Disorders of Lipid Metabolism
Lipid Metabolism

• Lipids are insoluble in water, for transport between the tissues in the aqueous blood plasma they are combined with amphipathic lipids and proteins to make water-miscible lipoproteins.
• Four major groups of lipoproteins are recognized:
  Chylomicrons transport lipids resulting from digestion and absorption. Derived from intestinal absorption of TG.
  Very low density lipoproteins (VLDL) : ( pre-β ) derived from liver for export of TG.
  Low-density lipoproteins (LDL) : ( β- lipoprotein ) synthesized in liver and deliver cholesterol to the tissues.
  High-density lipoproteins (HDL) ; ( α -lipoprotein ) synthesized in liver and intestine, remove cholesterol from the tissues in the process known as reverse cholesterol transport.
LIPOPROTEINS

• spherical particles with a hydrophobic core (TG and esterified cholesterol)

• apolipoproteins on the surface
  • large: apoB (B-48 and B-100) atherogenic
  • smaller: apoA-I, apoC-II, apoE

• classified on the basis of density and electrophoretic mobility (Chyl; VLDL; LDL; IDL; HDL)
The Apolipoproteins

• major components of lipoproteins, constitute the protein moiety of lipoproteins.
• often referred to as aproteins.
• classified by alphabetical designation (A thru E)
• the use of roman numeral suffix describes the order in which the apolipoprotein emerge from a chromatographic column.
• They act as enzyme activators (eg, apo C-II and apo A-I) or as ligands for cell receptors (eg, apo A-I, apo E, and apo B-100).
Lipoproteins

Micelle structures with apolipoproteins surrounding a lipid core
Core contains TG, phospholipid & cholesterol
## Classification of Lipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Function</th>
<th>Apolipoproteins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chylomicrons</strong></td>
<td>Large particles</td>
<td>A-I, II, IV</td>
</tr>
<tr>
<td></td>
<td>Carry lipid</td>
<td>B-48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C-I, II, III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E</td>
</tr>
<tr>
<td><strong>Very low density</strong></td>
<td>Carries endogenous TG</td>
<td>B-100</td>
</tr>
<tr>
<td>(VLDL)</td>
<td>and some cholesterol</td>
<td>C-I, II, III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E</td>
</tr>
<tr>
<td><strong>Intermediate density</strong></td>
<td>Carries cholesterol esters</td>
<td>B-100</td>
</tr>
<tr>
<td>(IDL)</td>
<td>and TG</td>
<td>C-III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E</td>
</tr>
<tr>
<td><strong>Low density</strong></td>
<td>Cholesterol esters</td>
<td>B-100</td>
</tr>
<tr>
<td>(LDL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High Density</strong></td>
<td>Cholesterol esters</td>
<td>A-I, II</td>
</tr>
<tr>
<td>(HDL)</td>
<td></td>
<td>C-I, II, III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D and E</td>
</tr>
<tr>
<td>Apolipoproteins</td>
<td>Major tissue sources</td>
<td>Functions</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Apo A-I</td>
<td>Liver and intestine</td>
<td>Co-factor LCAT</td>
</tr>
<tr>
<td>Apo A-II</td>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td>Apo A-IV</td>
<td></td>
<td>Activates LCAT</td>
</tr>
<tr>
<td>Apo B-48</td>
<td>Intestine</td>
<td>Secretion TG from intestine</td>
</tr>
<tr>
<td>Apo B-100</td>
<td>Liver</td>
<td>Secretion TG from liver; binding ligand to LDL receptor</td>
</tr>
<tr>
<td>Apo C-I</td>
<td>Liver</td>
<td>Activates LCAT; inhibits CETP</td>
</tr>
<tr>
<td>Apo C-II</td>
<td>Liver</td>
<td>Cofactor LPL</td>
</tr>
<tr>
<td>Apo C-III</td>
<td>Liver</td>
<td>Inhibits LPL</td>
</tr>
<tr>
<td>Apo D</td>
<td>Many sources</td>
<td>Reverse cholesterol transport</td>
</tr>
<tr>
<td>Apo E</td>
<td>Liver</td>
<td>Ligand for uptake of chylomicron remnants and IDL</td>
</tr>
</tbody>
</table>

*LCAT*, lecithin cholesterol acyl transferase; *TG*, triglyceride; *LDL*, low density lipoprotein; *CETP*, cholesteryl ester transfer protein; *LPL*, lipoprotein lipase; *IDL*, intermediate density lipoprotein
Lipoproteins

- Lipoproteins are important in diagnosis.
- They can be separated by electrophoresis, ultracentrifugation, and immunoelectrophoresis.

Electrophoretic mobility of plasma lipoproteins. The order of LDL and VLDL is reversed if ultracentrifugation is used as the separation technique.
LIPOPROTEINS

• A variety of factors can alter cholesterol and TG transport
  – Environmental
  – Genetic
  – Gender and age
  – Smoking habits
  – Body fat distribution
  – Diet
  – Medications
Lipid Metabolism

Two major pathways

The exogenous pathway of lipoprotein metabolism involves the absorption and transport of dietary lipids to appropriate sites within the body.

Nascent chylomicrons are secreted into the intestinal lymph and delivered through the thoracic duct directly to the systemic circulation, where they are extensively processed by peripheral tissues before reaching the liver.

The triglycerides of chylomicrons are hydrolyzed by LPL and free fatty acids (FFAs) are released; apoC-II, which is transferred to circulating chylomicrons from HDL, acts as a cofactor for LPL in this reaction.
The released FFAs are taken up by adjacent myocytes or adipocytes and either oxidized to generate energy or re-esterified and stored as triglyceride.

Some of the released FFAs bind albumin before entering cells, and are transported to other tissues, especially the liver.

The chylomicron particle progressively shrinks in size as the hydrophobic core is hydrolyzed and the hydrophilic lipids (cholesterol and phospholipids) and apolipoproteins on the particle surface are transferred to HDL, creating chylomicron remnants.

the chylomicron remnants are rapidly removed from the circulation by liver through a process that requires apoE as a ligand for receptors in the liver.
Metabolism of chylomicrons. CM = chylomicron; TAG = triacylglycerol; C = cholesterol; CE = cholesteryl esters. Apo B-48, apo C-II, and apo E are apolipoproteins found as specific components of plasma lipoproteins.
The exogenous pathway of lipoprotein metabolism involves the absorption and transport of dietary lipids to appropriate sites within the body.

The exogenous pathway: This pathway transports exogenous dietary fat from intestine to peripheral tissues as **chylomicron**.
The endogenous pathway of lipoprotein metabolism refers to the hepatic secretion of apoB-containing lipoproteins and their metabolism. VLDL particles resemble chylomicrons in protein composition but contain apoB-100 rather than apoB-48 and have a higher ratio of cholesterol to triglyceride. As with chylomicrons, the triglycerides of VLDL are hydrolyzed by LPL, especially in muscle and adipose tissue. After secretion into the plasma, VLDL acquires multiple copies of apoE and apolipoproteins of the C series by transfer from HDL. After the VLDL remnants dissociate from LPL, they are referred to as IDL, which contain roughly similar amounts of cholesterol and triglyceride. The liver removes approximately 40–60% of IDL by LDL receptor–mediated endocytosis via binding to apoE.
The remainder of IDL is remodeled by hepatic lipase (HL) to form LDL; during this process most of the triglyceride in the particle is hydrolyzed and all apolipoproteins except apoB-100 are transferred to other lipoproteins.

The cholesterol in LDL accounts for over half of the plasma cholesterol in most individuals.

Approximately 70% of circulating LDL is cleared by LDL receptor-mediated endocytosis in the liver.
Metabolism of VLDL and LDL. TAG = triacylglycerol; VLDL = very-low-density lipoprotein; LDL = low-density-lipoprotein; IDL = intermediate-density lipoprotein; C = cholesterol; CE = cholesteryl esters. Apo B-100, apo C-II, and apo E are apolipoproteins found as specific components of plasma lipoproteins.
The endogenous pathway: This pathway transports endogenous stored fat from liver to peripheral tissues as **VLDL**.
lipid Metabolism Summary

• Chylomicrons transport fats from the intestinal mucosa to the liver
• In the liver, the chylomicrons release triglycerides and some cholesterol and become low-density lipoproteins (LDL).
• LDL then carries fat and cholesterol to the body’s cells.
• High-density lipoproteins (HDL) carry fat and cholesterol back to the liver for excretion.
lipid Metabolism

• When oxidized LDL cholesterol gets high, atheroma formation in the walls of arteries occurs, which causes atherosclerosis.

• HDL cholesterol is able to go and remove cholesterol from the atheroma.

• Atherogenic cholesterol → LDL, VLDL, IDL
Levels of Plasma Lipids

• **LDL**
  - $< 100$ → Optimal
  - 100-129 → Near optimal
  - 130-159 → Borderline
  - 160-189 → High
  - $\geq 190$ → Very High

• **Total Cholesterol**
  - $< 200$ → Desirable
  - 200-239 → Borderline
  - $\geq 240$ → High

• **HDL**
  - $< 40$ → Low
  - $\geq 60$ → High

• **Serum Triglycerides**
  - $< 150$ → normal
  - 150-199 → Borderline
  - 200-499 → High
  - $\geq 500$ → Very High
Abnormalities in lipid metabolism

• Abnormalities of lipid metabolism occur at the sites of production or utilization of lipoproteins causing various hypo- or hyperlipoproteinemias.

• Other disorders affecting lipid transport are due to inherited defects in synthesis of apoprotein or lipoprotein receptors.
DYSLIPIDEMIA

Dyslipidemia (elevated blood lipid and lipoproteins [ ]s) has several forms:

• Hyperlipidemia: elevated blood TG & cholesterol
• Hypertriglycerideridemia: elevated TG only
• Hypercholesterolemia: only elevated blood cholesterol concentrations
• Hyperlipoproteinemia: elevated lipoprotein concentrations
Diorders of Lipoprprpteins

I  Hyperlipidemias:
1- Primary hyperlipidemias: in which the hyperlipidemia is the principal manifestation of the disease.
   It can be classified on the basis of plasma electrophoretic pattern after 12 hours fasting.
2- Secondary hyperlipidemias: in which the hyperlipidemia is result from another disease as in thyroid, liver or kidney diseases.

II  Hypolipidemias.
Causes for Hyperlipidemia

Secondary

- Obesity/diet
- Diabetes (IV, V)
- Alcohol (IV)
- Hypothyroidism (II, III)
- Estrogen therapy (IV)
- Glucocorticoids (IIa, IIb)
- Hypopituitarism (IIb)
- Acromegaly (IV)
- Anorexia Nervosa (IIa)
- Lipodystrophy (IV)
- Nephrotic syndrome (IIa, IIb)
- Hepatitis (IV)
- Systemic Lupus Erythematosus (I)
- Biliary obstruction or cholestasis (Lp)
- Acute intermittent porphyria (IIa)
- Glycogen storage disease (IV)
- Monoclonal gammopathy (IIa, III, IV)
Lipoprotein phenotypes of hyperlipidemia

<table>
<thead>
<tr>
<th>Lipoprotein phenotype</th>
<th>Elevated lipoprotein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Chylomicrons</td>
</tr>
<tr>
<td>Type IIa</td>
<td>LDL</td>
</tr>
<tr>
<td>Type IIb</td>
<td>LDL, VLDL</td>
</tr>
<tr>
<td>Type III</td>
<td>Cholesterol-enriched IDL</td>
</tr>
<tr>
<td>Type IV</td>
<td>VLDL</td>
</tr>
<tr>
<td>Type V</td>
<td>Chylomicrons, VLDL</td>
</tr>
</tbody>
</table>
## Classification of Hyperlipidemias

<table>
<thead>
<tr>
<th>Type</th>
<th>Predominant lipoprotein</th>
<th>Predominant lipid</th>
<th>Xanthoma</th>
<th>CHD risk</th>
<th>Pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chylomicrons</td>
<td>Triglycerides $&gt;1000$</td>
<td>Eruptive</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>IIa</td>
<td>LDL</td>
<td>Cholesterol $&gt;300$</td>
<td>Tendon; Xanthelasma</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>IIb</td>
<td>VLDL + LDL</td>
<td>TG and CH $&lt;1000 &gt;300$</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Remnants</td>
<td>TG and CH</td>
<td>Palmar and tuberous</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>CH</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Chylomicrons + VLDL</td>
<td>TG and CH $&gt;1000 &gt;300$</td>
<td>Eruptive</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
### Primary disorders of plasma lipoproteins (dyslipoproteinemias)

<table>
<thead>
<tr>
<th>Name</th>
<th>Defect</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypolipoproteinemias</strong>&lt;br&gt;Abetalipoproteinemia</td>
<td>No chylomicrons, VLDL, or LDL are formed because of defect in the loading of apo B with lipid.</td>
<td>Rare; blood acylglycerols low; intestine and liver accumulate acylglycerols. Intestinal malabsorption. Early death avoidable by administration of large doses of fat-soluble vitamins, particularly vitamin E.</td>
</tr>
<tr>
<td>Familial alpha-lipoprotein deficiency&lt;br&gt;Tangier disease&lt;br&gt;Fish-eye disease&lt;br&gt;Apo-A-I deficiencies</td>
<td>All have low or near absence of HDL.</td>
<td>Tendency toward hypertriacylglycerolemia as a result of absence of apo C-II, causing inactive LPL. Low LDL levels. Atherosclerosis in the elderly.</td>
</tr>
<tr>
<td><strong>Hyperlipoproteinemias</strong>&lt;br&gt;Familial lipoprotein lipase deficiency (type I)</td>
<td>Hypertriacylglycerolemia due to deficiency of LPL, abnormal LPL, or apo C-II deficiency causing inactive LPL.</td>
<td>Slow clearance of chylomicrons and VLDL. Low levels of LDL and HDL. No increased risk of coronary disease.</td>
</tr>
<tr>
<td>Familial hypercholesterolemia (type IIa)</td>
<td>Defective LDL receptors or mutation in ligand region of apo B-100.</td>
<td>Elevated LDL levels and hypercholesterolemia, resulting in atherosclerosis and coronary disease.</td>
</tr>
<tr>
<td>Familial type III hyperlipoproteinemia (broad beta disease, remnant removal disease, familial dysbetaproteinemia)</td>
<td>Deficiency in remnant clearance by the liver is due to abnormality in apo E. Patients lack isoforms E3 and E4 and have only E2, which does not react with the E receptor.</td>
<td>Increase in chylomicron and VLDL remnants of density &lt; 1.019 (β-VLDL). Causes hypercholesterolemia, xanthomas, and atherosclerosis.</td>
</tr>
<tr>
<td>Familial hypertriacylglycerolemia (type IV)</td>
<td>Overproduction of VLDL often associated with glucose intolerance and hyperinsulinemia.</td>
<td>Cholesterol levels rise with the VLDL concentration. LDL and HDL tend to be subnormal. This type of pattern is commonly associated with coronary heart disease, type II diabetes mellitus, obesity, alcoholism, and administration of gestational hormones.</td>
</tr>
<tr>
<td>Familial hyperalphalipoproteinemia</td>
<td>Increased concentrations of HDL.</td>
<td>A rare condition apparently beneficial to health and longevity.</td>
</tr>
<tr>
<td>Hepatic lipase deficiency</td>
<td>Deficiency of the enzyme leads to accumulation of large triacylglycerol-rich HDL and VLDL remnants.</td>
<td>Patients have xanthomas and coronary heart disease.</td>
</tr>
<tr>
<td>Familial lecithin:cholesterol acyltransferase (LCAT) deficiency</td>
<td>Absence of LCAT leads to block in reverse cholesterol transport. HDL remains as nascent disks incapable of taking up and esterifying cholesterol.</td>
<td>Plasma concentrations of cholesteryl esters and lyssolecithin are low. Present is an abnormal LDL fraction, lipoprotein X, found also in patients with cholestasis. VLDL is abnormal (β-VLDL).</td>
</tr>
<tr>
<td>Familial lipoprotein(a) excess</td>
<td>Lp(a) consists of 1 mol of LDL attached to 1 mol of apo(a). Apo(a) shows structural homologies to plasminogen.</td>
<td>Premature coronary heart disease due to atherosclerosis, plus thrombosis due to inhibition of fibrinolysis.</td>
</tr>
</tbody>
</table>
Disorders of Exogenous Lipoprotein Metabolism

Two disorders of exogenous lipoprotein metabolism are known. Both involve chylomicron removal.

**Lipoprotein Lipase Deficiency**

Patients present in the first several months of life with very marked hypertriglyceridemia, often ranging between 5,000 to 10,000 mg/dl. The plasma cholesterol level is usually 1/10 of the triglyceride level. Only the chylomicrons are elevated (type I phenotype) but occasionally the VLDL are also elevated (type V phenotype).

When chylomicrons are markedly increased, they can replace water (volume) in plasma, producing artifactual decreases in concentrations of plasma constituents; for example, for each 1,000 mg/dl increase of plasma triglyceride, serum sodium levels decrease between 2 and 4 meq/liter.
Lipoprotein Lipase
Role in Fatty Acid Transport

- Tg-rich lipoproteins: VLDL & Chylomicrons
- Free fatty acids
- Fatty acid albumin complexes
- Energy
- Tg storage
- Tg synthesis
Lipoprotein Lipase

Type I Hyperlipoproteinemia

LPL or apo CII deficiency
Lipoprotein Lipase deficiency

Clinical Phenotype

• Presents early in childhood
• Symptoms include
  – Colicky pain
  – Failure to thrive
  – Potentially lethal recurrent acute hemorrhagic pancreatitis
  – Eruptive xanthomata
  – Hepatosplenomegaly
Genetics

Familial LPL deficiency is a rare, autosomal recessive condition that affects about one in one million children.

Parents are often consanguineous.

Result from a variety of mutations in the LPL gene.
Diagnosis

1- Measurement of plasma TG after 12 hour fasting.
2- Detection of chylomicron band by electrophoresis.
3- Test for post-heparin lipolytic activity (PHLA).
LPL is attached to the surface of endothelial cells through a heparin-binding site. After the intravenous injection of heparin (60 units/kg), LPL is released and the activity of the enzyme is assessed in plasma drawn 45 min after the injection.
4- LPL released can also be assessed, using an ELISA assay.
Treatment

- Very low fat diet (10–15% of calories).
- Affected infants can be given Portagen, a soybean-based formula containing medium-chain triglycerides (MCT). MCT do not require the formation of chylomicrons for absorption, since they are directly transported from the intestine to the liver by the portal vein.
Apo C-II Deficiency

- Rare autosomal recessive disorder affecting apo C-II, the co-factor for LPL.
- Marked hypertriglyceridemia, patients have triglycerides levels ranging from 500 to 10,000 mg/dl.
- Apo C-II deficiency can be expressed in childhood but is often delayed into adulthood.
- The disorder is suspected by milky serum or plasma or by unexplained recurrent bouts of pancreatitis.
- Clinical symptoms as in LPL deficiency.
- A type V lipoprotein phenotype is often found (increased chy. and VLDL), but a type I pattern may also be present (increased chy.).
**Genetics**  Apo C-II deficiency is very rare autosomal disorder caused by a different number of mutations.

**Diagnosis**  by a PHLA test, and measuring apo C-II levels in plasma, using an ELISA assay. Apo C-II levels are very low to undetectable. The deficiency can be corrected by the addition of normal plasma to the in vitro assay for PHLA.

**Treatment**  is the same as for LPL deficiency. Infusion of normal plasma in vivo into an affected patient will decrease plasma triglycerides levels.
Disorders of Endogenous Lipoprotein Metabolism

These diseases comprise disorders of VLDL overproduction and of LDL removal.

**Disorders of VLDL Overproduction**
- Familial Hypertriglyceridemia
- Familial Combined Hyperlipidemia and the Small Dense LDL Syndromes
- Lysosomal Acid Lipase Deficiency: Wolman Disease and Cholesteryl Ester Storage Disease

**Disorders of LDL Removal**
- Familial Hypercholesterolemia (LDL Receptor Defect)
Familial Hypercholesterolemia
Type Ila
Familial Hypercholesterolemia

- Autosomal dominant disorder.
- Due to mutation in the gene encoding the LDL receptor.
- LDL receptor, a cell surface protein, is responsible for binding to LDL and delivering it to the cell interior.
- It is an example for protein receptor disorder.
- It is the most frequent mendelian disorder.
- Both homozygotes and heterozygotes develop premature heart disease as a result of Atheromas (deposits of LDL-derived cholesterol in coronary arteries), Xanthomas (cholesterol deposits in skin and tendons) and Arcus cornea (deposits of cholesterol round the periphery of cornea).
Heterozygous Familial Hypercholesterolemia (heFH)

- Autosomal dominant mode of inheritance
- Prevalence: 1 in 500 worldwide
- Total cholesterol: 270-500 mg/dL
- ~50% of men experience a cardiovascular event (CVE) by age 50 years
- Only 15% of men reach 65 years without experiencing a CVE
Homozygous Familial Hypercholesterolemia

- Total Cholesterol > 500 mg/dL
- Relatively normal TG
- Severe Defect in LDL receptor
- Occurs in about 1 in 1 million persons

- Tuberous or tendon xanthomas
- Symptoms of vascular disease before puberty
- Rarely survive beyond 2\textsuperscript{nd} decade of life
- Little or no response to drugs
- Respond to plasmapheresis and LDL-apheresis
Plasma cholesterol levels in normal and familial hypercholesterolemic individuals.

<table>
<thead>
<tr>
<th></th>
<th>Plasma cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>150-200 mg/dl</td>
</tr>
<tr>
<td><strong>FH Heterozygote</strong></td>
<td>250-500 mg/dl</td>
</tr>
<tr>
<td><strong>FH Homozygote</strong></td>
<td>600-1000 mg/dl</td>
</tr>
</tbody>
</table>
Familial Hypercholesterolemias
Physical examination

Lipoid arcus
Cholesterol uptake by the LDL receptor:

- Cholesterol is an essential lipid component of membranes and a precursor of steroid hormones and bile salts.
- Cells obtain cholesterol either by de-novo synthesis or by uptake from plasma through LDL receptors.
- Apoprotein B-100 in LDL receptor recognize LDL.
- The LDL receptor on the cell surface are localized to depressed regoins (coated pits) lined by the protein clathrin.
- Receptor bound LDL is brought into inside the cell by endocytosis, LDL is hydrolyzed in lysosomes and free cholesterol is released.
Representation of the LDL receptor

LDL molecule
• The increase in intracellular free cholesterol results in:

1- Reduced endogenous cholesterol formation by inhibition of enzyme hydroxy methylglutaryl Co A reductase; the rate limiting enzyme for cholesterol synthesis.

2- Activation of enzyme acyl Co :cholestrol acyltransferase (ACAT) to re-esterified the increased cholestrol for storage.

3- Reduced synthesis of the receptors.
Mutations on the LDL receptor

- About 900 different mutations have been identified and grouped into 5 classes.

Mutant alleles may:
1- Fail to produce LDL receptor proteins (null alleles).
2- Encode receptors blocked in intracellular transport between endoplasmic reticulum and Golgi, preventing the proper folding of the protein important for their transport (transport-defective alleles).
3- Produce proteins that cannot bind LDL normally (binding defective).
4- Those that bind LDL normally, but do not internalize LDL (internalization defects).
5- Those that disrupt the normal recycling of the LDL receptor back to the cell surface (recycling defects).
## Mutations in the LDL receptor

<table>
<thead>
<tr>
<th>Defect</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1 null alleles, synthesis</td>
<td>Most common defect, Receptor not synthesized in the ER</td>
</tr>
<tr>
<td>Class 2 , Transport</td>
<td>Receptor not transported to cell surface, accumulates inside cell</td>
</tr>
<tr>
<td>Class 3 , LDL Binding</td>
<td>Receptor on cell surface, can’t bind to apo B on LDL</td>
</tr>
<tr>
<td>Class 4 , Internalization</td>
<td>Receptor binds to apo B on LDL, can’t internalize LDL</td>
</tr>
<tr>
<td>Class 5 , Recycling</td>
<td>Receptor internalizes LDL, but isn’t recycled to cell surface</td>
</tr>
</tbody>
</table>
Diagnosis

• Measurement of plasma total cholesterol after 12 hour fasting.
• Detection of LDL (β- lipoprotein) band by electrophoresis.
• Direct DNA analysis of the molecular defect(s)
Treatment

• Treatment of FH includes a diet low in cholesterol and saturated fat that can be supplemented with plant sterols.

• **For heterozygotes:**
  1- By *diversion treatment* through administration of bile acid-binding resin as cholestyramin and colestipol which bind bile acids in the intestine and increase their fecal excretion, increasing the fraction of cholesterol that synthesized bile acids and the plasma cholesterol is decreased.
  2- **Inhibition treatment** by competitive inhibitor for the rate limiting enzyme of cholesterol synthesis (HMG Co A reductase) using drugs as lovastatin.

- **For homozygotes** by *depletion treatment*, by removal of plasma LDL through passage of plasma over columns that bind the protein component of LDL.