Important Doctors slides

Extra Information **Doctors notes**

Biochemistry

Biochemistry of Obesity: Role of Hormones

Editing file

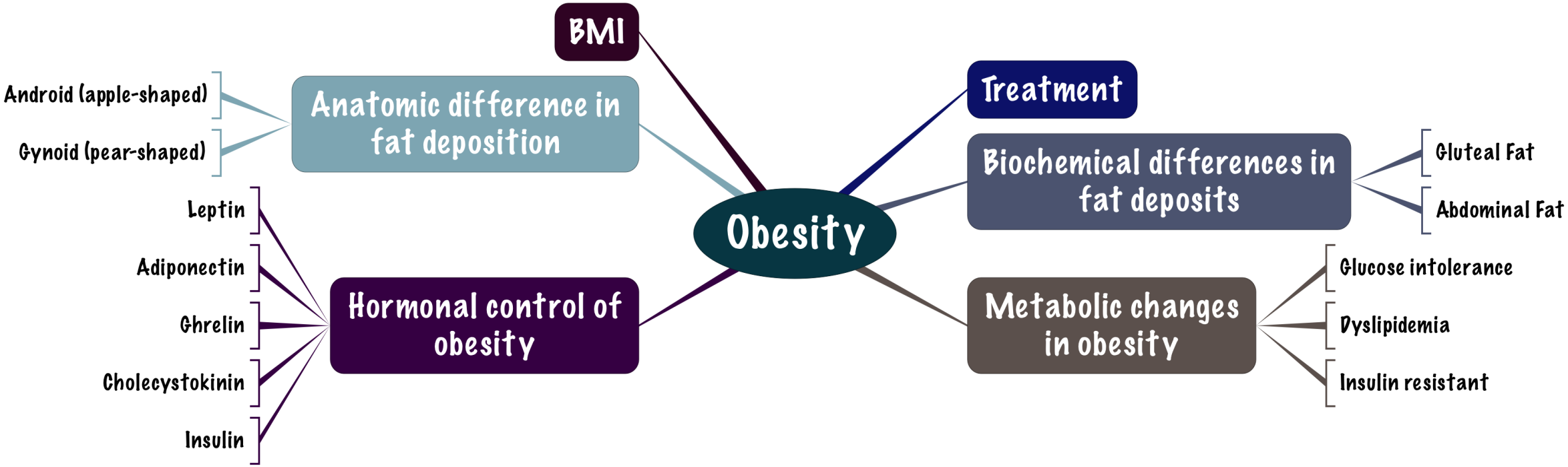
The best view comes after the hardest climb

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



This lecture contains too many notes but it's all super easy and understandable and most of it already known ..

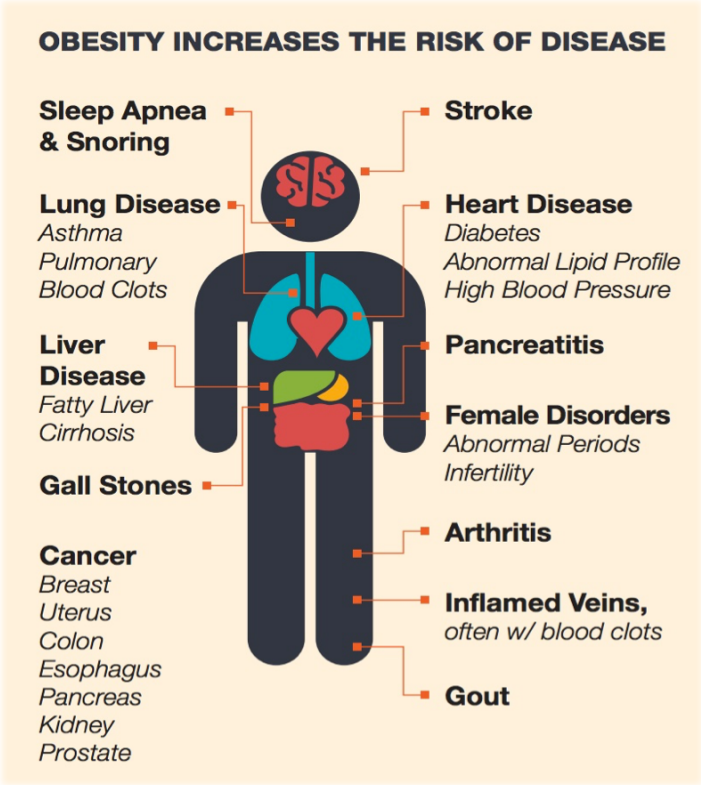
Obesity

- A **disorder** of body weight **regulatory systems.**
- Causes accumulation of **excess** body fat **>20%** of normal body weight.

  It should be **fat accumulation and not muscle mass**
  and it must be > 20% of the normal weight .

- **Obesity** is associated with a high risk of:

1. **Diabetes mellitus.**
2. **Hypercholesterolemia.**
3. **High plasma triglycerides.**
4. **Hypertension.**
5. **Heart disease.**
6. **Cancer.**
7. **Gallstones, arthritis, gout.**
8. **Mortality.**



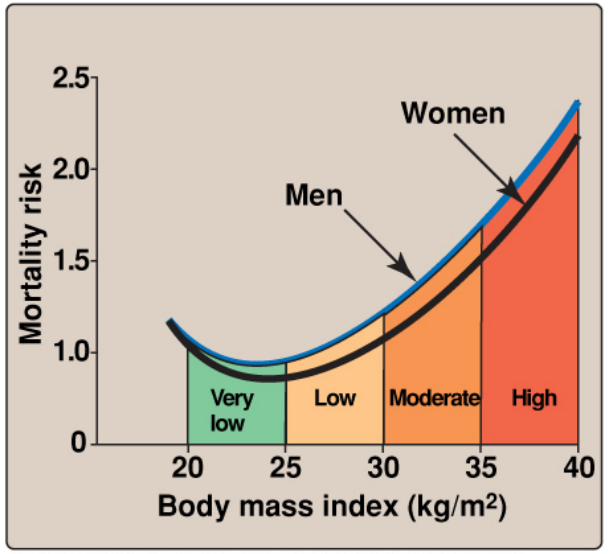
Is overweight same as obesity? obesity is more than overweight. Obese is when you cross the line of being overweight.

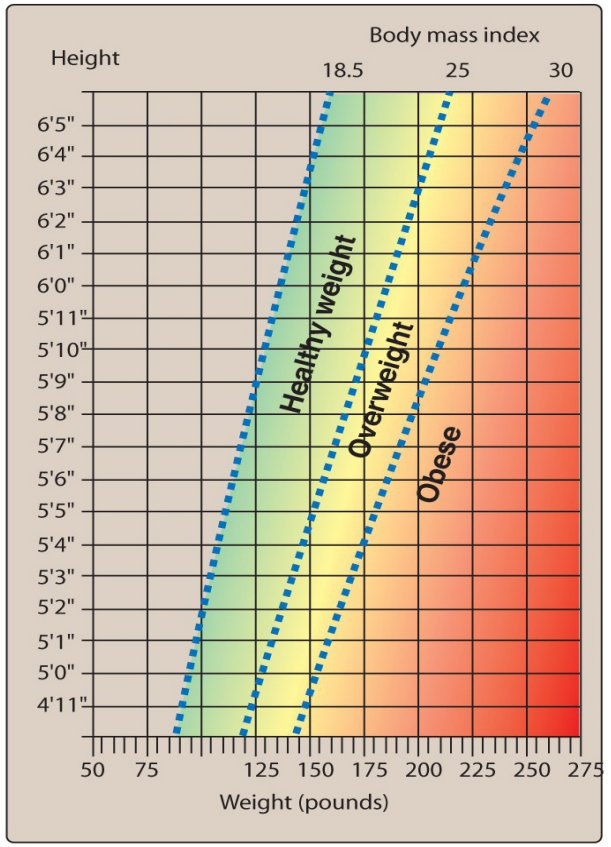
What do we mean by body weight regulatory system? The body has it's own regulatory system that controls a person's body so if a person has been maintaining a certain weight the body tries to go to it's memory and it becomes as a set point for it's body and if there is a transient point like: you have a set weight of 50KG and then you're stressed during the exam there is a chance that you're not eating well so you're starting loss weight in the end of the exams you have lost some weight but then as your exam finish and you're relieved you're start eating normally again then your body comes to it's original weight. You're on vacation your weight increase but then it comes to it's normal weight, as the change goes off. But when that **regulatory system** is not able to bring back your weight back to it's normal so, we've problem that causes obesity.

Body Mass Index (BMI)

- ❖ **BMI** is an **in**direct measure of obesity.
- ❖ **Correlates** **height**, **weight** and amount **of body fat** in an individual.
- High BMI is associated with increased mortality risk.

	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





BMI is and indirect measure of obesity:
Because muscular people have high BMI number because a muscle is much heaver than fat, so it sometimes gives a false positive that the person is obese.

When we talk about obesity and overweight we have to have certain measures to be able to differentiate the different people. There are different ways some people measure the waist circumference some people do a waist to hip ratio and one of the most generalized accepted and used ways are body mass index. What is BMI it's the weight in KG divided by the square of height in meters.

How did we comes to these numbers and rates. We actually did the research and found how the correlation of the body weight. How the body correlate with pre mature death. The reason of death shouldn't be accident so a natural pre-mature death so we have the weight and the height and it shows the BMI. If it's in the range of 18.5 to 25 it's a health range, we don't have the graft here but it's in Lippincott's it shows the curve. So you have the rate of premature death on the Y axis and you have the BMI on the X axis so if the BMI is lower than normal the mortality rate increases if the BMI in the health range it's the minimum mortality rate. And as the BMI increases the mortality rate increase. To have the least mortality rate your BMI should be in healthy range.

Anatomic differences in fat deposition

❖ Health risks depend on the pattern of fat deposition.

Android

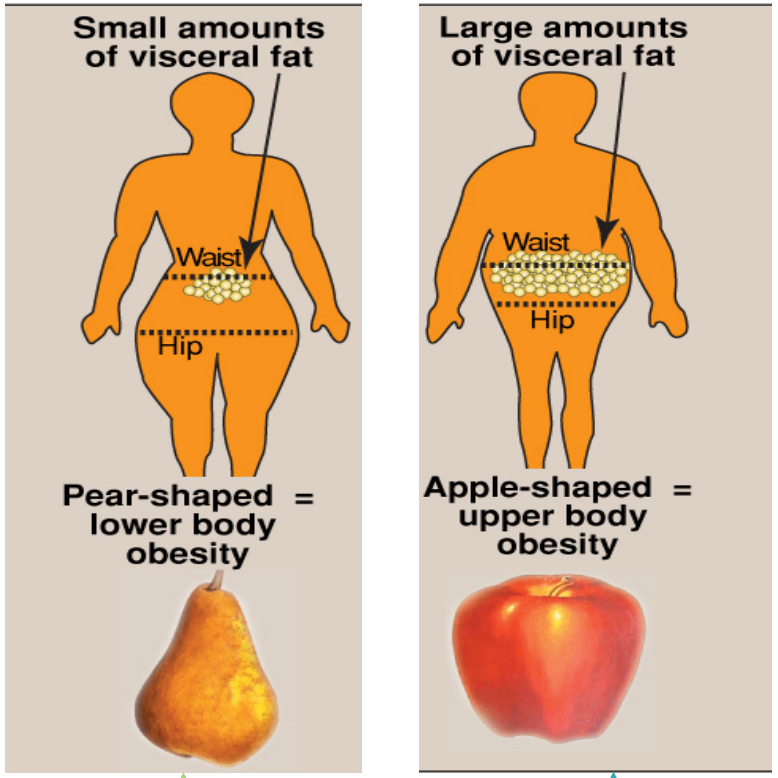
- "apple-shaped," or upper body obesity.
- Excess body fat deposited in **the central abdominal area.**
- Associated with risk of hypertension, insulin resistance, diabetes, dyslipidemia, and coronary heart disease.

Gynoid

- "pear-shaped," or lower body obesity.
- Fat deposited around the **hips** or **gluteal region.**
- Associated risks are **lower.**

It's risks are lower because the different regions of fat deposit it's biochemical differ. The fat that is located under the skin it's subcutaneous fat (it's just stored under the skin). The fat present in the abdominal area which is the fat around the digestive system it's the visceral omental fat, And this fat is much more dangerous because it's much more metabolically active than the gluteal femoral region fat.

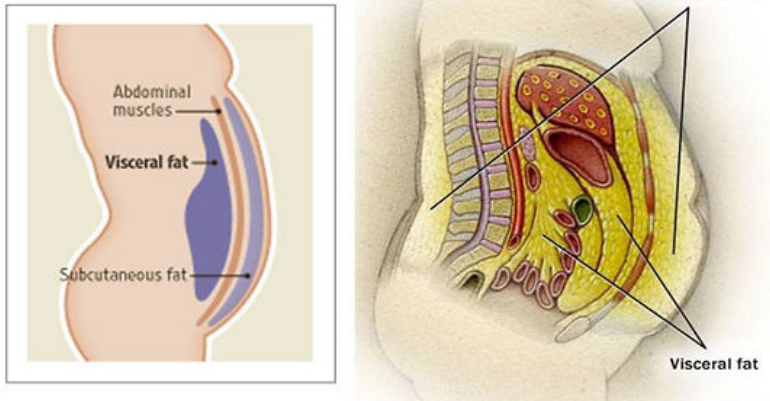
If the fat accumulate, when we see people Everybody has a different body type but we can put them into 2 categories in the sense of how the fat is deposited in the body. If we look to the most of females body the fat is accumulated in the hip region (pear shaped body) and for the males in the abdominal region (apple shaped body) or central body deposition, which is more dangerous than the first type.



Fat Deposits

❖ Different fat depots in the body

Subcutaneous Fat	Visceral 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.	• Composed of **omental** and **mesenteric** fat present in close association **with digestive tract.** • Visceral fat is hard to lose compared to subcutaneous fat.



❖ Biochemical differences in fat deposits

Abdominal Fat	Gluteal Fat
Smaller cell	**Larger cells**
More responsive to hormones (both visceral and subcutaneous)	**Less** responsive to hormones
Release substances via **portal** vein to liver affect it and cause dyslipidaemia and considered as high association with insulin resistance, That's why the abdominal fat is more dangerous because it release substances via portal vein to liver because this fat when it releases fatty acids and other things and the hormones everything goes to the liver so, it can cause insulin resistance and diabetes and dyslipidemia. Whether the gluteal fat what ever it releases it goes to the circulation it doesn't go directly to affect the liver.	Release substances to **circulation** with **no** effect on the liver

There is biochemical difference. So, by experience if you have seen obese people there is female has the same level of obesity and a male and both start exercising would you see a difference in their weight loss? Males loss weight faster. Because they have more muscles than fat. So even if they don't exercise and they depend only on diet they will loss fat why? Because the male accumulate the fat in the abdominal region while the female accumulate in the gluteal region. The abdominal fat is much more metabolically active and the gluteal fat is much more slow this region it takes the fat stores it and leave it's more difficult to loss the fat in this region (the gluteal region). Although the abdominal fat is dangerous and associated with pathological causes but it's also has a positive things to be lost much easier.

Adipocytes

Triacylglycerols are **deposited** in adipocytes (fat cells) which can **increase in size** up to a limit.

→ **Prolonged** overnutrition stimulates

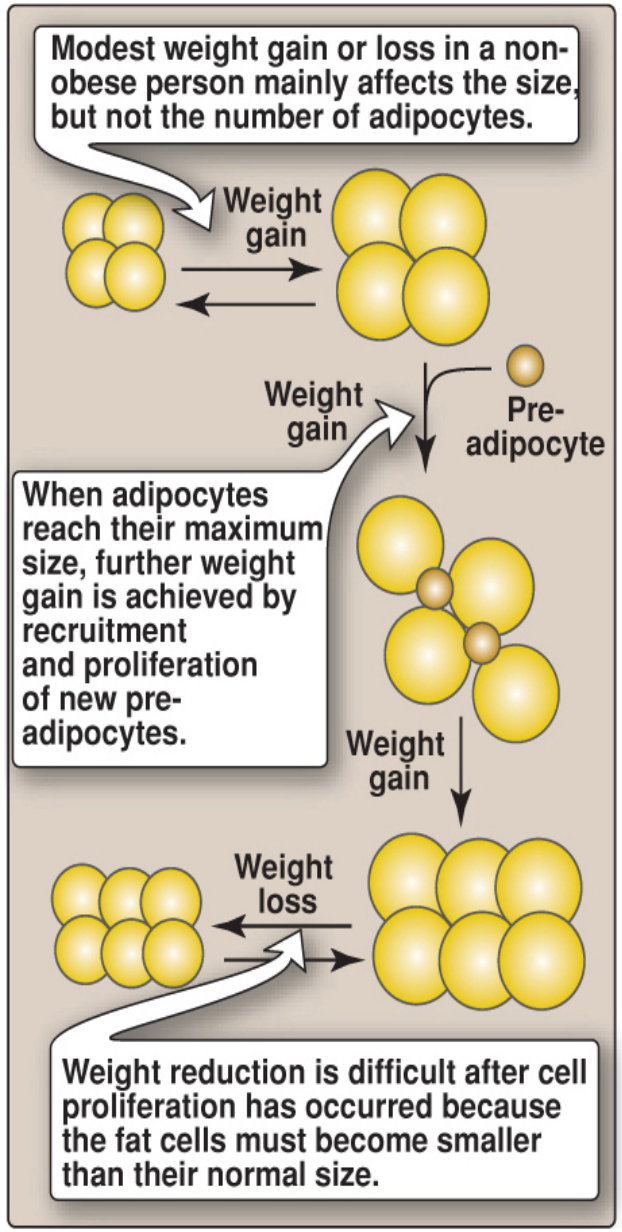
→ **Pre-adipocytes** in adipose tissue

→ **Proliferation / differentiation into mature fat cells**

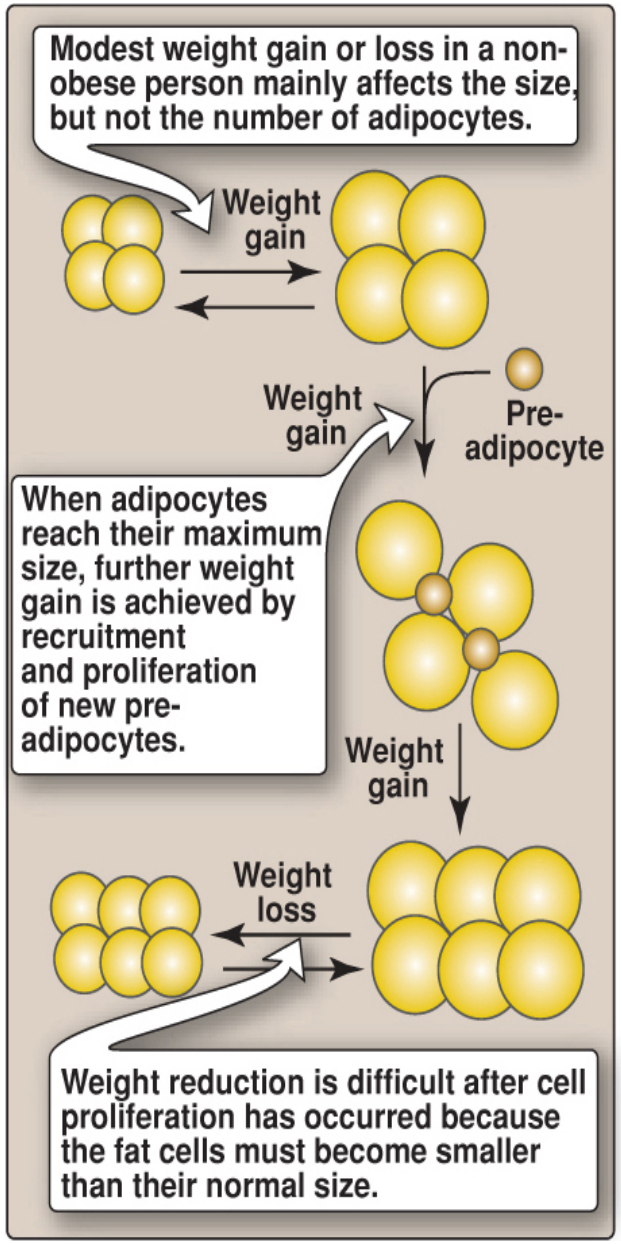
→ **Increases** adipocyte **number**

- 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.**

It is hard to lose weight when the fat cells increase in number. So abdominal fat cells are smaller cells, and gluteal fat cells are large and they have more capacity to store fat, but abdominal fat is more responsive than the subcutaneous fat and the fat present in the gluteal region is subcutaneous and therefore is less responsive.



Explanation



- When you eat too much all the excess fat will be stored in the adipocytes, these adipocytes they have a size where they can store up to limit. What happens after that –if the person continue in over eating- : The adipocytes will recruits the pre-adipocytes (the stem cells) and they differentiate into adipocytes
- So we have 2 things:

1. increase in size
2. increase in number.

- The amount od fat that is coming to the adipose tissue is so much that the tissue is overwhelmed and it cannot store in the adipocytes then this fat spells over and become what we know as ectopic fat around your organs.

- If a person is morbidly obese so, he has higher number and bigger adepocytes size then he starts losing weight There will be **decrease the size of adipocytes only** but the number stays the same.
- if a person lost too much this person is on the douply abnormal state because now to achieve that normal weight which that person had done he's still has the big number of his adipocytes but to reduce BMI range the size of adipocytes decreases .
- The moment they get any fat they will increase in size again.

Simple extra explanation:

Increased size of adipose tissue increases the production of new mature adipose tissue to help in fat storage (increased number), so when the individual loses weight there is higher normal of fat cells which are smaller than normal and has higher susceptibility to store fat to restore their normal size so because of their increased number the person will gain weight and become obese again.

Factor Contributing To Obesity

1. **Genetic**: familial tendency.
2. **Sex**: women more susceptible .
3. **Activity**: lack of physical activity.
4. **Psychogenic**: emotional deprivation/depression.
5. **Alcohol**: problem drinking.
6. **Smoking**

(cessation of smoking actually!!) after they quit it they start to taste the food better and eat more.

7. **Drugs**: e.g. tricyclic derivatives.

The genetic to prove it. They did an experiment the parents was obese and they had twins one of them raised with an obese parents and the other twin raised with lean parents, results showed that both twins were obese because of genetic causes. But genetic factors can be modified, if a person has a genetic obesity which is a predisposing factor he/she can modified his/her life style and prevent being obese.

Other causes:

- Stress.
- Some diseases like: hypothyroidism.
- Cushing's.
- The life style and eating habits

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**.

Causes of weight Gain

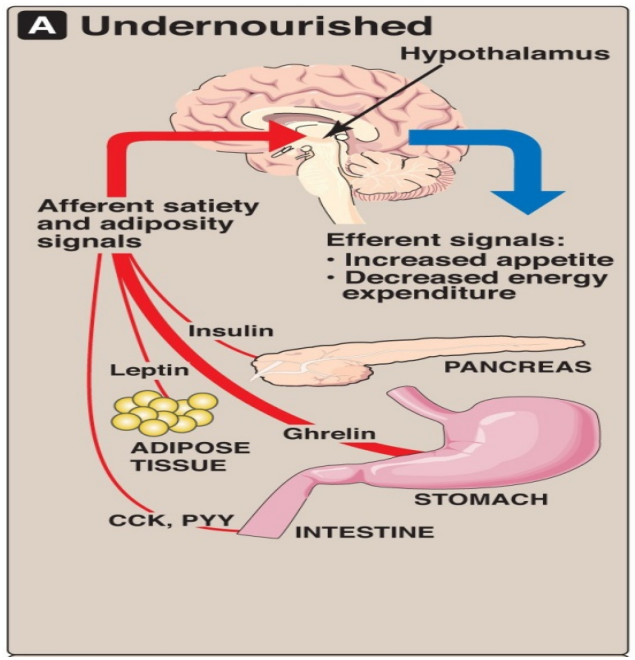
1. **Energy imbalance:**	• Calories consumed not equal to calories used. **Calories consumed higher than used, which makes fat accumulate in the body overtime.** • Over a long period of time.
2. **combination of several factors:**	• Individual behavior. • Social interaction. When you go out for a walk with your friends or go to resturant, it will contribute to your life style. • Environmental factors. e.g. hot weather (decrease physical activities) • Genetics.
3. **Hypothalamus:**	**Control center** for <u>hunger</u> and <u>satiety</u>.
4. **Endocrine disorder:** Adipose tissue it self is an endocrine organ	Hormonal **im**balance.
5. More in and less out = weight gain.	

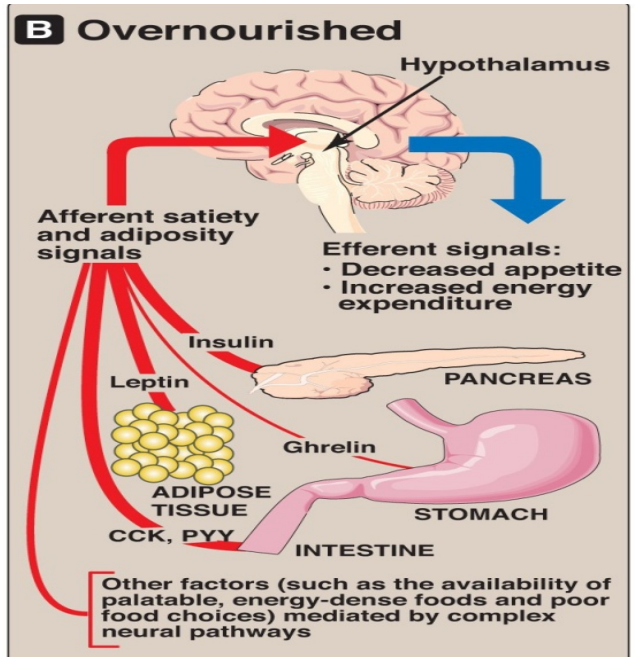
Hormonal control

❖ **Appetite is influenced by:**

1. **Afferent neural signals, circulating hormones, and metabolites.**
   - These signals cause the release of **hypothalamic peptides** and activate **efferent** neural signals.

2. **Adipocytes** also function as endocrine cells.
   - They release many regulatory molecules: **Leptin, Adiponectin, Resistin.**





There are signals that is going to your brain that control your feeling of your satiety or hunger. If the person is undernourished your stomach will increase the secretion of hormone **(ghrelin)** and other signals coming from the gut like **CCK, PYY** or the one coming from the adipose tissue which is **leptin or insulin** they will be low they go and tell the hypothalamus that the state of the body is undernuorishing and the hypothalamus will send signals that will increase the appetite and then you will feel hungery to eat. When the person is overnourished all of the hormones except the ghrelin (insulin – leptin – CCK – PYY) go and tell the hypothalamus that the person is fed and not hungry, so the hypothalamus will send the signals that decreases appetite (satiety) and the energy expenditure.

Leptin

- A **protein or peptide** hormone produced by **adipocytes** that is required to keep the body weight under control.
  - Signals the brain about **fat store levels**.
  - More fat in the body = more leptin secretion. So leptin tells the brain that body is will fed and induces satiety, decreases appetite and increases energy expenditure.
- **Regulates the amount of body fat by:**
  - **Controlling appetite and energy expenditure.**
- **Leptin secretion:**
  - **Suppressed** in **starvation** (depletion of fat stores).
  - **Enhanced** in **well-fed state** (expansion of fat stores).
- Leptin causes **overweight mice to lose weight** and maintain weight loss but not in humans.

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**.
- Mechanism? 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. Loss of fat stimulates leptin levels to go up and increases appetite and reduces metabolism.
  - **Reducing metabolism, stimulating appetite.**

Adiponectin

❖ **A protein hormone** exclusively and abundantly secreted by adipocytes .

❖ **Effect :**

- **Promotes** uptake and oxidation of **fatty acids** and **glucose** by muscle and liver.
- **Blocks** the synthesis of **fatty acids** and **gluconeogenesis** by hepatocytes.

Net effect is to increases insulin sensitivity / improve glucose tolerance.

- Adiponectin levels are inversely correlated with body fat percentage and parallels with **HDL levels** the good cholesterol (the good guy =P).

- Low levels are seen in **metabolic syndrome** and **diabetes mellitus.**

So, the fatty acids that present in the plasma it promotes the uptake of that and the glucose by tissues & that it's basically improving the glucose tolerance and insulin resistance .

(adiponectin regulates your fat metabolism and glucose metabolism so when it decreases the metabolism will be affected)

Other Hormones

GHRELIN	CHOLECYSTOKININ	INSULIN
A peptide hormone secreted by stomach. Right away before your meal time	Peptides	-
Secretion increases just before meals and drops after meals. Peaks and drops	released from the gut *after a meal*.	-
Stimulates appetite: It tells the body that you need to eat (= الام الحنون) increases food intake. Decreases energy expenditure and fat catabolism.	Sends satiety signals to the brain.	Promotes metabolism
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. When you loose large amount of weight in a very short time there will be an imbalance signals by your body which increases your ghrelin levels because the body is not adapted with the new weight with excess ghrelin you eat, and your weight returns rapidly	-	-

Metabolic Changes in Obesity → **Adipocytes send signals that cause abnormal metabolic changes such as:** →

1. **Dyslipidemia.**
2. **Glucose intolerance.**
3. **Insulin resistance.**

Benefits of weight loss in obesity

1. **Lower** blood pressure.
2. **Decreased** serum triacylglycerols.
3. **Lower** blood glucose levels.
4. **Increase** in HDL levels.
5. **Decreased** mortality.
6. Beneficial changes in BMR.
7. **Decreased** energy requirement.
8. Slow weight loss is more stable.

Tell the patient to eat healthy food not high calories food.

BMR = Basal metabolic rate

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**

The first thing to do is the modifying life style because if we go directly to the surgery or drugs without modifying the life style he will gain the weight again.

DRUGS	SURGERY
1. **Orlistat.** • **A pancreatic** and **gastric lipase inhibitor.** • Decreases **the breakdown of dietary fat.** • Causes fatty stool because it will not let the body to digest and absorb fat.	• Surgical procedures are designed **to reduce food consumption in patients with BMI >40** the last option • Used when other **treatment options fail** • Many clinics tell the patient to lose 5% of his weight before treatment because they want to make sure that he will modify his life style after the treatment. • Has multiple types: sleeve, bypass, ect..
1. **Lorcaserin**. • Promotes satiety.	

Summary

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)

Anatomic Differences in fat deposition:	
Android Obesity	**Gynoid obesity**
Apple shaped , central , upper bpdy 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

Summary

Fat deposits	
Subcutaneous fat	**Visceral fat**
Fat stored under the skin in abdominal and gluteal region Constituets 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 bia 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 obesed 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 apetite . The higher the weight loss the higher the ghrelin levels CCK: satiety signals to brain Insulin : promotes metabolisim
Treatment options Physical activity combones with healthy diet Drugs (Orlistat, Lorcaserin) Surgery		

QUIZ

Q1 : Which one of the following choices is associated with insulin resistance?

A. Abdominal fat
B. Gluteal fat
C. Ectopic fat
D. Subcutaneous fat

Q2 : 18 year old overweight teenager, came to your clinic complaining of inability to lose weight even though he tried dieting, he suggested that you do a sleeve for him.
But since you're a good doctor and understand the complications, you refused and gave him a therapy that would cause him to lose weight.
Which of the followings hormones when ***increased*** **,** causes weight loss?

A. Ghrelin
B. Leptin
C. Resistin
D. Adiponectin

Q3 : Which one of the following is expected to be in high levels **after** weight loss?

A. Ghrelin
B. Leptin
C. Resistin
D. Adiponectin

Q4 : Which one of the following is correct about Leptin?

A. Increases insulin sensitivity
B. Secretion suppressed in starvation
C. Secretion suppressed in expansion of fat stores
D. Causes thin mice to become overweight

Q5 : Which one of the following choices defines obesity?

A. Fat cell hypertrophy
B. Fat cell hyperplasia
C. Fat cell deposition
D. A+B

Q6 : Which one of the following is the function of Adiponectin?

A. Blocks synthesis of fatty acids
B. Decreases insulin sensitivity
C. Decreases glucose tolerance
D. Inversely correlated with HDL levels

QUIZ

Q7 : 21 year old girl came to your clinic because her medical student friend insisted you are the best endocrinologist on earth. (same girl in previous SAQs)
She says that she is worried about her body image because she is a bit overweight & unable to lose weight.
She came to ask you questions about how she can lose weight and how her current state of body affects her.

A) Can you tell me 3 disease associated with obesity?

- Diabetes mellitus
- Hypercholesterolemia
- High plasma triglycerides
- Hypertension
- Heart disease
- Cancer
- Gallstones, arthritis, gout

B) Tell me 3 hormones involved in appetite .

1. Leptin
2. Ghrelin
3. Cholecystokinin

C) What are the metabolic changes in obesity and what is responsible for them?

1. Dyslipidemia
2. Glucose intolerance
3. Insulin resistance

Adipocytes send signals that cause these abnormal metabolic changes.

D) What is the possible treatment for my current weight?

Physical activity combined with a healthy diet.

E) Tell me 2 drugs that can be used for losing weight & how do they work?

1. Orlistat: Pancreatic and gastric lipase inhibitor → decreases the breakdown of dietary fat
2. Lorcaserin: promotes satiety

Suggestions and recommendations

1) C 2) B 3) A 4) B 5) D 6) A

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THANK YOU

FOR CHECKING OUR WORK

PLEASE CONTACT US IF YOU HAVE ANY ISSUE

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