Obesity in Living Donors - Sustainable Interventions

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Disclosures

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Objectives

At the conclusion of this session, participants should be able to:

- Understand why weight management in living donors is important
- Recognize obesity as a chronic disease
- Review contributed factors to weight regulation, including uncontrollable ones
- Discuss the set point theory and why it is so difficult to lose weight and maintain it
- Describe current evidence-based treatment options for obesity, including their indications
- List the resources available at our Cedars Sinai Center for Weight Management and Metabolic Health
Understand why weight management in living donors is important
Obesity in Living Donors Poses Challenges and Potential Health Risks

- **“Most kidney donor** candidates with a BMI >35–40 kg/m² are rejected due to concerns regarding long-term renal functional deterioration in the donor.”

- **“Most centers use a threshold of BMI of ≥30 to 35 kg/m² to exclude potential liver donors.”** Previous studies have found that recipients who received liver from donors with obesity (BMI ≥30 kg/m²) had a higher incidence of early allograft dysfunction.”

- **Heart donors** with severe obesity (BMI ≥40 kg/m²) was not associated with adverse post-transplant outcomes, however long-term outcomes of allograft vasculopathy and graft coronary atherosclerosis is unknown.

3. Patel et al. 21st Century Cardiol, Volume 3 (1):128
Recognize obesity as a chronic disease
Obesity has complex pathophysiology

- Obesity affects every organ system
- Obesity is not only an underpinning of major chronic diseases, but a serious debilitating condition in its own right
- This is NOT due to a lack of willpower
- In 2013 - Obesity was designated a disease by AMA and numerous health organizations

2. Is Obesity a Disease” Cleveland Clinic Health Essentials. April 21 2022
3. AMA. House of Delegates. Recognition of Obesity as a Disease. Resolution 420(A-13);
Obesity is a chronic disease

#1: Similar to other chronic diseases, obesity has a pathophysiology that is complex and involves interactions among genes, biological factors, the environment, and behavior.

#2: It meets the 3 criteria that constitute a disease (per AMA)
   1. Must have outward signs or symptoms
   2. Cause morbidity or mortality
   3. Involve impaired function of one tissue
The adipose organ

Adipose tissue (AT) is now fully recognized as a metabolically active organ.
White adipose tissue (WAT)

- Primary site for energy storage in the form of lipid
- Major endocrine organ
  - produces and secretes adipokines
  - responds to a variety of circulating metabolites and hormones (i.e. lipids, growth hormone, cortisol, insulin, catecholamines, etc.)
  - plays a role in glucose homeostasis
Pathophysiology of adiposopathy

- **On cellular level, adiposopathy ("sick fat"), aka lipotoxicity** leads to excessive energy storage in the form of fat.

- **Exact mechanisms of the initial inflammatory trigger remains unknown at this time**

- Oxidative stress, mitochondrial dysfunction, immune dysfunction, chronic low-grade inflammation and metabolic dysfunction all contribute to the pathogenesis of obesity.

- Adiposopathy is sustained by adipocyte hypertrophy, visceral adiposity and/or ectopic fat deposition and secretion of hormones, like leptin, and proinflammatory protein, like the plethora of cytokines.
Inflammation Cascade in Adipocytes


Adipose Inflammation Leads to Organ Dysfunction

“Despite its low-grade nature, adipose tissue inflammation negatively impacts remote organ function, a phenomenon that is considered causative of the complications of obesity”
Signals reflecting energy stores, recent nutritional state, and other parameters are integrated in the central nervous system (i.e. hypothalamus) to coordinate energy intake and expenditure.
Obesity is a chronic, relapsing disease

#1: Similar to other chronic diseases, obesity has a pathophysiologic basis of interactions among genes, biological factors, the environment, and behavior.

#2: It meets the 3 criteria that constitute a disease (per AMA)

- Must have outward signs or symptoms
- Cause morbidity or mortality
- Involve impaired function of one tissue

Proposed by AACE and EASO
A New Diagnostic Term for Obesity: Adipose-Based Chronic Disease (ABCD)

Because it describes what we are treating: abnormalities in the mass, distribution, and function of adipose tissue—and why we are treating it, a chronic disease that leads to complications.
Review contributing factors to weight regulation, including uncontrollable ones
Obesity is a multifactorial pathology

The defect is in energy balance regulation
## Contributors to Weight – Uncontrollable and Controllable

<table>
<thead>
<tr>
<th>Genetics</th>
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<tbody>
<tr>
<td>Prenatal and Postnatal health</td>
</tr>
<tr>
<td>Environment</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Victim of Weight Bias and/or Stigma</td>
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<tr>
<td>Unhealthy diet</td>
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<tr>
<td>Eating patterns</td>
</tr>
<tr>
<td>Little or no exercise</td>
</tr>
<tr>
<td>Inadequate sleep/Circadian Rhythm disruption</td>
</tr>
<tr>
<td>Sedentary behaviors</td>
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<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Menopause</td>
</tr>
<tr>
<td>Life changing event</td>
</tr>
<tr>
<td>Weight Promoting Medications</td>
</tr>
<tr>
<td>Medical illness</td>
</tr>
<tr>
<td>Stress</td>
</tr>
<tr>
<td>Alcohol use</td>
</tr>
<tr>
<td>Quitting Smoking</td>
</tr>
<tr>
<td>Mental health</td>
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</tbody>
</table>
• To date >100 loci related to obesity have been identified

• Family, twin and adoption studies have consistently demonstrated that 40–70% of the variation in body weight can be attributed to heritable factors

• The presence or absence of genetic factors protect us from or predispose us to obesity. i.e. the fat mass and obesity-associated gene (FTO)

• It is the complex interplay of these loci and environmental factors ➔ EPIGENETICS

Findings:

• Thinness, like obesity, is a heritable trait with a polygenic component

• Slim individuals had a significantly lower genetic risk score

• Hence, this is first time in research that showed:

  "...thin people are generally thin because they have a lower burden of genes that increases a person’s chance of being overweight and NOT because they are morally superior, as some people like to suggest."
Prenatal and Early Life Health

Modifiable prenatal factors associated with childhood obesity:
- Mother’s smoking habits
  - Meta-analysis of 14 studies found 50% higher risk of childhood obesity
- Mother’s weight and rate of weight gain during pregnancy
- Pre-gestational and gestational diabetes

Modifiable postnatal factors associated with childhood obesity
- Rapid infant weight gain during first 6 mo. of life
- Breastfeeding and possibly duration
- Infant sleep duration

References:
Environment

- Built Environment: access & quality of foods, recreational facilities, urban design, transportation access, sedentary entertainment

- Organizational: rules, regulations, programs, practices in schools, worksite, community organizations, public policy

- Interpersonal: social networks, social norms, family norms, cultural beliefs, occupations

Obesity is a multifactorial pathology

The defect is in energy balance regulation.
Discuss the set point theory and why it is so difficult to lose weight and maintain it.
The brain is the primary organ responsible for body weight regulation operating mainly below our conscious awareness via complex endocrine, metabolic, and nervous system signals to control food intake in response to the body’s dynamic energy needs as well as environmental influences.
Why is it so hard to lose weight and keep it off?

www.rethinkobesity.com
Why is it so hard to lose weight and keep it off?

www.rethinkobesity.com
Sustained Changes in Peripheral Signals for Up to One Year Following Weight Loss

Long-Term Persistence of Hormonal Adaptations to Weight Loss


Figure 3. Mean (±SE) Fasting and Postprandial Ratings of Hunger and Desire to Eat at Baseline, 10 Weeks, and 62 Weeks. Ratings were based on a visual-analogue scale ranging from 0 to 100 mm. Higher numbers indicate greater hunger or desire.
Adaptive Responses to Weight Loss

<table>
<thead>
<tr>
<th>Domain</th>
<th>Parameter</th>
<th>Response to Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite</td>
<td>Subjective experience</td>
<td>Hunger increases</td>
</tr>
<tr>
<td></td>
<td>Hormones and neurotransmitters</td>
<td>Satiety falls</td>
</tr>
<tr>
<td></td>
<td>Rewarding properties of food</td>
<td>Leptin falls</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ghrelin rises</td>
</tr>
<tr>
<td>Energy expenditure</td>
<td>Total energy expenditure</td>
<td>Increased number of new adipocytes</td>
</tr>
<tr>
<td></td>
<td>Rest expenditure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physical activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thermic effect of food</td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>Insulin</td>
<td>Increased number of new adipocytes</td>
</tr>
<tr>
<td></td>
<td>Fat oxidation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adipocytes</td>
<td></td>
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</tbody>
</table>

**NET RESULT OF THESE ADAPTIVE RESPONSES:**

1) MAKES YOU WANT TO EAT MORE

2) BURN LESS ENERGY

3) STORE FAT

= HARDER TO loose and maintain your weight
Biological Adaptations

**Q: How long do these biological neurohormonal adaptations persist?**

- Evidence suggests adaption to sustained obesity often persist indefinitely
- Biological pressure to restore bodyweight to the highest-sustained lifetime level gets stronger as weight loss increases

**Q: Then is a patient ever truly “recovered” from obesity?**

- Few individuals ever fully recover from obesity
- Individuals with obesity who lose weight are essentially in “remission” and biologically very different than their counterparts

Describe current evidence based treatment options for obesity, including their indications
Components of Effective Weight Management Programs

- **RD/SW/Psychologist/ Sleep Medicine/ PT/OT:** Healthy Lifestyle
- **Obesity Medicine:** Medical Weight Management
- **Gastroenterology:** Bariatric Endoscopic Procedures
- **General Surgery:** Bariatric Surgery
- **Plastics:** Body Contouring

Treatment Modalities
Main Components of The Treatment Options

**Lifestyle is Foundation**
- Diet
- Exercise
- Sleep
- Stress management
- Work through barriers to achieving goals

**Medications**
- Medications in conjunction w/ lifestyle changes listed above
- Choice of medication depends on numerous variables
- Intended to be long-term treatment

**Endoscopic Bariatric Procedures**
- Endoscopic Sleeve Gastroplasty
- IntraGastric Balloon
- Revisions

**Weight Loss Surgery**
- Gastric Sleeve
- Gastric Bypass (Roux-en-Y)
- Revisions
## Indications for Treatment

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Treatment Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 25</td>
<td><strong>Reduced calorie diet, exercise, behavioral modification</strong></td>
</tr>
<tr>
<td>≥27-30 + co-morbidity</td>
<td><strong>Consider adding pharmacotherapy</strong>&lt;br&gt;<strong>Consider bariatric endoscopy procedure</strong></td>
</tr>
<tr>
<td>≥ 30</td>
<td><strong>Consider adding pharmacotherapy</strong>&lt;br&gt;<strong>Consider bariatric endoscopy procedure</strong></td>
</tr>
<tr>
<td>≥35-40 + co-morbidity</td>
<td><strong>Consider bariatric surgery</strong></td>
</tr>
<tr>
<td>≥ 40</td>
<td><strong>Consider bariatric surgery</strong></td>
</tr>
</tbody>
</table>

1. Apovian CM et al. JCEM online. 2015.
• **BMI ≥35** regardless of presence, absence, or severity of co-morbidities.

• **BMI of 30-34.9 with presence of metabolic disease**

• Asian population:
  • **BMI ≥25 kg/m²** suggests clinical obesity
  • **BMI ≥27.5 kg/m²** consider MBS

• Appropriate adolescents should be considered
<table>
<thead>
<tr>
<th>Agents</th>
<th>Mechanism of Action</th>
<th>Effect</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat (Xenical® or Alli®)</td>
<td>• Pancreatic lipase inhibition</td>
<td>• Reduces fat absorption</td>
<td>• 1999</td>
</tr>
<tr>
<td>Phentermine</td>
<td>• Sympathomimetic</td>
<td>• Appetite regulation</td>
<td>• 1959</td>
</tr>
<tr>
<td>Phentermine/topiramate ER</td>
<td>• Sympathomimetic</td>
<td>• Appetite regulation</td>
<td>• 2012</td>
</tr>
<tr>
<td>(Qsymia®)</td>
<td>• Anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naltrexone/bupropion SR</td>
<td>• Opioid receptor antagonist</td>
<td>• Appetite regulation</td>
<td>• 2014</td>
</tr>
<tr>
<td>(Contrave®)</td>
<td>• Dopamine/noradrenaline reuptake inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide (Saxenda®)</td>
<td>• GLP-1 receptor agonist</td>
<td>• Appetite regulation</td>
<td>• 2014</td>
</tr>
<tr>
<td>Semaglutide (Wegovy™)</td>
<td>• GLP-1 receptor agonist</td>
<td>• Appetite regulation</td>
<td>• 2021</td>
</tr>
</tbody>
</table>
Efficacy of existing weight loss interventions

Lifestyle intervention
Very low calorie diet
IBT
AOM
Surgery

Weight loss (%)
0 5 10 15 20 25 30

3–5%
6–10%
4–6%
3–20%
7–23%
25–35%
24–38%

*Based on mean weight loss achieved by the completer populations in the largest phase 3 clinical trial of each respective product’s clinical development program as reported in the AACE Guidelines (2016).

AACE, American Association of Clinical Endocrinology; AOM, anti-obesity medications; IBT, intensive behavioral therapy.

Approved anti-obesity medications

Sites of action

**Phentermine/Topiramate**[^1][^2]
Sympathomimetic amine anorectic and ER antiepileptic

**Liraglutide**[^1][^2]
**Semaglutide**[^3]
GLP-1 receptor agonists

**Bupropion/Naltrexone**[^1][^2]
Opioid antagonist/dopamine and norepinephrine reuptake inhibitor

**Orlistat**[^1][^2]
Pancreatic lipase inhibitor

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Percent Weight Loss (Drug versus Placebo) for 3 AOMs

Phen/TPM = phentermine + topiramate; NAL/BUP = naltrexone + bupropion
Lira = liraglutide; Sema = semaglutide

The data supporting these tables are derived from the Prescribing Information labeling approved by the U.S. Food and Drug Administration. *Data from randomized controlled trials >52 weeks in duration; † Adapted from Bray GA et al. Lancet 2016;387:1947–56.
Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group


Injected Drug Delivers Up to 20% Weight Loss in Trial

‘A Game Changer’: Drug Brings Weight Loss in Patients With Obesity

In a clinical trial, participants taking semaglutide lost 15 percent of their body weight, on average.

Diabetes medication almost twice as effective as other anti-obesity drugs, researchers say

A study from Northwestern Medicine found that, at a higher dosage, the diabetes medication semaglutide is more effective than FDA-approved weight-loss drugs currently on the market.

By Mari Devereaux  |  Feb 10, 2021, 8:00pm CST
## Emerging Anti-Obesity Pharmacological Therapies

<table>
<thead>
<tr>
<th>Category</th>
<th>Mechanism</th>
<th>Drug</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal</td>
<td>GLP-1 receptor agonist</td>
<td>Semaglutide</td>
<td>Approved 2021*</td>
</tr>
<tr>
<td></td>
<td>GLP-1/GIP receptor agonist</td>
<td>Tirzepatide</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>GLP-1/glucagon receptor agonist</td>
<td></td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>GLP-1/GIP/glucagon</td>
<td></td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Amylin analogue</td>
<td>Cagrilintide</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>GLP-1/amylin analogue</td>
<td></td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>Ghrelin antagonist</td>
<td></td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>PYY analogue</td>
<td>Danuglipron</td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>GLP-1 small molecule receptor agonist</td>
<td></td>
<td>Phase 1</td>
</tr>
<tr>
<td>Neuropeptide</td>
<td>Melanocortin-4 receptor agonist</td>
<td>Setmelanotide</td>
<td>Approved 2020 for rare genetic conditions*</td>
</tr>
<tr>
<td>Enzyme inhibition</td>
<td>Sodium-glucose transporter-1 and 2 (SGLT1, SGLT2 inhibitor)</td>
<td>Licoglifoxin</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Monoamine receptor uptake inhibition</td>
<td>Noradrenaline, dopamine, serotonin update inhibitor</td>
<td>Tesofensine</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Monoclonal antibody</td>
<td>Activin type II receptor antagonist</td>
<td>Bimagrumab</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

*selected approval according to local regulatory agencies
Intragastric Balloon (IGB)

- Silicone balloon inflated inside the stomach with either saline or gas
- Physically occupies space in the stomach and delays gastric emptying to cause early satiety
- Balloon left in place for 6 months and removed
- Total Body Weight Loss: 6-8 months: 7.1 - 14.9%
  12 months: 7.6 - 9.2%
Endoscopic Sleeve Gastroplasty (ESG)

- Reshaping and reducing the size of the stomach from within, using full thickness endoscopic sutures
- No cutting or removal of any part of the stomach
- All endoscopic and outpatient procedure (~1 hour)
- Expected total body weight loss at 1 year is 15-19%
Bariatric Surgeries

**Malabsorption**
Reduce Absorption
- Biliopancreatic diversion with Duodenal Switch

**Restriction**
Pouch Limits Quantity
- Gastric Banding
- Vertical Sleeve Gastrectomy

**Combination**
restrictive and malabsorptive
- Roux-en-Y Gastric Bypass
Different People Vary In Response to Treatment Options

- Obesity comes in many forms and flavors (think about cancer)
- Among proven options: Average response doesn’t matter so much as your response
- A good provider can find the options that work for you
Describe the resources available at The Cedars Sinai Center for Weight Management and Metabolic Health
Center for Weight Management and Metabolic Health – Multidisciplinary Treatment

RD/SW/Psychologist/ Sleep Medicine/ PT/OT:
Healthy Lifestyle

Obesity Medicine:
Medical Weight Management

Gastroenterology:
Bariatric Endoscopic Procedures

General Surgery:
Bariatric Surgery

Plastics:
Body Contouring
Extensive experience since 1999
- Over 4,000 weight loss operations
- 300+ per year
- Best-in-class outcomes

World-class research
- Electrical gastric pacemaker, LapBand® study, Realize™ band study, TOGa (first endoluminal weight loss procedure)
Center for Weight Management and Metabolic Health – Our Center’s Team Continued

Kristine Acorda Reece, NP  
Nurse Practitioner

Zsofia LaRue, NP  
Nurse Practitioner

Emily Cain, PA-C  
Physician Assistant

Albert Albayev, RD  
Dietitian

Carolina Castillo, RD  
Dietitian
High Quality and Evidence Based Care

Bariatric Surgery Center of Excellence:

Private Insurance Center of Excellence: Blue Cross, Blue Shield, Cigna, Aetna, Etc.
Take Away Points

- Addressing obesity in potential organ donors is critical
- Obesity is a chronic disease with complex pathophysiology
- Adipose tissue is an active endocrine organ and involved in the cross-talk between the gut, brain, and microbiome in energy regulation
- Dysregulation to energy homeostasis is multifactorial in origin, and results from controllable and uncontrollable factors
- Losing weight and maintaining it is challenging because of metabolic adaptations that counteract weight-loss efforts
- Numerous evidence-based treatments for obesity exist. Please feel free to refer those with medically complex obesity to our center!
“Patient success is dependent on a shift in the way healthcare professionals think about obesity, otherwise, patients are destined for failure.”

- Lee Kaplan, MD, PhD
Director, The Obesity and Nutrition Institute
Mass General Hospital
Past President of The Obesity Society
Thank you

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Session Survey

Amanda Velazquez, MD | April 19th 2:45 PM-3:30 PM