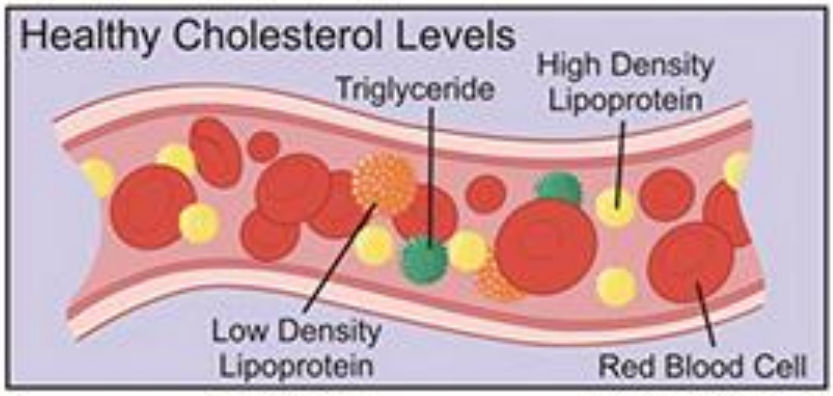
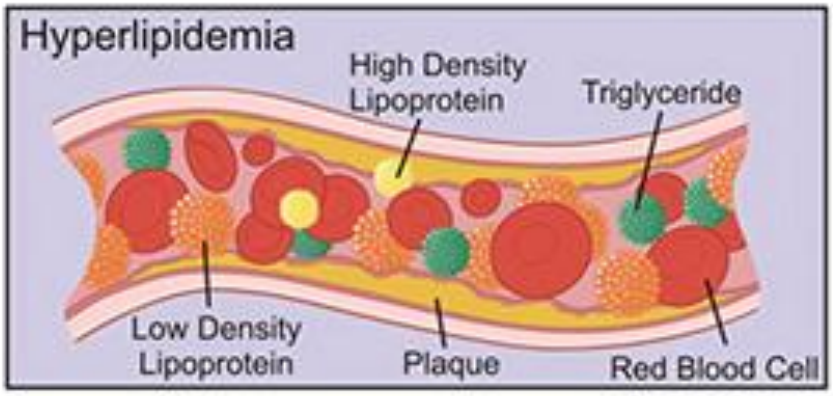
429 Medicine Team;





Dyslipidemia

By Dr. Anwar A. Jammah

Important If an MCQ-bearing point

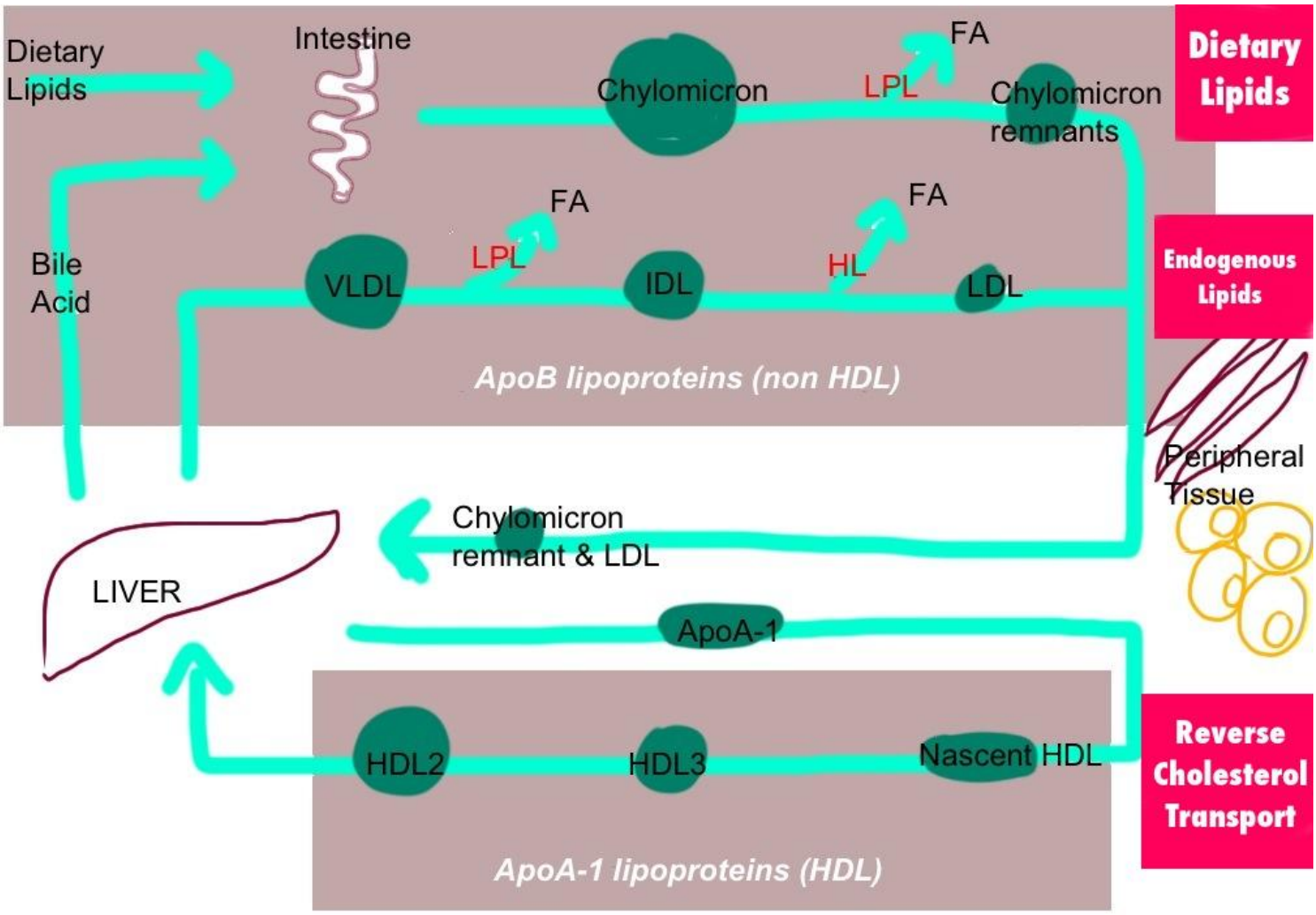
Sources include:

Davidson's Textbook of Medicine, Lecture Notes, physiology of lipoprotein metabolism video: http://www.youtube.com/watch?v=97uiV4RiSAY&feature=relmfu

Contents Page

"Lipoprotein metabolism has a key role in atherogenesis as it involves the transport of lipids, particularly cholesterol and triglycerides, in the blood"

Physiology of Lipid Metabolism and Transport



a) Dietary lipids Utilization Phase:

The dietary lipids are absorbed in the **intestines** after they undergo a process of lipolysis through different contributing factors (bile and pancreatic lipase) to formulate a mixed micelle (all lipid content in addition to fat-soluble vitamins ADEK). The enterocytes absorb the micelles and re-esterify the fatty acids into Triglyceride of which combines with the cholesterol ester, fat-soluble vitamins, phospholipids and apoproteins to form **chylomicrons** (large triglycerides-rich lipoproteins).

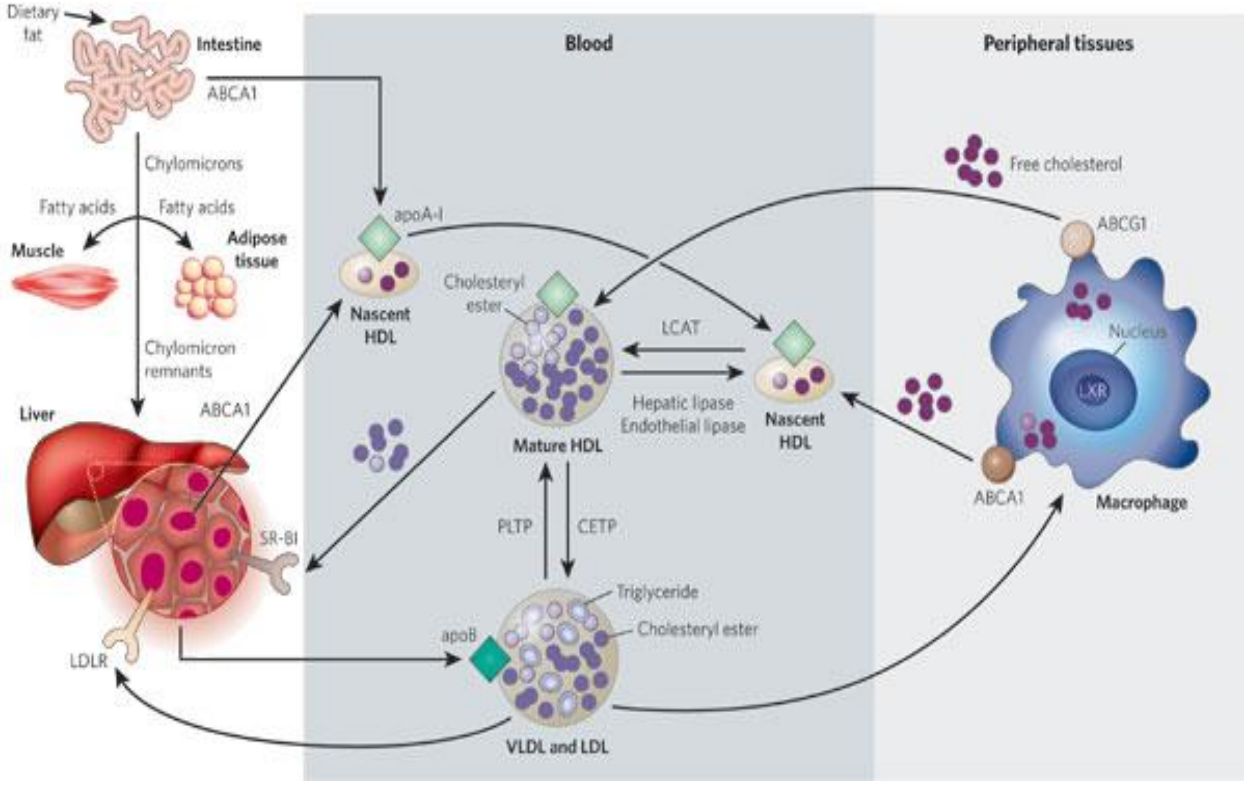
The Chylomicrons exit through lymphatics, passing the thoracic duct (do not pass to liver) and eventually, reaching the systemic circulation. At the peripheral tissue level; **Adipocytes** and **Muscle Tissue**, the enzyme ***lipoprotein lipase (LPL)*** breaks down chylomicrons into fatty acids that enter these tissues. The chylomicron remnants are subsequently taken up by the **liver** and cleared by LDLR (low density lipoprotein receptors).

b) Endogenous Lipids Utilization Phase:

When remnant Chylomicron reaches the liver, and in fasting state (6-10 hours after feeding), liver utilizes lipids by secretion of Very-Low Density Lipoproteins (VLDL; Triglycerides-rich lipoproteins, differ than chylomicrons with a different ApoB subtype) into the circulation and undergoes a similar metabolic process to that of the chylomicrons when the *LPL* hydrolyses it and releases Fatty Acids (FA) for peripheral tissue, and this converts the VLDL into Intermediate-Density Lipoprotein (IDL).

Furthermore, IDL is cleared by ***Hepatic Lipases (HL)*** and converted into Low-Density Lipoprotein (LDL; bad cholesterol) by removing more FAs. These lipoproteins are rich in cholesterol esters and are easily oxidized and ingested by Macrophages which might become a Foam Cell if too many LDL was ingested and so atheromas form.

c) Reverse Cholesterol Transport Phase:



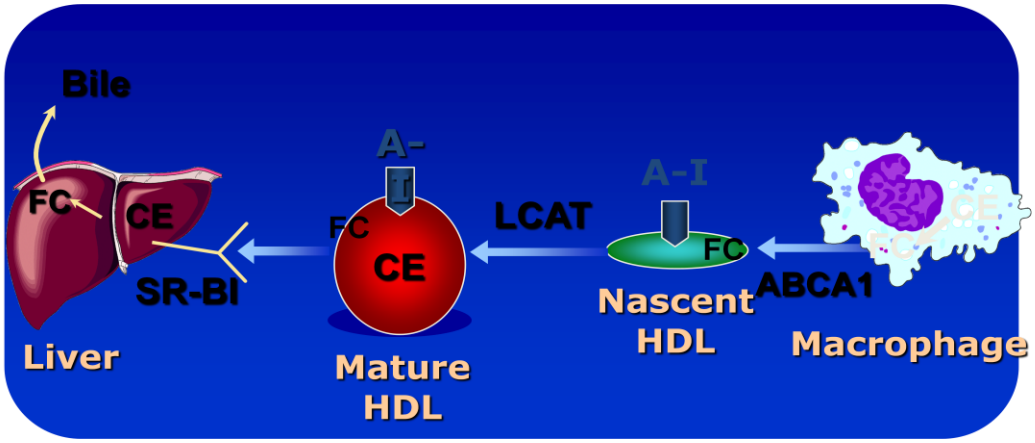
A Lipid-poor ApoA-1 lipoprotein (derived from liver, intestines, outer layer of chylomicrons and VLDL) protects peripheral tissue from excessive cholesterol accumulation. It's the precursor of the known High-Density Lipoprotein (HDL; good cholesterol) going through the following:

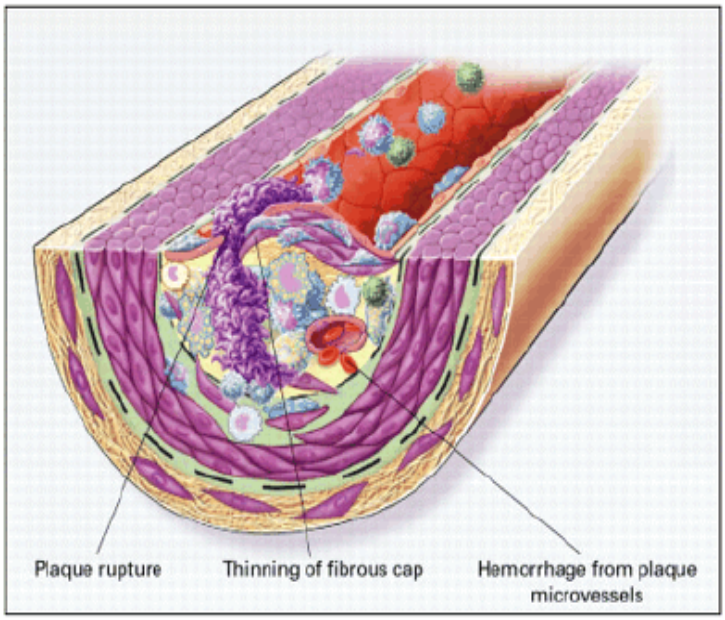
1- **The ApoA-1** (the lipid-free lipoprotein) attaches to the cell membrane at the peripheral tissues level and recruits the cholesterol through actions of a special membrane transporter; ABCA1 (ATP Binding Cassette A1 transporter).

2- After some cholesterol is obtained, **a nascent HDL** (small HDL) is formed, and this one is more able to accept cholesterol from cholesterol-rich regions via another membrane transporter called ABCG1.

3- When nascent HDL accepts further cholesterol, they are esterified into Cholesterol Ester via an enzyme called LCAT (Leicithin Cholesterol Acyl Transferase) and it becomes a **mature HDL (HDL3)** of which release their cholesterol content to liver and other requiring tissue through uptake by receptor SRB1 (Scavenger Receptor B1) (direct cholesterol return to liver).

4- The HDL3 can exchange their Cholesterol Ester components with the ApoB lipoproteins (VLDL, IDL and LDL) with the Triglycerides they are rich of, via its CTEB, and so it becomes **HDL2**. The lipid content of these HDLs is altered by the enzymes *hepatic lipase* and *endothelial lipase* and by the *transfer proteins CETP* and *phospholipid transfer protein (PLTP)*, affecting HDL catabolism.





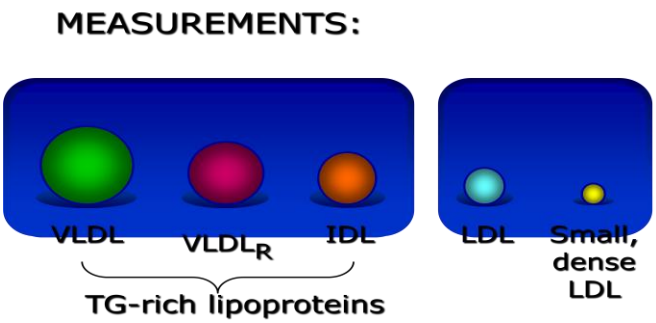
Long Story Short:

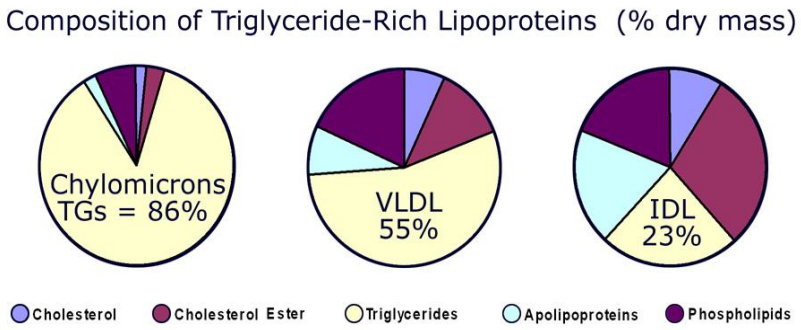
The **Lipoproteins** are two main types, **the ApoA-1** (HDL) and the **ApoB** (non HDL; VLDL, IDL and LDL) and their contents are the following:
VLDL: High TGs and low cholesterol ester (CE)
IDL: Moderate amounts of both TG and CE
LDL: Low TGs and high CE.
HDL: smallest lipoprotein, rich in CEs, but it collect the cholesterol from the body to the liver; anti-atherogenic (Good Cholesterol).
Chylomicrons: rich in TG with small amount of CE (high amount causes pancreatitis).

The bad cholesterol content in the body, carried by the ApoB lipoproteins (LDL, VLDL and IDL and especially dense LDL) is a precursor for atheromas formation while HDL reverses this process by ingesting the cholesterol and directing it into hepatic catabolism.

Atherogenecity

The danger lies in Triglycerides (TG) content of the lipoproteins. The richer the lipoprotein content, the higher the atherogenesis and so the greater the risk is for Heart Diseases when the coronary arteries acquire an atheroma.





Hyperlipidemias

(I) Hereditary Causes:

- **Familial Hyperlipidemia:**
  - A co-dominant genetic disorder, occurs in heterozygous forms (1 in 500 individuals)
  - The pathology lies due to a mutation in LDL receptor, resulting in elevated levels of LDL at birth and throughout life (LDL can't be shed out by the liver).
  - High LDL increases the risk for:
    1- Atherosclerosis (premature coronary disease → ischemia; IHD).
    2- Xanthomas: Tuberous, tendon and xanthelasmas of eyes (75% of the patients). *(Xanthomas is a deposition of yellowish cholesterol-rich material in tendons or other body parts in various disease states)*

Homozygous: is when two copies of the gene are affected (severe CVD), affects children at age of 15-16 yrs. A rare phenomena (1: million births)

Heterozygous: is when one copy is affected (pre-mature CVD), at age of 30-40 (1:5000).

- **Familial Combined Hyperlipidemia:**
  - Autosomal dominant genetic disorder (a rare disease)
  - Affects VLDL (increased secretions of VLDLs)

- **Dys-beta-lipoproteinemia**
  - Affects 1 in 10,000 (a rare disease)
  - Results in apo E2, a binding-defective form of apoE (which usually plays important role in catabolism of chylomicron and VLDL)
  - Increased risk for:
    1- Atherosclerosis
    2- Peripheral Vascular Disease
    3- Tuberous Xanthomas
    4- Striae Palmaris (deposits of cholesterol in the palmar creases).

Fredrickson Classification of the Hyperlipidemias *(for understanding only)*

Fredrickson phenotypes may be used to classify dyslipidemias on the basis of which lipoproteins are elevated. The Fredrickson classification system is not etiologic, does not distinguish between primary and secondary hyperlipidemias, and does not include HDL.

Fredrickson classification of hyperlipidemias (divided into primary and secondary)

Phenotype	Lipoprotein(s) elevated	Plasma cholesterol	Plasma TGs	Atherogenicity	Rel. freq.	Treatment
I	Chylomicrons	Norm. to ↑	↑↑↑↑	– pancreatitis	<1%	Diet control
IIa	LDL	↑↑	Norm.	+++	10%	Bile acid sequestrants, statins, niacin
IIb	LDL and VLDL	↑↑	↑↑	+++	40%	Statins, niacin, fibrates
III	IDL	↑↑	↑↑↑	+++	<1%	Fibrates
IV	VLDL	Norm. to ↑	↑↑	+	45%	Niacin, fibrates
V	VLDL and chylomicrons	↑ to ↑↑	↑↑↑↑	+ pancreatitis	5%	Niacin, fibrates

(II) Primary: Primary hypercholesterolemias

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
Familial hyper-cholesterolemia	LDL receptor	dominant	heteroz.:1/500 5% of MIs <60 yr homoz.: 1/1 million	premature CAD (ages 30–50) TC: 7–13 mM CAD before age 18 TC > 13 mM
Familial defective apo B–100	apo B–100	dominant	1/700	premature CAD TC: 7–13 mM
Polygenic hypercholesterolemia	multiple defects and mechanisms	variable	common 10% of MIs <60 yr	premature CAD TC: 6.5–9 mM
Familial hyper-alphalipoproteinemia	unknown	variable	rare	less CHD, longer life elevated HDL

Primary hypertriglyceridemias

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
LPL deficiency	endothelial LPL	recessive	rare 1/1 million	hepatosplenomegaly abd. cramps, pancreatitis TG: > 8.5 mM
Apo C–II deficiency	Apo C–II	recessive	rare 1/1 million	abd. cramps, pancreatitis TG: > 8.5 mM
Familial hyper-triglyceridemia	unknown enhanced hepatic TG-production	dominant	1/100	abd. cramps, pancreatitis TG: 2.3–6 mM

Primary mixed hyperlipidemias

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
Familial dysbeta-lipoproteinemia	Apo E high VLDL, chylo.	recessive rarely dominant	1/5000	premature CAD TC: 6.5 –13 mM TG: 2.8 – 5.6 mM
Familial combined	unknown high Apo B–100	dominant	1/50 – 1/100 15% of MIs <60 yr	premature CAD TC: 6.5 –13 mM TG: 2.8 – 8.5 mM

(III) Secondary

Secondary hyperlipidemias

Disorder	VLDL	LDL	HDL	Mechanism
Diabetes mellitus	↑ ↑ ↑	↑	↓	VLDL production ↑, LPL ↓, altered LDL
Hypothyroidism	↑	↑ ↑ ↑	↓	LDL-rec.↓, LPL ↓
Obesity	↑ ↑	↑	↓	VLDL production ↑
Anorexia	–	↑ ↑	–	bile secretion ↓, LDL catab. ↓
Nephrotic sy	↑ ↑	↑ ↑ ↑	↓	Apo B-100 ↑ LPL ↓ LDL-rec. ↓
Uremia, dialysis	↑ ↑ ↑	–	↓	LPL ↓, HTGL ↓ (inhibitors ↑)
Pregnancy	↑ ↑	↑ ↑	↑	oestrogen ↑ VLDL production ↑, LPL ↓
Biliary obstruction PBC	–	–	↓	Lp-X ↑ ↑ no CAD; xanthomas
Alcohol	↑ ↑ chylomicr. ↑	–	↑	dep. on dose, diet, genetics

Dietary Cholesterol:

Type of Fat	Main Source	Effect on Cholesterol levels
Monounsaturated (Healthiest)	Olives, olive oil, canola oil, peanut oil, cashews, almonds, peanuts and most other nuts; avocados	Lowers LDL, Raises HDL
Polyunsaturated	Corn, soybean, safflower and cottonseed oil; fish	Lowers LDL, Raises HDL
Saturated	Whole milk, butter, cheese, and ice cream; red meat; chocolate; coconuts, coconut milk, coconut oil , egg yolks, chicken skin	Raises both LDL and HDL
Trans (Dangerous Types)	Most margarines; vegetable shortening; partially hydrogenated vegetable oil; deep-fried chips; many fast foods; most commercial baked goods	Raises LDL

Causes of Hyperlipidemia:

- Diet and Obesity
- Hypothyroidism
- Obstructive Liver Disease and Acute Hepatitis
- Diabetes Mellitus
- SLE
- AIDs (Due to Protease Inhibitors' therapy)
- Pregnancy (a result of the metabolic adaptation of the maternal organism to pregnancy allowing to save glucose and energy for the fetus)
- Nephrotic Syndrome (due to the continuous loss of proteins, including the apolipoproteins, and this results in decreased lipids catabolism)
- Anorexia Nervosa

Checking Lipids Contents

- **Non-Fasting Lipid Content**
  Measures HDL and Total-Cholesterol only.

- **Fasting Lipid Content:** (fast for 12hours – water is ok)
  Measures HDL, Total-Cholesterol and Triglycerides, and the LDL is calculated as the following: LDL = Total-Cholesterol – [HDL + TG]

When Do We Check Lipids Content?

So many studies had been published on this regard, each suggests a different age group, but their conclusion is as the following:

- In High-Risk (has DM, HTN or a history of Hyperlipidemia); check at age of 20
- No risk; check ay age of 45

When to Check Lipid-Panel: *Different Recommendations:*

- Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP)
  - Beginning at age 20: obtain a fasting (9 to 12 hour) serum lipid profile consisting of total cholesterol, LDL, HDL and triglycerides
  - Repeat testing every 5 years for acceptable values
- United States Preventative Services Task Force
  - Women aged 45 years and older, and men ages 35 years and older undergo screening with a total and HDL cholesterol every 5 years.
  - If total cholesterol > 200 or HDL <40, then a fasting panel should be obtained
  - Cholesterol screening should begin at 20 years in patients with a history of multiple cardiovascular risk factors, diabetes, or family history of either elevated cholesteral levels or premature cardiovascular disease.

Management of Hyperlipidemia

Treatment Targets:

- **LDL** → to prevent CHD outcomes (myocardial infarction and coronary death).
- **Non-LDL (TG and HDL)** → to prevent CHD outcomes (myocardial infarction and coronary death).
- **TGs** → To prevent pancreatitis, and incase, coronary heart disease outcomes (myocardial infarction and coronary death)

Guidelines for Risk-Assessment and Treatments:

- **Framingham Heart Study; established a risk-assessment tool for Estimating a 10-year Risk of Developing CHD (Myocardial Infarction and Coronary Death) based on the following risk factors:**

1- Age
2- LDL cholesterol
3- Total Cholesterol
4- HDL cholesterol
5- Blood Pressure
6- Diabetes
7- Smoking

Adult Treatment Panel III Guidelines for Treatment of Hyperlipidemia:

Risk Category	Begin Lifestyle Changes If:	Consider Drug Therapy If:	LDL Goal
High: CAD or CAD equivalents (10-yr risk > 20%)	LDL ≥ 2.58 mM	LDL ≥ 2.58 mM (the drug is optional if < 2.58 mM)	< 2.58 mM; < 1.8 mM optional
Moderate high: ≥ 2 risk factors with 10-yr risk 10 to 20%*	LDL ≥ 3.36 mM	LDL ≥ 3.36 mM	< 3.36 mM; < 2.58 mM optional
Moderate: ≥ 2 risk factors with 10-yr risk < 10%*	LDL ≥ 3.36 mM	LDL ≥ 4.13 mM	< 3.36 mM; < 2.58 mM optional
Lower: 0-1 risk factor	LDL ≥ 4.13 mM	LDL ≥ 4.91 mM (the drug is optional if 4.13-4.88 mM)	< 4.13 mM

The New Canadian Guideline

Risk categories

Risk level	10-year CAD risk	Recommendations
High	≥20%	*Treatment targets:* Primary target: LDL-C <2.0 mmol/L Secondary target: TC/HDL-C <4.0
Moderate	10% - 19%	*Treat when:* LDL-C ≥3.5 mmol/L *or* TC/HDL-C ≥5.0
Low	<10%	*Treat when:* LDL-C ≥5.0 mmol/L *or* TC/HDL-C ≥6.0

High risk includes coronary artery disease (CAD), peripheral artery disease, cerebrovascular disease and most patients with diabetes.

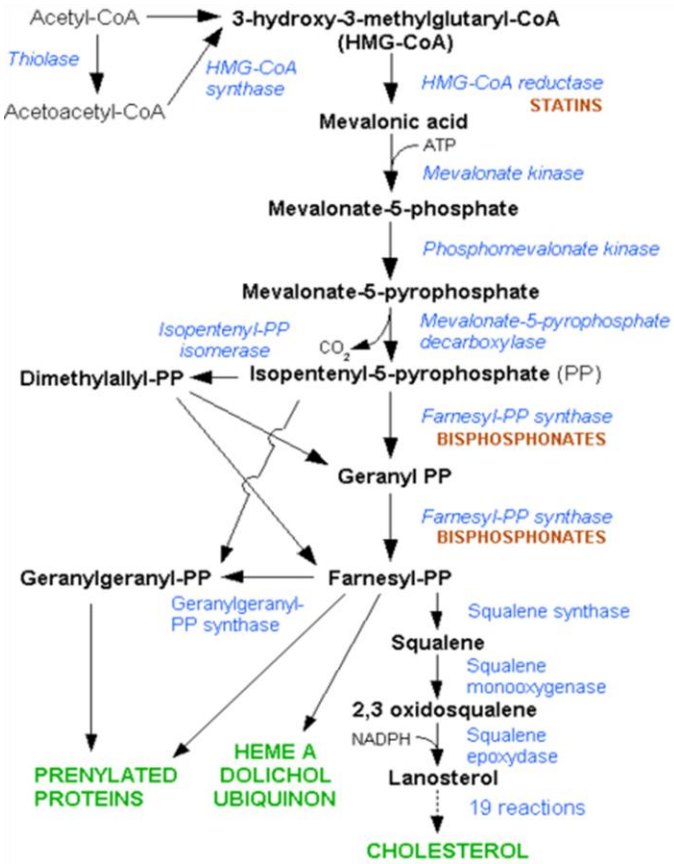
Therapeutic Approaches:

- **Lifestyle Modification:**
  - Low Cholesterol Diet
  - Exercise

- **Medical Therapy:**
  - HMG CoA Reductase inhibitos
  - Cholesterol absorption inhibitor
  - Nicotinic Acid
  - Fibric Acid
  - Bile Acid Sequestrants

Pharmaceulticals Table:

Drug Class	Agents	Effects (% change)	Side Effects
HMG CoA reductase inhibitors	Statins	↓LDL (18-55), ↑HDL (5-15) ↓ Triglycerides (7-30)	Myopathy, Increased LFT
Cholesterol absorption inhibitor	Ezetimibe	↓ LDL(14-18), ↑HDL (1-3) ↓Triglyceride (2)	Headache, GI distress
Nicotinic Acid		↓LDL (15-30), ↑HDL (15-35) ↓ Triglyceride (20-50)	Flushing, Hyperglycemia, Hyperuricemia, GI distress, hepatotoxicity
Fibric Acids	Gemfibrozil Fenofibrate	↓LDL (5-20), ↑HDL (10-20) ↓Triglyceride (20-50)	Dyspepsia, gallstones, myopathy
Bile Acid sequestrants	Cholestyramine	↓ LDL ↑ HDL No change in triglycerides	GI distress, constipation, decreased absorption of other drugs

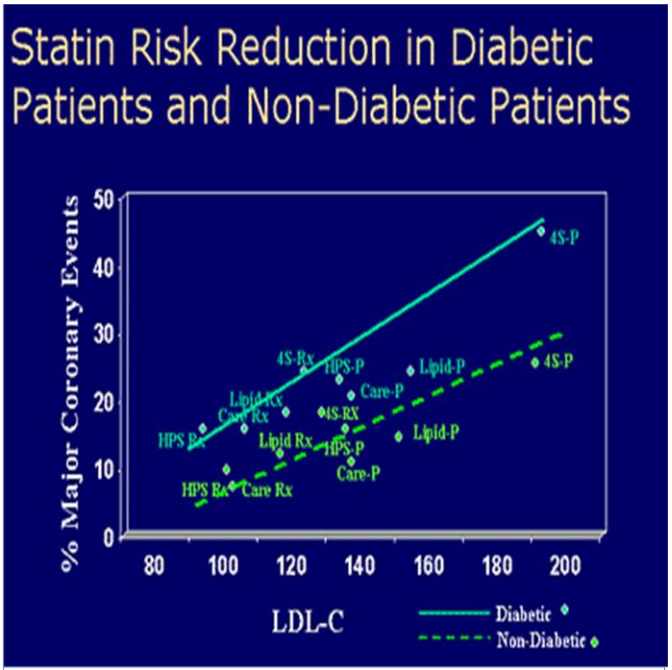


Mode of Action of Statins:

The action is *"HMG-CoA reductase" inhibitor "* that will decrease the cholesterol level in the Hepatic cells

→ LDL will be attracted to the Liver to be degraded (it produces cholesterol)

→end result: decreased cholesterol and LDL



This meta-regression analysis found that nonstatin (diet, bile acid sequestrants, and ileal bypass surgery) and statin interventions seemed to reduce CHD risk, consistent with a 1-to-1 relationship described by the National Cholesterol Education Program (NCEP).

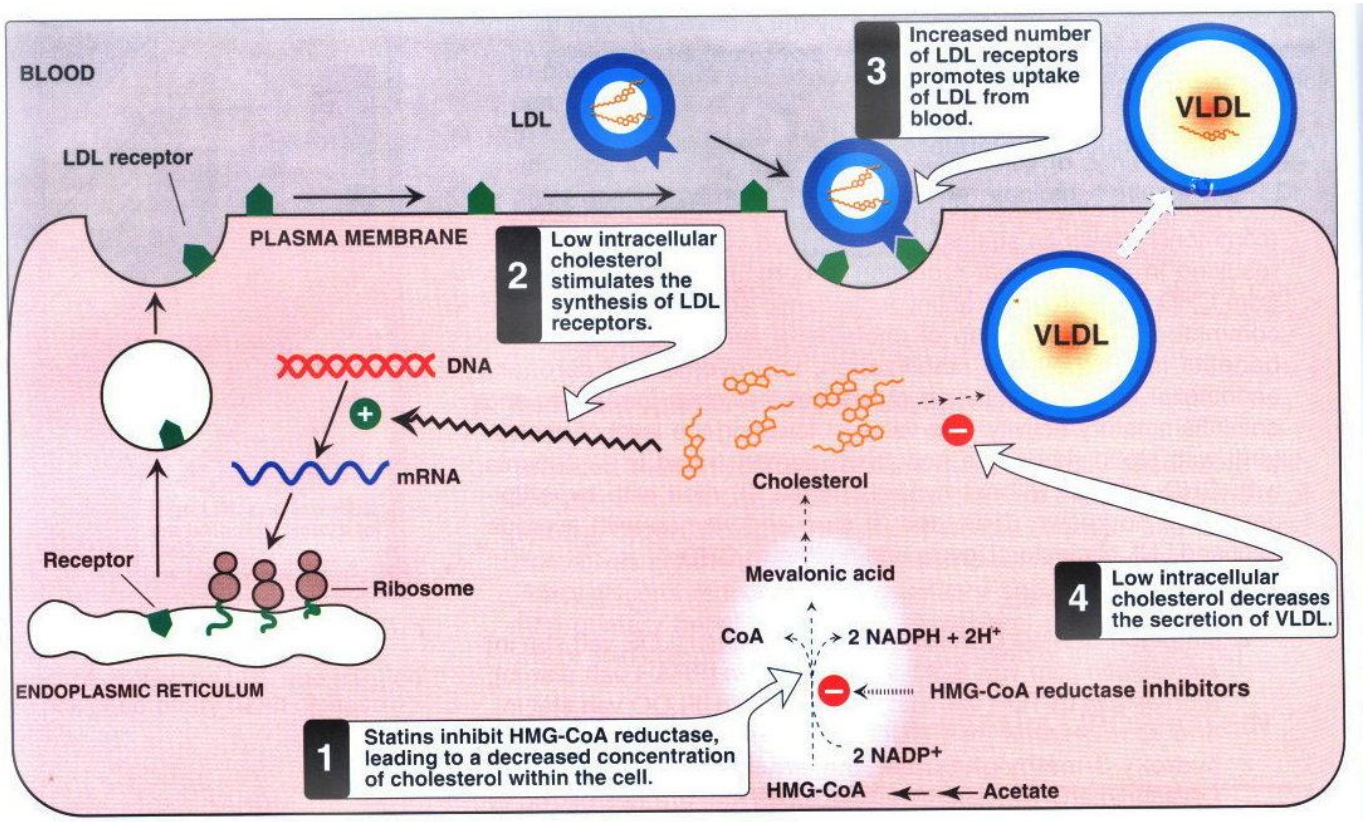


Figure 21.5
Inhibition of HMG-CoA reductase by the statin drugs.

Management with High Triglycerides (TG):

High TG increases the risk of:

1- IHD (>2mmol/L) **2-** Pancreatitis (>5mmol/L)

A management plan should be according to the following

- **TGs should be in normal levels (normal range is 0.5-1.9mmol/L), and if it remained lesser than 2mmol, we should continue whatever level of management the patient is on (if other lipids are high ..etc) and keep up a regular check up to ensure that it's still in range.**
- **If the TGs level is higher than 2 and lesser than 5 (2-5), three steps should be initiated:**
    1- Changing Lifestyle (weight loss, healthy lipid-less food and physical activity)
    2- Managing secondary factors (that might contribute to high lipid results) as some medications or glycemic control
    3- Pharmacological treatments initiation; LDL-lowering agents, fish-oil and niacin
- **When the TGs level is 5-10:**
    1- Make sure all the three previous steps are strictly followed (if TG is higher than 5, LDL-C can't be estimated by fasting-lipid content but by apoB levels)
    2- Start considering **Fibrate** Therapy; benzofibrate, fenofibrate and gemifibrozil.
- **When the TGs level is higher than 10:**
    1. Intensify the 1st three steps further more as this often presents with **Pancreatitis**. Fatty-diet should be severly lowered in addition to alcohol cessation, insulin for glycemic control and hospital admission to give IV-fluid (NPO).
    2. **Fibrate** therapy should be initiated
    3. Consider a specialist referral

[TG], mmol/L	Step	Action and comments	Retest interval, mo*
< 2		Continue current management • Reassess lipid profile regularly, to ensure that [LDL-C] is at target	6-12
≥ 2, < 5	1.	Therapeutic lifestyle measures • Weight control • Reduce dietary fat, simple sugars • Reduce alcohol intake • Increase physical activity Reassess lipid profile regularly, to ensure that [LDL-C] is at target	3-6
	2.	Manage other secondary factors • Control glycemia, if diabetic • Reassess medications; consider lipid-neutral alternatives	
	3.	Consider pharmacologic treatment • Intensify LDL-lowering (e.g., statin therapy) • Fish oil (omega-3 fatty acid) • Niacin (e.g., extended release)	
≥ 5, < 10	4.	Intensify steps 1-3, above • [LDL-C] cannot be estimated when [triglycerides] > 5 mmol/L • Apolipoprotein B determination might be helpful	2-3
	5.	Consider fibrate therapy, e.g., • Bezafibrate (Bezalip) 400 mg/d • Fenofibrate — Lipidil micro 200 mg/d — Lipidil supra 160 mg/d — Lipidil EZ 145 mg/d • Gemfibrozil (Lopid) 600-1200 mg/d	
≥ 10	6.	Further intensify steps 1-3 With acute pancreatitis: • Very-low-fat diet (10%-15% of energy intake) • Cessation of alcohol • Insulin, if indicated for glycemic control • Admit patient to hospital — Nothing by mouth: IV fluid replacement — Plasma exchange is unhelpful	1-2
	7.	Initiate fibrate therapy • Monitor serum [creatinine]	
	8.	Consider specialist referral