

"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all." – William Osler



430  
MEDICINE  
TEAMWORK

## OBESITY

Done By: Ruah AlYamany

# Obesity

## Adipocytes

- Adipocytes (Fat cells) in adipose tissue are storage spaces for Triacylglycerols. They increase in size and undergo division. Adipocytes, once gained are never lost. They may only decrease in size in weight loss.
- In obesity adipocytes increase in number and size
- They secrete several hormones (adipokines) that play important roles in energy balance and metabolism, e.g. Leptin, TNF and IL-6, Adiponectin and Resistin

## Hormonal Control

Appetite is influenced by afferent neural signals, circulating hormones, and metabolites  
These signals cause the release of hypothalamic peptides and activate efferent neural signals

### ❖ Leptin:

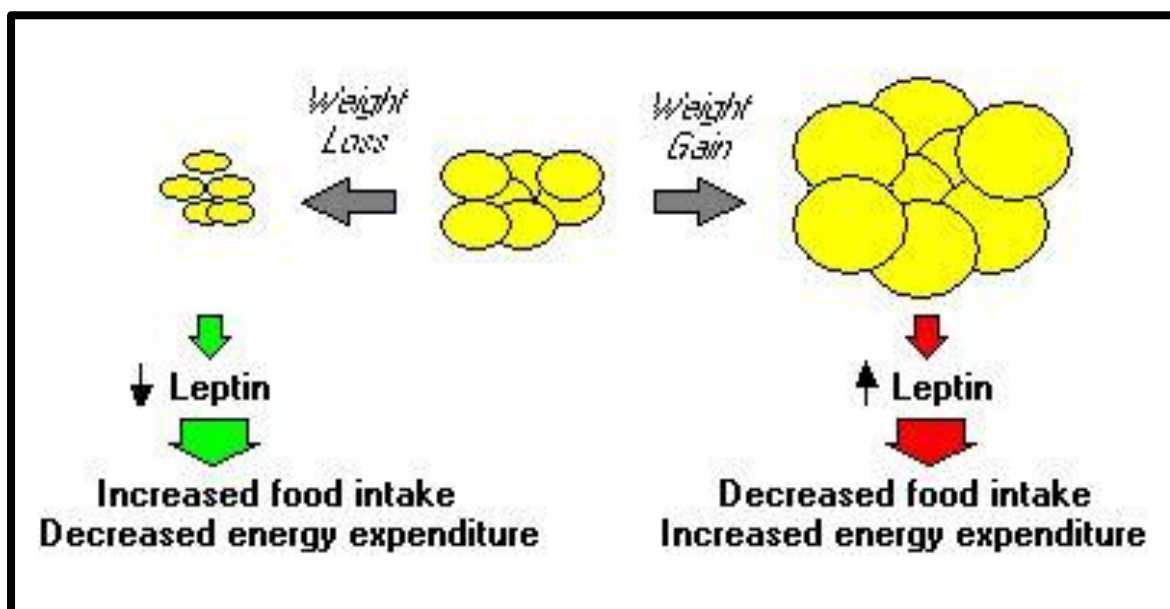
- Protein hormone essential for normal body-weight regulation (Leptin means “thin”)
- Amount of leptin indicates total amount of triglyceride

fat stored in adipocytes, the larger the fat stored the more leptin released into the blood

- Acts on hypothalamus to decrease food intake and stimulate energy expenditure
- Leptin suppresses appetite
- Leptin secretion regulation:
  - a. Suppressed in starvation (depletion of fat stores)
  - b. Enhanced in well-fed state (expansion of fat stores)

### Leptin Resistance

- Resistance to leptin has been found in obese humans
- The receptor for leptin in the hypothalamus is produced **db** gene
- Mutation in **db** gene causes leptin resistance in mice
- Leptin resistance may have some role in human obesity



### ❖ Adiponectin:

- Exclusively and abundantly secreted hormone from the adipocytes
- Promotes the uptake and oxidation of fatty acids and glucose by muscle and liver
- Adiponectin increases sensitivity to insulin, decreases body weight
- Adiponectin levels are inversely correlated with body fat percentage and parallels with the HDL level

- Low levels are seen in metabolic syndrome and diabetes mellitus

#### ❖ Ghrelin: "Hunger Hormone"

- A peptide hormone, a potent appetite stimulator secreted by the stomach and regulated by the feeding status
- Secretion of Ghrelin peaks before meals and makes people hungry, then decreases once food is eaten
- Increases food intake
- Decreases energy expenditure and fat catabolism

#### ❖ Cholecystokinin:

- Gastrointestinal Peptide hormone released from the duodenum during digestion of a meal
- Important satiety signal in regulating the size of meals
- Secreted in response to the presence of nutrients in the small intestine

#### ❖ Insulin:

- Secreted by the Pancreas
- Promotes metabolism

#### Weight loss effect on Ghrelin

- Levels of Ghrelin in dieters are *higher* after weight loss
- The body steps up Ghrelin production in response to weight loss
- The higher the weight loss, the higher the Ghrelin levels

#### Satiety:

Satiety is the feeling of being full. Satiety signals tell us when we have had enough and suppress the desire to eat

## Obesity

### ❖ Definition

Changes in body weight can occur through alteration of several variables, including:

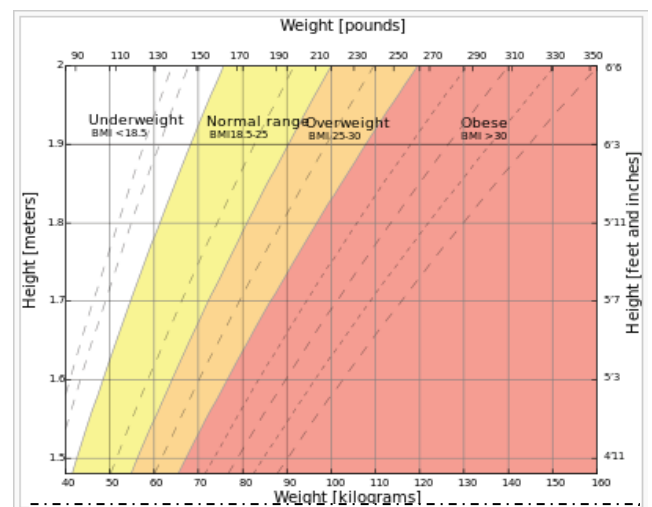
1. Amount and type of food ingested
2. Central control of satiety
3. Hormonal control of assimilation or storage
4. Physical activity and metabolic rate

- Obesity means excessive accumulation of fat in the body
- In other words, obesity is when your weight is 20% or more above your ideal body
- Once obesity is developed, it is difficult to "cure" and usually persists throughout life
- Obesity is usually diagnosed on the basis of the calculation of:
  1. Body Mass Index (BMI)
  2. Measurement of waist-hip ratio

### ❖ Body Mass Index (BMI)

Body mass index is a measure for human body shape based on an individual's weight and height. It is defined as the individual's body mass divided by the square of their height  
The formulae universally used in medicine produce a unit of measure of kg/m<sup>2</sup>

$$BMI = \frac{\text{mass(kg)}}{(\text{height(m)})^2}$$



Body mass index graph shows classifications and divisions of the classes.

### Classification of overweight and obesity by BMI, waist circumference, and associated disease risk

	BMI kg/m <sup>2</sup>	Obesity class	Disease risk* relative to normal weight and waist circumference	
			Men ≤102 cm (≤40 in)	>102 cm (>40 in)
			Women ≤88 cm (≤35 in)	>88 cm (>35 in)
Underweight	<18.5		-	-
Normal•	18.5- 24.9		-	-
Overweight	25.0- 29.9		Increased	High
Obesity	30.0- 34.9	I	High	Very High
	35.0- 39.9	II	Very High	Very High
Extreme Obesity	≥40	III	Extremely High	Extremely High

\* Disease risk for type 2 diabetes, hypertension, and CVD.  
 • Increased waist circumference can also be a marker for increased risk even in persons of normal weight.  
 Reproduced from: *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report*. National Institutes of Health. *Obes Res* 1998; 6:515.

UpToDate

### ❖ Anatomic Differences in Fat Deposition

Health risks depend on the pattern of fat deposition

There are 2 anatomical patterns of fat deposition:

Anatomical Patterns of Fat Deposition	
Android "apple-shaped" or Central obesity	Gynoid "pear-shaped" or below the waist obesity
More common in Males	More common in Females
Excess body fat deposited in the central abdominal area	Fat deposited around the hips or gluteal region
Associated with risk of hypertension, insulin resistance, diabetes, dyslipidemia, and coronary heart disease	Associated risks are lower. Associated more with mechanical problems

### ❖ Biochemical Differences in Fat Deposits

Biochemical Differences in Fat Deposits	
Abdominal Fat	Gluteal Fat
Larger cells	Smaller cells
More responsive to hormones	Less responsive to hormones
Release substances via portal vein to the liver	Release substances to circulation with no effect on the liver

### ❖ Prevalence and Epidemiology

- Well recognized as a serious and growing public health problem
- WHO estimates that over 1.7 billion people around the world are overweight, 310 million are obese
- Rates of obesity have tripled in the last 20

#### Obesity in young people

The prevalence of obesity in:

- Preschool children it increased from 5 to 10 % ( 1980 to 2008),
- School-aged children it increased from 5.6 to 19
- Adolescent's obesity reached between 5 to 18 % in the US

years in the developing world

- In US, 33.3 % of men and 35 % of women were found to be obese in 2007
- 15-25 % of American children are obese
- In SA: a study has been done between 1995-2000 in age group between 30-70 on 17000 subjects
- Prevalence of overweight: 36.9 % : 42% male, 31.8 % female
- Prevalence of obesity: 35.5 % , severe obesity 3.2 % with female of 44 %, male 26.4 %
- The prevalence of overweight and obesity was higher in a group of married women than those who were single women in Saudi Arabia

### ❖ Pathogenesis of Obesity

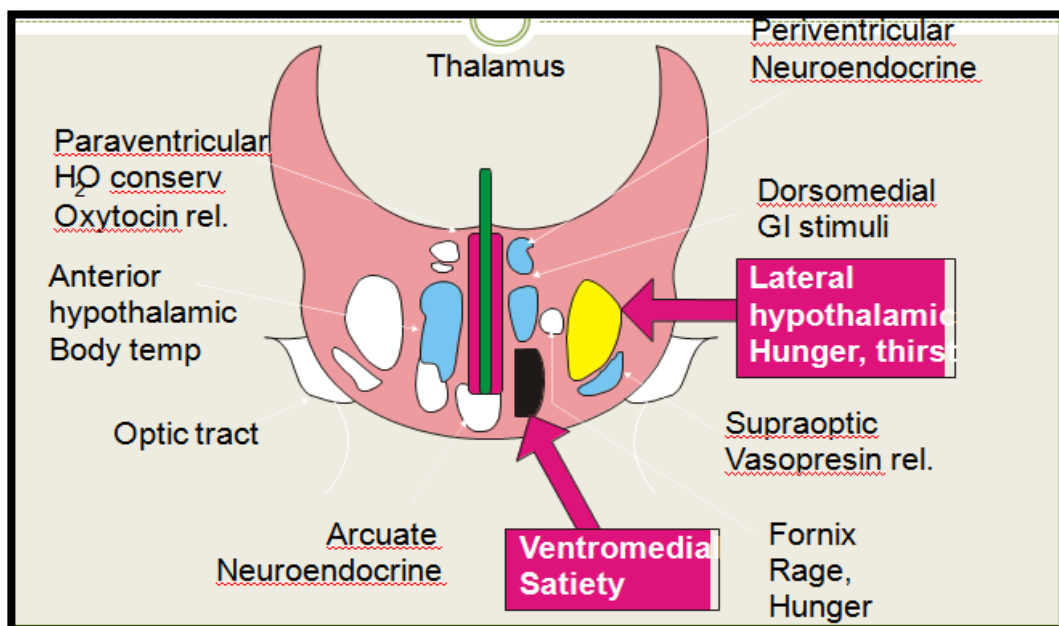
Generally, food intake and utilization is regulated by:

- Hormones (Mentioned previously)
- Neurotransmitters
- Central Nervous System

Mechanism of Obesity:

- Signals from peripheries are carried out by neurotransmitters and hormones to CNS in presence or absence of food
- Signals from fat cells (Leptin) are carried out to the hypothalamus to food intake and increase sympathetic activity and energy expenditure
- Gastric distension and contraction sends signals for satiety and hunger
- Fall in blood sugar sends signals to CNS for hunger
- Sympathetic activity from food thermogenesis leads to reduction in food intake

➤ Hypothalamus: The hypothalamus includes the centers for hunger and satiety



➤ Food intake:

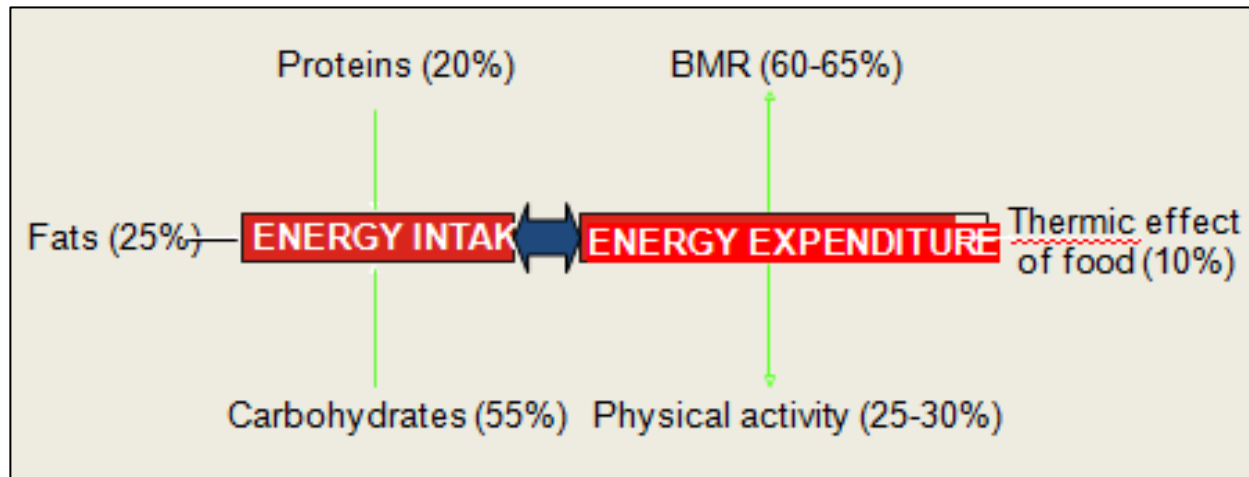
- More in and less out = weight gain
- More out and less in = weight loss

➤ Hormones

- Leptin and Ghrelin (Mentioned on Page 3 & 4)

➤ Energy expenditure:

The amount of calories we are burning compared to the calories we are consuming



Obesity mainly occurs because of the over consumption of calories and the reduction of physical activity over a long period. This may result due to combination of many factors, including:

1. Individual behaviors (10% to BMI)
2. Social interaction
3. Environmental factors
4. Genetic factors (40% to BMI and adiposity)

#### ❖ Factors predisposing to Obesity

1. Lifestyle
  - A sedentary lifestyle lowers the energy expenditure and as result, the enegry intake will become higher which leads to weight gain
  - 52% of Saudi women are inactive. Less than 19% of Saudi women do regular physical activity
  - Prolonged TV watching will lead to reduction of movement
2. Sleep deprivation
  - Studies showed that sleeping for **less than 7 hrs/day** might cause obesity, because the reduction of sleeping hours reduces the levels of leptin and increases the levels of Ghrelin which will lead to increased appetite and usually peopl t tend to eat Carbohydrates when this occurs
3. Cessation of smoking
  - People who stop smoking usullay gain weight (**average of 4 kg**) and that is because nicotine smoking reduces appetite so when a person stops smoking they will retain their normal appeitie
  - This can be prevented by calorie restriciton and exercising
4. Social influences:
  - Obese partents are most likely to have obese children
  - Obese individuals are usually surrounded by obese people
5. Diet:
  - Overeating and high frequency of consuming fatty meals, e.g. Fast food significantly leads to obesity (>2 fast food means/week)
  - Night eating syndrome

#### Night eating syndrome (NES)

NES, also known as “Midnight hunger” is an emerging eating disorder, diagnosed by an ongoing persistent pattern of late night binge eating (**>25% of intake is in the evening**)



**Table 1. Other Causes of Obesity**

1. Genetic disorders with obesity	Prader-Willi Syndrome
	Bardet-Biedl Syndrome
	Carpenter's Syndrome (Acrocephalopolysyndactyly type II)
	Cohen Syndrome
2. Endocrine disorders	Cushing's syndrome
	Hypothalamic tumors/inflammation/trauma/radiation
	Hypothyroidism
	Polycystic ovary syndrome
	insulinoma
3. Drugs	Antipsychotics, especially atypical agents
	Tricyclic antidepressants
	Sulfonylureas
	Insulin
	$\beta$ - Blockers
	Corticosteroids
	Estrogen
	Progestins

### ❖ Complications of Obesity

1. Obesity increases possibility of death from Cardiovascular diseases (CVD)
2. Obesity is associated with reduction in life expectancy during adulthood
3. Increased BMI is associated with increased mortality rate due to different types of cancers in both men and women. E.g. Cancer of Esophagus, colorectal, liver, gallbladder, pancreas, kidney, non-hodgkins lymphoma, and multiple myeloma
4. Increased cost rates on obese individuals, for food and medications for DM, HTN, CVDs and GI diseases
5. Obese individuals tend to have many sick leaves throughout the year
6. Increased number of hospitalization for obese individuals
7. Early age of retirement
8. Poor quality of life due to psychosocial issues
9. **Acanthosis Nigricans**: brown to black, poorly defined, velvety hyperpigmentation of the skin. It is usually found in body folds

### CVD's association with BMI

Each 5 kg/m<sup>2</sup> increase in BMI is associated with significant increase in mortality related to:

- IHD and stroke
- Diabetes and non-neoplastic kidney disease
- Different types of cancer
- Respiratory disease

Increase in BMI is associated with increase in morbidity and CVD

**Acanthosis nigricans**



Classic hyperpigmented axillary lesion in acanthosis nigricans.

Courtesy of Jeffrey Flier, MD.

## ➤ Systematic complications of Obesity:

**Table 2. Complications Associated with Obesity**

Cardiovascular	Coronary artery disease, stroke, congestive heart failure, hypertension, dysrhythmias, pulmonary embolism
Pulmonary	Obstructive sleep apnea and obesity hypoventilation syndrome
Endocrine	Metabolic syndrome, insulin resistance, dyslipidemia, diabetes mellitus type 2, polycystic ovary syndrome
Gastrointestinal	Gallstones, abdominal hernia, nonalcoholic fatty liver disease, gastroesophageal reflux disease
Bone, joint, and skin	Osteoarthritis, low back pain, gout, acanthosis nigricans
Vascular	Venous stasis
Neurologic	Pseudotumor cerebri
Gynecologic/genitourinary	Stress incontinence, sexual dysfunction, abnormal menses

NOTE: Obesity is also associated with cancer of the esophagus, colon, pancreas, liver, prostate, breast, endometrium, cervix, and ovaries.

## ❖ Assessment and Screening

It is important to screen adults for obesity. It should be part of the periodic health assessment.

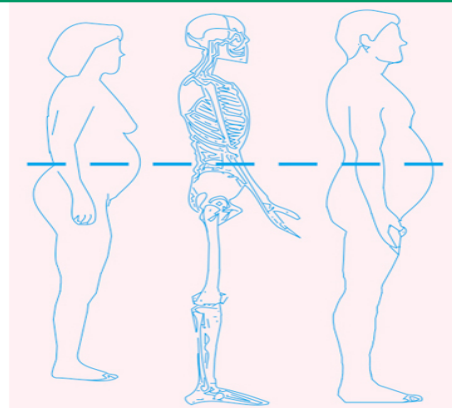
### ➤ Screening measurements:

1. BMI measurement:
  - Reliable, easy, correlated with percentage of body fat
  - Guide for selection of therapy
  - Varies among different races
  - Recent WHO classification applied to whites, hispanics and black
  - Asians are different: overweight BMI 23-24.9 kg/m<sup>2</sup> and obesity by BMI > 25 kg/m<sup>2</sup>
2. Waist circumference:
  - Measurement of central adiposity
  - Associated with increased risk of morbidity and mortality
  - Reflects visceral adiposity
  - Increase risk of heart disease, DM, hypertension, dyslipidemia
  - Important in identifying the risk in BMI 25-34.9 kg/m<sup>2</sup>
  - Risk increase with WC > 88 cm in women, 102 cm in men
  - Not useful if BMI > 35 kg/m<sup>2</sup>
  - In Asian population risk starts with WC > 80 cm in Asian women and > 90 cm in Asian men

### Screening for Obesity

Height, in or cm	_____
Weight, lb or kg	_____
Calculated BMI, kg/m <sup>2</sup>	_____
Waist circumference, in or cm	_____
Blood pressure SBP/DBP, mm Hg	_____
Fasting serum triglyceride, mg/dL or mmol/L	_____
Serum Hdl-cholesterol, mg/dL or mmol/L	_____
Fasting blood glucose, mg/dL	_____
Are there symptoms of sleep apnea?	_____
Are there medication(s) that increase body weight?	_____
Is there regular physical activity?	_____
Are there other etiologic factors?	_____

### Waist circumference measurement



Measuring-tape position for waist (abdominal) circumference in adults. To measure waist circumference, locate the upper hip bone and the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is made at the end of a normal expiration. Reproduced from: National Heart, Lung, and Blood Institute. *The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart Lung and Blood Institute, Bethesda, MD, October 2000.



3. Evaluation of overall medical risks: It is very important to identify the cause of obesity through obtaining an accurate history, physical examination and investigations.

A. History

- ✓ Medical history is important
- ✓ Age at onset of obesity, course of it
- ✓ Eating habits, activity habits
- ✓ Past medical history
- ✓ Medications
- ✓ Cessation of smoking history
- ✓ Ethnic background
- ✓ Family history of obesity

B. Physical examination and investigations:

- ✓ BP measurement
- ✓ Fasting lipid profile
- ✓ Fasting blood sugar

C. Identify comorbidities and risk factors:

- Presence of atherosclerosis
- Sleep apnoea
- GI, osteoarthritis, gout
- HTN
- DM2 ( fasting blood glucose 110-125 mg/dl)
- Smoking
- Dyslipidemia ( low HDL < 35 or high LDL> 130)
- Family history of premature CAD
- Physical inactivity

➤ The importance of assessing and screening for obesity:

- Obesity is a common disease with a significant morbidity and mortality rate, and without screening many high risk patients may not receive counseling about health risks, lifestyle changes, obesity treatment options, and risk factor reduction.
- Screening with BMI, waist circumference, and risk factor assessment is inexpensive and available to nearly all clinicians.

## ❖ Management of Obesity

➤ Treatment Goals:

1. Prevention of further weight gain
2. Weight loss to achieve a realistic, target BMI
3. Long-term maintenance of a lower body-weight

➤ How much loss in weight is considered significant?

- A 5-10% reduction in weight (within 6 months) is considered significant
- Weight maintenance should be stressed in any weight loss program and contributes significantly to decreased morbidity

➤ Management of obesity through 3 main interventions:

1. Lifestyle

### Goals and Cautions in Weight loss

- Initial goal: 10% weight loss
- Significantly decreases risk factors
- Rate of weight loss:
  - 1-2 pound per week
- Reduction of calories intake 500-1000 calories/day
- Slow weight loss is preferred approach
- Rapid weight loss is almost always followed by rapid weight gain
- Rapid weight loss is associated with gallstones and electrolytes abnormalities

a. Diet:

- Indicated for all with BMI > 30 and those with BMI 25- 30 with comorbidities
- Teaching about food composition ( fat, CHO, protein)
- Calories contents of food by reading labels
- Type of food to buy and to prepare
- Low calories diet-portion controlled
- Low fat diet
- Low CHO diet
- Meditarrean diet
- Average calorie consumption for women:  
1000-1200 kcal/day
- Average calorie consumption for men:  
1200-1600 kcal/day
- Adjust diet based on activity and weight
- After weight loss, weight maintenance

**How much calories should be consumed per day**

Gender	Age	Kcal/day
Male	20-49	2900 kcal/day
	50+	2500 kcal/day
Female	20-49	2300 kcal/day
	50+	1900 kcal/day

b. Physical activity:

- Helps in reducing the risk for DM, heart diseases and hypertension
- Physical activity alone is not efficient in weight reduction
- It helps preventing further weight regain

c. Behavior Changes

- \* Keep agenda of diet and activity
- Set specific goals regarding: diet, activity and related behavior
- Reminder system
- Reward yourself
- Don't deprive yourself, watch portion
- \* Track improvement:
- Weight measurement on regular basis

**Advices on Physical Activity**

- Start slowly
  - Change of daily living activities
  - Avoid injury
- Increase intensity and duration gradually
- Long -term goal:
  - 30-45 min or more of physical activity daily
  - 5 or more days per week
  - Burn 1000+ calories per week

2. Pharmacothreapy:

- Indications:
  - BMI > 30
  - BMI 27-30 with comorbidities
  - Should not be used for cosmetic weight loss
  - Used only when 6 months trial if weight and exercise fail to achieve weight loss
- Types of medications used in reducing weight:
  1. Sympathomimetics:
    - Stimulate release of norepinephrine or inhibits its reuptake by nerve terminals
    - Block serotonin and NE reuptake ( sibutramine)
    - Directly act upon adrenergic receptor
    - Reduced appetite by early satiety
  2. Pancreatic lipase inhibitor:
    - Orlistat: inhibits fat absorption
  3. Antidepressant

4. Antiepileptic
5. Diabetic drugs: metformin

#### Drugs approved by the FDA for treatment of obesity

Drug	Trade names	Dosage	DEA schedule
Pancreatic Lipase inhibitor approved for long-term use			
Orlistat	Xenical	120 mg three times daily before meals	-
Norepinephrine-serotonin reuptake inhibitor approved for long-term use			
Sibutramine	Meridia	5 to 15 mg/day	IV
	Reductil		
Noradrenergic drugs approved for short-term use			
Diethylpropion	Tenuate	25 mg three times daily	IV
	Tenuate Dospan	75 mg every morning	
Phentermine	Adipex	15 to 37.5 mg/day	IV
	Ionamin Slow Release	15 to 30 mg/day	
Benzphetamine	Didrex	25 to 50 mg three times daily	III
Phendimetrazine	Bontril	17.5 to 70 mg three times daily	III
	Prelu-2	105 mg daily	

#### Recommendation for use of drugs listed in the American College of Physicians guidelines

Drug	Net weight loss (kg) (statisticians view)	Gross weight loss (kg) (patients view)	Recommendation
Orlistat	-2.75	-6.25	Approved for long term use
Sibutramine	-4.45	-9.95	Approved for use up to two years
Phentermine	-3.6	-9.1	Approved for short term use (12 weeks)
Diethylpropion	-3.0	-8.5	Approved for short term use (12 weeks)
Fluoxetine	-14.5 to +0.4	-21 to -5.6	Not recommended
Bupropion	-2.77	-8.27	Not recommended

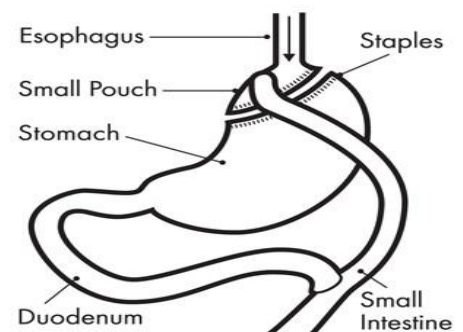
Net weight loss assumes an average weight loss of 5.5 kg with placebo. The 5.5 kg is then subtracted from the gross weight loss achieved with drug therapy.

With permission from: George Bray, MD. Data adapted from Li Z, Maglione M, Tu W, et al. Ann Intern Med 2005; 142:532. Snow, V, Barry, P, Fitterman, N, et al. Ann Intern Med 2005; 142:525.

### 3. Surgical intervention

- Indications:
  - Well-informed and motivated patients
  - Have BMI > 40
  - Acceptable risk of surgery
  - Failed previous non-surgical method
  - BMI > 35 with comorbidities like diabetes, sleep apnea, osteoarthritis, cardiomyopathy
  - BMI 25-29.9 with WC > 102 cm in male and 88 cm in women
  - Age 18-60
  - Psychologically stable
- Types of Surgical procedures for weight loss:
  1. Restrictive-type of surgery:
    - Vertical banded-gastroplasty
    - Gastric banding
  2. Malabsorptive and restrictive:
    - Roux-en-Y gastric bypass
    - Biliopancreatic diversion
- \* Follow up is crucial in surgical intervention

#### Roux-en-Y (RNY)



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