Obesity: Causes and Consequences

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Objectives

• WHAT is obesity?
• WHAT are the medical consequences of obesity?
• WHY do some people become obese?

What is Obesity?

Obesity is an excess of body fat

from L. obesitas "fatness, corpulence"

Body Mass Index (BMI)

• BMI = weight (kg)/height (m)²
• Measure of weight adjusted for height
• Highly correlated with body fat
  - Relationship varies with age, gender, ethnicity, and body build
• Easy to obtain
• Does not distinguish between body fat and muscle

One can be overweight but not overfat

OVERFAT: 220 LBS
OVERWEIGHT: 220 LBS

Relationship Between BMI and Percent Body Fat in Men and Women

By BMI, >65% of US Adults Are Overweight, >30% are Obese

Prevalence of obesity (BMI > 95th percentile) in children has tripled, but stable in girls over past 10 years

BMI-Associated Disease Risk

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>Increased</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 – 24.9</td>
<td>Normal</td>
</tr>
<tr>
<td>Overweight I</td>
<td>25.0 – 29.9</td>
<td>Increased</td>
</tr>
<tr>
<td>Obese II</td>
<td>30.0 – 34.9</td>
<td>High</td>
</tr>
<tr>
<td>Obese III</td>
<td>35.0 – 39.9</td>
<td>Very high</td>
</tr>
<tr>
<td>Obese I</td>
<td>≥ 40</td>
<td>Extremely high</td>
</tr>
</tbody>
</table>

Additional risks:
- Poor aerobic fitness
- Large waist circumference (men > 40 in; women > 35 in)

Fatness, Fitness, and Cardiovascular Disease Mortality

Visceral Adiposity:

Medical Complications of Obesity

- Pulmonary disease
  - Obstructive sleep apnea
- Hypoventilation syndrome
- Pancreatitis
- Nonalcoholic fatty liver disease
- Cholestasis
- Steatohepatitis
- Cirrhosis
- Gall bladder disease
- Cancer
  - Breast, uterus, cervix, prostate, kidney, colon, esophagus, pancreas, liver
- Gout
- Stroke
- Idiopathic intracranial hypertension
- Cataracts
- Coronary heart disease
- Diabetes
- Dyslipidemia
- Hypertension
- Gynecologic abnormalities
  - Abnormal menses
  - Infertility
  - Polycystic ovarian syndrome
- Osteoarthritis
- Osteoporosis
- Venous stasis
- Gastrointestinal disease
- Pancreatitis
- Idiopathic intracranial hypertension

Amount of intra-abdominal (visceral) fat is well correlated to the complications of obesity.
Why do people become obese?

Obesity Is Caused by Long-Term Positive Energy Balance

Energy Intake

Fat Stores

Energy Expenditure

America’s Weapons of Mass Destruction

Genetic Epidemiology of Human Obesity: Twin studies

- 50 - 80% of the variance in human body weight is accounted for by genetic variation
- The remainder is explained by common environmental factors

Indian family from Mexico

Pima Indian family in the US

Portion size and pediatric obesity

Number of Large-Size Portions Introduced


Percent overweight (> 95th centile)

12-19 year olds

6-11 year olds
Portion sizes have increased over the years

Environmental Changes in Physical Activity

- Decreased physical activity in schools/workplace/communities
  - Few schools offer daily P.E.
  - Fewer jobs require manual labor
  - Lack of sidewalks
- Increased sedentary behavior
  - Office and home
  - Computer, video games, television

Relative Risk of Developing Obesity and TV Viewing in Adults

Season Matters: Weight change is greatest during the winter holiday season
Why Do People Become Obese?

- Changes in our environment explain why obesity has become more common over the last 40 years.

- Our genes make us respond to our current environment by becoming obese.

Effects of Parental Obesity on Child Body Adiposity

Garn and Clark, Pediatr. 57: 443, 1976

Differential Diagnosis of Obesity

- Endocrinologic abnormalities
- Medication-related
- Hypothalamic damage related
- Genetic
  - Established syndromes
  - Leptin signaling pathway defects

Classical Endocrinologic causes of obesity

- Hypothyroidism
  - weight gain
  - fatigue
- Hypercortisolism
  - 1 in 1,000,000 prevalence
  - weight gain, striae, depression…
- Hyperinsulinemia (insulinoma)
  - Hypoglycemic episodes with weight gain
Medications associated with pediatric obesity

- Glucocorticoids
- Psychotropic Agents
  - Antipsychotics: phenothiazines, clozapine, risperidone
  - Mood stabilizers: lithium, gabapentin
  - Antidepressants: amitryptiline, mirtazapine
- Anticonvulsants: valproate, carbamazepine
- Serotonin Receptor Antagonist: cyproheptadine
- Antihypertensives: propranolol, nifedipine, clonidine

Genetic Syndromes Associated with Obesity

- Down Syndrome (trisomy 21)
- Prader Willi - (15 q 11.2-12)
- Bardet Biedl Syndromes
- Pseudohyoparathyroidism - inactivation of the stimulatory G protein α subunit (20-q13.3)
- Achondroplasia - FGF-R3 (4p16.3)
- Turner Syndrome (45 XO)

Down Syndrome

- Hypotonia, poor feeding neonatal period,
- After age 2y, obesity, “insatiable appetite, small hands/feet, hypogonadism,
- Abnormalities of 15q11-q12
  - Paternal deletions
  - Uniparental (maternal) disomy
  - Abnormal methylation

Prader Willi Syndrome

- Obesity
- Retinal degeneration
- Extra digits hands/toes
- Genital hypoplasia or hypogonadism (most males, 50% females)
- Mental retardation 75%

Bardet Biedel Syndromes

- Obesity
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New Genetic Syndromes Associated with Obesity

- Leptin deficiency
- Leptin Receptor Deficiency
- Prohormone Convertase 1 deficiency
- POMC processing mutation
- Melanocortin 4 Receptor mutation
- Melanocortin 3 Receptor mutation
Discovery of Leptin, Dec. 1994
Transforming Event in Obesity Research

Wild-Type Mice  \textit{ob/ob} (leptin deficient)


Leptin Signaling and Obesity

- Hypothalamic Leptin receptors
- POMC
- PC-1
- alpha-MSH
- Appetite
- Neuropeptide Y
- NPY Receptors
- Melanocortin Receptors
- Autonomic Nervous System
- Beta-3 Adrenergic receptors

Leptin Gene Deletion

- 2 cousins from a highly consanguineous Pakistani family
- Normal at birth, rapid weight gain
- Very low leptin despite high % fat
- Single base deletion introducing a premature stop codon


Plasma Leptin

- Healthy Children
- Leptin Mutation

Leptin-Deficiency

- Farooqi et al, NEJM 341:879-884, 1999

Leptin treatment
Leptin treatment

Effects of leptin injections in a child with leptin deficiency

Little efficacy of leptin in obese humans who are not leptin deficient

Leptin Signaling and Obesity

Human Leptin Receptor Mutations
• Early-onset obesity
• High leptin
• Failure to enter puberty normally

Patients with leptin receptor deficiency (LEPR/-) have significant hyperleptinemia


Leptin Receptor Deficiency – NIH Family

- Two siblings with early-onset obesity
- High leptin, even for obese children

Whole Exome Sequencing of affected siblings

- 36,100 shared single nucleotide variants
  - 1537 rare and non-synonymous
- 4,702 shared recessive indels
  - 1,213 both rare and functional (frameshift, amino acid insertion or deletion, or splice site)
- Filtering by pathogenicity and conservation:
  - Homozygous for 15 potentially damaging variants (10 SNVs and 5 indels)
- 1 Homozygous leptin receptor change

Mutation in Leptin Receptor

- Premature stop codon after insertion of 9 novel amino acids

Some obese humans with normal leptin receptor sequence are as obese and hyperleptinemic as those with leptin receptor deficiency

Bardet-Biedl syndrome (BBS): Obesity, leptin resistance & hyperleptinemia

- BBS: a pleiotropic, polygenic obesity syndrome

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- BBS: a pleiotropic, polygenic obesity syndrome
- BBS proteins essential for normal function of primary cilium
- Inactivation of BBS proteins in mice leads to aberrant leptin receptor trafficking in hypothalamic neurons, impaired leptin signaling, and hyperleptinemia

Hyperleptinemia consistent with leptin resistance in patients with Bardet-Biedl syndrome

- Leptin levels in Obese Controls vs. BBS patients
- Adjusted for age, sex, race, & body fat %

Leptin Signaling and Obesity

- Hypothalamic leptin receptors
- Appetite
- Autonomic nervous system
- Beta-3 adrenergic receptors
- Melanocortin receptors
- Serotonergic Neurons

POMC Processing

- Mutations disrupting ACTH / alpha MSH synthesis

Human POMC Mutations

- Can interfere with Processing of POMC into ACTH, alpha MSH, and beta-endorphin
- Red Hair (MC-1R)
- Congenital adrenal hypoplasia (MC-2R)
- Obesity (MC-4R)
**Leptin Signaling and Obesity**

- **Hypothalamic Leptin receptors**
- **PC-1**
- **α-MSH**
- **Neuropeptide Y**
- **Melanocortin Receptors**
- **Autonomic Nervous System**
- **Beta-3 Adrenergic receptors**

**POMC Processing**

- Mutations disrupting prohormone convertase 1

\[ \text{NH}_2 \text{ Pro-opio-melanocortin (POMC)} \rightarrow \text{COOH} \]

- 16 K Fragment
- ACTH
- β-lipotropin
- Gamma
- Alpha
- Beta
- MSH
- MSH
- Beta
- Endorphin

\[ \downarrow \text{normal processing cleavage sites} \]


**Human Prohormone Convertase 1 Mutations**

- Early-onset Obesity
- Abnormal post-translational hormone processing:
  - Hypogonadotropic hypogonadism
  - Low cortisol
  - Low insulin
  - High pro-insulin
  - High POMC


**Leptin Signaling and Obesity**

- Hypothalamic Leptin receptors
- **POMC**
- **PC-1**
- **α-MSH**
- **Neuropeptide Y**
- **Melanocortin Receptors**
- **Autonomic Nervous System**
- **Beta-3 Adrenergic receptors**
- **PPAR-γ2 receptors**

**Melanocortin 4 Receptor Knock-Out Mouse**

- MC4R +/- Wild Type

Photograph courtesy of Daniel Marks, M.D., Ph.D.

**9y old with homozygous MC4-R mutation and 16y old normal brother**

Melanocortin 4 receptor heterozygous inactivating mutations are common

- 1.4% of 140 obese adults (Gu et al Diabetes 48:635-9, 1999)
- 0.7% of 306 children with BMI 34 ± 7 kg/m² (Hinney et al, J Clin Endocrinol Metab 84:1483-6; 1999)
- 4.0% of 209 French adults with BMI > 40 kg/m² (Vaisse et al, J Clin Invest 106:253-62, 2000)
- 3.3% of 243 UK adults with history of onset of obesity before age 10y (Farooqi et al, J Clin Invest 106:271-9, 2000)

2.4% of severely obese may have heterozygous mutations of MC4 receptor

BMI-SD and DXA Fat Mass by Genotype of Function-Altering MC3R Polymorphisms in African American and Caucasian Children

- Increased fat mass
- Reduced lean mass
- Higher feeding efficiency


Double Mutant hMC3R knockin mice are more adipose than Wild Type hMC3R knockin mice

Plasma Leptin

...Back to our patient
Our Patient

• He has a function-altering variant of the melanocortin 3 receptor, (Thr6Lys+Val81Ile)
• He has hyperinsulinemia and hypercholesterolemia

How should he be treated?

AAP Recommended Weight Goals for Overweight Children and Adolescents

<table>
<thead>
<tr>
<th>BMI 85th–94th Percentile</th>
<th>BMI &gt;95th Percentile</th>
</tr>
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<tbody>
<tr>
<td>Mild Complication No</td>
<td>Mild Complication Yes</td>
</tr>
<tr>
<td>Weight Maintenance</td>
<td>Weight Maintenance</td>
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</tbody>
</table>

Mild complication=hypertension, dyslipidemia, increased liver enzymes, and insulin resistance


Our Patient

• Enrolled in a 6 month randomized placebo-controlled trial of orlistat
• Lost 7 kg over first 3 months
• Lost 2 kg over months 3-6
• Regained all of his lost weight over the next 24 months