The Science Behind Obesity and Diabetes

John P. Kirwan, Ph.D., FACSM

Director, Metabolic Translational Research Center
Endocrinology and Metabolism Institute, Cleveland Clinic

Staff, Department of Pathobiology
Lerner Research Institute, Cleveland Clinic

Professor, Molecular Medicine
Lerner College of Medicine, Cleveland Clinic and Case Western Reserve University
OBJECTIVES TODAY

Provide a broad overview of biomedical science in obesity and diabetes

• Define the problem
• Identify the causes of the problem
• Examine current treatments and preventions
Part 1 – Define the Problem
## The Science Behind Obesity & Diabetes

- Obesity: Body Mass Index (BMI) of 30 or higher.
  - A measure of weight in relation to height - body weight in kilograms divided by the square of height in meters (kg/m²)

<table>
<thead>
<tr>
<th>Weight classification</th>
<th>BMI (kg/m²)</th>
<th>Obesity Class</th>
<th>Risk Of illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>_</td>
<td>Increased</td>
</tr>
<tr>
<td>Ideal weight</td>
<td>18.5 to 24.9</td>
<td>_</td>
<td>Normal</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 to 29.9</td>
<td>_</td>
<td>Increased</td>
</tr>
<tr>
<td>Obesity (mild)</td>
<td>30.0 to 34.9</td>
<td>I</td>
<td>High/very high</td>
</tr>
<tr>
<td>(moderate)</td>
<td>35.0 to 39.9</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>Extreme obesity (severe)</td>
<td>40 &gt; 40</td>
<td>III</td>
<td>Extremely high</td>
</tr>
</tbody>
</table>
The Science Behind Obesity & Diabetes

Historical Perspective
Paleolithic Era > 25,000 years ago
# Obesity Trends* Among U.S. Adults
**BRFSS, 1990, 2000, 2010**

(*BMI ≥30, or about 30 lbs. overweight for 5’ 4” person*)

<table>
<thead>
<tr>
<th>Year</th>
<th>No Data</th>
<th>&lt;10%</th>
<th>10%-14%</th>
<th>15%-19%</th>
<th>20%-24%</th>
<th>25%-29%</th>
<th>≥30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Map showing obesity trends across the United States for 1990, 2000, and 2010.]
The Science Behind Obesity & Diabetes

Part 2 – Identify the Causes of the Problem
Regulation of Food Intake

**Brain**

**Central Signals**

<table>
<thead>
<tr>
<th>Stimulate</th>
<th>Inhibit</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPY</td>
<td>α-MSH</td>
</tr>
<tr>
<td>AGRP</td>
<td>CRH/UCN</td>
</tr>
<tr>
<td>galanin</td>
<td>GLP-I</td>
</tr>
<tr>
<td>Orexin-A</td>
<td>CART</td>
</tr>
<tr>
<td>dynorphin</td>
<td>NE</td>
</tr>
</tbody>
</table>

**Peripheral signals**

- Glucose
- CCK, GLP-1, Apo-A-IV
- Insulin
- Ghrelin
- Leptin
- Cortisol

**Peripheral organs**

- Gastrointestinal tract
- Adipose tissue
- Adrenal glands

**Food Intake**

**External factors**

- Emotions
- Food characteristics
- Lifestyle behaviors
- Environmental cues
Causes of Obesity

TOO INACTIVE!

TOO MANY CALORIES!

The eat-healthy secret your grandma knows

Hey, she has pots and pans older than you! Trust her advice.

WHEN GLAMOUR READER Julie Strongin asked her grandmother (pictured here in her early twenties) how she kept her figure, Harriet Strongin said, "I grew up in a time when people ate less. I'm amazed at how people eat today and then wonder how they've gained pounds. Movie theaters served popcorn in six-inch-high bags, not gallon tubs, and a hot dog was just that, not a combo meal." She's right. Portions have inflated during the last 50 years. According to research by Lisa Young, Ph.D., of New York University in New York City, what Grandma Harriet has to say about it.

1950s 1.5 cups 2002 3 cups
"The plates restaurant waiters put in front of you today would have been serving platters in my day," says Harriet Strongin.

1950s 3 ounces 2002 6.5 ounces
"The muffin pans that I used to bake with were cupcake-size, not big enough to feed three people like they are now."

1950s 6.5 ounces 2002 20 ounces
"I remember when soda came in the original, small bottles. Now servings are huge!"

1950s 1.5 ounces 2002 8 ounces
"The hamburgers we bought back then were just skinny little things."

1950s 1 ounce 2002 2.6 ounces
"We used to buy this little chocolate bars—for a nickel!"—SUNNY SEA GOLD
Working Model of Human Disease

Poor Nutrition
Inactivity

Obesity

Insulin Resistance

Diabetes
Cancer

Fatty Liver Disease
Cardiovascular Disease
Natural History of Type 2 Diabetes

Risk Factors
- Obesity
- Impaired glucose tolerance

Diagnosis
- 3 years of DM 2
- 9 years of DM 2
- Uncontrolled Hyperglycemia
- Decreased beta cell function

Lifestyle
- Monotherapy
  - HbA1c=8.5% or FPG=>240mm/dl
- Combined
  - HbA1c=<7.7% or FPG= 180mm/dl
- Insulin

Disease Progression
- 50%
- 100%

100% Risk Factors (Obesity)
50% Impaired glucose tolerance

The Science Behind Obesity & Diabetes

Part 3 – Current Treatments and Preventions
The Science Behind Obesity and Diabetes

Diet and Exercise can Treat and Prevent Obesity and Diabetes
Standard Exercise Prescription

Endurance Exercise

5 days/week; 60 min/day, 80-85% $HR_{\text{max}}$
Treadmill/cycle ergometry/ stationary rower
Energy Expenditure: ~500 kcal
Exercise Can Reverse Diabetes

Long-term exercise improves how insulin works in older (60-70 years), obese men and women

- Improved insulin sensitivity after a 3-month program of aerobic exercise
- After the exercise program the group with impaired glucose tolerance, were better than those who had normal glucose tolerance but were not exercising
- Likewise, those with type 2 diabetes were better than the impaired group when they were not exercising

Solomon/Kirwan et al. Diabetes Care, 33:1561-66, 2010
Role of Diet in Diabetes

I'm on a low-carb, low-fat, low-sodium, low-sugar diet.

So what can you eat?

Wallboard and straw.
Diet Composition
Glycemic Index & Glycemic Load

• **Glycemic Index (GI)** *is* a ranking of foods based on the ratio of the blood glucose response for each food expressed as a percentage of the response to the same amount (50 g) of a standard food (white bread or glucose) (Jenkins et al. *Am J Clin Nutr* 34: 362-6, 1981).
Comparison of Glycemic Index Value of Foods

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Glycemic Index Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barley</td>
<td>25</td>
</tr>
<tr>
<td>Prunes</td>
<td>29</td>
</tr>
<tr>
<td>Lentils</td>
<td>30</td>
</tr>
<tr>
<td>Whole Milk</td>
<td>31</td>
</tr>
<tr>
<td>Lima Beans</td>
<td>32</td>
</tr>
<tr>
<td>Yams</td>
<td>37</td>
</tr>
<tr>
<td>Apple</td>
<td>40</td>
</tr>
<tr>
<td>Sweet Potato</td>
<td>44</td>
</tr>
<tr>
<td>Instant Rice</td>
<td>46</td>
</tr>
<tr>
<td>Banana</td>
<td>51</td>
</tr>
<tr>
<td>Basmati Rice</td>
<td>58</td>
</tr>
<tr>
<td>Instant Oatmeal</td>
<td>61</td>
</tr>
<tr>
<td>Table Sugar (Sucrose)</td>
<td>68</td>
</tr>
<tr>
<td>White Bread Slice</td>
<td>70</td>
</tr>
<tr>
<td>Watermelon</td>
<td>72</td>
</tr>
<tr>
<td>French Fries</td>
<td>75</td>
</tr>
<tr>
<td>Baked Russet Potato</td>
<td>85</td>
</tr>
<tr>
<td>French Baguette</td>
<td>95</td>
</tr>
<tr>
<td>Mashed White Potato</td>
<td>97</td>
</tr>
<tr>
<td>Parsnips</td>
<td>100</td>
</tr>
<tr>
<td>Glucose</td>
<td>103</td>
</tr>
<tr>
<td>Dates</td>
<td>115</td>
</tr>
<tr>
<td>Tofu Frozen Dessert</td>
<td>125</td>
</tr>
<tr>
<td>Cornflakes</td>
<td></td>
</tr>
</tbody>
</table>
Role of Diet & Exercise in Insulin Resistance

Adding a low Glycemic Load diet to exercise has a synergistic effect on insulin sensitivity in older obese adults.

Change in the dietary glycemic load in a subset of obese subjects during a 12-week exercise intervention.

80% vs 20% improvement in insulin sensitivity ($\Delta$ mg/kg/min).

The increase in insulin sensitivity was inversely correlated with the decrease in glycemic load ($r = 0.84$, $P<0.009$).

Mouse Cloning Studies


When you increase the amount of a specific protein called PEPCK in the muscle of a mouse you change metabolism and the mouse can run for hours, eat all it wants without gaining weight, and reproduce well into old age.

Overexpression of PEPCK in Skeletal Muscle of the Mouse

More Powerful Than a Locomotive?

PEPCK-C$^{\text{mus}}$ Supermouse vs. Wild Type
BARIATRIC SURGERY & DIABETES
Surgery for Severe Obesity

- Gastric Banding: 35%
- RY-Gastric Bypass: 63%
- BPD: 2%
Figure 1. Mean Weight Change Percentages From Baseline for Controls and the 3 Surgery Groups Over 20 Years in the Swedish Obese Subjects Study

No. of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2037</td>
<td>1490</td>
<td>1242</td>
<td>1267</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banding</td>
<td>376</td>
<td>333</td>
<td>284</td>
<td>284</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertical banded gastroplasty</td>
<td>1369</td>
<td>1086</td>
<td>987</td>
<td>1007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>265</td>
<td>209</td>
<td>184</td>
<td>180</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sjöström, L. et al. JAMA 2012;307:56-65
Bariatric Surgery Versus Intensive Medical Therapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bariatric Surgery vs. Intensive Medical Therapy in Obese Patients with Diabetes

Philip R. Schauer, M.D., Sangeeta R. Kashyap, M.D., Kathy Wolski, M.P.H., Stacy A. Brethauer, M.D., John P. Kirwan, Ph.D., Claire E. Pothier, M.P.H., Susan Thomas, R.N., Beth Abood, R.N., Steven E. Nissen, M.D., and Deepak L. Bhatt, M.D., M.P.H.
Change in Body Mass Index

Schauer et al., NEJM, 2012
Average Number of Diabetes Medications

Average Number of Medications

Baseline | Month 3 | Month 6 | Month 9 | Month 12
---|---|---|---|---
IMT | 2.8 | 3.1 | 3.1 | 3.0 | 3.0
RYGB | 2.6 | 1.1 | 0.6 | 0.4 | 0.3
SG | 2.4 | 1.1 | 0.9 | 0.8 | 0.9

P<0.001

Schauer et al., NEJM, 2012
Reversal of Obesity and Diabetes

BMI

- Surgery
- Pharmacotherapy
- Lifestyle Modification
- Diet
- Physical Activity
Obesity & Diabetes in the US

• Over 30% of adults in the US are obese and another 30% are overweight

• Being overweight or obese is strongly associated with developing Type 2 Diabetes which is characterized by high blood sugar levels (hyperglycemia) as a result of the body’s inability to make or use insulin

• Nearly 24 million Americans have obesity-related diabetes

• Over 65% of people with diabetes die from heart disease or stroke

• Approximately one in three Americans born in 2000 will develop diabetes (Narayan et al. JAMA 2003 Oct 8;290(14):1884-1890)
Medical Complications of Obesity

- Pulmonary disease
  - abnormal function
  - obstructive sleep apnea
  - hypoventilation syndrome
- Idiopathic intracranial hypertension
- Stroke
- Cataracts
- Coronary heart disease
- Diabetes
- Dyslipidemia
- Hypertension
- Severe pancreatitis
- Cancer
  - breast, uterus, cervix
  - colon, esophagus, pancreas
  - kidney, prostate
- Gall bladder disease
- Gynecologic abnormalities
  - abnormal menses
  - infertility
  - polycystic ovarian syndrome
- Osteoarthritis
- Skin
- Gout
- Nonalcoholic fatty liver disease
  - steatosis
  - steatohepatitis
  - cirrhosis
- Phlebitis
  - venous stasis
The Obesity Problem

(PANT PANT) THIS CAN'T BE HAPPENING!
(HUFF) I'M ABOUT TO BE PASSED BY THE (PANT-WHEEZE) FAT GUY!!

SMOKING

RACING TO AN EARLY FINISH...

© 2004 PHOENIX TODAY
Caglecartoons.com
Thank you!