

Biochemistry  
Team 434

# Lipoproteins and Atherosclerosis

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# Introducon

A key element for cholesterol homeostasis is the balance between:

cholesterol transport from liver  $\longrightarrow$  peripheral tissue by LDL (bad cholesterol carrier)

reverse cholesterol transport from peripheral tissue  $\longrightarrow$  liver by HDL (good cholesterol carrier)

Imbalance results in cholesterol deposition in the wall of blood vessels, thickening of the wall and narrowing of the lumen “Atherosclerosis”

## composition of LDL and HDL

Low density lipoprotein (LDL)

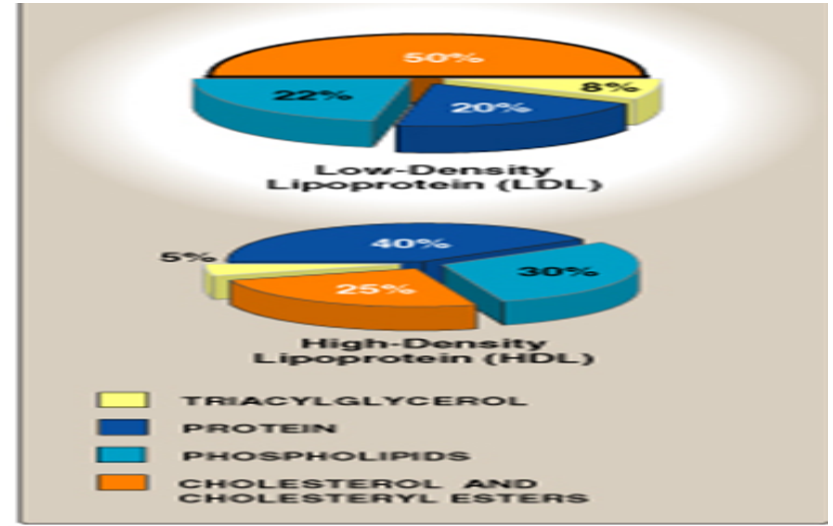
Mostly free cholesterol

High density lipoprotein (HDL)

Mostly cholesterol ester

More % protein

More % phospholipids



# low density lipoproteins LDL

-Produced in the circulation as the end product of **VLDLs**

-compared to **VLDLs**:

-It contains only apo **B-100**

-Smaller size and more dense

- Less **TG**

- More cholesterol & cholesterol ester

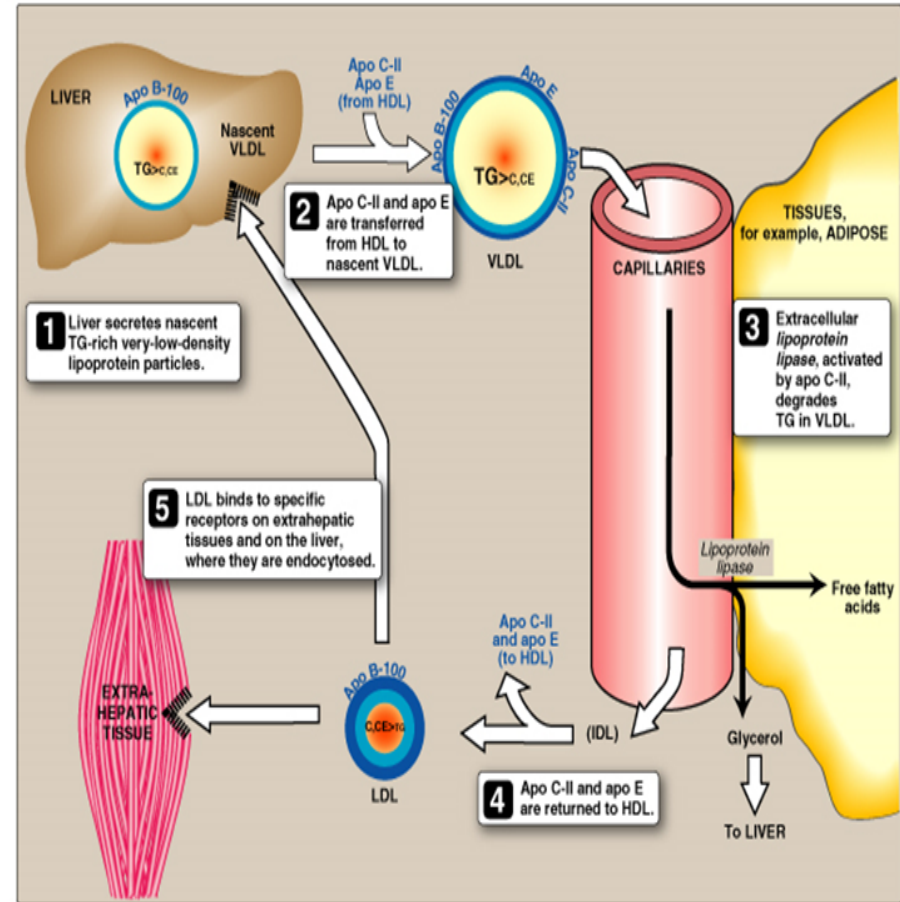
-Transport cholesterol from liver to peripheral tissues

-Uptake of LDL at tissue level by

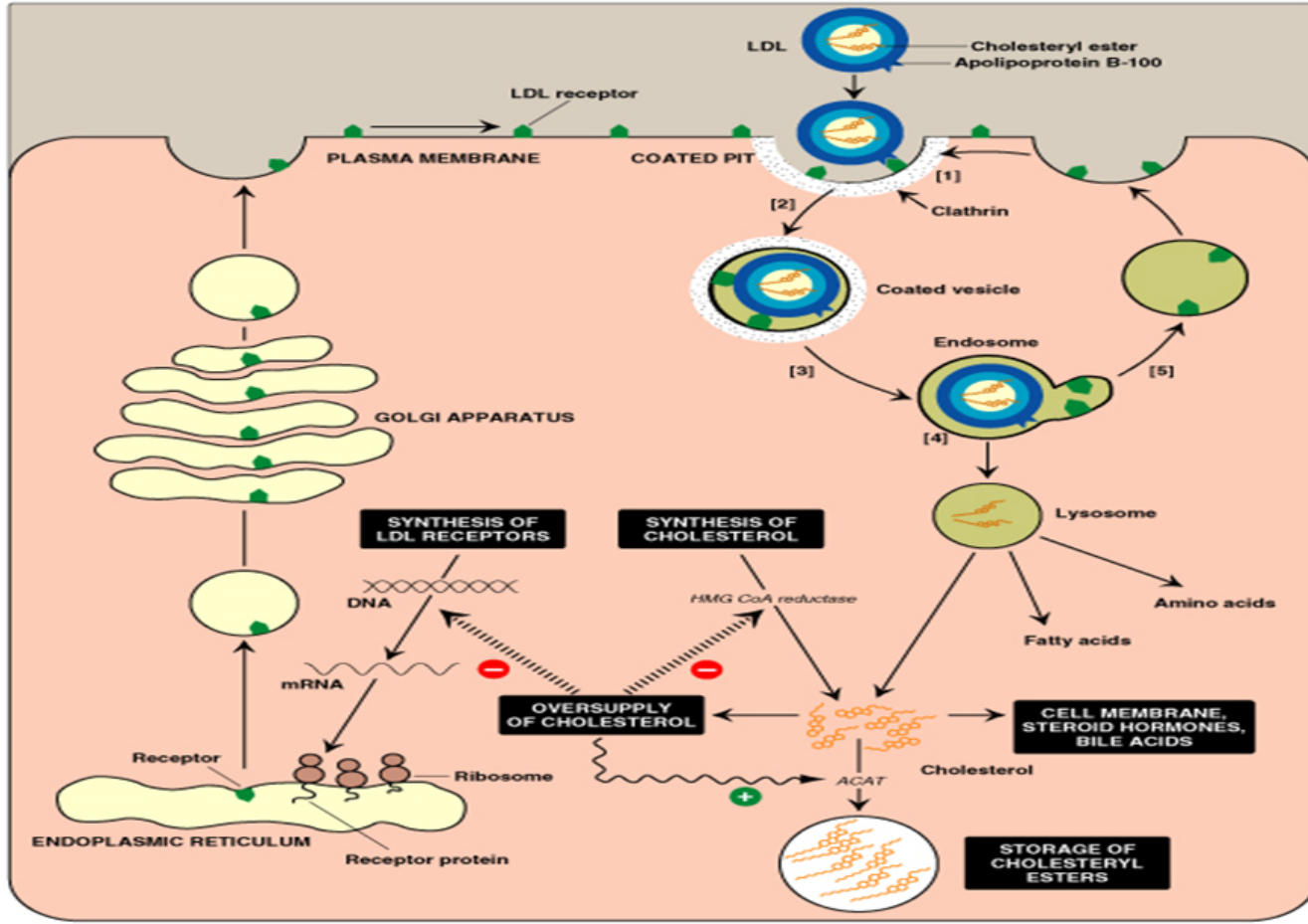
- **LDL receptor-mediated endocytosis**

Recognized by apo **B-100**

LDL metabolism



# Receptor-Mediated Endocytosis



LDL receptors :

- Cell surface glycoprotein
- High-affinity, tightly regulated

LDL/Receptor binding and internalization of the complex by endocytosis

Release of cholesterol inside the cells for:  
Utilization  
Storage as cholesteryl ester  
Excretion

Degradation of LDL:  
into amino acids,  
phospholipids and fatty acids

Degradation or recycling of receptor

## Down-regulation

**High intracellular cholesterol content**



-Degradation of LDL receptors.  
-Inhibition of receptors synthesis at gene level.



**Decrease No. of receptor at cell surface.**



**Decrease further uptake of LDL.**



**Decrease de novo synthesis of cholesterol.**

## Up-regulation

**Low intracellular cholesterol content.**



-Recycling of LDL receptors.  
-Stimulation of receptors synthesis at gene level.



**Increase No. of receptor at cell surface.**



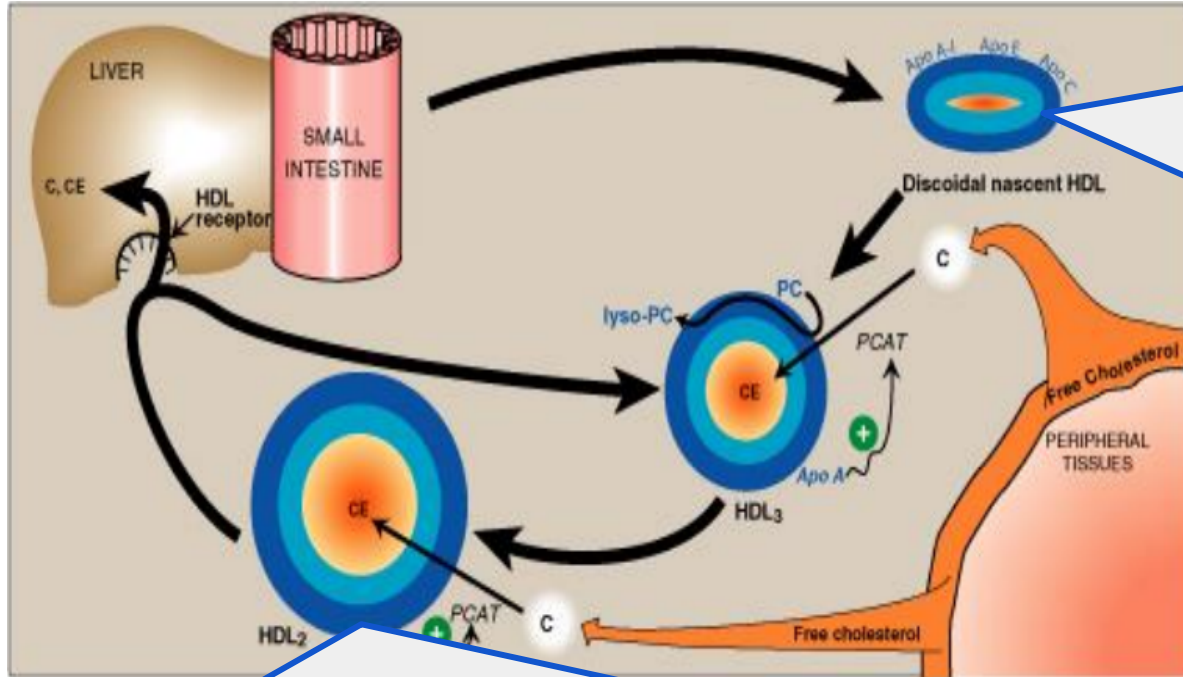
**Increase further uptake of LDL.**



**Increase de novo synthesis of cholesterol.**

# High Density Lipoproteins (HDL)

(produced by *intestine* & *liver*)



## Nascent HDL

-Disk-shaped

-Contains:

\***Apo A-I**

\***C-II**

\***E**

\*Primarily Phospholipid (**PC**)

## Mature HDL (HDL<sub>2</sub>)

**HDL<sub>3</sub>** collects **Cholesterol (C)** ⇒ **(C)** converted to **CE (C-ester)** ⇒ **HDL<sub>2</sub>** (spherical mature particle)

# Functions of HDL

## Reverse Cholesterol Transport

## Reservoir of Apoproteins

Apo C-II & E to VLDL

## Uptake of Cholesterol

*(from lipoproteins & cell membranes)*

**HDL** is suitable for **uptake of cholesterol** because of **high content of PC** that can:

- 1- Solubilize **cholesterol**.
- 2- Act as **source of fatty acid** for **cholesterol esterification**.

## Esterification of Cholesterol

- Enzyme: **PCAT/LCAT**
- Activator: **Apo A-I**
- Substrate: **Cholesterol**
- Co-substrate: **PC**
- Product: **Cholesterol ester** (& **Lyso-PC**)

# Why HDL Good Cholesterol Carrier?

⇒ Inverse relation between **plasma HDL levels** & **Atherosclerosis**

## Reverse Cholesterol Transport Involves:

- 1- Efflux of **cholesterol** from **peripheral tissues** and **other lipoproteins** to **HDL<sub>3</sub>**.
- 2- Esterification of **cholesterol** and binding of **HDL<sub>2</sub>** to **liver** and **steroidogenic cells** (by scavenger receptor class B (SR-B1)).
- 3- Selective transfer of **cholesterol ester** into these cells.
- 4- Release of lipid-depleted **HDL<sub>3</sub>**.



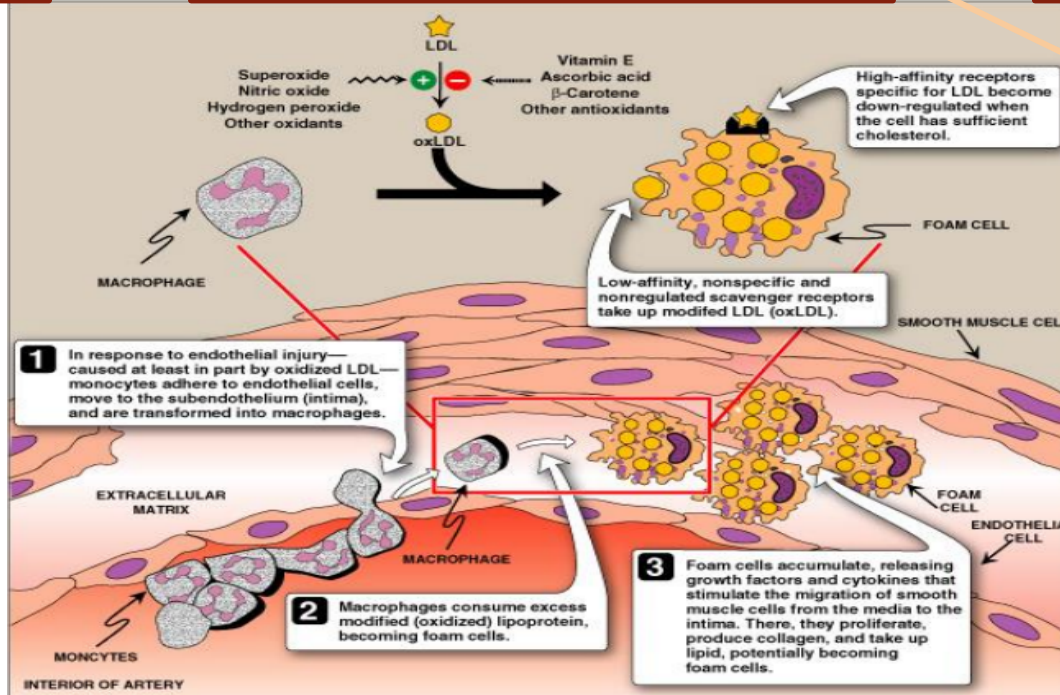
# Atherosclerosis

(pathogenesis & plaque formation)

**Modified (oxidized) LDL**  
(Oxidative Stress)

**Uptake of oxLDL**  
by macrophage scavenger receptor  
(Scavenger Receptor Class A (SR-A))

**Foam Cell Transformation**



-Low affinity.  
-Non-specific  
-Un-regulated

# Laboratory Investigation of Atherosclerosis

## Serum Lipid Profile: 10-12 hours (O/N) fasting

### Measurement of:

- 1- **Serum Triglyceride** level >> *reflect* >> **Chylomicron + VLDL** levels
- 2- **Serum Total Cholesterol** level >> *reflect* >> **LDL + HDL** levels
- 3- **Serum HDL-Cholesterol**
- 4- **Serum LDL-Cholesterol**

### Others:

Serum lipoprotein electrophoresis

Serum apoprotein levels e.g., Apo-B

# LDL-Related Diseases

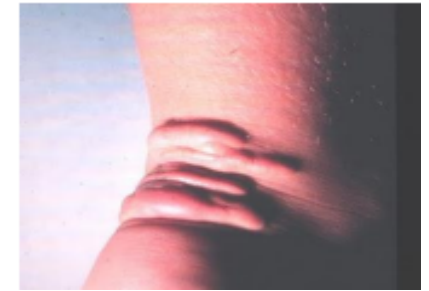
*(hyperlipoproteinemia)*

**Increase plasma LDL level**  
*(therefore plasma cholesterol level)*



**Premature Atherosclerosis & increased risk for early-onset Ischemic heart diseases**

**Functional defect of LDL-receptor**



Associated with **presence of tendon Xanthomas** on hands and ankles

**Type IIa Hyperlipoproteinemia**  
**(Familial Hypercholesterolemia)**

to develop atherosclerosis  
there is an imbalance between :

- 1- cholesterol transport from peripheral to the liver (HDL)

Action

- 2- cholesterol transport from the liver to the peripheral (LDL)

**LDL-Receptor :**

- tightly regulated
- high affinity
- endocytosis
- ends with degradation of LDL into (amino acids - fattyacids - phospholipids)
- release of cholesterol.

*Summary*

**HDL: has an inverse relation with atherosclerosis:**

- Nascent HDL
- Mature HDL

function:

- Reservoir of apoproteins
- Esterification of cholesterol
- Uptake of cholesterol
- Reverse cholesterol transport

**Atherosclerosis:**

- oxidized form of LDL.
- Uptake of oxLDL by macrophage scavenger receptor (lower affinity )
- Foam cell transformation
- Atherosclerotic plaque formation

**Laboratory Investigations:**

1- Serum lipid profile:

- Serum triglyceride level (VLDL -chylomicron)
- Serum total cholesterol level (HDL - LDL)
- Serum HDL-cholesterol level
- Serum LDL-cholesterol level

# Quiz your knowledge

<https://www.onlineexambuilder.com/lipoprotein-atherosclerosis/exam-23821>

## Some videos might help

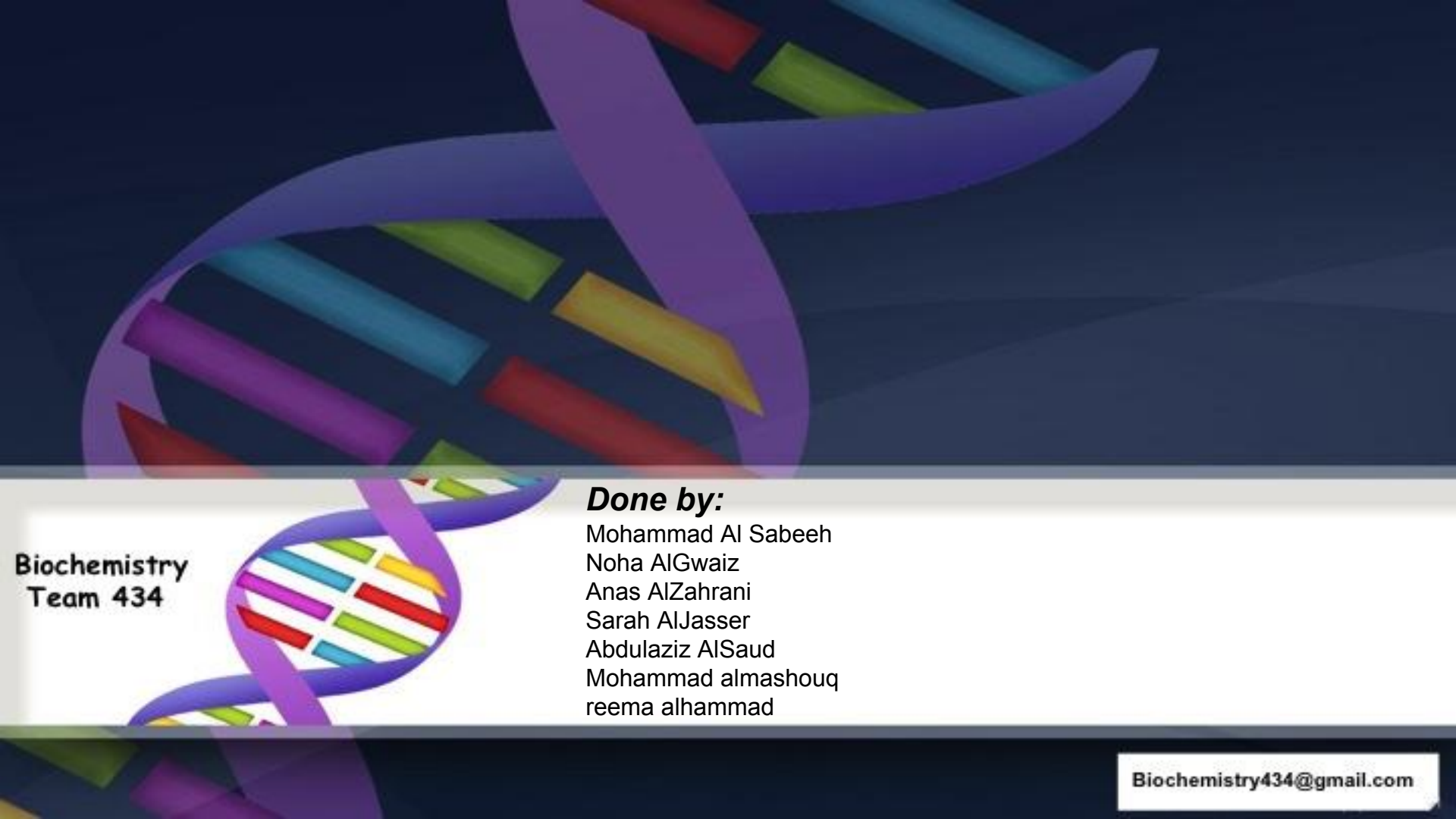
### **lipoproteins**

<https://www.youtube.com/watch?v=97uiV4RiSAY&spfreload=10>

<https://www.youtube.com/watch?v=wnK1Kv3XkZI&spfreload=10>

### **Atherosclerosis**

<https://www.youtube.com/watch?v=fLonh7ZesKs&spfreload=10>



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