Morbid Obesity and the Metabolic Syndrome

John P. Cello, MD
Professor of Medicine and Surgery, University of California, San Francisco

U.S. Adults: 1988
Nineteen states with 10-14% Prevalence of Obesity
(*BMI > 30, or ~ 30 lbs overweight for 5’4” woman)

U.S. Adults: 2000
Twenty-two states with > 20 % prevalence of obesity, 27 states with 15-19% obesity, one state with 10-14% obesity
(*BMI > 30, or ~ 30 lbs overweight for 5’4” woman)
Not Just a Problem for American Men!!

Women also!!

Relationship of BMI to Excess Mortality

But doctor why am I so fat? I just eat like a bird.

The Answer: First Law of Thermodynamics

- Matter and energy are interchangeable.
- They are neither created nor destroyed.
- Calories Ingested minus Calories Expended = Excess Caloric Intake.
- Energy (caloric) excess is stored principally as fat.

Basal Energy Requirements – Man @ 70 kg. (est. total 1940 kcal)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Weight</th>
<th>% B Weight</th>
<th>Kcal/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>1550</td>
<td>2.2</td>
<td>445</td>
</tr>
<tr>
<td>Brain</td>
<td>1400</td>
<td>2.0</td>
<td>420</td>
</tr>
<tr>
<td>Kidneys</td>
<td>300</td>
<td>0.4</td>
<td>360</td>
</tr>
<tr>
<td>Heart</td>
<td>300</td>
<td>0.4</td>
<td>235</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>28000</td>
<td>40</td>
<td>400</td>
</tr>
<tr>
<td>Adipose</td>
<td>15000</td>
<td>21</td>
<td>80</td>
</tr>
</tbody>
</table>

Factors Used to Estimate Thermal Effect of Physical Activity

- Resting 1.0
- Very light activity 1.1 – 2.0
- Light activity 2.1 – 4.0
- Moderate activity 4.1 – 6.0
- Heavy activity 10.0

Endogenous Fuel Stores in a 70 Kg. Man

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Fuel Source</th>
<th>Grams</th>
<th>Kcal.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose</td>
<td>Triglyceride</td>
<td>13000</td>
<td>120000 (60 d)</td>
</tr>
<tr>
<td>Liver</td>
<td>Glycogen</td>
<td>100</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>Protein</td>
<td>300</td>
<td>1200</td>
</tr>
<tr>
<td></td>
<td>Triglyceride</td>
<td>50</td>
<td>450</td>
</tr>
<tr>
<td>Muscle</td>
<td>Protein</td>
<td>6000</td>
<td>24000 (12 d)</td>
</tr>
<tr>
<td></td>
<td>Glycogen</td>
<td>400</td>
<td>1600</td>
</tr>
<tr>
<td></td>
<td>Triglyceride</td>
<td>50</td>
<td>450</td>
</tr>
<tr>
<td>Blood</td>
<td>Glucose</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Triglyceride</td>
<td>4</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Free fatty acids</td>
<td>0.5</td>
<td>5</td>
</tr>
</tbody>
</table>

Non-adipose/muscle energy stores = equivalent to 2 days!!
**Historical Background – Metabolic Syndrome**

- Vague (France) 1947 – first noted that upper body obesity predisposed to diabetes, atherosclerosis, gout
- Avogaro & Crepaldi (Italy) 1967 – describes 6 obese patients with DM, elevated chol. & TG – all responding to dieting with low carbohydrates
- Haller (Germany) 1977 - coined term “Metabolic Syndrome” in patients with obesity, DM, atherosclerosis, elevated TG & chol. Associated with hepatic steatosis
- Reaven (England) 1988 – proposed insulin resistance as the underlying factor for “Syndrome X”

**Components of the Metabolic Syndrome**

- Abdominal Obesity – increased visceral fat (premier feature)
- Insulin Resistance – with glucose intolerance and diabetes mellitus
- Dyslipidemia (consequential)
- Hypertension (consequential)

**Morbid Obesity and the Metabolic Syndrome**

- Markedly increased visceral fat is the core feature of the pathogenesis of the metabolic syndrome
- The key consequence of the increased visceral fat is insulin resistance

**Prevalence of Metabolic Syndrome Over 50 years old**

- United States – 40% of population
- Europe – 30% of population
- Developing world – not immune from the entity – India – now 27% of population
- Racial predisposition – Hispanics > African-Americans > Caucasians > Asians
- Sex predisposition – none: males = females
Younger Age Populations (20-25 years old) – Increased Prevalence World Wide: Not just an American and European Problem

- Saudi Arabia – 39%
- Turkey – 33%
- USA – 28%
- Venezuela – 31%
- Brazil – 25%
- India – 24%

Pathophysiology of the Metabolic Syndrome

- Visceral adipose tissue plays an important role in energy regulation – endocrine, paracrine and autocrine signals
- Adipokines released by visceral fat cause insulin resistance.
- Insulin antagonists – TNF-alpha, IL-6, resistin – (decrease insulin action)
- Insulin sensitzers – leptin, adiponectin

How Does Abdominal Obesity Cause Insulin Resistance

- Reduced Physical Activity
- Excessive food intake
- Inflammation
- insulin receptor substrate (IRS-1 & IRS-2)
- IL-6
- TNF-α
- various cytokines
- adiponectin
- leptin
- blood FFA

Insulin Resistance: Multisystem Disorder

- Adipose tissue
  - Increased NEFA and adipokine release
- Muscle
  - Decreased glucose disposal
- Liver
  - Increased gluconeogenesis and hepatic glucose output
  - Triglyceride accumulation in hepatocytes
- Endothelium
  - Endothelial dysfunction
### 2005 Revised ATP III Clinical Screening Criteria to Identify Metabolic Syndrome (AHA and NHLBI)

<table>
<thead>
<tr>
<th>Parameter (any 3/5 diagnostic)</th>
<th>Categorical cutpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference</td>
<td>≥ 40 inches in men</td>
</tr>
<tr>
<td></td>
<td>≥ 35 inches in women</td>
</tr>
<tr>
<td>Elevated triglycerides</td>
<td>≥ 150 mg/dl at baseline</td>
</tr>
<tr>
<td>Reduced HDL-cholesterol</td>
<td>&lt; 40 mg/dl in men</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 mg/dl in women</td>
</tr>
<tr>
<td>Or on drug treatment for reduced HDL-C</td>
<td></td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>≥ 130 mmHg systolic blood pressure</td>
</tr>
<tr>
<td></td>
<td>or ≥ 85 mmHg diastolic blood pressure</td>
</tr>
<tr>
<td>Or on antihypertensive drug treatment in a patient with a history of hypertension</td>
<td></td>
</tr>
<tr>
<td>Elevated fasting glucose</td>
<td>≥ 100 mg/dl at baseline</td>
</tr>
</tbody>
</table>

### What is NAFLD (Non-Alcoholic Fatty Liver)?

**How does it occur?**

**Why is it important?**

### Obesity & Pathogenesis of NAFLD/NASH

- **Low grade, chronic inflammatory state**
- **Circulating FFA**
- **Inflammatory cytokines, chemokines & adipokines (IL-6, TNFα, leptin, resistin, adiponectin)**
- **Oxidative Stress**
- **Impaired insulin responsiveness**
- **Insulin resistance**
- **Hyperinsulinemia**
- **NASH**
- **Steatosis**

**Fat**

**Inflammation/Necrosis**

- Mallory's Hyaline
- Ballooning/Fibrosis
Metabolic Syndrome - Treatment

- Expectant treatment – treat complications of diseases
- Dietary weight loss
- Exercise programs
- Pharmacotherapy
- Bariatric surgery

Dietary Changes

- Caloric restriction:
  - Total fat: 25-35% of total calories
  - Reduced consumption of simple sugars
  - Increased intakes of fruits, vegetables, and whole grains
- The relative amounts of carbohydrate and unsaturated fats is more controversial

Physical Activity

- Regular and sustained physical activity will improve all risk factors of the metabolic syndrome
- Current guidelines recommend 30-60 min moderate-intensity exercise daily (e.g., brisk walking)
- Best with a trainer under supervision

Medical Options: Non-Prescription

- Overall efficacy (unsupervised) – 20 kg loss per year
- Usual options: support groups, behavior modification, specialized (structured) diets, supervised very low calorie diets (usually inpatient).
Prescription Pharmacotherapy

- Unlicensed for bariatric use: thyroid derivatives, amphetamines
- Approved medications: orlistat (Xenical™)
- Withdrawn medications: Phen-Fen, Sibutramine, Rimonabant

Orlistat - Xenical™

- Pancreatic lipase inhibitor
- Dosage: 120 mg TID ($200/month)
- Side effects: steatorrhea, diarrhea, cramping, flatulence
- Overall efficacy: pts can lose 3-4 kg/year over that achieved by 1500 cal/day alone.
- Over-the-counter in Great Britain

Sibutramine (Meridia™)

- Mechanism of action: monoamine (serotonin and norepinephrine) reuptake inhibitor
- Side effects: tachycardia, hypertension, seizures, cholelithiasis, depression, suicidality (increased cardiovascular events)
- Efficacy: 4-5 kg extra weight loss over 1 year (with 1500 cal/day diet)
- WITHDRAWN FROM MARKET

Rimonabant

- Mechanism of action: selective cannabinoid receptor-1 antagonist
- Dosage: 20 mg QD
- Side effects: mood disorders
- Efficacy: about 4-5 kg added weight loss over one year (over that with 1500 cal/day diet)
- WITHDRAWN FROM MARKET
Why surgery?

Many if not most individuals with clinically severe obesity are refractory to conservative treatments

- Medical / pharmacological management
- Diet
- Exercise

Unadjusted Cumulative Mortality

Impact of Bariatric Surgery vs Medical Control on Excess Body Weight

Resolution of Comorbidities – 22,094 patients

- Diabetes
- Hyperlipidemia
- HTN
- Sleep apnea

Surgical options
- Malabsorptive procedure
  - Duodenal Switch
  - Biliopancreatic Diversion
- Restrictive procedure
  - Adjustable Lap-Band
  - Sleeve gastrectomy
- Combined procedure
  - Roux-en-Y gastric bypass

Malabsorptive Procedures
- Duodenal Switch/ Biliopancreatic Diversion
- Highest rate of longterm complications related to malnutrition / diarrhea
- Death rate highest of any bariatric procedure at 1.1 percent

Laparoscopic Gastric Bypass
Anatomical Changes in the Digestive Tract – Gastric Bypass

- Reduced stomach capacity – from 2 liters to 60-120 ml.
- Gastric stoma leads directly into mid jejunum (rather than duodenum)
- Bypass of 60-80 cm of small bowel absorptive surface
- Pancreatic juice and bile finally mix with chyme one meter downstream from stoma.

Stoma – the outlet of the stomach created surgically

Small Intestine just beyond the stoma

Consequences of Altered Anatomy on the Digestive Processes - Stomach

- Small gastric pouch means that the ingestion of a limited amount of food leads to sense of fullness – early satiety
- The fundus has little contractile activity (actually receptively relaxed with food) and slows the emptying rate of solid food.
- Liquids usually empty rapidly.
### Altered Digestion in Small Intestine
- Almost 1 meter of small intestine (principally the duodenum and few cms of jejunum) is never in contact with ingested food (loss of about 20% of small intestinal absorptive surface).
- An additional 1 meter of small intestine receives chyme but is without pancreaticobiliary secretion.
- Liquid food empties directly and rapidly into mid small intestine.

### The Consequences - Small Intestine Carbohydrate Foods
- Mismatching of starch-rich chyme and amylase
- Reduced surface area for absorption of sugars and other carbohydrates.
- Simple sugars (mono and disaccharides) in high concentration consumed as liquids are passed directly and rapidly into the mid small bowel produce early and late “dumping” – lightheadedness, diaphoresis, tachycardia, weakness.

### The Consequences – Small Intestine Proteins
- Poor mixing of pancreatic enzymes and ingested complex protein-containing foods (meats, poultry or fish). Limitation in hydrolysis to amino acids.
- Reduced surface area available for absorption of amino acids and small-chain polypeptides.

### The Consequences – Small Intestine Fats
- Dietary long-chain triglycerides require the following: pancreatic lipase, conjugated bile salts and an adequate small intestinal surface area. The small bowel cannot absorb long chain fats without all being present.
- Serious loss of effective surface area: nearly 2 meters of small intestine are either “bypassed” or without pancreaticobiliary secretions mixing with the ingested fat.
- Maldigested fat produces diarrhea and gas.
Consequences of Bariatric Surgery – Vitamins and Minerals

- Potential serious problem – fat soluble vitamins: Vitamin A, Vitamin D, Vitamin E and Vitamin K.
- Uniquely absorbed vitamin: Vitamin B12
- Minerals: iron (best absorbed in duodenum – now “bypassed”)
- Calcium – needs vitamin D for optimal absorption.

Fat Soluble Vitamins

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Dietary Source</th>
<th>Daily needs</th>
<th>Absorbed</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Liver, eggs, oils</td>
<td>1 mg</td>
<td>Micelles</td>
<td>Vision, immunity</td>
</tr>
<tr>
<td>D</td>
<td>Fish, eggs, milk, sun</td>
<td>200-600 IU</td>
<td>Micelles</td>
<td>Calcium Abs.</td>
</tr>
<tr>
<td>E</td>
<td>Oils, nuts grains</td>
<td>15-20 mg</td>
<td>Micelles</td>
<td>Anti-oxidant</td>
</tr>
<tr>
<td>K</td>
<td>Greens, dairy</td>
<td>unknown</td>
<td>Micelles</td>
<td>Clotting factors</td>
</tr>
</tbody>
</table>

Water-Soluble Vitamins

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Dietary Source</th>
<th>Daily needs</th>
<th>Absorbed</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Citrus</td>
<td>75-90 mg</td>
<td>Active/passive</td>
<td>Anti-oxidant, collagen synthesis</td>
</tr>
<tr>
<td>Thiamin</td>
<td>Cereals and grains</td>
<td>1.2 mg</td>
<td>Active/passive</td>
<td>Carbohydrate and ketogenic metabolism</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>meats, fish, fruits</td>
<td>1–2 mg</td>
<td>Passive diffusion</td>
<td>Amino acid metabolism</td>
</tr>
<tr>
<td>Niacin</td>
<td>Animal protein</td>
<td>15-20 mg</td>
<td>Passive diffusion</td>
<td>Redox reactions, FA biosynthesis</td>
</tr>
</tbody>
</table>

Vitamin B12

Vit B12 role in DNA replication, methyl donor, and neural function.