CHAPTER 4: Management of Obesity

Part 2: Pharmacotherapy and Bariatric Surgery

References:

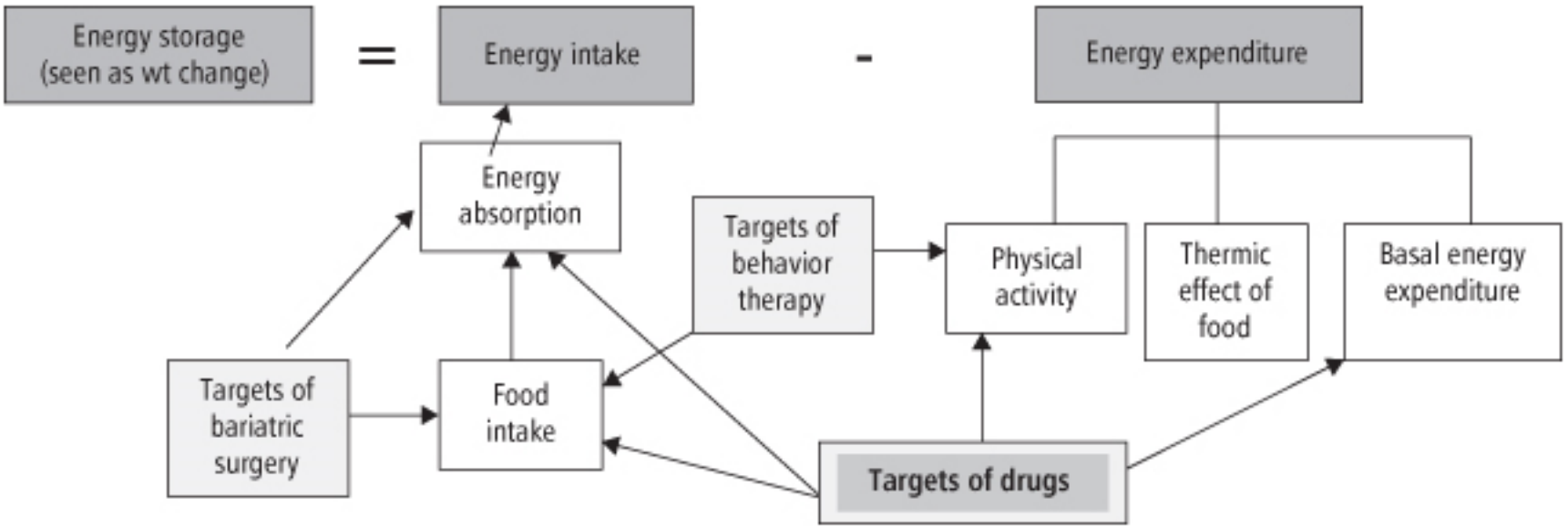
1. **Peter G. Kopelman, Ian D. Caterson, William H. Dietz - Clinical Obesity in Adults and Children 4e-Wiley-Blackwell (2022)**
2. **Sharon Akabas, Sally Ann Lederman, Barbara J. Moore - Textbook of obesity_ Biological, psychological and cultural influences-Wiley-Blackwell (2012)**

Outline

1. Pharmacotherapy
2. Bariatric Surgery

Introduction

- Drugs can, in theory, target and decrease food intake or energy absorption, or increase physical activity or basal metabolism/energy expenditure
- Drugs currently approved for weight-loss treatment target only a few of these.



Introduction

- **First line management**: diet, exercise, and behavioral support
- The role of anti-obesity drugs is as an adjunct to lifestyle and behavioral modification when these methods alone do not achieve weight loss
- The track record of anti-obesity drugs is far from spotless!

→ Many initially promising treatments being withdrawn

2020: Lorcaserin, a serotonin receptor agonist, was withdrawn in at the request of the FDA, 8 years after approval, following concerns of increased occurrence of malignancy, particularly with longer term use

1997: Fenfluramines: associated with increased cardiovascular conditions

Continued robust research is necessary to monitor current approved drugs and develop novel drugs with fewer side effects.

Introduction

- When should it be indicated?
  1. Patients with a BMI of >30 (or >27 with one or more comorbidities)
  2. Evidence of minimal success to lose weight despite continued lifestyle management
  3. Patients should be made aware of the potential benefits, limitations and adverse effects.
  4. Lifestyle and behavioral therapy support should continue.
  5. If after 3–4 months, clinically meaningful weight loss of 5% has not been achieved, prescription and management should be reviewed

Classification of obesity medication

- Drugs that inhibit intestinal fat absorption
  - Lipase inhibitors (e.g. orlistat)
- Drugs that suppress food intake by promoting satiety and controlling appetite can be divided into;
  - Those which work through the central and/or peripheral nervous system, modulating the production of neurotransmitters or interacting with their receptors.
  - Those which targets gastrointestinal neuroendocrine function
    - Glucagon-Like Peptide 1 receptor agonists (GLP1 RA, e.g. liraglutide)
    - Amylin receptor agonist (e.g. pramlintide).
- Drugs that increase energy expenditure, peripheral lipid metabolism and/or thermogenesis
  - Drugs such as epinephrine, caffeine, and thyroxine; however, they are associated with cardiovascular side effects and are not recommended for use in obesity management.
  - Thermogenesis in brown adipose tissue can be activated. Such approaches have repeatedly been shown to be ineffective in human and can cause side effects

Currently approved drugs

- Currently, four long-term and four short-term medications are approved for obesity treatment by the FDA, of which three are also approved by the EMA

Drug Name	FDA (US) Approval	EMA (EU) Approval
Orlistat	✓	✓
Phentermine-Topiramate	✓	✗
Naltrexone-Bupropion	✓	✓
Liraglutide	✓	✓
Semaglutide	✓	✗
Phentermine	✓*	✗
Benzphetamine	✓*	✗
Diethylpropion	✓*	✗
Phendimetrazine	✓*	✗

*Only approved for short-term use (12 weeks).

Lipase inhibitor

Appetite suppressant effects

Appetite suppressant effects

Currently approved drugs

Table 19.1 FDA-approved anti-obesity medications for chronic weight management

Medication	Primary mechanism of action	Dose	Placebo-subtracted weight loss at 1 year*
Orlistat	Pancreatic and gastric lipase inhibitor	120 mg with meals (three times daily)	2.6 kg
Naltrexone/bupropion	Opioid antagonist/dopamine and norepinephrine reuptake inhibitor	1 tablet (8 mg/90 mg) daily for 1 week; increase dose each week by 1 tablet until maintenance dose of 2 tablets twice per day at week 4	5.0 kg
Liraglutide	Glucagon-like peptide-1 receptor agonist	Starting dose of 0.6 mg daily; increase by 0.6 mg daily in weekly intervals to reach 3.0 mg daily	5.2 kg

Note: * Data on placebo-subtracted weight losses are from a meta-analysis of studies [65].

Orlistat

- Mechanism of Actions

A potent selective inhibitor of pancreatic lipase.

It increases fecal fat loss (approx. 30% on a diet that has 30% of its energy as fat).

- Notes

An over-the-counter version of orlistat is approved by the FDA. It is available in 60 mg doses to be used three times per day for up to six months.

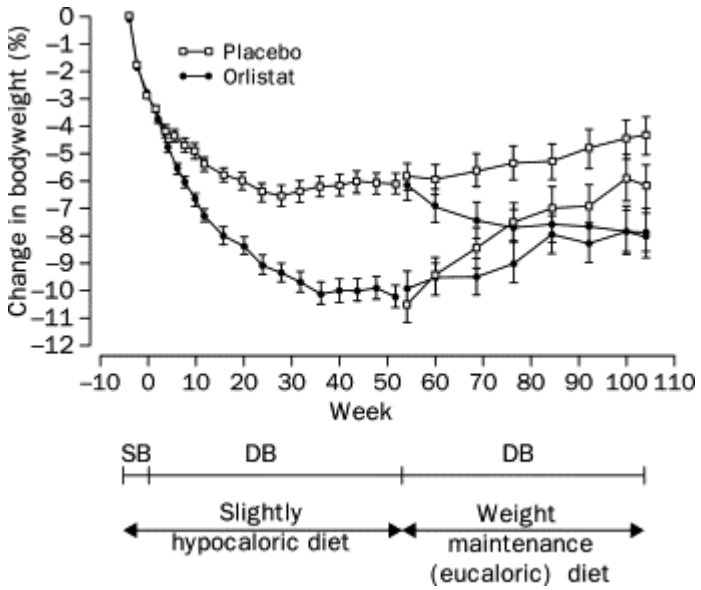
Its manufacturer showed that moderately overweight individuals (BMI 25–28 kg/m^2) who use over-the-counter orlistat three times per day could lose 50% more than the weight loss observed with placebo-treated patients when all of them were eating the same diet.

Orlistat

- Evidence from research

By the end of the first year: Orlistat vs. Placebo weight loss: 10.2% (10.3 kg) vs. 6.1% (6.1 kg).

In the second year, patients were re-categorized into either group: Weight gain occurred in both groups, those who continued with orlistat gained half as much as those who switched to placebo ($p < 0.001$), while those who continued with placebo gained an average of 2.5 kg ($p < 0.001$).



Orlistat

- Safety

the use of orlistat did not raise any major safety issues

Orlistat is not absorbed from the GI tract to any significant degree, and its side-effects are thus related to the blockade of triglyceride digestion in the intestine.

GI symptoms: flatulence, fecal incontinence, steatorrheal diarrhea. (depends on the amount of dietary fat consumed)

Orlistat

Additional notes:

- Mild to moderate gastrointestinal adverse events occurred in 9-50% of patients in the orlistat group
- Reduced absorption of fat-soluble vitamins, vitamin D in particular, observed with orlistat
- It is approved by the Food and Drug Administration for use in adolescents aged 12 years and older.

Clinical trials of orlistat in children

STUDY	DURATION	N	AGE	TYPE OF TRIAL	DOSE	BMI CHANGE
Chanoine et al,[10] 2005	12 mo	539	12–16 y	Randomized, double-blind, placebo-controlled	120 mg 3 times daily	−0.9 kg/m^2 (vs placebo)
Ozkan et al,[11] 2004	5–15 mo	42	10–16 y	Randomized, open-label, controlled	120 mg 3 times daily	−4.2 kg/m^2 (vs control)
Maahs et al,[12] 2006	6 mo	40	14–18 y	Randomized, double-blind, placebo-controlled	120 mg 3 times daily	−0.5 kg/m^2 (vs placebo, non-significant)
McDuffie et al,[13] 2004	6 mo	20	12–17 y	Single group	120 mg 3 times daily	−2.0 kg/m^2 (vs baseline)
Norgren et al,[14] 2003	3 mo	11	8–12 y	Single group	120 mg 3 or 4 times daily	−1.9 kg/m^2 (vs baseline)

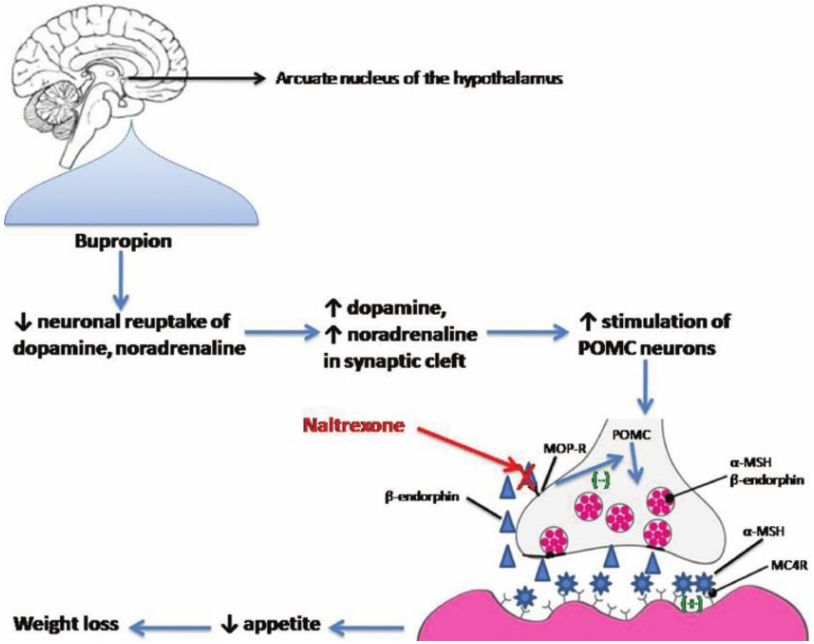
Rogovik AL, Goldman RD. Pharmacologic treatment of pediatric obesity. Can Fam Physician. 2011 Feb;57(2):195-7. PMID: 21642717; PMCID: PMC3038814.

Orlistat

- Though orlistat's effect on weight loss is modest, it has favorable effects on cardiometabolic risk factors such as:
  - Reduced blood pressure, cholesterol, blood glucose levels, and waist circumference
  - Reduced incidence of diabetes in those with prediabetes (37% reduction in the conversion of patients from impaired glucose tolerance to diabetes)

Naltrexone and bupropion

- Monotherapy of naltrexone has been used in the management of drug and alcohol abuse, whilst bupropion is licensed for use in depression and smoking cessation
- **Evidence of synergistic effect**
- Bupropion stimulates POMC neurons in the hypothalamus, enhancing the secretion of α-melanocytestimulating hormone (α-MSH) → anorexigenic properties
- Naltrexone augments this activation by preventing the inhibition of α-MSH → Prolongs the effect of bupropion → Weight loss, appetite regulation



Naltrexone and bupropion

- Experimental studies concluded:
  - The naltrexone/bupropion group showed significant weight reduction with an average placebo-adjusted weight loss of >6%
  - Patients reported greater control of overeating
  - HbA1c was reduced by 0.6% in comparison to 0.1% in the placebo cohort
- The maximum dose (32 mg/360 mg) did not appear to increase the risk of major adverse cardiovascular events (the cardiovascular safety of this therapy remains undefined and necessitates further evaluation)
- Common side effects: nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea

Naltrexone and bupropion

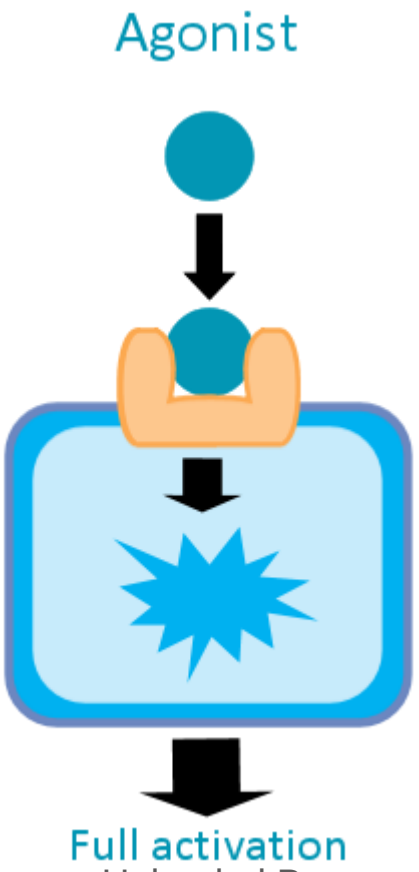
- Suicide: Bupropion has an FDA-issued warning label for suicide and suicide ideation. No sign of suicidality was presented in the studies. In addition, a positive shift in the quality of life was found. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/018644s039s040.pdf
- Blood pressure and heart rate should be monitored regularly. Development of depression and or suicidal ideation should also be closely monitored during treatment.

Liraglutide

- Glucagon-like peptide 1 (GLP1) is released by the L cells of the distal ileum and proximal colon following the ingestion of food.
- GLP1 receptors activation →
  - Stimulates a biochemical response resulting in blood glucose regulation through enhanced insulin secretion and inhibition of glucagon secretion
  - Decreased gastric secretion and delayed gastric motility → Increased postprandial satiety and fullness
  - Appetite suppression via stimulation of the hypothalamus, limbic system, and cortex

Liraglutide

- The use of GLP1 receptor agonists (GLP1 RA), liraglutide, was approved at a maximum dose of 3.0 mg for the management of obesity
- It is currently marketed by the brand name Saxenda.



Liraglutide

In one trial, patients with obesity without diabetes were given 3.0 mg liraglutide OD or placebo in conjunction with lifestyle modification counseling

- ✓ At 56 weeks, those assigned to liraglutide had lost 8.4 kg, compared to 2.8 kg with placebo
- ✓ 63.2% of patients taking liraglutide lost at least 5% of their body weight in comparison to 27.1% in the placebo arm ($p < 0.001$)
- ✓ 33.1 vs. 10.6% respectively lost more than 10% of body weight ($p < 0.001$)

Liraglutide

Additional Points:

1. Clinically significant weight loss by liraglutide has also been acknowledged in individuals with **heart failure** and in women with obesity and **polycystic ovaries**
2. Liraglutide was not associated with increased cardiovascular risk
3. Results published from the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular Results), which included patients with diabetes taking liraglutide for a median of 3.8 years, concluded:

The rate of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke (primary composite outcome) was significantly lower with liraglutide than with placebo (hazard ratio of 0.87 (95% CI, 0.78–0.97).

Conclusion: Pharmacotherapy

1. Obesity medications used alone have only small effects on weight and all have side-effects
2. The rationale for drug use is that they help more patients achieve 5–10% loss of initial body weight (in patients who are also making lifestyle changes to reduce weight)
3. Recommended in patients with a BMI of 30 kg/m^2 or more, or 27 kg/m^2 or more in those with an obesity-related comorbid condition.
4. Limitations of the currently available weight loss drugs include:
    1. lack of weight loss in some people using these drugs
    2. weight loss attained by responders is relatively modest
    3. they can have significant side-effects
    4. use may cause subtle health issues not readily detected in clinical trials lasting only 1 or 2 years
    5. 5) cost of life-long treatment can be substantial

2. Bariatric Surgery

Surgery is the only proven, effective treatment for long-term weight management in the severely obese

- **Patient Selection**

In 1991, the NIH consensus conference established guidelines and indications for surgical management of severe obesity, which include:

  - Body mass index (BMI) equal to or greater than 40 kg/m^2
  - Body mass index equal to or greater than 35 kg/m^2 with a significant obesity-related comorbidity

- **AND**

  - Demonstrated dietary attempts at weight loss, which have been ineffective.

2. Bariatric Surgery

- Obesity-Related Comorbidities
  1. Diabetes
  2. Hypertension
  3. Sleep apnea (snoring, daytime somnolence, tiredness on awakening)
  4. Obesity hypoventilation syndrome (extreme shortness of breath or exercise intolerance)
  5. GERD
  6. Osteoarthritis
  7. Menstrual irregularity/sterility
  8. Hypercoagulability of the blood
  9. Benign intracranial hypertension

Types of Bariatric Surgery

- Restrictive surgeries

– shrink the size of the stomach which reduces the amount of food it can hold.

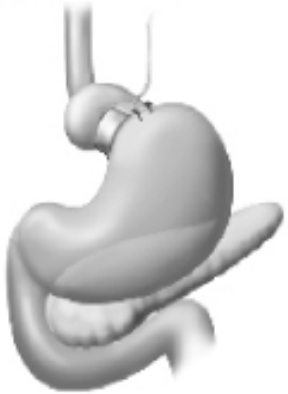
– This makes you feel full when eating much sooner than you did before surgery.

- Malabsorptive surgeries

– Rearrange and/or remove part your digestive system which then limits the amount of calories and nutrients that your body can absorb.

– Treatments with a large malabsorptive component result in the most weight loss but tend to have higher complication rates.

Surgical Options and Outcomes

Class and name of procedure		Description	Advantages	Disadvantages
Restrictive	Adjustable gastric band 	Implantation of adjustable band around upper part of stomach.	• Lowest mortality and complication rate • Adjustable • Reversible • No stomach stapling or cutting or re-routing of intestine or stomach • Least invasive surgical approach	• Slower initial weight loss than gastric bypass or BPD-DS • More frequent visits needed for adjustments • Foreign body • Band slippage • More frequent need for re-operation long term
	Sleeve gastrectomy 	Resection of fundus and body of the stomach, leaving a tubular pouch along the lesser curve of the stomach.	• No intestines are removed or bypassed • Shorter operative time • Can be used as a first stage procedure • No foreign body • Better patient compliance	• Requires cutting and stapling of stomach and bowel • Risk of leaks from resection line of stomach • Not reversible • Limited data available • Reflux post-operatively in about 30% of patients

https://www.youtube.com/watch?v=v0aHr5GuG7Y

https://www.youtube.com/watch?v=_viyWjQWL8M

Surgical Options and Outcomes

Class and name of procedure		Description	Advantages	Disadvantages
Combination	Gastric bypass 	Creation of a small gastric pouch with rearrangement of small intestine in a "Y" configuration to limit absorption.	• Better patient compliance • Greater and more rapid weight loss than purely restrictive procedures • Long term data available	• Requires cutting and stapling of stomach and bowel • Higher risk than adjustable gastric band • Not easily reversible • Requires many vitamin and mineral supplements • Nutrient deficiencies can occur • Dumping syndrome
Malabsorptive	BPD-DS biliopancreatic diversion with duodenal switch 	Distal stomach removed, but stomach volume remains (about 100 cc or more). Length of small intestine available for absorption is much shorter than with bypass, limited to about 75 to 150 cm. Also, a sleeve gastrectomy is performed and a duodenoileostomy is created to route ingested contents to the alimentary limb.	• Greatest amount of initial weight loss due to malabsorption • Allows larger meals because of larger stomach pouch	• Requires cutting and stapling of stomach and bowel • Portion of the digestive tract is bypassed, reducing absorption of nutrients • Requires many vitamin and mineral supplements • Nutrient deficiencies can occur • Highest rate of malnutrition • Frequent bowel movements • Cannot be completely reversed

https://www.youtube.com/watch?v=z8Ajg53fpkA

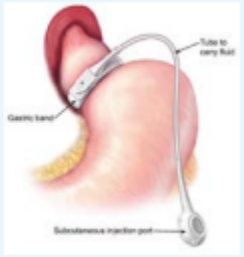
Expected weight loss / mechanism	EWL: 14% - 60% after 7-10 y	Use adjustable band to create upper gastric pouch of 15-45 mL and restrict inlet to stomach • Produce early satiety and limit food intake	
Expected weight loss / mechanism	EWL: 50% - 55% after 5-9 y	Excision of lateral aspect of stomach to create smaller gastric tube • Limits food intake • Increases GLP-1 and PYY; decreases ghrelin	
Expected weight loss / mechanism	EWL: 60%-70% after 7-10 y	Stomach transected to create proximal gastric pouch of 10-30 mL, which is anastomosed to a Roux-en-Y proximal jejunal segment, bypassing remainder of stomach and duodenum • Limits food intake • Induces micronutrient malabsorption • Decreases ghrelin and increases PYY and GLP-1	
Expected weight loss / mechanism	EWL: 60% - 80% after 7-10 y	Sleeve gastrectomy with intestinal bypass of all but ~100-150 cm of distal ileum • Limits digestion and absorption to 50-100 cm of small intestine • Induces extensive nutrient and caloric malabsorption	

Table 1: Weight Loss Surgeries[3]

	Adjustable gastric banding	Sleeve gastrectomy	Roux-en-Y gastric bypass	Duodenal switch
Total weight loss (%)	20	25	30	40
Resolution rate of T2DM (%)	20	30	40	80
Resolution rate of hypertension (%)	20	30	40	60
Resolution rate of sleep apnoea/ hypopnoea syndrome (%)	30	40	50	70
Mortality rate (%)	0.01	0.01	0.01	0.02
Serious adverse events (%)	2	3	3	5

Biertho L, Hong D, Gagner M. Canadian Adult Obesity Clinical Practice Guidelines: Bariatric Surgery: Surgical Options and Outcomes. Available from: https://obesitycanada.ca/guidelines/surgeryoptions

Nutritional Management and Follow-Up

- **Pre-Surgery Guidelines**

A small amount of weight loss over a short period of time can significantly reduce liver size and the amount of intra-abdominal adiposity, causing fewer complications.

In some programs, patients are placed on a diet 2–4 weeks prior to surgery.

- **Behavior Modification**

Bariatric surgery is a “tool” that will aid weight loss.

Nutritional guidelines and exercise are needed to achieve and maintain a healthier weight. The diet is slowly progressed during the first few weeks after surgery, from clear liquids to puréed foods, then to soft foods, and finally to foods of regular consistency.

Post-Surgery Guidelines

- Mean pre-surgery energy intake has been calculated to be 4,355 kcal/day.
- Daily postoperative intakes are about:
  - 100–200 kcal in the hospital
  - 400–600 kcal in the first six weeks
  - 600–800 kcal for the next three months
  - 800–1,000 kcal at six months
  - 1,000–1,200 kcal at 12 months after surgery.

Post-Surgery Guidelines

- Protein

Protein aids in wound healing, maintains lean body mass, prevents weakening of the immune system, provides a feeling of satiety, and prevents malnutrition.

Because the stomach will fill rapidly, they should select and consume foods of primary importance first.

Recommendations:

1. BPD/DS: 80–120 g of protein daily.
2. Others: 60–80 g of protein daily.

Post-Surgery Guidelines

- Supplements

Because this patient population is not able to consume sufficient nutrients from the foods they eat, vitamin and mineral supplementation in quantities greater than the DRI (dietary reference intake) is strongly recommended

Yearly measurements of a patient's levels of these nutrients is the best way to monitor and prevent deficiencies.

Post-Surgery Guidelines

- Supplements

Adjustable banding and sleeve gastrectomy: multi-vitamin and mineral supplement, and the DRI for calcium and 1,000 IU of vitamin D daily. As there is no change in absorption, the DRI should be adequate, however additional B_{12} is recommended for sleeve gastrectomy patients as well since decreased production of hydrochloric acid hinders the release of vitamin B_{12} from protein.

Malabsorptive operations: A multivitamin and mineral supplement, 1.5 times the DRI for calcium, 500 mcg sublingual B_{12} (or 1mg intramuscular injection monthly), and 150 mg of elemental iron, 50,000 IU dry vitamin D_3 weekly.

BPD: Two multivitamins, twice the DRI for calcium, additional fat-soluble vitamins (A, D, E, K), and 150 mg elemental iron that contains Vitamin B_{12} daily, and 50,000 IU dry vitamin D_3 weekly.

Recommended Supplementation

LAP-BAND®	Gastric Bypass	Sleeve	BPD-DS
Multi-vitamin/mineral	Multi-vitamin/mineral	Multi-vitamin/mineral	Multi-vitamin/mineral
Calcium/vitamin D	Calcium/vitamin D	Calcium/vitamin D	Calcium/vitamin D
Vitamin D alone	Vitamin D alone	Vitamin D alone	Vitamin D alone
	Iron	B_{12}	Fat-soluble vitamins (A, D, E, K)
	B_{12}		Iron with B_{12}

Expected Weight Loss

- https://bariatric-weight-trajectory-prediction.univ-lille.fr/

Changes in health after bariatric surgery

- **Type 2 diabetes mellitus**

Multiple studies have documented the benefit achieved by all the current bariatric procedures

The improvement is related to the dual effects of improvement in insulin sensitivity and pancreatic β cell function

Changes in health after bariatric surgery

- **Dyslipidemia of obesity**

Weight loss surgery produces substantial decreases in fasting triglyceride levels, an elevation of HDLcholesterol levels to normal, and improved total cholesterol to HDL-cholesterol ratio

- **Hypertension**

There is evidence of a reduction in both systolic and diastolic blood pressure (BP) following weight loss in association with a bariatric procedure. The fall in BP is sustained to at least 4 years after.

Changes in health after bariatric surgery

- **Ovarian dysfunction, infertility, and pregnancy**

In premenopausal women, weight loss significantly reduces active testosterone by reducing total testosterone and increasing the proportion of bound testosterone due to increased sex hormone-binding globulin.

- → Women are advised to use contraception and avoid pregnancy during the very active weight loss phase
- → Malabsorptive types of bariatric surgery were associated with a significantly increased risk of perinatal mortality, congenital anomalies, preterm birth, and NICU admission.
- → The adverse outcomes were not seen in women who had undergone either LAGB or sleeve gastrectomy (SG), although there were a small number of studies.

Changes in health after bariatric surgery

- **Obstructive sleep apnea**

There are major improvements in sleep quality, excessive daytime sleepiness, snoring, nocturnal choking, and observed OSA with weight loss following bariatric surgery.

A recent systematic review: After both RYGB and LAGB, with over 85% of patients having complete resolution of the disorder!

- **Quality of life**

Improvement in QOL is one of the most gratifying outcomes of bariatric surgery. Several studies clearly demonstrate major QOL and body image improvements following all bariatric procedures

Conclusion

- Unfortunately, there are no non-surgical options that are remotely as effective for long-term weight loss, and even modern, minimally invasive surgery carries some significant risk.

- For patients who do present for surgical treatment, careful evaluation, education, preparation, choice of operation, and consistent follow up will lead to the best outcomes.