Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

Hyperlipidemia

Objectives :

No objectives were found

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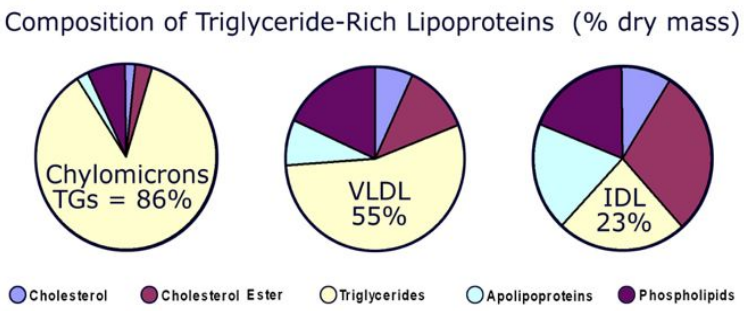
Books: Kumar + Step Up

Introduction.

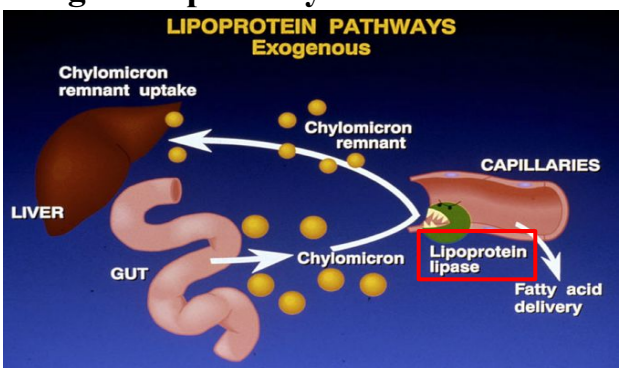
Lipids are insoluble in water, and are transported in the bloodstream as lipoprotein particles composed of:

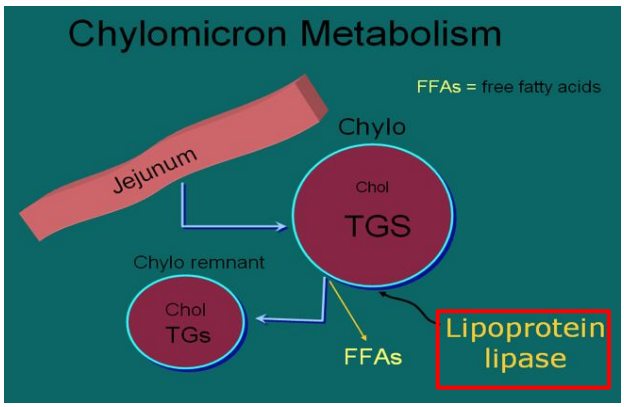
- **Lipids**
  - Mainly triglycerides, cholesterol and cholesterol esters
  - surrounded by a coat of phospholipids.
- **Proteins**
  - Called apo- proteins
  - embedded into the phospholipid coating exert a stabilizing function and allow the particles to be recognized by receptors in the liver and peripheral tissues.



Lipoprotein Pathway

Exogenous pathway: Source is diet





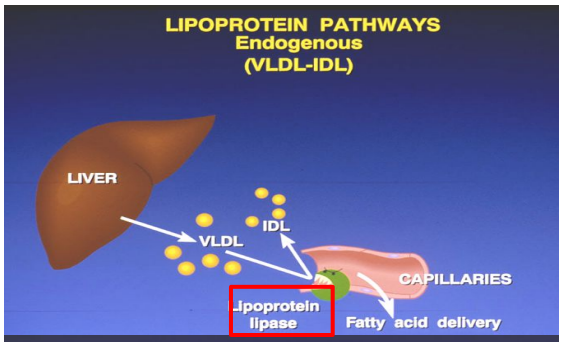
Chylomicrons transport fats from the intestinal mucosa to the liver, in the liver chylomicrons release triglycerides and some cholesterol and become low density lipoproteins (LDL).

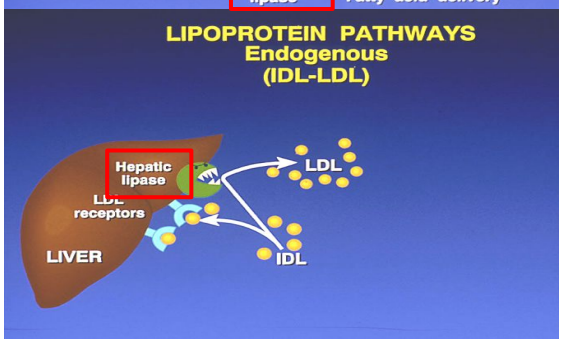
Chylomicron synthesized in the gut postprandially
> gets metabolized by **Lipoprotein Lipase**
> releases fatty acids from the chylomicrons into the vessels,
now Chylomicron remnant goes back to the Liver.

In case of **Lipoprotein lipase deficiency** >
↑↑ Chylomicrons in the blood >
↑↑ TGs > Pancreatitis

Cholesterol **percentage** is higher in Chylomicron remnant.

Endogenous pathway: Source is the liver





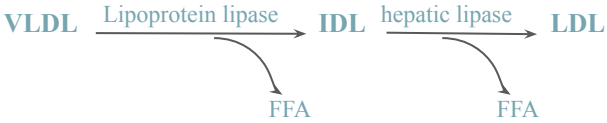
In the liver, **VLDL** released <u>to</u> blood stream to form LDL, IDL and LDL

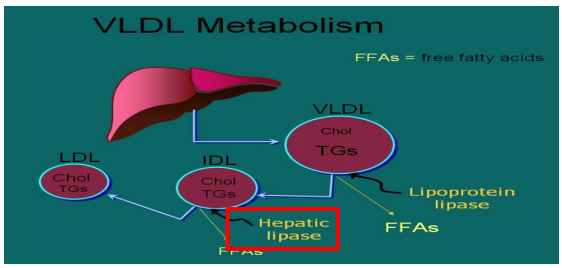
<u>VLDL</u> is released from the liver which transports endogenously synthesized TGs,

> broken down by **Lipoprotein lipase** to <u>ILD</u>, releasing FFA to the vessels in the process.

> The resulting <u>IDL</u> particles are either:

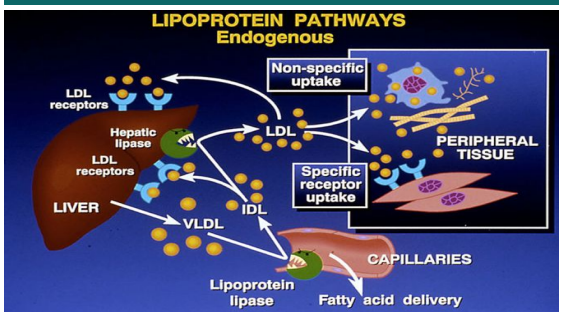
- Taken up in the liver by LDL receptors. Or
- Further metabolized by **Hepatic lipase** to <u>LDL</u> for transporting cholesterol to the peripheral tissues,





IDL: Cholesterol **percentage** is equal to TGs%

LDL: Cholesterol**%** > TGs**%**



LDL carries fat and cholesterol from the liver <u>to</u> the body's cells. LDL receptors in Liver take the LDL to Liver.

LDL uptake either:

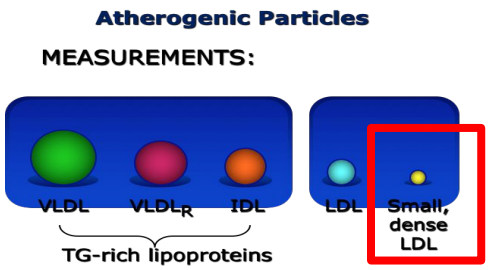
- To the liver via LDL receptors
- To the tissues
  - Two types of tissues :
    1. **Need specific receptors for LDL uptake**
       a. E.g. muscles.
    2. **Don't need receptors**
       a. Adrenal gland,
       b. Brain tissue
       c. Nerves

When <u>oxidized LDL **cholesterol**</u> gets high, atheroma formation in the walls of arteries occurs, which **causes atherosclerosis**. We worry about Cholesterol bc of atheroma, which leads to IHD.

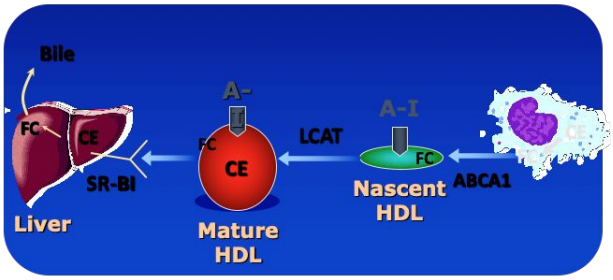
Atherogenic cholesterol → LDL, VLDL, IDL

<u>Small dense LDL</u> is the **most atherogenic**:

- High cholesterol concentration
- Very small size which makes it easier to go through blood vessels walls and accumulate



HDL and Reverse Cholesterol Transport



High-density lipoproteins (HDL) released from intestine and liver and carry fat and cholesterol **<u>from</u> blood vessels <u>to</u> the liver for excretion**.

HDL actually contain more cholesterol concentration than LDL but what makes it the better is its **<u>direction</u>** towards the liver

HDL is able to go and remove cholesterol from the atheroma. "Anti-atherogenic"

Extremely important note!!

HDL itself is not actually the good guy because its **already full** of cholesterol, unlike **<u>Nascent HDL</u>** **<u>"التاكسي الفاضي"</u>** which has room to go and collect cholesterol from blood vessels to the liver.

Tip: when studying tables in this lecture focus on what's red

Plasma lipoproteins

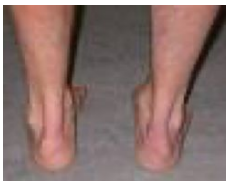
- ↑↑ TGs: causes pancreatitis
- ↑↑ Cholesterol: causes Atherosclerosis

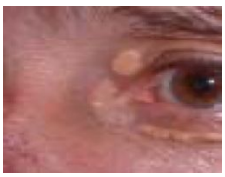
type	Source	Major lipid	Apoproteins	ELFO	Atherogenicity
Chylomicron	Gut	Dietary TGs	A-I, B-48, C-I, C-III, E	no mobility	No (pancreatitis)
VLDL	Liver	Endogenous TGs	B-100, E, C-II, C-III,	Pre-β	+
IDL	VLDL remnant	Ch esters, TGs	B-100, C-III, E	Slow pre- β	+
LDL	VLDL, IDL	Ch esters	B-100	β	+++
HDL	Gut, liver	Ch esters, PLs	A-I, A-II, C-II, C-III, D, E	α	anti-atherogenic

Hereditary causes of hyperlipidemia

- Familial Hypercholesterolemia
  - Mutation in LDL receptor, LDL will not be taken up by the liver resulting in elevated levels of LDL at birth and throughout life
  - **Heterozygous:**
    - Dominant genetic disorder, needs only one allele
    - Occurs in 1 in 500 individuals
    - High risk for atherosclerosis, tendon xanthomas especially in the extensors of the fingers + achilles tendon.(75% of patients), tuberous xanthomas and xanthelasmas of eyes.
    - Develop CADs in their 40's
  - **Homozygous:**
    - Total absence of LDL receptors
    - Cholesterol levels > 16 mmol/L
    - Die in their teens from CADs

Physical findings





- Familial Combined Hyperlipidemia the doctor skipped it
  - Autosomal dominant
  - Increased secretions of VLDLs
- Dysbetalipoproteinemia the doctor skipped it
  - Affects 1 in 10,000
  - Results in apo E2, a binding-defective form of apoE (which usually plays important role in metabolism of chylomicron and VLDL)
  - Increased risk for atherosclerosis, peripheral vascular disease
  - Tuberous xanthomas, striae palmaris

Primary hypercholesterolemia

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
Familial hypercholesterolemia	LDL receptor	dominant	hetero.: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** Coenzyme that helps LDL receptors	dominant	1/700	Same as heterozygous familial hypercholesterolemia premature CAD TC: 7-13 mM

Primary hypertriglyceridemia

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
Familial hypertriglyceridemia	unknown enhanced hepatic TG-production	dominant	1/100	abd. cramps, pancreatitis Or retinal vein thrombosis TG: 2.3-6 mM

Causes of secondary hyperlipidemia

- Diet
- Hypothyroidism affects hepatic lipase
- Nephrotic syndrome
- Anorexia nervosa
- Obstructive liver disease
- Obesity
- Diabetes mellitus Down regulation of lipoprotein lipase
- Pregnancy
- Acute hepatitis
- Systemic lupus erythematosus
- AIDS (protease inhibitors)

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 Everything will go up	↑↑	↑↑	↑	oestrogen ↑ VLDL production ↑, LPL ↓
Biliary obstruction PBC	-	-	↓	Lp-X ↑↑ no CAD; xanthomas
Alcohol	↑↑↑ chylomicron. Risk of pancreatitis	-	↑	dep. on dose, diet, genetics

When to check lipid panel

Different Recommendations but always remember when a patient has a family history or with high risk you need to check them as soon and as often as possible.

- 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 preventive 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 cholesterol levels or premature cardiovascular disease.

Treatment of hyperlipidemia

1- Lifestyle modification, Low-cholesterol diet, Exercise, Alcohol and Smoking cessation.
2- Medication

Goal of treatment:

- LDL: To prevent coronary heart disease outcomes (myocardial infarction and coronary death)
- Non LDL(TC/HDL): To prevent coronary heart disease outcomes (myocardial infarction and coronary death)
- Triglyceride: To prevent pancreatitis and may be coronary heart disease outcomes (myocardial infarction and coronary death)

Drug Class	***Agents***	***Effects (% change)***	***Side Effects***
HMG CoA reductase inhibitors*	Statins	LDL (18-55), HDL (5-15) Triglycerides (7-30)	Myopathy, increased liver enzymes
Fibric Acids	Gemfibrozil Fenofibrate	LDL (5-20), HDL (10-20) Triglyceride (20-50)	Dyspepsia, gallstones, myopathy
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
Bile Acid sequestrants	Cholestyramine	LDL, HDL No change in triglycerides	GI distress, constipation, decreased absorption of other drugs
PCSK9	Evolocumab Alirocumab	LDL (50-60%)	injection-site reactions, muscle pain, neurocognitive adverse events. These included memory impairment and confusion

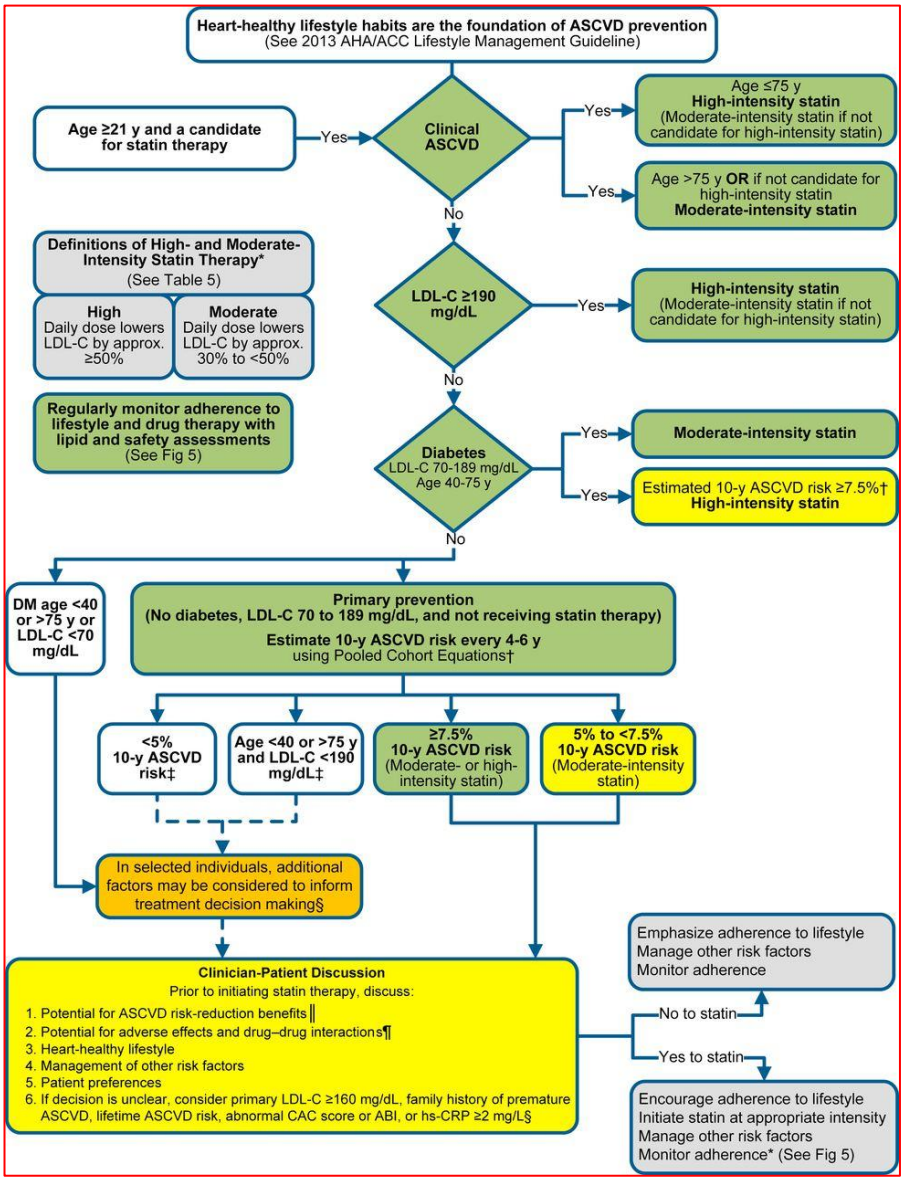
*Statins inhibits HMG-CoA reductase in the **hepatocytes** > ↓↓ Cholesterol concentration in the liver > Up regulation of LDL receptors on the surface of the liver > more cholesterol uptake to the liver for excretion.

Statins:

We use same drugs but in different doses to change intensity

Low-Intensity Statin Therapy	**Moderate-Intensity Statin Therapy**	**High-Intensity Statin Therapy**
Daily dose lowers LDL-C, on average, by <30% • Simvastatin 10 mg • Pravastatin 10–20 mg • Lovastatin 20 mg • Fluvastatin 20–40 mg • Pitavastatin 1 mg	Daily dose lowers LDL-C, on average, by approximately 30% to <50% • Atorvastatin 10 (20) mg • Rosuvastatin (5) 10 mg • Simvastatin 20–40 mg‡ • Pravastatin 40 (80) mg • Lovastatin 40 mg • Fluvastatin XL 80 mg • Fluvastatin 40 mg BID • Pitavastatin 2–4 mg	Daily dose lowers LDL-C, on average by approximately ≥50% • Atorvastatin (40†)–80 mg • Rosuvastatin 20 (40) mg

Treating Hypercholesterolemia :



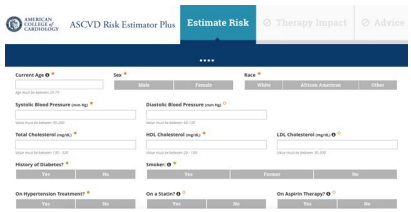
IMPORTANT

What you need to do:
1- Lifestyle modification.
2- Does this patient Clinical ASCVD? (Clinical means symptomatic eg; had prior MI, peripheral vascular diseases...etc)
✓ Yes?
High intensity statin!
Except if pt is old >75.
3- Is his LDL > 190?
✓ Yes?
High intensity statin!
No need for further questions
4- Has DM?
● More than 40 years?
✓ Yes?
High intensity statin!
5- Anything other than (2,3,4) above, we apply the 10 year risk assessment (done by websites and applications):-
● Less than 5% > No need for meds.
● between 5%-7.5% > **moderate** intensity statin.
● More than 7.5% > **High** intensity statin.

Estimate 10-year risk for ASCVD

Calculated using a website and these are the factors that are used for estimating:

- **AGE**
- **SBP/DBP**
- T cholesterol
- HDL
- LDL
- DM
- **Smoking**
- On Anti HTN
- On **statin**
- On **aspirin**



http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/

Don't skip this slide

Guideline Cont.

Patient	Risk Factors	Statin Intensity*
>29 Age	ASCVD	High
>29 years	LDL >190 mg/dl (4.9 mmol/l)	High
NO DM LDL <190	estimate 10-year risk for ASCVD <5%	No
	estimate 10-year risk for ASCVD 5-7.5%	Moderate
	estimate 10-year risk for ASCVD >7.5%	High

Recommendations in DM

Age	Risk Factors	Statin Intensity*
<40 years	None	None
	ASCVD risk factor(s)	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ACS & LDL ≥50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS & LDL ≥50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe

Treating Hypertriglyceridemia :

Table 1: Assessment and action strategies for elevated plasma triglyceride concentrations [TG]

[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	

Table 1: Assessment and action strategies for elevated plasma triglyceride concentrations [TG]

Treatment of **Hypertriglyceridemia** depends on the level of TGs:

- **200-500**
  - Risk of atherosclerosis and CAD only
  - no risk of pancreatitis
  - Give the patient **statin** to prevent atherosclerosis and CVD
- **> 500**
  - Risk of pancreatitis
  - Give the patient **fibrate** to prevent **pancreatitis** (Fibrate has no effect on CVD)

We rarely use statins and fibrate together, unless high levels of LDL

Skipped by the doctor...

Primary Hypercholesterolemia

Polygenic hypercholesterolemia	multiple defects and mechanisms	variable	common 10% of MIs <60 yr	premature CAD TC: 6.5-9 mM
Familial hyperalphalipoproteinemia	unknown	variable	Rere	less CHD, longer life elevated HDL

Primary Hypertriglyceridemia

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

Primary mixed hyperlipidemias

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
Familial dysbetalipoproteinemia	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

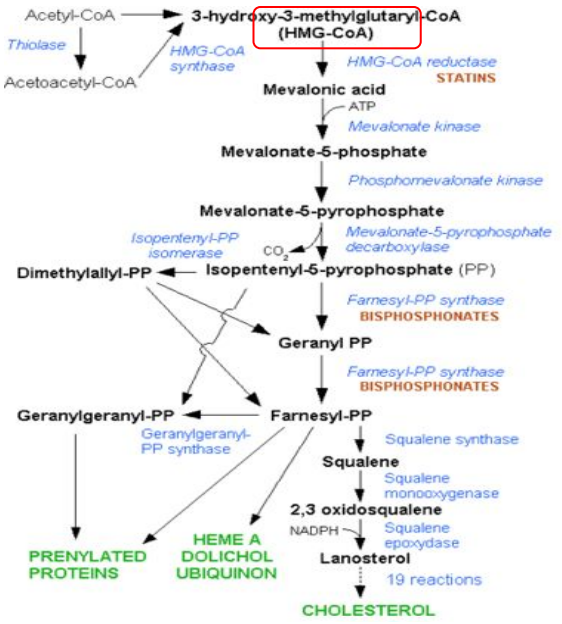
Fredrickson classification of hyperlipidemias

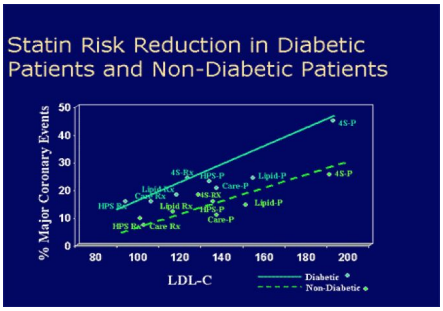
Phenotype	Lipoprotein(s) elevated	Plasma cholesterol	Plasma TGs	Athero-genicity	Rel. freq.	Treatment
I	Chylomicrons	Norm. to ↑	↑↑↑↑	– pancreatitis	<1%	Diet control
IIa	LDL	↑↑	Norm.	+++	10%	Bile acid sequestrants, statins, niacin
IIb	LDL and VLDL	↑↑	↑↑	+++	40%	Statins, niacin, fibrates
III	IDL	↑↑	↑↑↑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

Skipped by the doctor...

Dietary sources of cholesterol

Type of fat	Main source	Effect on Cholesterol levels
Monounsaturated the best type	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 the worst type	Most margarines; vegetable shortening; partially hydrogenated vegetable oil; deep-fried chips; many fast foods; most commercial baked goods	Raises LDL





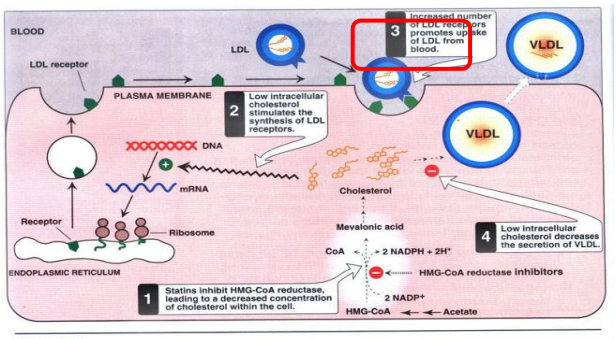
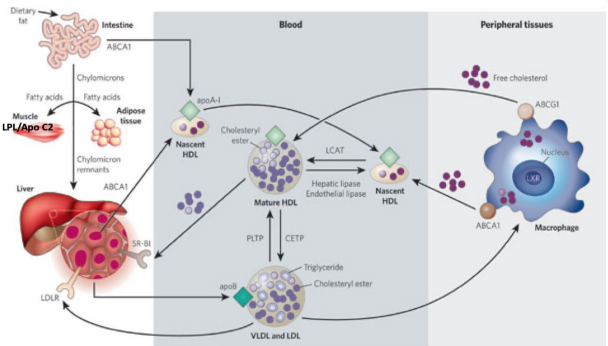
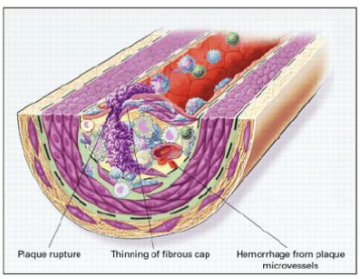


Figure 21.5
Inhibition of HMG-CoA reductase by the statin drugs.



Lipid Transport



Atherosclerosis

Summary

Primary hypercholesterolemia
● Familial hypercholesterolemia: LDL receptor mutation -> Elevated LDL + Family hx of premature CVD death

Primary hypertriglyceridemia
● LPL deficiency
● Familial hypertriglyceridemia: enhanced hepatic TG-production
● Apo-CII deficiency
(All can lead to pancreatitis)

Secondary hyperlipidemia
● DM: VLDL increased production
● Obesity: VLDL increased production
● Hypothyroidism: Mainly LDL increased production
● Anorexia : increased LDL ONLY

Aims of dyslipidemia treatment
1- LDL: prevent coronary heart disease (statins)
2- Non LDL (TC/HDL): prevent coronary heart disease
3- Triglyceride: prevent pancreatitis and may be coronary heart disease outcomes (fibrates)

Guidelines of Therapy
1- Lifestyle modification.
2- Does this patient have established coronary artery disease? (Had MI…)
✓ If yes? High intensity statin! except if pt is old >75.
3- Is his LDL more than 190?
✓ If yes? High intensity statin! No need for further questions
4- Has DM?
● More than 40 years? ✓ If yes? High intensity statin!
5- Anything other than that (2,3,4), we apply the 10 year risk assessment (done by websites & applications):-
● If its less than 5% > No need for meds.
● between 5%-7.5% > needs moderate intensity statin.
● More than 7.5% > needs High intensity statin.
● Best to prevent CAD/MI : Statins (reduce LDL)
● Best to prevent Pancreatitis: Fibrate (reduce TGs)

Thanks to 436 Medicine Team

Questions

1.Which one of the following is the good cholesterol?
A) Matures HDL
B) Nascent HDL
C) VLDL
D) IDL

2.The mechanism for the diabetes mellitus to causes hyperlipidemia is
A)Decreases the LPL
B)Decreases the bile secretion
C)Increases the Apo B-100
D)Decreases the HTGL

3.Ali is 40 years old male, his LDL level is 200 mg/dl and doesn't have ASCVD. His treatment should be?
A)High statin intensity
B)Moderate statin intensity
C)Strict diet
D)No treatment

4.Ali is 78 years old male, known to have DM for 25 years and does not have any risk for ASCVD. His treatment should be?
A)Moderate to high
B)Moderate to low
C)High
D)Non

5.Lovastatin 40mg consider as
A)High statin intensity
B)Moderate statin intensity
C)Low statin intensity
D)choose from the above

6.Dysbetalipoproteinemia results from
A) Mutation in LDL receptor
B) Increased secretions of VLDLs
C) Binding defective form of apoE
D) Unknown cause

7.Coconut oil causes
A) Lowers LDL, Raises HDL
B) Lowers HDL, Raises LDL
C) Raises HDL
D) Raises both

8.Chylomicrons transports fats from
A) The intestinal mucosa to the tissues
B) The intestinal mucosa to the liver
C) The liver to the tissues
D) The tissues to the liver

9.IDL converted to LDL by
A) Lipoprotein lipase
B) Hepatic lipase
C) Gastric lipase
D) Intestinal lipase

10.Which one of the following is the most triglycerides rich lipoprotein?
A) VLDL
B) IDL
C) Chylomicrons
D) HDL

11. Which of the following is the most atherogenic?
A) VLDL
B)LDL
C)IDL
D) small dense LDL

1. B
2. A
3. A
4. B
5. B
6. C
7. D
8. B
9. B
10. C
11. D