

# Obesity in Living Donors - Sustainable Interventions

**Amanda Velazquez, MD, DABOM**  
*Director, Obesity Medicine*  
**Department of Surgery**  
*Assistant Professor, Surgery*  
*Acting Assistant Professor, Medicine*

# Disclosures

**Velazquez - Advisory Board of Intellihealth, WeightWatchers; Consultant - Novo Nordisk**

# 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 contributing 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/m<sup>2</sup> are rejected due to concerns regarding long-term renal functional deterioration in the donor.”



- “Most centers use a threshold of BMI of  $\geq 30$  to  $35$  kg/m<sup>2</sup> to exclude potential **liver donors**. Previous studies have found that recipients who received liver from donors with obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) had a higher incidence of early allograft dysfunction.”

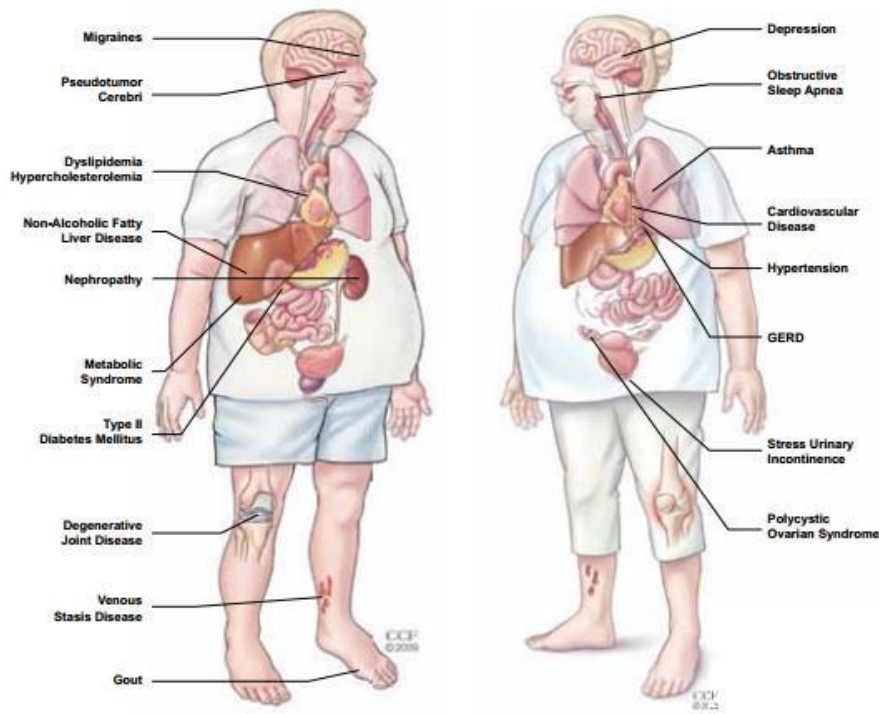


- **Heart donors** with severe obesity (BMI  $\geq 40$  kg/m<sup>2</sup>) was not associated with adverse post-transplant outcomes, however long-term outcomes of allograft vasculopathy and graft coronary atherosclerosis is unknown.

# 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



# 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.

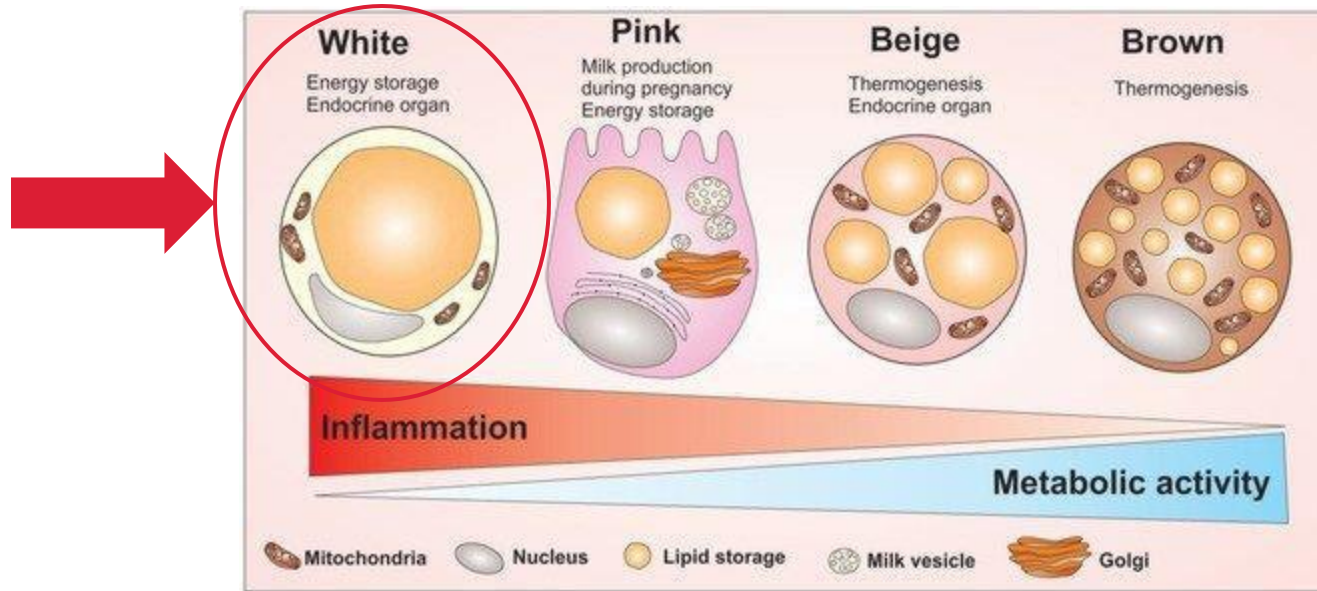
#2: It meets the 3 criteria that constitute a disease (per AMA)

- 1. *Must have outward signs or symptoms***
- 2. *Cause morbidity or mortality***
- 3. *Involve impaired function of one tissue***



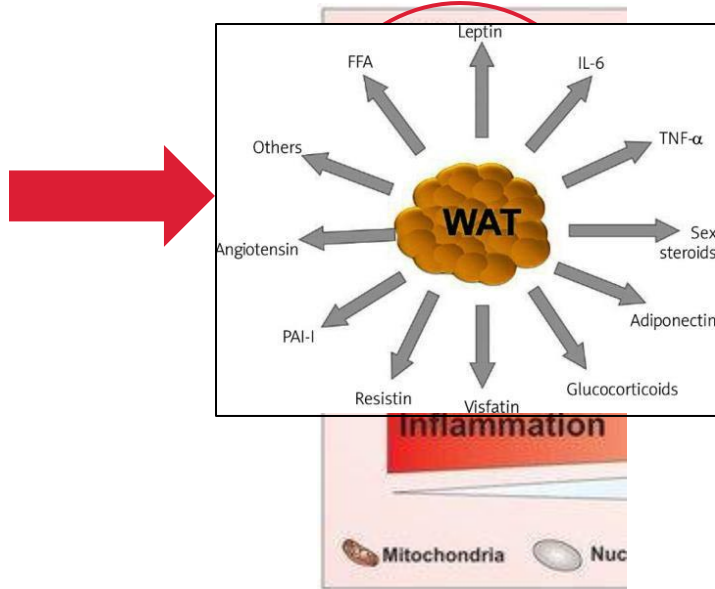


# The adipose organ



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

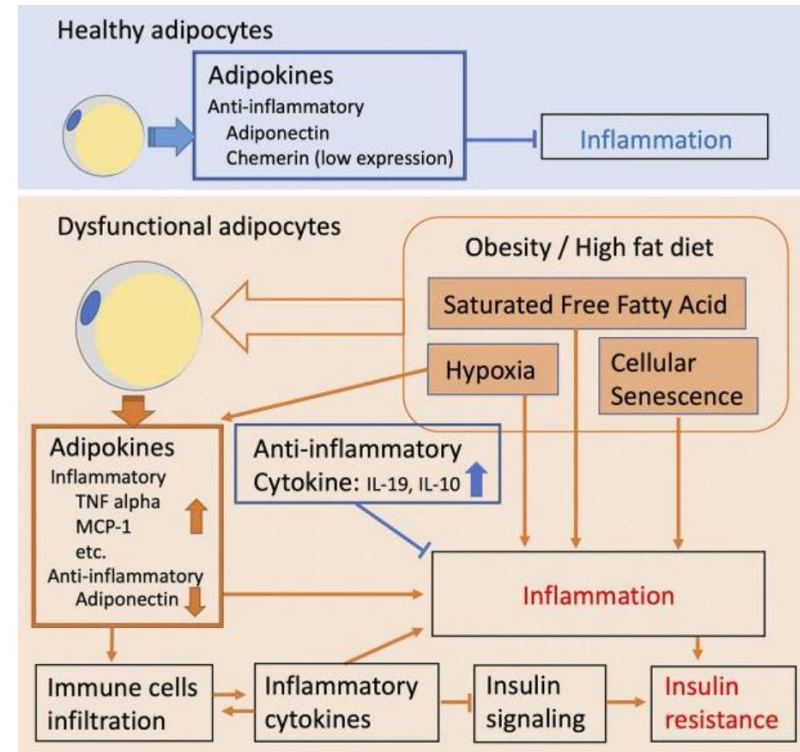
# White adipose tissue (WAT)



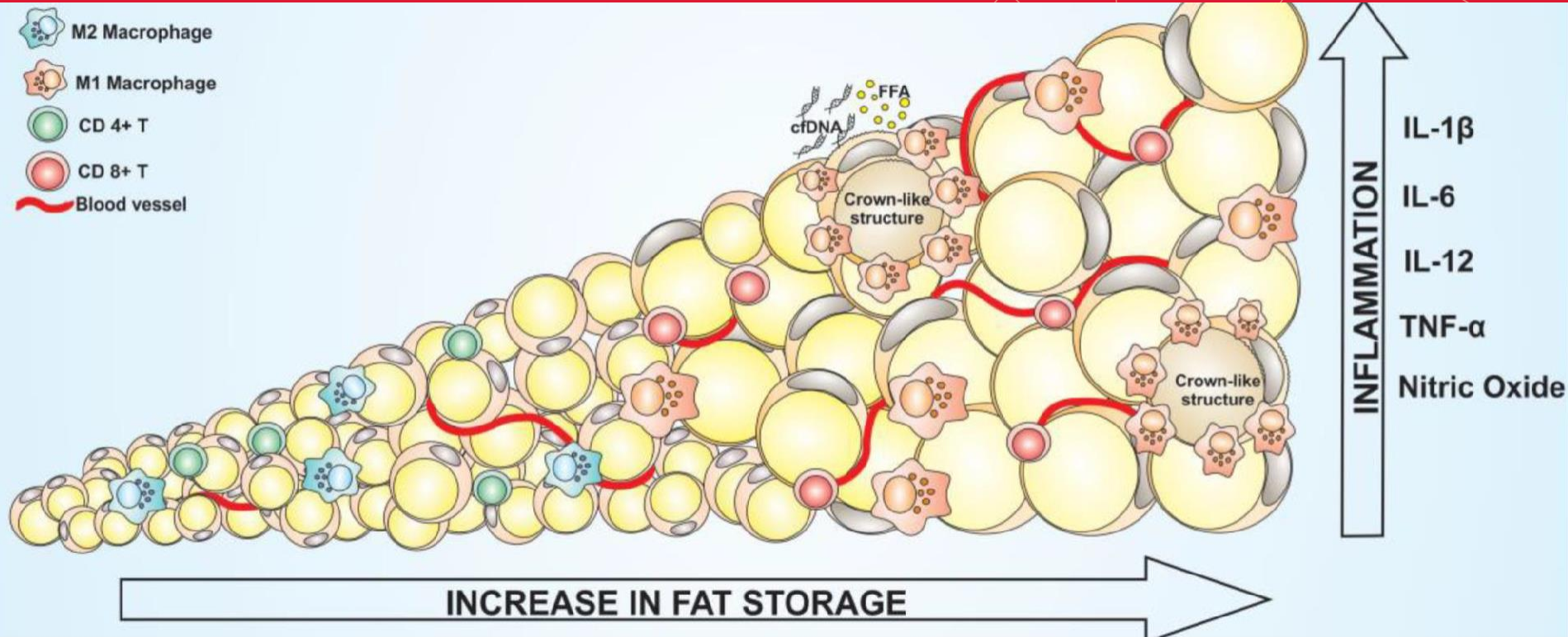
- ✓ Primary site for energy storage in the form of lipid
- ✓ Major endocrine organ
  - produces and secretes adipokines
  - responds to a variety of circulating metabolites and hormones (i.e. lipids, growth hormone, cortisol, insulin, catecholamines, etc.)
  - plays a role in glucose homeostasis

# Pathophysiology of adiposopathy

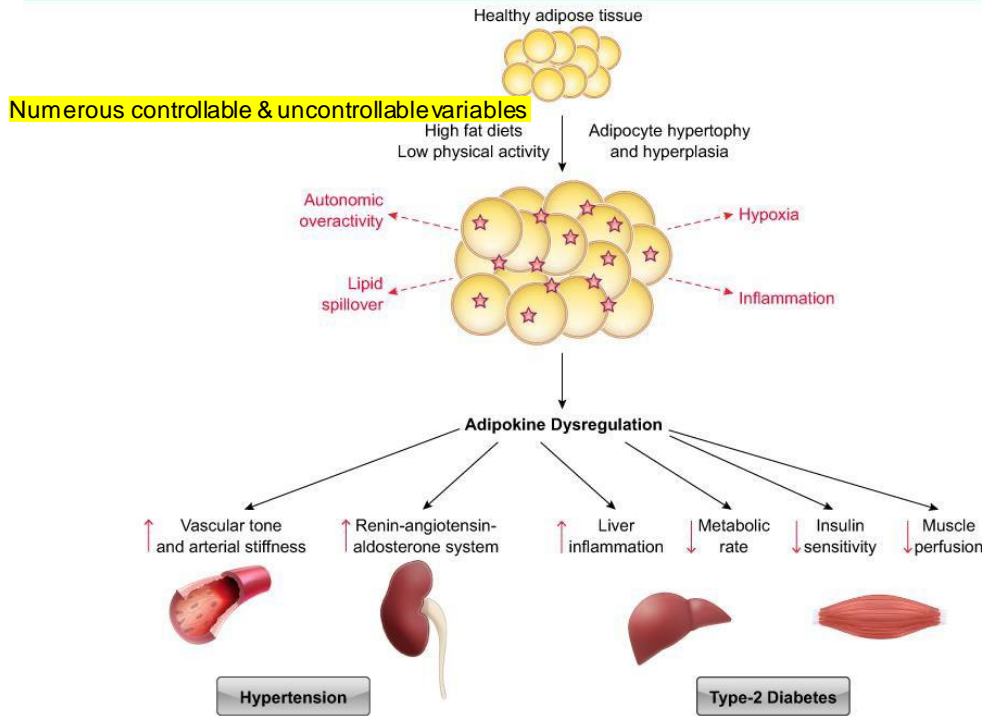
- **On cellular level, adiposopathy (“sick fat”), aka lipotoxicity** leads to excessive energy storage in the form of fat.
- **Exact mechanisms of the initial inflammatory trigger remains unknown at this time**
- Oxidative stress, mitochondrial dysfunction, immune dysfunction, chronic low-grade inflammation 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

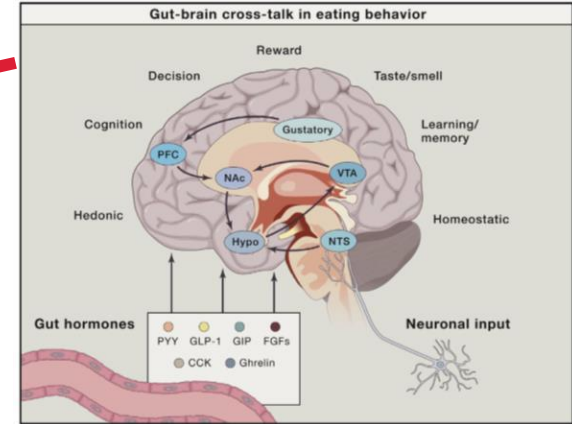
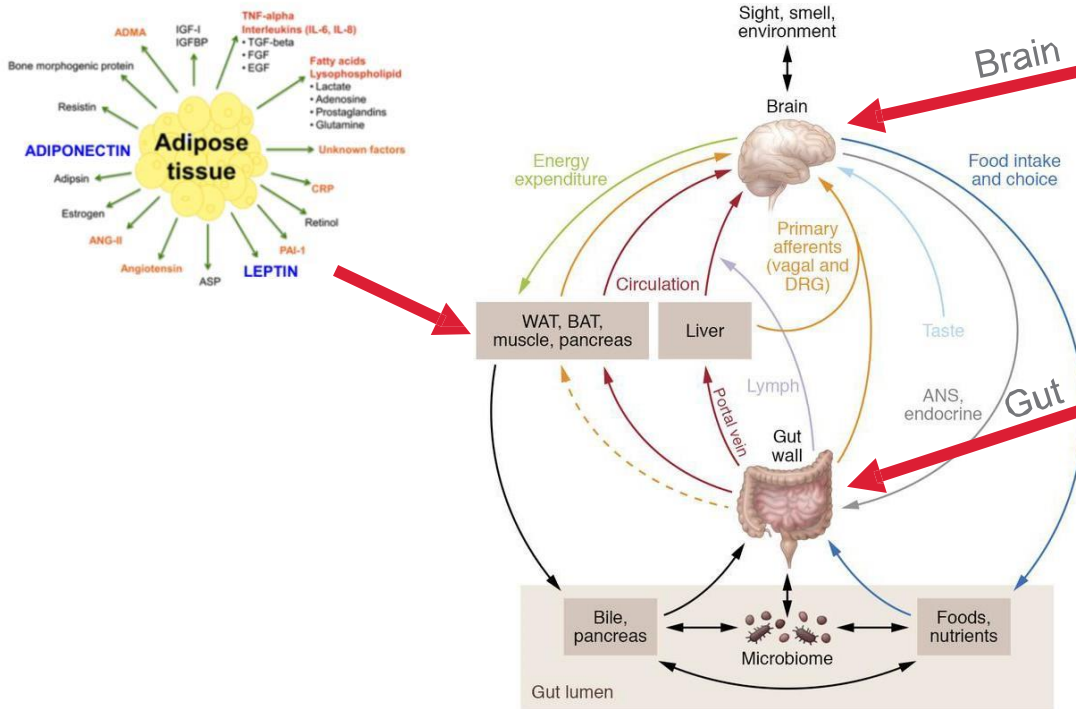


# Adipose Inflammation Leads to Organ Dysfunction



*“Despite its low-grade nature, adipose tissue inflammation negatively impacts remote organ function, a phenomenon that is considered causative of the complications of obesity”*

# The Interplay of Gut-Brain-Microbiota Axis and Adipose Tissue



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 pathophysiology involving complex interactions among genes, biological factors, the environment, and lifestyle.

#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***



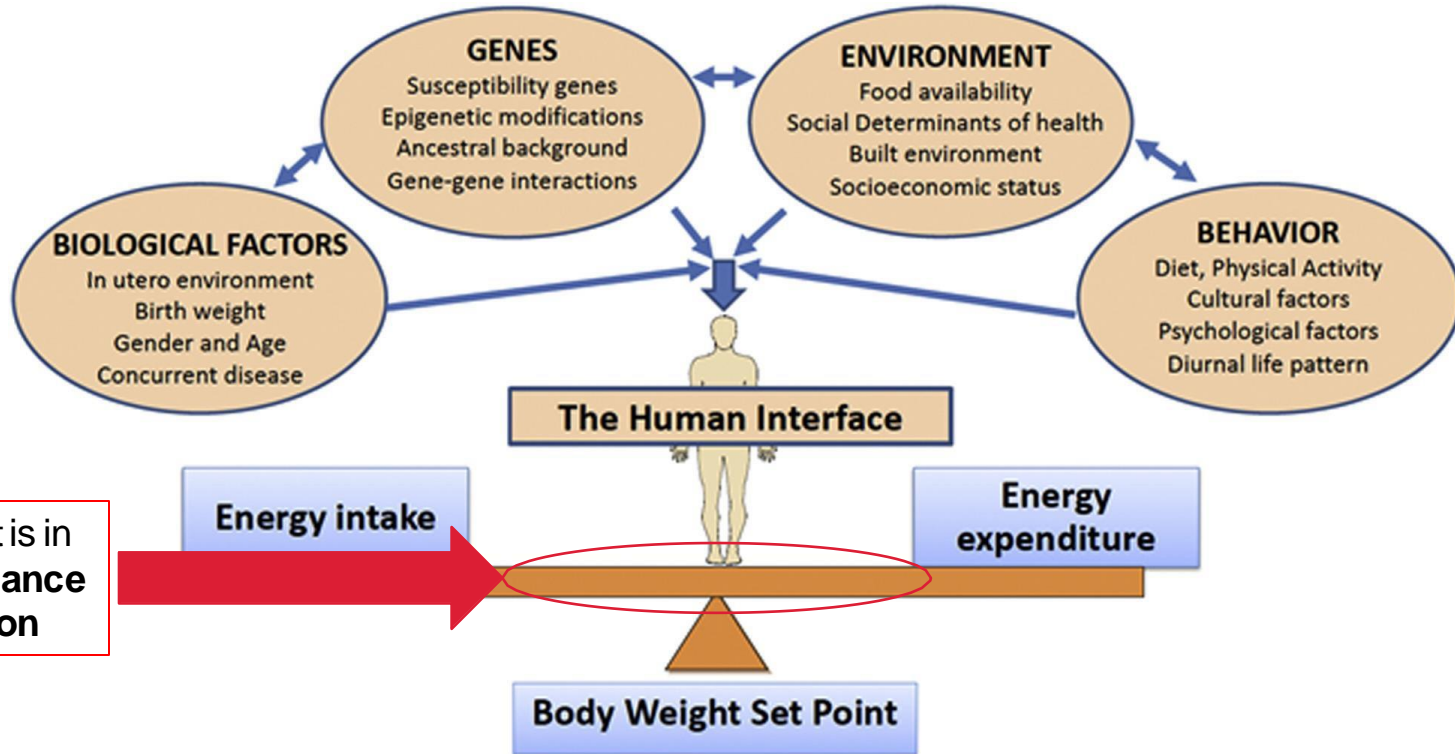
**Proposed by AACE and EASO**  
*A New Diagnostic Term for Obesity:*  
**Adipose-Based Chronic Disease  
(ABCD)**

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



# Contributors to Weight – Uncontrollable and Controllable

<b>Genetics</b>
<b>Prenatal and Postnatal health</b>
<b>Environment</b>
<b>Trauma</b>
<b>Victim of Weight Bias and/or Stigma</b>
<b>Unhealthy diet</b>
<b>Eating patterns</b>
<b>Little or no exercise</b>
<b>Inadequate sleep/Circadian Rhythm disruption</b>
<b>Sedentary behaviors</b>
<b>Pregnancy</b>
<b>Age</b>
<b>Menopause</b>
<b>Life changing event</b>
<b>Weight Promoting Medications</b>
<b>Medical illness</b>
<b>Stress</b>
<b>Alcohol use</b>
<b>Quitting Smoking</b>
<b>Mental health</b>

# Genetics

- 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



# 'Genetic dice are loaded against' ~~obese people~~ <sup>People with obesity</sup>

By Ana Sandoiu | Published Friday 25 January 2019

Fact checked by Isabel Godfrey

ADVERTISEMENT

## 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

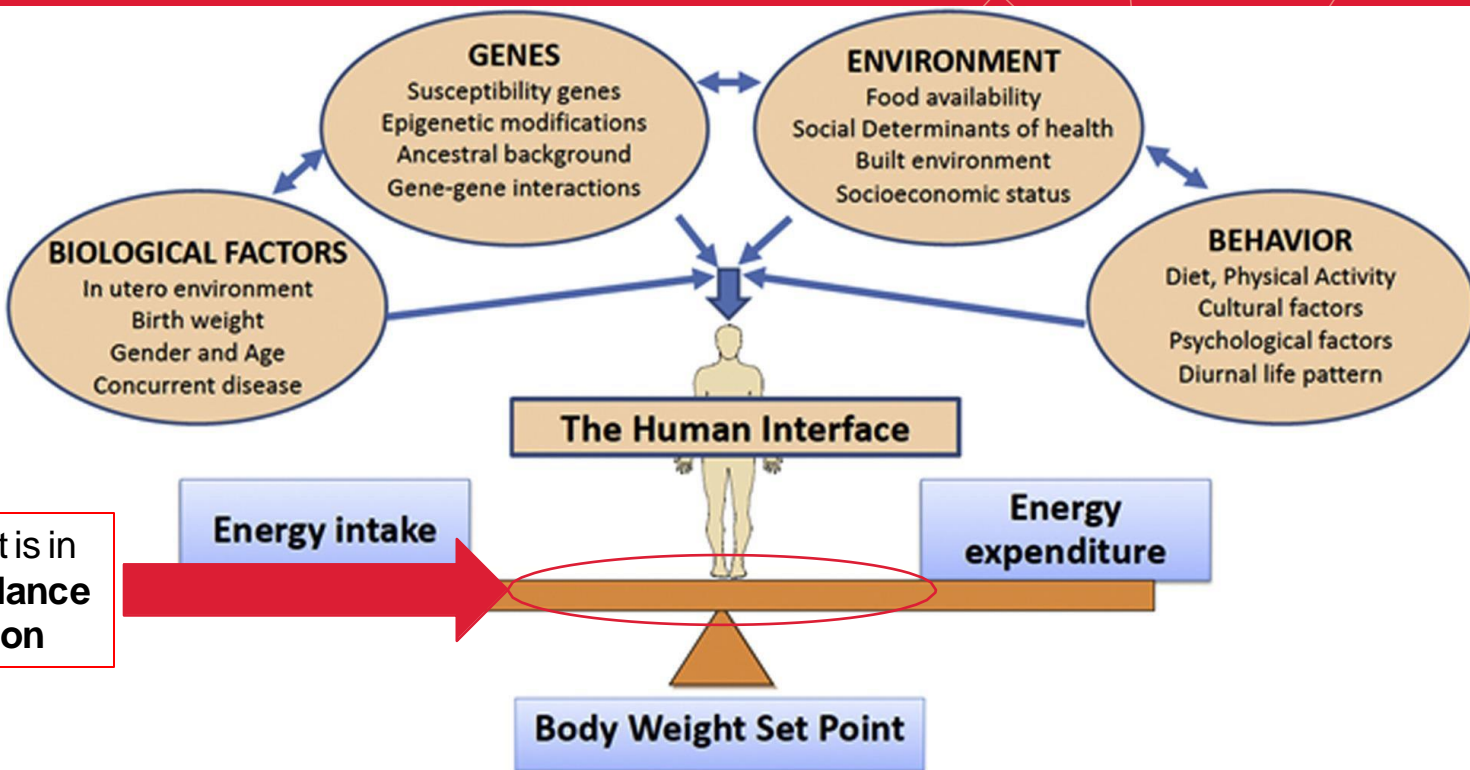


# Environment

- 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



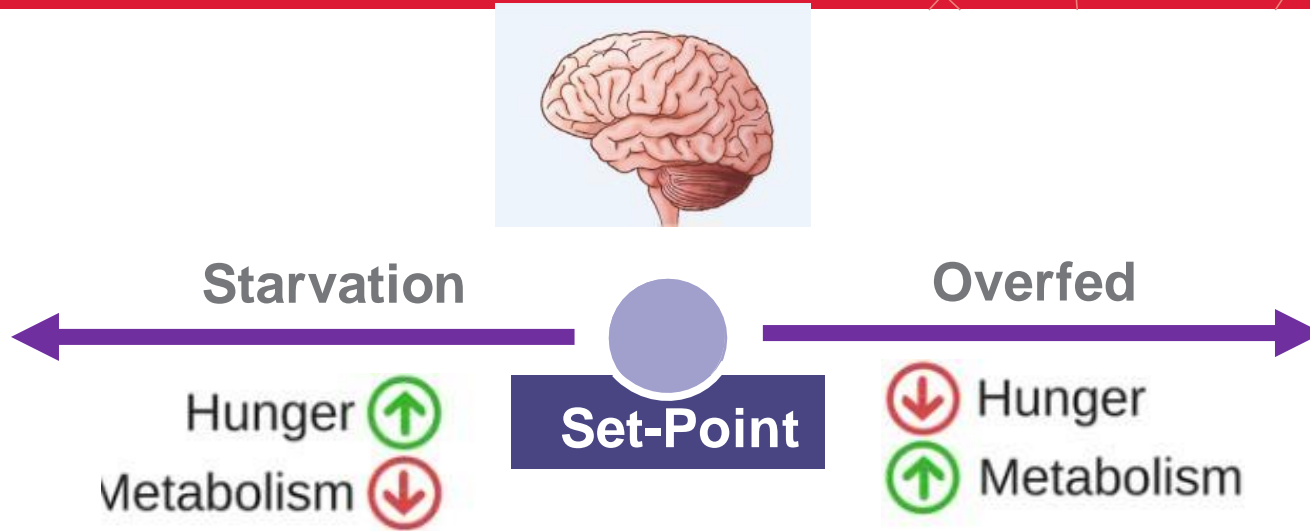
# Obesity is a multifactorial pathology



**Discuss the set point theory and why it is so difficult to lose weight and maintain it**

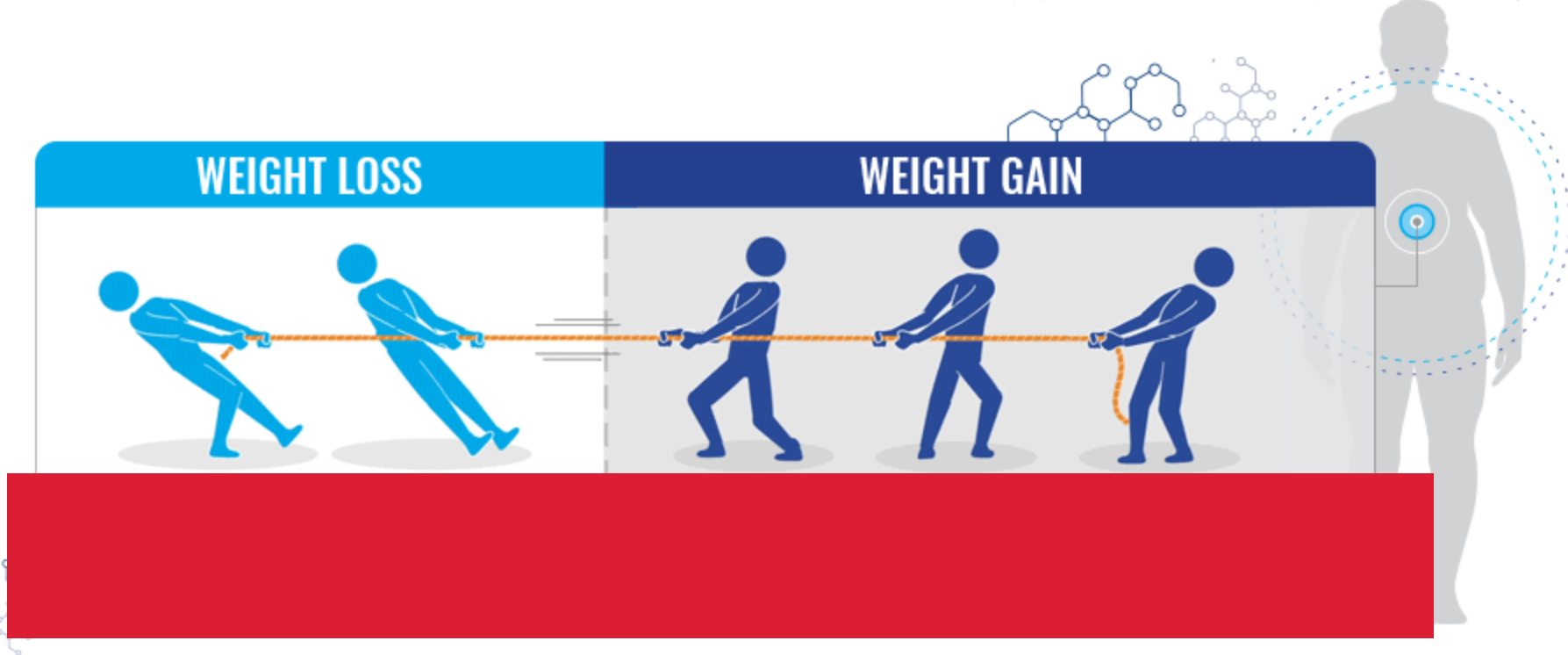


# The set-point theory

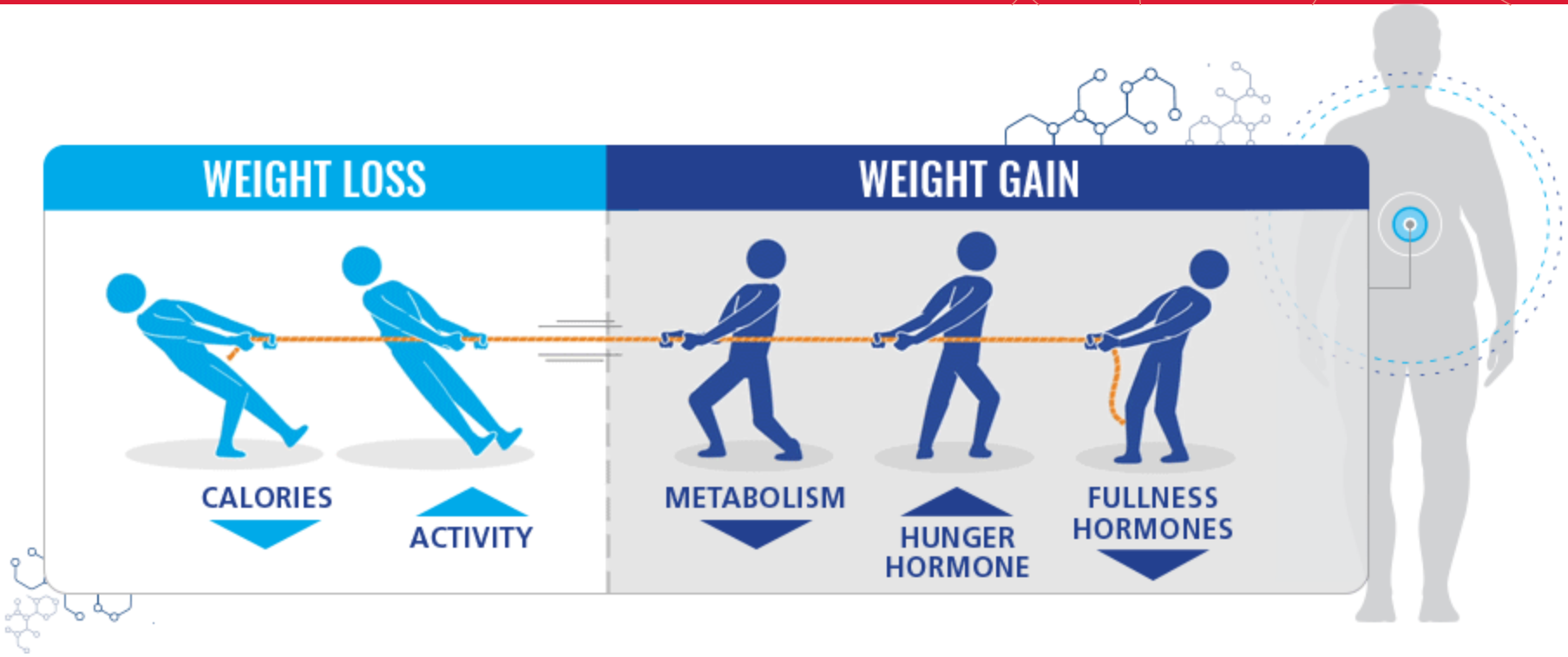


“The brain is the primary organ responsible for body weight regulation operating mainly below our conscious awareness via complex endocrine, metabolic, and nervous system signals to control food intake in response to the body’s dynamic energy needs as well as environmental influences”

# Why is it so hard to lose weight and keep it off?



# Why is it so hard to lose weight and keep it off?



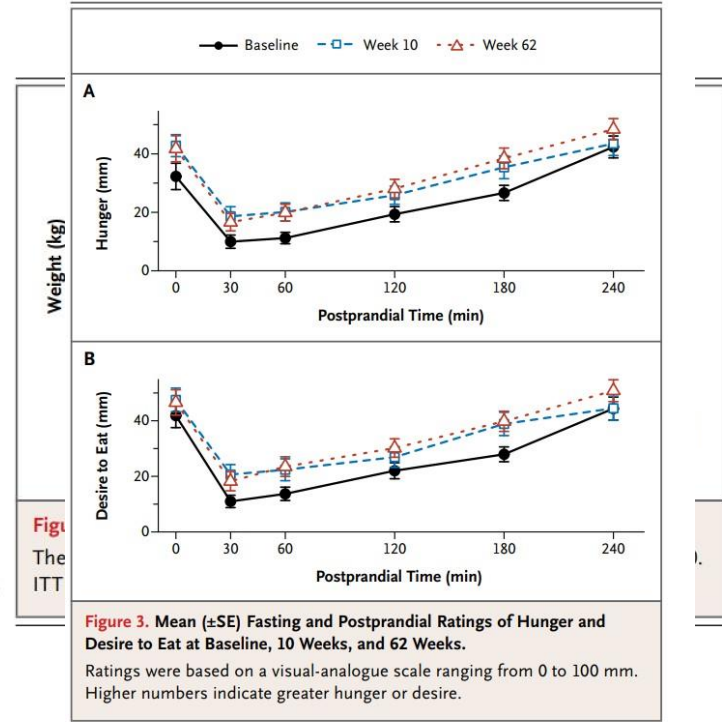
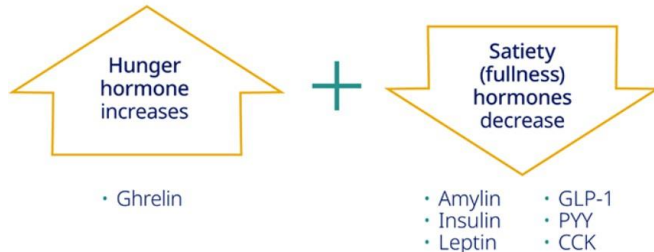
# Sustained Changes in Peripheral Signals for Up to One Year Following Weight Loss

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Long-Term Persistence of Hormonal Adaptations to Weight Loss

Priya Sumithran, M.B., B.S., Luke A. Prendergast, Ph.D., Elizabeth Delbridge, Ph.D., Katrina Purcell, B.Sc., Arthur Shulkes, Sc.D., Adamandia Kriketos, Ph.D., and Joseph Proietto, M.B., B.S., Ph.D.



# Adaptive Responses to Weight Loss

TABLE 1.2  
Adaptive Responses to Weight Loss That Promote Weight Regain

Domain	Parameter	Response to Weight Loss
Appetite	Subjective experience	Hunger increases
	Hormones and neurotransmitters	Satiety falls
	Rewarding properties of food	Leptin falls
		Ghrelin rises
Energy expenditure	Total energy expenditure	Decreases
	Resting energy expenditure	Decreases
	Physical activity, and thermic effect of food	Decreases
Metabolism	Insulin resistance	Increases
	Fat oxidation	Decreases
	Adipogenesis	Increases

**NET RESULT OF THESE ADAPTIVE RESPONSES :**

- 1) MAKES YOU WANT TO EAT MORE**
- 2) BURN LESS ENERGY**
- 3) STORE FAT**

**= HARDER TO LOSE AND MAINTAIN YOUR WEIGHT**

Increased number of new adipocytes

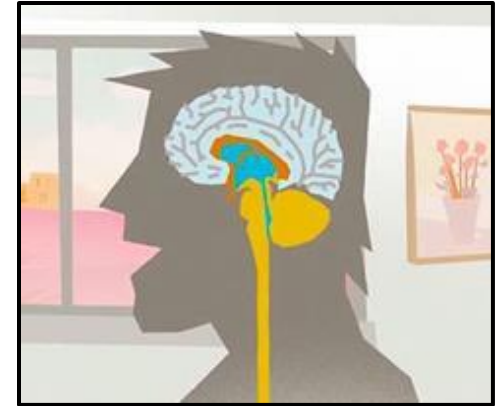
# Biological Adaptations

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

- Evidence suggests adaptations 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**

# Treatment Modalities

## 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





# 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

BMI (kg/m <sup>2</sup> )	Treatment Plan
> 25	Reduced calorie diet, exercise, behavioral modification
≥27-30 + co-morbidity	Consider adding pharmacotherapy Consider bariatric endoscopy procedure
≥ 30	Consider adding pharmacotherapy Consider bariatric endoscopy procedure
≥35-40 + co-morbidity	Consider bariatric surgery
≥ 40	Consider bariatric surgery

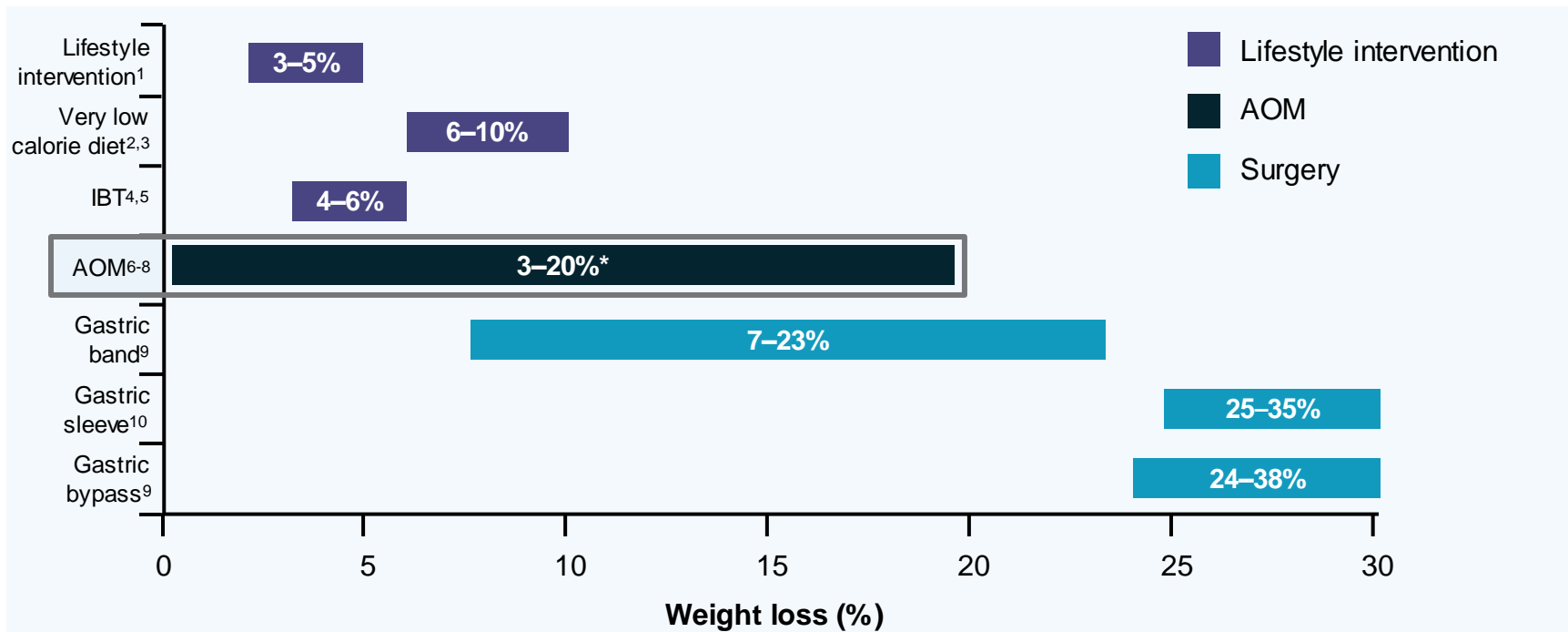
# 2023 ASMBS/IFSO Update to NIH Statement

- **BMI  $\geq 35$**  regardless of presence, absence, or severity of co-morbidities.
- BMI of 30-34.9 **with presence of metabolic disease**
- Asian population:
  - BMI  $\geq 25$  kg/m<sup>2</sup> suggests clinical obesity
  - BMI  $\geq 27.5$  kg/m<sup>2</sup> consider MBS
- Appropriate adolescents should be considered

# FDA Approved Medications for Weight Management

Agents	Mechanism of Action	Effect	Approval Date
Orlistat (Xenical® or Alli®)	<ul style="list-style-type: none"> <li>• Pancreatic lipase inhibition</li> </ul>	<ul style="list-style-type: none"> <li>• Reduces fat absorption</li> </ul>	<ul style="list-style-type: none"> <li>• 1999</li> </ul>
Phentermine	<ul style="list-style-type: none"> <li>• Sympathomimetic</li> </ul>	<ul style="list-style-type: none"> <li>• Appetite regulation</li> </ul>	<ul style="list-style-type: none"> <li>• 1959</li> </ul>
Phentermine/topiramate ER (Qsymia®)	<ul style="list-style-type: none"> <li>• Sympathomimetic</li> <li>• Anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)</li> </ul>	<ul style="list-style-type: none"> <li>• Appetite regulation</li> </ul>	<ul style="list-style-type: none"> <li>• 2012</li> </ul>
Naltrexone/bupropion SR (Contrave®)	<ul style="list-style-type: none"> <li>• Opioid receptor antagonist</li> <li>• Dopamine/noradrenaline reuptake inhibitor</li> </ul>	<ul style="list-style-type: none"> <li>• Appetite regulation</li> </ul>	<ul style="list-style-type: none"> <li>• 2014</li> </ul>
Liraglutide (Saxenda®)	<ul style="list-style-type: none"> <li>• GLP-1 receptor agonist</li> </ul>	<ul style="list-style-type: none"> <li>• Appetite regulation</li> </ul>	<ul style="list-style-type: none"> <li>• 2014</li> </ul>
Semaglutide (Wegovy™)	<ul style="list-style-type: none"> <li>• GLP-1 receptor agonist</li> </ul>	<ul style="list-style-type: none"> <li>• Appetite regulation</li> </ul>	<ul style="list-style-type: none"> <li>• 2021</li> </ul>

# Efficacy of existing weight loss interventions



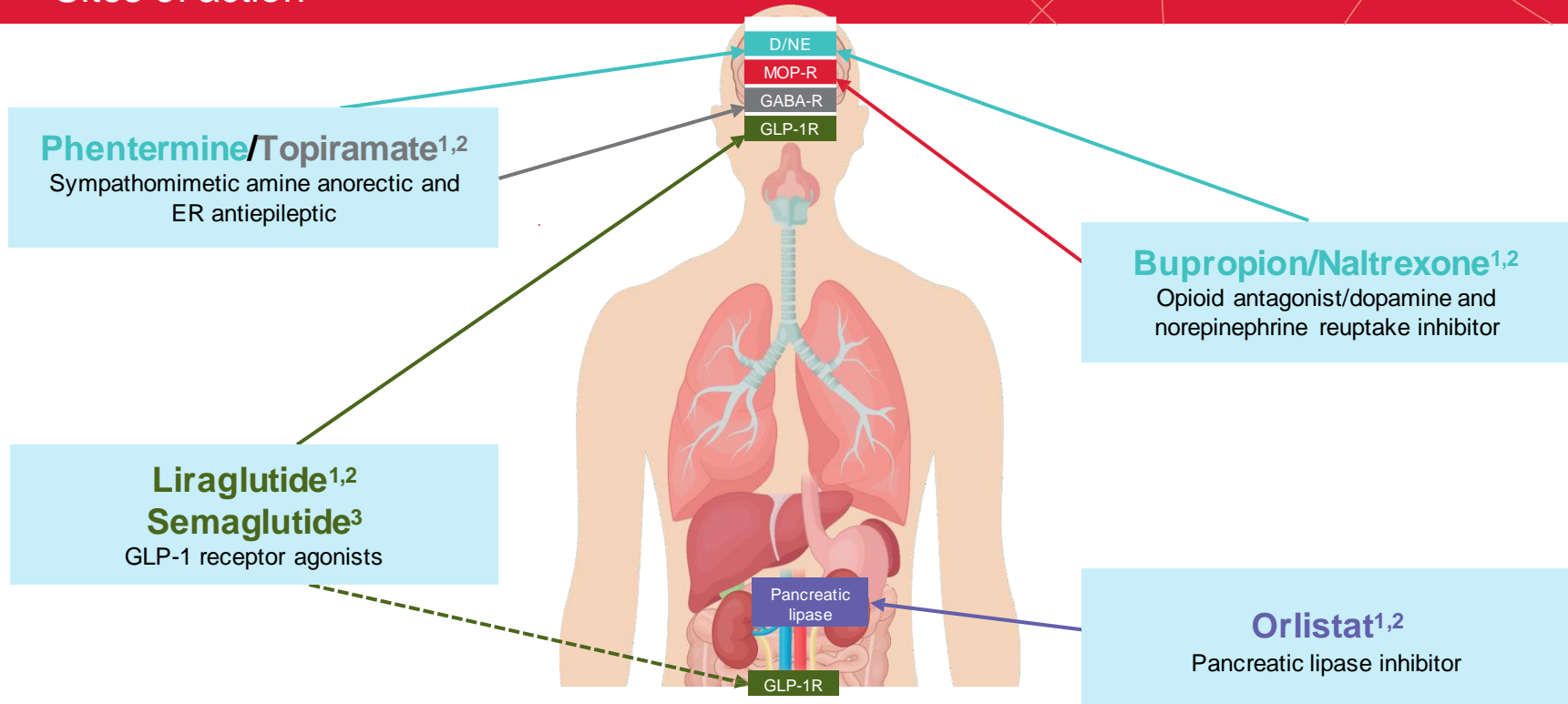
\*Based on mean weight loss achieved by the completer populations in the largest phase 3 clinical trial of each respective product's clinical development program as reported in the AACE Guidelines (2016).

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

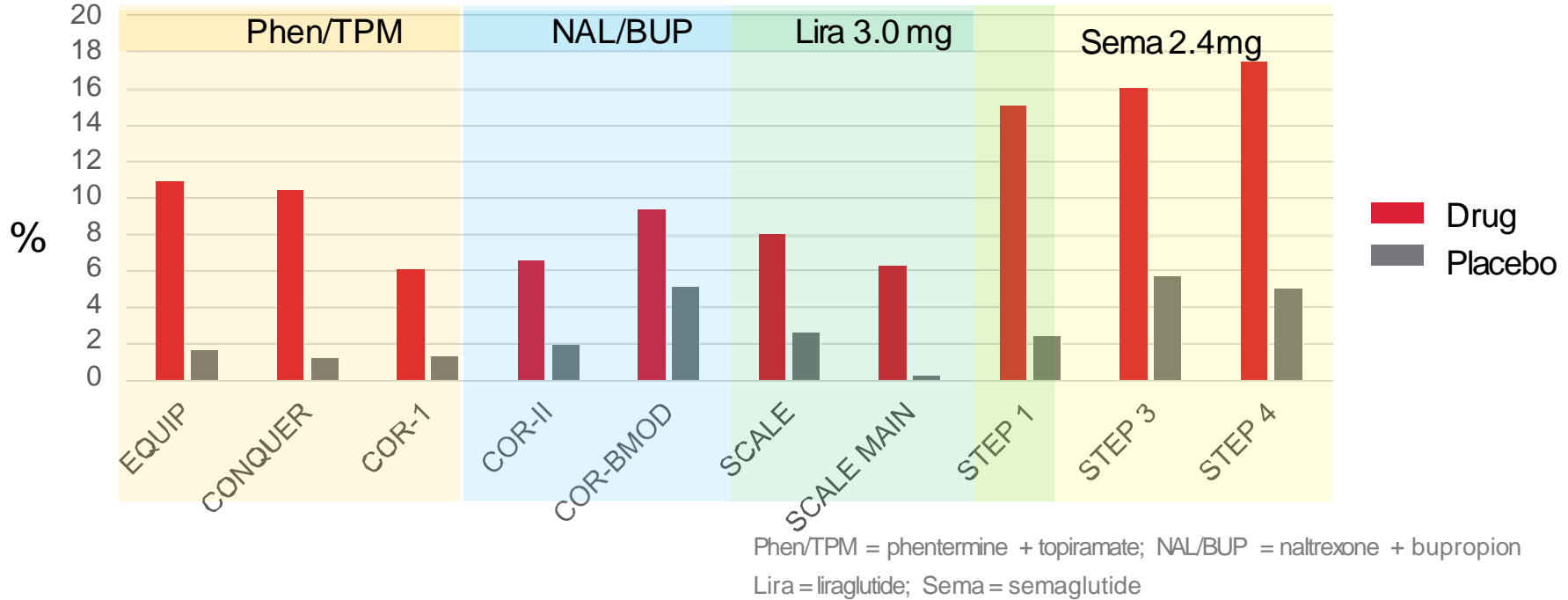
1. Le Roux CW et al. *Lancet* 2017;389:1399–409; 2. Lean ME et al. *Lancet* 2018;391:541–51; 3. Tsai AG and Wadden TA. *Obesity* 2006;14:1283–93; 4. Wadden TA et al. *Obesity* 2011;19:1987–98; 5. Wadden TA et al. *Obesity* 2019;27:75–86; 6. Garvey WT et al. *Endocr Pract* 2016;22(Suppl. 3):1–203; 7. Tak YJ and Lee SY. *Curr Obes Rep* 2021;10:14–30; 8.10. Novo Nordisk Wegovy (semaglutide). Package Insert. Available at: <https://www.novo-nordisk.com/wegovy.pdf>. Accessed August 2022; 9. Courcoulas AP et al. *JAMA* 2013;310:2416–25; 10. IFSO Sleeve Gastrectomy. Available at: <https://ifso.com/patient-sleeve-gastrectomy/>. Accessed August 2022;

# Approved anti-obesity medications

## Sites of action



# Percent Weight Loss (Drug versus Placebo) for 3 AOMs



ORIGINAL ARTICLE

## 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\*

N Engl J Med 2021;384:989-1002

### 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

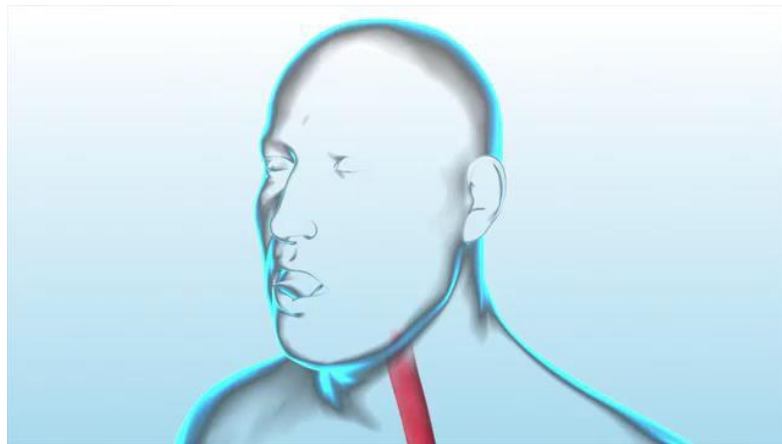


# Emerging Anti-Obesity Pharmacological Therapies

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

# 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%

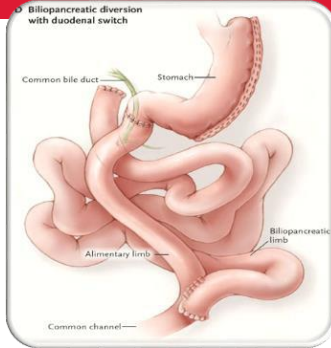


# Endoscopic Sleeve Gastroplasty (ESG)

- 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%



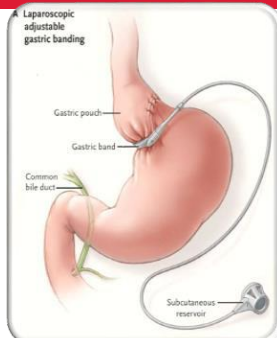
# Bariatric Surgeries



## Malabsorption

Reduce Absorption

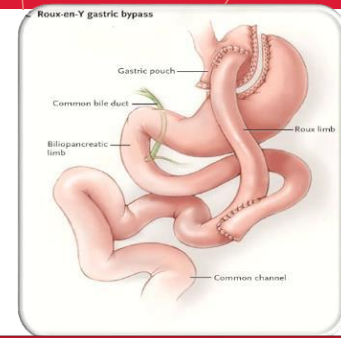
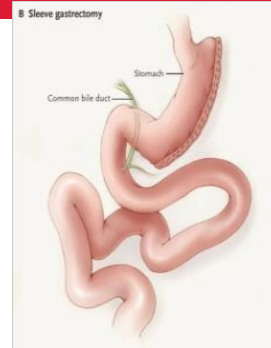
- Biliopancreatic diversion with Duodenal Switch



## Restriction

Pouch Limits Quantity

- Gastric Banding
- Vertical Sleeve Gastrectomy

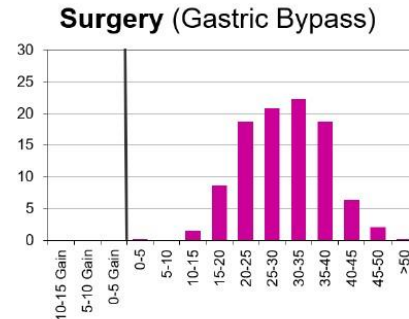
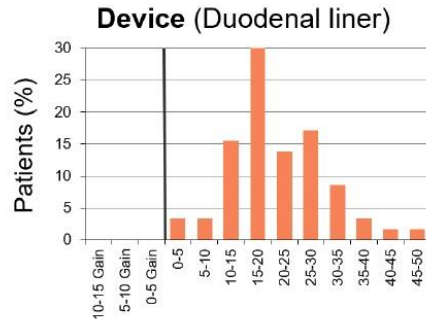
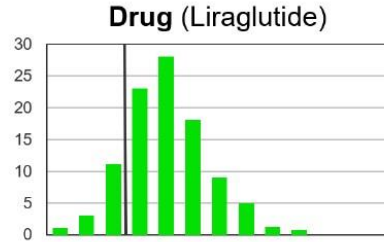
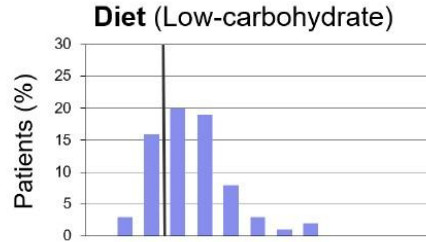


## Combination

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

Source: Presentation by Lee Kaplan, 30<sup>th</sup> Blackburn Course in Obesity Medicine, Treating Obesity 2017



**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



# Center for Weight Management and Metabolic Health – Our Team



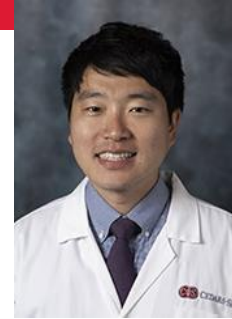
Miguel Burch, MD,  
FACS

Scott Cunneen, MD,  
FACS



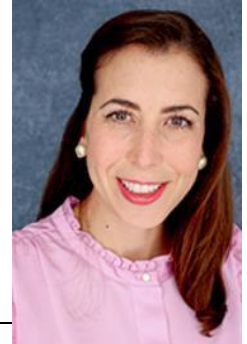
Kulmeet Sandhu, MD,  
FACS, FASMBS

Rabindra Watson, MD



Ken Park, MD

Amanda Velazquez, MD  
DABOM



- **Extensive experience since 1999**

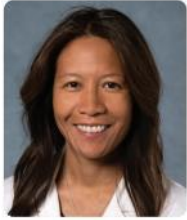
- Over 4,000 weight loss operations
- 300+ per year
- Best-in-class outcomes

- **World-class research**

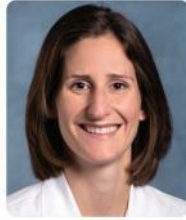
- Electrical gastric pacemaker, LapBand® study, Realize™ band study, TOGa (first endoluminal weight loss procedure)



# 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 19<sup>th</sup> 2:45 PM-3:30 PM



14<sup>th</sup> Annual Living Donation  
Conference