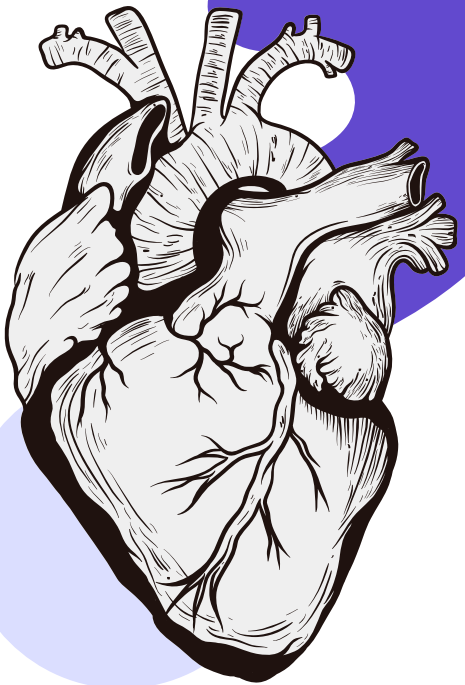
Lipoprotein and atherosclerosis



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COLOR INDEX:
MAIN TEXT (BLACK)
FEMALE SLIDES (PINK)
MALE SLIDES (BLUE)
IMPORTANT (RED)
DR'S NOTE (GREEN)
EXTRA INFO (GREY)

Objective

01 Correlate the imbalance in lipoprotein metabolism with the development of atherosclerosis.

02 Understand the functions and metabolism of LDL and HDL cholesterol.

03 Describe the receptor-mediated endocytosis of LDL and its regulation

04 Recognize how LDL is considered a bad cholesterol whereas HDL a good cholesterol.

05 Understand the biochemistry of atherosclerosis and its laboratory investigations.

06 Discuss the role of lipoprotein(a) in the development of heart disease.

Overview

- Receptor-mediated endocytosis of LDL and its regulation
- LDL is bad cholesterol
- High density lipoprotein (HDL) and its functions
- Metabolism of HDL
- HDL is good cholesterol
- Atherosclerosis
- Lipoprotein(a)

Cholesterol homeostasis is a balance between cholesterol transport:

Imbalance in Them leads to :

1. From the liver to peripheral tissues by LDL

2. From peripheral tissues to the liver by HDL

1- Cholesterol deposition in blood vessels.
2- Thickening and narrowing of the lumen of arteries.
3- Atherosclerosis.
4- Heart disease.

Receptor-mediated endocytosis of low density lipoprotein (LDL) particles

01 Binding of Apo B-100 to LDL receptor glycoprotein
(The LDL receptors are more concentrated on the coated pit of the cell surface (coated by clathrin).

02 Endocytosis.

03 Endosome formation (LDL vesicle fuses with other vesicles).

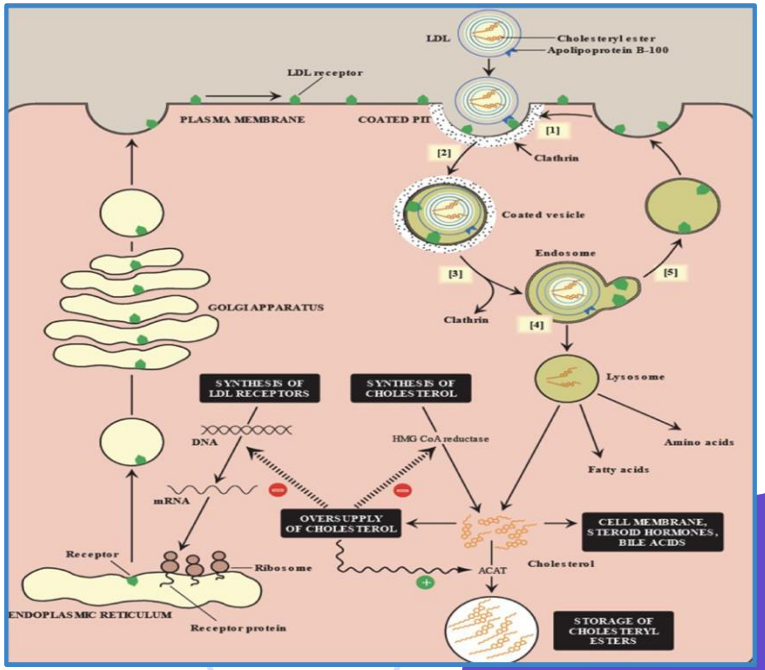
04 Separation of LDL from its receptor.

05 Receptor is recycled.

06 LDL degraded by lysosomes releasing: Free cholesterol, fatty acids, amino acids, phospholipids.

Summary for next 2 slides
High Intracellular Cholesterol:
1. Activate ACAT *(storage)*
2. Inhibit HMG-CoA Reductase *(de novo synthesis)*
3. Inhibit LDL-R Synthesis *(uptake)*

And Vice Versa



Video

Regulation of LDL endocytosis

Up regulation:

Low intracellular cholesterol level causes:

What will we do?	Recycling of LDL receptors (increase LDL-r to uptake more cholesterol)
How?	Increased receptor synthesis at gene level
What will happen?	Increase in cell surface receptors
The result?	Increase uptake of LDL by cells
Anything else can help?	Increased de novo synthesis of cholesterol

Regulation of LDL endocytosis

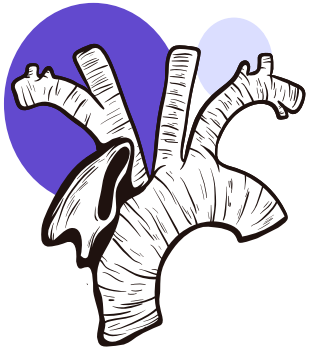
Down regulation:

High intracellular cholesterol level causes:

What will we do?	Degradation of LDL receptors
How?	Inhibition of receptor synthesis at gene level
What will happen?	Reduction in cell surface receptors
The result?	Decreased uptake of LDL by cells
Anything else can help?	Decreased de novo synthesis of cholesterol (de novo = new *in Latin*)

High density lipoprotein (HDL)

Nascent (newly formed) HDL:	Mature HDL:
Disk-shaped	Nascent HDL + cholesteryl esters = HDL3
Contains apo A-I, C-II /and E lipoproteins	HDL3 + more cholesteryl esters = Spherical HDL2
Mainly contains phospholipid	HDL2 transfers cholesterol to the liver



High density lipoprotein (HDL)

Functions of HDL

Transports cholesterol to liver from:

- Cell membranes
- Other lipoproteins
- Peripheral tissues

Reservoir of apoproteins (Apo C-II and Apo-E) (Apo C-II is for attachment to peripheral tissues while Apo E is for attachment to liver)

Suitable for cholesterol uptake due to:

1- High content of phospholipids

2- Phospholipids solubilize cholesterol and provide fatty acids for cholesterol esterification

(HDL) metabolism

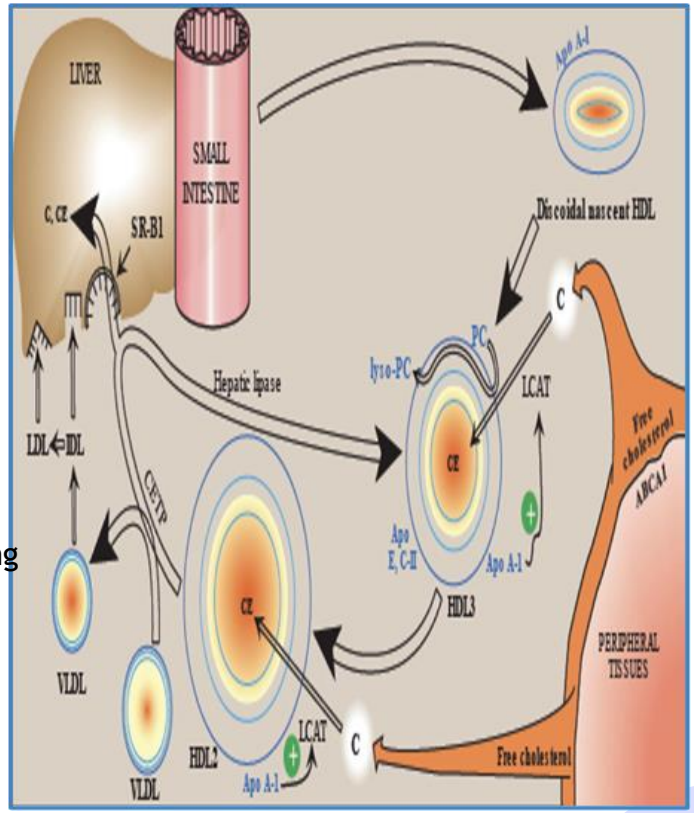
1. Small intestine releasing the discoidal nascent HDL (immature HDL).

2. Free cholesterol is removed from peripheral tissues by ABCA1.

3. The free cholesterol then is transformed to cholesteryl esters before it fuses with HDL by LCAT which takes a fatty acid from phosphatidylcholine (PC) and gives it to the free cholesterol the phosphatidylcholine is then converted to lysosomal phosphatidylcholine as a byproduct this mechanism allows the binding of free cholesterol to nascent HDL producing HDL3.

4. HDL3 collects more tissue cholesterol to form HDL2 (mature HDL).

5. HDL2 gives some of its cholesteryl esters to VLDL using cholesteryl ester transferase protein (CETP) and the rest goes to liver by binding to SR-B1 which converts HDL2 back to HDL3 using hepatic lipase.



PC =phosphatidylcholine) = (lecithin) so we can say LCAT or PCAT
LCAT = lecithin-cholesterol
Acyltransferase =scavenger receptor and some are found in macrophage and play a role in atherosclerosis (SR-A)

LDL "Bad cholesterol" deficiency of LDL receptors→ Type 2a hypercholesterolemia. deficiency of LDL → type 1	HDL"Good cholesterol"
Transports cholesterol to peripheral tissues	Transports cholesterol from peripheral tissues to liver for degradation
High LDL levels **increase** the risk of atherosclerosis / heart disease	High HDL levels have **inverse correlation with atherosclerosis**
Deficiency or defects in **LDL receptors** results in: ● Decreased uptake of cholesterol by cells ● Increased **accumulation** of cholesterol in **blood** vessels	**Reduces** cholesterol level in tissues and circulation (reverse cholesterol transport)
Deficiency of LDL receptors can lead to Familial **hypercholesterolemia**: ● Patients are unable to clear LDL from blood. ● Premature atherosclerosis and heart disease.	Reverse cholesterol transport includes: ● Cholesterol efflux from peripheral tissues to HDL ● Cholesterol esterification ● Binding and transfer of cholesteryl ester-rich HDL2 to liver ● Release of lipid-depleted HDL3

Extra slide to correct some misconceptions

- Despite being mentioned in slides, the terms “Good” and “Bad” **cholesterol** are inaccurate terms for doctors to use. Why is that?

- Because the cholesterol in LDL and the cholesterol in HDL are the **SAME** cholesterol. It is just that the particle (i.e. Lipoprotein) carrying it might be bad or good.

- And to emphasize that, remember that CETP exchanges cholesterol from HDL to VLDL which will then become LDL. does that mean that cholesterol suddenly changed from good to bad?

- So we agree that all cholesterol is the same, but the lipoproteins may be good and bad based on their function:

    - **Bad Lipoprotein (LDL):** because of its role of going into vessels and causing Atherosclerosis.

    - **Good Lipoprotein (HDL):** because of its role in doing the opposite (scavenger).

By: Khalid Alohali 44

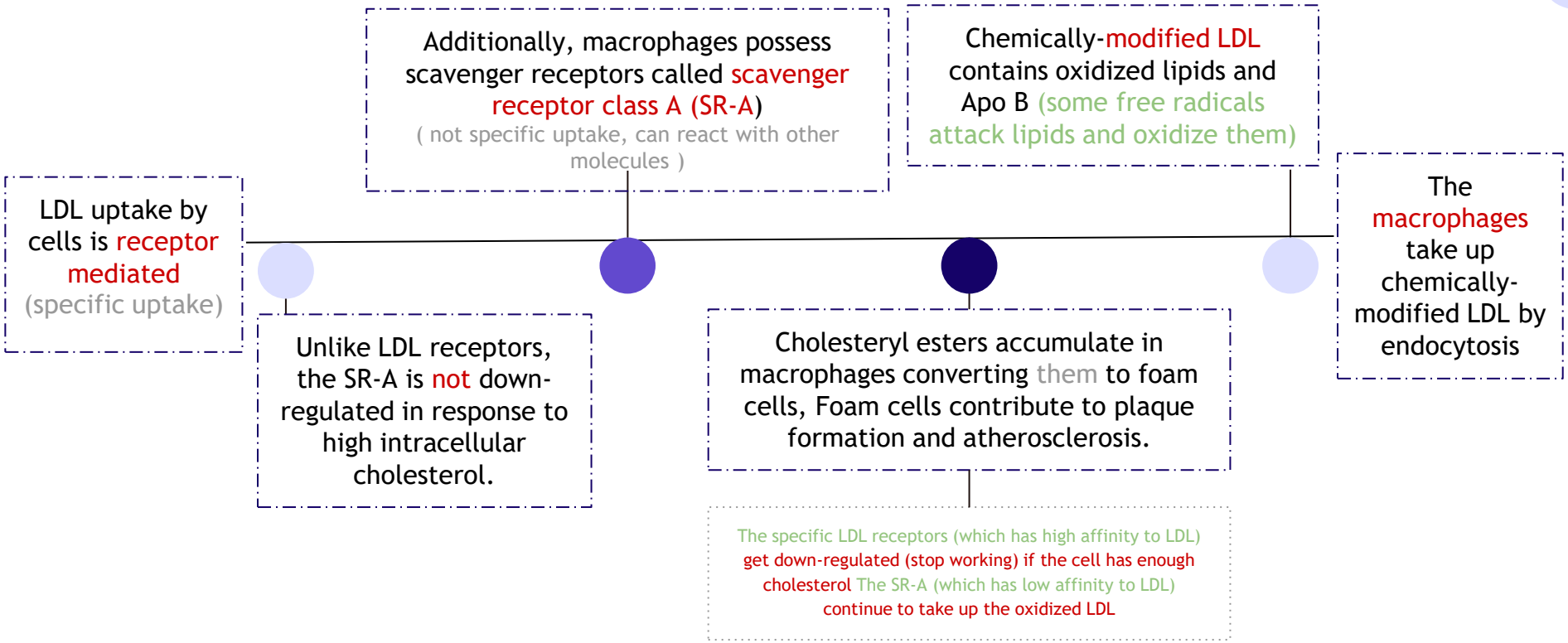
- Another thing that you should know as a doctor is that when you test someone's “LDL or HDL”. That test is actually called LDL-C or HDL-C ***(LDL-C = LDL Cholesterol)***

- And this means that total amount of cholesterol in LDL particles and **not the number of these particles.** And that amount is **calculated** with an equation and not measured

- Generally LDL-C correlates well with ASCVD risk and that's why it’s commonly used to assess risk. However, the number of LDL particles may be a better indicator of ASCVD risk than the amount of cholesterol in LDL particles. A test like ApoB-100 can measure the number of LDL particles.

for extra reading:
https://www.annlabmed.org/journal/view.html?doi=10.3343/alm.2023.43.3.221

Atherosclerosis



Atherosclerosis

01 In response to **endothelial injury** (caused at least in part by oxidized LDL) monocytes adhere to endothelial cells, move to the subendothelium (intima), and are converted into macrophages.

02 Macrophages consume excess modified (oxidized) lipoprotein, becoming foam cells.

03 Foam cells accumulate, releasing growth factors and cytokines that stimulate the migration of smooth muscle cells (SMCs) from the media to the intima. There, the SMCs proliferate; produce collagen; and take up lipid, potentially becoming foam cells.

04 Low-affinity, non-specific and non-regulated scavenger receptors take up modified (oxidized) LDL (oxLDL).

05 High-affinity receptors specific for LDL are downregulated when the cell has sufficient cholesterol.

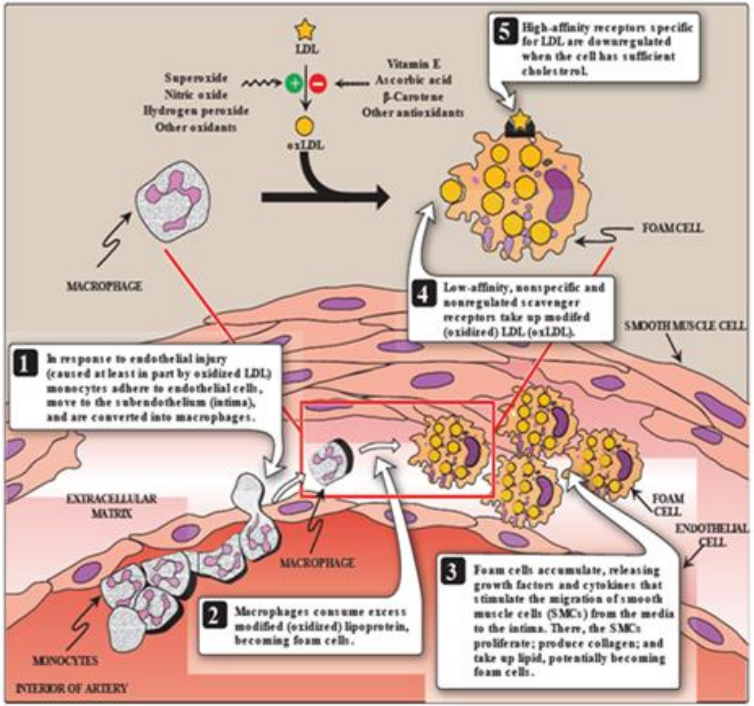
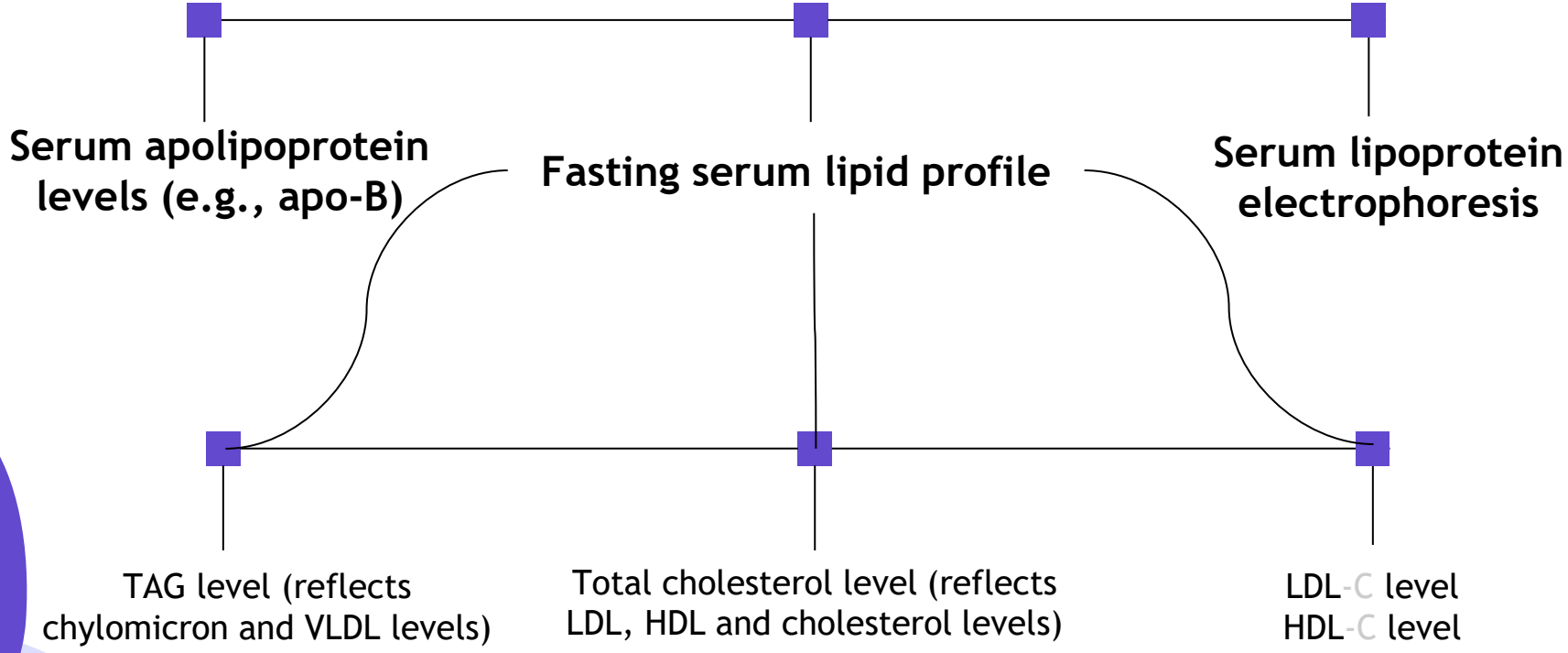


Figure 18.22
Role of oxidized lipoproteins in plaque formation in an arterial wall. LDL = low-density lipoprotein.

animation

Lab investigations of Atherosclerosis



It is pronounced “LP little a”

Lipoprotein (a)

LDL + apo a = Lp(a)

1. -Lp(a) is identical in structure to LDL particle
   -Contains apo(a) in addition to apo B-100

2. High plasma Lp(a) level is associated with increased risk of coronary artery disease

This one is highly atherogenic, and since it's mostly genetically predetermined if you test it once for a patient you most likely won’t need to test it again (unlike LDL-C)

3. Circulating levels of Lp(a) are determined by:
   - Genetics (mainly)
   - Estrogen (decreases Lp(a) levels)
   - Diet (trans FAs increase Lp(a) levels)

4. The apo(a) protein is structurally similar to plasminogen
   - Competes with plasminogen.
   - Slows the breakdown of blood clots.
   - Triggering heart attack.
   - A risk factor for CAD*.

Coronary artery disease

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 andatherosclerotic plaque.
- Individuals with high level of plasma Lp (a) are at higher risk for coronary heart disease.

MCQ

1- C 2- A 3- C

Q1: Deficiency of LDL receptors can lead to?			
A-Familial Hypocholestrolemia	B-Familial Hypertension	C-Familial Hypercholesterolemia	D-Familial Hypertension
Q2: What's the enzyme responsible for the transformation of free cholesterol to cholesteryl esters in Hdl metabolism?			
A-LCAT	B-HMG CoA reductase	C-CEPT	D-Apo B-100
Q3: Nascent HDL mainly contains?			
A-Proteins	B-Carbohydrates	C-Phospholipids	D-Lipids

MCQ

1-B 2-D 3-D

Q1: Increased levels of LP(a) are associated with?			
A-Decreased risk of coronary artery disease	B-Increased risk of coronary artery disease	C-Lower LDL cholesterol levels	D-Higher HDL cholesterol levels
Q2: In atherosclerosis, chemically-modified LDL contains …… and ……..?			
A-Oxidized phospholipids and Apo B	B-Oxidized lipids and Apo C	C-Deoxidized phospholipids and Apo C	D-Oxidized lipids and Apo B
Q3: Which ONE of the following is a characteristic of the scavenger receptors type A of macrophages?			
A-It is tightly regulated	B-It has a high affinity for HDL	C-It recognizes apo A	D-It binds to oxidized LDL

SAQ

Q1:Circulating levels of Lp(a) are determined by:

A1: Genetics (mainly), Estrogen (decreases Lp(a) levels), Diet (trans FAs increase Lp(a) levels).

Q2: Cholesterol transport Imbalance leads to:

A2: Cholesterol deposition in blood vessels, thickening and narrowing of the lumen of arteries, atherosclerosis, heart disease.

Q3: List 3 different facts about LDL and HDL:

A3: Slide 12.

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