# Obesity

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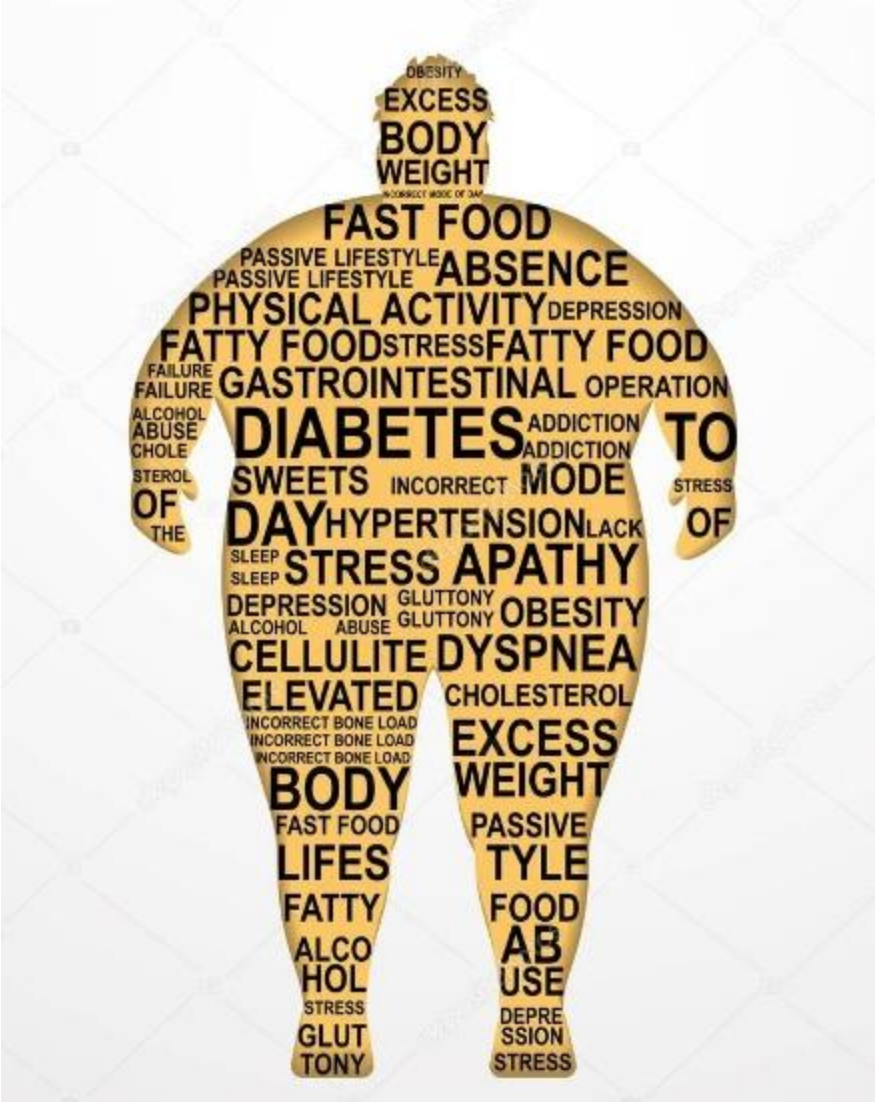


# Definition:

- Obesity is a complex medical condition marked by the excessive accumulation of body fat, leading to detrimental effects on overall health. This condition manifests in various clinical consequences that impact nearly every organ system and associated with a chronic low-grade inflammatory state and immune dysfunction.
- The extent of obesity is typically measured using the body mass index (BMI), calculated as the ratio of weight in kilograms to height in meters squared (BMI = weight [kg]/height $[m]^2$).
- The international classification of adult overweight and obesity according to body mass index (BMI):

❖ Normal range 18.50–24.99

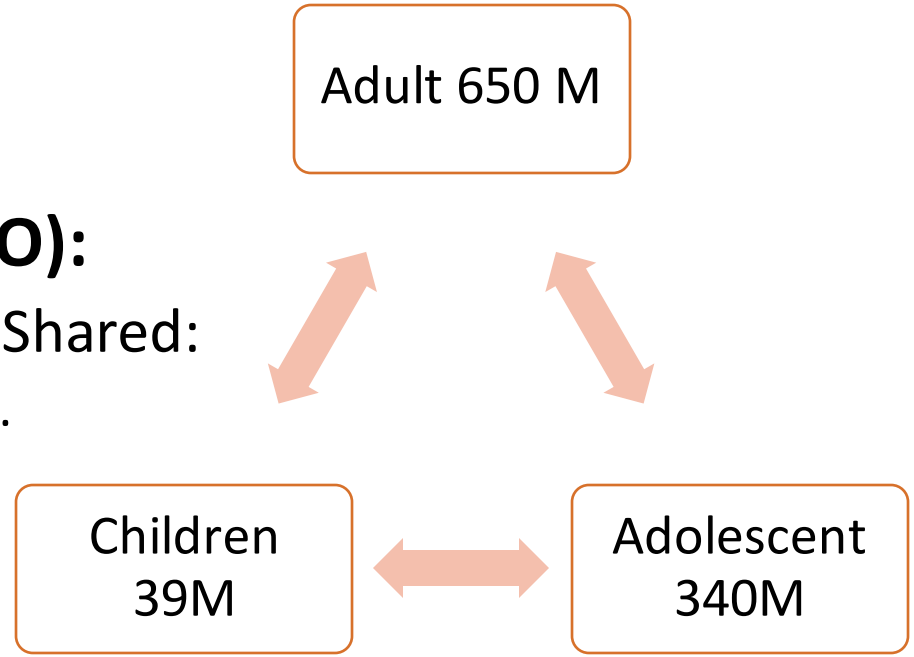
❖ Overweight (Pre-obese) 25.00–29.99

❖ Obese class I 30.00–34.99

❖ Obese class II 35.00–39.99

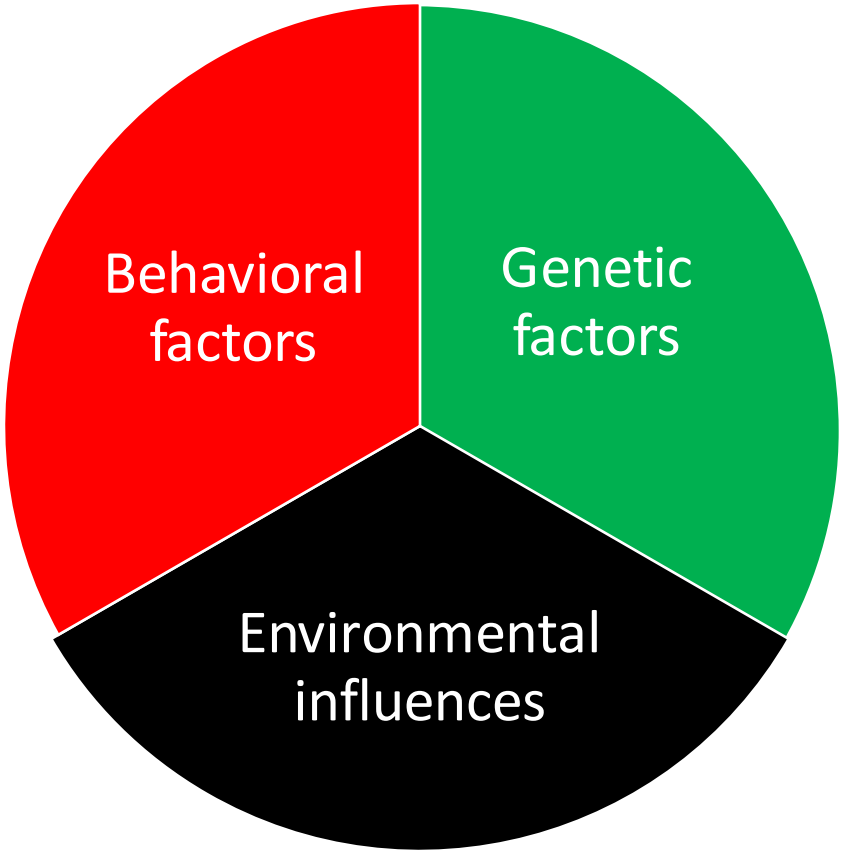
❖ Obese class III ≥40.00

# The global prevalence of obesity




- **In 2022:World Health Organization (WHO):**
  - Alarming Global Obesity Prevalence Figures Shared:
    - More than 1 billion people worldwide are obese.
      - 650 million adults
      - 340 million adolescents
      - 39 million children
    - This number is still increasing.
  - WHO Estimates by 2025:
    - Approximately 167 million people, both adults and children, will face health challenges due to being overweight or obese.

# Causes and Risk Factors:



## ➢ Genetic factors:

Individualized Genetic Impact: The development of obesity is not uniform across individuals exposed to the same environment, indicating a personalized genetic influence. Twin, family, and adoption studies reveal a high heritability rate of BMI, ranging from 40% to 70%.

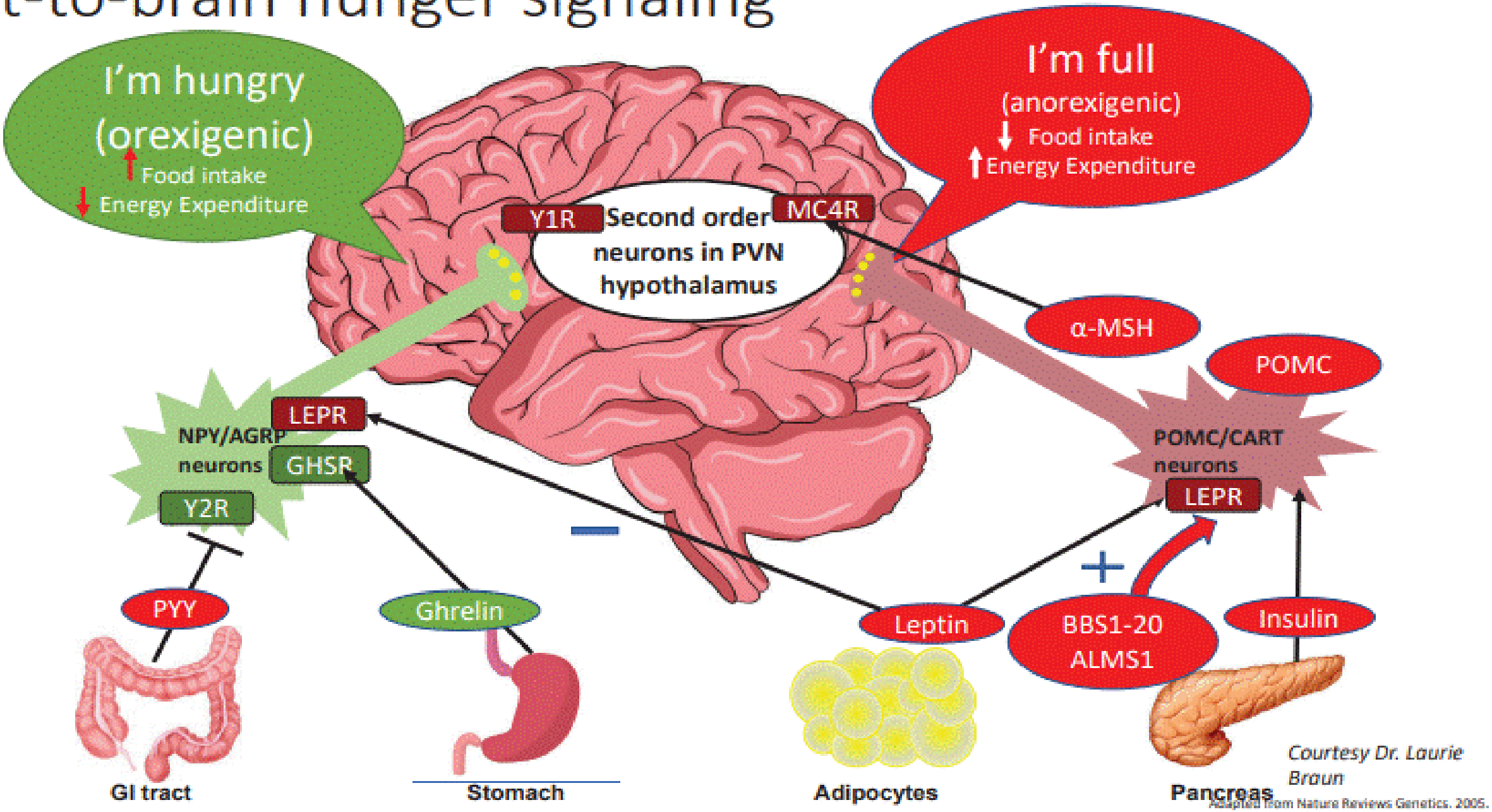
Eleven recognized rare and *monogenic forms of obesity* highlight specific genetic deficiencies, such as *leptin and melanocortin-4 receptors.* Heterozygous mutations in the melanocortin-4 receptor gene are currently the most common cause of *monogenic obesity*, affecting 2% to 5% of children with severe obesity

## ➢ Environmental influences & Behavioral factors:

- **Complex Responses to Caloric Restriction:** Reducing food intake or increasing physical activity initiates a negative energy balance, triggering compensatory adaptive mechanisms. These mechanisms include reductions in resting energy expenditure and increased appetite, limiting the expected weight loss associated with interventions like exercise programs.
- **Adipose Tissue Dynamics and Metabolic Implications:** Individuals with obesity display an excess of adipose cells, determined early in life. Adult-onset obesity primarily results from an increase in both the size and number of adipose cells. Distribution of adipose tissue, particularly central visceral fat, is associated with metabolic diseases such as diabetes, hypertension, and the metabolic syndrome, with gender differences in fat distribution.

- Neural circuits in the **hypothalamus** play a key role in the regulation of human energy homeostasis.
- A critical circuit involves **Leptin**-responsive neurons in the hypothalamic arcuate nucleus (the infundibular nucleus in humans) expressing the *appetite-suppressing neuropeptide* **ProOpioMelanoCortin (POMC)** and the *appetite-stimulating* **Agouti-related peptide.**
- In the fed state, the POMC-derived melanocortin peptide α-melanocyte-stimulating hormone stimulates **MelanoCortin-4 Receptors (MC4Rs)** expressed on second-order neurons in the **ParaVentricular Nucleus (PVN)** of the hypothalamus.
- Agonism of MC4R leads to reduced food intake and increased energy expenditure.
- Disruption of this hypothalamic circuit by inherited mutations in the genes encoding Leptin, the Leptin receptor, POMC, and MC4R can lead to severe obesity in humans.

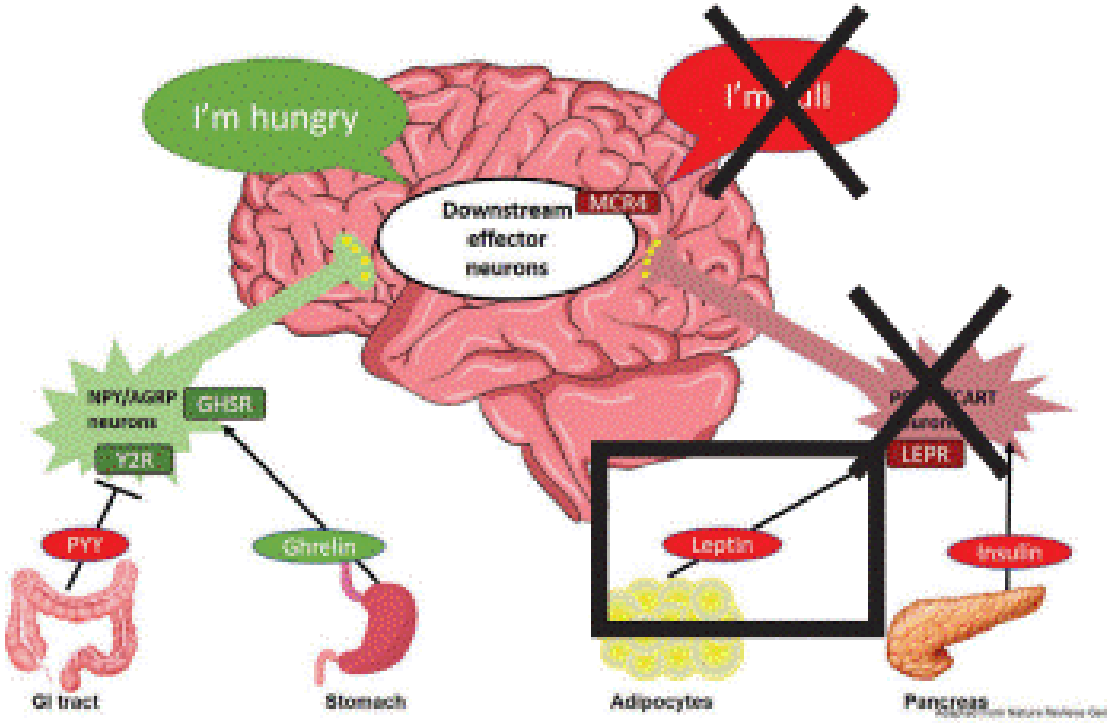
# Gut-to-brain hunger signaling




*Courtesy Dr. Laurie Braun*

Adapted from Nature Reviews Genetics. 2005.

# Monogenic Obesity

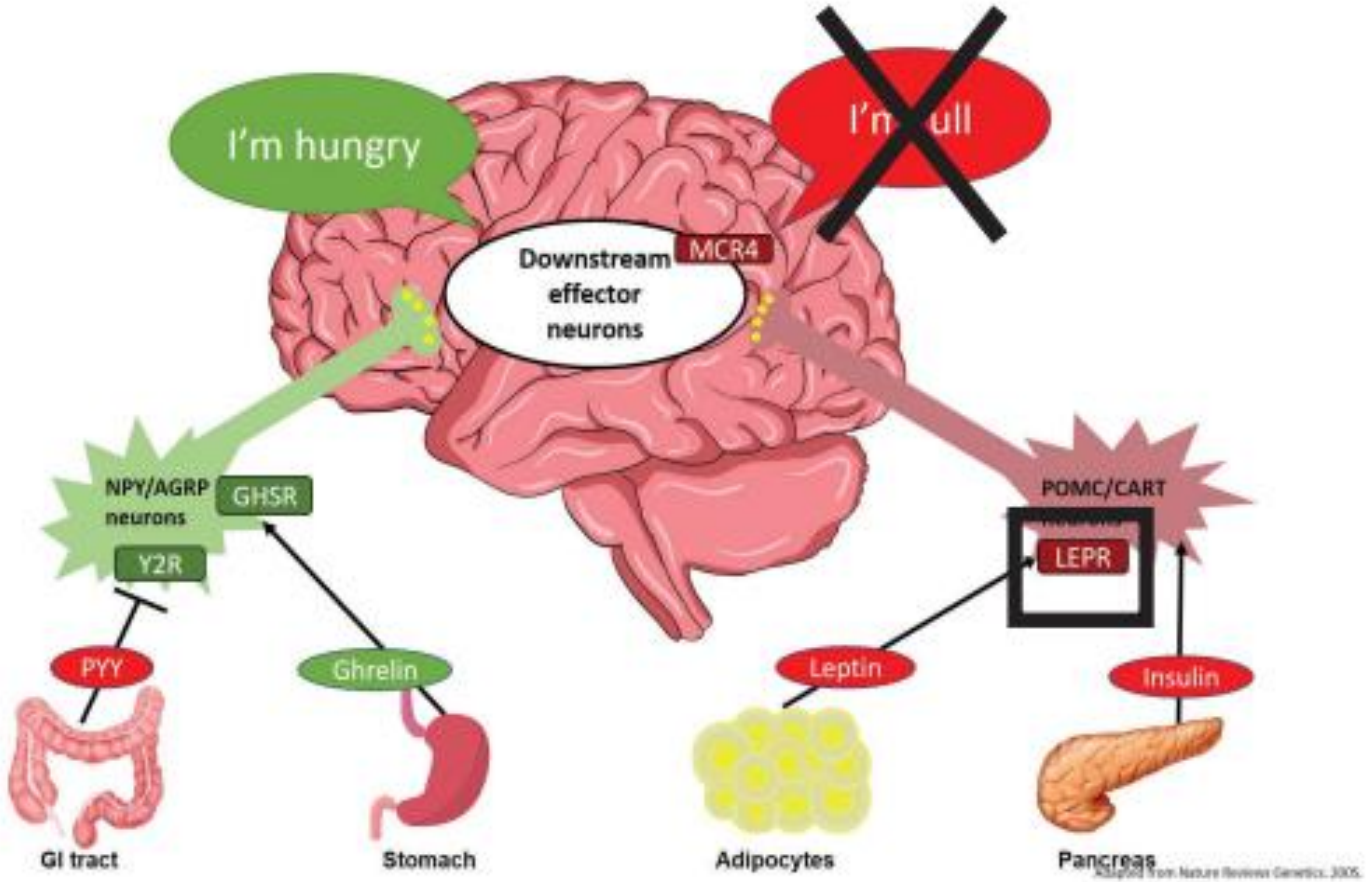



# Congenital Leptin Deficiency

- **Cause**: mutations in gene for leptin (*LEP*)
- **Phenotype**: Hyperphagia with severe, early onset obesity, altered immune function and delayed puberty
- **Prevalence**: EXTREMELY RARE – only several case reports in consanguineous families*
- **Diagnostic test**: leptin level (undetectable), genetic testing
- **Treatment**: recombinant leptin

*Mostly found in consanguineous families.

# Monogenic Obesity:




# Leptin receptor deficiency

- **Cause:** mutations in gene for leptin receptor (*LEPR*)
- **Phenotype:** Hyperphagia with severe, early-onset obesity and problems with sexual development [same as leptin deficiency]
- **Prevalence:** EXTREMELY RARE- only several case reports*
- **Diagnostic test:** leptin level [very high], genetic testing
- **Treatment:** none available, MC4R agonist in development

- Monogenic obesity is a **rare form of obesity that results from mutations in a single gene**.
- Monogenic obesity usually causes **severe and early-onset obesity**.
- Monogenic obesity can be non-syndromic, meaning obesity is the only symptom, or syndromic, meaning obesity is accompanied by other features, e.g. Prader Willi syndrome (PWS), the most common syndromic form of obesity.
- Other syndromes include: Bardet-Biedl syndrome (BBS) is a rare syndromic form of obesity, Alstrom syndrome, WAGR syndrome.

# OBESITY INCREASES THE RISK OF:

- ASTHMA
- CHRONIC OBSTRUCTI VE PULMONARY DISEASE
- OBSTRUCTIVE SLEEP APNOEA

- GOUT
- OSTEOARTHITIS
- LOWER BACK PAIN

- GALLSTONES
- PANCREATITIS
- LIVER DISEASE
- GASTRO-OESOPHAGEAL REFLUX DISEASE

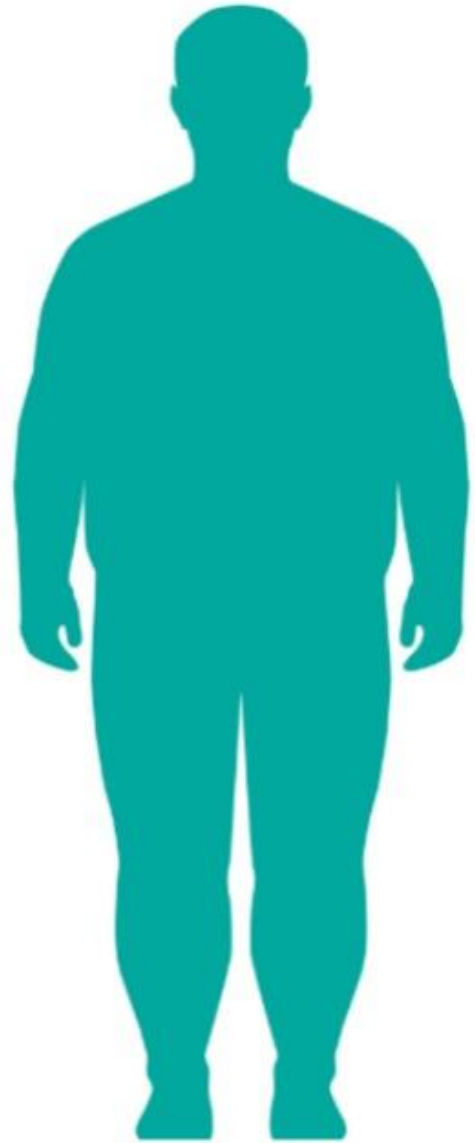
- INFERTILITY
- KIDNEY DISEASE
- COMPLICATIONS DURING PREGNANCY AND BIRTH

- HEART FAILURE
- HYPERTENSION
- ISCHAEMIC STROKE
- ISCHAEMIC HEART DISEASE

- DEMENTIA
- INTRACRANIAL HYPERTENSION
- DEPRESSION

- TYPE II DIABETES

- BREAST CANCER
- COLON CANCER
- ENDOMETRIAL CANCER
- OVARIAN CANCER
- RECTAL CANCER
- PROSTATE CANCER



# Obesity Clinical Presentation

## ❑History Taking:

1. **Clinical Presentation:**
   - Patients typically report weight concerns or challenges in sustained weight loss.
   - Some may present with complications or associated conditions (mentioned above).
2. **Key History Components:**
   - Detailed dietary inventory and activity analysis.
   - Screening for depression and eating disorders.
3. **Family History and Expectations:**
   - Exploration of family weight history.
   - Understanding patient expectations and motivation.
4. **Comorbidities.**

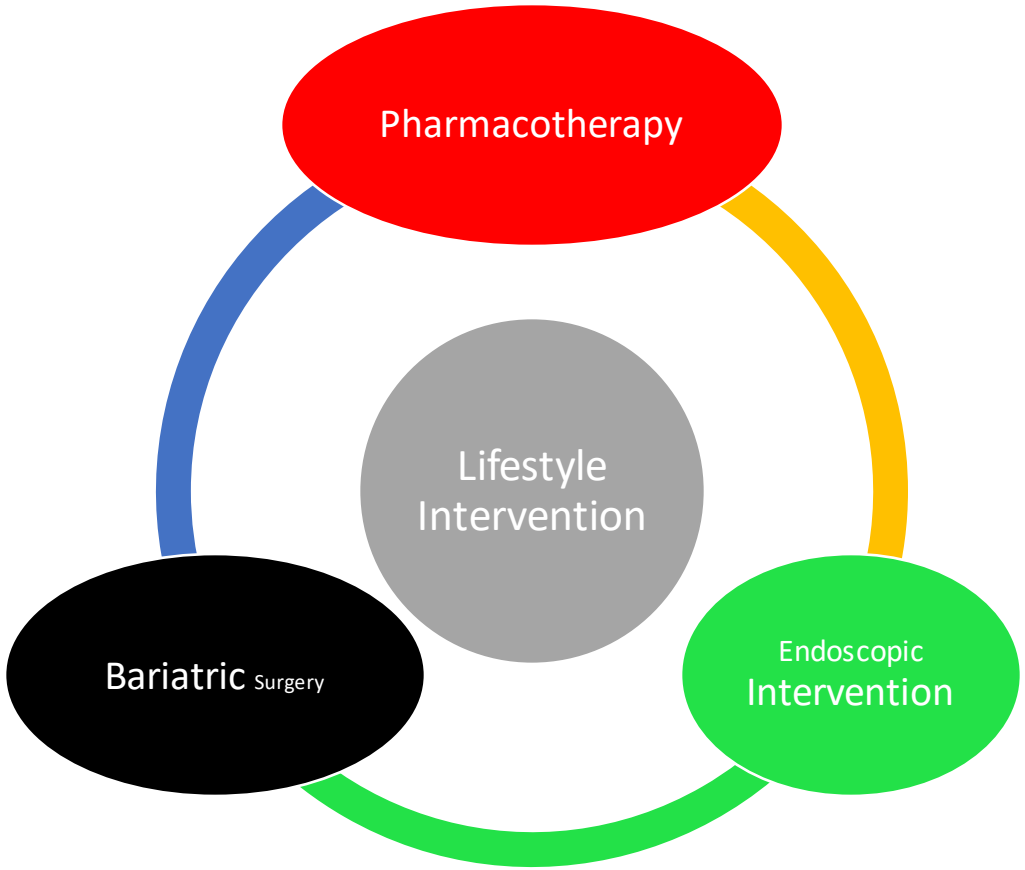
## ❑ Physical Examination:

- **Anthropometric Measurements:**
  - Measure waist and hip circumference for estimating visceral fat.
  - Neck circumference is predictive of sleep apnea risk and aids in risk stratification.
- **Organ System Examination:**
  - **Cutaneous:**
    - Look for intertriginous rashes, hirsutism in women, acanthosis nigricans, and skin tags indicating insulin resistance.
  - **Cardiac and Respiratory:**
    - Exclude cardiomegaly and respiratory insufficiency.
  - **Abdominal:**
    - Exclude tender hepatomegaly, indicating hepatic fatty infiltration or NASH.
    - Distinguish striae distensae from broad, pink striae suggesting cortisol excess.
  - **Extremities:**
    - Search for joint deformities , evidence of osteoarthritis, pressure ulcerations.
    - Identify localized and lipo-dystrophic fat distribution associated with insulin resistance.

- Standard laboratory studies in the evaluation of obesity should include the following:

- CBC
- Liver function studies
- Kidney Function tests.
- Thyroid Function tests
- Fasting glucose and hemoglobin A1c (HbA1c)

# ❑ MANAGEMENT OF OBESITY:



- **Lifestyle Intervention:**

*The first option for weight management, given their low cost and low risk.

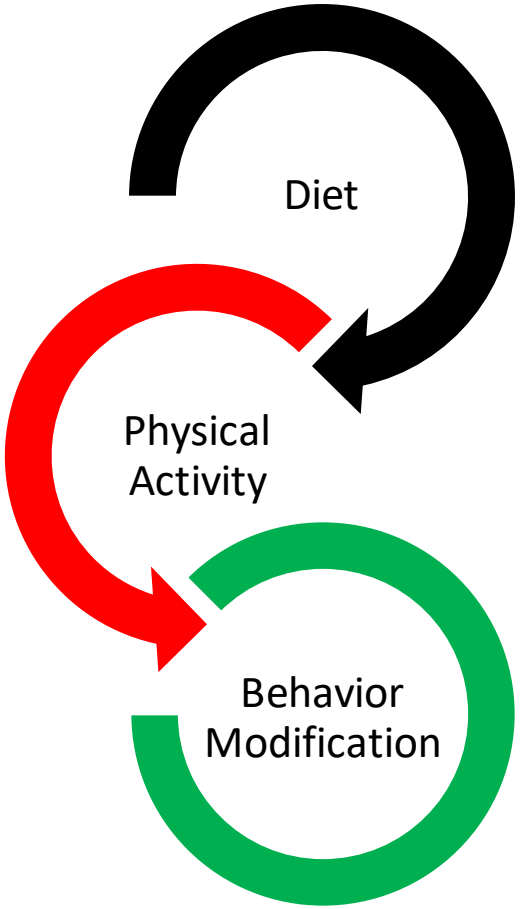
*Self-monitoring of caloric intake and physical activity

*Goal setting

*Stimulus control

*Nonfood rewards

*Relapse prevention



- ↑ CR Fitness
- ↑ Muscle Strength
- ↓ Cardiometabolic risk
- ↓ Bone loss
- ↑ Physical function
- ↑ Body composition
- ↑ Weight loss / ↓ weight recurrence
- ↑ Appetite & eating regulation
- ↓ Depression symptoms
- ↑ Energy/vitality

## ➢ Pharmacotherapy:

- Medications may be considered as an adjunct to lifestyle modification in adults who have a BMI of 30 or higher or a BMI of 27 to 29 with at least one obesity-related condition.
- **Evolution and Challenges of Obesity Pharmacotherapy:** Since the 1960s, obesity pharmacotherapy has seen both successes and failures. Many medications induced weight loss but were withdrawn due to safety concerns, such as cardiovascular issues or mood-related side effects. Orlistat was the only survivor until 2017, known for its tolerability. However, the landscape changed with the discovery of gut hormones, particularly GLP-1 analogues, which proved effective in treating type 2 diabetes and exhibited clinically meaningful weight loss with a favorable safety profile for obesity. This marks a transformative era in obesity treatment.
- **Revolution in Obesity Treatment:** The application of knowledge about gut-brain communication, especially regarding hunger and satiety signals, has revolutionized obesity treatment. GLP-1 analogues, initially used for diabetes, have shown remarkable effectiveness in weight loss with minimal side effects, unlike traditional hormonal treatments. The ability to combine and refine these gut hormones, anticipating additive or synergistic effects, represents the next frontier in obesity pharmacotherapy. While questions about long-term safety, impact on clinical outcomes, and personalization remain, the field is entering an exciting era of rapid advancement and innovation.

Categorical weight loss and other pre-specified metabolic efficacy measures in participants in randomized clinical trials of pharmacotherapy for obesity with at least 2 years duration

| Acronym of the RCT | Length of FU | Study Drug | >5% WL | >10% WL | >15% WL | >20% WL | Other pre-specified primary end points at the end of the study (active drug versus placebo) |
|---|---|---|---|---|---|---|---|
| XENDOS (3) | 4yrs | Orlistat 120mg TID | 52.8% | 41.0% | NR | NR | ↓ Incidence of T2DM |
| | | Placebo | 37.3% | 20.8% | NR | NR | |
| SCALE Prediabetes (4) | 3yrs | Liraglutide 3.0mg OD | 49.6% | 24.8% | 11.0% | NR | ↓ Incidence of T2DM |
| | | Placebo | 23.7% | 9.9% | 3.1% | NR | |
| SEQUEL (5) | 2yrs | Phen/Top 15/92mg OD | 79.3% | 53.9% | 31.9% | 15.3% | None |
| | | Phen/Top 7.5/46mg OD | 75.2% | 50.3% | 24.2% | 9.2% | |
| | | Placebo | 30.0% | 11.5% | 6.6% | 2.2% | |
| STEP-5 (6) | 2yrs | Semaglutide 2.4mg OW | 77.1% | 61.8% | 52.1% | 36.1% | None |
| | | Placebo | 34.4% | 13.3% | 7.0% | 2.3% | |

RCT: randomized clinical trial. FU: follow up. Phen/Top: phentermine-topiramate.
WL: weight loss. TID: three times per day. OD: once daily. OW: once weekly.
T2DM: type 2 diabetes mellitus. CRP: C-reactive protein.

- Endoscopic Intervention:

Gastric botox

Intra-gastric balloon

Endoscopic sleeve gastroplasty

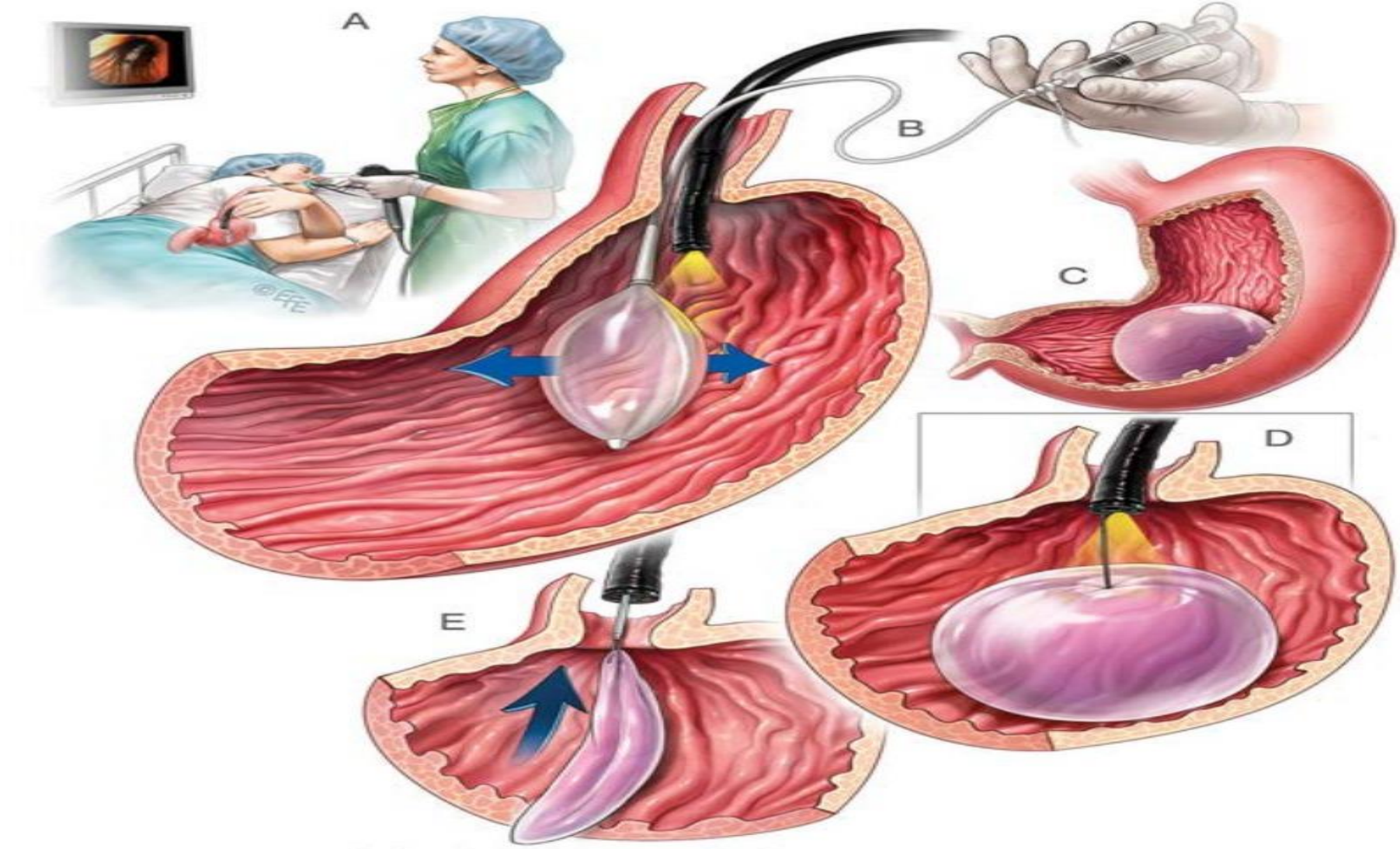



Figure 4-1: Intragastric Balloon

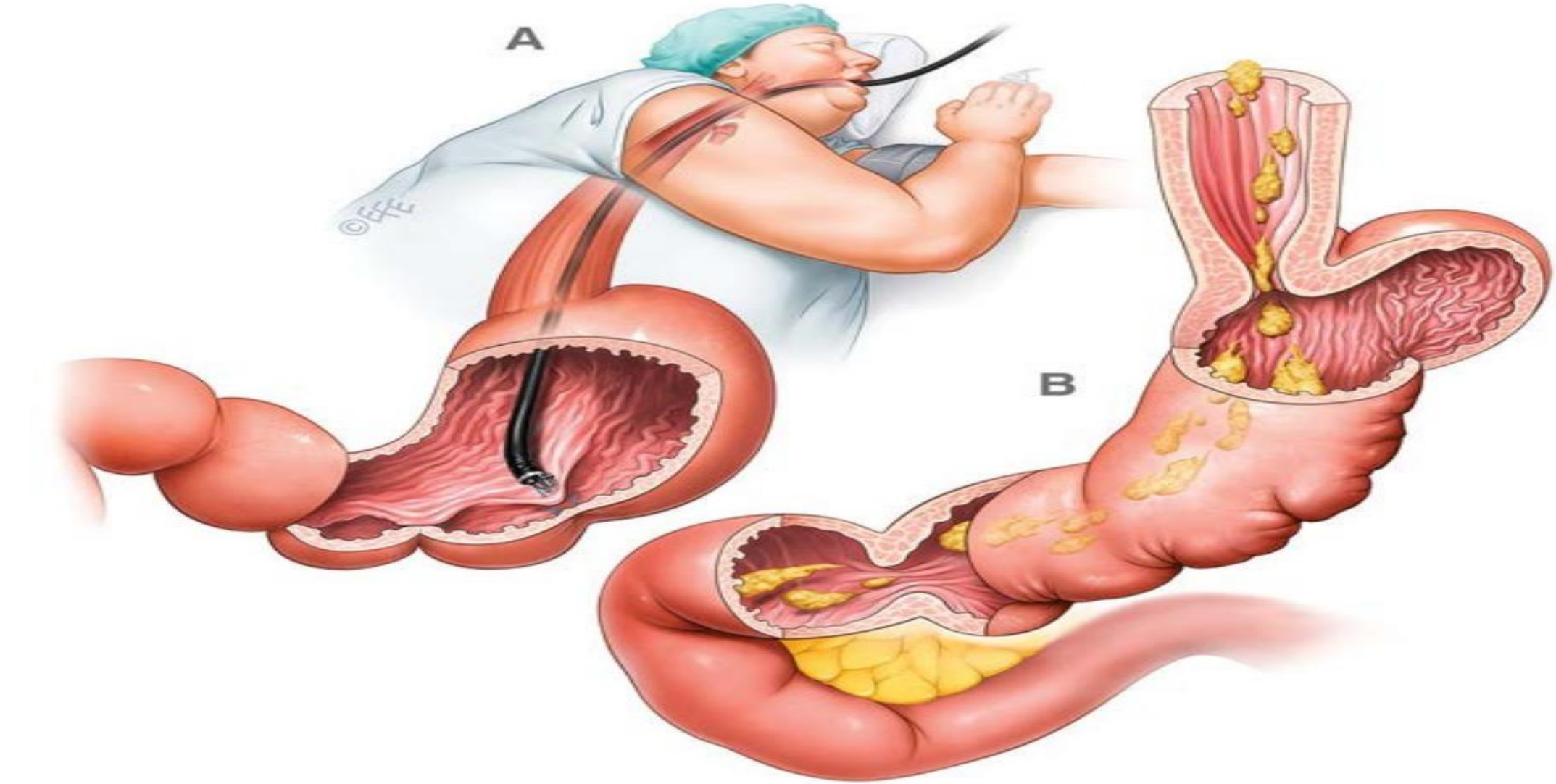



Figure 4-2: Endoscopic Sleeve Gastroplasty

# ➢ Metabolic Bariatric Surgery (MBS):

- Patient selection criteria for metabolic bariatric surgery:

1.Weight:

❖BMI >35

❖BMI >30 with metabolic complications

❖Asian population BMI >27.5

2. Weight loss history:

Failure of previous nonsurgical attempts at weight reduction, including nonprofessional programs

3. Commitment:

❖Expectation that patient will adhere to postoperative care

❖Follow-up visits with physician(s) and team members

❖Recommended medical management, including use of dietary supplements Instructions regarding any recommended procedures or tests

# Preoperative Preparation for Bariatric Surgery

The preoperative evaluation must be comprehensive and conducted by a multidisciplinary team.

This team could include: endocrinologists, dietitian, psychologists, anesthesiologists and surgeons.

Candidate selection criteria include body mass index, evaluation of comorbidities with respect to the patient's overall health.

# Psychological Evaluation

The assessment should include psychiatric history, screening for eating disorders and history of substance use.

Alcohol-dependent patients must start rehabilitation and detoxification before the procedure. One-year abstinence prior to surgery must be achieved.

Smoking cessation has proven improved outcomes and reduced postoperative complications.

# Nutritional Evaluation and Weight Loss Plan

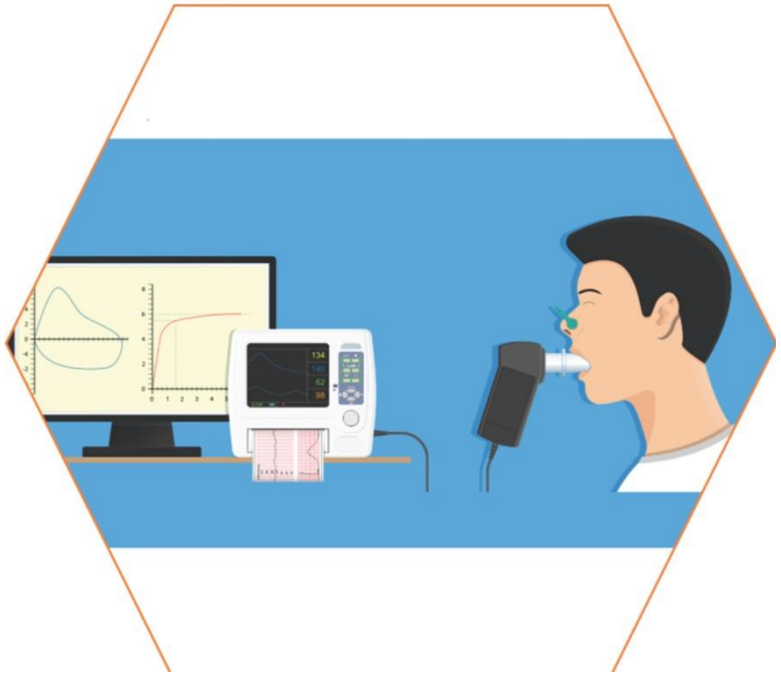
Prior weight loss attempts and adherence with therapy should also be discussed.

Bariatric surgery impacts on dietary intake and nutritional absorption and requires adherence to dietary guidelines, nutritional supplements and monitoring.

# Medical Clearance

Many patients present with obstructive sleep apnea and some of them may receive the diagnosis during the preoperative work-up.

It is not recommended universally, but in some centers a routine spirometry is performed.



# Abdominal Ultrasound (US):

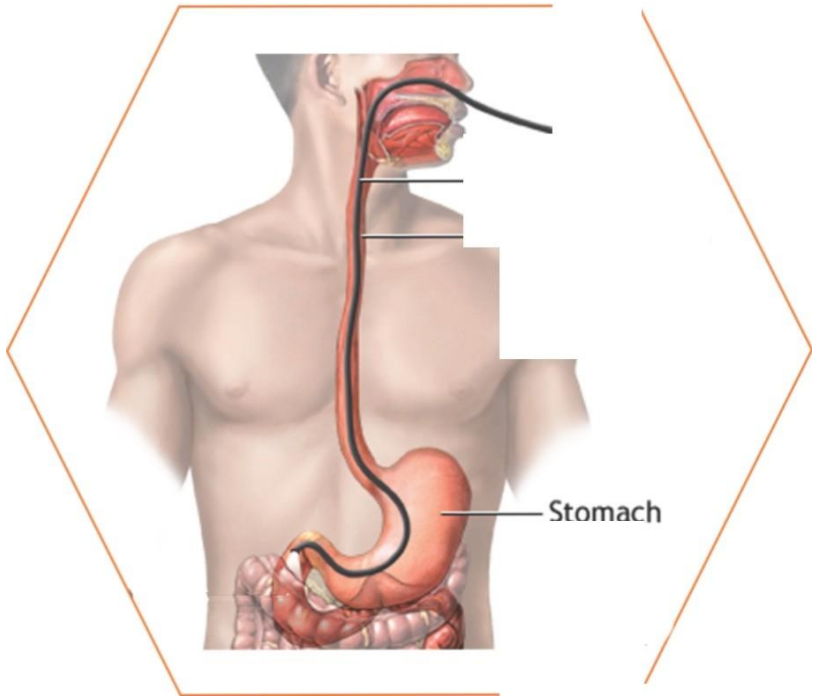
Patients with obesity have a high incidence of cholelithiasis, so US may be performed during the preoperative workout.

This is particularly important for patients undergoing Roux-en-Y gastric bypass because this procedure precludes the endoscopic exploration of the biliary tract in case of choledocholithiasis.

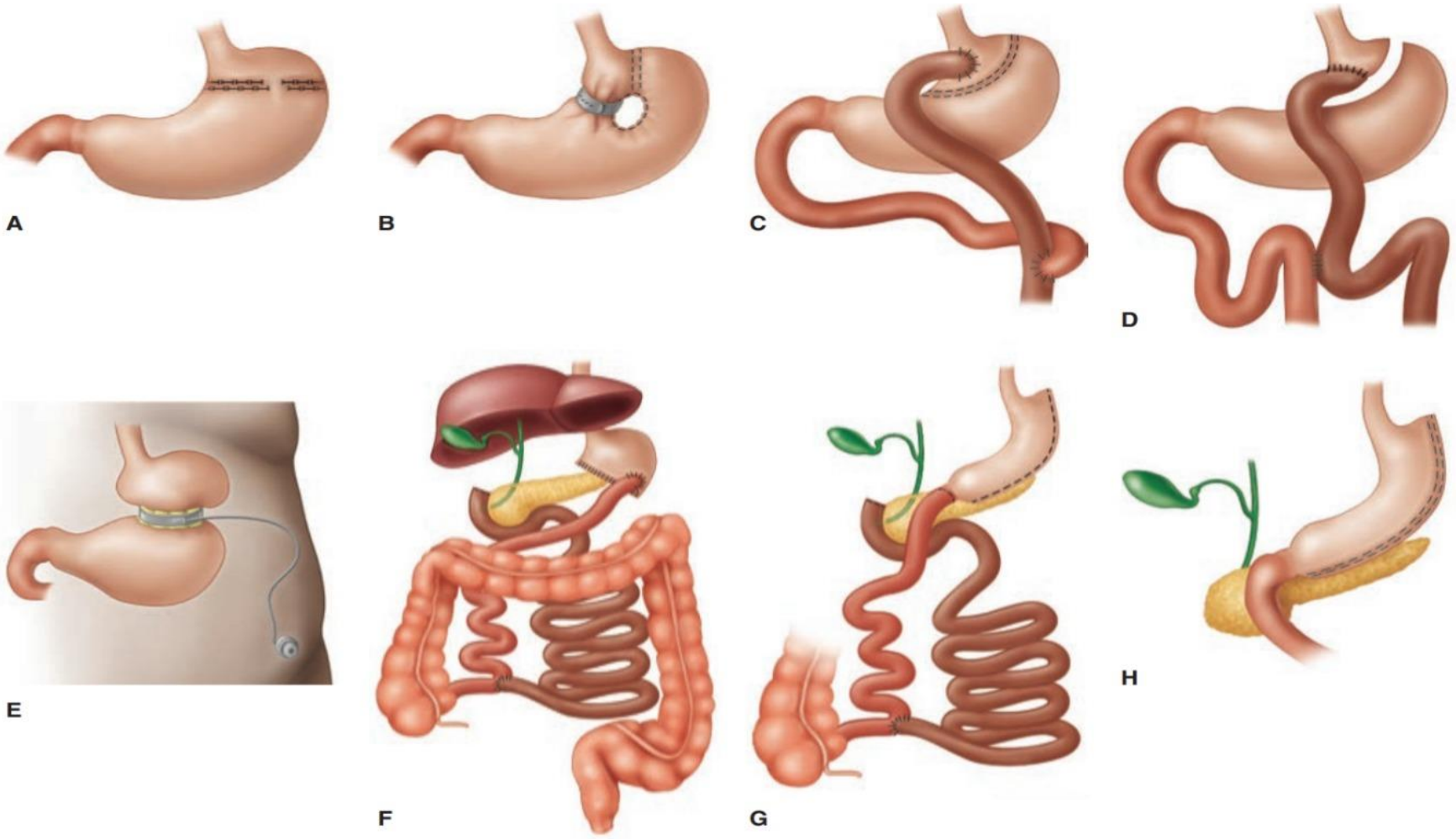
# Upper-GI Endoscopy:

A preoperative endoscopy may be recommended depending on the surgeon's discretion as obesity is a risk factor for many GI diseases.

Given the risk of developing GERD in some patients following Sleeve Gastrectomypatients with severe esophagitis or Barrett's disease should not be given the option of having Sleeve Gastrectomy.

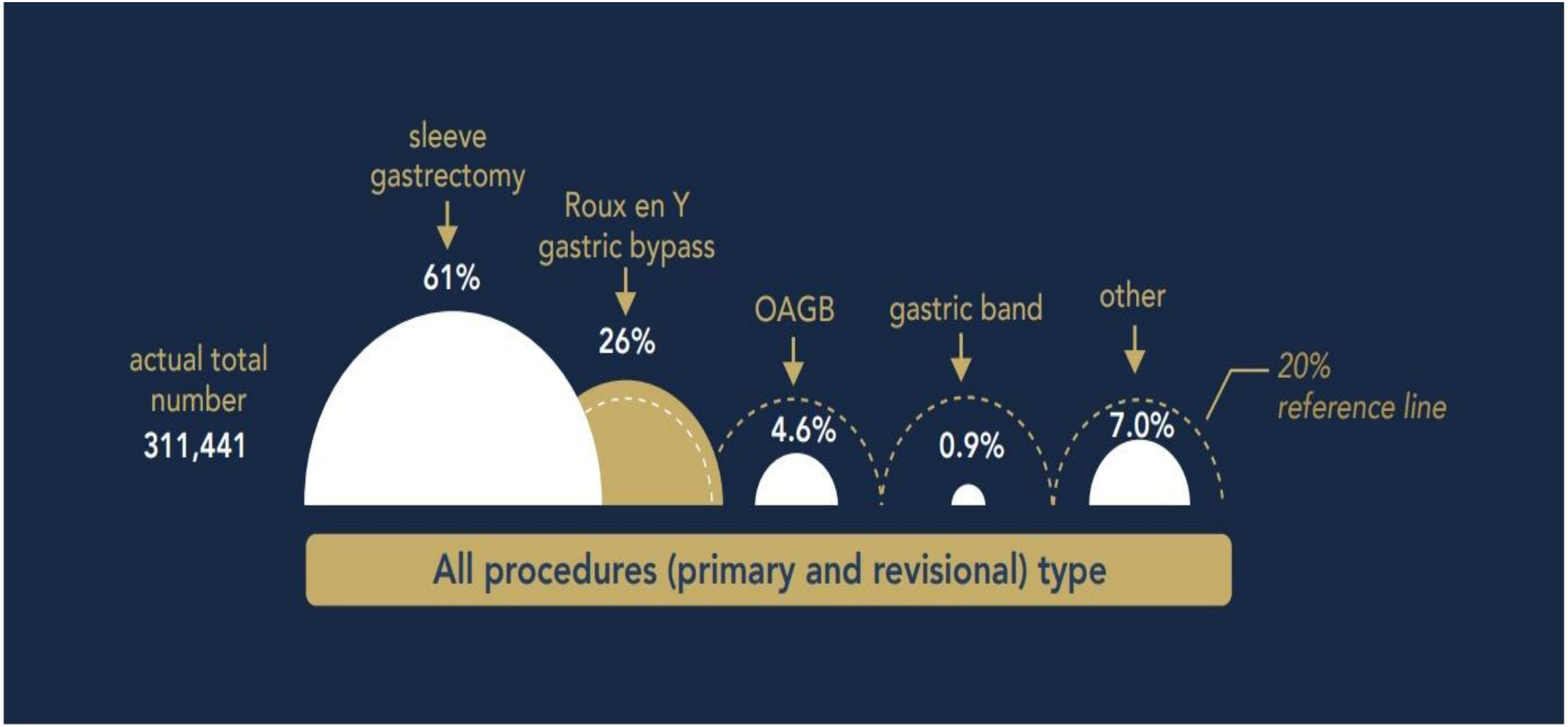


- Bariatric surgery procedure evolution:

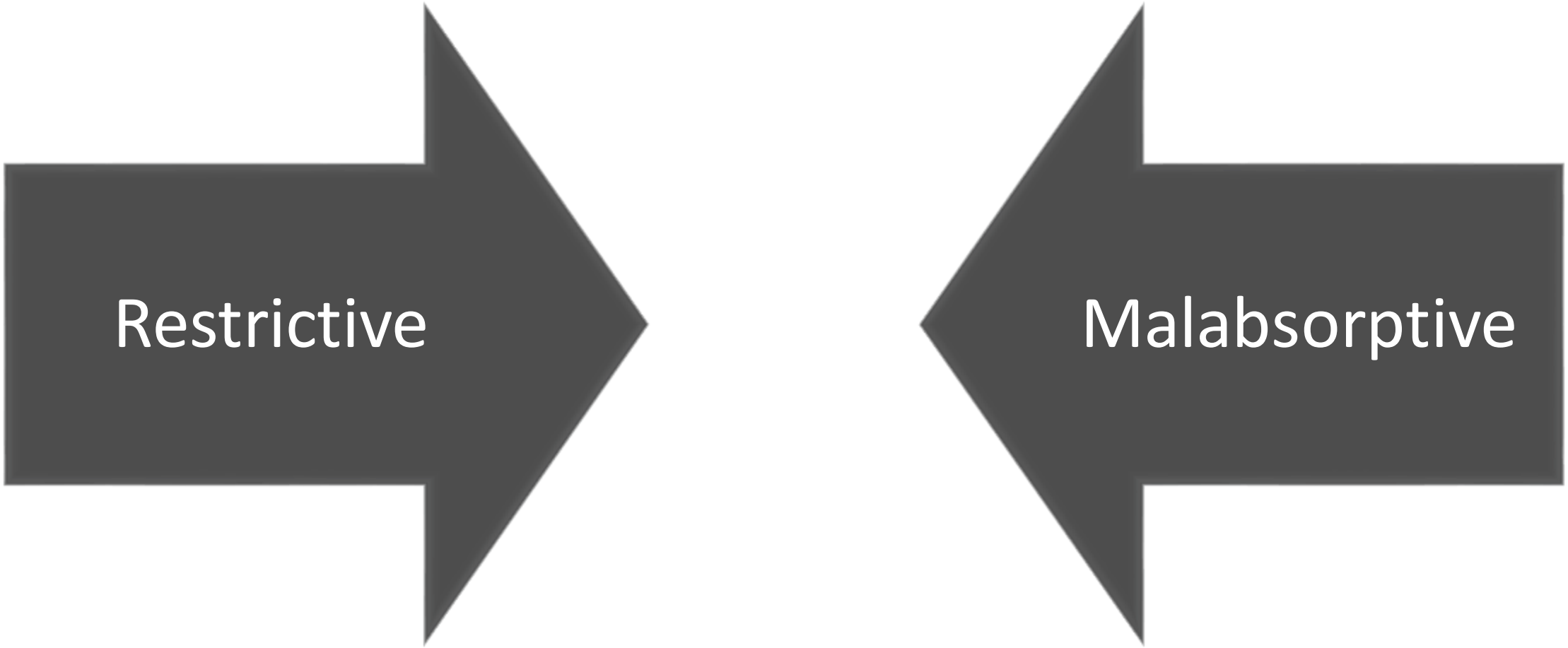



**Bariatric surgery procedure evolution**. **A.** Horizontal gastroplasty; **B.** vertical banded gastroplasty; **C.** Roux-en-Y gastric bypass; **D.** transected Roux-en-Y gastric bypass; **E** stric band; **F.** biliopancreatic diversion; **G.** biliopancreatic diversion with duodenal switch; **H.** vertical sleeve gastrectomy. *(Modified with permission from Arterburn D*

Frequency of use of various MBS procedures, as reported in the 7th IFSO Global Registry Report – 2022.



- Mechanisms of Bariatric Surgery:



## ➢ Laparoscopic Sleeve Gastrectomy (LSG):

- LSG was originally introduced as the first of a two-stage operative treatment for patients with super obesity (BMI >60 kg/m2 ).
- Its currently utilization is as a primary single-stage operation, but the possibility of a second-stage treatment remains, especially for the super obese patients, depending on the effectiveness of it as the primary operation.
- The sleeve gastrectomy typically results in 60 to 75 percent excess weight loss from your baseline starting point

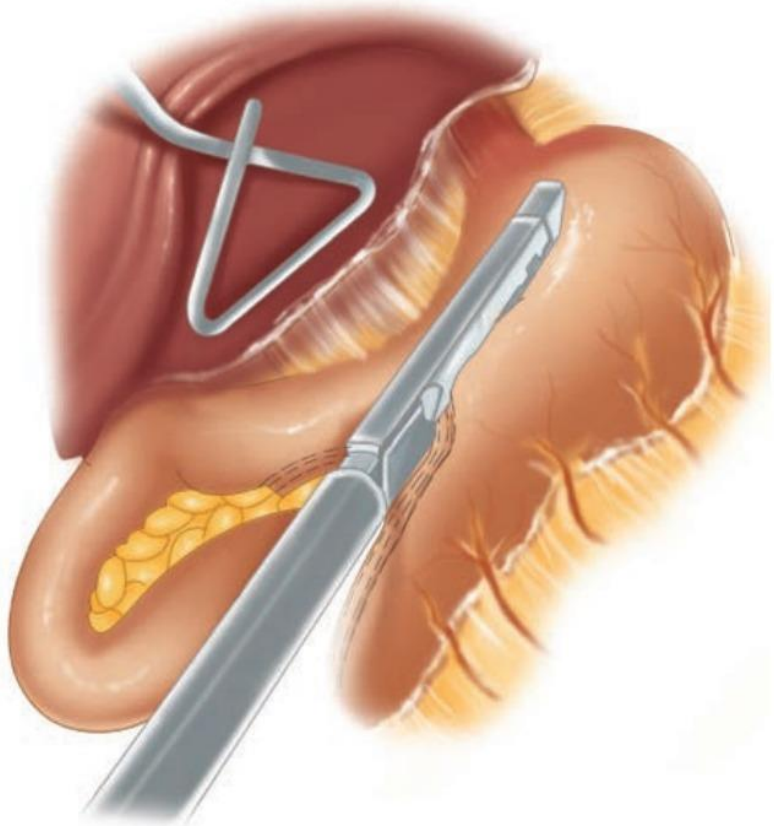
## ➢ Laparoscopic Sleeve Gastrectomy (LSG):

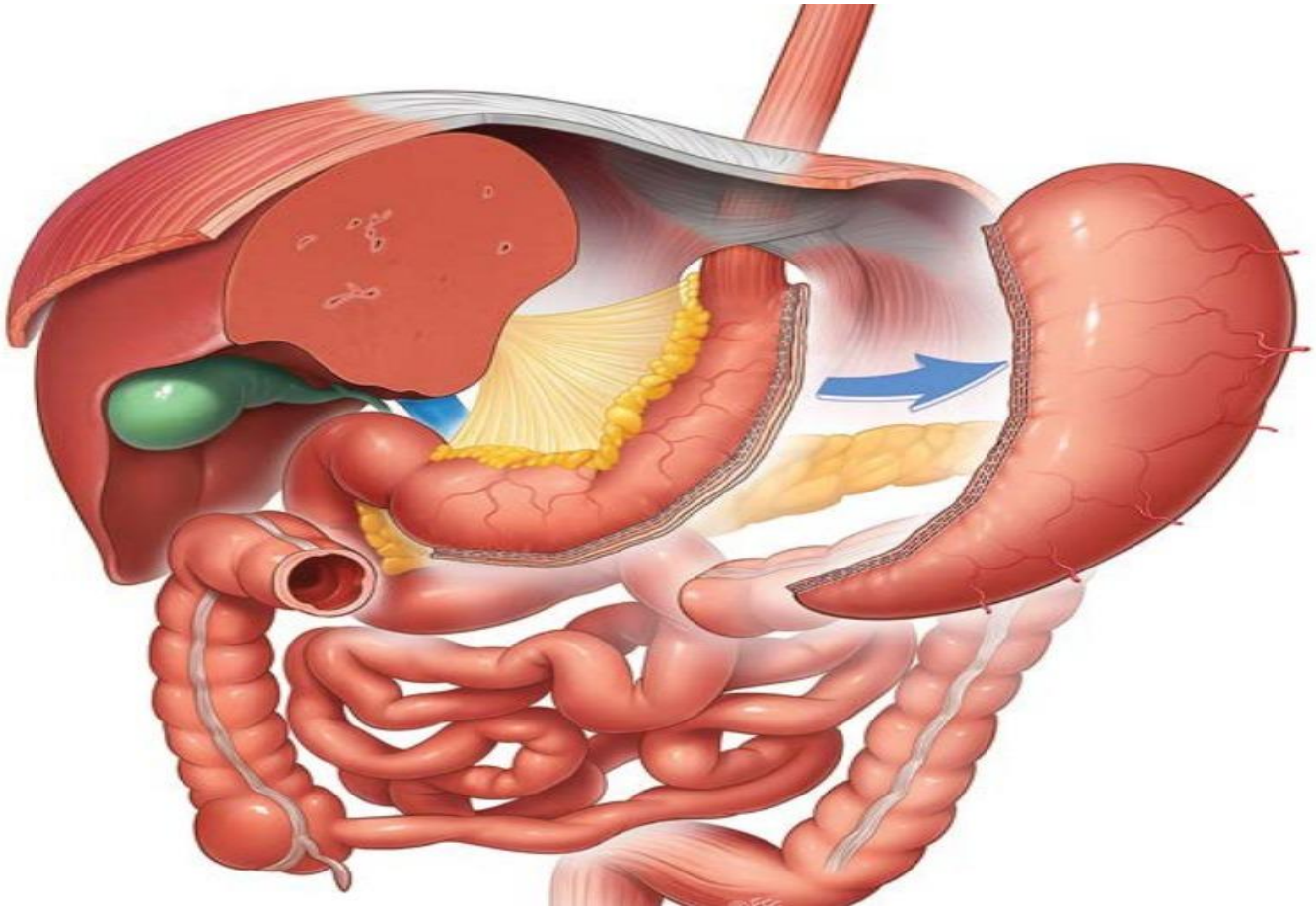
Sleeve gastrectomy (SG) is the most frequently performed of all of the primary MBS procedures worldwide.

The popularity of SG can be attributed to several factors, which include it being, relative to most other MBS procedures:

1) More economical
2) Technically simpler to perform
3) Free of any surgical anastomoses
4) Free of the risk of internal hernias
5) Easier to learn, with a shorter learning curve
6) Faster to perform, with shorter operating times
7) Feasible and relatively safe in patients considered at higher surgical risk.
8) Comparable to RYGB in terms of weight loss and metabolic outcomes .

➤ >>>

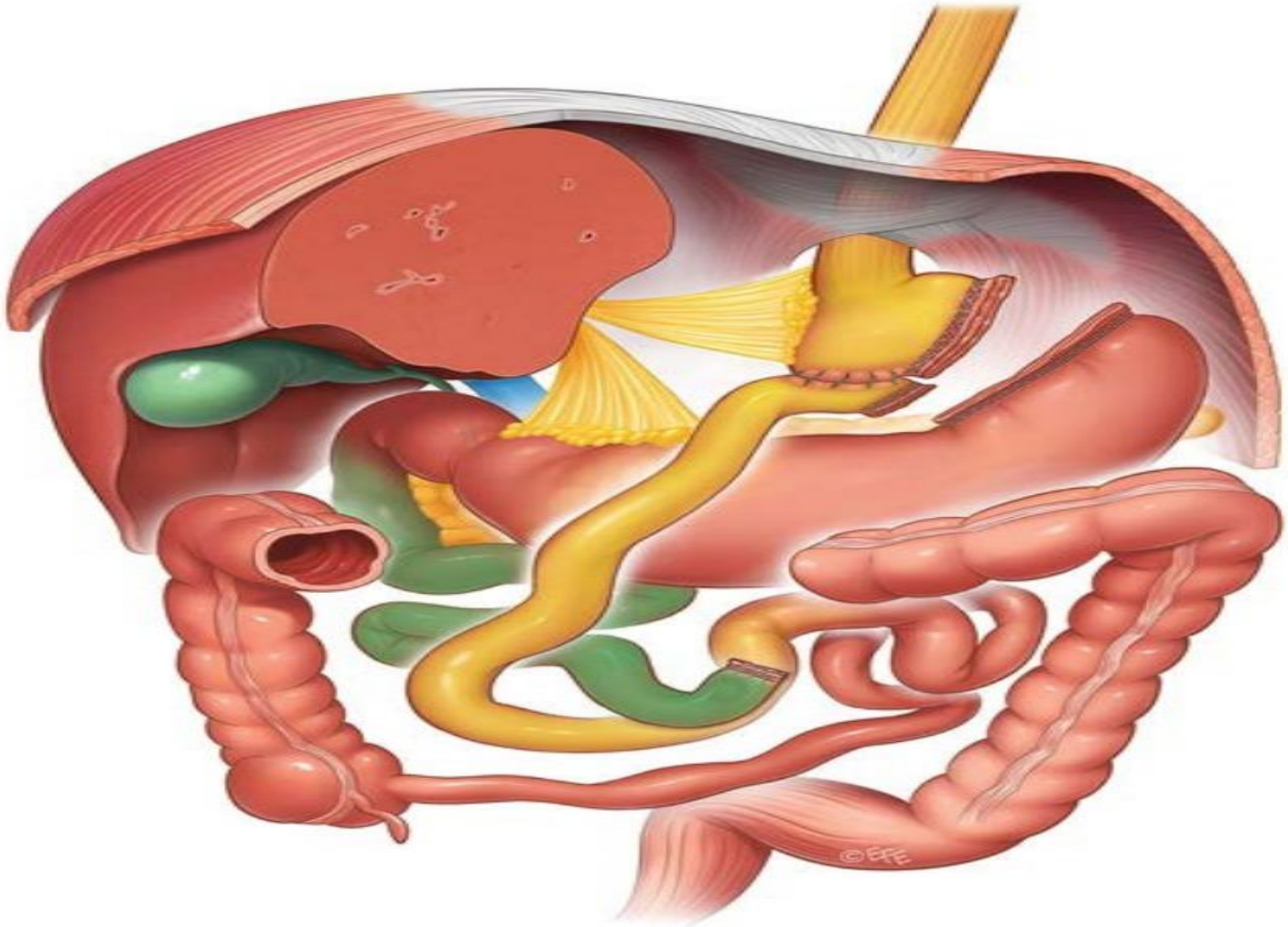




- Complications:

1. GERD
2. Leaks
3. Bleeding
4. stenosis
5. Suboptimal weight loss and weight recurrence

- Laparoscopic Roux-en-Y Gastric Bypass:



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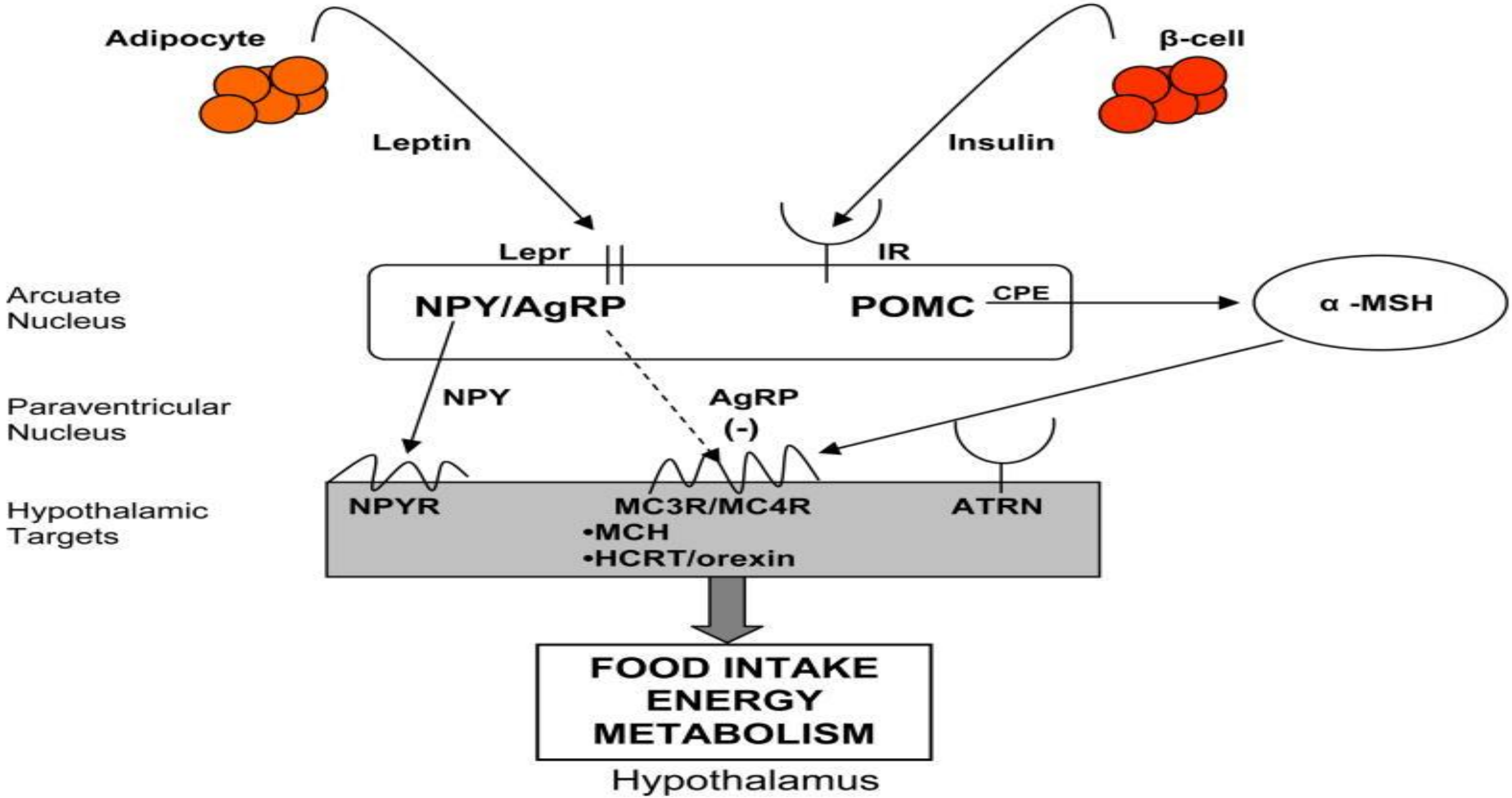
- During the procedure, gastric or stomach stapling creates a small, thumb-sized stomach pouch. The remainder of the stomach is not removed, but is completely divided from the pouch. The small intestine is divided about 18 inches below the stomach, and is rearranged to provide an outlet to the small stomach, while maintaining the flow of digestive juices.
- Food enters the second part of the small bowel within about 10 minutes of beginning the meal. There is very little interference with normal absorption of food. The technique works by reducing food intake and reducing the feeling of hunger. The result is an early feeling of fullness, followed by a profound sense of satisfaction.
- over 80% average weight loss of excess body weight one year after surgery
- Over 80% of people with type 2 diabetes enjoy remission; also highly effective at relieving or eliminating hypertension and other serious obesity-related conditions
- Disadvantages: Possible nutrition and vitamin deficiency and Dumping syndrome

# THE END


Adipocyte
β-cell
Leptin
Insulin
Lepr
IR
Arcuate Nucleus
NPY/AgRP
POMC
CPE
α -MSH
Paraventricular Nucleus
NPY
AgRP
(-)
Hypothalamic Targets
NPYR
MC3R/MC4R
•MCH
•HCRT/orexin
ATRN
FOOD INTAKE
ENERGY
METABOLISM
Hypothalamus