Disorders of Lipoprotein Metabolism

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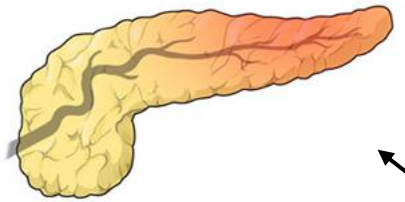
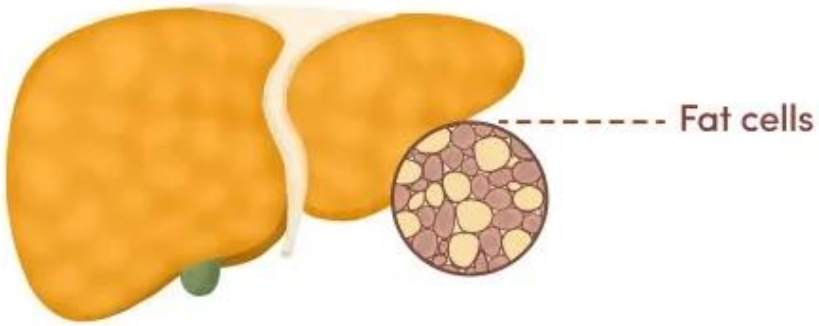
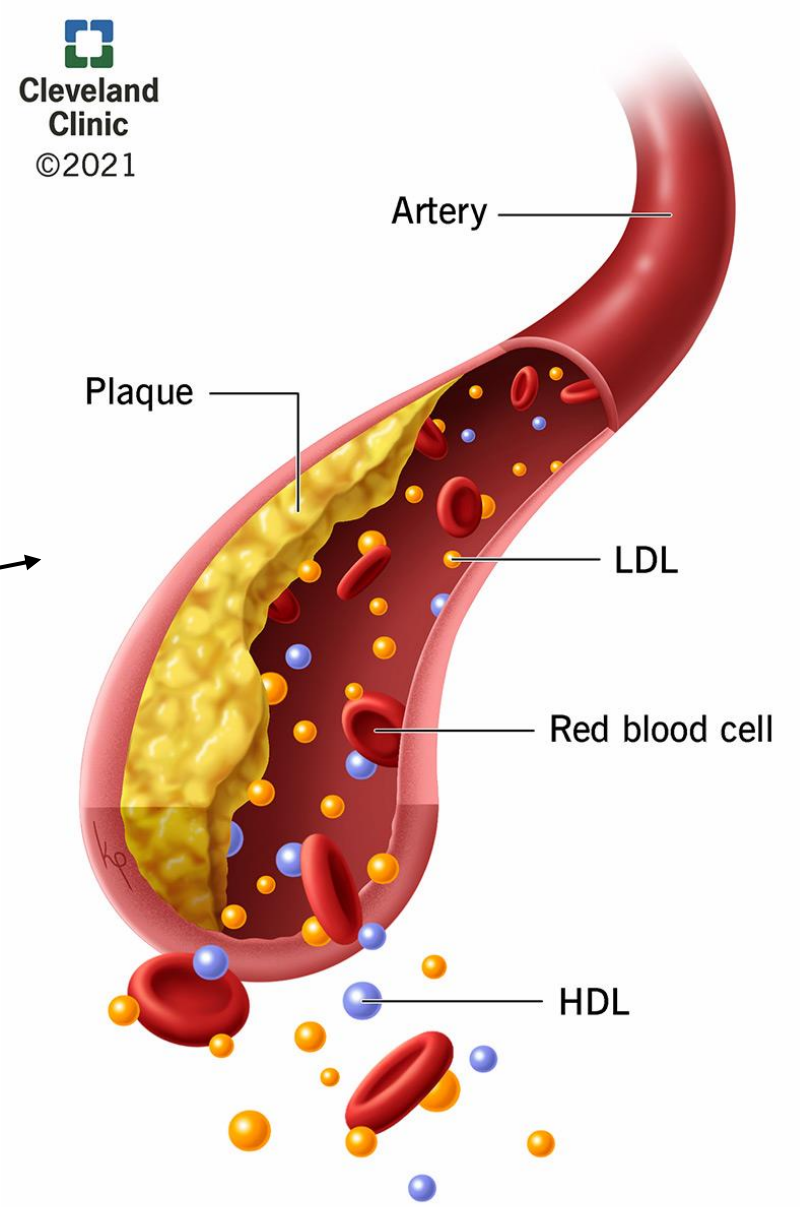
Introduction



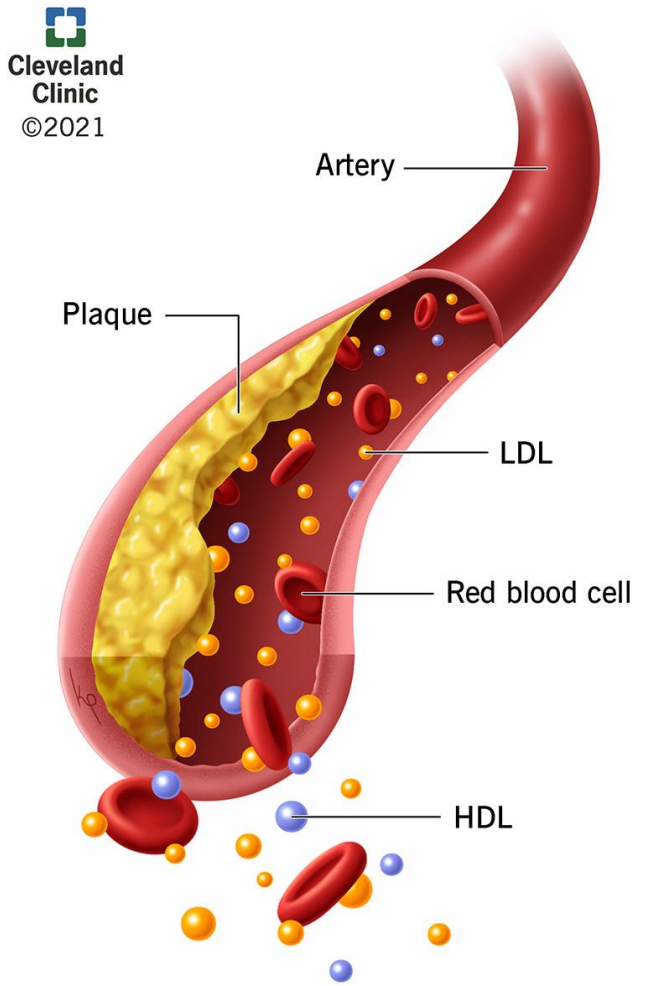
Dyslipidemia





https://www.hims.com/conditions/fatty-liver-disease,
Clinical impact of pancreatic steatosis measured by CT on the risk of post-ERCP pancreatitis: a multicenter prospective trial (Chung, Moon Jae et al.)

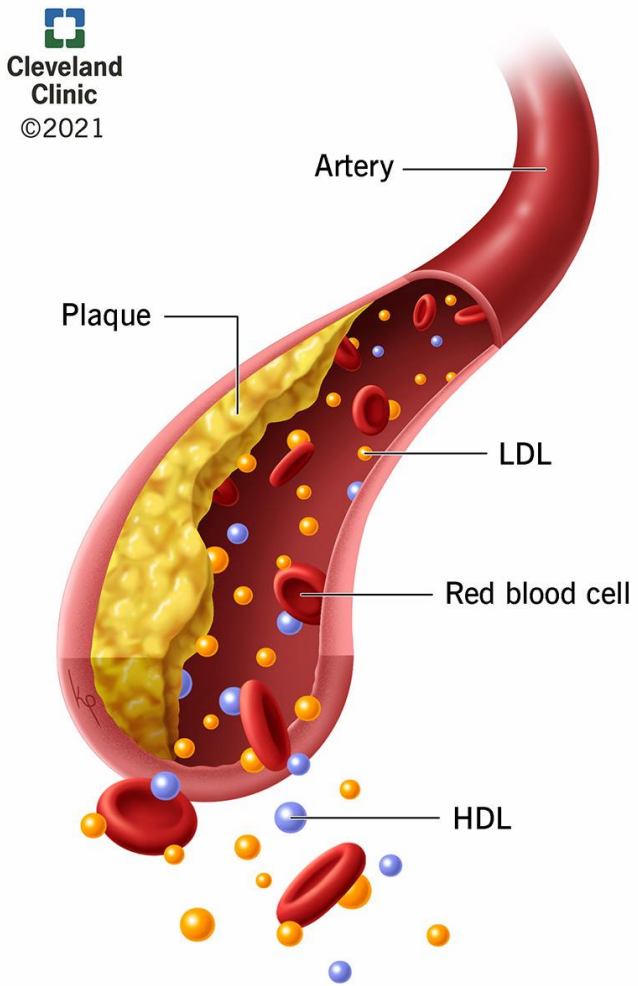
Atherosclerosis



Risk factors

- hyperlipidemia
- hypertension
- smoking
- diabetes
- physical inactivity
- decreased levels of HDL
- hyperhomocysteinemia
- hypercoagulable states

Pathogenesis of Atherosclerosis



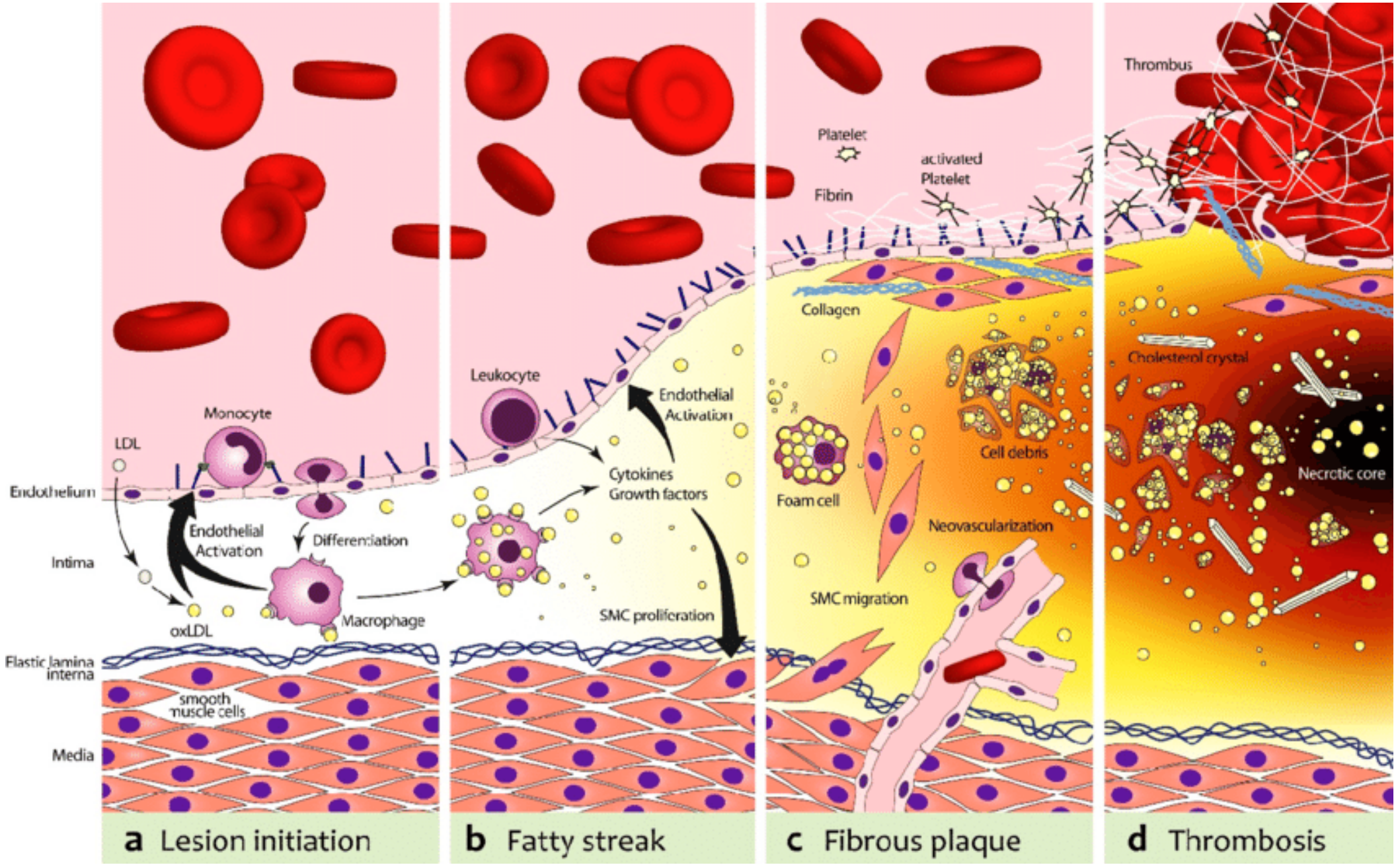
Atheroma

- containing cellular elements, collagen, and lipids

unesterified cholesterol and cholesteryl esters

- LDL, IDL, VLDL (Apo B-100)
- Chylomicron remnants (apoB-48)

The progression of atheroma



Steinl, David & Kaufmann, Beat. (2015). Ultrasound Imaging for Risk Assessment in Atherosclerosis. International Journal of Molecular Sciences (IJMS). 16. 9749-9769. 10.3390/ijms16059749.

Pathogenesis of Atherosclerosis

- **Tocopherols (vitamin E):** antioxidants in the surface of lipoproteins
- **Vitamin D:** prevents atherosclerosis, probably by influencing inflammatory activity of macrophages.
- **HDL:** cholesterol retrieval and in protecting lipoproteins against oxidation.

Pathogenesis of Atherosclerosis

- **Hypertension** increases access of lipoproteins to the subintima.
- **Smoking**: pro-oxidant effect, reducing HDL and increasing thrombogenesis by platelets. Activated platelets release platelet-derived growth factor (PDGF), stimulating proliferation and migration of cells of smooth muscle origin into the lesion.

Reversal of Atherosclerosis

Lipid-lowering therapy

- Trials have shown regression of atherosclerotic lesions / reductions in the incidence of new coronary events (both primary prevention and secondary prevention).
- Side-effects of treatment have been minimal in comparison with the magnitude of this benefit.

Differentiation of Disorders of Lipoprotein Metabolism

- Laboratory Analyses of Lipids and Lipoproteins
- Clinical Differentiation of Abnormal Patterns of Plasma Lipoproteins

Laboratory Analyses of Lipids and Lipoproteins

- Serum lipids and lipoproteins should be measured after a 10-hour fast.

  (chylomicrons present in plasma up to 10 hours after a meal, and contribute as much as 600 mg/dL (6.9 mmol/L) to the triglycerides measured during that period.)

- If blood glucose is not to be measured, patients may have fruit and black coffee with sugar (which provide no triglyceride) for breakfast.

Laboratory Analyses of Lipids and Lipoproteins

Inspection

- Opalescence is due to light scattering by large triglyceride-rich lipoproteins. Serum begins to appear hazy when the level of triglycerides reaches 200 mg/dL (2.3 mmol/L).

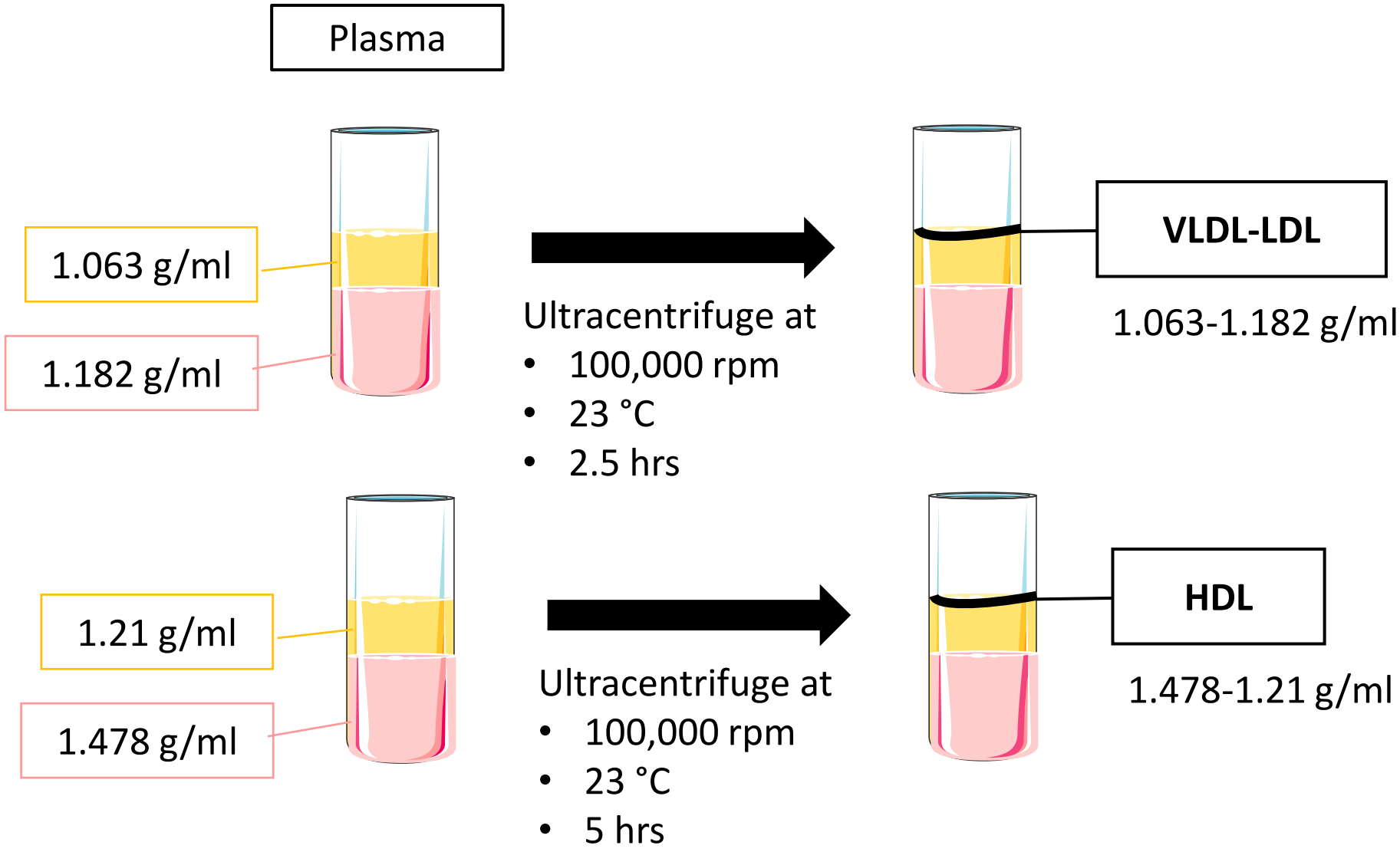
- Chylomicrons form a white supernatant layer after refrigeration.

http://clinical-laboratory.blogspot.com/2013/06/preventing-pre-analytical-errors.html
AL azkawi, Hanan & Alalwan, Ibrahim. (2010). Two Siblings with Familial Chylomicronemia Syndrome: Disease Course and Effectiveness of Early Treatment. Case reports in medicine. 2010. 807434. 10.1155/2010/807434.

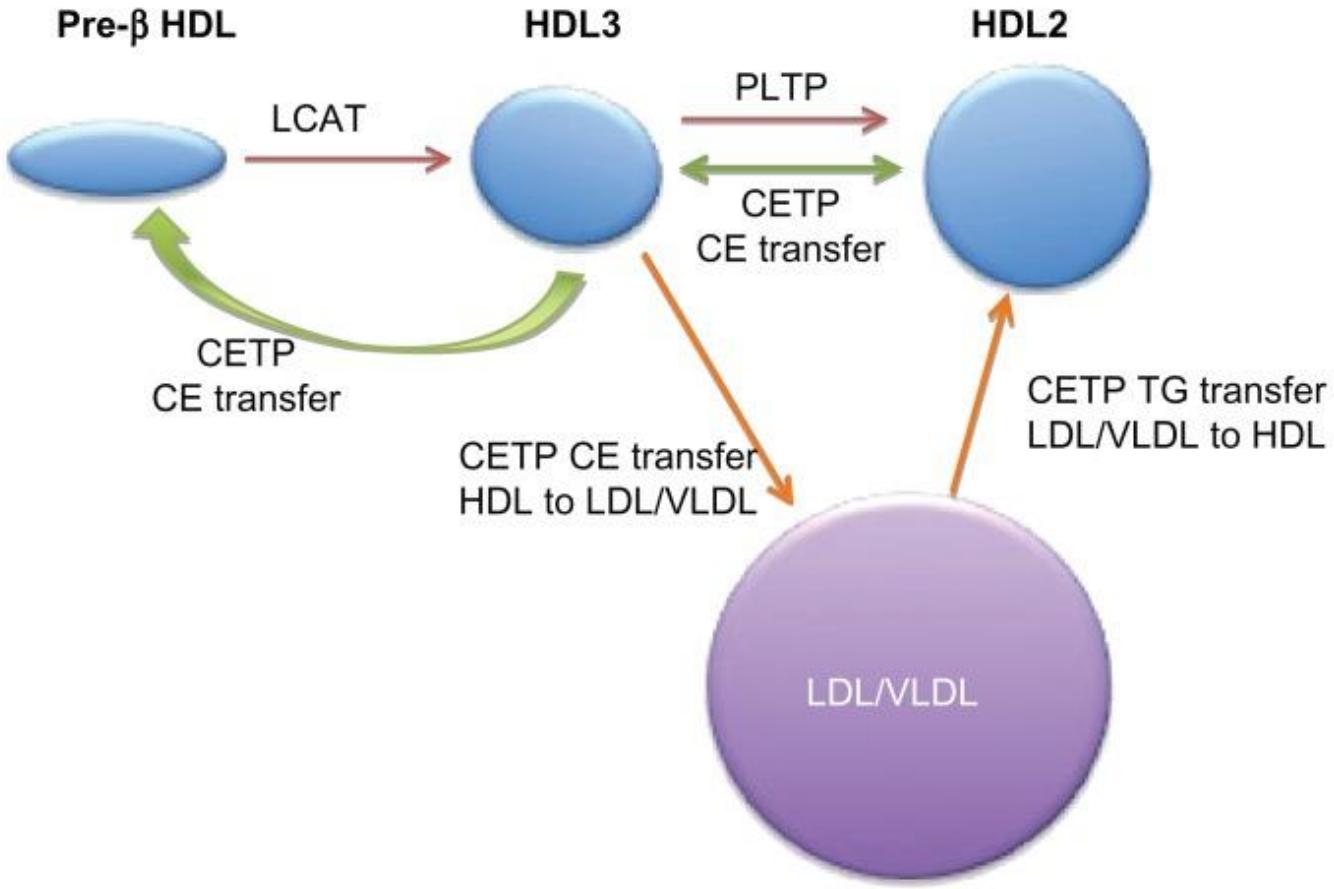
Laboratory Analyses of Lipids and Lipoproteins

Laboratory Techniques

- the total content of triglycerides and cholesterol (unesterified + esterified cholesterol) in serum
- individual lipoprotein fractions, separated by ultracentrifugation (only in research)
  - triglyceride and cholesterol contents
  - lipoprotein concentrations
  - particle diameters/size


Plasma
1.063 g/ml
1.182 g/ml
Ultracentrifuge at
• 100,000 rpm
• 23 °C
• 2.5 hrs
VLDL-LDL
1.063-1.182 g/ml
1.21 g/ml
1.478 g/ml
Ultracentrifuge at
• 100,000 rpm
• 23 °C
• 5 hrs
HDL
1.478-1.21 g/ml

Laboratory Analyses of Lipids and Lipoproteins



* HDL cholesterol cannot be interpreted without knowledge of the level of serum triglycerides.

Goldberg, Alyse & Hegele, Robert. (2012). Cholesteryl ester transfer protein inhibitors for dyslipidemia: Focus on dalcetrapib. Drug design, development and therapy. 6. 251-9. 10.2147/DDDT.S34976.

Laboratory Analyses of Lipids and Lipoproteins

Laboratory Techniques

- the ratio of cholesterol to triglycerides
- The ApoE genotype (PCR analysis)
- Clinically useful immunoassays are available for ApoB and Lp(a).

Clinical Differentiation of Abnormal Patterns of Plasma Lipoproteins

Identification of Abnormal Patterns

- The second step in investigation of hyperlipidemia is determination of the species of lipoproteins involved.
- The differentiation of specific primary disorders usually requires additional clinical and genetic information.
- HDL deficiency underscores the importance of controlling other risk factors and avoiding factors that reduce HDL, such as smoking, the use of some drugs, and obesity.

Case 1: Serum Cholesterol Levels Increased; Triglycerides Normal

- If the serum cholesterol level is modestly elevated (up to 260 mg/dL [6.72 mmol/L]), elevated levels of HDL may account for the observed increase in serum cholesterol.
- Very high levels of HDL can signal the presence of the abnormal lipoprotein of cholestasis (Lp-X). This disorder is characterized by elevated alkaline phosphatase activity. Rarely, deficiency of CETP or hepatic lipase can cause high levels of HDL.

Case 2: Predominant Increase of Triglycerides; Moderate Increase in Cholesterol May Be Present

- the primary abnormality is an increase in triglyceride-rich VLDL or chylomicrons or both (mixed lipemia).
- the increase in cholesterol due to the triglyceride-rich lipoproteins (TRL)
- Low levels of LDL often seen in hypertriglyceridemia.

Case 3: Cholesterol and Triglyceride Levels Both Elevated

- Familial combined hyperlipidemia (combined increase of VLDL and LDL)
- Familial dysbetalipoproteinemia
  - increase of remnant lipoproteins derived from VLDL and chylomicrons
  - partially depleted of triglyceride by LPL and enriched with cholesteryl esters by the LCAT system, such that the total content of cholesterol in serum is similar to that of triglycerides.

Clinical Descriptions of Primary and Secondary Disorders of Lipoprotein Metabolism

- Hypertriglyceridemia
- Hypercholesterolemia
- Hypolipidemia
- Other Disorders of Lipoprotein Metabolism

Hypertriglyceridemia

Atherogenicity

- Epidemiologic evidence supports the atherogenicity of VLDL and their remnants. They have been demonstrated in atherosclerotic plaques from humans.
- Impaired capacity of the VLDL of some individuals to accept cholesteryl esters from the LCAT reaction may also contribute to atherogenesis by impeding centripetal transport of cholesterol.

Hypertriglyceridemia

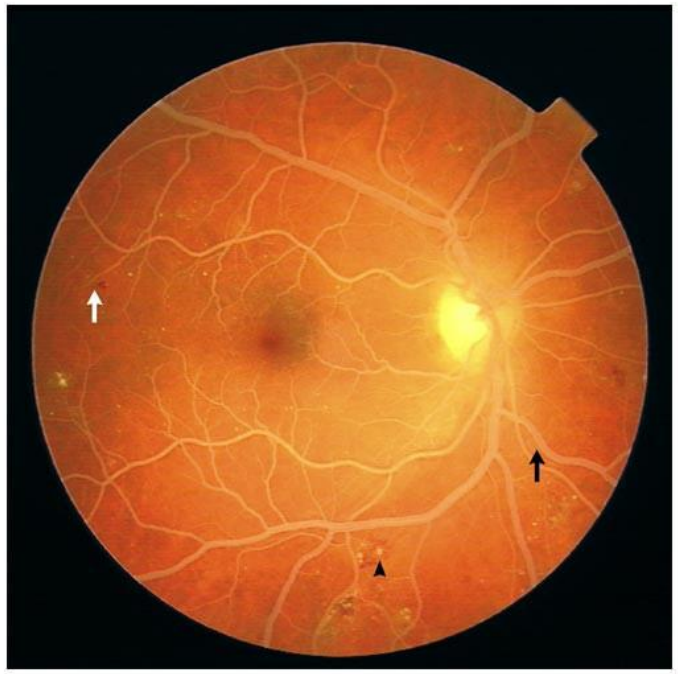
Cause of Pancreatitis

- probably from the local release of FFA and lysolecithin from lipoprotein substrates in the pancreatic capillary bed.
- When the concentrations of these lipids exceed the binding capacity of albumin, they could lyse membranes of parenchymal cells, initiating a chemical pancreatitis.
- The progression of pancreatitis can be prevented by rapid reduction of triglycerides, usually accomplished by restriction of all dietary fat.

Hypertriglyceridemia

Clinical Signs

- **lipemia retinalis**: triglyceride levels in serum exceed 3000 to 4000 mg/dL (34.5-46 mmol/L), light scattering by these particles in the blood lends a whitish cast to the venous vascular bed of the retina



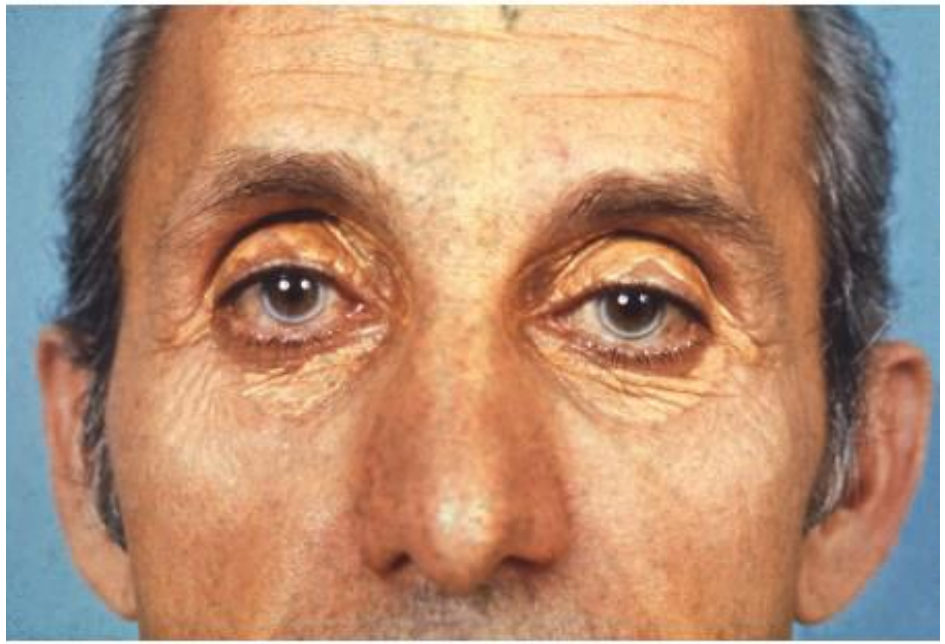
https://www.nejm.org/doi/full/10.1056/NEJMicm040437#f01

Xanthelasma

A

Source: Gardner DG, Shoback D: *Greenspan's Basic & Clinical Endocrinology, 9th Edition:* www.accessmedicine.com

B



Source: Gardner DG, Shoback D: *Greenspan's Basic & Clinical Endocrinology, 9th Edition:* www.accessmedicine.com

Xanthomas

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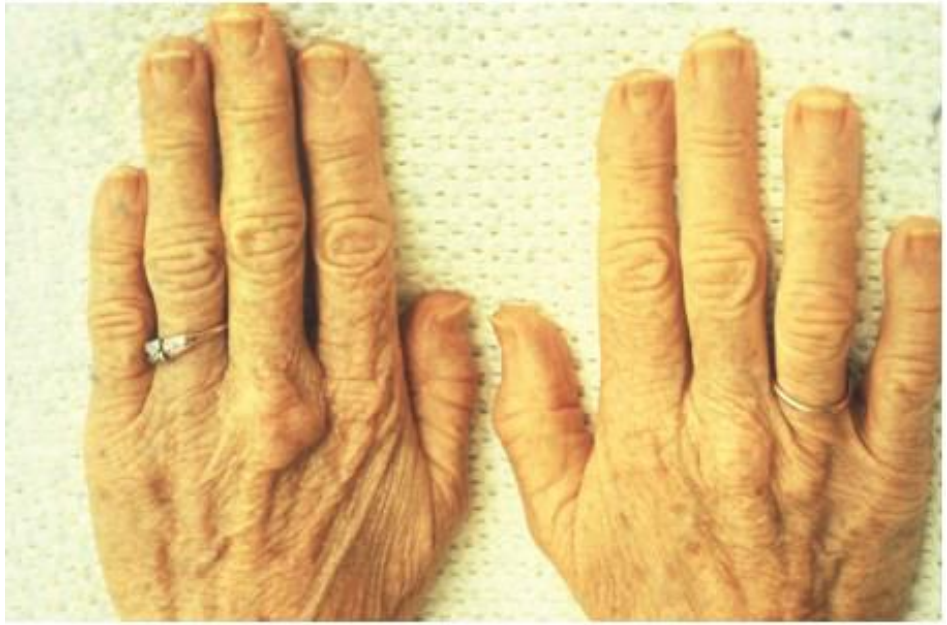

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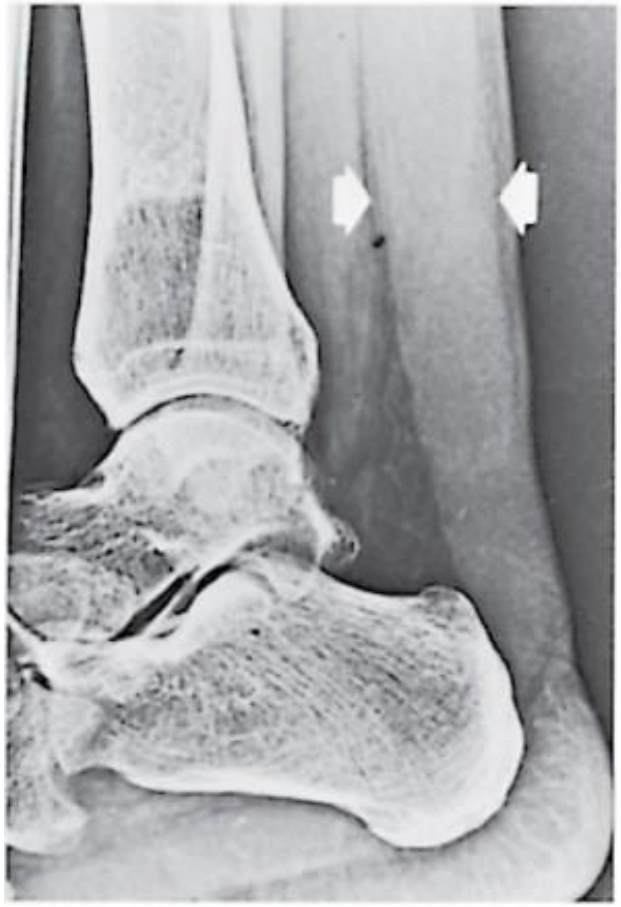

Source: Gardner DG, Shoback D: *Greenspan's Basic & Clinical Endocrinology, 9th Edition:* www.accessmedicine.com

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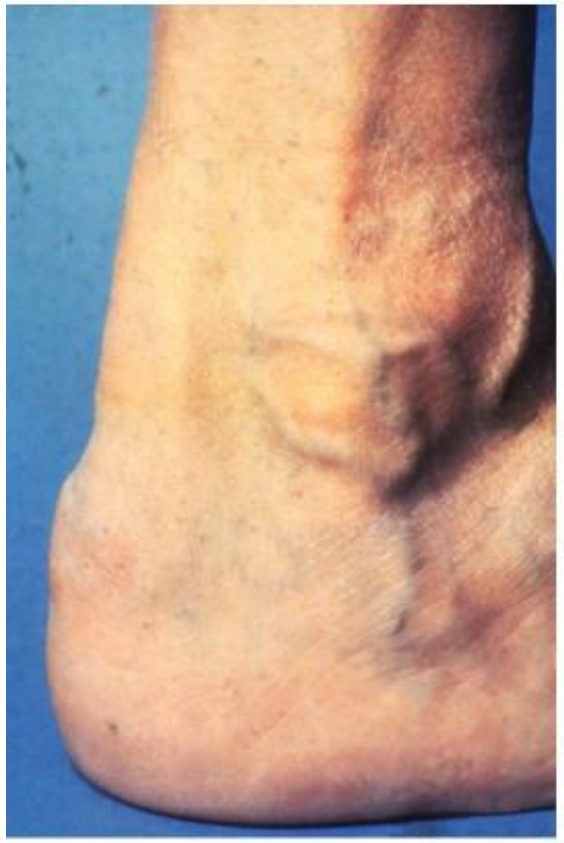

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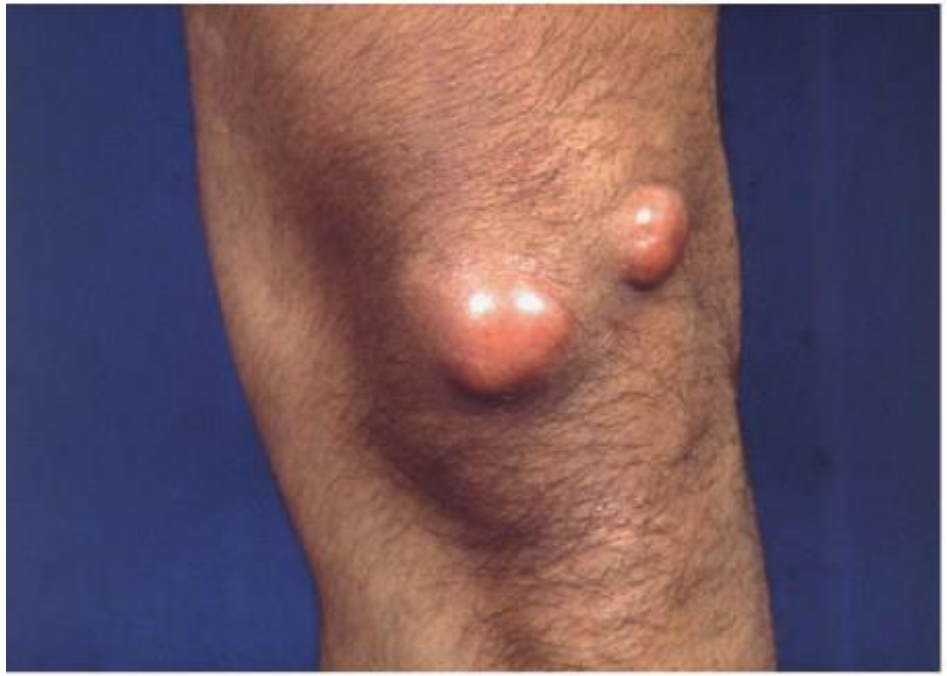

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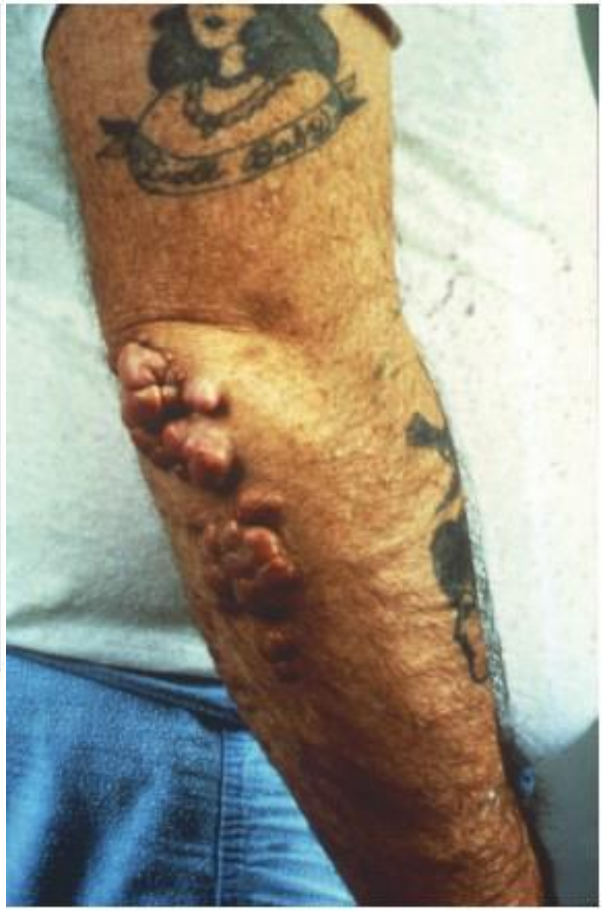

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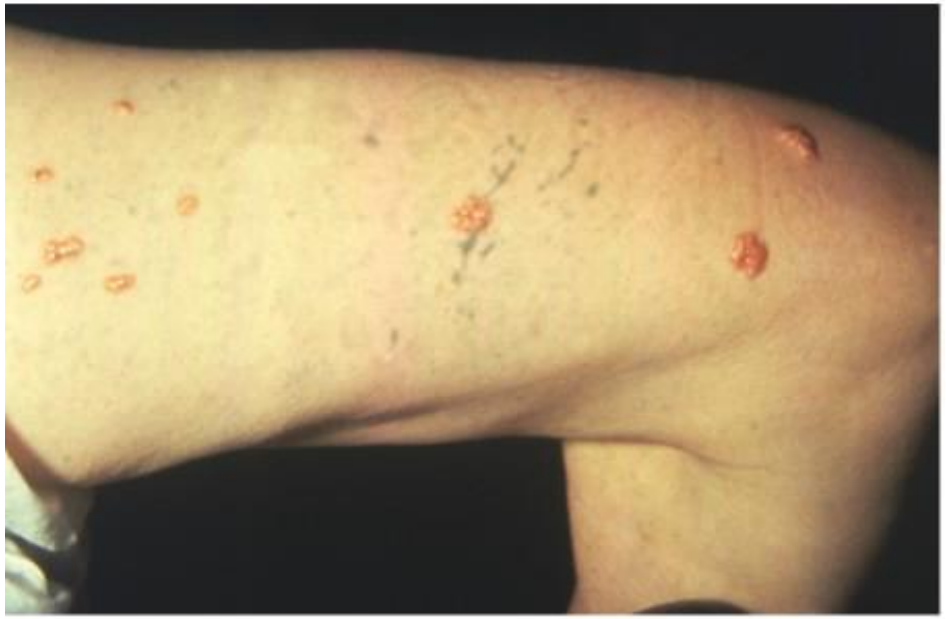


Source: Gardner DG, Shoback D: *Greenspan's Basic & Clinical Endocrinology, 9th Edition:* www.accessmedicine.com

Eruptive xanthomas

Tuberous xanthomas

Primary Hypertriglyceridemia

1. **Deficiency of LPL Activity**
2. **Endogenous and Mixed Lipemia**
3. **Familial Combined Hyperlipidemia**
4. **Familial Dysbetalipoproteinemia**

Primary Hypertriglyceridemia

1. Deficiency of LPL Activity

- The activity of LPL is dependent upon the integrity of the enzyme and its cofactor, ApoC-II.
- In addition, defects in ApoA-V, GPIHDLBP, and LMF1 proteins can result in severe impairment of LPL activity.

Primary Hypertriglyceridemia
1. Deficiency of LPL Activity

Clinical Findings

- Lipemia is usually severe (triglycerides of 2000-25,000 mg/dL) (23-287.5 mmol/L).
- Hepatomegaly and splenomegaly, splenic infarct, hypersplenism with anemia, granulocytopenia, and thrombocytopenia
- Pancreatitis *The risk of pancreatitis increases in pregnancy and lactation or during the administration of estrogenic steroids.
- Eruptive xanthomas
- usually not obese and have normal carbohydrate metabolism unless pancreatitis impairs insulinogenic capacity.

Primary Hypertriglyceridemia
1. Deficiency of LPL Activity

Laboratory Findings

- infranatant layer of serum refrigerated overnight may be nearly clear with a supernatant chylomicron layer.
- moderate increase in VLDL, decreased LDL and HDL cholesterol
- mixed lipemia (esp. in pregnant women or those receiving estrogens)
- Confirmation by measurement of the lipolytic activity of plasma (with and without 0.5 mol/L sodium chloride, which inhibits LPL but does not suppress the activity of hepatic lipase)
- absence of the ApoC-II cofactor (by electrophoresis or isoelectric focusing of the proteins of VLDL)

Primary Hypertriglyceridemia
2. Endogenous and Mixed Lipemia

Etiology and Pathogenesis

- Studies of VLDL turnover indicate that either increased production or impaired removal of VLDL may be operative in different individuals.
- Endogenous lipemia (increased VLDL) >> increased chylomicron >> mixed lipemia
  - VLDL and chylomicrons are competing substrates in the intravascular lipolytic pathway, saturating levels of VLDL impede the removal of chylomicrons.
- Factors that increase the rate of secretion of VLDL aggravate the hypertriglyceridemia (ie, obesity with insulin resistance, appearance of fully developed type 2 DM, alcohol, and exogenous estrogens).

Primary Hypertriglyceridemia
2. Endogenous and Mixed Lipemia

Clinical Findings

- depend on their severity
- eruptive xanthomas, lipemia retinalis, recurrent epigastric pain, acute pancreatitis.
- insulin resistance, central obesity
- low levels of HDL cholesterol (increased transfer of CE into circulating VLDL)
- hypertension , hyperuricemia

Primary Hypertriglyceridemia
3. Familial Combined Hyperlipidemia

Etiology

- overproduction of VLDL
- Some affected individuals have increased levels of both VLDL and LDL (combined hyperlipidemia). Some have predominantly increased levels of either VLDL or LDL.
- The level of ApoB-100 is increased. Patterns in the serum of an individual may change with time.
- Affected children often have hyperlipidemia. If the child is obese, hypertriglyceridemia is likely present, whereas a child of normal weight may have only an elevated LDL.

Primary Hypertriglyceridemia
3. Familial Combined Hyperlipidemia

Clinical Findings

- Xanthelasma
- Mendelian dominant trait
- Factors that increase the severity of hypertriglyceridemia in other disorders aggravate the lipemia in this syndrome as well.

Primary Hypertriglyceridemia
4. Familial Dysbetalipoproteinemia

Etiology and Pathogenesis

- homozygosity for ApoE-2 + environmental/possibly additional genetic determinants.
- heterozygous state >> dominant dysbetalipoproteinemia
- absence of the E-3 and E-4 alleles in genomic DNA confirms the diagnosis.

Primary Hypertriglyceridemia
4. Familial Dysbetalipoproteinemia

Etiology and Pathogenesis

isoforms of ApoE that are poor ligands for high-affinity receptors

↓

impaired hepatic uptake of TRL remnants

↓

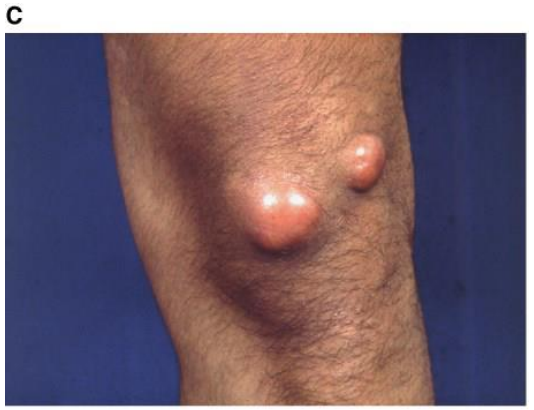
- accumulation of TRL remnants
- decreased LDL

- The remnant particles are enriched in cholesteryl esters such that the level of cholesterol in serum is often as high as that of triglycerides.

Primary Hypertriglyceridemia
4. Familial Dysbetalipoproteinemia

Clinical Findings

- Hyperlipidemia and clinical signs are not usually evident before age 20.
- In younger patients with hyperlipidemia: hypothyroidism or obesity
- Adults: tuberous or tuberoeruptive xanthomas (elbows and knees), planar xanthomas of the palmar
- impaired glucose tolerance, obesity
- often develop severe hyperlipidemia if they are hypothyroid.
- Atherosclerosis of the coronary and peripheral vessels occurs with increased frequency, and the prevalence of disease of the iliac and femoral vessels is especially high.



Secondary Hypertriglyceridemia

- Diabetes Mellitus
- Uremia
- Human Immunodeficiency Virus Infection
- Corticosteroid Excess
- Exogenous Estrogens
- Alcohol Ingestion
- Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis
- Nephrosis
- Glycogen Storage Disease
- Hypopituitarism and Acromegaly
- Hypothyroidism
- Immunoglobulin-Lipoprotein Complex Disorders

Clinical Descriptions of Primary and Secondary Disorders of Lipoprotein Metabolism

- Hypertriglyceridemia
- Hypercholesterolemia
- Hypolipidemia
- Other Disorders of Lipoprotein Metabolism

Primary Hypercholesterolemia

1. **Familial Hypercholesterolemia (FH)**
2. **Familial Combined Hyperlipidemia (FCH)**
3. **Lp(a) Hyperlipoproteinemia**
4. **Familial Ligand-Defective ApoB-100**
5. **Cholesterol 7α-Hydroxylase Deficiency**

Primary Hypercholesterolemia
1. Familial Hypercholesterolemia (FH)

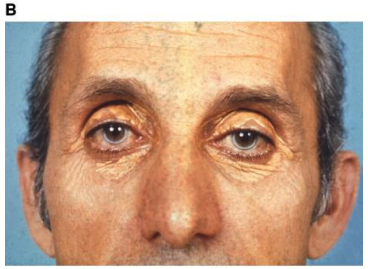
Etiology and Pathogenesis

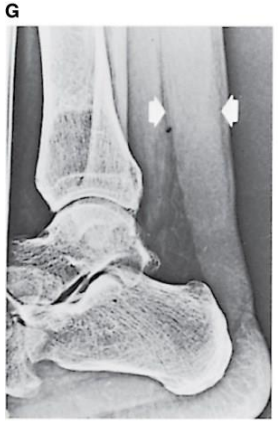
- heterozygous form occurs in approximately 1 in 500 individuals, is a codominant trait with high penetrance.
- half of first-degree relatives are affected, all members of a family should be screened.
- deficiency of normal LDL receptors on cell membranes - structure, translation, modification, or transport of the receptor protein
- A selective increase in LDL exists from birth >> increase during childhood and adolescence >> cholesterol in adult heterozygotes usually varies from about 260 to 400 mg/dL (6.7- 10.4 mmol/L).

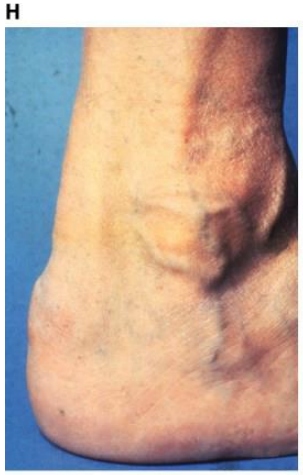
Primary Hypercholesterolemia
1. Familial Hypercholesterolemia (FH)

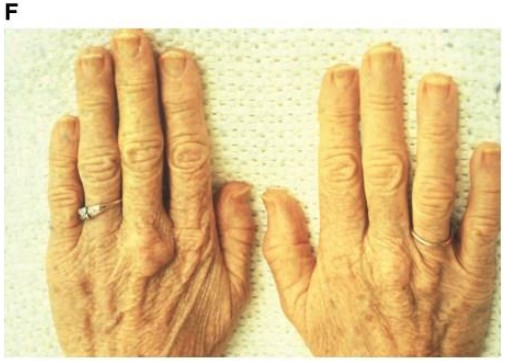
Clinical Findings

- Tendon xanthomas (the Achilles, patellar tendons, extensor tendons of the hands)
- Arcus corneae
- Xanthelasma









The finding of tendon xanthomas is nearly pathognomonic—beta-sitosterolemia, cerebrotendinous xanthomatosis (cholestanolosis), ligand-defective ApoB, and autosomal recessive hypercholesterolemia (ARH) are exceptions.

Primary Hypercholesterolemia
1. Familial Hypercholesterolemia (FH)

Clinical Findings

- **Homozygous FH**: xanthomatosis progresses rapidly, tuberous xanthomas, elevated plaque-like xanthomas of the extremities, buttocks, interdigital webs, and aortic valves.
- **Heterozygous FH**: Serum cholesterol in excess of 300 mg/dL (7.8 mmol/L) without hypertriglyceridemia and secondary cause hypercholesterolemia,
- The presence of affected first-degree is supportive of heterozygous FH
- Coronary atherosclerosis tends to occur prematurely in heterozygotes. It is particularly prominent in individuals who are relatively deficient in HDL.

Primary Hypercholesterolemia
2. Familial Combined Hyperlipidemia (FCH)

- The underlying mechanism involves increased secretion of VLDL.
- The pattern may vary: Predominant elevation of VLDL, combined elevations of LDL/VLDL or only elevated LDL/IDL
- In contrast to most cases of FH, the cholesterol level may be as low as 250 mg/dL (6.5 mmol/L)
- Xanthomas are absent in FCH.
- Coronary atherosclerosis is accelerated

Primary Hypercholesterolemia

3. Lp(a) Hyperlipoproteinemia

- Lp(a) contains ApoB-100 and the (a) protein, a homolog of plasminogen that can inhibit fibrinolysis.
- It has been demonstrated in atherosclerotic plaques
- an independent risk factor for coronary disease
- Increased plasma levels of Lp(a) >> an independent risk of coronary disease and stroke.

Primary Hypercholesterolemia
4. Familial Ligand-Defective ApoB-100

- Mutations involving the ligand domain in ApoB-100 impair the ability of LDL to bind to its receptor.
- less severe hypercholesterolemia than in FH because the removal of VLDL remnants is normal, resulting in a lower production of LDL.
- tendon xanthomas
- increased risk of coronary disease

Primary Hypercholesterolemia

5. Cholesterol 7α-Hydroxylase Deficiency

Loss of function mutations in cholesterol 7α-hydroxylase

↓

diminished catabolism of cholesterol to bile

↓

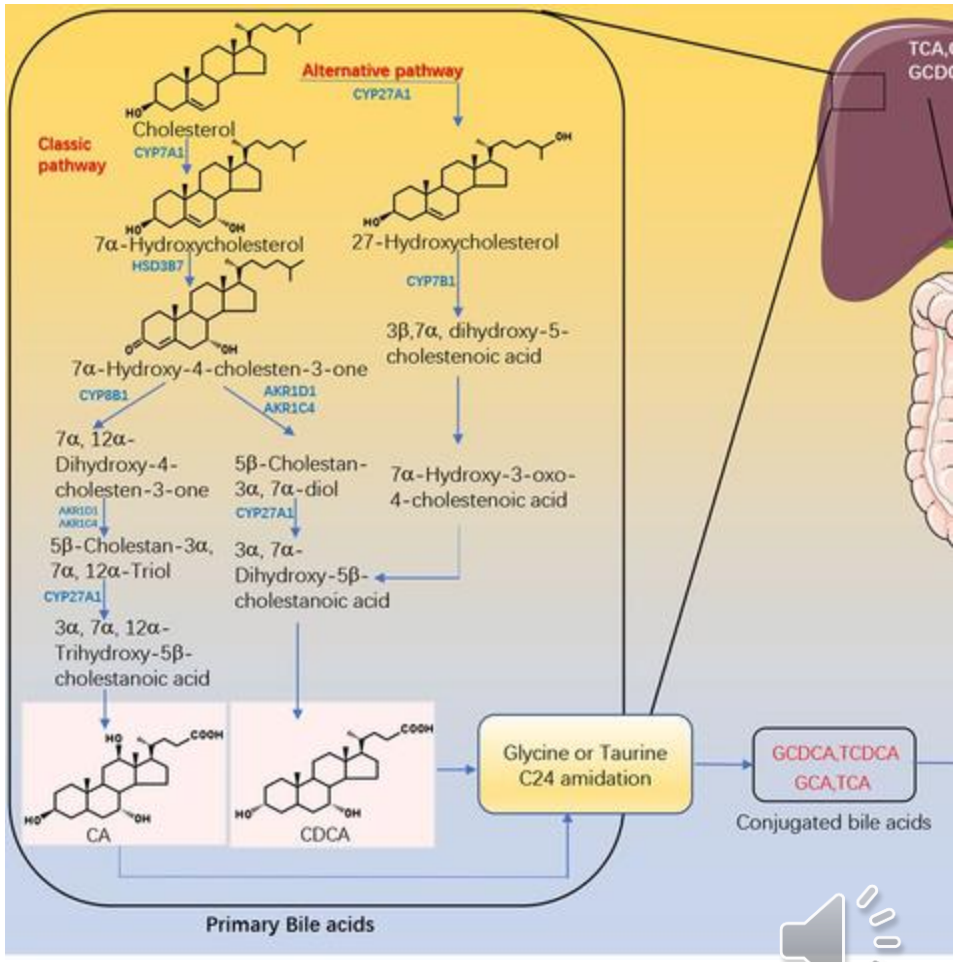
accumulation of cholesterol in hepatocytes.

↓

downregulation of LDL receptors

↓

elevated LDL in plasma.



Sun, Ruicong & Xu, Chunjin & Feng, Baisui & Gao, Xiang & Liu, Zhanju. (2021). Critical roles of bile acids in regulating intestinal mucosal immune responses. Therapeutic Advances in Gastroenterology. 14. 175628482110180. 10.1177/17562848211018098.

Secondary Hypercholesterolemia

- Hypothyroidism
- Nephrosis
- Immunoglobulin Disorders
- Anorexia Nervosa
- Cholestasis

Clinical Descriptions of Primary and Secondary Disorders of Lipoprotein Metabolism

- Hypertriglyceridemia
- Hypercholesterolemia
- Hypolipidemia
- Other Disorders of Lipoprotein Metabolism

Primary Hypolipidemia

due to Deficiency of HDL

1. Tangier Disease
2. Familial Hypoalphalipoproteinemia
3. Deficiency of LCAT

due to Deficiency of apoB-containing lipoproteins

1. Recessive Abetalipoproteinemia
2. Familial Hypobetalipoproteinemia
3. Chylomicron Retention Disease

Primary Hypolipidemia: due to Deficiency of HDL

1. Tangier Disease

Etiology and Pathogenesis

- rare autosomal recessive disease
- severe deficiency of HDL
- Heterozygotes lack clinical signs but have about one-half or less of the normal complement of HDL and ApoA-I in plasma.
- Homozygotes lack normal HDL, and ApoA-I and ApoA-II are present at extremely low levels.
- serum cholesterol is usually below 120 mg/dL (3.12 mmol/L)
- mild hypertriglyceridemia is usually present, and LDL is greatly enriched in triglycerides.

Primary Hypolipidemia: due to Deficiency of HDL

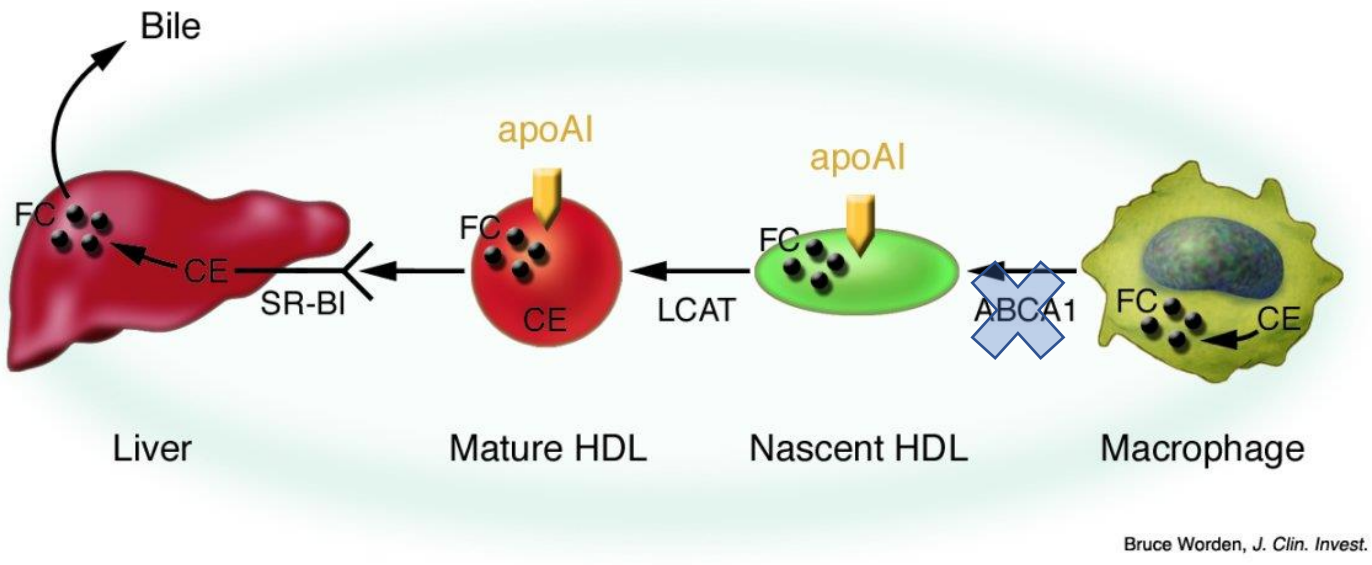
1. Tangier Disease

Etiology and Pathogenesis

mutations in the ATP-dependent transporter ABCA1

⬇

defective efflux of cholesterol from peripheral cells.



Primary Hypolipidemia: due to Deficiency of HDL

1. Tangier Disease

Clinical Findings

- large, orange-colored, lipid-filled tonsils
- accumulation of cholesteryl esters in the reticuloendothelial system
- episodic and recurrent peripheral neuropathy with predominant motor weakness in the later stages.
- carotenoid pigment may be apparent in pharyngeal and rectal mucous membranes.
- splenomegaly and corneal infiltration may also be present.
- some increase in risk of coronary atherosclerosis.

Primary Hypolipidemia: due to Deficiency of HDL

2. Familial Hypoalphalipoproteinemia

Etiology and Pathogenesis

- partial deficiency of HDL that may involve heterogeneous mechanism
- HDL cholesterol levels are usually below 35 mg/dL (0.9 mmol/L)
- moderately low levels of HDL may be seen in healthy individuals consuming a diet very low in fat.

*HDL cholesterol must also be interpreted in the light of the amount of triglyceride-rich lipoproteins in plasma. Because cholesteryl esters are progressively transferred to the cores of triglyceride-rich lipoproteins as triglyceride levels rise, HDL cholesterol decreases as an inverse function of the triglyceride level.

Primary Hypolipidemia: due to Deficiency of HDL
2. Familial Hypoalphalipoproteinemia

Etiologic Factor in Coronary Disease

- Mutations in several genes have been associated, including ApoA-I, PCPE-2 (a protease involved in the maturation of ApoA-I), and the WW domain oxidoreductase (a transcriptional regulator involved in HDL metabolism).
- important risk factor in atherosclerosis
- risk factor in many cases of premature coronary or peripheral vascular disease
- accelerates the appearance of coronary disease in patients with FH or other hyperlipidemias.
- strong familial incidence

Primary Hypolipidemia: due to Deficiency of HDL

3. Deficiency of LCAT

- rare autosomal recessive disorder
- not expressed in clinical or biochemical form in the heterozygote
- In the homozygote, clinical characteristics are variable.
- Proteinuria may be an early sign. Deposits of unesterified cholesterol and phospholipid in the renal microvasculature lead to progressive loss of nephrons and ultimate renal failure.
- mild to moderate normochromic anemia with target cells.
- hyperbilirubinemia or peripheral neuropathy may be present.
- red blood cell lipid composition is abnormal, with increased content of unesterified cholesterol and lecithin.

Primary Hypolipidemia: due to Deficiency of HDL

3. Deficiency of LCAT

- serum cholesterol vary from low normal to about 500 mg/dL (13 mmol/L), only a small fraction of which is esterified.
- Two abnormal HDL species are present: bilayer disks and small spherical particles.
- elevated plasma triglycerides (200-1000 mg/dL [2.3-11.2 mmol/L])
- the large TRL are unusually rich in unesterified cholesterol and appear to have abnormal surface monolayers.
- LDL are rich in triglycerides, and abnormal vesicular lipoproteins are present in the LDL density interval.

Primary Hypolipidemia: due to Deficiency of apoB-containing lipoproteins

1. Recessive Abetalipoproteinemia

Etiology and Pathogenesis

- mutations involving the microsomal triglyceride transfer protein >> defect in the incorporation of newly synthesized triglycerides into ApoB–containing lipoproteins
- heterozygous for mutations have no abnormalities
- homozygotes: no chylomicrons/VLDL/LDL, only HDL
- plasma triglycerides are usually less than 10 mg/dL (0.12 mmol/L) and fail to rise after a fat load.
- total cholesterol is usually less than 90 mg/dL (2.3 mmol/L).

Primary Hypolipidemia: due to Deficiency of apoB-containing lipoproteins

1. Recessive Abetalipoproteinemia

Clinical Findings

- a paucity of adipose tissue associated with malabsorption of long-chain fatty acids due to failure of the intestine to secrete chylomicrons.
- Low fat soluble vitamins - The neurologic and opthalmologic defects are due to deficiency of vitamin E (normally transported largely in LDL).
- develop steatorrhea with impaired growth in infancy.
- Red blood cells may be acanthocytic, with a high cholesterol-phospholipid ratio.
- progressive degeneration of the central nervous system, including cerebellar degeneration and posterior and lateral spinal tract disease.
- The neuromuscular disorder often appears in late childhood with ataxia, night blindness, decreased visual acuity, and nystagmus.
- Retinal degeneration may be severe.
- Cardiomyopathy with arrhythmias has been reported and may be a cause of death.

Primary Hypolipidemia: due to Deficiency of apoB-containing lipoproteins

2. Familial Hypobetalipoproteinemia

- defects at the ApoB locus, resulting in decreased production of protein or in the production of truncated gene products.
- LDL and ApoB in heterozygotes are often present at about half of normal levels.
- Homozygous: complete interdiction of ApoB synthesis
- the clinical and biochemical features may be indistinguishable from those of recessive abetalipoproteinemia
- Clinical features may be absent in patients who produce at least low levels of LDL-like particles.

Primary Hypolipidemia: due to Deficiency of apoB-containing lipoproteins

3. Chylomicron Retention Disease

- This disorder presents in the neonate
- based on the selective inability of intestinal epithelial cells to secrete chylomicrons.
- severe malabsorption of triglycerides with steatorrhea.
- Levels of LDL and VLDL are about half of normal, presumably secondary to malnutrition.
- Tocopherol levels may be very low and may be associated with neurologic abnormalities.

Secondary Hypolipidemia

- A wide variety of conditions leading to intestinal malabsorption produce hypolipidemia.
- chronic cachexia (eg, advanced cancer)
- myeloproliferative disorders
- massive parenchymal liver failure (eg, in Reye syndrome)
- drug treatment of hyperlipidemia can signal hepatic toxicity.
- immunoglobulin disorders (myeloma or macroglobulinemia but may have lymphomas or lymphocytic leukemia.

Clinical Descriptions of Primary and Secondary Disorders of Lipoprotein Metabolism

- Hypertriglyceridemia
- Hypercholesterolemia
- Hypolipidemia
- Other Disorders of Lipoprotein Metabolism

Other Disorders of Lipoprotein Metabolism

1. Lipodystrophies

a complete or partial loss of and/or abnormal distribution of adipose tissue in certain areas of your body

Associated Disorders

- tumors or other lesions of the hypothalamus
- HIV disease
- collagen-vascular disorders, including scleroderma and dermatomyositis

Other Disorders of Lipoprotein Metabolism

2. Rare disorders

- Autosomal Recessive Hypercholesterolemia
- Pcsk9 Variants
- Werner Syndrome, Progeria, Infantile Hypercalcemia, Sphingolipidoses, and Niemann-Pick Disease
- Wolman Disease and Cholesteryl Ester Storage Disease
- Cerebrotendinous Xanthomatosis
- Phytosterolemia
- Cholesteryl Ester Transfer Protein Deficiency

Treatment of Hyperlipidemia

Treatment of Hyperlipidemia

- Diet
- Medication

*LDL cholesterol and triglycerides should be below 70 mg/dL (1.8 mmol/L) and 130 mg/dL (1.5 mmol/L), respectively, in patients with known atherosclerosis.

Dietary Factors in the Management of Lipoprotein Disorders

Restriction of Caloric Intake

- The secretion of VLDL by liver is greatly stimulated by caloric intake in excess of requirements for physical activity and basal metabolism.
- There is a positive correlation between serum levels of VLDL triglyceride and various measures of obesity.
- Most patients with hypertriglyceridemia—except those with lipoprotein lipase deficiency—are obese.
- As obese patients lose weight, VLDL stabilize at lower levels.

Dietary Factors in the Management of Lipoprotein Disorders

Restriction of Fat Intake

- In primary chylomicronemia, all types of fats must be restricted rigidly.
- 10-15% fall in cholesterol is achieved when individuals who have been consuming a typical North American diet restrict their intake of saturated fats to 8% of total calories.
- In the acute management of mixed lipemia with impending pancreatitis, elimination of dietary fat leads to a rapid decrease in triglycerides.

Dietary Factors in the Management of Lipoprotein Disorders

Restriction of Fat Intake

- Most saturated and trans fatty acids cause increased levels of LDL cholesterol by downregulating hepatic LDL receptors.
- Polyunsaturated fatty acids may reduce levels of HDL and are potentially carcinogenic.
- Monounsaturated fatty acids increase HDL but do not increase LDL. Moderate use of monounsaturated fats such as olive oil, oleic acid–rich safflower oil, or canola oil is indicated.

Dietary Factors in the Management of Lipoprotein Disorders

Reduction of Cholesterol Intake

- The amount of cholesterol in the diet affects serum cholesterol levels, but individual responses vary.
- Restriction of dietary cholesterol to less than 200 mg/d (5.2 mmol/d) in normal individuals can result in a decrease of up to 10-15% in serum cholesterol, primarily reflecting a decrease in LDL.

Dietary Factors in the Management of Lipoprotein Disorders

Marine Omega-3 Fatty Acids

- ligands for peroxisome proliferator–activated receptor alpha (PPARα).
- Substantial decreases in triglyceride levels can be induced in some patients with severe endogenous or mixed lipemia at doses of 3 to 4 g/d of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, combined. This should be given in divided doses with meals.

Dietary Factors in the Management of Lipoprotein Disorders

Role of Carbohydrate in Diet

- When a high-carbohydrate diet is consumed, hypertriglyceridemia often develops within 48 to 72 hours, and levels of triglycerides rise to a maximum in 1-5 weeks.
- In persons with type 2 diabetes, a high-carbohydrate diet tends to increase insulin resistance. Substitution of monounsaturated fats for the carbohydrate improves insulin resistance and lipoprotein levels.

Dietary Factors in the Management of Lipoprotein Disorders

Alcohol Ingestion

- Alcohol intake >> overproduction of VLDL, increased cholesterol synthesis, decreased conversion to bile acids
- A positive correlation has been found between alcohol intake and HDL cholesterol levels in some individuals. Because alcohol-induced changes in HDL appear primarily to involve the HDL3 subfraction, there is no justification for the use of alcohol to increase the protective effect of HDL against atherosclerosis.

Dietary Factors in the Management of Lipoprotein Disorders

Antioxidants

- Vitamin E have recognized roles in the elimination of free radicals. & Vitamin C assists this activity by restoring the tocopheroxyl radical to active tocopherol.

restore normal vascular reactivity in hyperlipidemic patients, antiatherogenic effect

- Selenium: a cofactor for one species of superoxide dismutase.
- Diets rich in fruits and vegetables appear to be important, providing isoflavones, quinols, and a number of carotenoid species.

Dietary Factors in the Management of Lipoprotein Disorders

The Universal Diet

- A normal BMI should be achieved and maintained.
- Fat <35% and saturated fat <7% of total calories
- Monounsaturated oils should predominate and be used for all high-temperature cooking.
- Cholesterol should be reduced to <200 mg/d.
- Complex carbohydrates should predominate among total carbohydrates.
- Intake of trans fatty acids should be avoided.
- Alcohol should be avoided in patients with hypertriglyceridemia or those requiring weight loss.
- Peroxidized fats resulting from protracted heating should be avoided.

Drugs Used in Treatment of Hyperlipoproteinemia

Caution Regarding Drug Therapy

- Women of childbearing age should be advised of the potential risk of teratogenicity of statins and possibly other hypolipidemic agents. Treatment should be given only if pregnancy is being actively avoided.
- Nursing mothers should not be treated.
- Estrogen-containing contraceptives should be avoided or used with caution in patients with hypertriglyceridemia.

Drugs Used in Treatment of Hyperlipoproteinemia

Caution Regarding Drug Therapy

- In children, hyperlipidemias other than FH and severe cases of the metabolic syndrome usually do not require medication before age 16 years.
- Factors in the decision to start drug treatment include: the child's age and levels of lipoproteins; the severity and age at onset of symptomatic coronary disease in the child's family; and the presence in the child of other risk factors, especially diabetes or compound dyslipidemias [including hypoalphalipoproteinemia, hyper-Lp(a)lipoproteinemia, FH, and FCH].
- Dietary treatment is indicated for all children with hyperlipidemia

Drugs Used in Treatment of Hyperlipoproteinemia

1. Bile Acid Sequestrants
2. Niacin (Nicotinic Acid)
3. Fibric Acid Derivatives
4. HMG-CoA Reductase Inhibitors
5. Cholesterol Absorption Inhibitors

Drugs Used in Treatment of Hyperlipoproteinemia

1. Bile Acid Sequestrants

- useful only in disorders involving elevated LDL

bind bile acids in the intestinal lumen and not absorbed

↓

increase the excretion of bile acids in the stool up to 10-fold

↓

increased expression of high-affinity receptors on hepatic cell membranes

↓

decreased LDL levels in plasma

Drugs Used in Treatment of Hyperlipoproteinemia

2. Niacin (Nicotinic Acid)

- inhibits secretion of VLDL
- increases sterol excretion acutely, mobilizes cholesterol from tissue pools until a new steady-state is established, and decreases cholesterol biosynthesis.
- HDL (particularly HDL2) are usually significantly increased, reflecting a decrease in their fractional catabolic rate.
- stimulates production of tissue plasminogen activator, an effect that may be of value in preventing thrombotic events
- Small, dense LDL are converted to particles of larger diameter during treatment.
- Niacin is the only available agent that can reduce levels of Lp(a) significantly

Drugs Used in Treatment of Hyperlipoproteinemia

3. Fibric Acid Derivatives

- Gemfibrozil and fenofibrate: ligands for PPARα
- decrease lipolysis in adipose tissue, reduce levels of circulating triglycerides, and cause modest reductions in LDL.
- moderate increases in levels of HDL

Drugs Used in Treatment of Hyperlipoproteinemia

4. HMG-CoA Reductase Inhibitors

- competitive inhibitors of HMG-CoA reductase, a key enzyme in the cholesterol biosynthetic pathway.

Inhibition of cholesterol biosynthesis

increase LDL receptors in the liver

increased removal of LDL from plasma

Decrease LDL production

Drugs Used in Treatment of Hyperlipoproteinemia

4. HMG-CoA Reductase Inhibitors

- Modest increases in HDL cholesterol
- limited decreases in VLDL levels can be achieved.
- enhanced stability of atherosclerotic lesions and decreased oxidative stress and vascular inflammation, with improved endothelial function.
- Institution of treatment with a reductase inhibitor should begin immediately in all patients with acute coronary syndromes regardless of cholesterol level.

Drugs Used in Treatment of Hyperlipoproteinemia

5. Cholesterol Absorption Inhibitors

- Ezetimibe, the first of this class, inhibits the absorption of cholesterol and phytosterols by enterocytes.
- By interrupting the enterohepatic circulation of sterols secreted in bile, it increases sterol elimination.
- No outcome studies with this agent as monotherapy have been reported.

Drugs Used in Treatment of Hyperlipoproteinemia

Combined Drug Therapy

Combinations of drugs may be useful

(1) when LDL and VLDL levels are both elevated

(2) in cases of hypercholesterolemia in which significant increases of VLDL occur during treatment with a bile acid–binding resin

(3) where a complementary effect is required to normalize LDL levels, as in familial hypercholesterolemia or familial combined hyperlipidemia

(4) when a hyperlipidemia is accompanied by primary HDL deficiency or an elevated level of Lp(a)

Reference

- Greenspan’s Basic & Clinical Endocrinology, 9e

Chapter 19. Disorders of Lipoprotein Metabolism by Mary J. Malloy, MD; John P. Kane, MD, PhD