Obese, > 90% of stage 3 obese patients (BMI>40)

• More common in Men

• Truncal Obesity is risk factor (even with normal BMI!)
NAFLD - Diagnosis

• Liver enzymes (AST & ALT)
  – Neither sensitive or specific

• Imaging
  – No difference b/n US, CT and MRI
  – US favored

• Liver Biopsy – Gold standard
  – Invasive, expensive
NAFLD - Diagnosis

• How to screen for NASH non-invasively?
  
  – Transient Elastography
    • Measures fibrosis
    • Problems with obesity, inflammation, cholestasis etc
    • Not US FDA approved yet
  
  – Acoustic Force Impulse Elastography
    • Can be performed with US
NAFLD- Diagnosis

• Laboratory testing
  – CK-18 – testing for NASH
    • Musso Ann. Med 2011 – Meta-analysis
    • Sensitivity & specificity of 78 and 87%

  – Scoring systems
    • FibroTest, NAFLD Fibrosis Score, APRI and BARD etc

  – No test predicts NASH with sufficient accuracy and validation at this point to recommend.
NAFLD - Pathogenesis
NAFLD - Treatment

• Diet and Exercise!
  – Promrat, *Hepatology 2010*
    • 31 patients with NASH
      Randomized to Tx. vs counseling
    • Liver Biopsy before and after
    • Significant difference between groups and between more and less wt. loss!!!

  – Other studies show similar results
NAFLD - Treatment

- Coffee…!!
  - Inverse relationship noted 20 yrs ago in alcoholics
  - Malloy, Hepatology 2012
    - 306 patients – already biopsied – received questionnaire about coffee
    - Signif. Difference between IFL, early NASH, and Advance NASH
  - How much?
    - Between 2-3 cups
NAFLD - Treatment

• Medications
  – Thiazolidinediones (TZD’s)
    • Pioglitizone still available – Must be continued or histologic changes return
      – Beware of wt. gain
    • Metformin
      – Intial excitement tempered by recent Randomized trials showing no benefit.
NAFLD - Treatment

• Others? The Future?
  – Antioxidants
    • Vitamin E – Sanyal, NEJM 2010
      – Significant decrease in Lobular inflammation and steatosis
    • UDCA – Mixed results
  – Probiotics ??
Obesity and Cancer

• Increase in esophageal, colon/rectum, Hepatic, pancreas and Gall Bladder!

• Multiple potential mechanisms
  – Leptin
  – GERD, NAFLD, etc

• Risk of death higher in the obese