Obesity: Physiology and Treatment

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Guiding Principle 1

Obesity is a disease:

• Body weight is physiologically regulated
• Pathophysiology leads to unwanted weight gain
• Expression of weight gain has detrimental consequences
Two Approaches to Obesity Treatment

1) Prevention of unwanted weight gain:
   • Most important for society.
   • Improve environment: diet and activity.
   • Opportunities include: built environment, public education, legislation, individual motivation, cultural influences, economics.

2) After disease onset (in your clinic):
   • Follow traditional chronic disease approach

These are not mutually exclusive.
Weight Regulation—The Final Word Model

Body Weight

Energy In \[\rightarrow\] Energy Out

Weight loss = \[\downarrow\] Energy in
\[\uparrow\] Energy out
This is where we start...
Body Weight Regulation—1995

Food intake
EE

insulin

leptin

Fat cell
Gut-Brain-Adipose Tissue Axis

What Happens if I Put You on a 1200 Calorie Daily Diet?

↓ Energy Expenditure
↑ Appetite

↓ Leptin
↑ Ghrelin

↑ Fat

Caloric Restriction
Stability of Body Weight

Weight (lbs)

Time (years)

P. Barton Duell, MD
Weight Regain after Behavior Modification Diet Program: n=16 studies

% weight regain vs. Duration of follow-up (years)
Systematic Review of Commercial Weight Loss Programs

Duration of follow-up (years)
% weight lost
Overview of Obesity Treatment:
Chronic Disease Model

- Lifestyle
- Medications
- Surgery
Comparison of the Atkins, Ornish, Weight Watchers, and Zone Diets for Weight Loss

Variable Response Rates of Environment—Gene Interaction

- “Salt sensitive” hypertension 25%
- “Diet controlled” diabetes 8%

Individuals Successful at Long-Term Weight Loss Maintenance


<table>
<thead>
<tr>
<th>% Diet Fat</th>
<th>Energy (x10^3 kJ/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (n=629)</td>
<td>25</td>
</tr>
<tr>
<td>Men (n=155)</td>
<td>15</td>
</tr>
</tbody>
</table>

Exercise Energy (x10^3 kJ/wk)
Physical Activity and Weight Loss in Obese Subjects

Average weight loss = 2.4 kg
Sedentary phase “steady state”

Adjustment period

Re-equilibrium

Caloric intake \(_{SP} = \) Caloric Intake \(_{RE}\)
Lifestyle and Obesity: Effect on Body Weight in a “Set-Range”

BMI (kg/m²)

Worsening Lifestyle
Take Home Points

Once obesity is expressed:

- Lifestyle plays a modest role in weight loss...but continues to have an important impact on accompanying diseases.

- The mechanisms for responsiveness (or non-responsiveness) are being worked out.

- Medications and surgery play a much larger role for weight loss.
Guiding Principle 2

To achieve sustained weight loss, any therapy must ultimately alter the way that the brain senses and responds to feedback signals, preventing counter-regulatory processes from restoring baseline weight.
Recommendation For Consideration of Pharmacological Treatment

Body mass index (BMI) = weight / height² (kg/m²)
BMI normal range = 19 to 25 kg/m²

- BMI ≥ 30
- BMI 27 - 30 and
  - HTN
  - Dyslipidemia
  - Diabetes

www.nhlbi.nih.gov
Drugs for Obesity

Currently FDA Approved

- phentermine (Fastin, Ionamin, Adipex)
- tetrahydrolipstatin (Orlistat)
  - (now over the counter as “alli”-60 mg dose)
Drugs for Obesity

Not FDA approved but shown to cause weight loss

- Octreotide
- Wellbutrin (bupropion SR) + naloxone
- Topiramate
- Zonisamide
- Pramlintide
- Metformin

Under development or in clinical trials

- Cannabinoid receptor antagonists (rimonabant)
- GLP-1 / Excendin-4
- PYY$_{3-36}$
- Leptin
- CNTF
- MC4 agonists
- selective β3 receptor agonists
Sustained Weight Loss after Bariatric Surgery: 15-year Follow-up

Diabetes Improvement after Bariatric Surgery: 10-year Follow-up
Morbidity Reduction After Bariatric Surgery

- Obstructive sleep apnea
  - Improved 83.6%
  - Resolved 85.7%

Relative Risk Reduction

- Cardiovascular
  0.18 (p<0.001)
- Infectious Disease
  0.23 (p<0.001)
- Cancer
  0.24 (p<0.001)

(1035 cases vs. 5746 controls.
Hazards Ratios for Death: Surgery vs. Control Group


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

90% reduction
44 yo Obese Woman S/P RYGBP

Phentermine 30 mg q day
Therapeutic Potential

- **5%**
  - Minimum weight loss
  - Representative of weight loss with lifestyle
  - Benefit potential on comorbid conditions

- **10%**
  - Achievable with present therapies (orlistat, sibutramine, phentermine)
  - Some benefit on glucose and lipid metabolism

- **20%-30%**
  - Current weight loss range for bariatric procedures
  - Marked improvement in co-morbid conditions