Dysadiposity:
Pathophysiology and Treatment Strategies

> "***Obesity is a complex, multifactorial condition*** *characterized by excess body fat. It must be viewed as a* ***chronic disorder*** *that essentially* ***requires perpetual care, support, and follow-up****. Obesity causes many other diseases, and it* ***warrants recognition by health-care providers and payers****."*[10]

AACE. ACE

American Association of Clinical Endocrinologists
American College of Endocrinology Obesity Task Force

Eric S. Langer, D.O., MACOI, FACE, FEAA, C.C.D.
Past President – Michigan Chapter – American Association of Clinical Endocrinologists
Member, Board of Directors – American Diabetes Association, Michigan Chapter
Associate Clinical Professor, Department of Internal Medicine
Michigan State University-College of Osteopathic Medicine
Clinical Assistant Professor Internal Medicine – Oakland University –
William Beaumont School of Medicine

Disclosures

- **Compensated**
- **Speaker's Bureau**:
  - Novo Nordisk Pharmaceuticals
  - IBSA Pharmaceuticals
  - Medtronic Diabetes
- **Advisory Board**:
  - IBSA Pharma, Inc.
- **Non-Compensated**
- International Society of Clinical Densitometry (ISCD) Task Force Practice Analysis Committee for CCD Certification

Discussion Overview

Learning Objectives

- Recognize the “Paradigm Shift” of Obesity as a Weight/BMI-Centric Diagnosis to a clinically acknowledged **Adiposity-Based Chronic Disease**
- Define Obesity from its **Clinical Perspective**
- Appreciate the pathophysiology of Obesity in terms of **Dysadiposity** an its relevance to other chronic disease states.
- Highlight **Treatment Guidelines** specific to the pathology of Dysadiposity
- Review the **Pharmacologic Treatment** Strategies currently available for Dysadiposity

Key Phrases/Terms

- **Dysadiposity**
- **Central Obesity**
- **Visceral Obesity**
- **POM-C & AgRP-NPY Neuronal Pathways**

Evolution of a "Pathology Recognized"

- **2013**: ***American Medical Association*** (AMA) designated **Obesity as a Chronic Pathology**.

- **2014**: ***American College of Cardiology*** (ACC), ***American Heart Association*** (AHA), and ***The Obesity Society*** (TOS) published clinical practice **guidelines** for the management of **Adult Overweight and Obesity Pathology**.

- **2016**: ***American Association of Clinical Endocrinologists*** (AACE) and ***American College of Endocrinology*** (ACE) published **Evidence-based Clinical Practice Guidelines** **that expanded upon**:
  - The AMA's **"Pathology-recognized"** designation
  - AACE's novel **Diagnostic Paradigm: Integrating Body Mass Index (BMI) with Weight-related Complications**
  - AACE's **Clinical Approach: *Targeting Weight-related Complications* rather than a Weight-Loss** as the primary therapeutic objective.

The AACE/ACE documents

are currently the most accepted treatment standard for Obesity.

Evolution of a "Pathology Recognized"

- **2017**: **AACE** **Position Statement** clarified Obesity diagnostic terminology:
  - ***Adiposity-Based Chronic Disease*** (**ABCD**)
  - Merging **chronicity and adiposity** as the **clinical components responsible for the resultant morbidity**.

This **Paradigm Shift** now reflects a **Weight/BMI-centric Diagnostic transition** to a **Clinically-based** **ABCD** terminology that acknowledges:

- **What** **clinicians are treating:**
  - **"Dysadiposity"** → **Adipose Tissue as an "Operational Organ"** (**influenced by mass, distribution, and functionality)**
- **Why** **they are treating it** (***Chronic Disease with complications***).

Health Alert Perspective

As of 2021, the **WHO** reported (***based upon 2016 data***)

> 1 Billion people globally are obese:

- 650 million adults
- 340 million adolescents
- 39 million children

- **By 2025** → **≈ 167 Million more** will acquire an "obese status"

Obesity considered:

- **2nd most common** (soon to be 1st) **preventable cause of cancer** (after cigarette smoking)
  - Definitive catalyst for developing Type 2 Diabetes and CVD

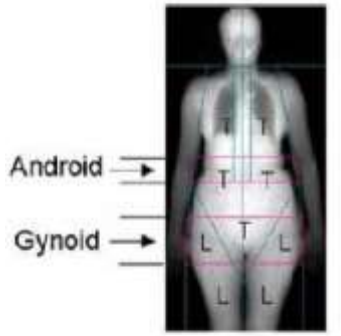
The estimated **Annual Medical Cost** of obesity in the United States:

Nearly $180 billion

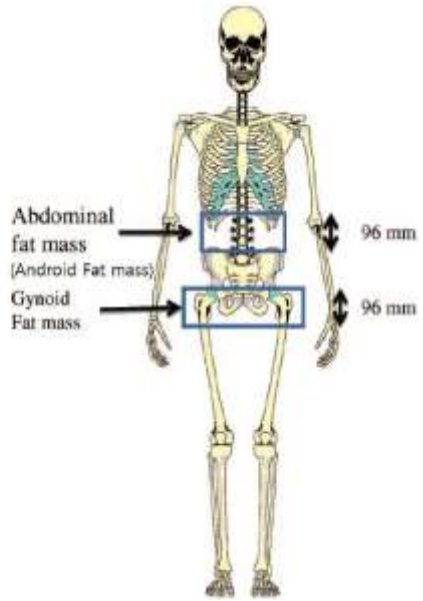
Evolution of a "Pathology Recognized"

- **March 2023**: **American Association of Clinical Endocrinology Consensus Statement was developed to:**
  - **Address the Stigma and Bias as Contributors of Disease Severity**
  - **Recognize Obesity as a**:
    - **Complex condition with variable clinical phenotypes**.
    - **Pathology of Diverse Behavioral and Neuroendocrine Influences that alter body's *Adipose "Set-Point"***.

- **"NEW" term of Adiposopathy ("Sick Fat Disease") → Dysadiposity**
  - Defines **Pathologic Role** of adipose tissue and "**Pro-inflammatory" physiology**
  - Result of "**Adipocyte Hypertrophy**"
  - Recognizes ***Regional Distribution*** concept **("Body Shape")**
    - **Android (*Central*) Adiposity**: **Visceral Fat**
      - ***Intra-abdominal** (i.e. omentum, mesentery, liver, and pancreas)*
      - ***Ectopic-abdominal** (i.e. pericardium, myocardium, and skeletal muscle)*
      - ***Pro-inflammatory***
    - **Gynoid (*Gluteal-Hip*) Adiposity**: Subcutaneous Fat
      - ***"Protective Distribution Depot"***
      - **Prevents "lipid spill-over" into Visceral sites**.



DXA fat regions



Evolution of a "Pathology Recognized"

Much has changed since the evolution of our current framework of Interventional Guidelines:

- **The FDA approved 4 new medications (2012 → 2014) for Long-term Treatment of Obesity**:
  - **Phentermine + Topiramate** (**Qsymia®**; VIVUS)
  - **Naltrexone + Bupropion** (**Contrave®**; Currax Pharmaceuticals)
  - **Liraglutide** (**Saxenda®**; Novo Nordisk)
  - **Lorcaserin** (**Belviq®**; Arena Pharmaceuticals/Eisai)

- **An Anti-Obesity Medication was withdrawn from the market**: **2020**
  - **Lorcaserin** (**Belviq®**; Arena Pharmaceuticals/Eisai)

- **Another long-term Anti-Obesity Medication was approved**: **2021**
  - **Semaglutide** (**Wegovy®**; Novo Nordisk)

- **Several Procedures for Weight Loss & Weight Management were recommended/FDA-approved**:
  - ***American Society for Metabolic and Bariatric Surgery***-Endorsed and/or FDA-Approved Procedures for Weight-Loss

Approved Procedural Treatment Strategies for Weight-Loss

TABLE 4. ASMBS-Endorsed and/or FDA-Approved Procedures for Weight-Loss[15,16,AAA]

Procedure	Target weight loss, %	Favorable aspects	Unfavorable aspects
Laparoscopic adjustable gastric banding	20%-25%	No anatomic alteration Removable Adjustable	High explant rate Erosion Slip/prolapse
Sleeve gastrectomy	25%-30%	Easy to perform No anastomosis Reproducible Few long-term complications Metabolic effects Versatile for challenging patient populations	Leaks difficult to manage Little data beyond 5 yr 20%-30% GERD
Roux-en-Y gastric bypass	30%-35%	Strong metabolic effects Standardized techniques <5% major complication rate Effective for GERD Can be used as second stage after sleeve gastrectomy	Few proven revisional options for weight regain Marginal ulcers Internal hernias possible Long-term micronutrient deficiencies
Biliopancreatic diversion with duodenal switch	35%-45%	Very strong metabolic effects Durable weight loss Effective for patients with very high BMI Can be used as second stage after sleeve gastrectomy	Malabsorptive 3%-5% protein-calorie malnutrition GERD Potential for hernias Duodenal dissection Technically challenging Higher rate of micronutrient deficiencies than roux-en-Y gastric bypass
Single anastomosis duodeno-ileal bypass with sleeve gastrectomy	35%-45%	Single anastomosis Simpler to perform than biliopancreatic diversion with duodenal switch Strong metabolic effects Low early complication rate	Little long-term data Nutritional and micronutrient deficiencies possible Duodenal dissection
Intragastric balloon	10%-12%	Endoscopic or swallowed Good safety profile	Temporary (6 mo) therapy Temporary nausea/vomiting, pain Early removal rate of 10%-19%
One-anastomosis gastric bypass	35%-40%	Simpler to perform than roux-en-Y gastric bypass More malabsorptive Strong metabolic effects No mesenteric defects	Potential for bile reflux Malabsorptive (long biliopancreatic limb) Little experience in the United States
Transpyloric bulb	14%	Endoscopic Delays gastric emptying	6-mo data Gastric ulcers
Aspiration therapy	12%-14%	Endoscopic Changes eating behavior	1-yr therapy Tube-related problems/complications 26% early removal
Vagal nerve blocking therapy	8%-9%	No anatomic changes Low complication rate (4%)	Pain at neuroregulatory site Explant required for conversion to another procedure

ASMBS, American Society of Metabolic and Bariatric Surgery; BMI, body mass index; GERD, gastroesophageal reflux disease; mo, month; vBloc, vagal nerve-blocking device; yr, year.

[A]ASMBS also endorses bariatric reoperative procedures.[15]

[B]In a 2019 clinical practice guidelines update, the American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, ASMBS, Obesity Medicine Association, and American Society of Anesthesiologists also discussed use of primary obesity surgery endoluminal, Geloxia100 ingested hydrogel capsules (Genesis), and endoscopic sleeve gastroplasty.[16] Endorsements for these procedures and this device do not appear in ASMBS' most recent update.[15]

Reprinted from Endocrine Practice, Vol25/12, Mechanick JI, Apovian C, Brethauer S, et al, Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists, Pages No. 175-247, Copyright (2020), with permission from Elsevier.

Future Pharmacologic Treatment Strategies

Name	Class/Mechanism	Indication	Pros	Cons	Dose
Retatrutide (Eli Lilly)	GIP/GLP-1/Glucagon Receptor **Triagonist** Attaches to GIP and GLP-1 receptors (Like Tirzepatide) and also targets glucagon receptors.	Treatment of obesity	**18% weight loss by 24 weeks, 17% loss by 36 weeks, and 24% reduction by 48 weeks**; meaningful improvements in glycemic control, robust weight reductions; safety profile consistent with GLP-1 and GIP/GLP-1 receptor agonists	**Side effect profile consistent with GLP-1 receptor agonists** and GIP/GLP-1 receptor agonist; mostly gastrointestinal and include mild to moderate nausea, constipation, vomiting and diarrhea	Weekly injection therapy
Orforglipron (Eli Lilly)	Oral **Non-peptide GLP-1 Receptor Agonist** Small non-peptide molecule that is not degraded in the G.I. tract; action at GLP-1 receptor produces cAMP signaling similar to native GLP-1, but promotes low activation of β-arrestin pathway to enhance receptor internalization	For chronic weight management in people with obesity/overweight, and Glucose-lowering in Type 2 diabetes	**dose-dependent 8.6-12.6% weight reduction at 26 weeks and 9.4%-14.7% at 36 weeks**; compared to Liraglutide (9.2% weight reduction at 56 weeks) & Semaglutide (16.9% weight reduction at 68 weeks)	Mild-moderate nausea, constipation, vomiting, diarrhea, and belching most common adverse events; **10-17% across all dose cohorts reported G.I. event as reason for discontinuation**	Daily dose options of 12-mg, 24-mg; 36-mg; and 45-mg; **administered q a.m. as an oral capsule without food or water restrictions**
Tirzepatide (Eli Lilly)	GIP receptor and GLP-1 receptor agonist; Action at the GLP-1 receptor produces cAMP signaling similar to native GLP-1, but promotes low activation of β-arrestin pathway that enhances receptor internalization.	An adjunct to diet and exercise to improve glycemic control in T2D; eventually for obesity or overweight + weight-related comorbidities	**15% weight reduction by 72 weeks**; being studied for treatment of obesity/overwt patients with preserved-EF heart failure, obstructive sleep apnea, and NASH	**mild to moderate nausea, diarrhea, vomiting, constipation, and abdominal pain.** Most stomach side effects lessen/resolve after several weeks of treatment	Weekly injection therapy
Danuglipron (Pfizer)	Organic **low molecular weight compound** with advantage of oral administration and ability to more readily pass through cell membranes to reach intracellular targets;	An adjunct to diet and exercise to improve glycemic control in T2D	Oral agent; no refrigeration; **Doesn't require fasting before or after taking the pill**; using 120 mg dose bid → **loss of ≈10 pounds in 16 weeks**	**Bid dosing**; most common side effects were nausea, diarrhea and vomiting; 34% discontinuation rate.	**40 mg, 80 mg, and 120 mg bid**??

"**Diagnosing**" Obesity/"Dysadiposity"

TABLE 1. Classification of Obesity by BMI in Adult Patients[2,3,12]

BMI,* (kg/m²)	Classification
18.5-24.9	Normal weight
25-29.9	Overweight
30-34.9	Class 1 obesity
35-39.9	Class 2 obesity
≥40	Class 3 obesity

BMI, body mass index.
*BMI values are not dependent upon age or sex. Values may not correspond to the same amount of adiposity in different populations, including certain ethnic groups (specifically, South Asian, Southeast Asian, and East Asian adults).

- **Body Mass Index** (BMI): **Weight:Squared Height (kg/m²) ratio**

- **NOT the optimal diagnostic tool**:
  - Does not address Percent Body Fat; **"crude" measure only**
  - **Confounded by** body frame, muscularity, fluid retention, spinal deformities, physical and transcultural differences.
  - Does not account for CV risk implications

  - Formula developed by **Adolphe Quetelet** (**1832**; Belgian Mathematician) → the ***Quetelet Index***
    - **Probability calculus applied to human physical characteristics and social aptitudes**
    - **Designated BMI by Ancel Keys (1972; nutritionist, epidemiologist) → post WWII concerns of weight and CVD risk in *life insurance policy holders*.**

"**Diagnosing**" Obesity/"Dysadiposity"

- **Endocrine and Inflammatory Role of Adipose Tissue** require:
  - Classifying obesity based upon Body Fat vs. Lean Muscle **Composition** & **Distribution** (***Regional Distribution Concept***)
  - Using ***Waist-to-Hip Ratio*** and ***Waist-Circumference*** as **Co-Proxy Measures of Body Fat Distribution**
  - Characterizing degree of ***Body Fat Percentage*** & ***Genetic Polymorphisms*** to customize interventional strategies

- **Waist-to-Hip Ratio** relates to the ***Regional Distribution Concept***:
  - **Android Conformation: HIGH** waist:hip ratio; **UPPER** (***centripetal***) body obesity
    - **Waist-circumference → Intra**- and **Ectopic-Abdominal Visceral Fat**
    - Adipocytes **EXPAND** (**Hypertrophy**)
  - **Gynoid Conformation: LOW** waist:hip ratio; **LOWER**-body obesity)
    - **Hip-circumference → Subcutaneous Gluteo-femoral Region** (i.e., muscle mass, bone, and fat mass).
    - Adipocytes **INCREASE in number** (**Hyperplasia**)

Hypertrophic Adipocytes

Generate Adipogenic Transcription Factors

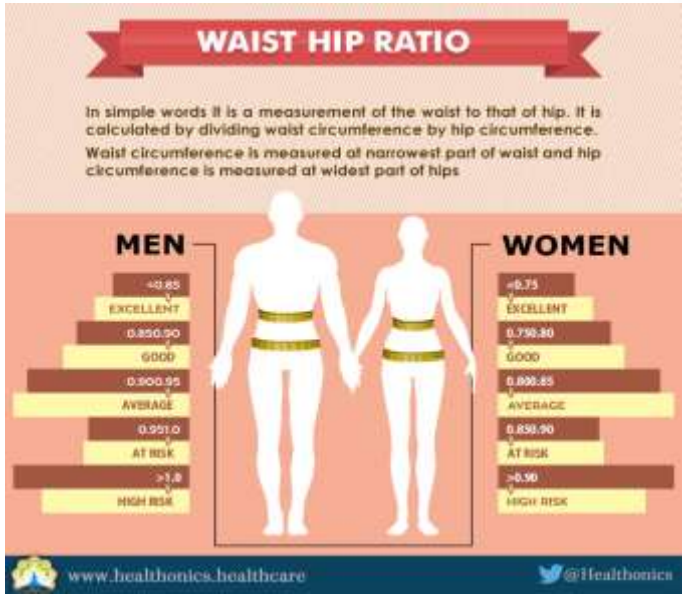
Promote Dysmetabolic Ramifications

"Diagnosing" Obesity/"Dysadiposity"

- **Waist Circumference Scores**
  - **Basic Indicator of CV Risk (↑sensitivity with BMI + Triglyceride "co-marker"):**
    - **Waist circumference ≥40 inches in men → Central Obesity**
    - **Waist circumference ≥35 inches in women → Central Obesity**
      - **Waist circumference alone may underestimate risk on a regional/cultural basis**
      - **≈ 34 inches (Men) and 29-32 inches (Women) → South, Southeast, East Asian pop.**

Criteria for Waist Circumference in Adults				
Waist Circumferences				
Risk Category	Females		Males	
	cm	in	cm	in
Very Low	<70	28.5	<80	31.5
Low	70-89	28.5-35.0	80-99	31.5-39.0
High	90-109	35.5-43.0	100-120	39.5-47.0
Very High	>109	>43.0	>120	>47.0

- **Waist-to-Hip Ratio Scores**
  - **Women: waist should be narrower than hips (≤ 0.80)**
  - **Men: waist should be narrower or same as hips (≤ 0.90)**
  - **Better Implicator of Central Obesity (and CVD risk)**



- **Waist-to-Height Ratio**
  - **BEST Diagnostic/screening tool for Central Obesity (less dependent on age & sex)**
  - **Optimal is ≤ 0.49 (associated with increased life expectancy)**
  - **Preferred risk predictor** of Type 2 Diabetes and CVD.

Providers now rely on a combination of measures to advise on Weight-Related Risk.

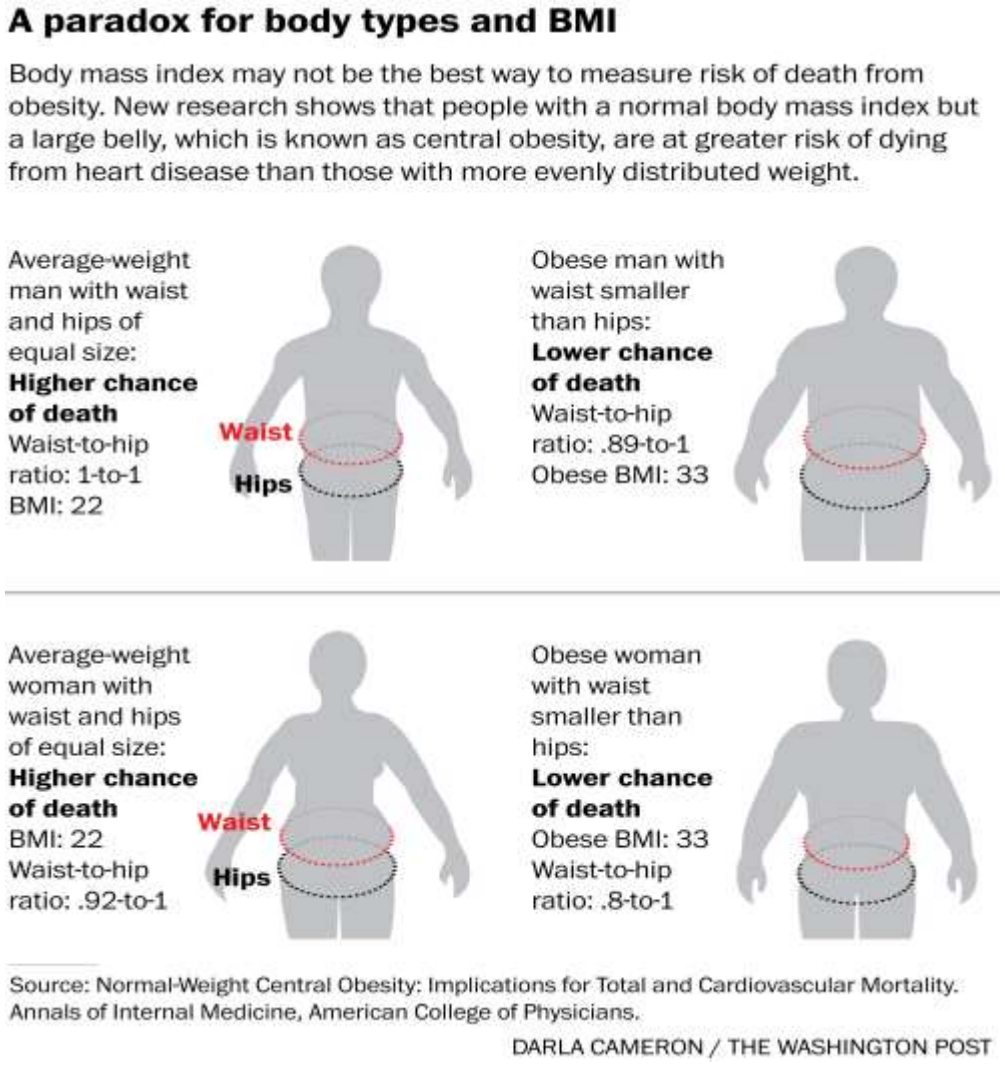
("Overweight" Category in particular)

“Diagnosing” Obesity/“Dysadiposity”

Waist-Hip Circumference Ratio (WHR):

Simple index of Body Fat Distribution

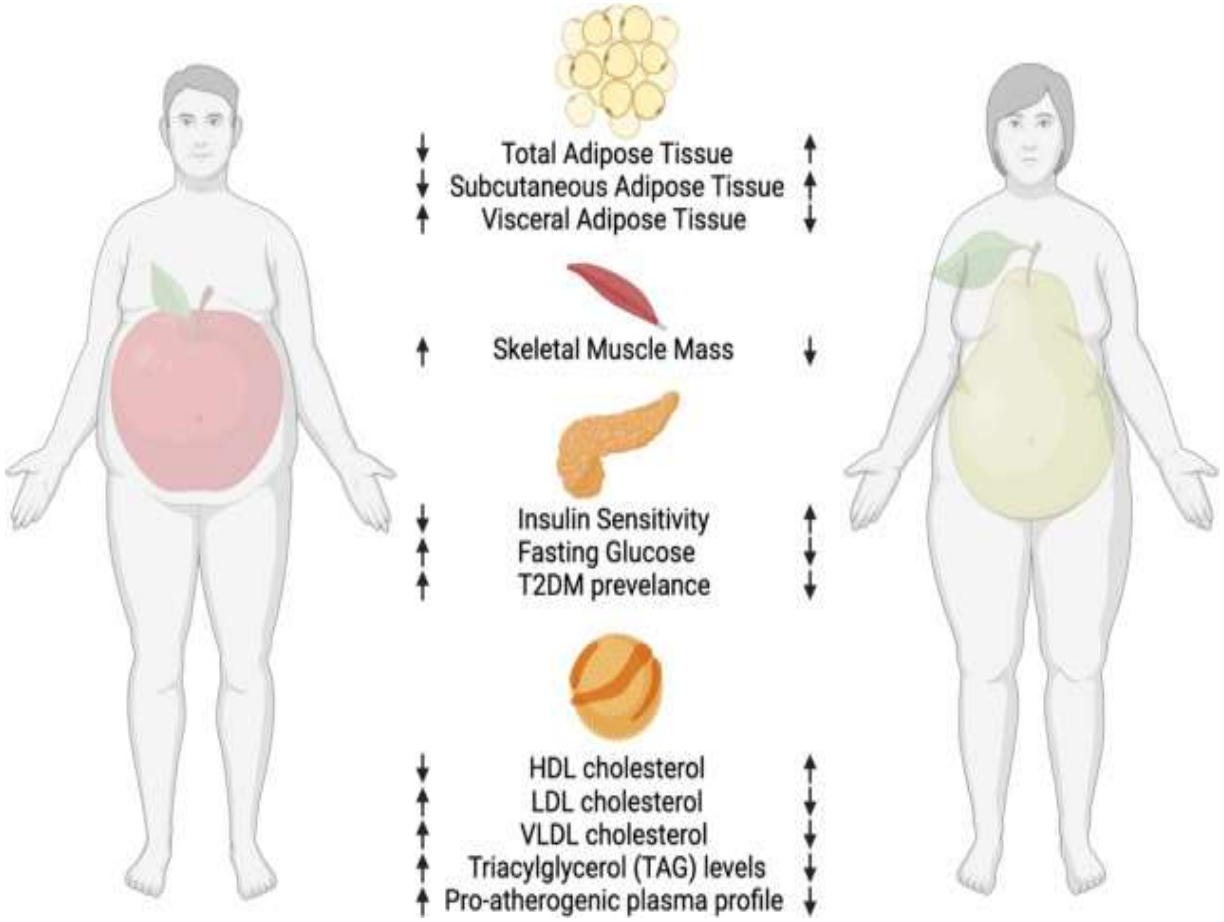
(1984 Swedish Study)



Android Obesity vs. Gynoid Obesity

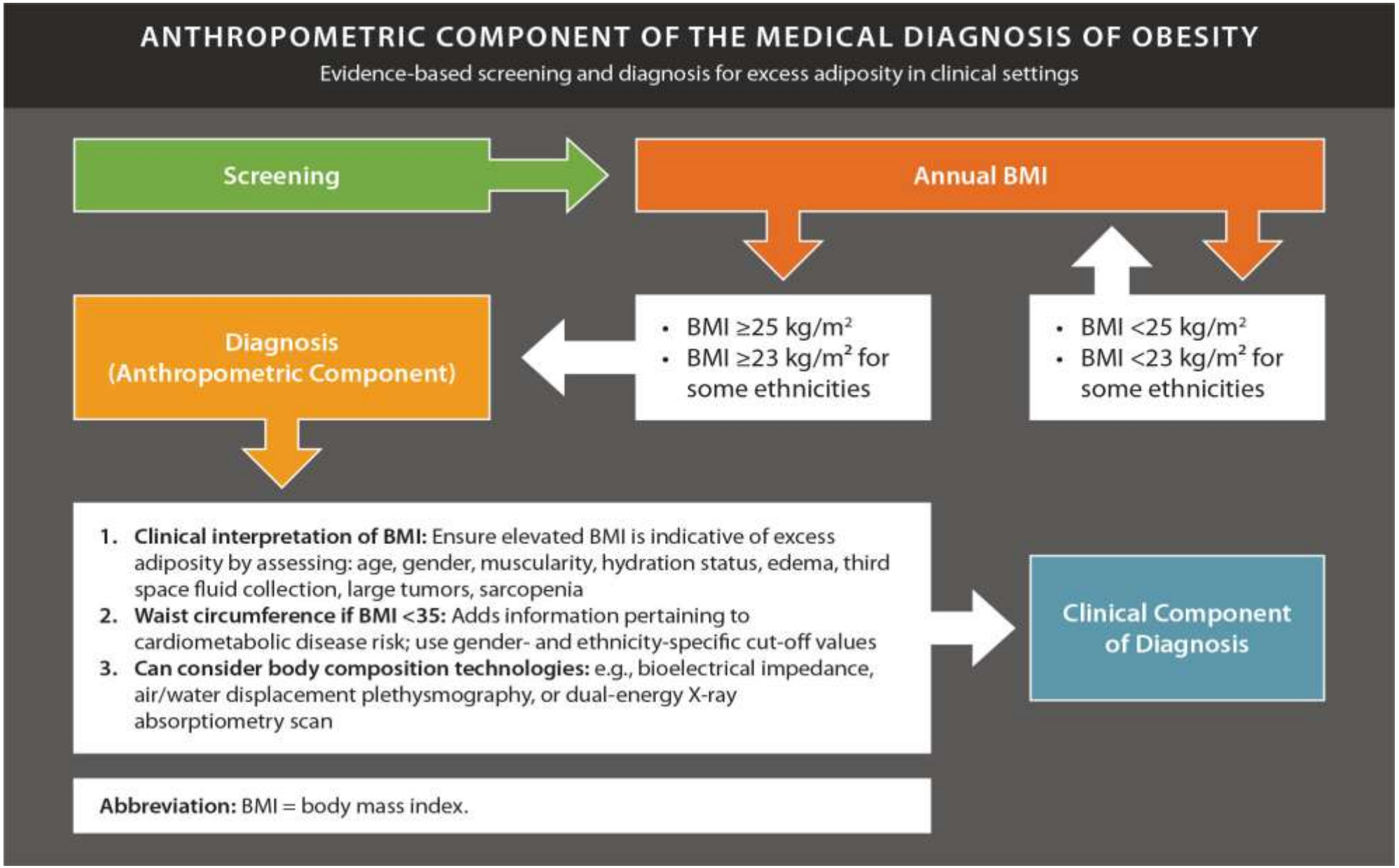
Regional Adipose Tissue Distribution → Dysmetabolic Outcomes

(proposed mid-1980s)



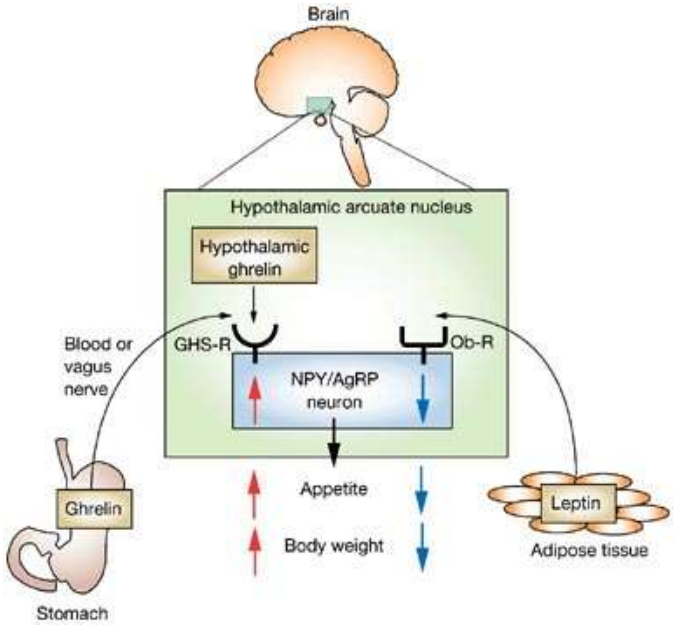
Treatment

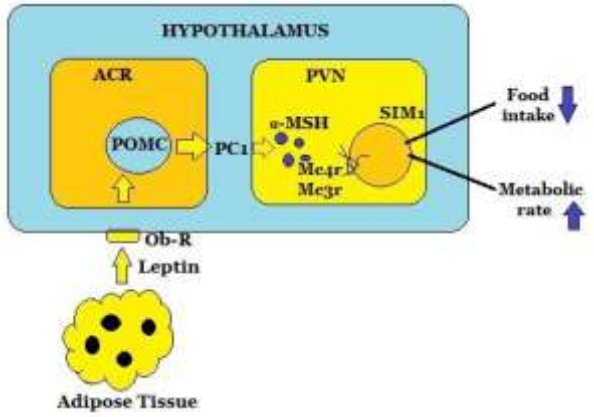
3-phase Paradigm for Chronic Disease Prevention and Treatment



Physiology of Weight Homeostasis: 3 Tier Interplay
Neuronal, Hormonal, Adiposity

- **Hormonal Signaling**
  - **Ghrelin**
  - **Leptin**
  - **Insulin**
  - **GLP-1**
- **Neuronal Circuitry**
  - **Brain Stem**
  - **Hypothalamus**
    - Arcuate Nucleus
    - Paraventricular Nucleus
- **Adiposity Influence**
  - **Visceral Adiposity**
    - **Hypertrophic Adipocytes**
    - **Proinflammatory**
  - **Subcutaneous Adiposity**
    - **Hyperplastic Adipocytes**
    - **Protective**





Physiology of Weight Homeostasis

Neuronal, **Hormonal**, Adiposity

- **Ghr**elin ("**Gr**owling" stomach when hungry)
  - **Produced by Gastric X cells**
  - **Stimulates** Hypothalamic **AgRP & NPY** Neurons → triggers **Hunger** and↑ **FEEDING**
  - **Stimulates PVN → Reduce Energy Expenditure**
  - **Inhibited** stomach distention

- **Leptin** (suppresses appetite; think **"L" for "LESS")**
  - **Produced by Adipose Tissue**
  - **Stimulates** Hypothalamic **POM-C** Nuclei → **REDUCED EATING** & Burn More Energy

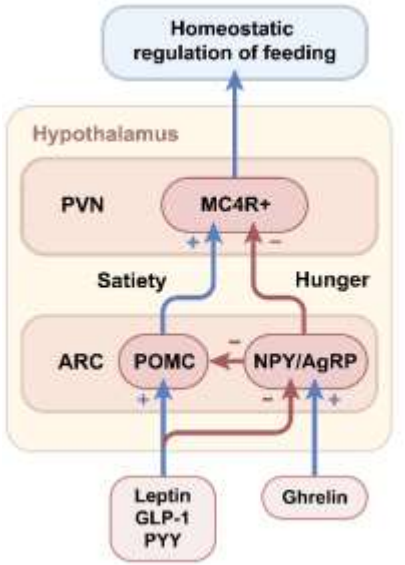
  - **OBESITY → Leptin Resistant Pathology → "Paradoxical Sense of Starvation" → ↑ Hunger**
    - High-Fat; Energy Dense Diets → ↑ Saturated Fatty Acids
    - **Low-Grade Hypothalamic Inflammation → ↑*Matrix Metalloproteinase-2*** (MMP-2) → ***cleaves Leptin Receptor*** **→ impairs Leptin signaling**

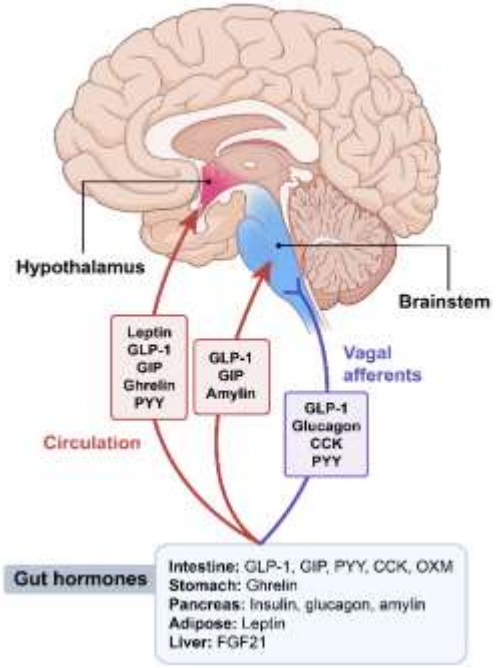
- **Insulin**
  - **Produced by Pancreas**
  - Released upon food ingestion/rising sugar
  - **Stimulates** Hypothalamic **POM-C** Nuclei → ↑***α-MSH*** → ↑***Melanin-Concentrating Hormone*** neurons **(PVN) → REDUCED EATING**

- **GLP-1**
  - **Produced by the Intestinal L-cells (**differential processing of proglucagon)
  - **Stimulates** Hypothalamic **POM-C** Nuclei
  - **Indirectly inhibits** (via ***GABAergic*** transmission) the **AgRP** and **NPY** neurons **→ REDUCED EATING**

Physiology of Weight Homeostasis
Neuronal, Hormonal, Adiposity

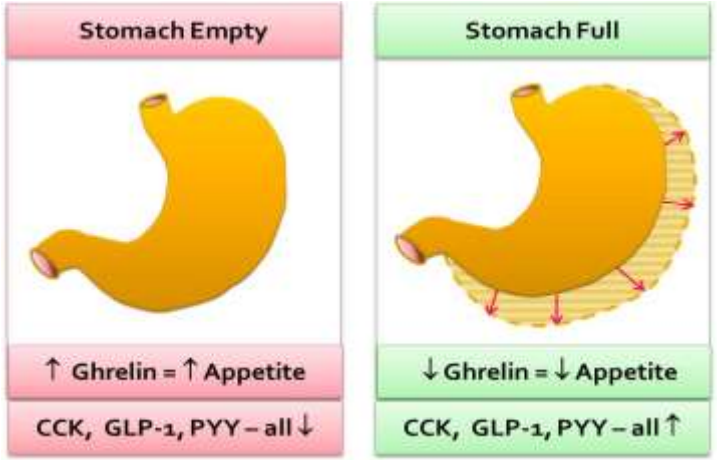
- ***Central Reward and Motivation Pathways***:
  - **Hypothalamus**: Receives Hormonal & Nutritional Signals
    - **Arcuate Nucleus (Major Control Center)**
      - Appetite **Stimulating** **("Hunger")** Neurons (***AgRP* & *NPY* Neurons**)
      - Appetite **Suppressant** **("Satiety")** Neurons (***POM-C* Neurons**)
    - Para-Ventricular Nucleus **(Information Processing Center)**
      - **Projects to circuits Outside Hypothalamus**
      - ***Coordinates Energy Intake & Expenditure***
  - **Brain Stem**: Receives Signals from Digestive Tract
    - **Vagus Nerve** stimuli via **GLP-1**/CCK/Glucagon/PYY **enhancement**
    - **Direct** stimuli from **GLP-1**, **GIP** and Amylin





Physiology of Weight Homeostasis

Neuronal, Hormonal, Adiposity

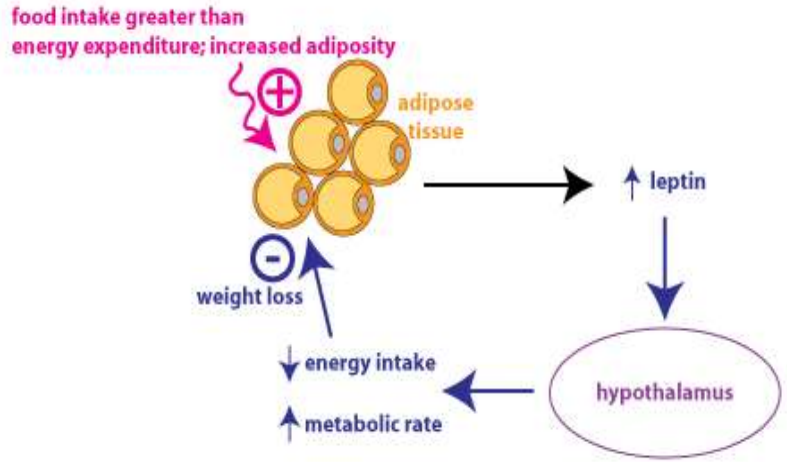


- **Short-Term Regulation of Feeding**: **ques from Stomach**
  - **Empty Stomach** → encourages Feeding
  - "Stretch" information to **Brain Stem** → signals "Hunger"
  - **↑Ghrelin** → Arcuate Nucleus → **AgRP** & **NPY** neurons → **↑ FEEDING**
    → **PVN** → Reduce Energy Expenditure

  - **Full Stomach** → **Satiety**
  - Stomach "Distention" → **Brain Stem** → **↓Ghrelin** production
  - **↑GLP-1 (CCK, PYY)** → Arcuate Nucleus → **stimulates POM-C** neurons → ↑ **Satiety**
    → **PVN** → Increase Energy Expenditure

- **Long-Term Regulation of Feeding**: **ques from Body Fat**
  - **LOW Fat** → Encourages Feeding
  - **↓ Leptin** Production
  - ↓ Energy Expenditure

  - **HIGH Fat** → Discourages Feeding
  - **↑ Leptin** Production
  - ↑ Energy Expenditure

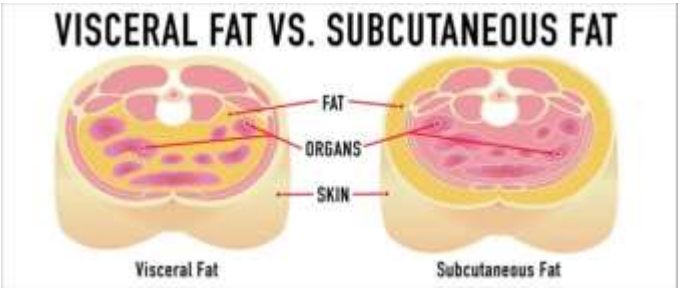


Physiology of Weight Homeostasis

Neuronal, Hormonal, Adiposity

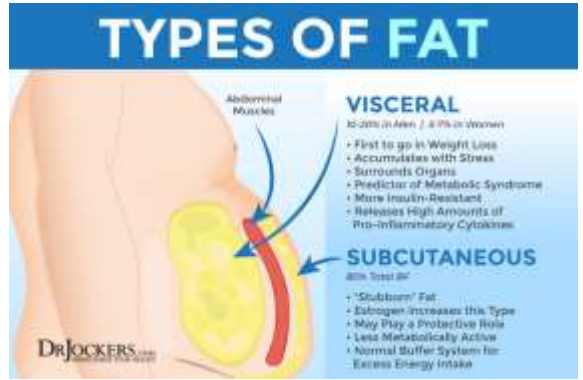
Adipose Tissue Stores Excess Energy in 2 ways:

- **Adipocyte Hypertrophy** (catalyst of "**Dysadiposity**"):
  - Pathological **Expansion** of adipocytes → **Android Visceral** Adiposity
  - Accelerate secretion of ***Chemokines*** (**Monocyte Chemoattractant Protein**):
    - Recruits Monocytes and Tissue-resident Macrophages
    - Promotes de-differentiation into pro-inflammatory **MI-Macrophages**
    - **MI-Macrophages**:
      - **Pro-inflammatory/pathogen-killing**
      - Key catalyst of adipocyte dysfunction



  - **↑Release FFAs into circulation** → incites chronic low-grade systemic inflammatory state,
  - Fosters ***metabolic syndrome***, ***CVD risk***, ***malignancy risk*** (breast, prostate, colon, liver), ***NAFLD***

- **Adipocyte Hyperplasia:**
  - **Increased** Extra-abdominal (**Gynoid**) **Subcutaneous** Adiposity
  - "***Protective Distribution Depot***" → **prevents "lipid spill-over"** into Visceral sites
  - Ameliorates insulin sensitivity and T2D risk



Physiology of Dysadiposity

- **M1 Pro-inflammatory Activated Tissue Macrophages** → **incite** Adipocyte **secretion of Pro-inflammatory Cytokines** (**TNF-a, IL-6, IL-8, plasminogen activator inhibitor-1 (PAI-1), resistin, IL-1b, etc.**)
  - **Inhibit Insulin Receptor activation → insulin resistance → Diabetes**
  - **Activate Kupffer cell** (liver-resident macrophage-like cells) **cytokine production → local inflammation → Hepatic Insulin Resistance & NAFLD**

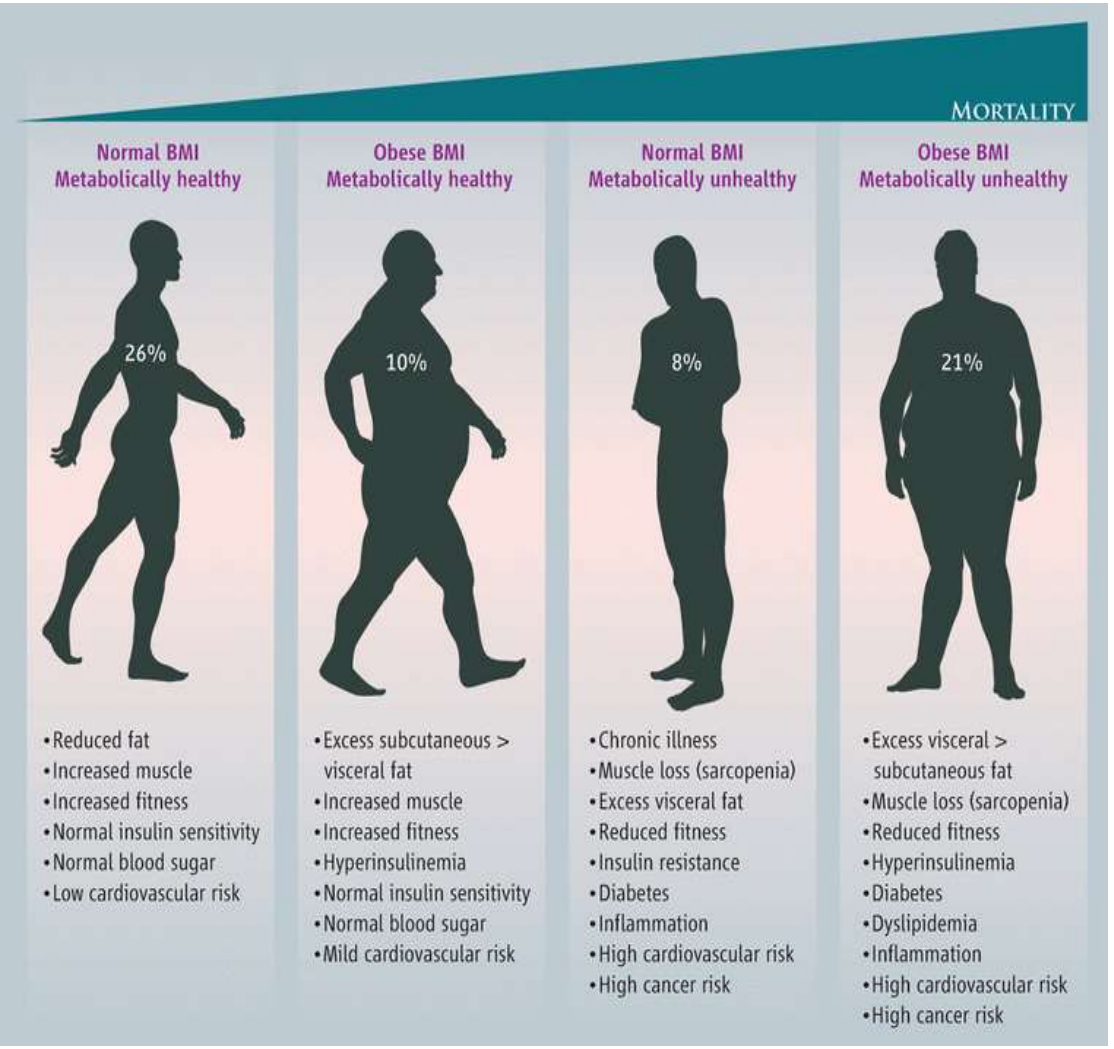
- **↑ Free Fatty Acids** from accelerated **Adipocyte Lipolysis**:
  - **↑ Vascular Endothelial Growth Factor-A & Vimentin → promote tumor initiation/growth → Malignancy predisposition**
  - **Inhibit insulin receptor activation → insulin resistance → Diabetes**
  - **↑ Superoxide Anion Free Radicals via Cellular Mitochondrial Oxidation →** DNA instability/**Tissue Oxidative Impairment**
  - **Downregulate Genes** that guide intracellular antioxidant defenses **→ Insulin resistance → Diabetes**
  - **Esterified into Adipocyte-stored Triglycerides → Non-Alcoholic Fatty Liver Disease**
  - **Accumulate in Cardiomyocytes** → Mitochondrial dysfunction → **↑ Superoxide Free Radicals** → **impaired Angiogenesis**, **localized Hypoxia**, and **M1 macrophage infiltration** → tissue inflammation/**CVD**.

- **Leptin Resistance** due to a **defect in intracellular signaling** (***genetic defect in JAK2–STAT3 pathway?***), **impairs Leptin Receptor functionality**, and **Leptin Transport** (***negative feedback inhibition by high Leptin levels?***) **across the blood–brain barrier**
  - Encourages ***growth-promoting and mitogenic capabilities*** → **Malignancy predisposition/transformation**
  - **Increases pro-inflammatory cytokine expression → insulin resistance → Diabetes**
  - **Inactivates IRS/PI3K pathway** and **translocation of intracellular GLUT4** to cell surface to assist glucose uptake **→ Insulin resistance → Diabetes**
  - **Upregulates pro-inflammatory TGF-β1** which provokes hepatic fibrosis → **Non-Alcoholic Fatty Liver Disease**

- **Adiponectin paucity**:
  - **Normally produced & secreted by adipocytes** and **Fosters insulin sensitivity** at liver and muscle
  - Effects anti-inflammatory and anti-oxidant properties
  - **Synthesis** adversely influenced by epigenetic certain genetic alterations (p.G48R, P.Y111H, p.R112C, and p.G90S mutations)
  - **Low levels → vascular remodeling**, **low nitric oxide levels**, **inhibit macrophage-to-foam cell transformation**, and **increased levels of TNF-a** → **insulin resistance** and **atherosclerotic vascular disease**.

Obesity/"Dysadiposity": Phenotypic Presentations

Body-Weight Phenotypes



6 "Spectral" Presentations

1. **Normal Weight Lean**:
   - a. Normal weight
   - b. Metabolically healthy

2. **Metabolically Healthy Obese ("Fat-Mass Disease")**:
   - a. Obese Phenotype
   - b. Absent insulin resistance-related metabolic abnormalities
   - c. ≥ 50% may progress to Metabolic Syndrome with ↑ CVD risk by 10-years

3. **"Metabolically Obese" Normal Weight ("Sick-Fat Disease")**:
   - a. Normal Weight & BMI; HIGH Visceral Fat content; Sarcopenia?
   - b. Metabolic Syndrome-related ramifications

4. **Metabolically Unhealthy Obese ("Sick-Fat Disease")**:
   - a. BMI ≥ 30; % Body Fat >30%; HIGH Visceral Fat content
   - b. Metabolic Syndrome ramification; ↑ CVD

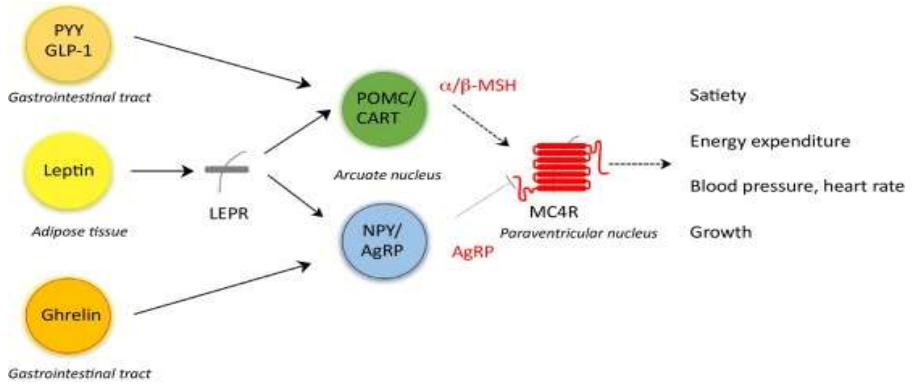
5. **"Normal Weight Obese" ("Fat-Mass Disease") – subset of #2**:
   - a. Normal weight + Central Obesity (Visceral > SubQ Fat content); Sarcopenic
   - b. Genetic/Epigenetic Polymorphisms → Vascular Inflammation, CVD, Cancer

6. **Sarcopenic Obese (*applicable to all above phenotypes*)**:
   - a. Normal BMI
   - b. Visceral Fat-derived CATABOLIC pro-inflammatory Cytokines → ↑ Sarcopenia
   - c. Weight-loss strategies directed toward Muscle Mass recovery

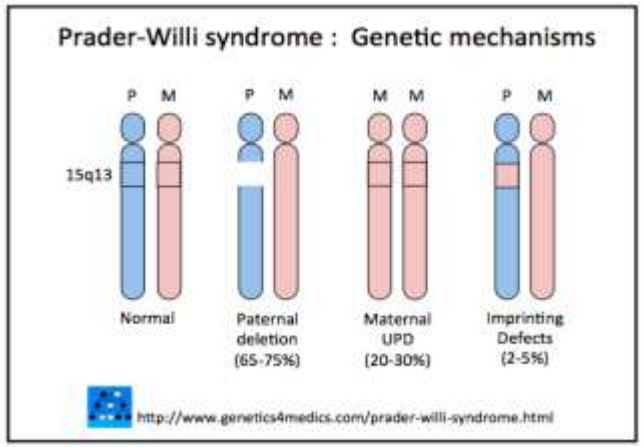
"Dysadiposity": Predisposing Etiologies

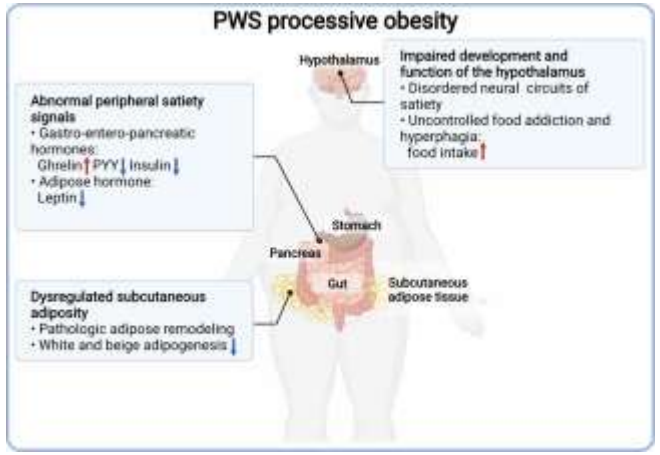
- **Genetic Factors: 3 broad categories**
  - **Monogenic Obesity** (rare): Mutation or deficiency of a single gene
  - **Polygenic Obesity** (common):
    - **Polygenes** (gene variants) and **Environmental Factors** variably converge on CNS and Neuronal Pathways to alter food intake.

Genetic Obesity		
Non-Syndromic Forms		Syndromic Form
Monogenic Obesity	**Polygenic Obesity**	**Chromosomal or Pleiotropic Forms**
Leptin deficiency LEPR mutation POMC deficiency PC mutation MC4R mutation SIM1, BDNF, TRKB mutations	MC4R mutation FTO mutation INSIG2 mutation	Bardet Biedl syndrome Prader Willi syndrome Alstrom syndrome Smith–Magenis syndrome



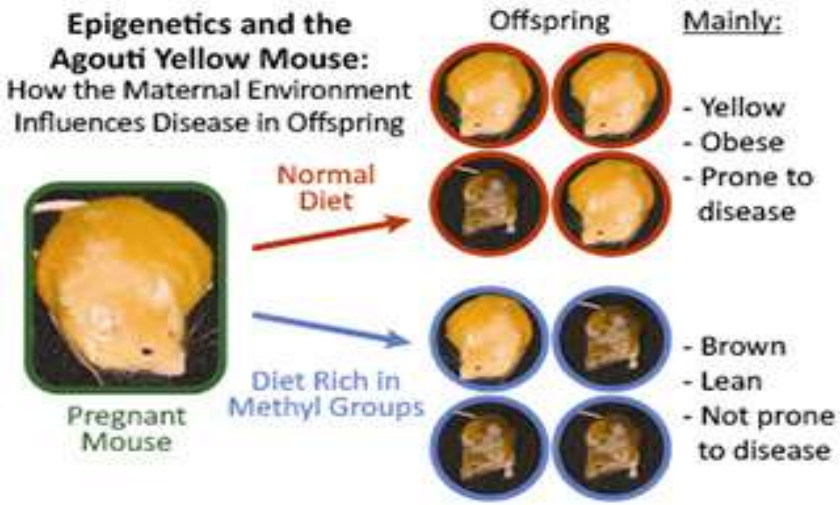
- **Syndromic Obesity**: Chromosomal Rearrangements
  - **Prader Willi Syndrome** (Paternal Gene Deletion; Maternal Uni-Parental Disomy) → ***Most common Syndromic Life-threatening Obesity Disorder***)



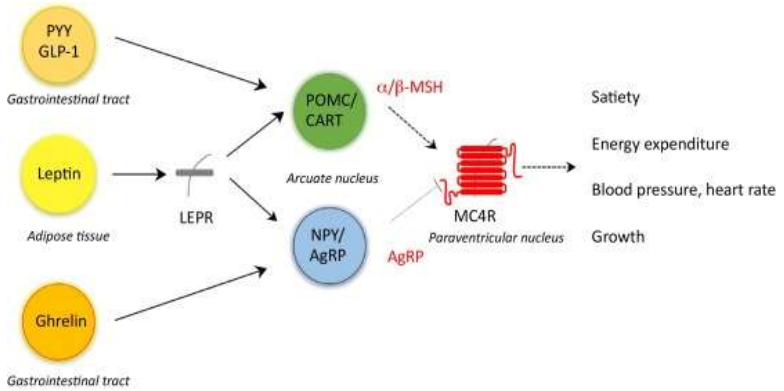


"Dysadiposity": Predisposing Etiologies

- **Epigenetic Factors: Modern Life-Style Influences**
  - **Impact DNA transcription without altering its sequence (i.e. "*Gene Expression*")**
  - **Most common alterations to "*Gene Expression*" are derived through:**
    - **DNA methylation**
    - **Histone modifications**
    - **Non-coding RNAs**
  - **"Dynamic" interplay between body and surroundings**
    - **Energy-dense foods, sedentary behavior, chemical endocrine disruptors**
  - **REVERSIBLE**



- **Best Paradigm: The Agouti Mouse Model**
  - **DNA Hypomethylation Mutation of Agouti Viable Yellow (Avy) Gene (guides mouse coat color)**
  - **Altered expression of Agouti Signaling Protein (ASIP) at Hypothalamus**
  - **AISP blocks Melanocortin-4 Receptor (MC4R) → triggering Hyperphagic Obesity.**
  - **Diet rich in "methyl donors" (folate and methionine) fosters DNA methylation:**
    - **↓ Hyperphagia**
    - **↑Insulin Sensitivity**
    - **"Coat color" Restoration**



Trends in Molecular Medicine

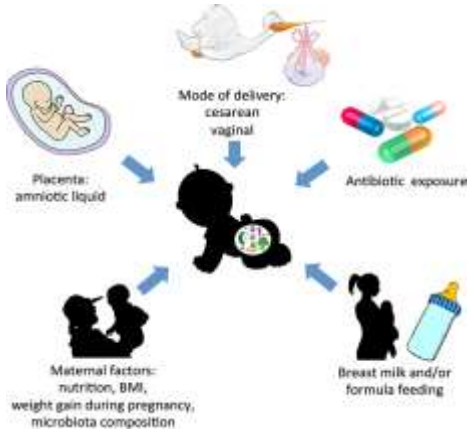
“Dysadiposity”: Predisposing Etiologies

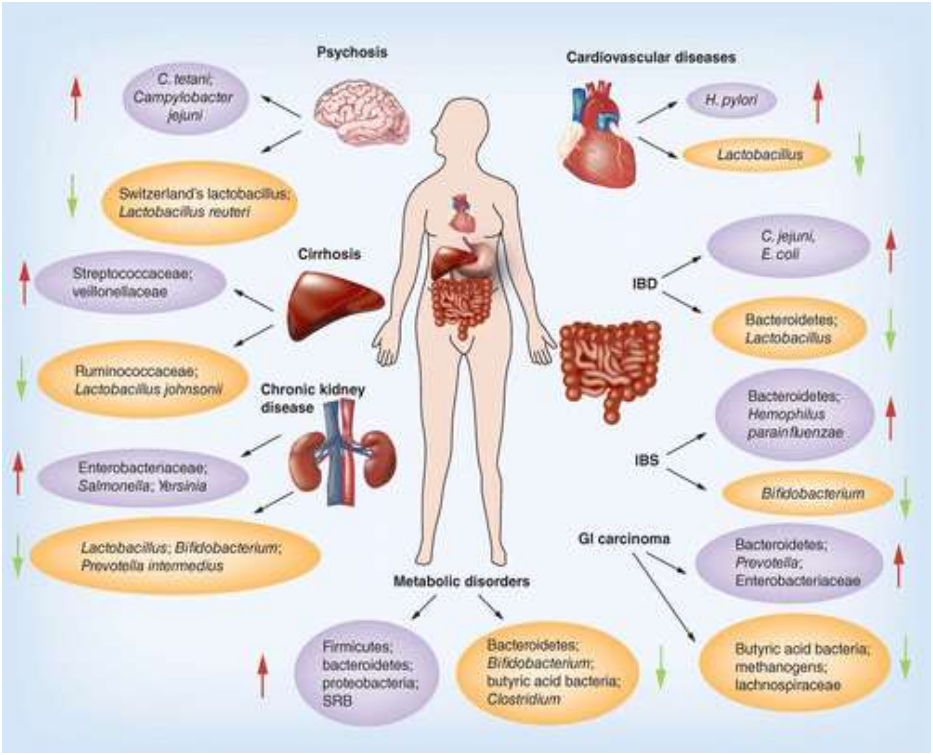
- **Medical Factors**
  - **Hypothyroidism**
  - **Diabetes**
  - **Hypopituitarism**
  - **Hypercortisolemia (endogenous/exogenous)**
  - **Obstructive Sleep Apnea/Sleep deprivation (i.e. metabolic dysregulation, pro-inflammatory markers, endogenous cortisol dysregulation)**

- **Iatrogenic Causes**
  - **Various medications can encourage weight gain.**
    - **Antipsychotics**
    - **Antidepressants**
    - **Antiepileptics**
    - **Insulin/Insulin secretagogues**
    - **Hydrocortisone/Prednisone**
    - **Antihypertensive medicines**

“Dysadiposity”: Predisposing Etiologies

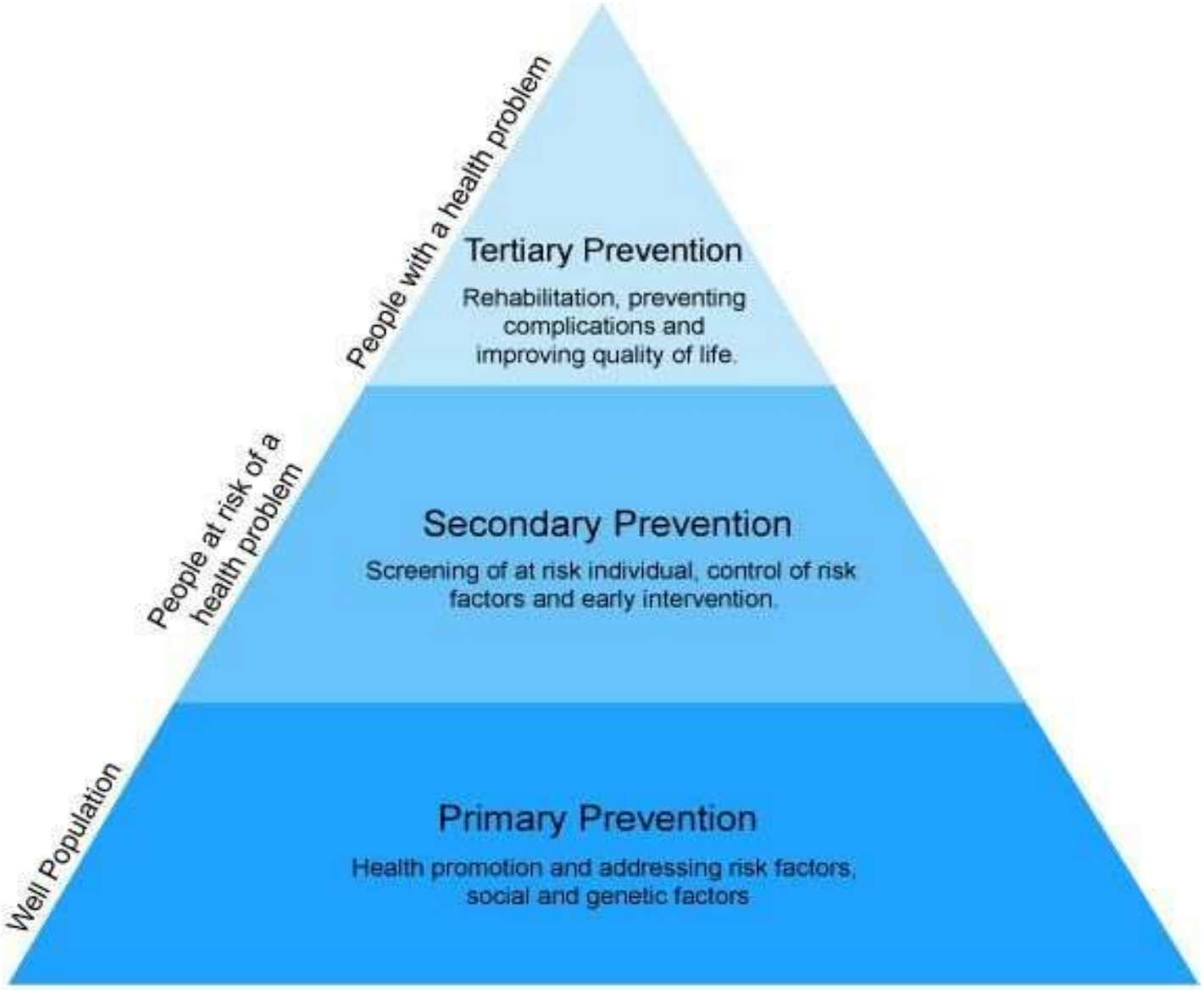
- **Socio-Cultural Factors**
  - Substantially contributes to an effective transmission of obesity from parents to offspring
  - Areas of primary influence
    - Social adversity **within the family**
    - Increasing levels of **personal insecurity**
    - **Refractory weight gain** eliciting further social stress and weight stigma
- **Psychological Factors**
  - Individuals confronted with weight pathology often possess a **traumatic history** (i.e. abuse, bullying, job loss, romantic difficulties, mistreatment by the medical field)
  - “Binge Eating” → a common ramification
- **Gut Microbiota**
  - **Obese and lean people have different gut microbiota**.
  - **Microbiome determined early in life**
  - **Antibiotics alter** microbiome; influence metabolic derangements
- **Life-Style Factors**
  - Eating out; consuming processed foods
  - Eating late
  - Eating rapidly
  - Inactivity





Treatment

3-phase Paradigm for Chronic Disease Prevention and Treatment



Treatment

3-phase Paradigm for Chronic Disease Prevention and Treatment

DIAGNOSIS		COMPLICATION-SPECIFIC STAGING AND TREATMENT		
Anthropometric Component (BMI kg/m²)	Clinical Component	Disease Stage	Chronic Disease Phase of Prevention	Suggested Therapy (based on clinical judgment)
<25 <23 in certain ethnicties waist circumference below regional/ ethnic cutoffs		**Normal weight** (no obesity)	**Primary**	• **Healthy lifestyle:** healthy meal plan/ physical activity
25–29.9 23–24.9 in certain ethnicities	Evaluate for presence or absence of adiposity-related complications and severity of complications • Metabolic syndrome • Prediabetes • Type 2 diabetes • Dyslipidemia • Hypertension • Cardiovascular disease • Nonalcoholic fatty liver disease • Polycystic ovary syndrome • Female infertility • Male hypogonadism • Obstructive sleep apnea • Asthma/reactive airway disease • Osteoarthritis • Urinary stress incontinence • Gastroesophageal reflux disease • Depression	**Overweight stage 0** (no complications)	**Secondary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions
≥30 ≥25 in certain ethnicities		**Obesity stage 0** (no complications)	**Secondary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Weight-loss medications:** Consider if lifestyle therapy fails to prevent progressive weight gain (BMI ≥27)
≥25 ≥23 in certain ethnicties		**Obesity stage 1** (1 or more mild to moderate complications)	**Tertiary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Weight-loss medications:** Consider if lifestyle therapy fails to achieve therapeutic target or initiate concurrently with lifestyle therapy (BMI ≥27)
≥25 ≥23 in certain ethnicties		**Obesity stage 2** (at least 1 severe complication)	**Tertiary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Add weight-loss medication:** Initiate concurrently with lifestyle therapy (BMI ≥27) • **Consider bariatric surgery:** (BMI ≥35)

a. All patients with BMI ≥25 have either overweight or obesity stage 0 or higher, depending on the initial clinical evaluation for presence and severity of complications. These patients should be followed over time and evaluated for changes in both anthropometric and clinical diagnostic components. The diagnoses of overweight/obesity stage 0, obesity stage 1, and obesity stage 2 are not static, and disease progression may warrant more aggressive weight-loss therapy in the future. BMI values ≥25 have been clinically confirmed to represent excess adiposity after evaluation for muscularity, edema, sarcopenia, etc.

b. Stages are determined using criteria specific to each obesity-related complication; stage 0 = no complication; stage 1 = mild to moderate; stage 2 = severe.

c. Treatment plans should be individualized; suggested interventions are appropriate for obtaining the sufficient degree of weight loss generally required to treat the obesity-related complication(s) at the specified stage of severity.

d. BMI ≥27 is consistent with the recommendations established by the US Food and Drug Administration for weight-loss medications.

Abbreviation: BMI = body mass index.

Treatment

- **Behavioral Interventions**
  - **Adequate Sleep** – 7-9 hours per night
  - **Reduce Caloric Intake** – Foundation of any weight-loss strategy
  - **Aerobic exercise** and **Resistance Training**
    - **150 minutes** of weekly aerobic physical activity
    - **2-days** of resistance training
    - Reduce sedentary periods
  - **Encourage Support mechanisms**:
    - "Home Gym" vs. Fitness Club membership
    - "Exercise Partner"
    - Professional Health-Care conduits (i.e. Psychologists, Psychiatrists, and Dietitians)

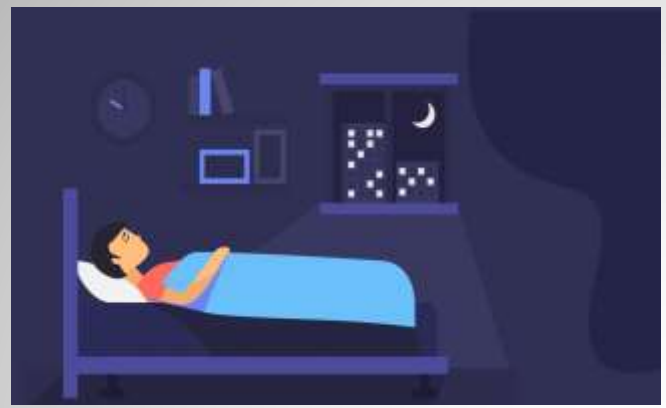
  - **Cognitive Behavioral Therapy**:
    - **Evaluates and treats interaction between thoughts, feelings, behaviors, and physical sensations**.
    - Emphasis on weight-loss **achievement** vs. diet and exercise alone
    - **Implements measurable, action- and time-oriented goals**
      - Re-defining success
      - Planning physical activity
      - Changing foods purchased and cooking at home
      - Adjusting portion sizes (food portioning plates; diet diaries)
      - How to order when eating out
      - Addressing sleep patterns

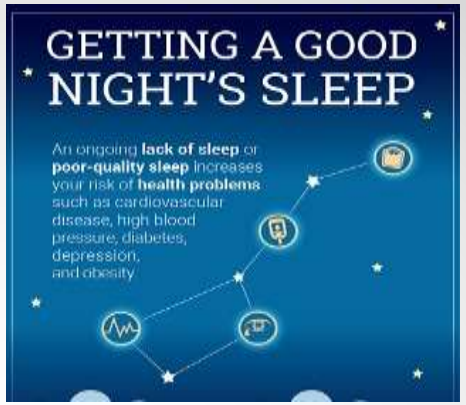
Treatment

- **Nutritional Tactics**:
  - Different diet strategies are variably popular, confusing, and counter-productive.
    - **Adkins** (high protein/low-carbohydrate diet can lead to **hyperuricemia** (leading to joint pain and gout) and **hypercalcuria** (leading to kidney stones, hypocalcemia, and osteoporosis)
    - **South Beach** (**restrictive first phase**, driven by glycemic index, expensive, **limited structure**, could contribute to disordered eating)
    - **Ketogenic** (despite the favorable effect on HDL-C, the **concomitant increases in LDL-C and VLDL** may lead to increased cardiovascular risks; the dietary restrictions required to sustain ketosis impedes its sustainability)
    - **Paleolithic diet** (**restrictive** nature & **high saturated fat content** can promote fatigue/CVD; **alters gut microbia**; variable bowel habits)
    - **Low fat** (**very low-fat diets create vitamin/mineral deficiencies**, dry skin, labile moods, fatigue; best to consume a balance of mono- and polyunsaturated fats)
    - **Intermittent Fasting** (can encourage hunger, fatigue, insomnia, irritability, headaches, and nausea; **fasting at the wrong time of day**)
  - **HEALTHY DIET**:
    - Ample water
    - **Balanced Variety** (***vegetables, fruits, whole grains, lean proteins, healthy fats***)
    - **Limited exposure to sodium, processed sugars/saturated fats**.
  - **Best Diet Plan**? **Mediterranean Diet**
    - **BALANCE**: **nutrient-dense fruits**, **vegetables**, **lean protein**, **whole grains**, and **healthy fats**
    - **AVOIDS**: saturated fat, added sugars and sodium common to standard American diet.
    - **PROMOTES**: **longer lifespans** and **risk reduction of chronic health conditions**
    - **FRIENDLY**: to family, budget, environment, Vegan/Gluten-free preferences, Halal/Kosher requisites

The "SEE" Food Diet of Healthy Living

- **SLEEP**

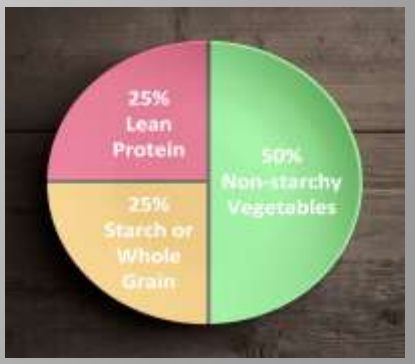




Average Sleep Needs by Age	Age Hours Needed	May be appropriate
Newborn to 3 months old	14 - 17 hrs	11 - 19 hrs
4 to 11 months old	12 - 15 hrs	10 - 18 hrs
1 to 2 years old	11 - 14 hrs	9 - 16 hrs
3 to 5 years old	10 - 13 hrs	8 - 14 hrs
6 to 13 years old	9 - 11 hrs	7 - 12 hrs
14 to 17 years old	8 - 10 hrs	7 - 11 hrs
Young adults (18 to 25 years old)	7 - 9 hrs	6 - 11 hrs
Adults (26 to 64 years old)	7 - 9 hrs	6 - 10 hrs
Older adults (65+)	7 - 8 hrs	5 - 9 hrs
Source: National Sleep Foundation		

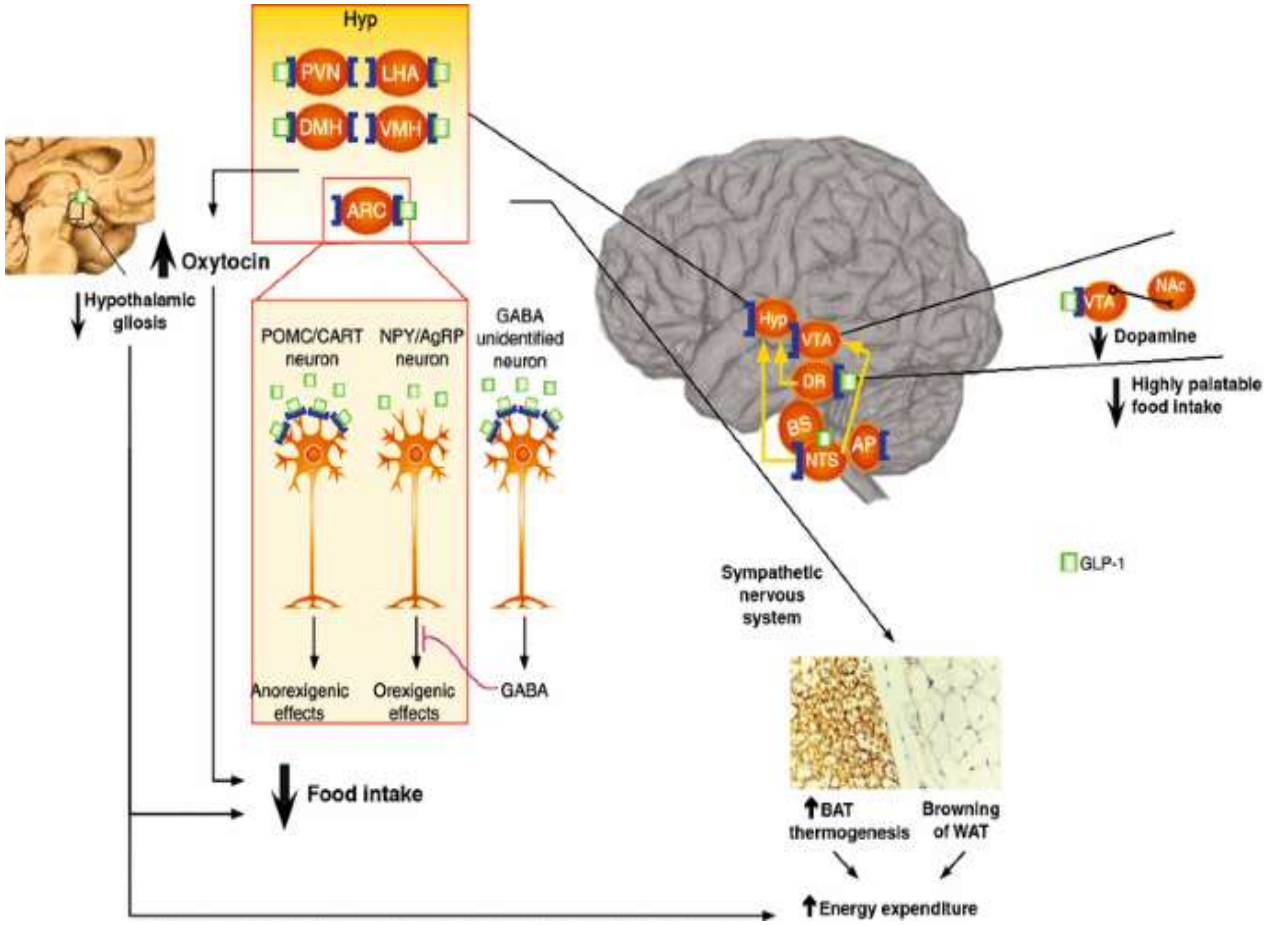
- **Exercise**

- **Eat**



Basic Pharmacologic Mechanisms of Action

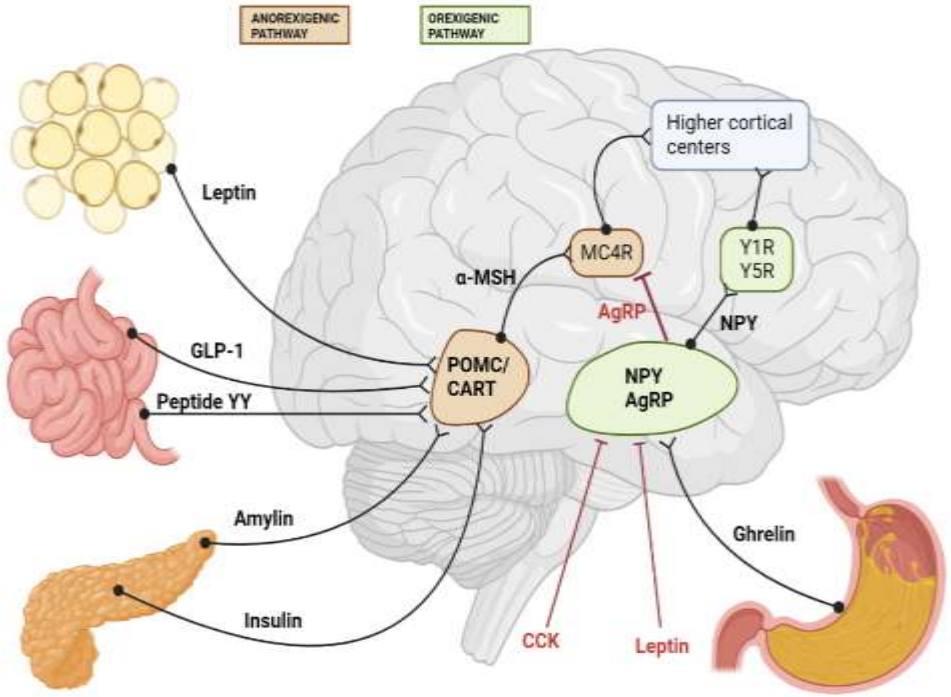
GLP-1 Receptor Agonists



Oral Weight-loss Promoting Agents

Oral agents for obesity treatment work primarily in the arcuate nucleus to **stimulate**:

- **Pro-opiomelanocortin (POMC) neurons and promote satiety.**
- **Cocaine Amphetamine Related Transcript (CART) neurons in the arcuate nucleus to decrease food intake and increase energy expenditure.**



Pharmacologic Treatment Strategies

Name	Class/Mechanism	Indication	Pros	Cons	Dose
Orlistat OTC (Alli)	Gastric/Pancreatic Lipase inhibitor	Weight loss with + Diet modification	With consistent dietary adherence, can effectively ↓ weight, BMI, cholesterol, waist circumference; modest ↓ in BP; improved glycemic control	**Ave. 12-month weight loss with a behavioral weight control program + low-fat diet is ≈ 5.5 lbs. > placebo, or ≈2.3% initial weight**; **weight is slowly regained after 1st year of treatment**; Flatus, fecal urgency; oily stool AEs	60 mg tid with meals
Orlistat (Xenical)	Gastric/Pancreatic Lipase inhibitor	Refractory weight gain; Adults with BMI ≥30 kg/m² or ≥27 kg/m² + risk factors	With consistent dietary adherence, can effectively ↓ weight, BMI, cholesterol, waist circumference; modest ↓ in BP; improved glycemic control	**Ave. 12-month weight loss with a behavioral weight control program + low-fat diet is ≈ 7.5 lbs. > placebo, or ≈3.1% initial weight**; **weight is slowly regained after 1st year of treatment**; Flatus, fecal urgency; oily stool AEs	120 mg tid with meals
Plenity	superabsorbent hydrogel; thousands of hydrogel particles/capsule which disintegrate and release the particles that occupy ≈ 25% stomach volume	Weight loss + diet modification in adults with BMI 25-40 kg/m²	effective in making person feel fuller/longer; 60% lose at least 5% of their body weight; mean weight loss of **6.4% after 24 weeks** and up to **7.6% after 48 weeks**	**Digestive issues**: bloating, gas, nausea, constipation, and stomach pain	3-capsules with 16 oz. of water 20 min. before lunch & dinner

Pharmacologic Treatment Strategies

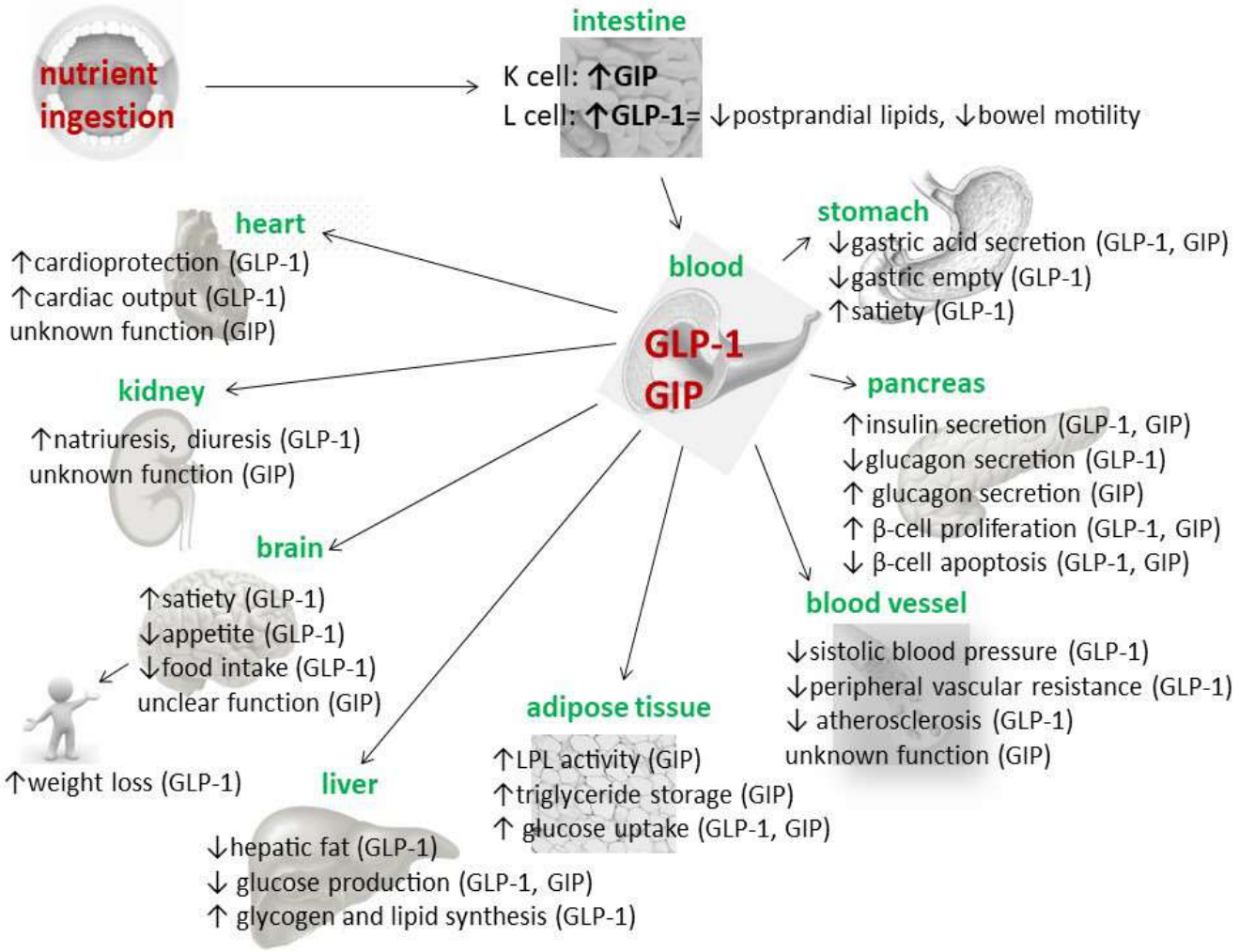
Name	Class/Mechanism	Indication	Pros	Cons	Dose
Phentermine (Adipex)	Sympathomimetic Amine Anorectic	Short-term adjunct to exercise + behavioral and caloric restriction; Adults with BMI ≥30 kg/m² or ≥27 kg/m² + risk factors	effectively suppresses appetite; **After 2-3 months: ≈90% taking phentermine lose ≥ 5% of body weight and ≈ 50% lose ≥ 10% of body weight**	**Addictive**, **pulmonary hypertension**; anxiety, palpitations, **SVT**, **atrial fibrillation**, headache and insomnia	37.5 mg before or 1-2 hrs. post-breakfast; Or 8 mg tid 30 mins. a.c. meals
Phentermine + Topiramate (Qsymia)	Sympathomimetic Amine Anorectic/anti-epileptic analogue	Adjunct to efforts at caloric restriction + exercise; Adults with BMI ≥30 kg/m² or ≥27 kg/m² + risk factors	adults and children ≥ 12 years old; Effective appetite suppression; **By 56-weeks: average weight loss of 9.6% using 7.5 mg/46 mg dose, and 12.4% using 15 mg/92 mg dose**	May cause **depression or mood problems**, constipation, dry mouth, and trouble sleeping; possible **seizures if stop too fast**; discontinue by taking every other day for 1 week	One 3.75 mg/23 mg capsule q a.m. for first 2 weeks, then increase to one 7.5 mg/46 mg capsule q a.m.; may titrate to 11.25 mg/69 mg & 15 mg/92 mg dose options
Naltrexone + Bupropion (Contrave)	Opioid Antagonist/Aminoketone Antidepressant	Adjunct to efforts at caloric restriction + exercise; Adults with BMI ≥30 kg/m² or ≥27 kg/m² + risk factors	Weight loss achieve by 4-weeks; 2%-4% more weight loss than placebo; **By 1-year: average weight loss of 5-8%**	**Behavioral changes**, suicidal thoughts & actions; **seizures**; nausea, constipation, headache, insomnia	Start with one 8mg/90mg tablet; titrate by 1-tablet weekly until maximum of 2-tablets bid by week 4

Pharmacologic Treatment Strategies

Name	Class/Mechanism	Indication	Pros	Cons	Dose
Liraglutide (Saxenda)	GLP-1 Receptor Agonist	Adjunct to efforts at caloric restriction + exercise; Adults with BMI ≥30 kg/m² or ≥27 kg/m² + risk factors	**After 8-weeks: ≈5% weight loss; after 1-year: 85% of patients lose an average of 9.2% body weight**	**Nausea, Diarrhea. Constipation. Vomiting.** Injection site reaction. Hypoglycemia, Headache, **dyspepsia**, fatigue	Weekly dose titration of 0.6 mg qd → 1.2 mg → 1.8 mg → 2.4 mg → 3.0 mg qd
Semaglutide (Wegovy)	GLP-1 Receptor Agonist	Adjunct to efforts at caloric restriction + exercise; Adults with BMI ≥30 kg/m² or ≥27 kg/m² + risk factors	Effective reduction in hunger and increased sense of fullness; **After 17 months: average 15% loss of body weight**	mild to moderate **nausea, diarrhea, vomiting, constipation, and abdominal pain.** For most people, stomach side effects lessen or resolve after several weeks of treatment	Monthly dose titration of 0.25 mg q weekly → 0.5 mg → 1.0 mg → 1.7 mg → 2.4 mg q weely

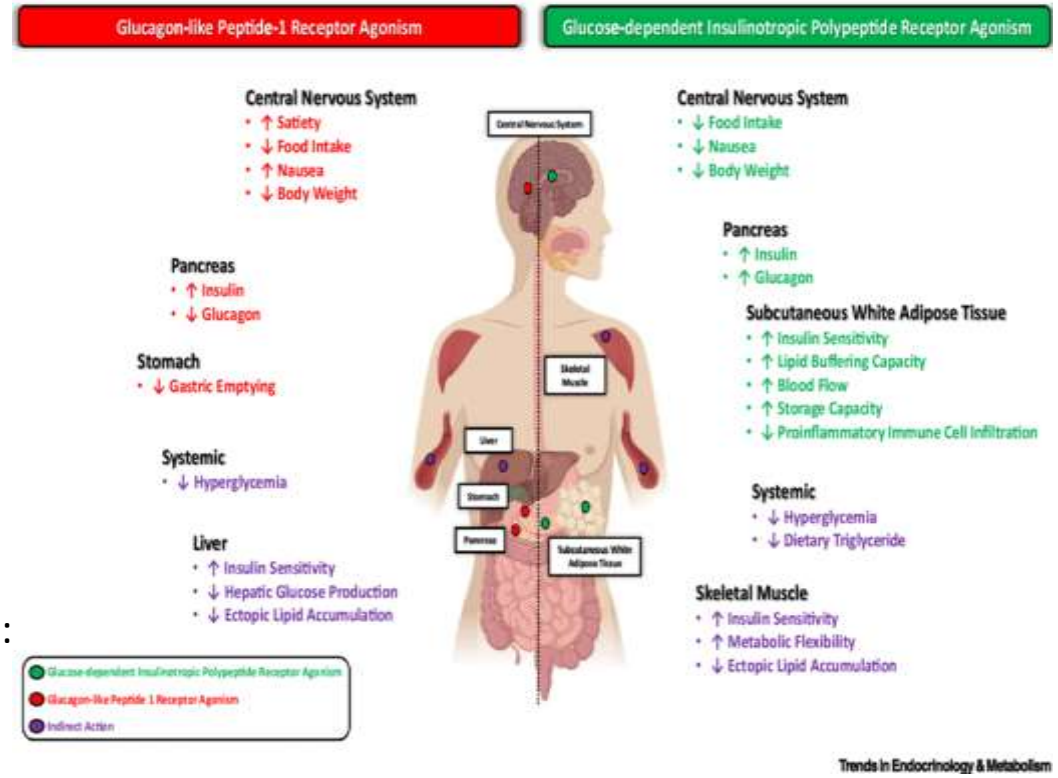
What Makes Incretins so Effective?

GIP & GLP-1 Gut-produced Factors upon Meal Ingestion Influence Post-prandial Metabolism and Weight Homeostasis



What Makes Incretins so Effective?

- **Activation of Receptors ON/AT**:
  - **Pancreatic β-cells** (**GLP-1 & GIP**) to enhance efficiently the glucose-dependent insulinotropic response
  - **GUT** (**GLP-1**) **to facilitate transient post-prandial delay of Gastric Emptying**
  - **White Adipose Tissue** (**GIP**) to:
    - Enable **differentiation & development of Pre-adipocytes**
    - **Modulate WAT Physiologic Function:**
      - **Hyperplastic" remodeling** to **buffer circulating lipids**
      - **Economic FFA delivery** → manage systemic energy needs
    - **Increase WAT Blood Flow**
      - **Sensitize GLUT-4**-mediated glucose uptake
      - **Enhance Lipoprotein Lipase**-directed Triglyceride storage
      - **Reduce "lipid spillover" into Visceral Fat depot → ↓ Insulin Resistance**
  - **Hypothalamus** (**GLP-1**):
    - **Direct Satiation Stimulus (POMC/CART neurons)**
    - **Indirect Satiation and Hunger-suppression (*GABAergic neurons*)**
  - **Hypothalamus Dual** (**GLP-1 & GIP**) **Action** (***modulate Satiety & Hunger***):
    - **Arcuate**, **Paraventricular**, **Ventromedial** and **Dorsomedial** nuclei
      - Classic signaling (separate cells)
      - Synergistic signaling (same cells)
      - Integrated signaling (downstream locations)



- **Preserving Free Leptin levels** (**GLP-1**) → proposed mechanism for **SUSTAINABILITY**

Thank You

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Slide Appendix

Clinical Approach to Treatment

Medication	Unique Mechanism	Contraindications	Relative Contraindications
Orlistat (Xenical; Alli)	Binds covalently to the serine residue of the active site of gastric and pancreatic lipases; may inhibit NF-κB-mediated inflammation; lowers proatherogenic Oxysterols.	Chronic G.I. issues (i.e. IBS, colitis, gallbladder pathology)	Variable history of digestive issues
Plenity	Modified cellulose is cross-linked with citric acid, which creates a three-dimensional gel matrix which mixes with food, creating a larger volume, with higher elasticity and viscosity, in the stomach & small intestine, promoting satiety and fullness.	< age 22, pregnancy, allergy to cellulose, citric acid, sodium stearyl fumarate, gelatin, titanium dioxide	History of digestive issues

Clinical Approach to Treatment

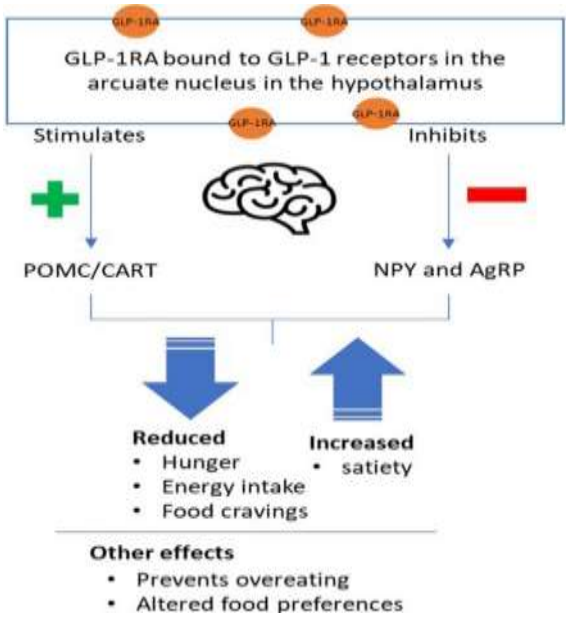
Medication	Unique Mechanism	Contraindications	Relative Contraindications
Phentermine (Adipex)	Sympathomimetic amine that stimulates release of norepinephrine in the hypothalamus; no effect on serotonin; may inhibit neuropeptide, a principal signaling pathway for hunger induction.	Teratogenic; glaucoma; hyperthyroidism; use within 14 days of MAOI treatment; sensitivity to sympathomimetic amines	Labile glycemia in diabetes; alcohol exposure; caffeine; may interact with MAOIs, SSRIs, and SNRIs
Naltrexone + Bupropion (Contrave)	(Bupropion) stimulates hypothalamic POMC-producing neurons to release α–melanocyte-stimulating hormone (MSH) which mediates POMC anorectic effect, and (Naltrexone) blocks β-endorphin autoinhibitory feedback that normally inactivates anorectic effect.	uncontrolled hypertension; history of seizures; bulimia or anorexia nervosa, chronic opioid/opiate agonist use.	NASH; diabetes→ hypoglycemia; labile moods; renal dysfunction
Phentermine + Topiramate (Qsymia)	Sympathomimetic amine (Phentermine) stimulates release of norepinephrine in the hypothalamus; no effect on serotonin; may inhibit neuropeptide signaling pathway; (Toprimate) augments neurotransmitter gamma-aminobutyrate activity, modulates voltage-gated ion channels, inhibition of AMPA/kainite excitatory glutamate receptors, and inhibition of carbonic anhydrase.	pregnancy; glaucoma; hyperthyroidism; use within 14 days of MAOI treatment; sensitivity to sympathomimetic amines	Patients on antidepressants and/or psychotropics; dysrhythmias

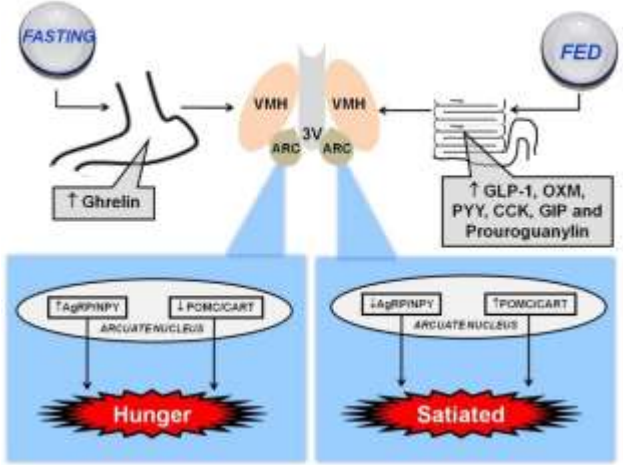
Clinical Approach to Treatment

Medication	Unique Mechanism	Contraindications	Relative Contraindications
Liraglutide (Saxenda)	Stimulates POMC/CART satiety neurons and indirectly (via GABA-dependent signaling) suppresses neuropeptide Y (NPY) and agouti-related peptide (AgRP) "hunger signaling" neurons; enacts preservation of free leptin levels to mediate weight loss maintenance.	Personal/family history of Thyroid Medullary Carcinoma MEN-2	Chronic G.I. issues (i.e. IBS, colitis, gallbladder pathology, gastroparesis, pancreatitis)
Semaglutide (Wegovy)	Stimulates POMC/CART satiety neurons and indirectly (via GABA-dependent signaling) suppresses neuropeptide Y (NPY) and agouti-related peptide (AgRP) "hunger signaling" neurons; enacts preservation of free leptin levels to mediate weight loss maintenance.	Personal/family history of Thyroid Medullary Carcinoma MEN-2	Chronic G.I. issues (i.e. IBS, colitis, gallbladder pathology, gastroparesis, pancreatitis)

Basic Pharmacologic Mechanisms of Action

GLP-1 Receptor Agonists

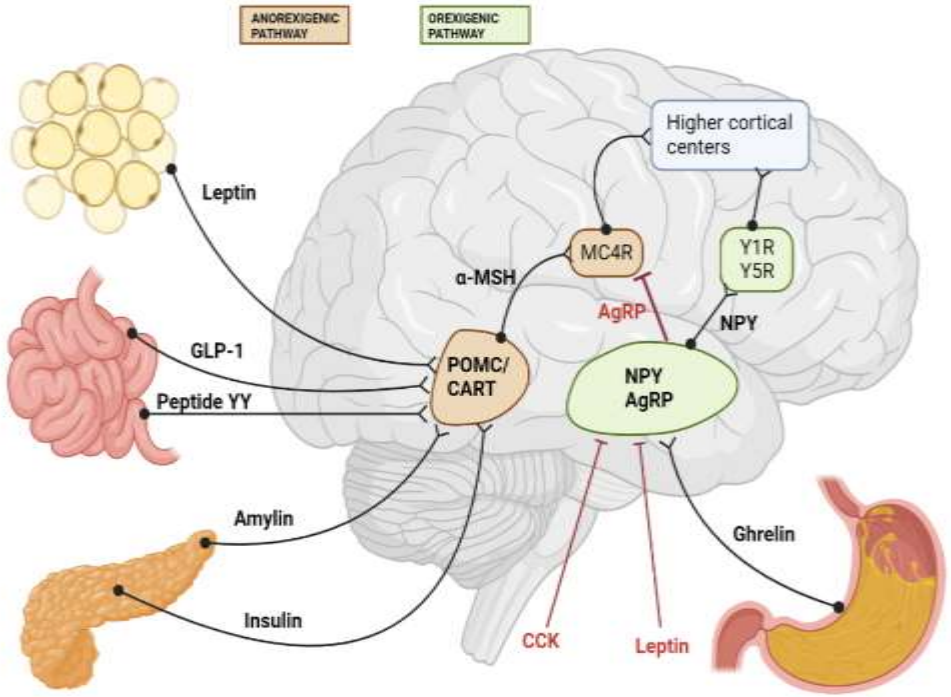




Oral Weight-loss Promoting Agents

Oral agents for obesity treatment work primarily in the arcuate nucleus to **stimulate**:

- **Pro-opiomelanocortin (POMC) neurons and promote satiety.**
- **Cocaine Amphetamine Related Transcript (CART) neurons in the arcuate nucleus to decrease food intake and increase energy expenditure.**



What Influences Refractory Weight-Loss Efforts

- **GENETICS**:
  - **150 genetic variants** adversely influence pathways **affecting CNS processing, Neural Regulation of Feeding**, and **Fasting Insulin Secretion/Action**.

- **Leptin Levels**:
  - Free Leptin levels decrease within 24-hours of energy restriction (or ***"relatively" with "Leptin Resistance"***).
    - **Leptin's primary role** is the prevention of starvation (vs. weight regulation).
  - Reductions in leptin secretion **increases appetite**, excess food intake, and weight regain.

- **Insulin levels:**
  - Levels decrease **(**or ***"relatively" with insulin resistance*****)** → slowing fat metabolism.

- **Adaptive Thermogenesis** (Metabolic Adaptation):
  - **Compensatory slowing of Resting Metabolic Rate** (RMR)
  - Promotes decrease in energy expenditure.
  - Formerly obese individuals have 3–5% lower RMR than non-obese.

- **Increased Neural Dopamine Signaling:**
  - Decrease in **"*Rewards from Food*"** encourages increased ***Neural Dopamine Signaling***
  - Rekindles **increased** **"*compensatory desire*"** for consumption

Focus of Nutritional Therapy for all individuals:

Reduced energy intake – emphasis on **Nutrient-dense, Fiber-rich Foods** – **Regular Physical Activity**

What Predisposes to Visceral Fat Acquisition?

- **Age**:
  - **Body weight increase observed with age** is **more likely to accumulate in the abdominal area** vs. gluteo-femoral.
  - **Deterioration in plasma glucose and insulin homeostasis** seems to closely reflect the **age-related increase in visceral adiposity seen**.

- **Gender**:
  - **Men are more** likely to accumulate adipose tissue in the **upper body** (trunk, abdomen), whereas **women usually** accumulate adipose tissue in the **lower body**.
  - Well established is a **sex-dimorphism in LDL particle size** whereby women exhibit larger LDL particles than men.

- **Sex-Hormones**:
  - **Female-to-male transsexuals** treated with intramuscular testosterone injections have shown a progressive shift in body fat distribution **favoring an android pattern**. Conversely, estrogen treatment of **male-to-female transsexuals increases subcutaneous fat** deposition with little effect on the visceral fat compartment.
  - **Reduced estrogen levels after menopause** have been associated with **increased visceral fat deposition**.

- **Genetics**:
  - **Up to 150 candidate genes** have been identified as being **linked to obesity-related phenotypes**, including 253 quantitative trait loci **(*DNA region associated with specific phenotype/trait that varies within a population*)**.
  - Studies have identified **genetic variants** possibly related to **preferential accumulation of visceral fat** and its metabolic complications.

What Predisposes to Visceral Fat Acquisition?

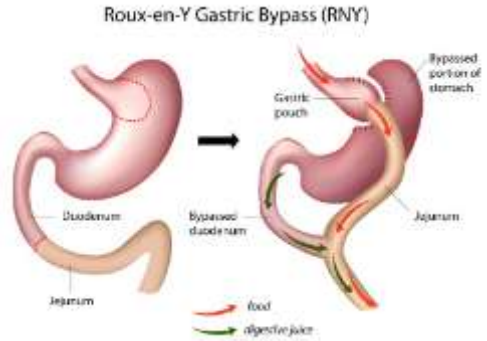
- **Hypercortisolemia**:
  - Studies suggest that **chronic distress/**stressful situations are **associated with mild hypercortisolemia** and **accelerated systemic sympathetic tone**, which may favor accumulation of visceral fat.
  - A genetic predisposition toward **increased local cortisol synthesis in adipose tissue** (absent central HPA axis alterations) is clearly recognized as an etiologic factor for **non-Cushing abdominal obesity**.

- **Nutrition**:
  - **Increased saturated fat intake** might predispose to preferential accumulation of visceral fat.
  - **Soft drink consumption** and the concomitant **intake of fructose** may encourage visceral fat acquisition.

- **Sedentary Life-Style**:
  - The peculiar **β-adrenergic responsiveness inherent to visceral adipose tissue** as driven by the sympathetic drive associated with **vigorous exercise**, could explain the **selective mobilization of the visceral lipid depot** versus subcutaneous fat.

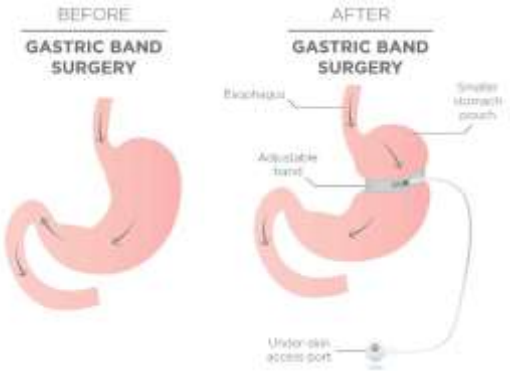
Bariatric Surgery: 3 Primary Approaches

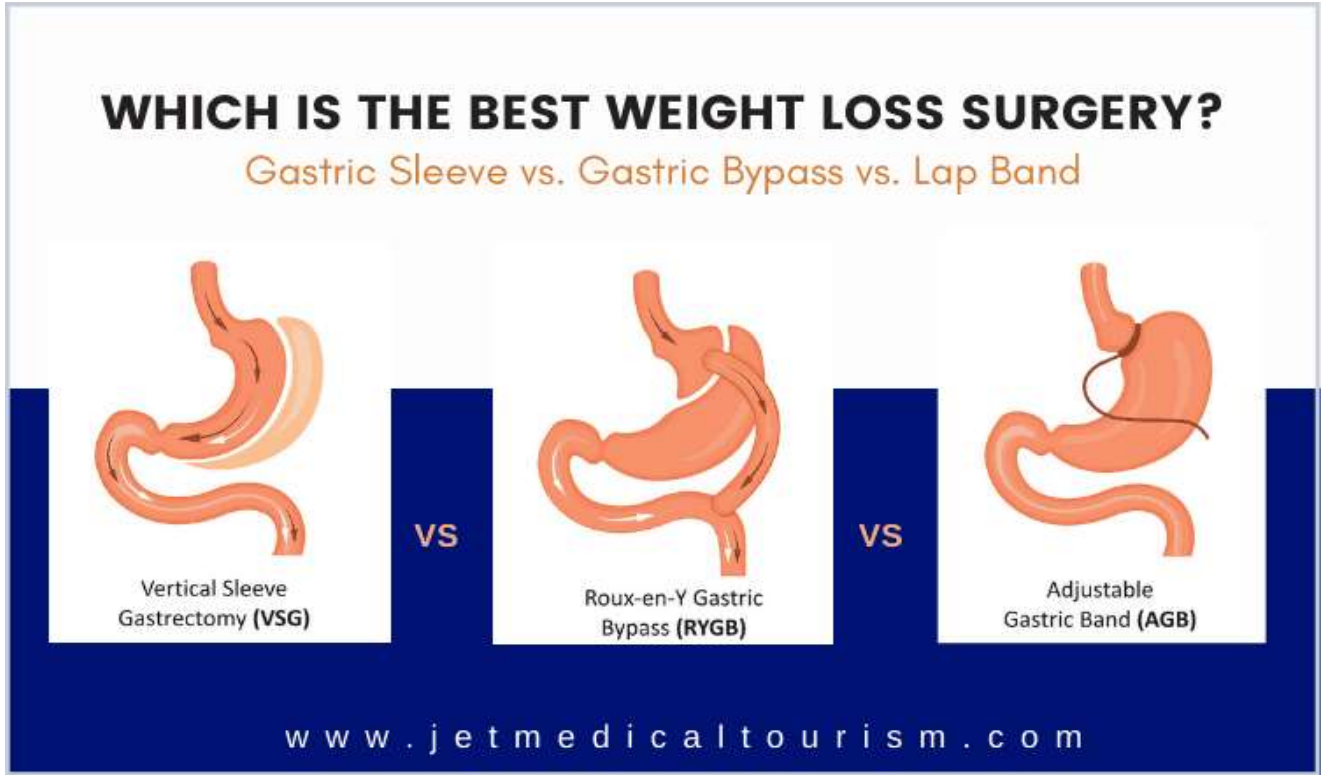
- **Roux-en-Y Gastric Bypass** (RYGB):



- **Vertical Sleeve Gastrectomy** (VSG):

- **Adjustable Gastric Banding** (AGB):





Bariatric Surgery: 3 Primary Approaches

- **Roux-en-Y Gastric Bypass (RYGB): 30-35% weight reduction**
  - Creation of a small gastric pouch (~30 mL) anastomosed to proximal jejunum; forms the "alimentary limb."
  - Continuity of intestine restored via a jejuno-jejunal anastomosis
  - Food bypasses most of stomach, duodenum, and proximal jejunum.
  - **Rapid delivery of nutrients** to jejunum and ileum (highest number of GLP-1-secreting L-cells) **triggers enhanced GLP-1 secretion**.

- **Vertical Sleeve Gastrectomy (VSG): 25-30% weight reduction**
  - Dividing stomach along its vertical length to create a sleeve and remove ~75% of its volume
  - Rapid emptying of high-pressure gastric remnant creates "**functional intestinal bypass**".
  - Exhibits consistent **decrease in** the postprandial concentration of **Ghrelin**.

- **Adjustable Gastric Banding (AGB): 20-25% weight reduction**
  - Placing a silicone ring around proximal stomach, bellow the gastroesophageal junction.
  - Ring pressure adjusted through fluid injected or withdrawn from subcutaneous port
  - **Mechanism of action** is exclusively via **altered vagal signaling** by the extraluminal pressure **(by "band & food")** on vagal afferents that send anorexigenic signals to brainstem;
  - Limited success with AGB (compared to RYGB/VSG) because the **AGB activates only 1 signaling system** to the brain.

Bariatric Surgery: Weight-Loss Mechanisms (RYGB, VSG, AGB)

- **Eating Behavior** (Body-weight Set-Point theory):
  - **Set-point theory:** body-weight trajectory influenced by genetic make-up and nonbiological factors (i.e. social, psychological) to determine final phenotype.
  - Weight loss below or above setpoint is perceived as an alarm by hypothalamus and brainstem to modulate eating response.
  - Similar to caloric restriction during acute negative-calorie phase of eating, there is a decrease in hunger and increase in satiety.
  - Different than dieting, obesity **surgery reduces setpoint 20%-30%.**
  - Manipulation of stomach and small intestine prompts **change in humoral and neural signals** from gut to brain and **maintain new setpoint**.

- **Hypothalamic Gene Expression** of **AgRP** and **NPY decline (POM-C unchanged)** following **RYGB** surgery

- **Food selection**:
  - After **RYGB** and **VSG** surgery (not AGB) patients shift from energy-dense sweet and fatty foods to less energy-dense options.
  - Food choices further altered by **modulation of brain "reward cue areas"** after **RYGB** and **VSG** (via direct **GLP-1** and **PYY** receptor stimulation)
  - **Reduced** production of **Oleoylethanolamide** (small intestine fat satiety molecule) coupled with Vagus nerve–driven **increase in** dorsal striatal **dopamine release**

Bariatric Surgery: Weight-Loss Mechanisms (RYGB, VSG, AGB)

- **Energy Expenditure**:
  - **Increased energy expenditure** through enhanced glucose utilization by **hypertrophied small intestine** and change in body composition (increased lean-to-fat-mass ratio)
  - **Increased Brown Fat deposition** (**RYGB**) → ↑**Thermogenesis** and **Triglyceride clearance**.

- **Gut Hormones**:
  - After RYGB, absent mechanical restriction at level of the gastrojejunal anastomosis enables **rapid delivery of nutrients to jejunum and ileum** (highest number of **GLP-1**-secreting L-cells) triggering **enhanced GLP-1 secretion**.
  - **VSG** thought to engage same mechanism (though less robust) through rapid emptying of the high-pressure gastric remnant creating a "**functional intestinal bypass**".
  - **VSG** more than RYGB, exhibits a consistent **decrease in** the postprandial **Ghrelin levels**.
  - **Accelerated post-prandial secretion of Oxyntomodulin** a dual agonist of glucagon and GLP-1 receptors, may act **additively to GLP-1** to reduce food intake, appetite, and desire for energy-dense foods.

Bariatric Surgery: Weight-Loss Mechanisms (RYGB, VSG, AGB)

- **Bile Acids**:
  - **Total Bile Acids** and **Fibroblast Growth-Factor-19 (FGF19) increase** after **RYGB** and **VSG**
  - Bile acids increase energy expenditure by promoting intracellular thyroid hormone activation
  - **FGF-19 signals energy-replete state to suppress hypothalamic AgRP/NPY neurons** and reduce feeding
  - **Bile acids inhibit appetite** through **stimulation of GLP-1 and PYY** secretion

- **Gut Microbiota**:
  - After **RYGB**, studies in humans consistently demonstrate **an increase in gut microbiota diversity**, spatial organization and stability; specifically, Proteobacteria
  - Gut microbiota **increase short-chain fatty acids**, which **stimulate GLP-1** via free fatty acid receptor-2.
  - **Duodenal-jejunal bypass** with **minimal gastric resection** component of **RYGB** is presumed catalyst for **increased microbial richness/abundancy**.