Clinical Benefits of Weight Loss

AACE Obesity Resource Center
Defining Obesity

• Obesity is a chronic relapsing progressive disease defined by abnormal or excessive adiposity that may impair health.¹,²

• Multiple pathophysiological aspects¹
  • Genetic
  • Environmental
  • Physiological
  • Psychological

• Abundance of food + low physical activity + genetics/environmental factors → positive energy balance
  • Excess energy stored as fat in enlarged/more numerous adipocytes and ectopically¹,²
  • Enlarged fat cells/ectopic fat produce/secrete metabolic, hormonal, inflammatory products that damage organs

Evolving Terminology of Obesity

Obesity historically diagnosed as BMI $>30$ kg/m$^2$
- BMI not optimally predictive of health
- Ethnic differences
- Does not recognize cardiometabolic risks associated with waist circumference
- Stigmatization of term ‘obesity’

“Obesity” does not provide sufficient information of conditions associated with excess adiposity

Adiposity-Based Chronic Disease (ABCD): New Diagnostic Term for Obesity

• **ABCD** as the new diagnostic term for obesity by AACE/ACE
• **Adiposity** - obesity (excessive accumulation of fat within the body)
• **Based** – a point at which something can develop
• **Chronic** – persisting over a long period of time
• **Disease** – interruption of the normal function of the body or structure of a body part or system

ABCD: Relevant Diagnostic Term for Obesity

Adiposity-Based Chronic Disease:
A clinically relevant diagnostic term for the disease of obesity

- Adiposity-Based
- Chronic Disease

- Disease based on adipose tissue pathophysiology involving abnormalities in:
  1. Mass
  2. Distribution
  3. Function

- Lifelong disease with complications that confer morbidity and mortality including:
  - Biomechanical Complications
  - Cardiometabolic Disease Complications

- Pathophysiology and natural history consistent with opportunities for primary, secondary, and tertiary phases of chronic disease prevention
AACE Blueprint for Complications-Centric Approach

- Lifestyle medicine positioned as central pervasive action to promote overall health
- Develop standardized protocols to address weight loss and management of adiposity-based complications
- Contextualize patient care in light of environmental, socioeconomic, ethnic/cultural differences
- Develop evidence-based strategies for implementation, monitoring, and optimization of patient care over time

Obesity: Overview

- >35% of men and 40% of US women have obesity
- Obesity is associated with many health problems/morbidity
- Obesity is associated with increased risk for death
  - especially adults <65 years

USPSTF et al; JAMA 2018 Sep 18;320(11):1163-1171.
Childhood and Adolescent Obesity

• Inherited Obesity:
  • For most people, genetics account for a small percentage of obesity risk
    • Even if genetics contributes up to 40% of risk, 60% of risk associated with lifestyle factors
  • Rare inherited conditions: Prader-Willi, Bardet-Biedl syndromes, monogenetic obesity

• Childhood/Adolescent Obesity
  • CDC: ~1 in 5 children/adolescents (6-19 yrs) in US has obesity
  • Obese children more likely to grow up to be obese adults; more severe obesity and more extreme obesity-related health problems
  • Factors that contribute to childhood/adolescent obesity
    • Genetics.
    • Metabolism.
    • Eating and physical activity behaviors.
    • Community and neighborhood design and safety.
    • Short sleep duration.
    • Negative childhood events

https://www.cdc.gov/healthyschools/obesity/facts.htm
Peri- and Post-Menopausal Obesity

Obesity prevalence significantly increases in women after age 40:
~65% between 40-59 yrs
~74% in women > 60 yrs

Healthy Women Study: average weight gain in perimenopausal women ~5 lbs; 20% women gained ≥10 pounds

Possible explanations of increased weight with menopause:
decreased estrogen levels and decrease in energy expenditure

Estrogen deficiency enhances metabolic dysfunction → T2D, MetS, CVD.
Estrogen affects fat storage and distribution.
- Before perimenopause, estrogen deposits fat in your thighs, hips, and buttocks.
- During/after menopause: decreasing estrogen leads to overall increase in total body fat and especially fat around waistline
- Abdominal fat: linked to increase in insulin resistance, diabetes, and inflammatory diseases
Racial/Ethnic/Socioeconomic Disparities

- Prevalence of obesity in US differs among racial/ethnic groups\(^1,2\)
- Disparities in health consequences of obesity by race/ethnicity\(^3\)
- Different average BMIs by ethnicity:\(^1,2\)
  - US-born Asians:
    - Chinese: 24.9,
    - Asian Indians: 25.8
    - Filipinos: 27.3
  - US-born Hispanics:
    - Cubans: 29.5
    - Puerto Ricans: 30.6
    - Mexicans: 31.1

Racial/Ethnic Disparities: Obesity Prevalence

Adults >20 years

Adults

Children (2-19 years)

Children

Race/Ethnic/SES Disparities in Obesity

- Possible mechanisms explaining disparities
  - Health behaviors: knowledge about nutritional food
  - Biological/developmental factors: genetics
  - Social environment
    - Opportunity for physical activity in and after school
    - Access to healthy (vs fast) food
- Socioeconomic status: having a college degree nearly doubles the risk of obesity vs not having a high school diploma
- Cultural norms promoting big-boned, fat/thick adults
- Food as center of community unity

Consequences of Overweight/Obesity

- **Physical**
  - Increased body fat mass/loss of lean muscle
  - Joint pain/osteoarthritis
  - Impaired mobility/Disability
  - Urinary incontinence
- **Medical**
  - Metabolic/Altered metabolism
  - Digestive disorders
  - Lung function and Sleep impairments
  - Cancers
  - CVD/Hypertension
  - Hormonal
- **Psychiatric/Psychologic**
  - Low self-esteem, depression, anxiety, binge-eating disorder
Physical Consequences of Obesity

- Increased body fat mass
- Joint pain
- Impaired mobility, Disability
- Urinary Incontinence
Increased Body Fat Mass

- Biologic aging associated with progressive increase in body fat mass, loss of lean body mass\(^1\)
  - Intra-abdominal fat increases by over 300% between ages 25-65 years
- Metabolic consequences of reduced muscle mass
  - Low muscle mass strong predictor of morbidity and mortality\(^2\)
    - Lower physical function
    - Shorter survival
    - Poorer quality of life
- Can interfere with lower extremity physical performance
- Location of body fat distribution: central obesity carries greater risks\(^3\)

Joint Pain and Osteoarthritis

- Obesity accelerates development of hip and knee osteoarthritis (OA)
- Obesity increases risk of hand osteoarthritis

Causes: 1-3
- Biomechanical effects
- Systemic inflammatory changes
  - Low-grade systemic inflammatory state
  - Production and secretion of adipocytokines involved in OA development
- Obesity comorbidities (hypertension, impaired glucose and lipid metabolism) - alter joint tissue homeostasis

**Impaired Mobility, Disability**

**OBESITY:**

| Limits optimal function of cardiopulmonary and metabolic systems → exertion dyspnea and impairments in functional abilities |
| Affects balance and movement control |
| Is associated with mobility disability: difficulty walking 400 m or climbing stairs¹ |
| Interferes with functional mobility and ability to participate in activities of daily living (ADL): standing, bending, walking, climbing, grabbing objects while standing.²⁻⁴ |
| Affects postural stability. |
| Impedes motor control, speed |
| Increases risk of fall-related injuries requiring medical treatment – including sprains, strains, dislocations⁴ |
| Implies sedentary lifestyle – impaired exercise tolerance |

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Urinary Incontinence

• Obesity associated with stress urinary incontinence (SUI)\(^1\)
  • Increased intra-abdominal pressure
  • Neurogenic and metabolic pathways also contribute

• ACP recommends weight loss and exercise for obese women with UI\(^2\)

• Overweight associated with 1/3 increased risk of UI, and risk doubled with obesity\(^3\)

Medical Consequences of Obesity
Metabolic/Altered Metabolism

- Overweight and Obesity are associated with higher risks of prediabetes (HbA1c = 5.7-6.4%) and T2D (HbA1c >6.5%)
  - Insulin resistance
- Increasing body weight $\rightarrow$ increased insulin resistance and eventually development of high blood sugar:
  - Prediabetes: Impaired Glucose Tolerance (IGT) or Impaired Fasting Glucose (IFG).
  - Individuals with prediabetes have an increased risk of developing T2D, hypertension and stroke.
  - An estimated 79 million Americans age 20 years or older have prediabetes

Digestive disorders: Obesity and Dyslipidemia

- Increased triglycerides (TG) and free fatty acids (FFA)
- Decreased HDL-C, normal/slightly increased LDL-C
- Increased concentrations of plasma apolipoprotein (apo) B
- Elevated fasting and postprandial TG with small dense LDL-C and low HDL-C.
- Increased FFA and obesity-induced inflammation are important in the development of insulin resistance.

Increased triglycerides (TG) and free fatty acids (FFA), decreased HDL-C with HDL dysfunction, normal or slightly increased LDL-C with increased small dense LDL.

The concentrations of plasma apolipoprotein (apo) B are often increased, partly the result of hepatic overproduction of apo B containing lipoproteins.

The hallmark characteristics = elevated fasting and postprandial TG in combination with the preponderance of small dense LDL and low HDL-C.

Hypertriglyceridemia may be the major cause of the other lipid abnormalities; leads to delayed clearance of the TG-rich lipoproteins and formation of small dense LDL.

Plasma FFA elevated in obese people as result of an increased fatty acid release from adipose tissue and a reduction in plasma FFA clearance.

Increased FFA + obesity-induced inflammation play important role in the development of insulin resistance.

Digestive disorders: GERD

• Obesity is associated with significant increased risk for gastroesophageal reflux disease (GERD) symptoms and GERD-related complications\(^1,2\):
  • Barrett’s esophagus
  • Erosive esophagitis
  • Esophageal adenocarcinoma

• Central/abdominal obesity more closely related to GERD vs BMI\(^3,4\)

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Digestive Disorders: Gallbladder Disease

- Obesity is a risk factor for the formation of cholesterol gallstones and gallstone-related complications\(^1\)-\(^3\)
- However, rapid weight loss via very low-calorie diets (VLCD) or bariatric surgery increases risk for cholelithiasis in obese patients\(^1\),\(^2\)
  - Risk increases with higher BMI prior to weight loss
  - Prophylactic treatment with oral ursodeoxycholic acid may be recommended\(^1\)
- Obesity increases risk of acute pancreatitis\(^1\),\(^2\)

Nonalcoholic fatty liver disease (NAFLD)  
Nonalcoholic steatohepatitis (NASH)

- NAFLD is the most common cause of chronic liver disease; affects >30% adults\(^1,2\)
- NAFLD: hepatic manifestation of metabolic syndrome
  - Central abdominal obesity common\(^1,2\)
  - Up to 80% of patients with NAFLD are obese\(^2\)
  - Obesity associated with initial stages and severity of NAFLD\(^3\)
  - High prevalence NAFLD if increased visceral adipose tissue (VAT),\(^2\) insulin resistance, dyslipidemia
- Most patients with NAFLD have simple steatosis (SS); up to 1/3 progress to more severe form of NASH\(^1\)

Lung Function and Sleep Impairments

- Obesity interferes with lung function\(^1\)
  - Stiffens respiratory system, reduces lung/chest wall compliance
  - Reduced lung volume and vital capacity
  - Increased risk of airway closure and ventilation distribution abnormalities

- Obesity associated with Obstructive Sleep Apnea (OSA)\(^2\)
  - Excess fat reduces diaphragm mobility, promotes soft tissue edema
  - Obesity reduces lung volume\(^3\)
  - Increased BMI lowers forced expiratory volume in 1 second (FEV\(_1\)), forced vital capacity (FVC), functional residual capacity (FRC), and the expiratory reserve volume (ERV)\(^3\)
  - Poor sleep promotes production of IL-6 and cortisol (stress hormone) which exacerbates insulin resistance

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Obesity and Cancer

- Obesity has been associated with at least 13 different types of cancers:¹ ²
- In 2012, estimated 28,000 new cases of cancer in men (3.5%) and 72,000 new cases in women (9.5%) were due to overweight or obesity¹
- Obesity lowers survivorship/increases mortality from cancer

## Obesity: Cancer Type and Associated Risk

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial cancer</td>
<td>2-4x risk vs normal weight</td>
</tr>
<tr>
<td>Esophageal adenocarcinoma</td>
<td>2x greater risk; morbid obese—4x</td>
</tr>
<tr>
<td>Gastric cardia cancer</td>
<td>2x greater risk</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>Up to 2x greater risk, especially in men</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>Up to 2x greater risk</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Slight increased risk – 10% - 20%</td>
</tr>
<tr>
<td>Meningioma</td>
<td>20% increased risk in overweight, 50% increased risk in obese</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1.5x increased risk</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Slightly - ~30% increased risk</td>
</tr>
<tr>
<td>Gallbladder cancer</td>
<td>~20% increased risk in overweight, ~60% increased risk in obese</td>
</tr>
<tr>
<td>Breast cancer in postmenopausal women</td>
<td>20-40% increased risk (also increases breast cancer risk in men)</td>
</tr>
<tr>
<td>Ovarian or Thyroid cancer</td>
<td>Slight increased risk (ovarian especially if never used Hormone Therapy), (thyroid - ~10%)</td>
</tr>
</tbody>
</table>

Obesity and Cancer: Possible Mechanisms

• Chronic low-level inflammation
• Fat (adipose) tissue produces excess estrogen – increases risk breast, endometrial, ovarian, other cancers
• Increased blood levels insulin, insulin-like growth factor-1 (IGF-1) = hyperinsulinemia or insulin resistance; predisposes to T2D
  • May increase risk colon, kidney, prostate, endometrial cancers
• Fat cells produce adipokines (hormones that stimulate or inhibit cell growth)
  • Leptin: promotes cell proliferation, level increases with increasing fat
  • Adiponectin: antiproliferative effects, lower level in obese vs normal weight persons
• May directly/indirectly effect other cell growth regulators

Cardiovascular Disease

- Obesity and overweight linked to several factors that increase risk for CVD (coronary artery disease and stroke):
  - High blood lipids, especially high triglycerides, LDL cholesterol, and total cholesterol and low HDL cholesterol
  - High blood pressure
    - Can be challenging to accurately measure blood pressure in obese patients
  - Impaired glucose tolerance or type-2 (also called adult onset) diabetes
  - Metabolic syndrome (MetS)
  - Enlarged left ventricle (left ventricular hypertrophy) → increased risk for heart failure.
- AACE recommends weight loss of 5% to 10% to reduce CVD risk

Obesity and Hypertension

• ~50% of hypertensive patients are obese in US
• >1/3 obese patients in US have diagnosis of hypertension (vs <20% normal weight)
• Hypertension in obesity contributes to end organ damage including cardiovascular and chronic kidney disease.
• Very challenging to treat hypertension in obese patient – may require multiple agents

Bidirectional Relationship: Obesity and Blood Pressure

- Obesity is important risk factor for hypertension\(^1\)
  - Waist-to-height ratio and waist circumference are most strongly associated with risk of developing hypertension
- Hypertension is major factor in morbidity/mortality associated with obesity\(^2\)
  - Obesity strongly correlated with treatment-resistant hypertension\(^3\)
- Mechanisms:
  - Sympathetic nervous system, alteration of renal function, insulin resistance\(^4\)
  - Altered hemodynamics, impaired sodium homeostasis, renal dysfunction, autonomic nervous system imbalance, endocrine alterations, oxidative stress/inflammation, vascular injury\(^5\)

Hormonal Alterations: Males

- Male hypogonadism/Androgen deficiency
  - Total testosterone <280-300 ng/dL and/or free T <5-9 ng/dL
  - Decreased muscle mass, bone mineral density, increased fat mass
  - Weight loss of >5% to 10% needed to significantly increase serum testosterone
  - Testosterone therapy can facilitate weight loss, decrease waist circumference, improve metabolic parameters (for men not seeking fertility)

Hormonal Alterations: Females

- Polycystic ovary syndrome (PCOS)$^{1,2}$
  - Anovulation, irregular menstrual cycles, may worsen with overweight/obesity
  - Weight loss of $\geq 5\%$ to $15\%$ can improve hyperandrogenism, oligomenorrhea, anovulation, insulin resistance, hyperlipidemia

- Female Infertility$^{1,3}$
  - Weight loss effective in treating some infertility; target for weight loss goal of $\geq 10\%$ to improve likelihood of conception/live birth

- Obesity as a “modifiable” risk factor for breast cancer risk in postmenopausal women$^4$

Obesity Medical Consequences Summary

- Altered Metabolism
- Digestive Disorders
  - Obesity and Dyslipidemia
  - GERD
  - Gallbladder Disease
- NAFLD and NASH
- Lung function and sleep impairment

- Cancer
- Cardiovascular disease
- Hypertension
- Hormonal alterations (males and females)
Psychiatric/Psychologic Consequences of Obesity
Obesity and Mood Disorder

- Blame/shame from family, friends and professionals
- Stigma (low self-esteem)
- Bias and Social Isolation
- Depression
- Anxiety
Bidirectional Relationship: Obesity and Depression

- Depression results in weight gain/obesity; overweight/obesity increases likelihood of developing depression\textsuperscript{1-4}
- Prevalence of depression in obesity - as high as 2X that in individuals of normal weight\textsuperscript{1}
- High prevalence mental illness and comorbid obesity\textsuperscript{5}
- Study found 43% adults with depression are obese – vs 33% adults without depression\textsuperscript{6}
  - As increase severity of depression, increase % of people with obesity.
  - Moderate-to-severe depressive symptoms associated with higher rate obesity – if not taking antidepressant Rx.
  - Highest prevalence of obesity (54.6\%) in persons with moderate or severe depressive symptoms on antidepressants.\textsuperscript{6}

Obesity and Binge Eating Disorder

• Online survey of people with overweight/obesity\textsuperscript{1}
  • Nearly 1/3 met criteria for binge-eating disorder (BED), food addiction (FA) or BED+FA
  • Disordered eating: greater psychiatric pathology, impulsivity, self-control, depression

• DSM-5 recognizes strong association between obesity and psychiatric syndromes\textsuperscript{2}:
  • Strong association with bipolar spectrum disorders (BSD) and BED.
  • Distinctive pathological eating behaviors may be warning signals in obese patients

• Disordered eating (eg BED) is associated with weight gain over time, increased risk of diabetes and metabolic dysfunction;
  • Patients also have higher risk of psychopathology – mood, anxiety, sleep problems.\textsuperscript{3}

Benefits of Weight Loss

Physical
Medical
Psychiatric/Psychologic
USPSTF Recommendation Statement

• Adequate evidence that intensive, multicomponent behavioral interventions in adults with obesity can lead to clinically significant improvements in weight status and reduce incidence of T2D among adults with obesity and elevated plasma glucose levels: moderate benefit

• Adequate evidence that behavior-based weight loss maintenance interventions are of moderate benefit

• Adequate evidence that the harms of intensive, multicomponent behavioral interventions (including weight loss maintenance interventions) are small to none

• Adults with BMI >30 should be referred to intensive, multicomponent behavioral weight loss interventions

USPSTF et al; JAMA 2018 Sep 18;320(11):1163-1171.
Physical Benefits of Weight Loss

- Improved ability to engage in activities of daily living (ADLs)
- Improved mobility
  - Physical activity abdominal fat (around the waist) and total body fat; slows the development of abdominal obesity.
- Easier to engage in physical activity
  - Exercise
  - NEAT (non-exercise activity thermogenesis)
- Reduced symptoms of:
  - Obstructive sleep apnea (OSA)
  - Bladder incontinence
  - Joint pain
Effect of Weight Loss: Asthma

- Weight loss (via caloric restriction) of >7.5% --> improvements in asthma disease factors$^{1-4}$
  - Reduced asthma severity
  - Improved disease control
  - Improved quality of life
  - Improved airway hyperresponsiveness
  - Peak expiratory flow
  - Pulmonary function
  - Markers of oxidative stress, inflammation

Relationship between Weight Loss and OSA

- Complex interaction between obesity and weight loss\(^1\)
  - Weight loss is associated with significant reduction in apnea-hypopnea index (AHI)\(^2\)
  - Long-term treatment of OSA with CPAP is associated with a small but significant weight gain\(^1,2\)
  - Weight loss may only benefit a small percentage of patients with sleep apnea\(^1\)
  - Screening for OSA before attempting weight loss is recommended\(^3\)

Benefits of Weight Loss

Weight loss reduces symptoms of:¹

• Dyslipidemia
• GERD (symptoms and complications)
• Gallbladder disease
• Nonalcoholic fatty liver disease (NAFLD)
• Nonalcoholic steatohepatitis (NASH)
• Colon cancer

Weight loss and dyslipidemia

- Markedly reduces fasting and non-fasting TG concentrations
- Small reduction in LDL-C
- Weight loss of ~9-22 lbs in obese subjects resulted in a 12% reduction in LDL-C and a 27% increase in LDL receptor mRNA levels
- Modest 5% weight loss leads to substantial reductions in adipose visceral fat tissue (AVT) and adipose subcutaneous tissue (AST) which reduce TG concentrations, cholesterol

Weight Loss and Gallbladder Disease

• Weight loss can reduce risk of gallbladder disease
• Dietary contribution: Eating foods high in fiber, healthy fats, can reduce risk of gallbladder disease
• Rapid weight loss can cause gallstones
Weight Loss and NAFLD/NASH

• Weight loss is cornerstone for disease prevention and treatment\(^1,^2\)
• Diet and exercise initial steps; often need for pharmacologic and/or surgical intervention
• Importance of reducing visceral (abdominal) fat to reduce risk of progression from simple steatosis (SS)/NAFLD to NASH\(^2\)
• Mean weight loss of ~12.5 lb via lifestyle intervention led to significant reduction in intrahepatic triglycerides and significantly greater number of patients achieving NAFLD remission vs Control group\(^3\)

NAFLD/NASH (continued)

- AACE Gx recommend patients with overweight or obesity and NAFLD should be primarily managed with lifestyle interventions
  - Calorie restriction and moderate-to-vigorous physical activity
  - Target 4% to 10% weight loss
- Weight loss as high as 10% to 40% may be required to decrease hepatic inflammation, hepatocellular injury, and fibrosis (Rx, surgery)
- A Mediterranean dietary pattern or meal plan can have a beneficial effect on hepatic steatosis independent of weight loss.

Obesity and Cancer

- People who have lower weight gain in adulthood have lower risk of colon cancer, kidney cancer, and (postmenopausal women) breast, endometrial, ovarian cancers\(^1,2\)
  - Weight loss may reduce inflammation and protect against cancer
  - Reduced adipose tissue prevents excess amounts of estrogen, reduced risk numerous cancers
- Obese people who undergo bariatric surgery have reduced risk many cancers vs those who do not undergo bariatric surgery\(^1\)

Weight Loss and Hypertension

- ~50% of hypertensive patients are obese in US
- >1/3 obese patients in US have diagnosis of hypertension (vs <20% normal weight)
- Hypertension in obesity contributes to end organ damage including cardiovascular and chronic kidney disease.
- Weight loss is strongly associated with improvements in blood pressure.
- Weight loss medications may not be as beneficial as lifestyle or surgical interventions
  - Unpredictable effects medications

Metabolic Benefits of Weight Loss

• Decreased insulin resistance
• Decreased blood glucose
• Decreased cholesterol
• Decrease in fatty liver
Weight Loss To Prevent Diabetes

- Weight loss is highly effective to prevent, treat T2D\(^1-3\)
  - ADA recommends loss ≥ 7% of body weight with increased PA ≥150 min/week\(^1\)
  - Weight loss of ~10% maximally beneficial to prevent future diabetes
  - Weight loss via lifestyle therapy, pharmacotherapy, or bariatric surgery\(^3\)
- Weight loss in high-risk patients with prediabetes and/or MetS\(^2\)
  - Prevents progression to T2D
  - Improves insulin resistance
  - Improves CV risk factors
  - Metabolic health benefits – even in absence of classic CV risk factors.
- Weight loss in persons with diabetes\(^3\)
  - Improves glycemic control in patients with T2D
  - Improves features of NAFLD and NASH

Weight Loss in Patients with T2D

• Benefits of weight loss:¹
  • Improves glycemia
  • Enhances glucose homeostasis via reversing defects in insulin action and secretion from glucose toxicity
    • As increase % weight loss, progressive improvements in glucose homeostasis²
  • Reduces need for conventional glucose lowering medicines
• Metabolic benefits of bariatric surgery generally more pronounced vs lifestyle/medical treatments²
• Hypocaloric feeding via very-low calorie diet or bariatric surgery leads to rapid improvement in insulin sensitivity

## Effect of Differing Amounts of Weight Loss

<table>
<thead>
<tr>
<th>5% Weight Loss</th>
<th>&gt;10% Weight Loss</th>
</tr>
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<tbody>
<tr>
<td>Improved adipose tissue, liver and muscle insulin sensitivity, β-cell function</td>
<td>Further improvements in β-cell function and insulin sensitivity in muscle</td>
</tr>
<tr>
<td>No change in systemic or subcutaneous adipose tissue markers of inflammation</td>
<td>Changes in intrahepatic triglycerides, adipose tissue biological pathways</td>
</tr>
<tr>
<td>Simultaneous improvement in metabolic function in multiple organs</td>
<td>Continued improvement in metabolic function in multiple organs</td>
</tr>
</tbody>
</table>

Diabetes Prevention Program (DPP)

- 2 major goals of DPP lifestyle intervention:
  - Minimum 7% weight loss/weight maintenance
  - Minimum of 150 min physical activity similar in intensity to brisk walking.

- Program methods
  - Individual case managers or “lifestyle coaches”
  - Frequent contact with participants
  - Structured 16-session core-curriculum on behavioral self-management strategies
  - Supervised physical activity sessions
  - Flexible maintenance intervention
  - Individualization through a “toolbox” of adherence strategies
  - Tailored materials and strategies to address ethnic diversity
  - Extensive network of training, feedback, and clinical support

Diabetes Prevention Program (DPP)

- DPP program reduced diabetes incidence by 58% after 2.8 years of follow up
  - Sustained improvements in HbA1c, blood pressure, lipid levels.
  - After 15 years follow-up – DPP’s lifestyle intervention sustained a 27% risk reduction in progression to diabetes
- In light of many DPP-like studies that consistently demonstrate weight losses of 7% at 1-year, as of April 2018 Medicare covers CDC-recognized DPP lifestyle programs

Look AHEAD: Lifestyle intervention

- Significantly reduced HbA1c, BP, TG; reduced c-reactive protein (CRP)
- Lowered the amount/costs Rx
- Less self-reported retinopathy
- Reduced risk nephropathy, less sexual dysfunction, decreased incidence UI, decreased incidence fatty liver, remission of sleep apnea, remission of diabetes
- Improved physical functioning, less knee pain, reduced incidence depression, less body image dissatisfaction, improved QoL.
Weight Loss and Women

- Academy of Nutrition and Dietetics: Counsel all women of reproductive age regarding risks of pre-pregnancy obesity, excessive gestational weight gain, postpartum weight retention\(^1\)
  - Weight loss before pregnancy improves fertility, decreases risk of poor maternal/fetal outcomes\(^1\)
  - Maternal pre-pregnancy obesity increases risk preterm birth; varies by age and race/ethnicity\(^2\)
- PCOS\(^3,4\)
  - Low dose OCs and lifestyle interventions \(\rightarrow\) weight loss and significant improvements in psychosocial parameters;
    - Changes in serum testosterone, FG and body weight had greatest benefits\(^3\)
    - Combining OC + lifestyle interventions had greatest benefit to HRQoL\(^3\)
    - Weight loss of even 2% to 5% improves ovulation and spontaneous pregnancy\(^4\)

Weight Loss Effects: Postmenopausal Women

- Women’s Health Initiative (WHI) observational study and follow-up: 61,335 postmenopausal women had their weight change determined over a 3-year period with subsequent follow-up.
  - Breast cancer:
    - Women with weight loss ≥ 5% had significantly lower breast cancer incidence vs women with stable weight.
    - WHI Dietary Modification randomized clinical trial (n=48,835 postmenopausal women): following low-fat eating pattern significantly reduced deaths after breast cancer.
    - Moderation regarding dietary composition and body weight maintenance can reduce a postmenopausal woman's risk of being diagnosed with breast cancer and of dying after breast cancer.
  - Mortality:
    - Normal-weight central obesity associated with excess risk of mortality (~same as women with BMI-defined obesity with central obesity).
    - Importance of prevention and control of central obesity even if normal BMI.
  - Cardiovascular disease (2683 postmenopausal women with normal BMI (18.5 to <25 kg/m2) with no known CVD at baseline):
    - Median 18 years of follow-up: postmenopausal women with normal BMI: elevated trunk fat and reduced leg fat associated with increased risk of CVD.

Menopausal hormone therapies (MHT) may prevent T2D.

Hormonal Benefits: Testosterone

• Testosterone therapy in men with testosterone deficiency and obesity:¹
  • Increases lean body mass, decreases fat mass, improves overall body composition

• Long-term testosterone therapy in men with testosterone deficiency:
  • Significant/sustained weight loss, marked reduction in waist circumference and BMI, improvement in body composition¹,²
  • T therapy more effective for weight loss vs bariatric surgery
  • Ameliorates components of the metabolic syndrome

Psychiatric/Psychologic Benefits of Weight Loss

• Improved mood, decrease in anxiety and depressive symptoms
• Improved mental clarity, focus and attention
• Weight loss decreases depression symptoms (if non-clinically depressed)$^1$
• Treatment of one comorbidity (obesity/depression) improves the course of the other condition$^2$
• Among patients going for bariatric surgery – high prevalence of depression (19%) and binge eating disorder (17%).
  • Bariatric surgery consistently associated with postop decreases in prevalence of depression (8-74% decrease) and severity of depression symptoms (40-70% decrease)$^3$

Racial and Ethnic Differences

- Majority of obesity studies predominantly involve White participants\(^1\)
  - Results of studies may not be generalizable to non-Whites
- Effect of food insecurity, lack of physical activity, type of foods eaten (sugar/sugar sweetened) can increase risk childhood/adolescent obesity risks\(^2\)
- Need to address infrastructure and access to physical activity and nutritious food


\(^2\) Au LE. J Nutr. 2019 Jun 7
Weight loss approaches

• Diet/lifestyle intervention/exercise
  • Importance of weight training and other exercises with diet-induced weight loss – to minimize risk of losing muscle strength\(^1\)

• Pharmacotherapy

• Bariatric surgery

Role of NEAT

• Physical activity (PA) is either exercise-related thermogenesis (EAT) or non-exercise activity thermogenesis (NEAT)\(^1\)
• Most individuals get very little formal exercise\(^2\)
• Energy is expended with spontaneous NEAT\(^1\)
• NEAT is major component of daily activity-related thermogenesis
  • Examples: leisure time activity, sitting, standing, ambulation, toe-tapping, shoveling snow, playing piano, dancing, washing, cooking, fidgeting, etc.\(^1\)

Weight-Loss Medications

- Overall, weight loss medications are associated with:
  - Modest decrease in fasting blood glucose (FBG) and waist circumference (WC)
  - No clinically meaningful changes in systolic/diastolic BP or cholesterol profile vs PBO.
- NO drug improves all cardiometabolic risk factors.

# Weight Loss Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Benefits</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine-topiramate</td>
<td>Substantial decrease WC</td>
<td>Minimal effect on cholesterol</td>
</tr>
<tr>
<td></td>
<td>Modest decrease in FBG, HbA1c, BP</td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Substantial decrease FBG, HbA1c, WC</td>
<td>Minimal effect on blood pressure, cholesterol</td>
</tr>
<tr>
<td>Naltrexone-bupropion</td>
<td>Moderate increase HDL-C</td>
<td>Minimal effect FBG, WC</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Decrease in LDL-C</td>
<td>Decrease in HDL-C</td>
</tr>
</tbody>
</table>

Aerobic training: with/without weight loss

- Study found greater improvement in insulin sensitivity in adults who performed exercise training with at least moderate weight loss (≥3%) vs exercise training alone.
  - Benefits to acute insulin response, triglycerides, non-HDL cholesterol concentration, low density lipoprotein (LDL) particle size, high density lipoprotein (HDL) particle size.
  - Modest weight loss needed with exercise for improved cardiovascular benefits.

Amount of Weight Loss Needed for Benefit

- Even small amounts of weight loss have benefit to glycemic measures, TG
  - PCOS: 2% to 5% can improve menstrual irregularities, infertility
  - For 1kg (2.2 lb) weight loss: 16% reduction in risk for T2D
    - No clear benefit for weight loss >10kg (22lb) regarding T2D prevention

- Clinically meaningful weight loss: at least 5%

- Modest weight loss (5% to 10%):
  - Associated with improved systolic and diastolic BP, HDL-C
  - Improvements in QoL, depression, mobility, sexual dysfunction, urinary stress incontinence

- Additional weight loss (>10% to 15%) needed for improvements to OSA, NASH
  - Reduction in mortality

AACE/ACE ALGORITHM

Medical Care of Patients with Obesity
Algorithm for Medical Care of Patients with Obesity

Garvey, W. Timothy et al. AACE Endocrine Practice. 22(7) 842-884.
Algorithm Components

Access the interactive AACE/ACE Obesity Algorithm
Summary

- Benefits of weight loss are extensive, extend over multiple areas of physiology
- No magic bullets that can mimic or replace weight loss
- Ideal body weight does NOT need to be achieved to experience benefits
  - Weight loss of at least 5% or 10% can have substantial health benefits
- Weight loss without exercise is STILL important
  - Exercise is NOT required
  - NEAT: Non-exercise activity thermogenesis