Dyslipidemia

Saturday, November 1, 2014
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Learning Objectives:
- 3 pathways of lipid transport & metabolism
  - exogenous
  - endogenous
  - reverse cholesterol transport
- main lipoproteins involved in lipid transport & metabolism
- primary vs. secondary dyslipidemia
- primary defect of dyslipidemia
- atherogenesis development/progression & complications
- targets for treatment of dyslipidemia

Epidemiology
- leading cause in morbidity/mortality (CVD, cancer, etc)
- ↑ cholesterol, ↑ heart issues

CHOLESTEROL - cell membrane formation, hormone synth, source of FAs

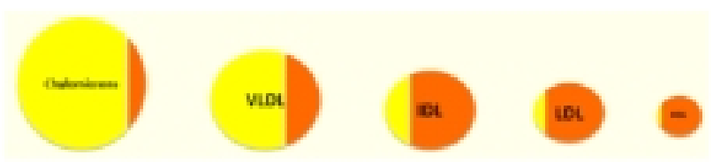
TC = LDL + HDL + (TG/5)

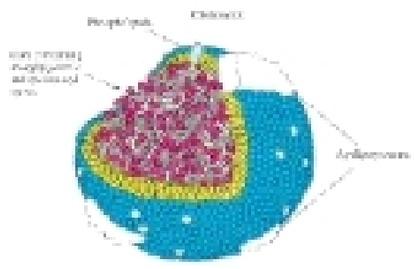
Total Cholesterol
1) LDL-C (60-70%) - most atherogenic
2) HDL-C
3) TRIGLYCERIDES - major component of CHYLOMICRONS; major source of energy; atherogenic

TG, LDL = atherogenic

Classes of Lipoproteins
LIPOPROTEIN - complexes used to transport lipids via lymph & blood

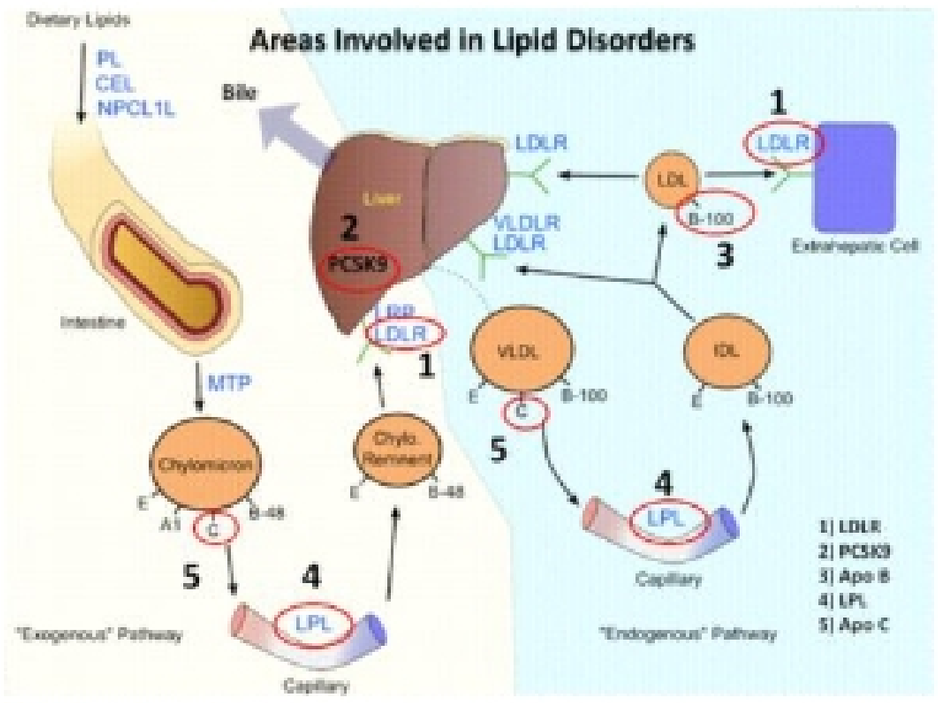
	Density	%TG
Chylo	<0.94	80-95
VLDL	0.94-1.006	55-80
IDL	1.006-1.019	23-30
LDL	1.019-1.063	5-15
HDL	1.063-1.21	5-10

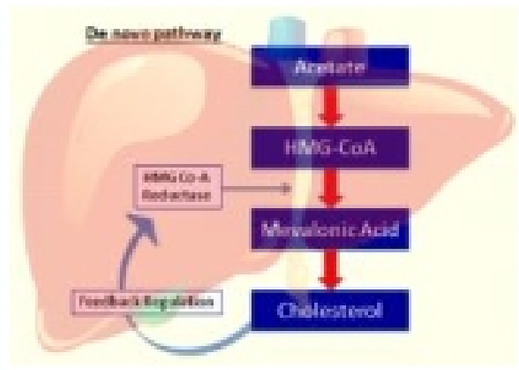


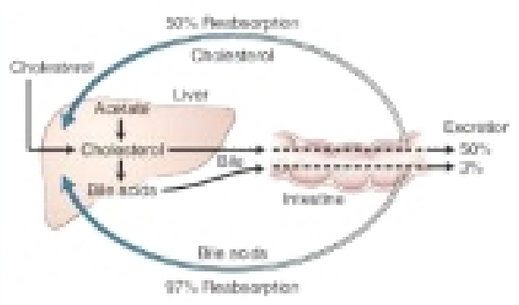


Lipid Disorders
LIPID DISORDER - defect in lipoprotein synth/processing/clearance
DYSLIPIDEMIA = hyperlipidemia = hypercholesterolemia
- ↑ TC/LDL/TG, ↓ HDL

Pathways of Lipid Transport
EXOGENOUS ENDOGENOUS







MTP - transfer protein
LPL - enzyme in blood/lymph that converts (Chylo --> Chylo Remnant)/(VLDL --> IDL)

Involved in Lipid Disorders
1) LDLR
2) PCSK9 gene mutation
3) Apo B
4) LPL
5) Apo C
6) SR
7) LCAT
8) CEPT

LDLR - receptor for LDL

Liver Cells	- cholesterol excretion
Extrahepatic/Peripheral Cells	- LDL is broken down to release cholesterol, which is used by cell, stored, or excreted

PCSK9 - protein that destroys LDLR (liver); dominant

↑ PCSK9	↓ LDLR*	↑ cholesterol (hyper)

APOLIPOPROTEINS (A, B,C,E) - membrane-bound proteins of lipoproteins
- stabilize membrane
- cofactors
- interacts with receptors to promote lipid metabolism

APO B - estimates #atherogenics

	Location	Lipoprotein	Function
APO B-48	Intestine	Chylo	- Chylo secretion
APO B-100	Liver	VLDL, IDL, LDL	- VLDL secretion - LDLR ligand

*B-100 competes with LDL for LDLR, prolonging LDL life & ↑LDL oxidation

LPL - H_2O-soluble enzyme on capillary wall; TG (Chylo & VLDL) --> (2 FAs + 1 monoacylglycerol)

APOC2	activates LPL	(bound to Chylo & VLDL)
APOC3	inhibits LPL	

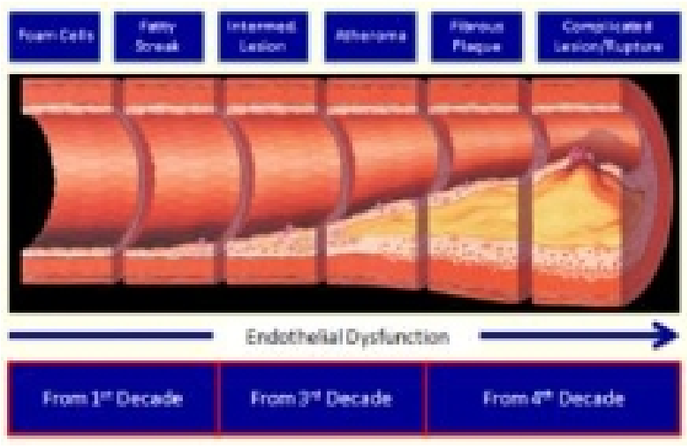
LDL Oxidation

1) LDL oxidized by free radicals Cu^{+2}/Fe^{+2}

↑plasminogen inhibitor	coagulation
↑endothelin	vasoconstriction
↓NO	vasoconstriction, platelet promotion

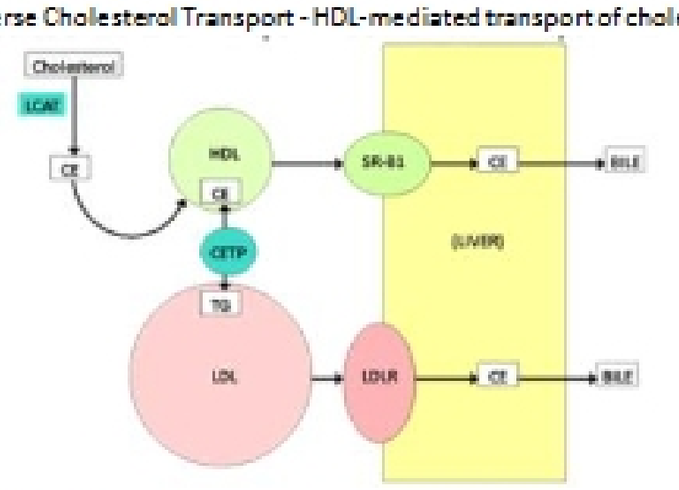
2) oxLDL binds CD36
3) taken up by macrophage --> "foam cell" formation
4) cholesterol put under endothelium
5) *ARTHERO*

CD36 - macrophage "scavenger receptor"; binds oxLDL
ATHEROGENESIS/ATHEROSCLEROSIS - hardening of blood vessels, puss & platelet aggregation, vessel narrowing



HDL - liver & intestine; "cardioprotective"; involved in Reverse Cholesterol Transport
- Reverse Cholesterol Transport - HDL-mediated transport of cholesterol (heart --> liver)

Reverse Cholesterol Transport:
http://www.youtube.com/watch?v=h18qaShTZU



LCAT - Cholesterol --> CE
SR-B1 - liver "scavenger receptor"; binds HDL
CETP - exchanges CE &TGs between lipoproteins

Dyslipidemia Classifications

FREDERICKSON CLASSIFICATION - based on genetic makeup; no longer used
PRACTICAL CLASSIFICATION - primary vs. secondary

	Elevations	Causes	
Primary ("Familial")	LDL/TG	- gene mutations: - LDLR - LDLR adapter protein - Apo B - PCSK9 - xanthomas/atheromas - rare: premature/fatal CHD <20 yrs	Symptoms: - xanthomas/atheromas - pacreatitis, abdominal pain, hepatosplenomegaly - TG > 1,000 > 10,000
Secondary (common)	LDL/TG	- obesity - diet - DM - alcohol - Liver disease - anabolic steroids - anorexia - smoking - hypothyroidism	4 Risk Groups: 1) CVD 2) (190<LDL) 3) (70<LDL>189) + (DM (40-75 yrs)) 4) (70<LDL>189) + (CVD 10Risk>7.5%)

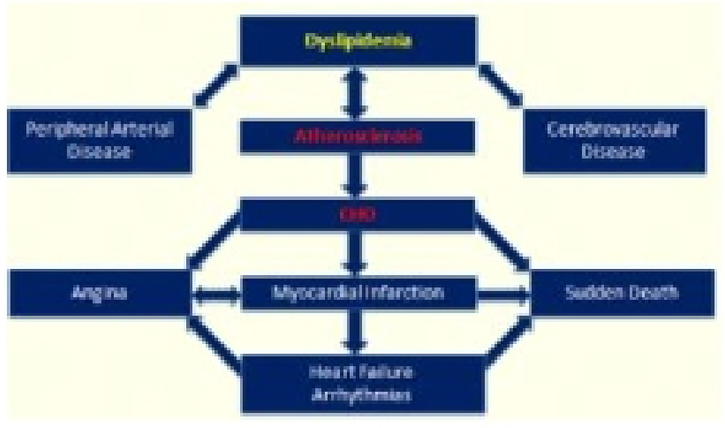
XANTHOMAS - clumping of LDL-C in tendons
ATHEROMAS - clumping of LDL-C in arteries

CVD - ACS, MI, angina, revascularization, stroke, TIA, PAD

Treatments

- diet
- bile acids reabsorption
- PCSK9
- De Novo (HMG-CoAR)
- LDLR
- MTP
- Apo B

Complications


Dyslipidemia
Peripheral Arterial Disease
Atherosclerosis
Cerebrovascular Disease
CHD
Angina
Myocardial Infarction
Sudden Death
Heart Failure
Arrhythmias