Last edited: 3/9/2024

HYPERLIPIDEMIA

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I. PATHOPHYSIOLOGY

1. LDL

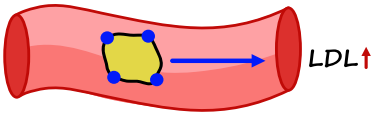
- **Pathophysiology of ↑LDL:**
  - ↑ Atherosclerotic plaque formation

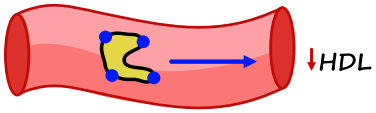
2. HDL

- **Pathophysiology of ↓HDL:**
  - ↑ Atherosclerotic plaque formation

3. Triglycerides

- **Pathophysiology of ↑TG:**
  - ↑Risk of tissue deposition, such as pancreatitis and NAFLD





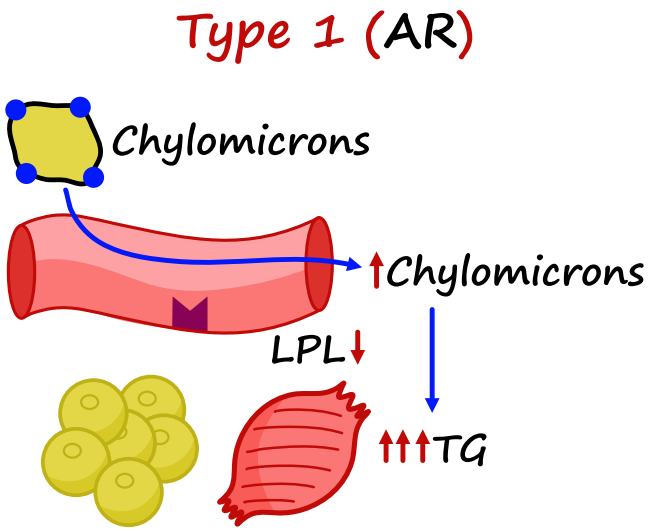
Hyperlipidemia is associated with either:
1. ↑LDL
2. ↓HDL
3. ↑Triglycerides

A. Inherited Hyperlipidemia

- Inherited hyperlipidemia is more commonly seen in the younger patient population

1. Type I

- **Pathophysiology:**
  - Autosomal recessive disorder leading to ↓Lipoprotein lipase activity (LPL) → ↓Break down of triglycerides of chylomicrons and VLDL → **↑↑↑Triglycerides in blood** → ↑ Risk of hepatomegaly and pancreatitis
- **Fun fact:**
  - When obtaining a lipid panel → The blood sample has a **creamy layer** on top signifying increased triglycerides



2. Type II

- **Pathophysiology:**
  - Autosomal dominant disorder leading to a **defect in LDL receptor** → ↓LDL-R on hepatocytes available → ↑LDL in the blood → ↑Accelerated Atherosclerosis

3. Type III

- **Pathophysiology:**
  - Autosomal recessive disorder leading to a **defect in Apo-E protein**
    - →Inability to uptake chylomicron remnants and VLDL
    - →↑Triglycerides and total cholesterol
    - →↑Accelerated atherosclerosis

4. Type IV

- **Pathophysiology:**
  - Autosomal dominant disorder leading to **↑Hepatic synthesis of VLDL**
    - → ↑↑Triglycerides in the blood
    - → ↑Risk of pancreatitis and possibility of premature atherosclerosis

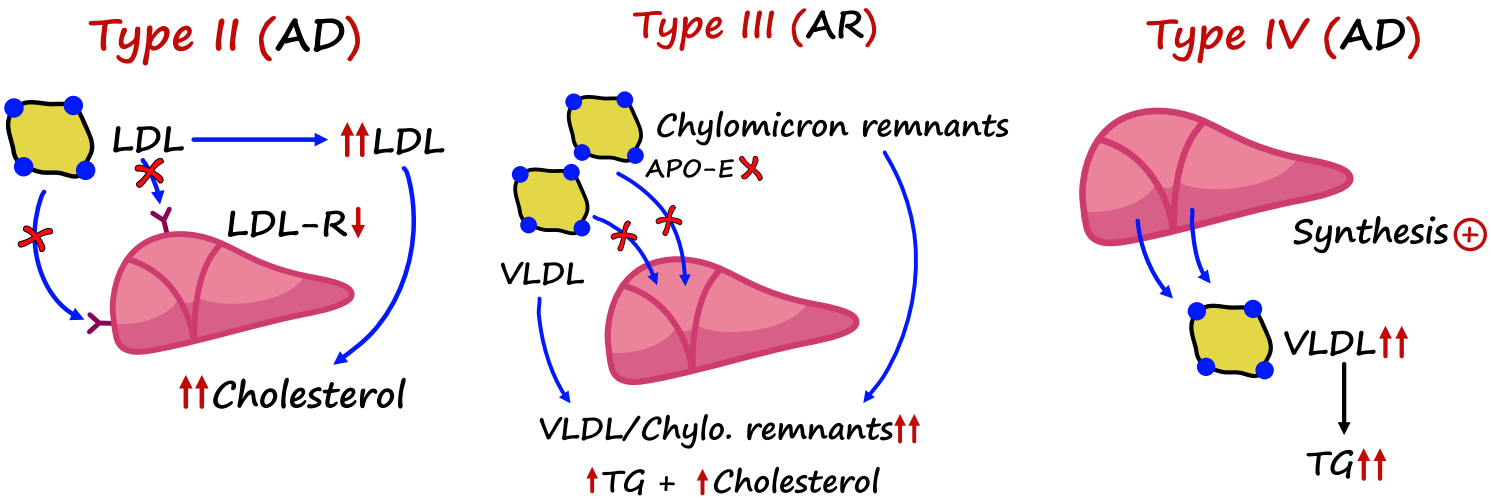


Table 1. Types of Inherited Hyperlipidemia.

	Pattern of Inheritance	Pathophysiology		Remarks
Type I	Autosomal recessive	Defect in **lipoprotein lipase**	↑chylomicrons → ↑↑↑**TG**	Blood samples have a **creamy** layer on top
Type II	Autosomal dominant	Defects in **LDL receptors**	↑LDL → ↑↑↑**cholesterol**	LDL receptors take up LDL in the liver
Type III	Autosomal recessive	Defect in **ApoE protein**	↑ VLDL and ↑chylomicron → ↑TG and ↑cholesterol	ApoE proteins take up chylomicron remnants and VLDL
Type IV	Autosomal dominant	↑**hepatic synthesis of VLDL**	↑VLDL → **↑↑TG**	

B. Acquired Hyperlipidemia

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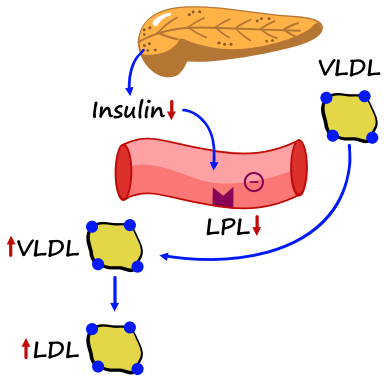
1. Diabetes Mellitus Related

- **Pathophysiology:**
  - Insulin resistance → ↓Effectiveness of insulin → ↓LPL activity → ↓Breakdown of VLDLs → ↑VLDLs lead to increased triglycerides and ↑LDL formation → ↑Accelerated atherosclerosis

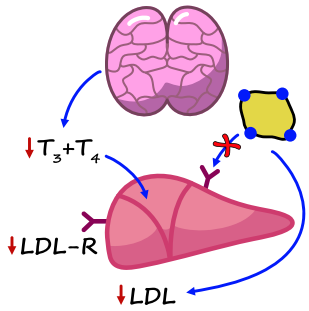
DM-related



2. Hypothyroid Related

- **Pathophysiology:**
  - ↓T3 and T4 → LDL- R down-regulation → ↓LDL uptake → ↑LDL → ↑Accelerated atherosclerosis

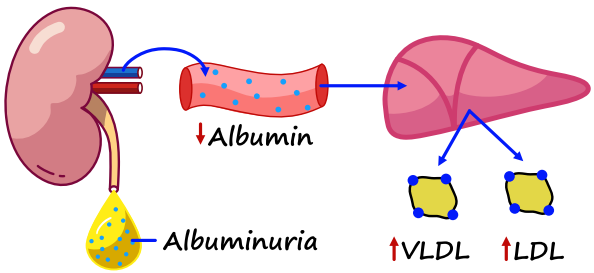
Hypothyroid related



3. Nephrotic Syndrome Related

- **Pathophysiology:**
  - Podocyte damage → ↑ Albuminuria → ↓Serum albumin → ↑Synthesis of liver proteins → ↑VLDL and LDL → ↑ Accelerated atherosclerosis

Nephrotic syndrome related



4. Medications

- Beta-Blocker
- Oral Contraceptives
- Thiazide Diuretics

II. COMPLICATIONS

A. Atherosclerosis

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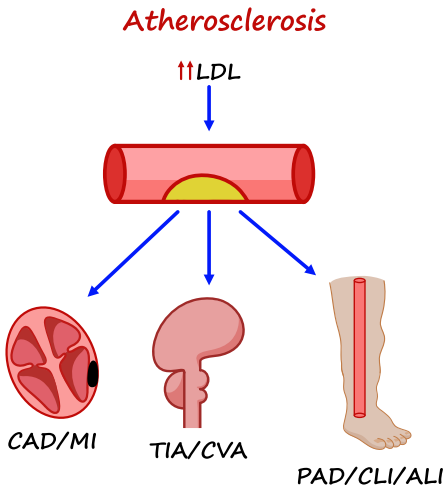
- **Pathophysiology:**
  - ↑↑LDL → ↑Atherosclerotic plaques → Luminal narrowing of blood vessel → Ischemia of organ affected
    - Myocardium: CAD or MI
    - CNS: TIA or CVA
    - Lower extremity: PAD or ALI



B. Pancreatitis

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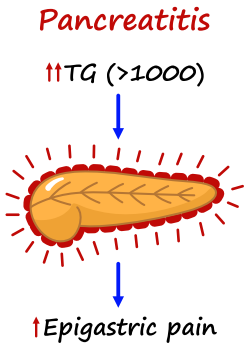
- **Pathophysiology:**
  - **↑↑TG** (> 1000 mg/dL) → Activate pancreatic enzymes → Massive pancreatic inflammation



C. Steatosis

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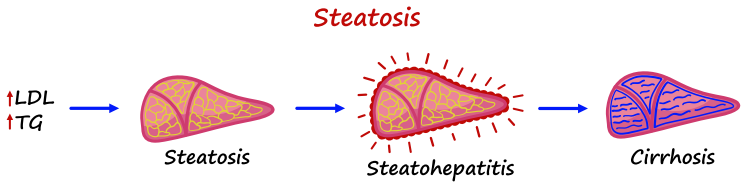
- **Pathophysiology:**
  - ↑LDL and ↑TG → **Steatosis** occurs which triggers inflammation → **Steatohepatitis** occurs which triggers fibrosis → **Cirrhosis** of the liver

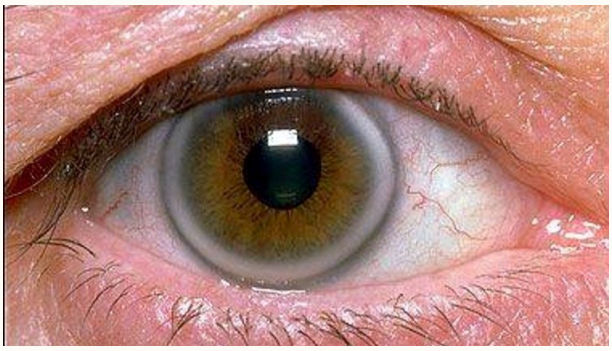


D. Soft Tissue Deposition

- Deposition of cholesterols or triglycerides into different soft tissues
  - **Xanthomas**: Deposition into tendons

  - **Xanthelasma**: Deposition into nasal side of eyelids

  - **Corneal arcs:** Deposition into the cornea



III. DIAGNOSIS AND TREATMENT

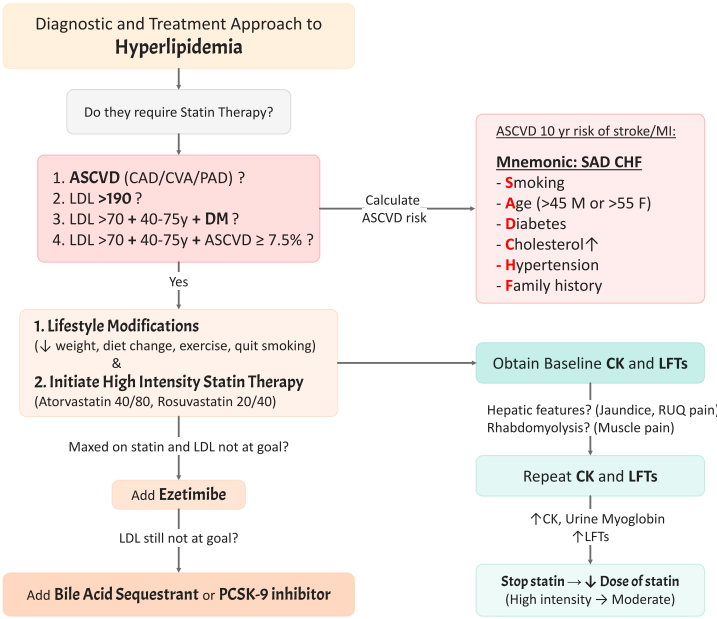


FIGURE 1. APPROACH TO DIAGNOSIS AND TREATMENT OF HYPERLIPIDEMIA.

A. STATIN REQUIREMENT

- **Four reasons for initiating statin therapy:**
  - **ASCVD:** Do they have evidence of CAD, MI, TIA, CVA, PAD or ALI?
    - (+) ASCVD → Statin therapy
  - **LDL > 190**? → Statin therapy
  - LDL > 70 + 40-75 y/o + **DM**? → Statin therapy
  - LDL > 70 + 40-75 y/o + **ASCVD risk ≥ 7.5%**? → Statin therapy

1. ASCVD Risk:

- **Purpose:** Calculates the 10-year risk of stroke or MI
- **Mnemonic: SAD CHF**
  - **S**moking
  - **A**ge (> 45/M or > 55/F)
  - **D**iabetes
  - **C**holesterol ↑
  - **H**ypertension
  - **F**amily history

B. TREATMENT APPROACH

1. Lifestyle Modification

- Change the modifiable risk factors:
  - ↓Weight
  - Diet
  - Exercise
  - Quit smoking

2. Initiate High-Intensity Statin Therapy

- Indications discussed in statin requirements
- Agents used:
  - **Atorvastatin 40/80**
  - **Rosuvastatin 20/40**

Obtain Baseline CK and LFTs

- Statins can cause **rhabdomyolysis** and **hepatitis** as adverse effects → Obtain baseline **CK** and **LFTs**
- The patient presents with hepatic features such as **jaundice** and **RUQ pain** or rhabdomyolysis such as **dark urine** and **muscle pain** → Repeat CK and LFTs
- If there is ↑CK, urine myoglobin, and LFTs → **Stop statin** and restart on a **↓Dose statin** such as moderate intensity

3. Add Ezetimibe

- If statin is maxed and LDL remains ↑↑ → Add **Ezetimibe**

4. Add Bile Acid Sequestrant or PCSK9-Inhibitor

- If statin and ezetimibe are maxed and LDL remains ↑↑ → Add Bile Acid or PCSK9-inhibitor

C. Lipid-Lowering Medications

25:46

a) Statins

- Primary drug class
- Examples: Atorvastatin, Rosuvastatin
- **Main effect:** ↓↓LDL
- **Mechanism of action:** inhibits HMG-CoA
  - HMG-CoA is needed in cholesterol synthesis
- **Pitfalls:**
  - ↑LFTs
  - ↑rhabdomyolysis

b) Bile Acid Sequestrants

- **Example:** Cholestyramine
- **Main effect:** ↓LDL
- **MOA:** Inhibits bile acid absorption → Loss of bile acid in stool
- **Pitfalls:**
  - ↑Diarrhea

c) Ezetimibe

- Primary drug class
- **Main effect:** ↓↓LDL
- **MOA:** Inhibits cholesterol absorption → Loss of cholesterol in stool
- **Pitfalls:**
  - ↑Diarrhea

d) Fibrates

- Examples: Gemfibrozil, Fenofibrate
- **Main effect:** ↓↓TG
  - Patient is on statin with the LDL goal reached, but **not** the TG goal
- **MOA:** ↑Lipoprotein lipase
  - ↑Conversion of TG to free fatty acids
- **Pitfalls:**
  - ↑LFTs and ↑rhabdomyolysis (if added to statins)
  - ↑Gallstones

e) Niacin

- **Main effect:** ↓TG and ↑HDL
- **MOA:** ↓Lipolysis
- **Pitfalls:**
  - Flushing
    - Niacin causes ↑Prostaglandin pathway stimulation
    - Treat with Aspirin
  - ↑Uric acid → Gout

f) PCSK-9 Inhibitors

- Example: Evolocumab
- **Main effect:** ↓↓↓LDL
- **MOA:** Inhibits LDL-R breakdown → ↑LDL uptake by the liver
- **Pitfalls:**
  - Very expensive

Table 2. Drug Classes used to treat Dyslipidemia.

Drug class	Main effect	Mechanism	Pitfalls
Statins (Atorvastatin, Rosuvastatin)	↓↓LDL	HMG-CoA inhbitor	↑ LFTs and Rhabdomyolysis
Bile Acid Sequestrants (Cholestyramine)	↓LDL	Inhibit Bile absorption	↑Diarrhea (cholesterol malabsorption)
Ezetimibe	↓LDL	Inhibit Cholesterol absorption	
Fibrates (Gemfibrozil, Fenofibrate)	↓↓TG	↑Lipoprotein Lipase	↑LFTs and Rhabdomyolysis (if added to statins) ↑gallstones
Niacin	↓TG ↑HDL	↓Lipolysis	Flushing (PG mediated)→Rx w/ ASA ↑uric acid→ gout
PCSK-9 Inhibitors (Evolocumab)	↓↓↓LDL	↓LDL-R breakdown	$ $ $