Epidemic of Obesity: What Can We Do?

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Obesity

- Obesity is the leading public health crisis of our time
  - Prevalence of obesity (BMI > 30 kg/m²) among adults is 34% for extreme obesity, the figure is 6%.
  - 53% of non-Hispanic African American women and 51% of Mexican American women 40 to 59 years of age are obese compared with an estimated 39% of non-Hispanic white women of the same age.
  - Overweight and obesity affect more than 66% of the adult population.
- Modern therapies have reduced the rate of mortality due to heart disease in the United States
  - Concerning trends in both nonfatal events and the disability that results from major cardiovascular events
  - Risk factor levels continue to rise at alarming rates.
Obesity

- Obesity is the leading public health crisis in US in the 21st century
- Obesity is an independent risk factor major cardiovascular events, including coronary heart disease, heart failure, and stroke
- Framingham risk score assessment for cardiovascular disease does not account for obesity. Risk assessment should include:
  - body mass index
  - waist circumference
  - blood serum inflammatory biomarkers
  - physical fitness

Prevalence of Obesity* Among U.S. Adults

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>1990</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>1996</td>
<td>10%-14%</td>
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<tr>
<td>2003</td>
<td>&gt;14%</td>
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Prevalence of Diabetes* Among U.S. Adults

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>&lt;4%</td>
</tr>
<tr>
<td>1996</td>
<td>4%-6%</td>
</tr>
<tr>
<td>2003</td>
<td>6%-8%</td>
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Obesity

- Major studies show that lifestyle change leading to weight loss can reduce or reverse risks associated with cardiovascular disease, including sleep apnea, hypertension, type 2 diabetes, and coronary heart disease.
- Patients intractable to lifestyle intervention alone, pharmacotherapy can facilitate weight loss to reduce risk of comorbid conditions
- In cases of severe obesity, bariatric surgery is associated with significant weight loss and improvement in diabetes, hypertension, and obstructive sleep apnea.
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Walking the dog

Obesity

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Risk Factors for Obesity

- Hypertension
- Dyslipidemia
- Diabetes mellitus (type 2)
- Obstructive sleep apnea
- Hyperinsulinemia, insulin resistance
- Low levels of plasminogen activator inhibitor
- High levels of C-reactive protein
- Hyperviscosity
- Framingham risk score

Patient: "Doctor the problem with me is that obesity runs in my family."
Doctor: "No, the problem with you is that no one runs in your family."
Etiology & Pathophysiology

Risk Factors - Visceral Adiposity

- Central obesity more significant CVD risk than total obesity and that waist circumference and waist-to-hip ratio may be better predictors of atherosclerosis and CVD risk than BMI
- Inflammatory adipokines
  - increases insulin resistance and diabetes in obesity
  - Increase risk for thrombosis
  - Affects progression of endothelial dysfunction, increasing inflammation and the risk for atherosclerosis
- Free fatty acids, produced in visceral abdominal fat, may decrease insulin sensitivity, impair vascular reactivity, and also increase endothelial dysfunction.
Low Birth Weight

- Large number of studies have linked low birth weight to the later development of central adiposity.
- Landmark cohort study of 300,000 men coworkers that exposure to the Dutch famine of 1944-1945 during the first half of pregnancy resulted in low birth weight associated with significantly higher obesity rates at the age of 19 years.
- Research has confirmed the relationship between low birth weight and development of:
  - visceral or central adiposity
  - Oligo-olig syndrome
  - higher blood pressure later in life.

Hypertension

- In 2003-2006, 36% of men and women between the ages of 45 and 54 years had hypertension compared with 65% of men and 80% of women 75 years of age and older.
- The National Health Interview Survey found that in 2007, 23% of U.S. adults had been told by a physician or health professional on two or more visits that they had hypertension.
- Children and adolescents with severe elevation of blood pressure are at risk for CVA & CHF.
  - Two autopsy studies in adolescents and young adults found significant relationships between the level of blood pressure and the presence of atherosclerotic lesions in the aorta and coronary arteries.
  - Childhood levels of blood pressure are also associated with carotid intima-media thickness, large artery compliance, decreased brachial artery flow-mediated vasodilation,
Sleep Apnea

- Obstructive sleep apnea is independently associated with increased cardiovascular risk, also linked to:
  - insulin resistance and glucose intolerance
  - impaired glycemic control and type 2 diabetes in patients who report excessive sleepiness.
- Obstructive sleep apnea is strongly correlated with intra-abdominal fat and serum lipid levels are elevated in patients who have obstructive sleep apnea.
- Population-based prospective cohort study from 1989-2000 found that a 10% weight gain predicted an approximate 32% increase in the apnea-hypopnea index and a sixfold rise in the risk for development of moderate to severe obstructive sleep apnea.

Dyslipidemia

- Metabolic syndrome is closely associated with obesity CVD risk factors.
- Individuals with obesity and metabolic syndrome present with increased concentrations of very-low-density lipoprotein (VLDL) particles, increased triglycerides and small-particle LDL, increased LDL particle number, and decreased HDL particle size.
- Elevated triglyceride concentrations are associated with greater circulating numbers of triglyceride-rich VLDL particles and higher levels of VLDL cholesterol, an environment that alters the metabolism of LDL-C and HDL-C and contributes to atherogenic potential.
- Atherogenic dyslipidemia, characterized by elevated triglycerides and low levels of HDL-C, often with elevated apolipoprotein B and non-HDL-C, is common in patients with established CVD, type 2 diabetes, or metabolic syndrome and contributes to both macrovascular and microvascular residual risk.

Lifestyle, and Exercise Interventions: Diet, Behavioral Modification

- A study examined the risk of CHD associated with excess weight in 42,351 men from the Health Professionals Follow-up Study and 76,703 women from the Nurses’ Health study. A total of 2771 incident cases of CHD among the men and 2359 among the women were documented during 16 years of follow-up.
  - Relative risk of CHD associated with a BMI ≥ 30 compared with a BMI of 18.5 to 22.9 was 2.13 among men and 2.48 among women. The risk of CHD increased with BMI, with and without hypercholesterolemia, hypertension, or diabetes. The authors estimated that more than a third of all incident CHD in U.S. men and women may be attributed to excess weight.
- For prevention of CVD and CVD risk factors, dietary choices that improve the overall quality of the diet are preferred to specific dietary components. AHA recommendation:
  - variety of fruits, vegetables, and whole grain products
  - fat-free and low-fat dairy products, legumes, poultry, and lean meats as well as fish, preferably oily fish, at least twice a week.
Lifestyle Interventions: Diet, Behavioral Modification, and Exercise

- The “whole diet” approach greatly increases the odds of achieving a “prudent diet.”
  - Large 18-year prospective study of 72,113 women, greater adherence to the prudent pattern was related to a lower risk of cardiovascular and total mortality.
  - Greater adherence to the Western pattern (i.e., high intake of red and processed meat, refined grains, French fries, and sweets and desserts) was linked to a higher risk of CVD, cancer, and total mortality.

- Consumption of diets rich in saturated fatty acids is highly correlated with metabolic syndrome and an increased expression of genes involved in inflammation processes in adipose tissue.
  - High-fat, high-protein, low-carbohydrate diets have been associated with short-term improvement in LDL-C, HDL-C, and blood pressure; recent evidence suggests that this diet profile can elevate risk of CVD without altering classic CVD risk factors.
  - High-fat, high-protein diets can elevate circulating nonesterified fatty acids and increase arterial plaque.

Comparison of the Atkins, Ornish, Weight Watchers, and Zone Diets for Weight Loss and Heart Disease Risk Reduction: A Randomized Trial


Study description

- Single-center one-year randomized trial at an academic center in Boston, Mass
- Enrolled July 2000- January 2002
Methods: Inclusion Criteria

- Adults with BMI between 27 and 42
- At least one of the following metabolic risk factors:
  - Fasting glucose ≥ 110 mg/dL
  - Total cholesterol ≥ 200 mg/dL
  - LDL cholesterol ≥ 130 mg/dL
  - HDL cholesterol ≤ 40 mg/dL
  - Triglycerides ≥ 150 mg/dL
  - SBP > 145 or DBP > 90
- Or current use of oral medications to treat HTN, DM, or dyslipidemia
- 160 final participants; 40 participants randomized to each diet group

Methods: Dietary Intervention

- Less than 20 g of carbohydrate daily with a gradual increase to 50 g daily
- 40-30-30 balance of percentage calories from carbohydrate, fat, and protein respectively
- Vegetarian diet containing 10% calories from fat
**Results: Weight Loss**

<table>
<thead>
<tr>
<th>Diet</th>
<th>Weight loss in kg (SD) at 12 months</th>
<th>Percentage participants completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkins</td>
<td>2.1 (4.8)</td>
<td>53%</td>
</tr>
<tr>
<td>Zone</td>
<td>3.2 (6.0)</td>
<td>65%</td>
</tr>
<tr>
<td>Weight Watchers</td>
<td>3.0 (4.9)</td>
<td>65%</td>
</tr>
<tr>
<td>Ornish</td>
<td>3.3 (7.3)</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Results: Cardiac Risk Factors**

<table>
<thead>
<tr>
<th>Diet</th>
<th>Decrease of LDL at 1 year (SD)</th>
<th>Increase in HDL at 1 year (SD)</th>
<th>Decrease of LDL/ HDL ratio at 1 year (SD)</th>
<th>Decrease of C-reactive protein at 1 year (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkins</td>
<td>-7.1 (24)</td>
<td>3.4 (7.1)</td>
<td>-0.39 (0.81)</td>
<td>-0.70 (2.1)</td>
</tr>
<tr>
<td>Zone</td>
<td>-11.8 (34)</td>
<td>3.3 (10.3)</td>
<td>-0.40 (0.81)</td>
<td>-0.58 (2.1)</td>
</tr>
<tr>
<td>Weight Watchers</td>
<td>-9.3 (27)</td>
<td>3.4 (9.9)</td>
<td>-0.55 (1.39)</td>
<td>-0.58 (1.3)</td>
</tr>
<tr>
<td>Ornish</td>
<td>-12.6 (19)</td>
<td>3.0 (6.5)</td>
<td>-0.31 (0.68)</td>
<td>-0.88 (2.4)</td>
</tr>
</tbody>
</table>

Statistically significant

**Food Choices to Make**

Instead of…
- Soft drinks
- Fried foods
- Whole milk
- Salad dressings
- Cookies
- Chips

Choose…
- 100% juice
- Grilled/Baked
- Low-fat milk
- Low fat dressings
- Soft serve yogurt
- Veggies with dip
**Steps to Fix Bad Eating Habits**

- Start each day with a nutritious breakfast.
- Get 8 hours of sleep each night, fatigue can lead to overeating.
- Eat your meals seated at a table, without distractions.
- Eat more meals with your partner or family.
- Teach yourself to eat when you’re really hungry and stop when you’re comfortably full.
- Reduce your portion sizes by 20%, or give up second helpings.
- Eat a nutritious meal or snack every few hours.
- Use nonstick pans and cooking spray instead of oil to reduce the fat in recipes.
- Try different cooking methods, such as grilling, roasting, baking, or poaching.
- Drink more water and fewer sugary drinks.
- Eat smaller portions of calorie-dense foods (like casseroles and pizza) and larger portions of water-rich foods (like broth-based soups, salads, and veggies).
- Flavor your foods with herbs, vinegars, mustards, or lemon instead of fatty sauces.
- Limit alcohol to 1-2 drinks per day.

**Pharmacotherapy**

- Drug treatment should be considered only part of a systematic weight management program that includes dietary and lifestyle changes
  - Recommended for patients with cardiometabolic risk and a BMI of 27 to 29.9 OR
  - those with a BMI ≥30.
FDA approves lorcaserin for weight loss

- FDA has approved lorcaserin (Belviq) as an adjunct to a calorie-reduced diet and exercise for chronic weight management.
  - Works by activating the serotonin 2C receptor in the brain and does not appear to activate the serotonin 2B receptor when used at the recommended dose of 10 mg twice daily.
  - First weight-loss drug available since 1999 and is approved for adults with a body mass index (BMI) >30.
  - Can also be used in adults who have at least one weight-related condition, including hypertension, type 2 diabetes, or dyslipidemia, and a BMI >27.
- The approval of lorcaserin is based on three randomized clinical trials that included approximately 8000 overweight and obese patients with and without diabetes treated with lorcaserin for 52 to 104 weeks in addition to a calorie-reduced diet and recommendations to get physically active.

Phase 3 Results

- Study 009 & 011 (non diabetics)
  - >5% weight loss
    - Lorcaserin 47% vs Placebo 23%
  - ≤10 weight loss
    - Lorcaserin 22% vs Placebo 9%

- Study 010 (Diabetics)
  - >5% weight loss
    - Lorcaserin 38% vs Placebo 16%
  - ≤10 weight loss
    - Lorcaserin 16% vs Placebo 4%
**Lorcaserin**

- Most common side effects of lorcaserin in nondiabetic patients
  - Non diabetics: Headache, dizziness, fatigue, nausea, dry mouth, and constipation.
  - Diabetics: hypoglycemia, headache, back pain, cough, and fatigue.
- Condition of the FDA approval includes the initiation of six long-term post-marketing studies, including a cardiovascular outcomes study to assess the effect of the weight-loss drug on hard clinical outcomes, such as myocardial infarction and stroke.

**Qsymia - PHEN/TPM CR**

- Phentermine/topiramate controlled-release (Qsymia) is a fixed-dose combination under investigation for the treatment of overweight or obesity.
  - PHEN is a sympathomimetic amine, an anorectic agent, approved by the FDA (37.5 mg/day) as a short-term therapeutic adjunct to a weight loss regimen.
  - TPM is approved by the FDA for the treatment of epilepsy (200-400 mg/day) and migraine headache prophylaxis (100-200 mg/day) and has demonstrated weight loss and cardiometabolic benefits in clinical trials.
- PHEN/TPM CR was given in three doses: 3.75 mg/23 mg daily, 7.5 mg/46 mg daily, and 15 mg/92 mg daily. A total of 3,879 overweight and obese individuals were studied.
- Compared to placebo, treatment with PHEN/TPM CR at different doses was associated with significant weight loss in obese individuals (between 4.7% and 10.4% from baseline to 56 weeks; p<0.0001 vs. placebo).
- Reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were seen at all doses of PHEN/TPM CR in both patients with and without hypertension.
Weight Loss Surgery

- Bariatric surgery is associated with significant weight loss and improvement in diabetes, hypertension, and obstructive sleep apnea and reversal of type 2 diabetes.
- Laparoscopic Roux-en-Y gastric bypass is the most effective procedure for weight loss and is considered the “gold standard” operation for long-term weight control, accounts for more than 90% of all bariatric operations.
- Laparoscopic adjustable gastric banding is the second most commonly performed procedure.
- Laparoscopic sleeve gastrectomy, which is becoming popular as a stand-alone operation for the treatment of severe obesity is safe and effective, with results similar to those of gastric bypass.

- A recent systematic review summed up the risks and benefits of weight loss surgery.
  - Comorbidities in all groups improved after procedures
  - Fewer people had metabolic syndrome
  - Higher remission of type 2 diabetes than in nonsurgical groups.
  - Mortality ranged from none to 10%.
  - Major postoperative adverse events, some necessitating reoperation, included anastomosis leakage, pneumonia, pulmonary embolism, band slippage, and band erosion.

STAMPEDE

- Single site, prospective, randomized controlled trial (Cleveland Clinic), 150 patients
- Compared the efficacy of three treatments for patients with T2DM and BMI between 27-42 kg/m²
- Intensive Medical Therapy
- Intensive Medical Therapy + Laparoscopic Sleeve Gastrectomy
- Intensive Medical Therapy + Gastric Bypass
- Primary Endpoint: Proportion of patients with a glycated hemoglobin level of 6.0% or less at 12 months after treatment.
### STAMPEDE

#### Increased Weight Loss

<table>
<thead>
<tr>
<th></th>
<th>Medical Therapy</th>
<th>Medical Therapy + Gastric Bypass</th>
<th>Medical Therapy + Sleeve Gastrctomy</th>
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</thead>
<tbody>
<tr>
<td><strong>Mean % Weight Loss</strong></td>
<td>5.2%</td>
<td>27.5%*</td>
<td>24.7%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*p&lt;0.001</td>
<td>*p&lt;0.001</td>
</tr>
<tr>
<td><strong>Mean % Excess Weight Lost</strong></td>
<td>13%</td>
<td>88%*</td>
<td>81%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*p&lt;0.001</td>
<td>*p&lt;0.001</td>
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</table>

Table adapted from study data

#### Results: Significantly More Diabetic Patients at Glycemic Control with Bariatric Surgery

- In obese patients with uncontrolled type 2 diabetes, 12 months of medical therapy plus bariatric surgery achieved glycemic control in significantly more patients than medical therapy alone.

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<th>Medical Therapy + Sleeve Gastrectomy</th>
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<tbody>
<tr>
<td><strong>Patients at Glycemic Control, 12 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Therapy</td>
<td>12%</td>
<td>*42%</td>
<td>37%</td>
</tr>
<tr>
<td>Medical Therapy + Gastric Bypass</td>
<td></td>
<td>*p=0.002</td>
<td></td>
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<tr>
<td>Medical Therapy + Sleeve Gastrectomy</td>
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Glycemic control: HbA1c < 6.0% with or without diabetes medications, 12 mo after randomization. Figures adapted from study data.

#### STAMPEDE

- No deaths in the study
- 4 surgery patients required re-operation to address adverse events:
  - Cholelithiasis (gallstones)
  - Self-limited bleeding
  - Nausea & vomiting
  - Gastric leak
- No episodes of serious hypoglycemia
Myths of Obesity
Casazza et al, NEJM 2013

- "False and scientifically unsupported beliefs about obesity are pervasive in the scientific literature and popular press"
- Small changes over time produce big benefits of weight loss—it takes more exercise and less intake as we lose weight
- Realistic weight loss goals improve success but those with ambitious goals are often more successful
- Slow weight loss improves success when the opposite appears true (16% vs 10% at 6 mos lass 18 mos)
- Eating breakfast prevents obesity
- Intense sex is effective in burning calories—NOT! 21 kcal in 6 min to orgasm vs. 7 kcal lying on the couch
- Yo yo dieting increases mortality
- Eating fruits and vegetables increase weight loss

Consensus Evidence about Weight Loss

- TLC can promote = wt loss to meds
- Adherence to diet more important than specific diet for successful weight loss with best diets based on Mediterranean concept
- Exercise yields health benefits and can accelerate weight loss when accompanied by hypocaloric lifestyle
- Childhood obesity is a family issue
- Meals/replacements work
- Weight loss drugs should be considered and are effective in the right subgroups of pts with BMI >27 with RFs or >30 who have failed TLC
- Bariatric Surgery is extremely effective with reversal of metabolic derangements and DM and elimination of need for RF meds in those who fail TLC and meds and have BMI>35 with RF or 40

Future Directions…

- Early childhood education
- Public education focus
- Calorie Counting, labeling
- Portion Size Control - NYC experience with softdrinks
- Healthy eating alternatives in public places
- ???Balancing public health concerns vs individual rights
Simple Conclusions

• Eat Less
• Move More
• Live Longer
• Live Better

• THANK YOU!