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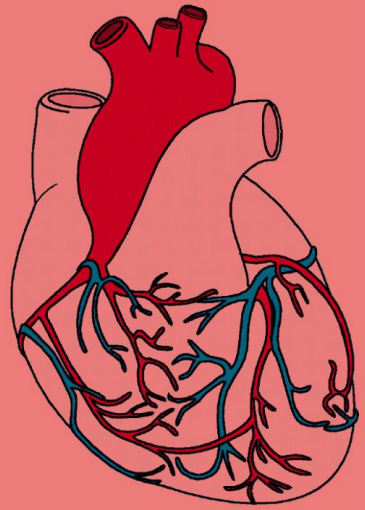
Lipoproteins and Atherosclerosis



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Main text

IMPORTANT

Extra Info

Drs Notes

Cardiovascular Block - Biochemistry Team

Revised & Approved by: Shaima Abdullah Alhassan, Faisal Alotaibi

MED439

Objectives:

- Correlate the imbalance in lipoprotein metabolism with the development of atherosclerosis
- Understand the functions and metabolism of LDL and HDL cholesterol
- Describe the receptor-mediated endocytosis of LDL and its regulation
- Recognize how LDL is considered a bad cholesterol whereas HDL a good cholesterol
- Understand the biochemistry of atherosclerosis and its laboratory investigations
- Discuss the role of lipoprotein(a) in the development of heart disease

Introduction (Overview)

Cholesterol homeostasis is a balance between cholesterol transport from the liver to the peripheral tissue and vice versa.

Liver

By LDL

By HDL

Peripheral Tissue

Our cardiac cell in the previous lecture , do you remember who drew it ?

Imbalance in this transport leads to:

- Cholesterol deposition in blood vessels
- Thickening and narrowing of the lumen of arteries
- Atherosclerosis
- Heart disease

Normally there is a cholesterol homeostasis. When the Body is unable to maintain cholesterol homeostasis there will be an accumulation of cholesterol in the blood which will be deposited in the blood vessels which leads to atherosclerosis.

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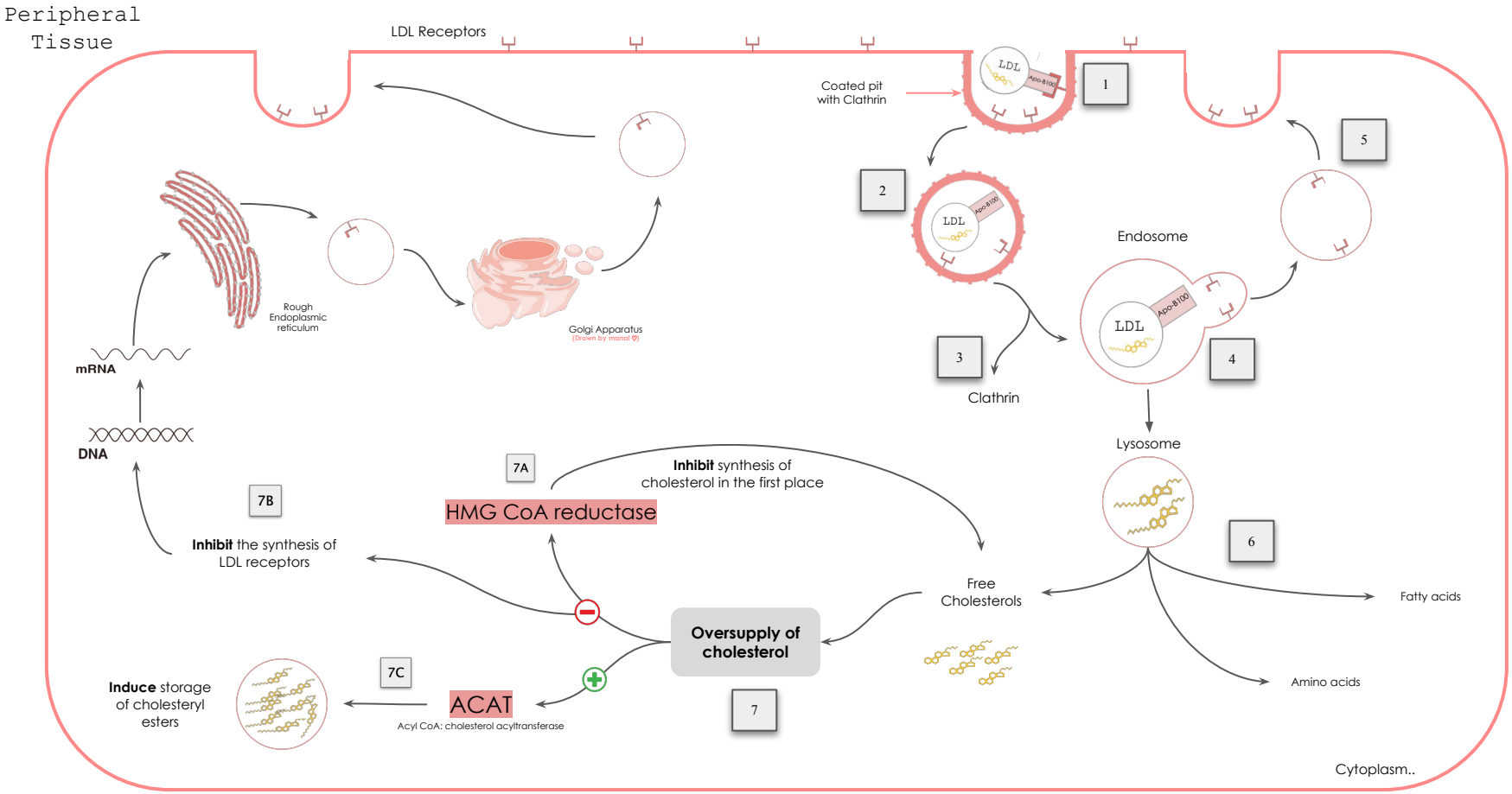
Cellular uptake and degradation of low-density lipoprotein (LDL) particles.



★ important slide

Cellular uptake & regulation of LDL particles

A helpful video

A) Receptor mediated endocytosis:

1. **Binding** of Apo B-100 to LDL receptor glycoprotein. LDL receptors are clustered in pits (depressions on the cell surface), which are coated with the protein Clathrin.
2. After binding, LDL receptors are taken in by **endocytosis.** The pits of clathrin pinch on itself forming a coated vesicle inside the cell
3. **Endosome formation** (LDL vesicle fuses with other vesicles). The vesicle containing LDL loses its Clathrin coat, forming an endosome.
   (Clathrin is responsible for maintaining and protecting the vesicle from being degraded or detached).
4. **Receptors Separation** from LDL. Endosomal ATPase enzyme will reduce the pH leading to the separation of receptors from the molecule.
5. Receptor is **recycled** The receptors migrate to one side of the endosome, whereas the LDL stay free within the lumen of the vesicle.
6. Endosomal vesicle containing LDL will **fuse with a lysosome** that has plenty of degrading enzymes and gets degraded, then it will give rise to amino acids, fatty acids and cholesterol (which will be used for cell requirements).

B) Regulation:

7. Let's suppose cholesterol increases inside the cell and there is **overproduction**, what is going to happen? (We will talk more about it next slide)

   7A **Inhibition** of the gene expression for enzyme HMG CoA reductase, this will lead to inhibition of cholesterol synthesis in the first place.
   this will also decrease De novo cholesterol synthesis, thus the degradation of the reductase is accelerated. (more details in cholesterol metabolism lecture)

   7B **Inhibition** and reduction of the synthesis of new LDL receptors. Also promoting the degradation of old receptors. This will limit further entry of LDLs into cells . You already know that LDL receptors are made up of proteins, too much cholesterol will stop the process of LDL receptors protein synthesis; replication, transcription, and translation, etc.....

   7C **Induction** of the esterification process and the storage of these cholesterols by activating the enzyme ACAT (Acyl CoA: cholesterol acyltransferase)
   ACAT transfers a FA " fatty acids " from a fatty acyl CoA to cholesterol, producing a cholesteryl ester that can be stored in the cell

Also, note that the cell might **pump the excess amounts of free cholesterol into the blood circulation.** (and it will be taken by HDL, we will discuss this in a few slides).

★ important slide

Regulation of LDL Endocytosis

Level of cholesterol present inside the cell (intracellular cholesterol level)

↓ **Down Regulation** High intracellular cholesterol level causes:	↑ **Up Regulation** Low intracellular cholesterol level causes:
Degradation of LDL receptors	Recycling of LDL receptors
Inhibition of receptor synthesis at gene level	Increase of receptor synthesis at gene level
Reduction in cell surface receptors (Less recycling)	Increase in cell surface receptors (More recycling)
Decreased uptake of LDL by cells	Increased uptake of LDL by cells
Decreased *de novo* synthesis of cholesterol By inhibition the gene expression of HMG CoA Reductase	Increased *de novo* synthesis of cholesterol

High Density Lipoprotein (HDL)

1

Nascent HDL:

- Disk-shaped
- Mainly contains phospholipids
- Contains apo A-I, C-II and E lipoproteins

2

Mature HDL: (will be explained in details in the next two slides)

- Nascent immature HDL **+** cholesteryl esters **=** HDL_3
- HDL_3 **+** more cholesteryl esters **=** spherical HDL_2
- HDL_2 then transfers cholesterol to the liver (Unloading)

Functions of HDL:

Transports cholesterol to the liver from:

- Peripheral tissues, cell membranes, and other lipoproteins.

Reservoir of apoproteins (Apo C-II and E)

- Gives Apo C-II and Apo E to chylomicron and VLDL. " as we discussed in the previous lecture "

Suitable for cholesterol uptake due to:

- High content of phospholipids. Which will solubilize cholesterol and provide fatty acids for cholesterol esterification

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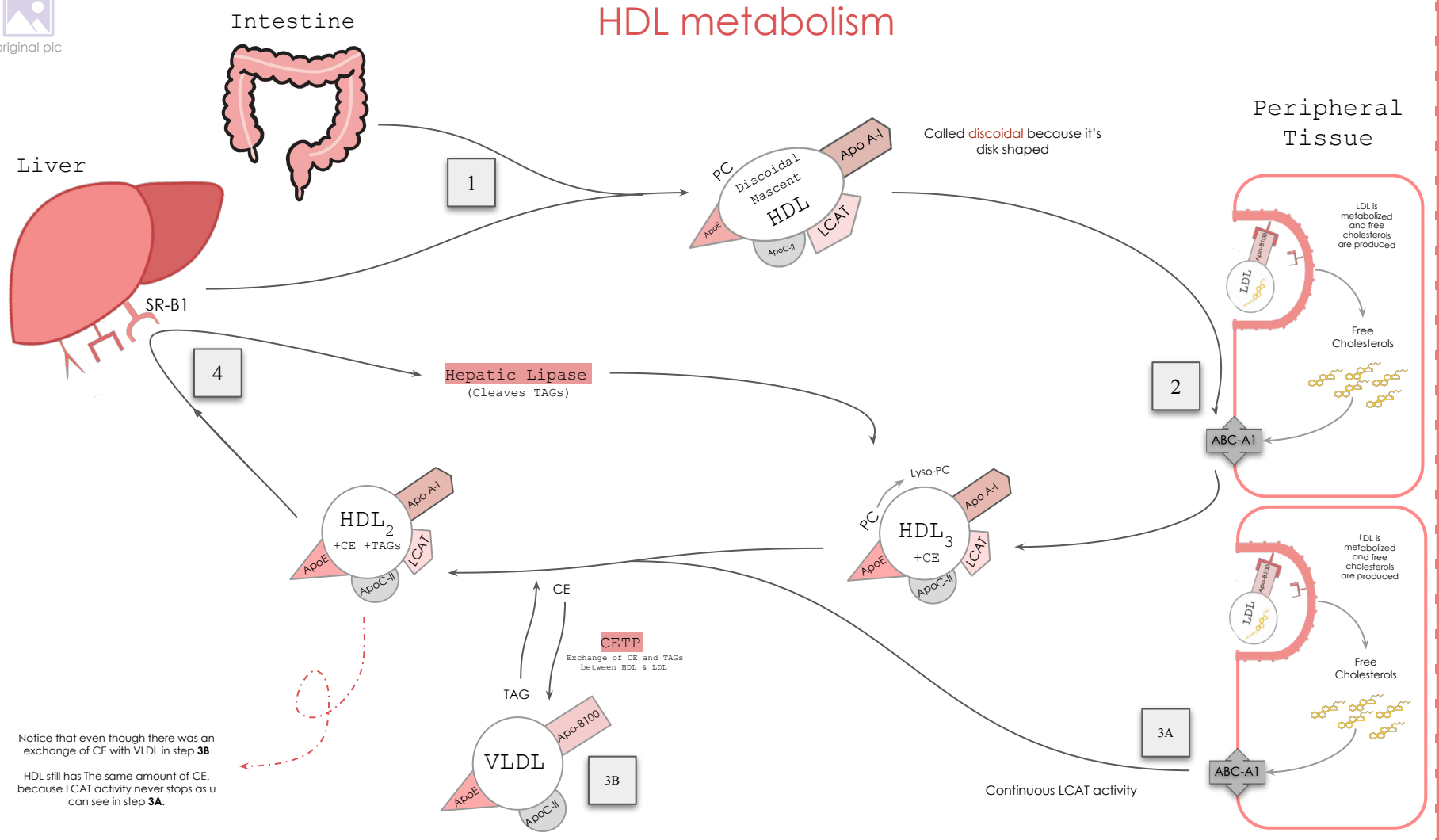
HDL metabolism



HDL metabolism

A helpful video

1 HDL is synthesized in the liver and intestine, then it goes through the circulation to the peripheral tissues with a disk shape (that's why it's called discoidal).

2 Cholesteryl esters are obtained from peripheral tissues and the nascent HDL will become → HDL_3

- The **Cholesterol is released** from the tissue to circulation via a transporter enzyme called **ABC-A1**.
- Because HDL shell contains too many phospholipids, it will grab this free cholesterol and it will stick to the shell (not in the core).
- In order for us to get this cholesterol in the core of the HDL molecule, we need to convert it to cholesteryl esters first.
- **PC** (Phosphatidylcholine, [Aka. lecithin], which is the phospholipid present in the shell of HDL) will be converted into **Lyso-PC** (Lyso-Phosphatidylcholine, [Aka. lyso-lecithin]) How? **by losing a fatty acid**. (we will need this fatty acid in the next step).
- **Now, Apo A1** will activate **LCAT** enzyme (Lecithin–cholesterol acyltransferase), which will then catalyze the addition of the fatty acid (that was taken from PC) to the free cholesterol on the shell and **transform it into → Cholesteryl ester (CE)** and get it inside the HDL! Now, **nascent HDL became HDL_3.** This mechanism allows more cholesterol intake by keeping a sufficient gradient.

3 HDL_3 (with only CE) will become → HDL_2 (more CE + some TAGs) by:

3A Further addition of cholesteryl esters by **LCAT**. (just as in step 2)

3B Addition of TAGs from VLDL will convert it to HDL_2.

LCAT is found extracellularly (in circulation)
While **ACAT** is found intracellularly (inside the cell).

(as we studied in previous lecture, there is exchange of TAGs and CEs between VLDL and HDL. This exchange is mediated by CETP enzyme).

4 Finally, HDL_2 goes to the liver and binds there via the **SR-B1 receptor** (scavenger receptor) to unload the cholesterol it collected.
Then, Hepatic lipase will act on it, cleaving the TAGs that it got from the VLDL, and converting it back to HDL_3.
(This HDL_3 will then take up free cholesterols in the same way again, take TAGs from VLDL, and unload again via SR-B1 & Hepatic lipase. **The cycle continues over and over again…**)

HDL increases by exercise

Good cholesterol **VS.** Bad cholesterol

HDL	LDL
Good cholesterol	Bad cholesterol
Transports cholesterol from peripheral tissues to the liver for **degradation** degraded into bile acids , bile salt and different types of steroids	Transports cholesterol from the liver to peripheral tissues " stores cholesterol "
High HDL levels decrease the risk for atherosclerosis & heart disease (inverse correlation with atherosclerosis)	High LDL levels increase the risk for atherosclerosis & heart disease (direct correlation with atherosclerosis)
Reduces cholesterol level in tissues and circulation by reverse cholesterol transport. Which include: - Cholesterol efflux from peripheral tissues to HDL - Cholesterol esterification - Binding and transfer of cholesteryl ester-rich HDL_2 to the liver - Release of lipid-depleted HDL	Increase cholesterol level in tissues and circulation (Which might lead to atherosclerosis when it's s oxidized in walls of arteries). - Binding through LDL receptors on peripheral tissue - Endocytosis & recycling of LDL receptors - Fusing with lysosome - Free cholesterols are released.
Tangier disease is a rare inherited disorder characterized by significantly reduced levels of (HDL) in the blood. Read more about it here. Familial LCAT deficiency, also known as fish eye disease is a genetic disorder that affects the body's ability to process metabolize cholesterol due to mutations in LCAT gene. It is characterized by cloudiness of the clear front surface of the eye. Read more about it here.	**Deficiency or defects in LDL receptors results in:** Decreased uptake of cholesterol by cells & Increased accumulation of cholesterol in blood vessels. For example: **Familial hypercholesterolemia (Deficiency in LDL receptors):** اذا تسمعون يقولون هالعائلة الـ high "bad" cholesterol levels عندهم وراثه YUP هذا هو - Patients are unable to clear LDL from blood - Premature atherosclerosis and heart disease

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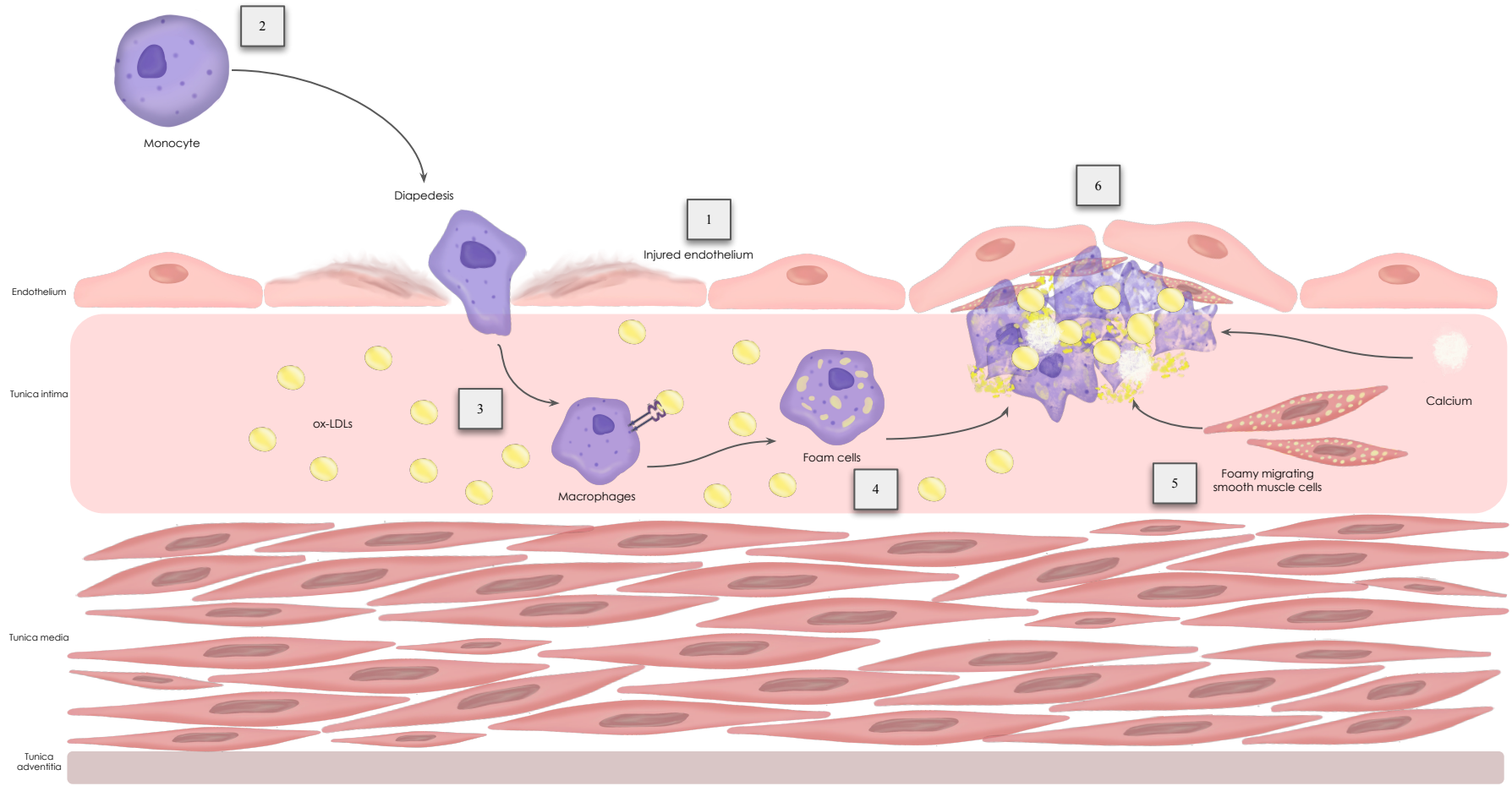
This illustration is drawn by the **AMAZING** Duaa ♡

Atherosclerosis



Atherosclerosis

A helpful video

1. There has to be some irritant present first, which will lead to **damaged endothelium** (e.g. toxins from cigarettes, or chronic hypertension). And some LDLs will be settled in the Intima **already**. (LDL uptake by cells is by receptor mediated endocytosis) which was explained in slide 4 & 5.

2. These **LDLs will get oxidized** becoming oxidized-LDLs (Modified LDL) by the action of free radicals. Oxidized LDL stimulates the local release of growth factors, cytokines, and chemokines, **increasing monocyte recruitment.** (LDL oxidation is induced by the action of superoxide, nitric oxide, hydrogen peroxide, and other oxidants. In contrast, it's inhibited by the action of antioxidants such as Vitamin E, ascorbic acid, beta carotene, and other antioxidants). *Bear in mind that if the LDLs are not oxidized, there will be no atherosclerosis (oxidation of LDL is the problem, not the LDL itself).

3. Monocytes will adhere to the epithelium and get inside to the intima by diapedesis, and then **differentiate into macrophages**.

4. Macrophages have a **scavenger receptor class A (SR-A)**, which **can only recognize ox-LDLs.** Once the ox-LDLs are recognized, macrophages will avidly engulf the ox-LDLs (chemically modified LDL) becoming **foam cells**. (Activated macrophages also produce toxic oxygen species that drive LDL oxidation more and elaborate growth factors). (Chemically-modified LDL contains oxidized lipids and Apo B).
   * Unlike LDL receptors, the SR-A is not down-regulated in response to high intracellular cholesterol

5. These foam cells will accumulate and release growth factors and cytokines that will also **promote the migration of smooth muscle cells** and matrix synthesis. Smooth muscle cells from the media will migrate into the intima, proliferate, produce collagen, calcium crystals, and **take up lipids and become foam cells as well**.

6. The foamy dead macrophages , foamy smooth muscle cells, collagen, elastic fibers, and proteoglycans, intracellular and extracellular lipids, and sodium crystals will all **accumulate and form plaque that will cause narrowing of blood vessels**.

Lab Investigations of Atherosclerosis

1

Fasting serum lipid profile

- TAG level
  (reflects chylomicron and VLDL levels because they are carrying it).
- LDL, HDL levels.
- Total cholesterol level
  (reflects LDL, HDL and cholesterol levels).

2

Serum apoprotein levels (e.g. Apo-B)

This test measures the amount of apo B in the blood. (the protein portion of apolipoprotein)

3

Serum lipoprotein electrophoresis

Measures lipoprotein fractions to determine abnormal distribution and concentration of in the serum by Electrophoresis is an electrokinetic process which separates charged particles in a fluid using a field of electrical charge.

Pay attention that the letter a is **small** / lower case

Lipoprotein (a)

- Lipoprotein (a) is identical in structure to LDL particle (It is also bad, just as LDL).
- It contains Apo(a) in addition to apo B-100. Apo (a) is covalently attached to Apo B-100.
- Its physiological function, its role, and how is it synthesized in the body, all are still unknown.. but what's known is that **high plasma Lp (a) level is associated with increased risk of coronary heart disease.**
- The apo(a) protein is structurally similar to plasminogen (A protein that attacks fibrin to breakdown blood clots).
    - It competes with plasminogen to attack fibrin
    - Slows the breakdown of blood clots. its structure is similar to plasminogen. however, it opposes the function of plasminogen.
    - Triggering heart attack
    - A risk factor for CAD " coronary artery disease "
- Circulating levels of Lp(a) are determined by:
    - Genetics (Mainly)
    - Diet (consumption of trans fatty acids increase Lp(a) levels) (Trans fatty acids are not saturated fatty acids but act like saturated fatty acids in the body and they're used a lot in the bakery products . they become solidified in room temp.)
    - Estrogen (decreases Lp(a) levels)

Take Home Messages

- Imbalance in the LDL and HDL metabolism causes increased accumulation of lipids in the body
- LDL is bad cholesterol whereas HDL is good cholesterol
- The pathogenesis of atherosclerosis includes the uptake of oxidized LDL by macrophages through scavenger receptor class A (SR-A) producing foam cells and atherosclerotic plaque
- Individuals with high level of plasma Lp (a) are at higher risk for coronary heart disease

Summary

Lipoproteins

LDL

Endocytosis Of LDL

Major steps

- Binding of Apo B-100 to LDL receptor glycoprotein
- Endocytosis
- LDL degraded by lysosomes releasing: Free cholesterol, fatty acids, amino acids, phospholipids

Regulation

Up regulation

- ↑ receptor synthesis at gene level
  - ↑ cell surface receptors
  - ↑ Uptake of LDL by cells
- Recycling of LDL receptors

Down regulation

- Inhibition receptor synthesis at gene level
  - ↓ cell surface receptors
  - ↓ uptake of LDL by cells
- Degradation of LDL receptors

Level of LDL in the blood

Increase level of LDL

Lead to

- Transports cholesterol Liver → peripheral tissues.

Risk factor

- ↑ risk for atherosclerosis / heart disease

HDL

Functions

- Reservoir of apoproteins
- Transports of cholesterol to liver
- Suitable for cholesterol uptake

Metabolism

1- In Liver and intestines the Nascent HDL synthesized and then it's transported to the circulation then

2-In Tissue ABCA1 enzyme will release the cholesterol to the circulation

3-In Circulation

A- Nascent HDL will take up cholesterol from nonhepatic (peripheral) tissues.

B- Apo A-1 activate LACT enzymes that will convert the cholesterol to Cholesteryl ester and therefor transforming nascent HDL to HDL3

C- this Esterification will allow efflux of cholesterol to HDL3 so it will convert it to HDL2

4-In tissue Unloading of the cholesterol from HDL2 through SR-B1

Quiz

Q1 LCAT enzyme is activated by:			
A) Apo C-I	B) Apo C-II	C) Apo A1	D) Apo E
Q2 : The ox-LDL receptor that is possessed by macrophages is:			
A) SR-B1	B) SR-B2	C) SR-A	D) SR-B
Q3 : HDL2 binds to the liver via ..... to unload the cholesterol it collected.			
A) SR-B1	B) SR-B2	C) SR-A	D) SR-B
Q4 : All are mechanism of the downregulation of high cholesterol levels except:			
A) Decreased de novo synthesis of cholesterol	B) Decreased uptake of LDL by cells	C) Inhibition of receptor synthesis at gene level	D) Decreased breakdown of LDL receptors
Q5 : Cholesterol is released from the tissue to circulation via a transporter enzyme called			
A) Lipoprotein lipase	B) ABC-A1	C) ABC-A2	D) LCAT
Q6 : The condition where patients are unable to clear LDL from blood:			
A) Familial hypercholesterolemia	B) Familial hypocholesterolemia	C) Tangier disease	D) Familial LCAT deficiency

SAQs :

Q1: What does the imbalance in transporting cholesterol from the liver to the peripheral tissues and vise versa lead to?

Q2: what does the down regulation of cholesterol level cause?

Q3: List the functions of HDL?

Q4: Enumerate lab investigations of atherosclerosis?

★ **MCQs Answer key:**

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

★ **SAQs Answer key:**

1) Cholesterol deposition in blood vessels, thickening of arterial lumen, atherosclerosis, and heart disease.
2) Check **Slide 6**
3) Transport cholesterol to the liver, reservoir of Apo C-II and Apo E, and suitable for cholesterol uptake
4) Fasting serum lipid profile, serum apoprotein levels, and serum lipoprotein electrophoresis

Girls team:

Manal Altwaim
Duaa Alhumoudi
Rania Almutiri
Alia Zawawi
Noura Alshathri
Reem Alamri
Renad Alhomaidi
Fatimah Alhelal

Boys team:

Omar Alsuliman
Abdullaziz Alomar
Hamad Almousa
Homoud Algadheb
Abdullah Alanzan
Abdullah Almazro
Ahmad Alkhayatt
Abdullaziz Alrabiah

Click here for a ridiculous website, yet faaaaaaar more important than your to-do list. **Obviously you should click "MAKE IT RAIN"!!!**

Revised by Shatha Aldhohair

Made by Abdulaziz Alsalem

Biochemistry439@gmail.com
@Biochemistry439