"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Obesity: Role of Hormones

Biochemistry Team 437

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

Endocrine block

Objectives:

By the end of this lecture, the students should be able to know:

- Define and characterize obesity in terms of BMI and risk factors
- Compare the anatomic and biochemical differences in fat deposition
- Understand the role of adipocytes in fat storage and release of hormones
- Discuss the hormonal control of obesity by leptin, adiponectin and other hormones
- Discuss the management and treatment options for obesity

Overview:

- Introduction
- Body Mass Index (BMI)
- Types of fat deposition in the body
- Metabolic changes in obesity
- Adipocytes (fat cells) and weight gain
- Hormones in obesity
- Leptin, adiponectin, ghrelin, cholecystokinin
- Treatment options

Obesity

- **Obesity:** Increase in body weight that is attributable to fat and not muscle mass
- A disorder of body weight regulatory systems
- Causes accumulation of excess body fat
  - >20% of normal body weight

- Everything in our body is regulated including body weight.
- Usually each body has a set point where the body tries to maintain its weight around this point even during lifestyle changes, for example if someone is not eating well due to a stressful new job which lead to weight loss, the body will try to increase the the person's appetite to try and bring the weight back to the set point.
- In case of prolonged lifestyle changes, the body's weight set point changes.

Body Mass Index (BMI)

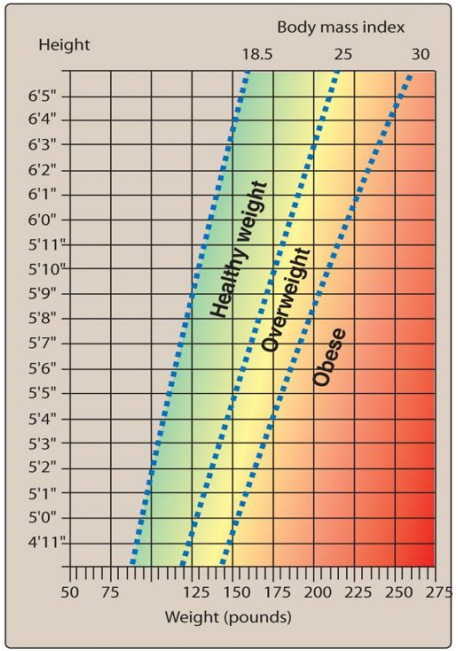
- BMI is an indirect* measure of obesity
- Correlates height, weight and amount of body fat in an individual

You have to know the numbers in the table

$$BMI = \frac{Weight\ (kg)}{[Height(m)]^2}$$

Extra

	BMI	GRADE
UNDER WEIGHT	≤ 18.5	
NORMAL	18.5 – 24.9	
OVER WEIGHT	25.0 – 29.9	
OBESE	30.0 – 34.9	I
OBESE	35.0 – 39.9	II
HIGHLY OBESE	≥ 40	III



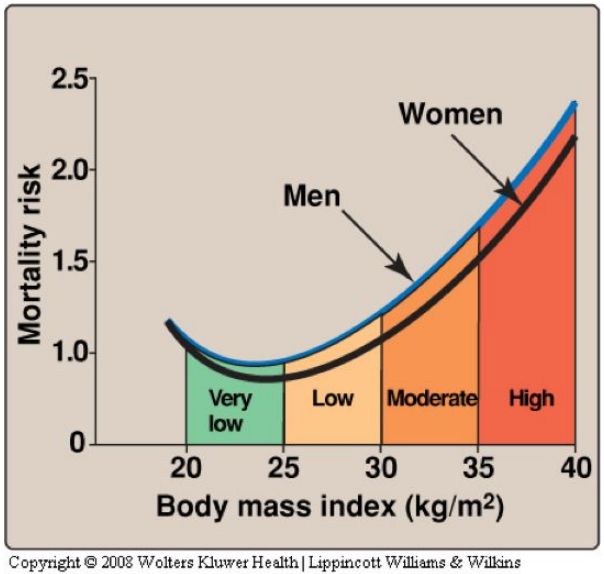
Graph showing BMI measurements for different heights

- Weight alone is not enough to screen for obesity, since other factors like height and body fat percentage should be taken into account, that is why we use BMI.
- *Because it doesn't show you the exact measurement of fat, , which can be done by a full body MRI but this is not available everywhere.

High BMI is associated with increased mortality

Obesity is associated with a high risk of:

- Diabetes mellitus
- Hypercholesterolemia
- High plasma triglycerides
- Hypertension
- Heart disease
- Cancer
- Gallstones, arthritis, gout
- Mortality
- Many other diseases



↑ BMI will lead to ↑ Mortality risk

Obesity can affect metabolic activity by:
↑ increase in lipolysis > ↑ Free fatty acids > ↑ Hormones release

Anatomical Differences in Fat Deposition

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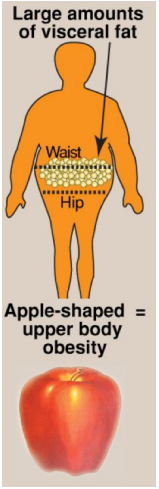
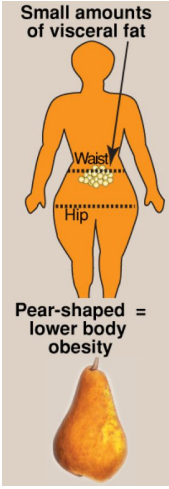
Health risks depend on the pattern of fat deposition

People have different tendencies for fat deposition

Sometimes Waist to hip ratio is a better diagnostic tool of obesity:
If the ratio is less than 1 → gynoid obesity
If it was more than 1 → android obesity



Android, "apple-shaped", or upper body obesity	Gynoid, "pear-shaped", or lower body obesity
• Excess body fat deposited in the central abdominal area • Associated with risk of hypertension, insulin resistance, diabetes, dyslipidemia, and coronary heart disease • More in men	• Fat deposited around the hips or gluteal region • Associated risks are lower • More in women



These two types of fat are biochemically different, and their metabolism is different
- Gluteal fat is less metabolically active so
  - It is more hard to lose
  - But it doesn't increase the risk of diseases, because the increased risk Of diseases is associated with circulating fatty acids that are released after metabolism
- Android or upper body fat:
  - More metabolically active, easier to lose but associated with many diseases

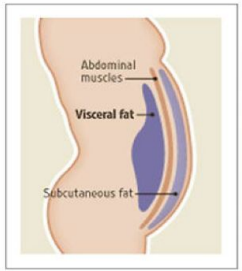
Different Fat Depots in the Body

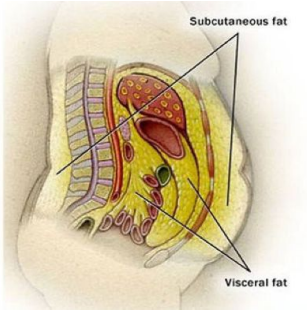
Subcutaneous Fat

- The fat stored just under the skin in the abdominal and gluteal-femoral region
- Constitutes 80-90% of the total fat in the body

Visceral Fat

- Composed of omental and mesenteric fat present in close association with digestive tract



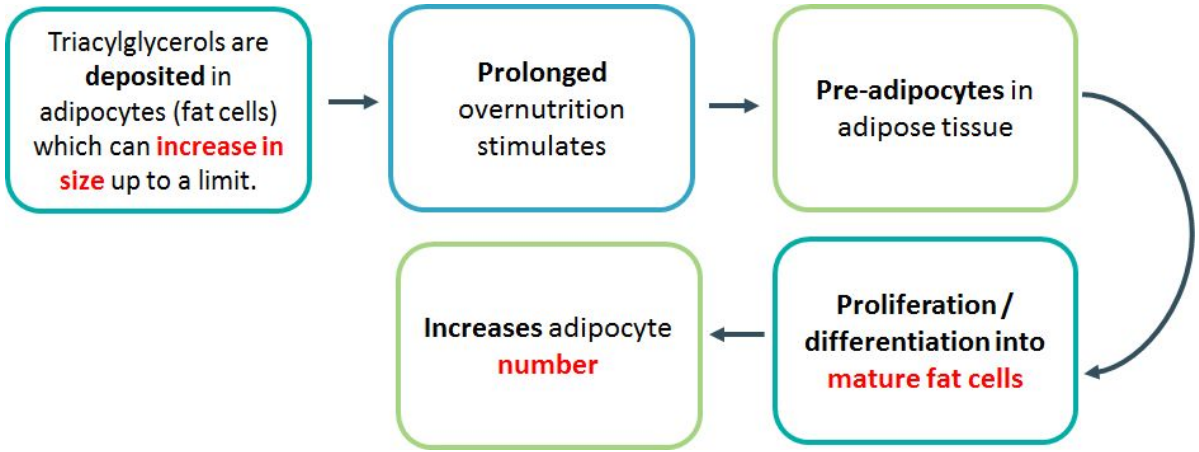


Biochemical Differences in Fat Deposits

Abdominal fat	Gluteal Fat
Smaller cells	Larger cells
More responsive to hormones* (both visceral and subcutaneous)	Less responsive to hormones
Release substances via portal vein to the liver May cause fatty liver disease	Release substances to circulation with no effect on the liver

*Metabolically active
- When we say abdominal fat, we mean both subcutaneous and visceral, both of which here are more metabolically active.

Adipocytes



- Thus obesity is due to a combination of increased fat cell size (hypertrophy) and number (hyperplasia).
- Fat cells, once gained, are never lost*.
- Reduction in weight causes adipocytes to reduce in size but not in number.

Adipocytes

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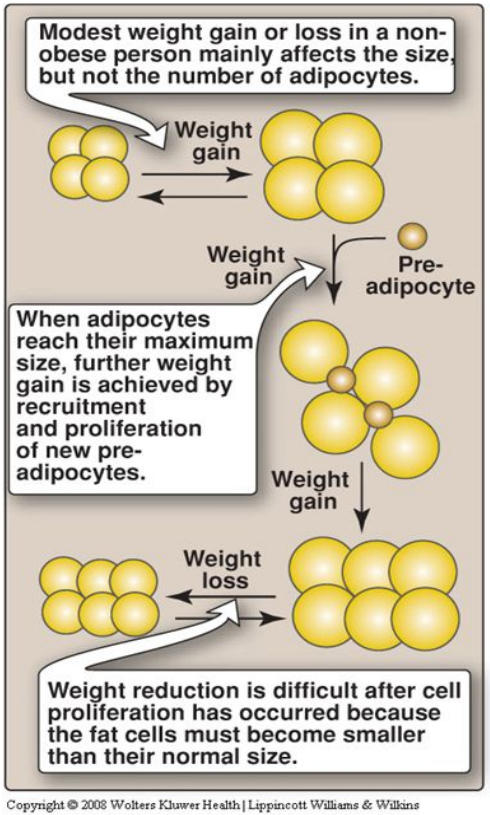
Read the picture



Picture:

- So weight gain includes both hypertrophy and hyperplasia of the adipocytes
- If a person with increased number of adipocytes is trying to lose weight, the adipocytes will shrink but will not decrease in number, so to get to a healthy fat percentage, the person must have smaller adipocytes than normal. This makes it harder to maintain the weight loss.

*This is actually an old statement, adipocytes have a lifespan of 10 years.

Ectopic fat

- Excessive calories that cannot be stored in adipose tissue “spill over” into other tissues such as muscle and liver
- It is called “ectopic fat” that is strongly associated with insulin resistance

Factors Contributing to Obesity

- **Genetic:** familial tendency
- **Environmental and behavioral :-**
  - **Sex:** women more susceptible
  - **Activity:** lack of physical activity
  - **Psychogenic:** emotional deprivation/depression
  - **Alcohol:** problem drinking
  - **Smoking**
- **Drugs:** e.g. tricyclic derivatives "antidepressants"

Causes of Weight Gain

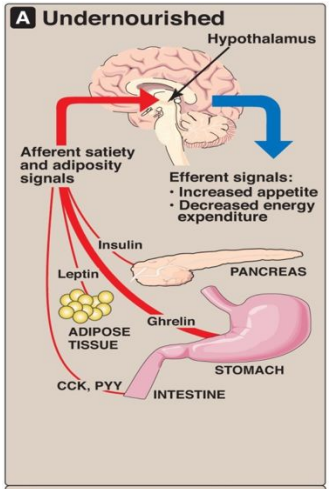
- **Energy imbalance:**
  - calories consumed not equal to calories used

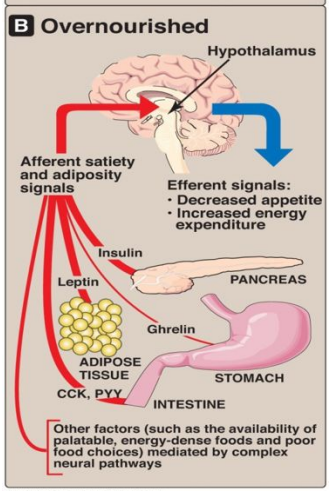
  Over a long period of time
- **Due to a combination of several factors:**
  - Individual behavior
  - Social interaction
  - Environmental factors
  - Genetics
- **More in and less out = weight gain**
- **More out and less in = weight loss**
- **Hypothalamus**
  - Control center for hunger and satiety
- **Endocrine disorder**

  "obesity is considered endocrine disorder"
  - Hormonal imbalance

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
- Adipocytes also function as endocrine cells
- They release many regulatory molecules:
  - Leptin, adiponectin, resistin, We call them adipokines





Long term hormone control:
- Leptin
- Insulin

Short term:
- Ghrelin, CCK

A) **Undernourished**
- High ghrelin which increases appetite"
- Low CCK,PYY which slows the gastric emptying
- Low leptin and insulin

Which send signals to satiety and adiposity signals, Net effect: increase appetite and decrease energy expenditure.

B) Overnourished: the opposite happens

Leptin

Definition	A protein hormone produced by adipocytes
Function	1. Required to keep the body weight under control 2. Signals the brain about fat store levels 3. Regulates the amount of body fat by: a. Controlling appetite (decrease) and energy expenditure (increase) b. Leptin causes overweight mice to lose weight and maintain weight loss
Secretion is:	• Suppressed in starvation (depletion of fat stores) • Enhanced in well-fed state (expansion of fat stores)

It is stimulated by increase in fat and it regulates its amount.
"it's a good hormone, it tells you when to stop eating"
↑ Leptin = ↓ Ghrelin

Leptin Resistance

- Leptin increases metabolic rate and decreases appetite in humans
- Plasma leptin level in obese humans is usually **normal** for their fat mass
- Resistance to leptin has been found in **obese humans**
- The receptor for leptin in the hypothalamus is produced by **db gene** and mutation in the **db gene** causes leptin resistance in mice
- Leptin resistance may have some role in human obesity
  - Dieting decreases leptin levels
  - Reducing metabolism, stimulating appetite

The person either:

- Can't produce enough leptin due to genetic abnormality and they become obese, so if you give leptin, The Person will lose weight
- Receptors are defected, so the person has enough leptin but no usage "leptin resistance"

Obese people have the same amount of Leptin, but they have a **delayed Leptin response.**

"It is helpful to tell the patient to take a small break in the middle of eating a meal to allow leptin secretion"

Adiponectin

Definition	**A protein hormone** exclusively and abundantly secreted by adipocytes
Effect	1. Promotes uptake and oxidation of fatty acids and glucose by muscle and liver 2. Blocks the synthesis of fatty acids and gluconeogenesis by hepatocytes. **Net effect is to increases insulin sensitivity / improve glucose tolerance**
Relations to level	1. Adiponectin levels are inversely correlated with body fat percentage and parallels with HDL levels 2. Low levels are seen in metabolic syndrome and diabetes mellitus

Increases metabolism, causing weight loss

Other Hormones

GHRELIN: A peptide hormone secreted by stomach

- Secretion increases just before meals and drops after meals
- Stimulates appetite: A-increases food intake B-Decreases energy expenditure and fat catabolism
- Levels of ghrelin in dieters are higher after weight loss
  When we lose weight, our body wants us to restore it. So it secretes high amounts of Ghrelin
- The body steps up ghrelin production in response to weight loss
- The higher the weight loss, the higher the ghrelin levels

Levels elevate during starvation

Cholecystokinin:
Peptides released from the gut after a meal.
Sends satiety signals to the brain

Insulin:
Promotes metabolism
Also suppresses the appetite immediately

Metabolic Changes in Obesity

Adipocytes send signals that cause abnormal metabolic changes such as:

- **Dyslipidemia**
- **Glucose intolerance**
- **Insulin resistance**

Findings in obese patients
(Both adiponectin and leptin will be LOW)

Benefits of weight loss in obesity

Weight loss decreases risk factors for obesity leading to:

- Lower blood pressure
- Decreased serum triacylglycerols
- Lower blood glucose levels
- Increase in HDL levels
- Decreased mortality
- Beneficial changes in BMR
- Decreased energy requirement
- Slow weight loss is more stable*

*To allow the set point to change, and the weight loss to be maintained

Treatment Options

- **Physical Activity combined with healthy diet decreases level of obesity**
- Reduces risk of heart disease and diabetes
- **Dieting:**
  - Use of low-calorie diet
  - Restriction of excessive energy intake

Actually, calorie restriction is the most important factor, and combining it with exercise helps in weight loss maintenance

Drugs

- **Orlistat**
  - A pancreatic and gastric lipase inhibitor
  - Decreases the breakdown of dietary fat
- **Lorcaserin**
  - Promotes satiety

Other drugs:
Liraglutide which is a Glucagon-Like-Peptide agonist

Surgery

- Surgical procedures are designed to reduce food consumption in patients with BMI >40
- Used when other treatment options fail

Extra Explanation

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How can obesity cause insulin resistance?

When a person is obese, initially adipocytes or adipose tissue are storage for TAGs, whatever excess of carbohydrates or fat, are all stored in adipocytes.

It's not just for storage it's an endocrine organ releasing a whole lot of hormones and other molecules some of them are adiponectin, lectin, resistin, IL-6, IL-1B and a lot more cytokines.

All these put together and called adipokines (**not all of them are bad some of them increase insulin sensitivity such as :Leptin and adiponectin (will be low in DM).**
most of these molecules are pro-inflammatory molecules So, obesity can be considered as a Low grade chronic inflammation.

All these signals coming from adipocytes cause a metabolic abnormalities such as dyslipidemia, glucose intolerance, insulin resistance and hypertension.

Another reason due to the ectopic fat in **Liver** and other tissue.

Summary

Anatomic Differences in fat deposition:	
Android Obesity	**Gynoid obesity**
Apple shaped , central , upper body obesity .	Pear shaped , or lower body obesity
In the Abdominal area	Around the gluteal and hips region
Most common in men	Most common in women

Definition	•A disorder of body weight regulatory system . •Accumulation of body fat >20%.
Risk factors	1.Diabetes 2.Hypocholesteremia 3.High plasma Triglycerols 4.Hypertension 5.Heart disease 6.Cancer 7.Gallstones , arthritis , gout 8.Mortality
Causes	1.Energy imbalance 2.Individual behavior , Environmental factors , Genetics 3.Hypothalamus (Controls satiety and hunger) 4.Endocrine disorders (Hormonal imbalance)
Factors Contributing	1.Genetic (Familial tendency) 2.Sex (Women are susceptible) 3.Activity (Lack of physical activity) 4.Psychogenic (Emotional deprivation) 5.Alcohol (Problem drinking) 6.Smoking (Cessation of smoking) 7.Drugs (Tricyclic derivatives)

Summary

Fat deposits	
Subcutaneous fat	**Visceral fat**
Fat stored under the skin in abdominal and gluteal region Constitutes 80-90% of total fat in body	Composed of omental and mesenteric fat present in close association with digestive system

Biochemical differences in fat deposition	
Abdominal fat	**Gluteal fat**
Smaller cells	Large cells
More responsive to hormones (both visceral and subcutaneous)	Less responsive to hormones .
Release substances via portal vein to liver	Release substances to circulation with no effect on liver

Leptin	Adiponectin	Others
Keeps body weight under control . Signals brain about fat level stores . Controls appetite and energy expenditure . Leptin resistance is due to db gene mutation and has been found in obese humans .	Promotes the uptake and oxidation of fatty acids and glucose by muscles and liver . Blocks synthesis of fatty acids and gluconeogenesis by hepatocytes . Net effect increases the sensitivity to insulin and improve glucose tolerance	Ghrelin : Secretes between meals , stimulates appetite . The higher the weight loss the higher the ghrelin levels CCK: satiety signals to brain Insulin : promotes metabolism

Treatment options

Physical activity combined with healthy diet

Drugs (Orlistat, Lorcaserin)

Surgery

MCQs:

1- A man's BMI is 36.9 what grade of obese is he according to the measurement

A- grade I
B- grade II
C- grade III
D- grade IX

2- Which of the following is NOT a feature of abdominal fat ?

A- Small cells
B- More responsive to hormones
C- Release substance in the in circulation
D- Release substance via portal system

3- Excessive calories that cannot be stored in adipose tissue "spill over" into other tissues such as muscle and live is the definition of?

A- Ectopic fat
B- Subcutaneous fat
C- Visceral fat
D- None of the above

4- Which of the following hormones secretion increases before meals and decrees after a meal ?

A- Leptin
B- Adiponectin
C- Ghrelin
D- Cholecystokinin

4- C
3- A
2- C
1- B

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