New Perspectives on the Pathogenesis of Obesity

Cardiometabolic Congress

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April 23, 2013
No Financial Disclosures

Body Mass Index (BMI): weight (kg) / height (m²)

Lean
BMI < 25

Overweight
BMI 25 - 30

Obese
BMI 30 - 40

Morbidly Obese
BMI > 40

* Caveat: An athletic, fit person may have a high BMI without excess adiposity

Agenda

- Definitions and the Scope of the Problem
- Physiological Determinants of Body Weight
- Molecular Mediators of Body Weight
- Gene – Environment Interactions
  – The Role of Dietary Composition
  – The Social Environment

Obesity Increases the 10 Year Risk of Death in Men ages 50 - 71


Obesity Increases the 10 Year Risk of Death in Women ages 50 - 71


Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults Aged 18 Years or older

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Social Stigma of Obesity

- Negative perception that obese people are lazy, unmotivated, lacking self-discipline, less competent.
- The prevalence of weight discrimination is comparable to rates of racial discrimination, especially among women:
  - Discrimination in hiring and employment decisions
  - Lower wages
- In a study of 600 primary care physicians in France:
  - 30% considered overweight and obese patients to be lazier and more self-indulgent than normal weight people
  - 60% identified lack of patient motivation as the most common problem in treating overweight and obese patients.

Observations:
- Obesity and its associated comorbidities have clear negative health consequences, yet they are also highly heritable.

Queries:
- Why is the Prevalence of Obesity Increasing?
- How could natural selection favor the spread of genes with such negative consequences?

Why is the Prevalence of Obesity Increasing?
- The "thrifty gene" hypothesis? (J. Neel, 1962)
  - In our early evolutionary development, genes that promoted efficient fat storage would be adaptive to protect against intermittent famine.
  - In modern society, with an overabundance of cheap nutrients and absent famine, this efficiency is maladaptive and results in obesity.
- The "predation release" hypothesis? (J. Speakman, 2007)
  - Genes favoring obesity have not been positively selected, but have occurred due to random genetic "drift" as a result of the absence of selection
  - ~ 2 million years ago, with the discovery of weapons and fire, the selection against obesity which might put us at risk for predation largely ceased.
- Protection from chronic infections like tuberculosis? (J. Roth, 2009)
  - The thrifty hypothesis fails to explain why obesity predisposes to the metabolic syndrome and why it is associated with increased "inflammation.
  - Increased adiposity associated with intensified proinflammatory defenses may provide a survival benefit against infectious agents like tuberculosis.

Body Weight is Determined by Energy Balance

- Energy Intake
  - Feeding
- Energy Expenditure
  - Basal Metabolism
  - Physical Activity
  - Adaptive Thermogenesis

* For body weight to increase such that obesity develops, energy intake must exceed energy expenditure.

Energy Expenditure

- Resting Energy Expenditure: ~ 60% of total
  - "Basal Metabolism"
  - Maintenance of transmembrane ion gradients
  - Resting cardiopulmonary activity
- The Thermic Effect of Feeding: ~ 10%
  - Digestion, transport, and deposition of nutrients
- Non-Resting Energy Expenditure: ~ 30%
  - Physical activity
- Adaptive Thermogenesis: ~ 80%
  - Major fraction of energy consumption in small mammals, but unclear in humans

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Can Small Changes in Energy Intake Cumulatively Produce Large Changes in Body Weight?

Example:
- Average daily caloric intake: 2200 kcal / day
- If a person eats 1 extra Ritz Crackers per day (16 kcal / day) without changing energy expenditure
  - This is a 0.7% increase in daily energy intake
- 16 kcal / day for 5 years => 29,200 kcal
  - 1 gram of stored fat is equivalent to 9 kcal
  - \( \frac{29,200}{9} = 3,244 \) grams of stored fat
  - \( \frac{3,244 \times 9}{7000} \approx 3.24 \) kg (7 pounds)

** Without a change in energy expenditure, eating 1 extra Ritz Cracker per day would lead to a 7 pound weight gain over the course of 5 years.

When Does Weight Gain Occur - Slow Drift Versus Sudden Change?

- Sudden changes in weight?
  - “The Freshman 15” is largely a myth
  - Weight gain averages ~ 2.5 lbs during the freshman year
- Weight generally increases slowly

Common Experience: Energy Balance is Largely Self-Regulating

- Despite short-term and long-term variability in energy consumption, body weight, in most people, remains generally stable over long periods of time
  - A feedback system must exist to auto-regulate energy consumption and energy expenditure
- The normal maintenance of body weight is not a matter of “willpower”
  - We do not need to “think” about regulating our food intake or energy expenditure for the maintenance of energy balance on a meal to meal basis. This process occurs subconsciously.

Query:

- Does Each Individual Have a Body Weight “Set Point?”

Energy Expenditure Increases Disproportionately with Weight Gain

Energy Expenditure Increases Disproportionately with Weight Loss
Weight Loss Increases Appetite Sensations

**How is Unbalanced Energy Status Sensed and How is Rebalancing Controlled?**

![Diagram showing energy intake and expenditure](Diagram)

**Molecular / Genetic Evidence for the Regulation of Energy Balance**

**Parabiosis Rescues Obesity in ob/ob Mice, but not db/db Mice**

**Ob/ob Mice are Deficient in the Adipose Secreted Hormone Leptin**

**Recombinant Leptin Replacement Cures Obesity in a Leptin Deficient Child**

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Obsessing is a State of Leptin Resistance

Mutations in Members of the Leptin Signaling Pathway Cause Monogenic Forms of Severe Obesity in Humans

- **FAT**
- **Hypothalamic Leptin**
- **Hypothalamic Appetite Suppressing Neurons Expressing POMC**
- **Other areas of brain, frontal cortex, hindbrain**
- **Effector Neurons Expressing MC4R**

Leptin, Leptin Receptor, POMC Mutations
Severe, early onset morbid obesity
Extremely rare

**MC4-Receptor Mutations**
Heterozygous coding mutations in MC4R account for ~5-7% of early onset (before age 5) obesity

Queries:
- Do Genetics Play a Role in Common Forms of Obesity?
- Is Adiposity a polygenic trait?
  - The predisposition to common obesity may be the result of relatively common mutations in many genes, each of which has individually a small impact on body weight.

Changes in Adiposity with Overfeeding is Strongly Heritable

- 12 pairs of monozygotic twins overfed by 1000 kcal per day for 84 days
- ~10-fold variation in adiposity with overfeeding across pairs
- Strong correlation within twin pairs ($R = 0.72$)

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Genome-Wide Association Studies

- A large number of genetic loci contribute to the regulation of BMI
- Individually, each of these loci has a small effect
- The largest effect is for a loci that contains the gene FTO.
  - This polymorphism explains 0.34% of the variance in BMI


On Average, People are Overweight Whether they have the Most or Least Number of Obesity Risk Alleles

Observations:
- Energy balance and body weight are tightly controlled by genetic / molecular mechanisms.
- However, the prevalence of obesity has increased dramatically over the last four decades.
- Our genes have not changed significantly over this time period.

Conclusions:
- Changes in Environmental Variables must account for the increase in obesity.

Queries:
- What Environmental Variables have changed over the last few decades contributing to the obesity epidemic?
- How do these environmental variables alter the homeostatic processes that normally regulates body weight within a narrow range?

Environmental Variables

- Decline in activity level
  - Cars, decline in manual labor, sedentary lifestyles
- Changes in Nutrient Intake / Composition
  - Increased portion sizes
  - Increased availability and reduced cost of highly palatable, energy dense foods
- Social and Cultural Factors
- Maternal-Fetal Environment and Epigenetic Imprinting
  - The Dutch Famine?
- Viral or other Communicable Causes
- Disrupted Sleep-Wake Cycles and Circadian Rhythms
- Changes in the Microbiome
- Environmental Toxins

Changes in Physical Activity Level?

- Occupation related physical activity has been slowly, but steadily trending down over the last 5 decades, inconsistent with the rapid increase in BW beginning in 1980
- “suburbanization” – cars, TV, washing machines and dishwashers, vacuums... became prevalent in the 1950s

TS Church et al., PloS one 6, e19657 (2011).
Query:
• Do Changes in Energy Intake or Dietary Composition Explain the Obesity Epidemic?

- Expectation of larger portions evolved over time.
- Related to cheapness of food.
- More food for the same amount of money is perceived as a positive value.
- “Supersizing” adds 1337 calories to the meal.

Pepsi (20 ounces):
- 259 calories
- 69 grams of sugar

Dannon Frusion (10 ounces):
- 240 calories
- 3.4 grams of fat
- 45 grams sugar

Baseline consumption of sugar-sweetened beverages (SSBs) correlated with BMI

For each additional daily serving of SSB consumed over 19 months
- BMI increased by 0.24 kg/m²
- Odds ratio for obesity 1.6
Queries:

- Is There Hope for Effective Treatment of Obesity?
- Can we use our knowledge of genetics and molecular physiology to enhance weight loss?

** Without a change in energy expenditure, eating 1 extra Ritz Cracker per day would lead to a 7 pound weight gain over the course of 5 years.

- Sustained marginal reductions in energy intake coupled with maintenance of or small increases in energy expenditure should produce large cumulative weight losses over long periods of time
- Short-term we are capable of helping people reduce caloric intake and increase energy expenditure
- We must learn to decouple weight loss from the compensatory homeostatic mechanisms

FDA Guidelines for Effective Anti-Obesity Therapy

- In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:
  - The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant
    - For a 250 pound person, that would require a 12.5 pound weight loss in 1 year
  - The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant