What Is the Disease of Obesity?

Obesity Pathophysiology
Obesity Has Multiple Pathophysiologic Origins

- Epigenetic
- Genetic
- Physiologic
- Behavioral
- Sociocultural
- Environmental

Obesity Pathophysiology

Genetic and Epigenetic Origins
## Genetic Determinants of Obesity Supported by Genome-Wide Association Studies

<table>
<thead>
<tr>
<th>Gene</th>
<th>Tissue expressed</th>
<th>Gene product / role in energy balance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MC4R</strong></td>
<td>Adipocyte, hypothalamus, liver</td>
<td>Melanocortin 4 receptor / Appetite stimulation; monogenic cause of obesity</td>
</tr>
<tr>
<td><strong>ADRB3</strong></td>
<td>Visceral adipose tissue</td>
<td>β3-Adrenergic receptor / Regulates lipolysis</td>
</tr>
<tr>
<td><strong>PCSK1</strong></td>
<td>Neuroendocrine cells (brain, pituitary and adrenal glands)</td>
<td>Proprotein convertase 1 / Conversion of hormones (including insulin) into metabolically active forms</td>
</tr>
<tr>
<td><strong>BDNF</strong></td>
<td>Hypothalamus</td>
<td>Brain-derived neurotrophic factor / Appetite stimulation; regulated by MC4R signaling and nutritional state</td>
</tr>
<tr>
<td><strong>LCT</strong></td>
<td>Intestinal epithelial cells</td>
<td>Lactase / Digestion of lactose</td>
</tr>
<tr>
<td><strong>MTNR1B</strong></td>
<td>Nearly ubiquitous</td>
<td>Melanotinin receptor 1 B / Regulation of circadian rhythms</td>
</tr>
<tr>
<td><strong>TLR4</strong></td>
<td>Adipocyte, macrophage</td>
<td>Toll-like receptor 4 / Lipolysis, inflammatory reactions</td>
</tr>
<tr>
<td><strong>ENPP1</strong></td>
<td>Nearly ubiquitous</td>
<td>Ecotnucleotide pyrophosphatase/phosphodiesterase 1 / Inhibits tyrosine kinase activity of the insulin receptor, downregulating insulin signaling and decreasing insulin sensitivity</td>
</tr>
<tr>
<td><strong>FGFR1</strong></td>
<td>Adipose, hypothalamus</td>
<td>Fibroblast growth factor receptor 1 / Hypothalamic regulation of food intake and physical activity</td>
</tr>
<tr>
<td><strong>LEP, LEPR</strong></td>
<td>Adipocyte</td>
<td>Leptin, leptin receptor / Appetite inhibition</td>
</tr>
</tbody>
</table>
Epigenetic Perturbations of Genes Associated with Obesity

- Environmental toxins
- Nutrient deficiency
- Obesogenic (high fat) diet

Decreased energy expenditure
Genes affected: ODC, SSAT

Abnormal adipocyte differentiation
Genes affected: CEBPA, PPARG, FASN

↓ Leptin transcription
Genes affected: CEBPA, PPARG, FASN

↓ Hypothalamic POMC
(homeostatic appetite inhibition*)
Genes affected: POMC, ST8SIA4

↓ POMC neuronal response to leptin
(homeostatic appetite inhibition)
Genes affected: POMC

Dysregulation of dopaminergic neuronal signaling (hedonic appetite control)
Genes affected: TH, SLC6A3, CDKN1C

↑ Adiposity

↑ Food intake

*Homeostatic appetite increase partially offset by upregulation of ST8SIA4. †Folate, vitamin D, vitamin A. ‡BPA, fetal alcohol exposure, POPs. See notes view for abbreviations.

Mechanisms of Epigenetic Regulation

Environmental toxins
- Nutrient deficiency
- Obesogenic (high fat) diet

H3K4 methylation

DNA methylation

Histone acetylation

Leptin transcription and affects on POMC
- Known epigenetic regulators: DNMT1, MBD2, RNA polymerase II, miR-132, -143, -145, 200a, 200b

Dysregulation of dopaminergic neuronal signaling
- Known epigenetic regulators: Dnmt1, Mecp2, histone marks, KAT8, miR-103

Decreased energy expenditure
- Gene affected: NNMT
- Epigenetic regulator: Not determined

Abnormal adipogenesis or adipocyte differentiation
- Known epigenetic regulators: histone methyltransferases, miR-27a, 27b

↑ Adiposity

↑ Food intake

Footnotes:
- †Folate, vitamin D, vitamin A. ‡BPA, fetal alcohol exposure, POPs. See notes view for abbreviations.
Obesity Pathophysiology

Physiologic Origins: Energy Storage and Release
Energy Homeostasis

Body Weight

Increase

Energy intake
Ingestion of:
• Proteins
• Fats
• Carbohydrates

Decrease

Energy expenditure
• Physical activity
• Diet-induced thermogenesis
• Basal metabolic rate
## Adipose Tissue Types

<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>Beige/Brite</th>
<th>Brown</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shape</strong></td>
<td>Round</td>
<td>Round</td>
<td>Polygonal</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>Larger</td>
<td>Larger</td>
<td>Smaller</td>
</tr>
<tr>
<td><strong>Lipid droplets</strong></td>
<td>Single, large</td>
<td>Intermediate</td>
<td>Numerous, small</td>
</tr>
<tr>
<td><strong>Nucleus</strong></td>
<td>Peripheral</td>
<td>Peripheral</td>
<td>Central</td>
</tr>
<tr>
<td><strong>Mitochondria</strong></td>
<td>Few</td>
<td>Numerous, well-developed</td>
<td>Numerous, well-developed</td>
</tr>
<tr>
<td><strong>Precursor</strong></td>
<td>Myf5(–) lineage, BMP4-stimulated adipogenesis</td>
<td>Depot-specific origin: Myf5(–) or Myf11 and/or other(?)</td>
<td>Myf5(+) lineage, BMP7-stimulated adipogenesis</td>
</tr>
<tr>
<td><strong>Body location</strong></td>
<td>Subcutaneous, visceral</td>
<td>Subcutaneous, visceral</td>
<td>Neck, shoulders, spine</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>Energy storage</td>
<td>Energy release, regulated by mitochondrial UCP1</td>
<td>Energy release, regulated by mitochondrial UCP1</td>
</tr>
</tbody>
</table>

White Adipose Tissue

- Main form of adipose tissue
  - Important endocrine organ that interacts with most other body organs

- Normally found in subcutaneous adipose tissue
  - ~50% adipocytes
  - ~50% other cells
    - Stem/precursor cells
    - Preadipocytes
    - Vascular, neural, and immune cells
    - Leukocytes

SAT = subcutaneous adipose tissue.
Ectopic White Adipose Tissue

- Due to limited SAT expandability, may accumulate in ectopic tissues
  - Viscera
  - Heart
  - Liver
  - Pancreas
  - Skeletal muscle
- Ectopic accumulation leads to increased insulin resistance and metabolic complications

Consequences of WAT Expansion

Positive energy balance

Healthy SAT

WAT hypertrophy

Increased physical stress, ROS, FFAs, chemokines, inflammatory cytokines

WAT apoptosis, macrophage infiltration, lipolysis, and fibrosis

Lipid accumulation in ectopic tissues (visceral cavity, heart, pancreas, liver, skeletal muscle)

FFA = free fatty acid; IL = interleukin; MCP-1 = monocyte chemoattractant protein 1; ROS = reactive oxygen species; SAT = subcutaneous adipose tissue; TG = triglyceride; TNF-α = tumor necrosis factor α; VAT = visceral adipose tissue; WAT = white adipose tissue.

Inflammation and Adipose Tissue Remodeling

Increasing obesity

Angptl2 = angiopoietin-like protein 2; CXCL14 = CXC motif chemokine ligand 14; MCP-1 = monocyte chemoattractant protein 1; TLR4 = Toll-like receptor 4; TNF-α = tumor necrosis factor α; TNF-R = tumor necrosis factor receptor.

Brown Adipose Tissue

- Functional PET and histological analyses show that nearly all adult humans have UCP1-expression BAT deposits in the cervical and superclavicular (neck) regions

- There is a significant negative correlation between UCP1 mRNA abundance and BMI, accounting for 44% of BMI variance ($P=0.004$)

BAT = brown adipose tissue; BMI = body mass index; mRNA = messenger ribonucleic acid; UCP1 = uncoupling protein 1.
Brown Fat Prevalence and Activity Decrease With Increasing Age and BMI

Prospective Cross-sectional Human Study
(N=162)

Adiposity increases with age in BAT-negative individuals but not in BAT-positive individuals

*BAT not discernable with function positron emission tomography.

BAT = brown adipose tissue; BMI = body mass index; SUV$_{\text{max}}$ = maximal standardized uptake value.

Obesity Pathophysiology

Physiologic Origins: Adipose Tissue Inflammation and Adipose Dysfunction
Ectopic Fat Deposits Associated With Metabolic Disorders

<table>
<thead>
<tr>
<th>Systemic effects</th>
<th>Local effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased metabolic risk factors</td>
<td>Increased risk for vascular diseases</td>
</tr>
<tr>
<td><strong>Pancreatic fat</strong></td>
<td><strong>Perivascular fat</strong></td>
</tr>
<tr>
<td>Systemic and intramuscular insulin resistance, mitochondrial dysfunction, impaired lipid and glucose metabolism</td>
<td>Inflammation, macrophage infiltration, insulin resistance, altered release of adipokines, altered FFA metabolites, RAS activation, oxidative stress</td>
</tr>
<tr>
<td><strong>Intramuscular fat</strong></td>
<td><strong>Epi/pericardial fat</strong></td>
</tr>
<tr>
<td><strong>Fatty liver</strong></td>
<td><strong>Myocardial steatosis</strong></td>
</tr>
<tr>
<td>Hepatic insulin resistance, oxidative stress, inflammation, ↑ lipogenic transcription factors, ↑ VLDL-TG</td>
<td>Inflammation, ↑ TNF-α, IL-6, leptin, MCP-1, cell adhesion molecules, calcification, decreased diastolic function, coagulation defects</td>
</tr>
<tr>
<td><strong>Visceral fat</strong></td>
<td><strong>Renal sinus fat</strong></td>
</tr>
<tr>
<td>Inflammation, macrophage infiltration, insulin resistance, altered release of adipokines, altered FFA metabolites, RAS activation, oxidative stress</td>
<td>Hypertension, vascular resistance, glomerulosclerosis, proteinuria, ↑ intra-renal pressure</td>
</tr>
</tbody>
</table>

FFA = free fatty acid; IL = interleukin; MCP-1 = monocyte chemoattractant protein 1; RAS = renin angiotensin system; TG = triglyceride; TNF-α = tumor necrosis factor α; VLDL = very low density lipoprotein;

Pathogenesis of the Metabolic Syndrome Trait Complex

Central Adiposity

Metabolic Consequences

Dyslipidemia
- Increased large VLDL
- Increased small LDL
- Decreased large HDL

Endothelial Dysfunction
- Vascular reactivity
- Dysfibrinolysis
- Inflammation
- Foam cell proliferation

Insulin Resistance
- Glucose intolerance

Secreted Adipocyte Factors
- Adiponectin
- Leptin
- Resistin
- Free fatty acids
- PAI-1
- IL-6
- TNFα
- Angiotensinogen
- CETP

CETP = cholesteryl ester transfer protein; HDL = high-density lipoprotein; IL-6 = interleukin 6; LDL = low-density lipoprotein; PAI-1 = plasminogen activator inhibitor 1; TNF-α = tumor necrosis factor α; VLDL = very-low-density lipoprotein.

WT Garvey, 2013.
Association Between Visceral Fat and Insulin Resistance

CT scans courtesy of Wilfred Y. Fujimoto, MD.
Factors Secreted by Adipose Tissue Under Inflammatory Conditions

ADMA = asymmetric dimethyl-arginine; ANG-II = angiotensin II; ASP = acylation-stimulating protein; CRP = C-reactive protein; EGF = epidermal growth factor; FGF = fibroblast growth factor; IGF-1 = insulin-like growth factor 1; IGFBP = insulin-like growth factor binding protein; PAI-1 = plasminogen activator inhibitor 1; TGF-β = transforming growth factor β; TNF-α = tumor necrosis factor α.

Physiologic Origins: Peripheral and Central Signals Controlling Energy Intake
Peripheral and Central Regulation of Energy Intake

Adaptations to Weight Loss: Obesity Protects Obesity

Eating Behavior Changes
↑ Hunger, preference for calorie dense foods

Metabolism Changes
↓ Fat oxidation, ↑ cortisol

Nervous System Changes
↓ SNS activity, increased mesolimbic reward center activity

Orexigenic Hormones
Ghrelin

Anorexigenic Hormones
Leptin, PYY, CCK, GLP-1, amylin, insulin

Energy intake
Energy expenditure

Body Weight

CCK = cholecystokinin; GLP-1 = glucacon like peptide 1; NREE = nonresting energy expenditure; PYY = peptide YY; SNS = sympathetic nervous system; REE = resting energy expenditure; T4 = thyroxine; TEE = total energy expenditure.

## Key Hormone Changes Associated with Weight Gain and Regain

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Source</th>
<th>Normal function</th>
<th>Alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholecystokinin (CCK)</td>
<td>Duodenum</td>
<td>Suppress appetite</td>
<td>Levels decrease during dieting and weight loss</td>
</tr>
<tr>
<td>Glucose-dependent insulinotropin polypeptide (GIP)</td>
<td>Duodenum, jejunum</td>
<td>Energy storage</td>
<td>Levels increase during dieting and weight loss</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Gastric fundus</td>
<td>Stimulate appetite, particularly for high-fat, high-sugar foods</td>
<td>Levels increase during dieting and weight loss</td>
</tr>
<tr>
<td>Glucagon-like peptide 1 (GLP-1)</td>
<td>Ileum</td>
<td>Suppress appetite and increase satiety</td>
<td>Decreased functionality</td>
</tr>
<tr>
<td>Insulin</td>
<td>Pancreas</td>
<td>Regulate energy balance, Signal satiety to brain</td>
<td>Insulin resistance in obese persons</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduced insulin levels after dieting</td>
</tr>
<tr>
<td>Leptin</td>
<td>Adipocytes</td>
<td>Regulate energy balance, Suppress appetite</td>
<td>Levels decrease during weight loss</td>
</tr>
<tr>
<td>Peptide YY (PYY)</td>
<td>Distal small intestine</td>
<td>Suppress appetite</td>
<td>Levels decreased in obese persons</td>
</tr>
</tbody>
</table>
Hormonal Changes After Diet-Induced Weight Loss May Contribute to Regain

Prospective Observational Study
(N=50)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Change from BL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>95.4±13.5</td>
<td>−13.5±0.5</td>
</tr>
<tr>
<td>Change from BL</td>
<td></td>
<td>−7.9±1.1</td>
</tr>
</tbody>
</table>

*P* values shown in graphs are for mean postprandial period at 10 and 62 weeks vs baseline, except for amylin, which was not significantly different from baseline at 62 weeks.

Obesity Pathophysiology

Physiologic Origins: Metabolic Consequences of Aging
Age-Related Changes in Body Composition

## Age-Related Sarcopenia and Sarcopenic Obesity

### Characteristics
- Specific type II muscle fiber atrophy, fiber necrosis, and fiber-type grouping
  - Reduced satellite cell proliferation and differentiation may contribute to age-dependent decreases in muscle regenerative capacity
- Lipid infiltration into muscle tissue and increase in satellite cells with adipocytic phenotype

### Etiologic Factors
- Decreased physical activity
- Altered nutritional intake
- Oxidative stress
- Hormonal changes
- Disruption of positive regulators (eg, Akt and serum response factor)

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Resistance Training Improves Body Composition in Elderly, Obese Patients

**Adults, BMI 25-39 kg/m², Age 60-75 Years (N=27)**

<table>
<thead>
<tr>
<th></th>
<th>DASH diet alone (n=11)</th>
<th>DASH diet + resistance training (n=15)</th>
<th>Between group difference (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body weight, kg</strong></td>
<td>-1.7 ± 0.9</td>
<td>-3.3 ± 0.8</td>
<td>0.137</td>
</tr>
<tr>
<td><strong>Fat mass, kg</strong></td>
<td>-0.2 ± 1.0</td>
<td>-4.1 ± 0.9</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Lean mass, kg</strong></td>
<td>-1.4 ± 0.4</td>
<td>+0.8 ± 0.4</td>
<td>0.002</td>
</tr>
</tbody>
</table>

DASH = Dietary Approaches to Stop Hypertension.
Gut Microbiota and Metabolic Health

Healthy gut microbiota

- Gut permeability
- Endotoxemia
- Pro-inflammatory cytokines
- Beneficially active molecules (SCFAs, indole)
- Insulin sensitivity

Dysbiotic gut microbiota

- Gut permeability
- Endotoxemia
- Pro-inflammatory cytokines
- Adiposity
- Insulin resistance
- Calorie intake
- Obesity
- Metabolic syndrome

Gut microbial ecology

Pathobionts
- *Bacteroides* spp (Bacteroidetes phyla)
- *Clostridium difficile* (Firmicutes phyla)

Symbionts
- *Bifidobacteria*
- *Lactobacilli*
- *F. prausnitzii* (Clostridiaeaceae phyla)
- *Bacteroides thetaiotamicron* (Bacteroidetes phyla)

Anti-inflammatory species

- Bacterial gene count

Pro-inflammatory species

- High fat and high sugar diet, stress, antibiotics

Environmental factors

Healthy diet and lifestyle, prebiotics, probiotics, fecal transplantation

High fat diet and stress

Metabolic diseases
- Type 2 diabetes, cardiovascular diseases, inflammatory bowel diseases, ...

Improved gut and metabolic health

Contributions of Altered Gut Microbiota to Obesity Pathogenesis

Obesity Pathophysiology

Behavioral, Sociocultural, and Environmental Origins
Sociocultural and Environmental Contributors to Obesity

**Sociocultural**
- Preference for foods high in fat and/or carbohydrates
- Large portion sizes (value meals)
- Work-life circumstances
  - Sedentary occupations and leisure activities
  - Heavy time commitments to work, social, and family obligations
  - Sleep deprivation

**Environmental**
- Community design and infrastructure not conducive to physical activity
  - Lack of safe, convenient areas for outdoor activities
  - Distances between homes and work/shops too far for walking
  - Lack of public transportation
  - Ubiquity of escalators, elevators, etc
Effects of Alcohol, Sleep Deprivation, and TV Watching on Food Intake

Lifestyle Effects Meta-analysis

<table>
<thead>
<tr>
<th>Effect size (95% CI)</th>
<th>P value</th>
<th>No. studies / subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>1.03 (0.66, 1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleep deprivation</td>
<td>0.49 (0.11, 0.88)</td>
<td>0.01</td>
</tr>
<tr>
<td>TV watching</td>
<td>0.20 (0.04, 0.37)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Possible Neurobehavioral Mechanisms Underlying Development of Obesity

**Normal**

- Conditioned memory
- Reward signals
- Inhibitory control
- Drive to eat

**Chronic exposure to obesity-promoting behaviors (e.g., alcohol abuse, sleep deprivation, TV)**

- Conditioned memory
- Reward signals
- Inhibitory control
- Drive to eat

Obesity Pathophysiology

Summary
Summary

- Obesity has a genetic basis as well as environmental and behavioral origins
- Age contributes to shift in balance between fat and muscle mass
- Various negative feedback loops contribute to obesity
  - Increased caloric intake and reduced physical activity
    - Alters energy homeostasis → reduced metabolic rate
    - Alters neurohormonal signals → increased appetite
  - Increased visceral adiposity
    - Promotes insulin resistance
    - Promotes inflammation
      - Worsens insulin resistance
      - Leads to macrophage mobilization into adipose tissue, which worsens inflammation
  - Together, inflammation and insulin resistance contribute to development of cardiovascular disease, type 2 diabetes, cancer, and other poor outcomes