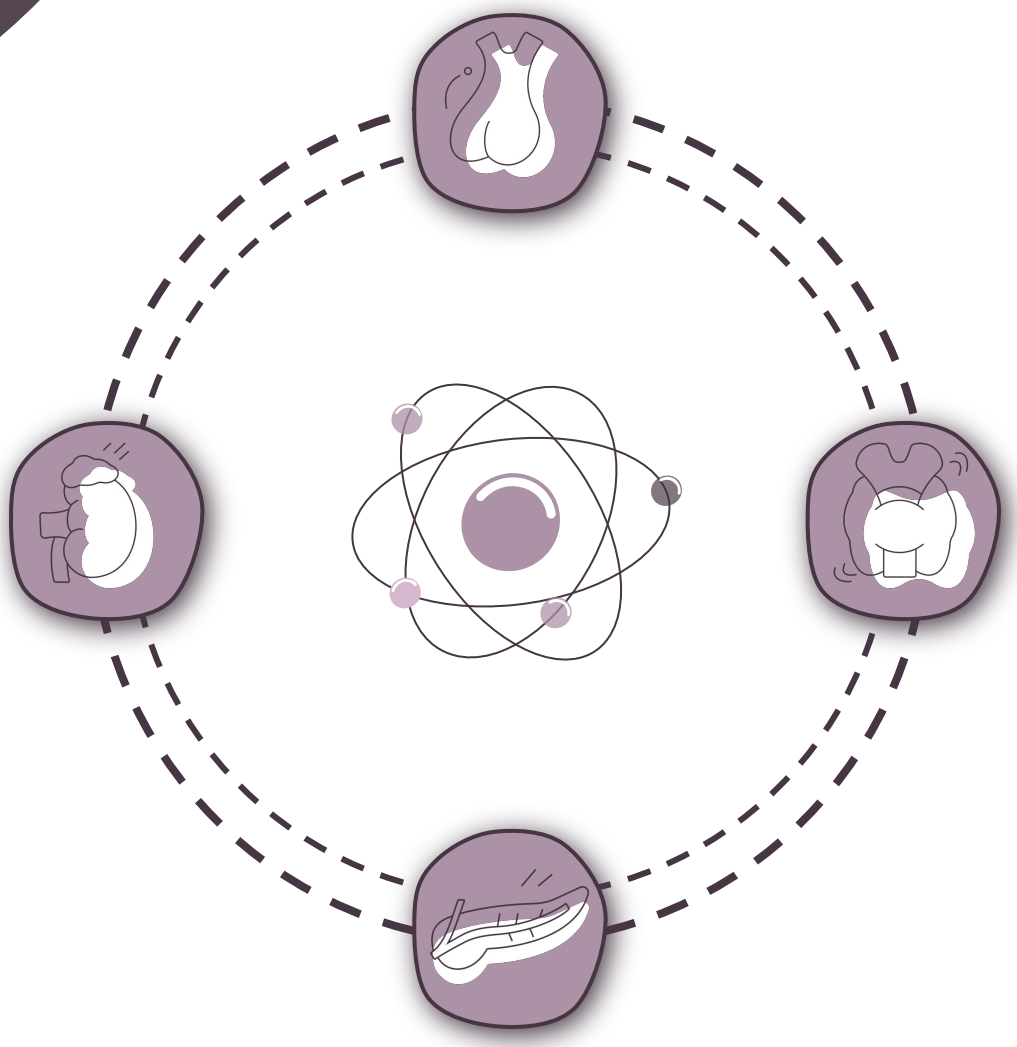

L7: Obesity: role of hormones

Presented by:
Dr. Sumbul & Dr. Usman Ghani

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Objectives

1. **Define and Characterize Obesity in terms of BMI and Risk Factor.**
2. **Compare the Anatomic and Biochemical differences in fat deposition.**
3. **Understand the role of adipocytes in fat storage and release of hormones.**
4. **Discuss the hormonal control of obesity by leptin, adiponectin and other hormones.**
5. **Understand the mechanism of leptin signaling.**
6. **Discuss the management and treatment options for obesity.**

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1

Obesity

* Obesity is an endocrine problem.

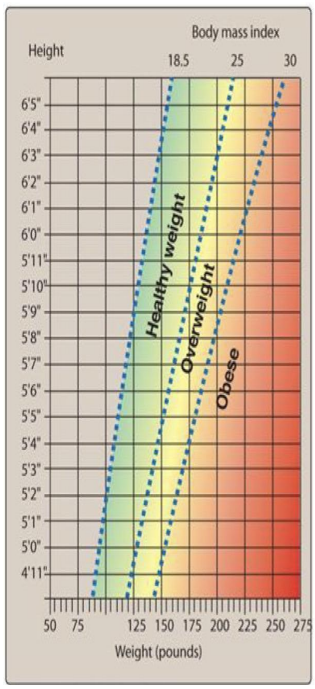
Definition

A disorder of body weight regulatory systems causes accumulation of excess body fat more than >20% of normal body weight.

Body Mass Index (BMI)

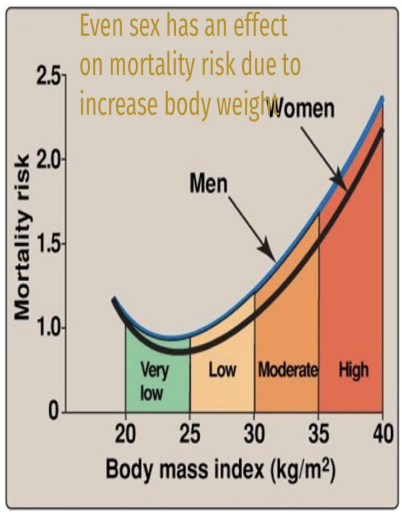
- **BMI is an indirect measure of obesity.**
  - **BMI = Weight (kg) / Height²**
- **Correlates height , weight and amount of body fat in an individual.**
  - **Doesn't take other things in account e.g. difference between muscle mass or fat mass.**
- **High BMI is associated with increased mortality risk**

	BMI	Grade
Underweight	≤ 18.5	-
Normal	18.5-24.9	-
Overweight	25-29.9	It's a warning sign
Obese I	30-34.9	I
Obese II	35-39.9	II
Highly Obese	≥40	III



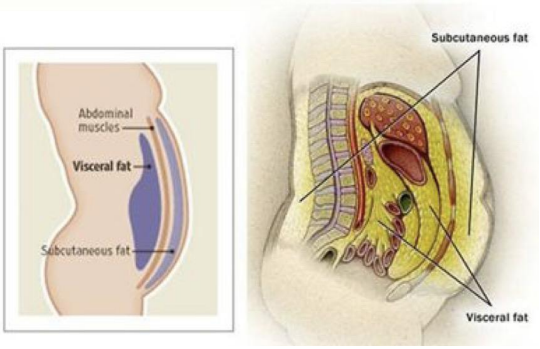
Risk factors associated with obesity

- Mortality — Depending on how much obese the person is
- Diabetes mellitus
- Hypercholesterolemia
- Gallstones, arthritis, gout
- Hypertension
- Heart disease
- Cancer — Most of the types
- High plasma TAGs



2 Different fat depots in the body

Visceral fat	Subcutaneous fat
Composed of omental and mesenteric fat	The fat is stored just under the skin in the abdominal and gluteal-femoral region
Present in close association with digestive tract around and in between the organs	Constitutes 80% - 90% of the total fat in the body. Mainly Gynoid because there is no organs in these areas



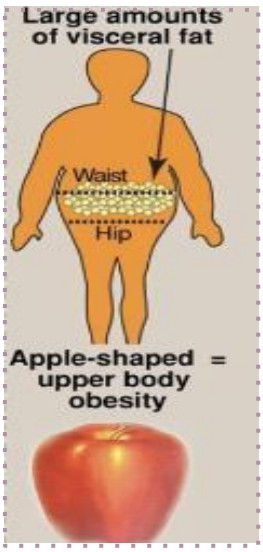
Both types present in Android pattern

Anatomic difference in fat deposition
(Health risks depend on type of deposition)

1 Android

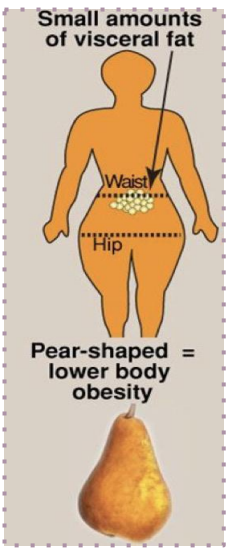
- **(Apple shaped)** or upper body obesity. More dangerous
- Excess body fat deposited in the **central abdominal area.**
- **Associated risk factors** are : hypertension , coronary heart disease, dyslipidemia, diabetes and insulin resistance.

Because these adipocytes releases substances (cytokines and fatty acids) and start inflammatory signaling to other organs.



2 Gynoid

- **(Pear shaped)** or lower body obesity.
- Fat deposited around the **hips or gluteal region** and the femoral region.
- Associated risks are **lower.**



Biochemical differences in fat deposits

1 Abdominal fat

- Smaller cells.
- More responsive to hormones (Both visceral and subcutaneous) metabolically active! And easily lost. that's why it's more dangerous.
- Release substance (pro-inflammatory molecules) via **portal vein to the liver** and contributes in Insulin resistance.

2 Gluteal Fat

- Larger cells Can take up larger amount of fat
- Less responsive (subcutaneous) less metabolically active! (stubborn fat).
- Release substance **to circulation with no effect on the liver.**

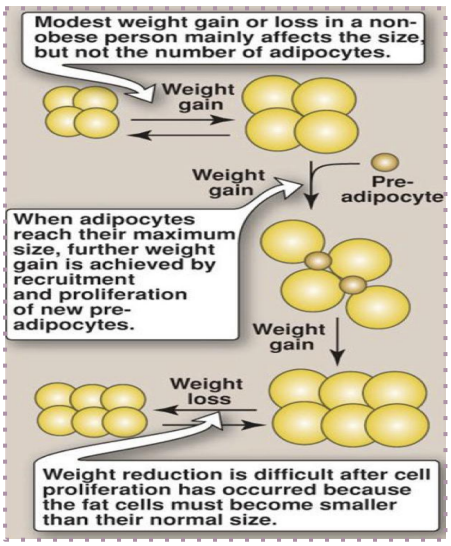
3

Adipocytes

- Excess Triacylglycerols (Fats) are deposited in adipocytes (fat cells) Which can increase in size up to a limit :

  Prolonged overnutrition stimulates –> Pre-adipocytes in adipose tissue a kind of stem cells –> proliferation/differentiation into mature fat cells Recruitment of more fat cells –> Increases adipose number. + in size

- Thus obesity is due to a combination of increased fat cell size (hypertrophy) and number (hyperplasia).
- Fat cells, once gained, are never lost. Fat cells have lifespan = 10 years
- Reduction in weight causes adipocytes to reduce in size but more in number



Ectopic fat

- Excessive calories that cannot be stored in adipose tissue "spill over" into other tissues such as muscle and liver. In liver, this is called Non-Alcoholic fatty liver disease (NAFLD).
- It is called "ectopic fat" that is strongly associated with insulin resistance.

Dr's notes: When you gain weight the cell will increase in size (hypertrophy), and when you lose weight the cell will return to the normal size without change in number of cells. But when the amount of fat is beyond the storage capacity of the cell, a new adipocytes will be formed (hyperplasia) which will make it hard for the person to lose weight because the cells should be smaller than normal since these cells are never lost. People who lose weight will easily regain it because the (hyperplasia) is already there and that's why weight is much easier controlled in early stages (hypertrophy) before (hyperplasia) starts. When adipocytes aren't enough to store all the fat then the fat spread out to other regions in the body(rather than adipose tissue) such as liver and muscles and they become fatty.

Factors Contributing To Obesity

Environmental and Behavioral

- Sex : Women more susceptible.
- Activity : Lack of physical activity.
- Psychogenic : Emotional deprivation/ depression
- Alcohol : Problem drinking.
- Smoking.

Genetic

Familial tendency

Polygenic disease

Diseases

Hypothyroidism and cushing syndrome.

Drugs

E.g. tricyclic derivation

4

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**
- **Environment factors**
- **Genetics** *Non-modifiable factor
- **Social interaction**

Hypothalamic Hormonal control

IMP

Appetite is influenced by :
- Afferent neural signals.
- Circulating hormones.
- Metabolites.

1

These signals cause the release of hypothalamic peptide and activate efferent neural signals.

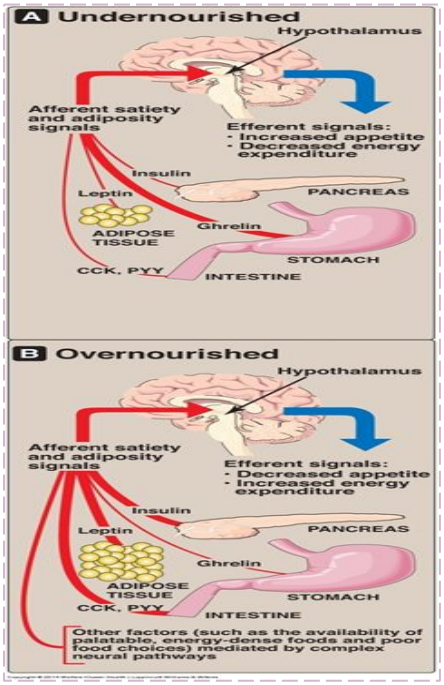
2

Adipocytes also function as endocrine cells.

3

They release many regulatory molecules :
- **Leptin**
- **Adiponectin**
- **Resistin** Antagonizes Insulin

4



Hormones

- **Insulin**
- **Adipocytes**
  - **Leptin**
  - **adiponectin**
  - **resistin**
- **Cholecystokinin**
- **Ghrelin**

5 Leptin

- A protein hormone produced by adipocytes

Secretion

-Suppressed in starvation (depletion of fat stores). Leads to ↓ in energy and ↑ in appetite
-Enhanced in well-fed state (expansion of fat stores).

Function

-Required to keep the body weight under control. It tells the brain how much fat is stored
-Signals the brain about fat store levels.
-Regulates the amount of body fat by controlling appetit (↓ appetite) and energy expenditure (stimulating effect)
-Leptin causes overweight mice to lose weight and maintain weight loss.

Leptin signaling (hypothalamic leptin action)

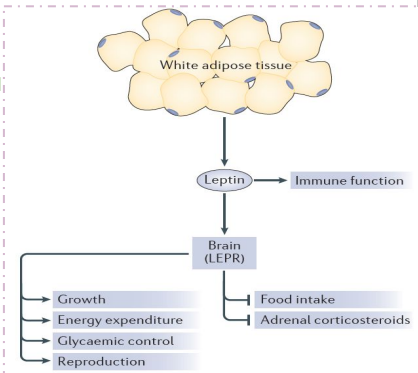


Figure 1 | **Leptin action.** Cells of white adipose tissue secrete leptin in approximate proportion to their triglyceride content. Circulating leptin binds to the long form of the leptin receptor (LEPR) in the brain and, in doing so, promotes growth, energy expenditure, glycaemic control and reproduction. Leptin also suppresses food intake and the production of adrenal corticosteroids. Leptin also influences the production and function of immune cells.

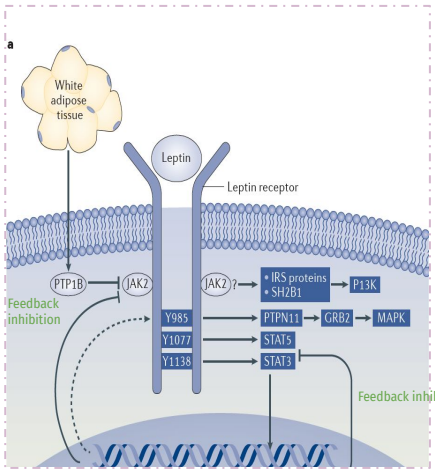
Dr's notes :

- The function of leptin is to make feel full, it decreases your appetite.
- The amount of leptin in the body is proportional to the amount of fat levels and adipose tissue, so it levels will increase in obese people and after meals, but when you are hungry your fat levels will decrease so there's NO action of leptin on the hypothalamus.

Leptin signalling and mechanisms that mediate its inhibition In individuals with normal body weight

The LEPR-STAT3 pathway : IMPORTANT

- Leptin + Receptor (LEPR) → Activates JAK2 → Phosphorylation of LEPR tyrosine residues (Y985, Y1077, Y1138).
- Y1138 → Activates STAT3 transcription factor → Gene expression → Control of energy balance. And change the BMR
- STAT3 → activates suppressor of cytokine signaling 3 (SOCS3) → Binds to Y985 → Inhibits leptin signaling (by inhibiting JAK2 and Y985).
- PTP1B from WAT and TCPTP → dephosphorylate JAK2 and STAT3.



- Leptin Receptor (LEPR)
- White adipose tissue (WAT)
- Janus kinase 2 (JAK2)
- Signal transducer and activator of transcription 5 (STAT5)
- Suppressor of cytokine signalling 3 (SOCS3), inhibits **JAK2** and **Y985**
- **PTP1B (Protein tyrosine phosphatase 1B),** inhibits **JAK2**
- **TCPTP (T cell protein-tyrosine phosphatase),** inhibits **STAT3** and **STAT5**

Dr's notes :

- Leptin binding to his receptor, which is present in the hypothalamus, will phosphorylate (activate) a phosphorylating enzyme (**JAK2**) then it will phosphorylate (activate) the **tyrosine residues** (Y985, Y1077, Y1138), after the activation they will activate transcription factors to act on certain genes resulting in effects on energy control .
- **TCPTP** : a gene involved in growth and glycemic control

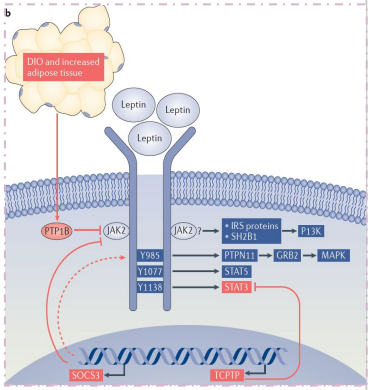
Leptin and obesity

- **Leptin increases metabolic rate and decreases appetite in humans.**
- Plasma leptin levels are in **proportion** to adipose tissue mass.
- Two mechanisms by which this leptin-adiposity balance is lost:

1. Leptin resistance:

- The receptor for leptin in the hypothalamus (Arcuate nucleus) is produced by **db** gene.
- Mutation in the **db** gene causes leptin resistance in mice.
- **Leptin resistance may have some role in human obesity:**
  - Dieting decreases leptin levels. (One of the reasons of diet failure) same in Undernourished Reducing metabolism, stimulating appetite.

2. Defect in leptin signaling.



<u>Leptin signalling and mechanisms that mediate its inhibition In Individuals with diet-induced obesity (DIO) :</u>

- Increased adipose mass →increases leptin levels → high LEPR signaling → increased expression of SOCS3, TCPTP and PTP1B → Decrease the amplitude of leptin response.

Dr's notes :

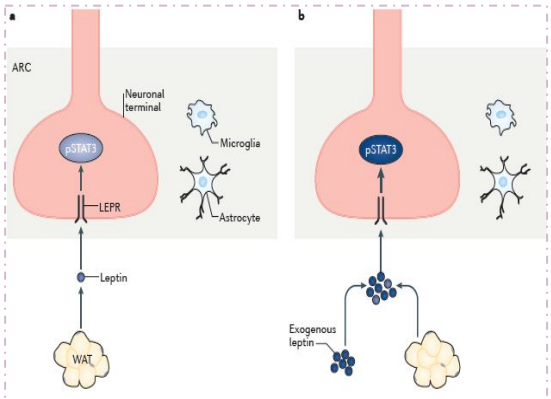
- Obese individuals will have higher levels of Leptin, initially they will have its effects, but it will stop quickly because of the strong activation to the inhibitory process , resulting in almost NO effect.
- **Negative feedback inhibition** on the leptin receptor signaling (PTP1B, TCPTP and SOCS3)

6

Male's Slides

Hypothalamic leptin action and changes during diet-induced obesity.

- **In lean individuals:**

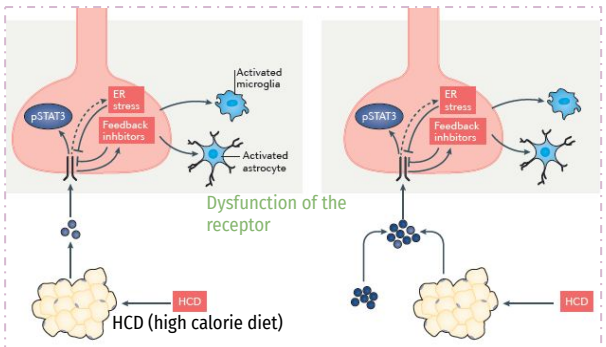


- ↑The expression and weight will be managed.
- Exogenous leptin will potentiate the response.

- **In obese individuals:**

Inflammation presents in the neurons

Counteract the effect of leptin signaling



No benefits from giving them exogenous leptin because the inhibition will increase as will.

Adiponectin

- A protein hormone exclusively and abundantly secreted by adipocytes.

Function	-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	**-Adiponectin levels are inversely correlated with body fat percentage and parallels with HDL levels.** -Low levels are seen in metabolic syndrome and diabetes mellitus.

Ghrelin

- A peptide hormone secreted by stomach.

Secretion	• Secretion increases just before meals and drops after meals. • The body steps up ghrelin production in response to weight loss. • Levels in dieters are higher after weight loss. It recommended to start dieting gradually with small goals. • The higher the weight loss, the higher the ghrelin levels.
Function	• **Stimulates appetite.** • Increases food intake. • Decreases energy expenditure and fat catabolism.

Cholecystokinin

- Peptides released from the gut after a meal.
- Sends satiety signals to the brain and slows gastric emptying.

Insulin

- Promotes metabolism.

7

Benefits of weight loss in obesity

Weight loss decreases risk factors for obesity leading to:

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

Metabolic changes in obesity

Adipocytes send cytokine signals to liver and other organ causing:

1. Dyslipidemia
2. Glucose intolerance
3. Insulin resistance

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

Drugs:

- **Orlistat :**

-A pancreatic and gastric lipase inhibitor
-Decreases the breakdown of dietary fat and the amount of the absorbed fat.

Surgery

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

Take home messages

1. Obesity is correlated to an increased risk for a number of chronic conditions and mortality.
2. Defect in leptin signaling is prevalent in obesity.
3. Energy balance in the body is hormonally controlled.

Test Yourself!

MCQs

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

Q1: Which of the following can be used to signal the percentage of body fat?
A. Leptin
B. Adiponectin
C. Ghrelin
D. CCK

Q2: Which one of the following hormone is inversely correlated with body fat percentage and parallels with HDL ?
A. Adiponectin
B. leptin
C. gastrin
D. ghrelin

Q3: What is the range of BMI that causes moderate increase in the mortality rate?
A. 20-25%
B. 25-30%
C. 30-35%
D. 35-40%

Q4: which one of the following is a genetic factor contributing to obesity?
A. Drugs
B. Familial tendency
C. Depression
D. Smoking

SAQs

Q1: mention three differences between Android and Gynoid deposition?
Slide 2

Q2: Enumerate some of the risk factors associated with obesity?
Slide 1

Q3: leptin is a protein hormone produced by ..... in response to..... ?
adipocytes - well-fed state (expansion of fat stores)

Meet The Team!

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