تفريغ علم وظائف الأعضاء المرضي

اسم الموضوع: Hyperlipidemia P 2

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لجان الدُّفعات

7,2

	Chylomicron	VLDL	LDL	HDL
Density (g/mL)	<0.94	0.94–1.006	1.006–1.063	1.063–1.210
Composition (%)				
Protein	1–2	6–10	18–22	45–55
Triglyceride	85–95	50–65	4–8	2–7
Cholesterol	3–7	20–30	51–58	18–25
Phospholipid	3–6	15–20	18–24	26–32
Physiologic origin	Intestine	Intestine and liver	Product of VLDL catabolism	Liver and intestine
Physiologic function	Transport dietary CH and TG to liver	Transport endogenous TG and CH	Transport endogenous CH to cells	Transport CH from cells to liver
Plasma appearance	Cream layer	Turbid **"Lipemia"**	Clear	Clear
Electrophoretic mobility	Origin	Pre-beta	Beta	Alpha
Apolipoproteins	A-IV, B-48, C-I, C-II, C-III	B-100, C-I, C-II, C-III, E	B-100,	A-I, A-II, A-IV

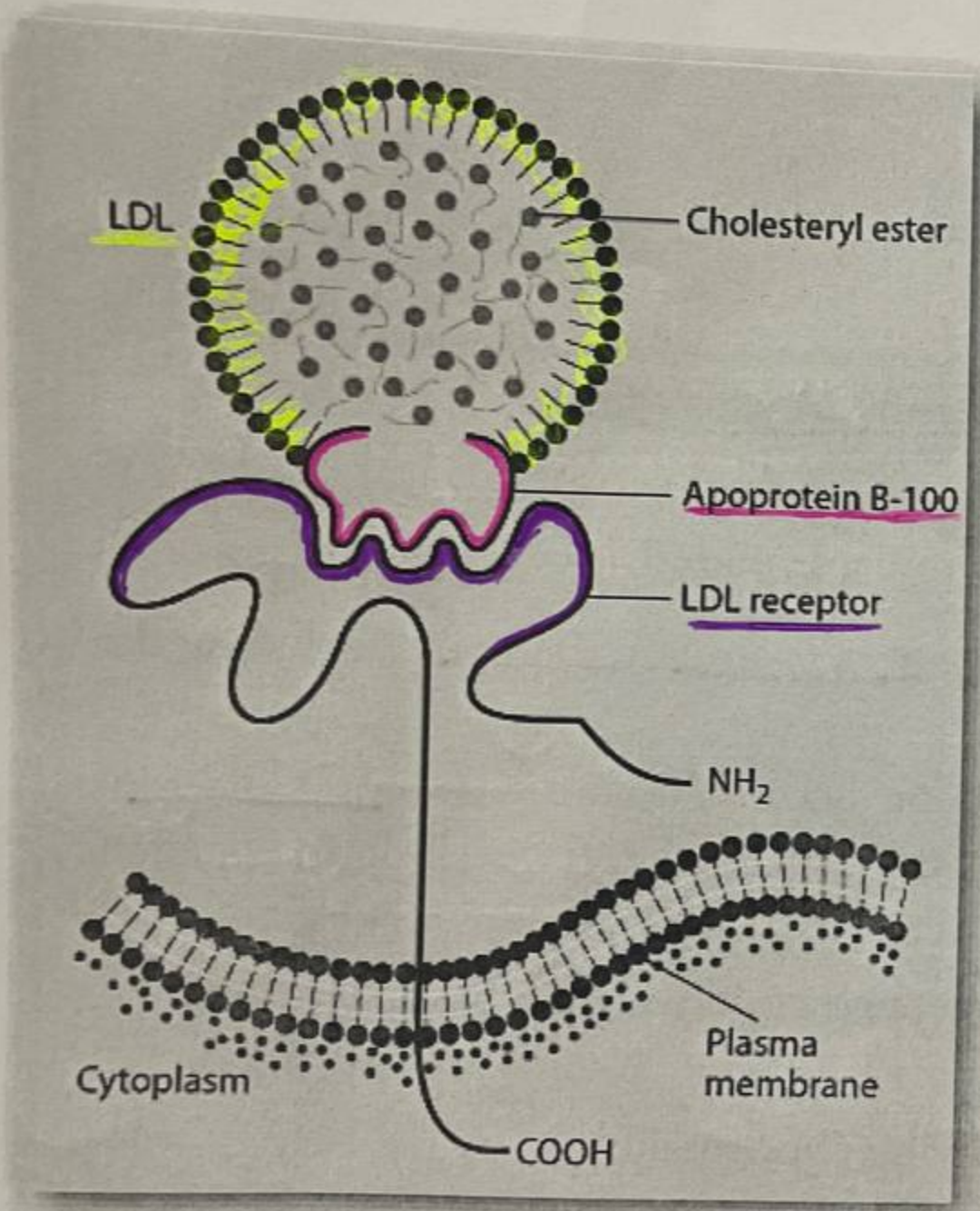
Background & Pathophysiology

LDL → IDL → LDL

- **VLDL** secreted from the liver: converted to IDL then LDL

- Plasma **LDL** has taken up by receptors on the liver, adrenal, & peripheral cells:
  1. recognize LDL apolipoprotein B-100 → (apolipoprotein B100) بروتين
  2. LDL internalized & degraded by these cells → internalized (الاحتواء)
  3. Increased intracellular cholesterol levels inhibits HMG-CoA reductase & decreases LDL receptor synthesis.

بزيادة (LDL) يثبط (HMG-CoA reductase) وبالتالي يقل من إنتاج مستقبلات (LDL).



The figure shows a diagrammatic representation of the structure of low-density lipoprotein (LDL), the LDL receptor, and the binding of LDL to the receptor via apolipoprotein B-100.

ارتباط (LDL) في المستقبل عن طريق (apolipoprotein B-100).

Background & Pathophysiology

- LDL also excreted in bile:
  - joins the enterohepatic pool.
  - eliminated in stool
- LDL can be oxidized in subendothelial space of arteries:
  - *Oxidized* LDL in artery walls provokes *inflammatory* response.
  - Monocytes recruited & transformed into *macrophages*.
    - results in *cholesterol laden foam cell accumulation*
  - Foam cells: beginning of arterial fatty streak.
  - If processes continue angina, stroke, MI, peripheral artery disease, arrhythmias, death.

Etiology

- **There are two major ways in which dyslipidemia are classified:**

السبب غير معروف

1. Primary: when the disorder is not due to an identifiable underlying disease.

ممكن تكون

a) **Phenotype** (Fredrickson-Levy-Lees), or the presentation in the body (including the specific type of lipid that is increased).

الظاهرة

b) **Genetic,** this classification can be problematic, because there are over 500 different mutations of the apolipoprotein gene. However, there are a few well-defined genetic conditions that are usually easy to identify.

الواضح

2. Secondary: should be initially managed by correcting underlying abnormality when possible.

- Current laboratory values can not define underlying abnormality.

السبب معروف

- **Primary lipoprotein disorders: 6 Phenotype categories:**

Fredrickson Classification of the Hyperlipidemias

Phenotype	Lipoprotein(s) elevated	Serum cholesterol concentration	Serum triglyceride concentration	Relative frequency, %
I	Chylomicrons	Normal to ↑	↑↑↑↑	<1
IIa	LDL	↑↑	Normal	10
IIb	LDL and VLDL	↑↑	↑↑	40
III	IDL	↑↑	↑↑↑	<1
IV	VLDL	Normal to ↑	↑↑	45
V	VLDL and chylomicrons	↑ to ↑↑	↑↑↑↑	5

- **Primary lipoprotein disorders: 6 Phenotype categories:**

Type I	Hyperchylomicronemia
Type IIa	Elevated LDL (familial hypercholesterolemia)
Type IIb	Elevated LDL and VLDL (familial combined hypercholesterolemia)
Type III	Broad β-VLDL (Familial dysbetalipoproteinemia)
Type IV	Elevated VLDL (Familial hypertriglyceridemia)
Type V	Elevated chylomicrons and VLDL (mixed hyperlipidemia)

WHO: World Health Organization, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein

lipoprotein ⟶ هو الناقل اللي بينقل (lipids).

- Primary lipoprotein disorders: 6 Phenotype categories:

Frederickson	Classification	Lipid Profile
Type		
I	Familial lipoprotein lipase deficiency (hyperchylomicronemia, hypertriglyceridemia)	TG++, C normal, CM++, HDL–/normal
IIa	Familial hypercholesterolemia	TG normal, C+, LDL+
IIb	Familial combined hyperlipidemia	TG+, C+, LDL+, VLDL+
III	Familial dysbetalipidemia (remnant particle disease)	TG+, C+, IDL+, CM remnants+
IV	Familial hypertriglyceridemia	TG+, C normal/+, LDL++, VLDL++
V	Familial combined hypertriglyceridemia	TG+, C+, VLDL++, CM++

TG, triglycerides; C, cholesterol; CM, chylomicrons; HDL, high-density lipoproteins; LDL, low-density lipoproteins; VLDL, very low density lipoproteins; IDL, intermediate-density lipoproteins; +, raised; –, lowered.

https://doctorlib.info/medical/fitzpatrick-atlas-dermatology/18.html

Disorders of lipid metabolism

- Prolonged hyperlipidemia results in the accumulation of lipid in tissues and causes cell damage.

- **Lipids may accumulate in:**

a. **Xanthomatosis:** subcutaneous tissue (**tuberoeruptive xanthomata** (over knees and elbows- **type III hyperlipidemia**)-triglyceride), tendons (**tendon xanthomas**-familial hypercholesterolemia- **type II hyperlipidemia**), palm (**palmar xanthomata-type III hyperlipidemia**), the cornea (**corneal arcus, xanthomas, type II hyperlipidemia**).

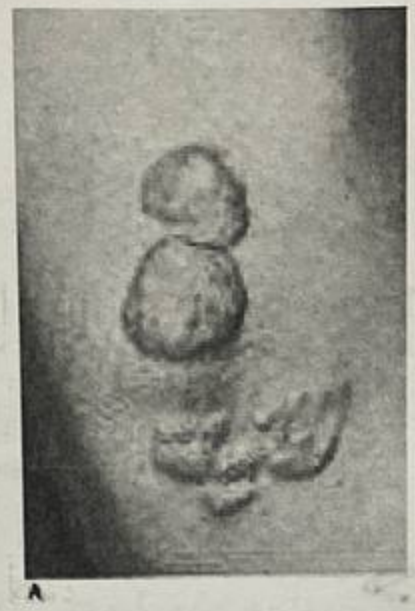
b. **Atherosclerosis:** Arterial wall (Cholesterol).

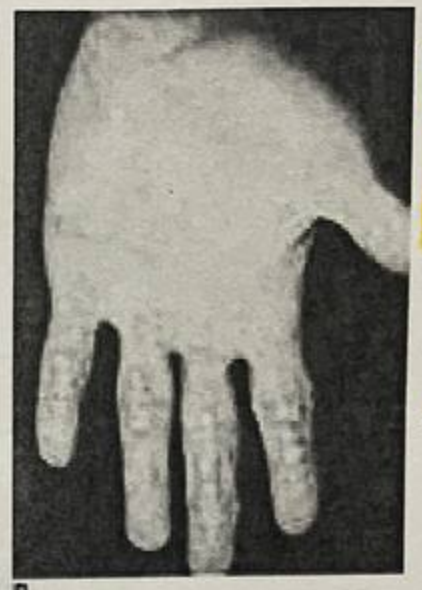
Xanthomas

تفرحات

- Xanthomas are plaques or nodules consisting of abnormal lipid deposition and foam cells. They do not represent a disease but rather are symptoms of different lipoprotein disorders or arise without an underlying metabolic effect.
- Clinically, xanthomas can be classified as:
  - Eruptive, tuberoeruptive or tuberous,
  - Tendinous or planar xanthoma.
- Planar xanthomas include:
  - Xanthelasma palpebrarum/xanthelasma,
  - Xanthoma striatum palmare,
- There are characteristic clinical phenotypes associated with specific metabolic defects.

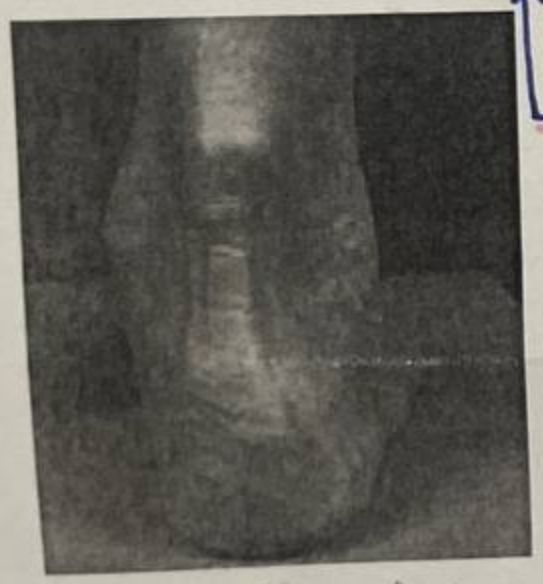
Eruptive skin xanthomata characteristic of severe chylomicronemia.



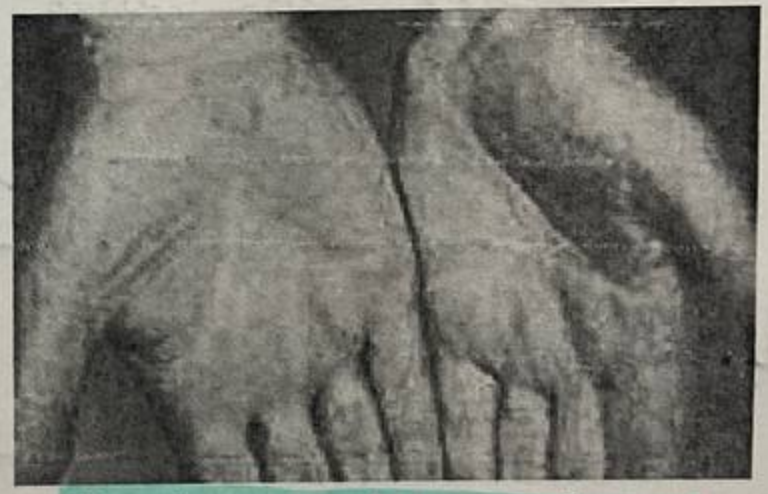


Tuberoeruptive and tuberous xanthomata typical of familial dysbetalipoproteinemia. A. Knee B. Palm.

يحل اليل واحد للمرض



Tendon xanthomata: typical of heterozygous familial hypercholesterolemia. Similar xanthomata occur in patients with familial defective apolipoprotein B-100, cerebrotendinous xanthomatosis, and sitosterolemia.



Xanthoma striatum palmare characteristic of familial dysbetalipoproteinemia.

يتكون على شكل خطوط
~~أبيض~~ أصفر ما دلة الى
الأصفر في كف اليد.

السائد

لازم يكونوا باجتماع متنحي الذليين

Dominant trait	Recessive trait
1. The trait which appears in F1 generation are called dominant trait.	1. The trait which does not appear in F1 generation are called recessive trait.
2. It appears in more number.	2. It appears in less number.
3. Dominant trait can express itself in the presence of recessive trait.	3. Recessive trait cannot express itself in the presence of dominant trait.
4. The presence of another similar allele is not required to produce its phenotype.	4. The presence of another similar allele is required to produce its phenotype.

Familial LPL deficiency

- **LPL** is normally released from vascular endothelium or by heparin and hydrolyzes chylomicrons and VLDL.

- Familial LPL deficiency is rare.

- Diagnosis is based on low or absent enzyme activity with normal human plasma or apolipoprotein C-II, a cofactor of the enzyme.

عملية تشخيص المرض نشاط للإنزيم . وعملية قياس نشاطه باستخدام (apolipoprotein C-II) أو باستخدام عينة من (human plasma) الطبيعية

← هو عامل مساعد للإنزيم

Familial LPL deficiency

- Type I (1)
- Type V (5)

- **Type- I lipoprotein pattern (chylomicrons):** نوع زيادة متزامنة

  - Characterized by a massive accumulation of chylomicrons and a corresponding increase in plasma **triglycerides. VLDL concentration is normal.** تراكم كبير — النقص الكبد

  - Presenting manifestations include repeated attacks of (1) pancreatitis and abdominal pain, (2) eruptive cutaneous xanthomatosis, and (3) hepatosplenomegaly beginning in childhood. الأعراض — تضخم في الطحال والكبد

  - Symptom severity is proportional to dietary fat intake and consequently to the elevation of chylomicrons. شدة الأعراض

  - **Accelerated atherosclerosis is not associated with the disease.**

* ما في علاقة بين (atherosclerosis) وهاد المرض

Familial LPL deficiency

- **Type V (VLDL and chylomicrons):**
  - Abdominal pain, pancreatitis, eruptive xanthomas, and peripheral polyneuropathy.
  - Symptoms may occur in childhood, but usually the disorder is expressed at a later age.
  - **The risk of atherosclerosis is increased with the disorder.**
  - Patients commonly are obese, hyperuricemia, and diabetic, and alcohol intake, exogenous estrogens, and renal insufficiency tend to be **exacerbating factors.**

Familial hypercholesterolemia

- **Characterized by:**
  a. Selective elevation in the plasma level of LDL.
  b. Deposition of LDL-derived cholesterol in tendons (xanthomas) and arteries (atheromas).
  c. Inheritance as an autosomal dominant trait with homozygotes more severely affected than heterozygotes.

- The primary defect in familial hypercholesterolemia is the inability to bind LDL to the LDL receptor (Apo B-100) or, rarely, a defect of internalizing the LDL receptor complex into the cell after normal binding.

Familial hypercholesterolemia

(LDL receptors) ابدًا ابدًا ماعندهم

- **Homozygotes** have essentially **no** functional LDL receptors
  - This leads to lack of LDL degradation by cells and unregulated biosynthesis of cholesterol, with total cholesterol and LDL-C inversely proportional to the deficit in LDL receptors.

- **Heterozygotes** have only about **half** the normal number of LDL receptors, total cholesterol levels in the range from 300 to 600 mg/dL.

Dysbetalipoproteinemia

- **Familial type III hyperlipoproteinemia** (also called, *broad-band*, or β-*VLDL*)
- **Patients develop the following clinical features after age 20 years:**
  - **Xanthoma striata palmaris** (yellow discolorations of the palmar and digital creases);
  - **Tuberous or tuberoeruptive xanthomas** (bulbous cutaneous xanthomas);
  - **Severe atherosclerosis** involving the coronary arteries, internal carotids, and abdominal aorta.

Dysbetalipoproteinemia

- A **defective structure of apolipoprotein E** does not allow normal hepatic surface receptor binding of remnant particles derived from chylomicrons and VLDL (known as IDL).

عوامل تحفز/تزيد السمنة البثرة الحمل

- **Aggravating factors** such as obesity, diabetes, and pregnancy may promote overproduction of apolipoprotein B–containing lipoproteins.

Familial combined hyperlipidemia

- Characterized by elevations in total cholesterol and triglycerides, decreased HDL, increased apolipoprotein B, and small, dense LDL.

- It is associated with premature CHD and may be difficult to diagnose because lipid levels do not consistently display the same pattern.

Type IV hyperlipoproteinemia

- Two genetic patterns:
  - **Familial hypertriglyceridemia**, which does not carry a great risk for premature CVD,
  - **Familial combined hyperlipidemia**, which is associated with increased risk for cardiovascular disease.

Type IV hyperlipoproteinemia

- Type IV hyperlipoproteinemia is common and occurs in adults, primarily in patients who are obese, diabetic, and hyperuricemia and do not have xanthomas.

- It may be secondary to alcohol ingestion and can be aggravated by stress, progestins, oral contraceptives, thiazides, or β-blockers.

Lipoprotein Abnormalities: 2° Causes

- **Hypercholesterolemia:**
  - Hypothyroidism
  - Obstructive liver disease
  - Nephrotic syndrome
  - Anorexia nervosa
  - Acute intermittent porphyria

- **Medications:**
  - Progestins
  - Thiazide diuretics
  - Glucocorticoids
  - β-blockers
  - Isotretinoin
  - Protease inhibitors
  - Cyclosporine
  - Mirtazipine
  - Sirolimus

Hypertriglyceridemia

- Obesity.
- DM.
- Lipodystrophy → تشحم الدهون في الجسم بمكان غلط
- Glycogen storage disease. → الجسم ما بيفرز الجلايكوجين (Glycogen) بكمية كافية
- Ileal bypass surgery → عملية حصلت قبل
- Sepsis → التهاب الدم
- Pregnancy.
- Acute hepatitis → التهاب الكبد
- Systemic lupus erythematous. → مرض مناعي

Medications

- Asparaginase
- Interferons
- Azole antifungals
- Mirtazipine
- Anabolic steroids
- Sirolimus
- Alcohol
- Estrogens
- Isotretinoin
- β-blockers
- Glucocorticoid
- Bile acid resins

Hypocholesterolemia:

- Malnutrition.
- Malabsorption.
- Myeloproliferative diseases.
- Chronic infectious diseases:
  - Acquired immune deficiency syndrome
  - Tuberculosis
- Monoclonal gammopathy.
- Chronic liver disease.

Low high-density lipoprotein:

- Malnutrition
- Obesity
- Medications
  - non-ISA β-blockers
  - anabolic steroids
  - isotretinoin
  - progestins

Total cholesterol	
<200	Desirable
200–239	Borderline high
240	High
LDL cholesterol	
<100	Optimal
100–129	Near or above optimal
130–159	Borderline high
160–189	High
190	Very high
HDL cholesterol	
<40	Low
60 mg/dL	High
Triglycerides	
<150	Normal
150–199	Borderline high
200–499	High
500	Very high

All values unit are mg/dL

Major risk factors – exclusive of LDL-C – that modify the LDL goals

Age Men: ≥ 45 years Women: ≥ 55 years or premature menopause without estrogen replacement therapy
Family history of premature CHD (definite myocardial infarction or sudden death before age 55 years in father or other male first-degree relative, or before age 65 years in mother or other female first-degree relative)
Cigarette smoking Within the past month
Hypertension (140/90 mm Hg or taking antihypertensive medication)
Low HDL cholesterol (<40 mg/dL)[b]

[a]Diabetes regarded as coronary heart disease (CHD) risk equivalent.
[b]HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.
Metabolic syndrome is considered as CHD risk

Goals & Cutpoints

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate TLC (mg/dL)	LDL Level at Which to Consider Drug Therapy
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 (optional goal: <70)	>100	>100 (<100 mg/dL; consider drug options)[a]
Moderately high risk: 2+ risk factors (10-year risk >10%–20%)	<130 (optional goal <100)	≥130	≥130 (100–129: consider drug options)
Moderate risk: 2+ risk factors (10-year risk <10%)	<130	≥130	≥160
Lower risk: 0–1 risk factor[b]	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

Risk is estimated from Framingham risk score

[a]Some authorities recommend use of LDL-lowering drugs in this category if LDL cholesterol <100 mg/dL cannot achieved by **therapeutic lifestyle changes (TLC).** Others prefer to use drugs that primarily modify triglycerides ar high-density lipoprotein, e.g., nicotinic acid or fibrates. Clinical judgment also may call for deferring drug therapy this subcategory.

[b]Almost all people with 0–1 risk factor have a 10-year risk <10%; thus,10-year risk assessment in people with 0–1 risk factor is not necessary.