HEADLINE NEWS:
Bull giraffe returns home after brief stay at the NYC zoo
Objectives

- Review some statistics on obesity
- Etiologies of obesity
- Treatment modalities for obesity
- Review bariatric surgery
- Review NAFLD/NASH
Obesity and Increased Disease Risks

Hypertension (drop diastolic BP by 1 mm Hg decreased MI risk by 2-3%)
Osteoarthritis
Dyslipidemia (low HDL, high TG)
Type 2 diabetes (BMI >30)
Heart disease (Increase BMI by 1.1=increased CV risk by 6%
Stroke
Gallbladder disease (1 kg fat synthesizes 20 mg cholesterol)
Sleep apnea and respiratory problems/pneumonia

Some cancers: pancreas, esophageal, kidney, prostate, endometrial (due to increased estrogen), breast, liver/GB and colon/rectal CA

Reference:
Obesity is a “Worldwide” Crisis

- Many industrialized countries seeing increased obesity

Prevalence of overweight people in the Anglosphere

Obesity is a “National” Crisis

* US has the highest obesity rate of all countries
  * 1962: 13%
  * 1997: 19.4%
  * 2004: 24.5%
  * 2007: 26.6%
  * 2008: 33.8%, with 17% of children obese
  * 2010: 35.7%, with 17% of children obese
Prevalence of Self-Reported Obesity Among U.S. Adults
BRFSS, 2011

Source: Centers for Disease Control and Prevention, Behavioral Risk Factor Surveillance System 2011
Obesity Trends* Among U.S. Adults
BRFSS, 1985
(*BMI ≥30, or ~ 30 lbs. overweight for 5′ 4″ person)
The Costs of Obesity (Direct and Indirect Costs)

* 1995: $51 Billion
* 2000: $61 Billion
* 2003: $75 Billion
* 2006: $117 Billion
* 2011: $165 Billion
Prevalence of Obesity in the US

- **Severe Obesity (BMI >40 kg/m2)**
  - 1986: 1 in 200
  - 2000: 1 in 50

- **Extreme Obesity (BMI >50 kg/m2)**
  - 1986: 1 in 2000
  - 2000: 1 in 400
**Obesity by Age**

- **Children (2-5 year olds)**
  - 1980: 5%
  - 2006: 12.4%

- **Children (6-11 year olds)**
  - 1980: 6.5%
  - 2008: 19.6%

- **Teenagers**
  - 1980: 5%
  - 2008: 18.1%

- Up to 40% of daily nutrient intake occurs during school hours. *(National School Lunch Act of 1946)*
I WANT YOU

TO LOSE SOME WEIGHT
16% of active duty US military personnel were obese in 2004

US military spent $15 million in 2002 for bariatric surgery

Obesity is the largest single cause for the discharge of uniformed personnel

2005, 9 million adults ages 17-27 years old, or 27%, were too overweight to be considered for military service

Obesity is the MCC of rejection for military service


What Causes Obesity?

* **Cultural Habits**
  * Favorite foods are carbohydrate and fat “loaded”
    * Easy to make, package, cheap
  * Deep fried
  * Volume/Size/Want more for our money. In 1955 McDonalds cup size was 7 oz. (Original Coke bottle was 6.5 oz)

* **Social Habits**
  * Interact/socialize over food
    * Business, parties, sports events, medical events
    * Social status, wealthy vs poor. Times have changed
Soda

Original 8-ounce bottle
97 calories

12 ounce can
145 calories

20-ounce bottle
242 calories
Two Slices of Pizza

Twenty years ago
500 calories

Today
850 calories

Those extra 350 calories, if eaten two times a month, would put on two extra pounds a year, or forty pounds in the next two decades.
Movie Popcorn

Twenty Years Ago
3-5 cups

~270 calories

Today
Tub

~800 calories
(up to 1600 calories with butter)
Cup of Coffee

Twenty years ago
Coffee with milk and sugar
8 ounces
45 calories

Today
Grande café mocha with whipped milk
16 ounces
330 calories
What Causes Obesity?

* Environmental Factors
  * US has many labor saving devices, less calorie expenditure
  * “Hurried” life-styles
  * Children and exercise (or lack thereof), video games, etc
* Medications
  * Anti-convulsants, -depressants, -diabetics, neuroleptics
  * Adenovirus? (AM-36)
* Genetics (~100 genes implicated)
  * Prader-Willi (chromosome 15)
  * Bardet-Biedl Syndrome
CHICO'S MEXICAN RESTAURANT
THE BEST PIZZA IN TOWN
How Do We Combat Obesity?

- Let’s Move! campaign. February 9, 2010/Exercise
- Medications
- Surgery
- Diets (3500 kcal/wk = 1 lb loss)
- Taxation?
The Overweight American

The Overweight Government

Y'know...you really ought to consider trimming down a bit, Bud.
NYC: (Non-Diet) Soda Ban Proposal, Summer 2012

* Obesity Kills ~5,800 NYC residents/year

* 16 oz soda = 27 gm sugar
* 8 oz Ocean Spray cranberry cocktail = 33 gm
* Carton of flavored milk = 25-30 gm
* 8 oz cup of granola = 30 gm
* Craisins = 29 gm

* Does not address coffees, Slurpees, fruit drinks, etc
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Medications for Obesity

* Sibutramine (Meridia), SSNRI
* Orlistat (Xenical 120 mg/Alli OTC 60 mg TID), inhibits intestinal lipase
* Sympathomimetic Amines (4)
  * Phentermine (remember Phen/fen-fluramine)
  * Qsymia (Phentermine + Topiramate)
* Cannabinoid Antagonists: Rimonabant, pulled 2008 (psychiatric side effects)
* Fluoxetine (Prozac): SSRI
* Buproprion (Wellbutrin/Zyban): Norepi/dopamine RI
* Topiramate (Topamax): Anti-epileptic
* Zonisamide (Zonegran): Anti-epileptic, serotonin/dopaminergic activity
* Metformin
* Exenatide
* Pramlintide (Amylin), Pancreatic beta-cell hormone
HEADLINE NEWS:
Michelangelo’s *David* after his tour in the United States
GI Problems Related to Obesity

* Cholelithiasis
  * Cholesterol turnover directly related to total body fat
  * 20 mg cholesterol is synthesized for each kg of extra adipose
  * Precipitates, cholesterol stones
  * Rapid weight loss is lithogenic
    * Wt loss → increased CH excretion in bile → precipitates → stones

* GERD
* Erosive Esophagitis
* Barrett’s Esophagus
* Esophageal Adenocarcinoma
GI Problems Related to Obesity

* Cancer
  * Esophagus
  * Pancreas
  * Gallbladder
  * Liver
  * Colon/Rectum

* Prostate
* Endometrial
* Breast
How Do We Combat Obesity?

- Bariatric Surgery
  - Laparoscopic adjustable gastric banding
  - Vertical banded gastroplasty
  - Biliopancreatic diversion-duodenal switch (high risk surgery)
  - Roux-en-Y, 88% of bariatric procedures
    - DM2: 84%
    - HTN: 75%
    - DL: 94%
    - GERD: 96%
    - Steatosis: 89%
    - OSA: 87%
GI Problems Related to Bariatric Surgery

* Intraoperative Complications
  * Splenic Injury
  * PV Injury
  * Bowel Ischemia
  * Bowel Misconstruction

* Early Complications
  * Anastomotic Ulcers
  * Anastomotic Leaks
  * Obstruction
  * Bleeding
GI Problems Related to Bariatric Surgery

* Late Complications
  * Gastric Remnant Distension/Obstruction
  * Anastomotic Stenosis/Leaks
  * Marginal Ulcers
  * Dumping Syndrome (50% of patients)
    * Nausea, shaking, diaphoresis, diarrhea, light-headed, flushing, tachycardia, possible syncope
  * Prolonged Vomiting
  * Cholelithiasis
  * Hernias
  * Short Bowel Syndrome
Nutritional Deficiencies after RYGB

- **Vitamin A**: 500 mcg (1600 units). Night blindness, Bitot’s spots, xerosis
- **Vitamin D3**: Rickets, osteomalacia
- **Vitamin E**: 10 mg. Sensory and motor neuropathy, ataxia, hemolytic anemia, retinal degeneration
- **Vitamin K**: 120 mcg in males, 90 mcg in females. Bleeding problems

- **Vitamin B1 (thiamine)**: 1.2 mg. Intractable vomiting, Wernickes
- **Vitamin B12 (cyanocobalamin)**: 400 to 1000 mcg. Megaloblastic anemia, atrophic glossitis, neuropathy, CNS demyelination. (Also seen in strict vegans and in infants that are exclusively breastfed.)
* Nutritional Deficiencies after RYGB
  * Folate (childbearing females): 400 mcg. Neural tube defects
  * Biotin: 30 mcg.
  * Selenium: 55 mcg
  * Zinc: 11 mg in males, 8 mg in females. Chronic diarrhea
  * Copper: 2 mg. Fatigue, neuropathy
  * Calcium: 1200 to 1500 mg (elemental). Citrate better absorbed than carbonate in low acid conditions. Do not take within 2 hours of iron supplement. Osteopenia/Osteoporosis

* Iron: Ferrous fumarate, 40-65 mg or ferrous gluconate, 18-27 mg. Vitron-C (ferrous fumarate, 65 mg + ascorbic acid, 125mg)
  * Ascorbic acid 100-150 mg enhances iron absorption in conditions of reduced gastric acidity. Microcytic anemia
GI Problems Related to Bariatric Surgery

- Medication Use Post-RYGB
  - Don’t use delayed/extended release, enteric coated meds
  - Avoid sulfonylureas/meglitinides (hypoglycemia). Metformin is safest
  - BP meds: Hypotension common post-RYGB
  - Reflux meds: Usually can be stopped. (If reflux returns w wt gain consider gastrogastric fistula)
  - NO NSAIDS! Remember, it’s extremely difficult to get back into the stomach post-RYGB
  - ERCP extremely difficult post-RYGB! (Why GBs removed with surgery)
GI Problems Related to Obesity

* Nonalcoholic Fatty Liver Disease (NAFLD)
  * Presence of hepatic steatosis with no cause of secondary hepatic fat accumulation
  * MC liver disorder in industrialized countries
  * In US
    * NAFLD: 10-46%
    * NASH: 3-5%
  * Prevalence in US (NAFLD) % of Chronic Liver Dz
    * 1988 to 1994: 5.5% 47%
    * 1999 to 2004: 9.8% 63%
    * 2005 to 2008: 11% 75%

Worldwide

6-35%
Definitions

* **NAFLD**: Entire spectrum of fatty liver disease in people without significant alcohol consumption. Encompasses fatty liver to steatohepatitis and cirrhosis

* **NAFL**: Presence of hepatic steatosis with no evidence of hepatocellular injury (no balloon degeneration of hepatocytes, no fibrosis)

* **(Steatohepatitis)**: “Fatty liver disease.” Fat deposition in the liver with subsequent liver inflammation

* **NASH**: Clinical disorder in which pt has no significant EtOH hx but liver biopsy resembles alcoholic steatohepatitis. Fatty liver + inflammation with hepatocyte injury (ballooning), +/-fibrosis = Cirrhosis
Fatty Liver
Steatohepatitis with Fibrosis
**Risk Factors for NASH**

- Central obesity (69-100% of pts)
- Dyslipidemia (20-80% of patients)
- DM2 (34-75% of patients)
- Slight male predominance
- Older age (most cases seen in ages between 40-60)
- Metabolic disorders
  - TPN, rapid weight loss, acute starvation, hypothyroidism, Wilson’s Disease
- Drugs/Toxins
  - Amiodarone, tamoxifen, glucocorticoids, estrogens, HAART, tetracycline/minocycline
Pathogenesis

- Insulin resistance (hormonal)

- “Second Hit” of subsequent oxidative stress is considered to be a key mechanism of hepatocellular injury and disease progression in NASH patients
  - Iron
  - Antioxidant deficiencies
  - Intestinal bacteria/overgrowth
Clinical/Lab Manifestations

* Malaise
* Fatigue
* Mild RUQ pain
* ~75% are asymptomatic!
* Hepatomegaly (on CT = liver span of >18 cm)

* Elevated Aminotransferases (MC presentation)
  * High in about 90% with NASH, but could be normal (in ~10%)
  * AST/ALT ratio <1 (with EtOH is >2, ~2.7)
  * Alk Phos/GGT may be up 2- to 3-fold (but could be normal)
  * Bilirubin/albumin usually normal
  * Degree of aminotransferase elevation does not predict grade or stage of liver injury!
Differential for LFT Abnormalities

- Alcohol
- Viral hepatitis (A, B, C and D)
- Hereditary hemochromatosis
- Wilson’s disease
- Alpha-1 antitrypsin deficiency
- Autoimmune hepatitis
- Drug/toxin history
- NASH
Imaging Studies

* **US**
  * Hyperechoic texture or bright liver (fat)

* **CT**
  * Non-contrasted images worse with higher BMIs
  * Contrasted images does not accurately reflect steatosis

* **MRI**
  * Normal MRI can exclude significant steatosis but may not reflect slight fatty changes

* **MR Spectroscopy**
  * Can be more quantitative with fat appearance

* **Tissue Elastography (with trans-abdominal or EUS)**
Fatty Liver on CT
Liver Biopsy

- Only way to confirm or exclude NASH
- Shows severity of disease and may offer prognosis
- If cirrhotic then need...
  - Screening for esophageal/gastric varices
  - US/AFP q 6 months
  - Vaccinations for HBV/HAV (and other vaccines)

Perform in Patients with:

- Physical stigmata of chronic liver disease
- Splenomegaly
- Cytopenia
- Abnormal iron studies
- DM, Obesity, age >45
Treatment

* Weight Loss + Increased Physical Activity
  * Can help improve LFTs, histology, lower serum insulin levels and improve quality of life
  * 7% wt reduction showed histologic improvement in 72% (of 31 pts). 3-5% wt decrease improves steatosis, 10% wt loss needed to improve necro-inflammation

* Bariatric Surgery
  * Histologic improvement (inflammation and fibrosis) noted with wt loss 1-2 years post-op on repeat liver biopsy
  * Not contraindicated if NASH/NAFLD present but not recommended for treatment of NASH

* Gradual wt loss
  * Not exceed 3.5lbs or 1.6kg/week in adults
  * Too rapid can worsen liver disease
Vitamin E

- Vitamin E (alpha-tocopherol) at dose of 800IU/day improves liver histology in non-diabetic adults with biopsy proven NASH and should be considered as a first-line pharmacotherapy for this pt population.

- Vitamin E is **NOT recommended** to treat NASH in diabetic pts, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis until further data is available.

- Controversial whether Vitamin E increases all-cause mortality (meta-analyses)
  - Recent RCT demonstrated 400IU daily increased risk of prostate CA in healthy men with absolute risk of 1.6/1000 person years of Vitamin E use.
Metformin

- 110 pts with NASH, Metformin 2gm/day vs. Vit E 800IU/day vs. dietary wt loss over 12 months
  - LFTs improved with metformin more than with vit E or wt loss
  - Only mild change in steatosis/inflammation
- Other studies failed to show major benefit from metformin on hepatic insulin sensitivity, LFTs or histology

Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH
TZDs (Actos (pioglitazone) and Avandia (rosiglitazone))

- Rosiglitazone improved AST/ALT and steatosis but not inflammation and fibrosis.
- Pioglitazone improved AST/ALTs and steatosis, ballooning and inflammation and NAFLD activity score (NAS) and trend toward improved fibrosis.
  - Some pts had wt gain of 2.5-4.5kg.
  - Pts in the trials were non-diabetic!
  - Long-term safety and efficacy not established.
  - Caution in cardiac/CHF pts.

- **Actos can be used to treat steatohepatitis** in pts with biopsy-proven NASH!
Treatment

* **URSO:** Not recommended

* **Omega-3-Fatty Acids**
  * Can treat hypertriglyceridemia with NAFLD but not recommended for NASH or treatment of NAFLD
Alcohol/Statins Use in Patients with NAFLD and NASH

* Alcohol
  * Heavy consumption is risk factor, should be avoided
    * More than 4 drinks/day or > 14 drinks/week in men
    * More than 3 drinks/day or >7 drinks/week in women

* Statins: Can be use to treat dyslipidemia in patients with NAFLD and NASH
  * No evidence that pts with chronic liver disease are at higher risk for serious liver injury from statins than those without liver disease
Summary

- Obesity is a national problem and only becoming more prevalent.
- Multiple etiologies of obesity.
- Multiple therapeutic modalities for treating obesity.
- Bariatric surgery can have subsequent morbidities.
  - Follow these patients closely post surgery.
- NASH likely to be MCC of cirrhosis and subsequently MCC of liver transplant in next 5-10 years.
- Not many therapies for this other than weight loss.
“So then I says to Borg, ‘You know, as long as we’re under seige, one of us oughta moon these Saxon dogs.’”