Disclosures

Novo Nordisk: Consulting Fee
Weight Regulation Physiology

The body weight **Set Point** is tightly regulated:

- **Sensing mechanisms** detect environmental changes in food intake (type, quantity) and activity level, as well as adipose tissue content.
- **Effector systems** respond (adapt) with changes in appetite and energy expenditure.
- Weight loss (or gain) is kept $\pm 5$ lbs of a set point (range)
Weight Regulation (Patho)Physiology

Overweight and obesity results when leptin resistance (deficiency) occurs, establishing a higher body weight Set Point.
To achieve **sustained weight loss**, any therapy must ultimately “interfere” with the way that the brain senses and responds to feedback signals, **preventing counter-regulatory appetite and energy expenditure adaptations** from restoring baseline weight.

(and be continued **long-term**)
Overweight and Obesity as a Chronic Disease

- Treatment of Overweight and Obesity
  - Lifestyle (diet and exercise)
  - Medications
  - Bariatric Surgery
Overweight and Obesity as a Chronic Disease

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Systematic Review of Commercial Weight Loss Programs

Duration of follow-up (years)

• ↑ Ghrelin, ↓ leptin, insulin, PYY (↑ Hunger) (↓ Fullness)
• ↓ Total Energy Expenditure (~ 15-20%) (“adaptation”)
• ↑ Lipolysis (fat loss > lean loss) but NO ↑ in fat oxidation capacity (poor fat utilization)
• ↓ T3, T4 levels (cold intolerant, hair loss, dry skin)
• ↓ Sympathetic nervous system (bradycardia)
Approaches to Weight Loss

Yes, but, patients with obesity need to exercise more...
Constrained Total Energy Expenditure During Metabolic Adaptation to Physical Activity
Exercise, Weight Loss, and Weight Regulation

- Sedentary phase “steady state”
- Adjustment period
- Re-equilibrium

Caloric intake_{SP} = Caloric Intake_{RE} ± 2.4 kg

Body Weight

Weeks of exercise

0 1 2 3 4 5 6 7 8 9 10 ........
Weight Loss
Comparison of "Named Diets."

Average weight loss: 2 - 3 kg

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Weight Change by Diet Type

$r = 0.07, P = .40$

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Atkins "Lo-carb"  Zone "Hi-protein"  Weight Watchers  Ornish "Lo-fat"
Diabetes Prevention Program: Modest Effect on Weight (Low-fat Diet + Exercise)


Four years: - 4%
Diabetes Incidence Best Lowered by Lifestyle (Low-fat Diet + Exercise)
Weight Loss Averages by Approach

Overweight and Obesity as a Chronic Disease

• Treatment of Overweight and Obesity
  – Lifestyle (diet and exercise)
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  – Bariatric Surgery
Recommendation For Consideration of Pharmacological Weight Management

• BMI 27 - 30 kg/m\(^2\) and a weight-related comorbidity:
  – HTN
  – Dyslipidemia
  – Diabetes
  – Other

OR

• BMI \(\geq 30\) kg/m\(^2\)

Anti-Obesity Medicines (AOMs)

Currently FDA Approved

- tetrahydrolipstatin (Orlistat) $$$
  - (now over the counter as “alli”-60 mg dose)

- phentermine (Fastin, Ionamin, Adipex) $

- phentermine + topiramate (Qsymia) $$

- bupropion + naltrexone (Contrave) $$

- liraglutide 3.0 (Saxenda)

- Semaglutide 2.4 mg (Wegovy)
Weight Loss Medications Enhance CNS Signaling to Meal-related Signals

- phentermine
- phentermine + topiramate
- bupropion + naltrexone
- liraglutide
- semaglutide

↓ CNS Hunger Signaling

↑ CNS Satiety Signaling
Weight Loss With Phentermine

- 8 and 37.5 mg tablets
- 15 and 30 mg capsules

~ 9-10% wt loss
Phentermine + Topiramate (Qsymia)
Liraglutide 3.0 for Weight Management and Type 2 Diabetes Risk Reduction in Pre-diabetes
Liraglutide 3.0 for Weight Management and Type 2 Diabetes Risk Reduction in Pre-diabetes

~80% risk reduction for diabetes
Semaglutide 2.4 for Weight Management in Overweight and Obesity

No. at Risk
Placebo  655  649  641  619  615  603  592  571  554  549  540  577
Semaglutide 1306 1290 1281 1262 1252 1248 1232 1228 1207 1203 1190 1212

~14.9%
Weight Loss Averages by Approach

Diagnosis and Management of Obesity

Key Practice Recommendations

**Recommendations**

Screen all adults for obesity. Offer or refer patients with a body mass index (BMI) of 30 kg/m² or greater to intensive, multicomponent behavioral interventions.¹

Screen children 6 years and older for obesity, and offer or refer them to comprehensive, intensive behavioral interventions to promote improvement in weight status.²

A 5% to 10% weight loss can reduce risk of heart disease and diabetes and should be encouraged for all patients who are overweight and obese.³ ⁴

Consider pharmacotherapy in adults who have not been able to lose weight through diet and physical activity alone and who have:

- BMI of ≥30 kg/m² or greater
- BMI of ≥27 kg/m² or greater, and obesity-related comorbidity² ⁴

Consider bariatric surgery in adults who have not been able to lose weight through diet and physical activity alone and who have:

- BMI of ≥40 kg/m² or greater
- BMI of ≥35 kg/m² or greater, and obesity-related comorbidity²

Regardless of body weight or weight loss, all patients should be encouraged to be physically active for improved health and weight maintenance.²

**Comments**

This recommendation applies to all adults, not just those with known cardiovascular risk factors.

Regular physical activity is strongly related to maintaining normal weight. Exercise also mitigates health-damaging effects of obesity, even without weight loss.

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Low Adoption of Weight Loss Medications

Of the 829,962 active physicians in the United States IMS Health Xponent database:
  n=129,414 (16%) prescribed phentermine
  n=79,624 (10%) prescribed a new antiobesity medication

34%-42% Family Practice
19%-27% Internal Medicine
7%-13% OB/Gyn
2%-13% Endocrinology

Low Adoption of Weight Loss Medications: A Regional Thing

Prescribing Physicians by Region

- Phentermine
- New AntiObesity Meds

South: 50%
MidWest: 20%
West: 10%
Northeast: 5%
Pacific: 1%

Reasons for Underutilization of Weight Management Medications

- Previous weight loss drugs had poor safety record (fenfluramine, sibutramine, rimonabant)
- Perceived need for frequent follow-ups needed for AE monitoring
- Some are controlled substances:
  - Phentermine is a DEA schedule IV (low potential for abuse and low risk of dependence)
  - Compared to Adderall, Concerta, and Vyvanse (all schedule II)
- Lack of understanding of current guideline recommendations
- Misperception that meds are only used “short-term,” leading to weight regain
- Variable response among patients, including many “non-responders”
- Poor and inconsistent insurance coverage

Slide credit: clinicaloptions.com
Overweight and Obesity as a Chronic Disease

• Treatment of Overweight and Obesity
  – Lifestyle (diet and exercise)
  – Medications
  – Bariatric Surgery
Recommendation For Consideration of Bariatric Surgery

• BMI 35-40 kg/m² and a weight-related comorbidity:
  – HTN
  – Dyslipidemia
  – Diabetes
  – Other (sleep apnea, GERD, OA, etc)

OR

• BMI ≥ 40 kg/m²

Long-Term Weight Loss Durability After Bariatric Surgery

Sustained Appetite Reduction after Bariatric Surgery: 10-year Follow-up
Primer on Mechanisms/Effects of Bariatric Surgery

Primer on Mechanisms/Effects of Bariatric Surgery: Gut Adaptation

Weight Change and Health Outcomes after Bariatric Surgery: The Longitudinal Assessment of Bariatric Surgery (LABS) Study


Roux-en-Y gastric bypass

![Graph showing remission rates for various health outcomes after Roux-en-Y gastric bypass.](image)

<table>
<thead>
<tr>
<th>Health Outcome</th>
<th>Median (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>High LDL cholesterol level</td>
<td></td>
</tr>
<tr>
<td>High triglyceride level</td>
<td></td>
</tr>
<tr>
<td>Low HDL cholesterol level</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk

- Diabetes: 379, 327, 320, 342, 345, 219
- High LDL cholesterol level: 292, 246, 253, 253, 260, 167
- High triglyceride level: 201, 166, 162, 161, 164, 120
- Low HDL cholesterol level: 437, 353, 342, 341, 354, 241
- Hypertension: 960, 786, 741, 751, 782, 520
Hazards Ratios for Death: Surgery (n=7000) vs. Control Group (n=7000)


- All Cause Death: 0.63
- CVD Death: 0.5
- Cancer Death: 0.38
- Diabetes Death: 0.1

90% reduction
Association Between Bariatric Surgery and Long-term Survival: VA Study

Arterburn D et al., *JAMA* January 6, 2015

Graph showing 53% reduction in mortality with bariatric surgery compared to matched control patients.
Obesity (as a disease) Management: Timeline

Pre-modern

“Eat less And Exercise”

1994

Modern

Lifestyle: 

Ave. Weight Loss

~ 4%

Pharmacology:

~ 6-15%

Bariatric surgery:

~ 20-30%
Weight Loss Averages by Approach

- **Lifestyle:** ~ 4%
- **Lifestyle + weight loss medications:** ~ 6-15%
- **Lifestyle + Roux-en-Y gastric bypass:** ~ 25-30%

Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline

Caroline M. Apovian, Louis J. Aronne, Daniel H. Bessesen, Marie E. McDonnell, M. Hassan Murad, Uberto Pagotto, Dennis E. Rao, and Christopher D. Still

(J Clin Endocrinol Metab 100: 342–362, 2015)
Eat food. Not too much. Mostly plants.
Weight is regulated through the interaction of three major organ systems:

1. **Gastrointestinal (GI) System**
2. **Brain: Hypothalamus and Brainstem**
3. **Adipose Tissue Stores**
Nutrient Absorption Triggers Secretion of Gut Hormones: “Sensing Food” and Conveying Biologic Appetite Signals to CNS

- **Ghrelin** → ↓ hunger
- **CCK**, **Insulin**, **Amylin**, **PYY**, **GLP-1** → ↑ satiety
- ↓ Ghrelin → ↓ hunger
Signals from the GI tract have a key role in body weight regulation

**Duodenum**
- CCK
- GIP
- Ghrelin

**Jejunum**
- GIP
- GLP-1
- ApoA-IV
- Guanylin
- Uroguanylin

**Ileum**
- GLP-1
- ApoA-IV
- Guanylin
- Uroguanylin
- PPY
- Oxyntomodulin
- Neurotensin

**Stomach**
- Ghrelin
- Nesfatin-1
- Leptin

**Colon**
- GLP-1
- GLP-2
- PPY
- Oxyntomodulin

**Lipid derived molecules**
- Endocannabinoid agonists
- Anorexic lipid OEA
Meal-related Satiety Gut Hormone Appearance: “Sensing Food Availability”
Meal-related Gut Hormone Appearance: Level of Suppression (Stimulation) Determined by Total Calories
Meal-related Satiety Gut Hormone Appearance: Sensing Food Availability and Calories Consumed

Time After Meal (Minutes)

Satiety
Fullness
Satisfaction

Hunger

Normal Meal Calories
Normal Fullness
Normal Hunger Suppression
Meal-related Satiety Gut Hormone Appearance: Sensing Food Availability and Calories Consumed

↓ 50% Meal Calories
↓ 50% Fullness / Satisfaction
↓ 50% Hunger Suppression and quicker return

Satiety
Fullness
Satisfaction
Hunger

Time After Meal (Minutes)
CNS Body Weight Regulation Center Receives Adiposity Signal from Fat Depots

Leptin

Adipose Tissue Stores
CNS Integrates Adiposity and Meal-related Signals to Maintain Body Weight Set Point (Range)

“Are you weighing what I think you should?”

+ 5 lbs.

- 5 lbs.

“Are you eating enough (or too much) to maintain that weight?”

Leptin

Ghrelin

CCK

Insulin

Amylin

PYY

GLP-1

..others

OHSU