Why Do We Treat Obesity?

Organ-Specific, Hormonal, and Biomechanical Complications
## Treatment Based on Clinical Judgment

### Treatment Goals Based on Diagnosis in the Medical Management of Patients with Obesity

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthropometric Component</td>
<td>Clinical Component</td>
</tr>
<tr>
<td>Overweight or Obesity BMI ≥25</td>
<td>Polycystic ovary syndrome 5% to 15% or more</td>
</tr>
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<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
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</tr>
<tr>
<td>Female infertility BMI ≥25</td>
<td>10% or more</td>
</tr>
<tr>
<td>Male hypogonadism BMI ≥25</td>
<td>5% to 10% or more</td>
</tr>
<tr>
<td>Obstructive sleep apnea BMI ≥25</td>
<td>7% to 11% or more</td>
</tr>
<tr>
<td>Asthma/reactive airway disease BMI ≥25</td>
<td>7% to 8% or more</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis BMI ≥25</td>
<td>≥10%</td>
</tr>
<tr>
<td></td>
<td>• 5% to 10% or more when coupled with exercise</td>
</tr>
<tr>
<td>Urinary stress incontinence BMI ≥25</td>
<td>5% to 10% or more</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease BMI ≥25</td>
<td>10% or more</td>
</tr>
<tr>
<td>Depression BMI ≥25</td>
<td>Uncertain</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

**Abbreviations:** A1C = hemoglobin A1c; BMI = body mass index; BP = blood pressure; HDL-C = high-density lipoprotein cholesterol; T2DM = type 2 diabetes mellitus.
Organ-Specific, Hormonal, and Biomechanical Complications

Gallbladder Disease
The Paradox of Obesity and Gallbladder Disease

Effect of Obesity

- Increased risk of cholesterol gallstones, cholecystis, and gallbladder cancer, especially in women
  - Increased biliary fat may increase cholesterol in the gallbladder
- Risk increases with higher BMI

Effect of Weight Loss

- Increased risk of gallstones
  - 10% to 25% of patients on diet-exercise regimens and up to 30% undergoing bariatric surgery develop gallstones
  - Higher risk in patients with a high BMI prior to weight loss or those who lose weight rapidly
- Oral ursodeoxycholic acid during weight loss may prevent gallstone formation

BMI = body mass index.

Organ-Specific, Hormonal, and Biomechanical Complications

Sex Hormone Disorders
# Polycystic Ovary Syndrome

## Disease Features

- Characterized by anovulation or irregular menstrual cycles with hyperandrogenism
  - Not a consequence of obesity, but may worsen with weight gain
  - Pathophysiologically linked to insulin resistance
- Increased risk for T2D, dyslipidemia, hypertension, inflammation, and CVD

## Treatment

- Increase insulin sensitivity
  - Aerobic exercise and weight loss
  - Metformin,* pioglitazone,*† or GLP-1 receptor agonist*†
- Spironolactone or other nonandrogenic oral contraceptive for skin manifestations (hirsutism, acne)

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*Not FDA-approved for PCOS.

†Recommended only for women with IGT or T2D. Pregnancy category C—use with contraception in women of childbearing age.

CVD = cardiovascular disease; PCOS = polycystic ovary syndrome; T2D = type 2 diabetes.

Effect of Weight Loss on Female Infertility

Women With Obesity Presenting for Fertility Treatment (N=49)

Weight Change After 12 Weeks

<table>
<thead>
<tr>
<th>Weight Change After 12 Weeks</th>
<th>Intensive lifestyle intervention* (n=22 completers)</th>
<th>Control† (n=17 completers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Δ Weight (kg)</td>
<td>-6.6 P&lt;0.001</td>
<td>-1.6</td>
</tr>
</tbody>
</table>

Pregnancy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>48</td>
<td>14</td>
<td>0.002</td>
</tr>
<tr>
<td>Live birth</td>
<td>44</td>
<td>14</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Very-low-energy diet for first 6 weeks followed by a hypocaloric diet for next 6 weeks, with weekly multidisciplinary group meetings.
† Weight loss recommendations plus the same printed materials as intervention group.

Obesity and Testosterone Deficiency

**Disease Features**

- Total testosterone <280-300 ng/dL and/or free testosterone <5-9 ng/dL*

- Signs and symptoms: fatigue, decreased libido, ED, altered mood/cognition, decreased muscle mass and BMD, increased fat mass

- Strongly associated with metabolic syndrome

- Increased risk for T2D, dyslipidemia, hypertension, and CVD

**Treatment**

- Weight loss

- Testosterone replacement therapy

*Reference range varies with laboratory; use lower limit of normal.

BMD = bone mineral density; CVD = cardiovascular disease; ED = erectile dysfunction; T2D = type 2 diabetes.

Androgen Deficiency and BMI

Pooled Data From 2 Lipid Treatment Studies
(N=864 men)

Mean Total Serum Testosterone (ng/dL)

*P<0.05 vs no metabolic syndrome.

BMI = body mass index.
Effects of Obesity, Metabolic Syndrome, and Age on Testosterone Levels

Multiple Linear Regression Analysis
(N=864 men participating in 2 lipid treatment studies)

BMI

-58
P<0.0001

-112
P<0.0001

-26
P=0.0193

-1
P=0.0444

BMI = body mass index, in kg/m²; Met Syn = metabolic syndrome.
Effect of Weight Loss on Male Hypogonadism

Observational Data
(N=33 men, mean WL = 18.8% [59.1 kg])

**Hypogonadism Before and 12 Months After Bariatric Surgery**

**Change in Sex Hormones 12 Months After Bariatric Surgery**

*P*<0.001, †*P*=0.01 vs value before surgery.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Mean Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>164.2</td>
</tr>
<tr>
<td>FT</td>
<td>51</td>
</tr>
<tr>
<td>SHBG</td>
<td>34.8</td>
</tr>
<tr>
<td>E2</td>
<td>-17</td>
</tr>
<tr>
<td>FSH</td>
<td>-5</td>
</tr>
<tr>
<td>LH</td>
<td>-28</td>
</tr>
<tr>
<td>PRL</td>
<td>3.1</td>
</tr>
<tr>
<td>IB</td>
<td>10.2</td>
</tr>
<tr>
<td>AMH</td>
<td></td>
</tr>
</tbody>
</table>


AMH = anti-Müllerian hormone; E2 = estradiol; FSH = follicle-stimulating hormone; FT = free testosterone; IB, inhibin B; LH = luteinizing hormone; PRL = prolactin; SHBG = sex hormone binding globulin; TT = total testosterone; WL = weight loss.
Organ-Specific, Hormonal, and Biomechanical Complications

Pulmonary Disorders
Obesity Adversely Affects Lung Function

- Stiffening of total respiratory system
  - Reduced lung and chest wall compliance
  - Reduced tidal volume and short, rapid breathing pattern
- Reduced lung volume and vital capacity
- Increased risk of airway closure and ventilation distribution abnormalities

Flow-Volume Loops
(Healthy, obese woman, age 35 years)

Predicted lung volumes

- TLC
- FRC
- RV

Flow (L/min)

Volume (L)

Predicted flow at VC$_{50}$

Actual flow at VC$_{50}$

FRC = functional residual capacity; RV = reserve volume; TLC = total lung capacity; VC = vital capacity.

Obstructive Sleep Apnea

**Mechanisms**
- Feedback loop involving interplay between excess visceral adipose tissue, insulin resistance, and inflammatory cytokines
  - Excess fat reduces diaphragm mobility and promotes soft tissue edema, which in turn lead to depression of ventilation
- Ventilation depression causes sleep apnea and poor sleep, which contributes to daytime sleepiness and fatigue
- Poor sleep promotes stress hormone and interleukin 6 production, which exacerbates insulin resistance

**Risk Factors**
- Obesity
- Neck circumference >44 cm
- Narrowed airway
- Hypertension
- Smoking
- Male sex
- Age
- Family history
- Alcohol or sedatives

**Treatment Options**
- Continuous positive airway pressure (CPAP)
- Adjustable airway pressure devices
- Oral appliances
- Surgery
  - Uvulopalatopharyngoplasty (UPPP)
  - Maxillomandibular advancement
  - Tracheostomy

Effect of Weight Loss on OSA

Sleep AHEAD Study
(N=264 Patients With T2D)

Weight Change After 12 Months

<table>
<thead>
<tr>
<th>Weight Change After 12 Months</th>
<th>Change in OSA After 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive lifestyle intervention</td>
<td>Diabetes support and education</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>Mean change in index</td>
</tr>
<tr>
<td>-10.8</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>-10.4</td>
<td>4.2</td>
</tr>
<tr>
<td>-2.5</td>
<td>6.1</td>
</tr>
</tbody>
</table>

DSE = diabetes support and education; ILI = intensive lifestyle intervention.

Effects of Weight Loss on Asthma and Reactive Airway Disease

- Calorie restriction with an average of 8% weight loss associated with improvements in asthma disease factors
  - Asthma symptoms
  - Quality of life
  - Peak expiratory flow
  - Markers of oxidative stress and inflammation

- After RYBG (WL ~23%), significant reductions in expression of:
  - Asthma-related genes
    - Interleukin-4
    - Disintegrin
    - Metalloproteinase 33
  - Rumor necrosis factor (ligand) superfamily member 14
  - Matrix metallopeptidase-9
  - C-C chemokine receptor type-2
  - Nitric acid metabolites

RYGB = Roux-en-Y gastric bypass; WL = weight loss.
Organ-Specific, Hormonal, and Biomechanical Complications

Biomechanical Disorders
Effect of Weight Loss on Osteoarthritis

18-Month Randomized, Controlled Weight Loss Study (N=399)

**Knee Compressive Force**

- Low: $-4.9\%$ to $9.9\%$
- Medium: $-9.8\%$ to $-5.0\%$
- High: $-32.5\%$ to $-10.1\%$

**IL-6**

- Low: $-4.9\%$ to $9.9\%$
- Medium: $-9.8\%$ to $-5.0\%$
- High: $-32.5\%$ to $-10.1\%$

**Pain**

- Low: $-4.9\%$ to $9.9\%$
- Medium: $-9.8\%$ to $-5.0\%$
- High: $-32.5\%$ to $-10.1\%$

**Function**

- Low: $-4.9\%$ to $9.9\%$
- Medium: $-9.8\%$ to $-5.0\%$
- High: $-32.5\%$ to $-10.1\%$

IL-6 = interleukin 6.
Effect of Weight Loss on Urinary Incontinence in Women

6-Month Randomized, Controlled Weight Loss Study (N=338)

Weight Loss

Frequency of Incontinence

-8
-1.6

P<0.001

-47
-42

P=0.01

P=0.14

-58
-33

P=0.02

-26

Weight loss
Control

Any incontinence
Stress incontinence
Urge incontinence

Δ Weight (%)

Effect of Weight Loss on Gastroesophageal Reflux Disease

6-Month Prospective Observational Weight Loss Study
(N=332; mean WL: 13 ± 7.7 kg)

GERD Prevalence

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Before WL</th>
<th>After WL</th>
</tr>
</thead>
<tbody>
<tr>
<td>P&lt;0.001</td>
<td>37</td>
<td>15</td>
</tr>
</tbody>
</table>

GERD Severity

<table>
<thead>
<tr>
<th>GERD symptom score</th>
<th>Before WL</th>
<th>After WL</th>
</tr>
</thead>
<tbody>
<tr>
<td>P&lt;0.01</td>
<td>5.5</td>
<td>1.8</td>
</tr>
</tbody>
</table>

GERD = gastroesophageal reflux disease.
Organ-Specific, Hormonal, and Biomechanical Complications

Cancer
## Obesity and Cancer

### Increased Risks

- Obesity increases risk of the following cancers:
  - Colon
  - Endometrium
  - Postmenopausal breast
  - Kidney
  - Esophagus
  - Pancreas
  - Gallbladder
  - Liver
  - Hematological malignancies

- Obesity worsens prognosis and mortality risk

### Mechanism

- Obesity increases levels of leptin, IGF-1, and proinflammatory cytokines
  - These activate PI3K/Akt, which promotes cancer cell proliferation through mTOR
  - Caloric restriction decreases levels of leptin, IGF-1, and proinflammatory cytokines
  - Signaling through AMPK is enhanced, promoting cancer cell apoptosis

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AMPK = adenosine 5’-monophosphate–activated protein kinase; IGF-1 = insulin growth factor 1; mTOR = mammalian target of rapamycin; PI3K/Akt = phosphoinositide 3 kinase protein kinase B.

Summary

- Numerous organ-specific and mechanical complications accompany obesity
  - Gallbladder disease
  - Sex hormone–related disorders
    - Polycystic ovary disease
    - Female infertility and male hypogonadism
  - Pulmonary disorders
    - Obstructive sleep apnea
    - Asthma/reactive airway disease
  - Biomechanical disorders
    - Osteoarthritis
    - Urinary stress incontinence
    - Gastroesophageal reflux disease

- Weight loss ameliorates all of these conditions