Disorders of Lipid Metabolism

Dr D.M.Vidanapathirana
MBBS, Dip Chem Path,MD Chemical Pathology,
FRCPath(UK)
Visting Senior Lecturer /Consultant Chemical Pathologist

Objectives

- Describe the basic structure and metabolism of lipoproteins in plasma
- Explain the pathological basis of common dyslipidemias, both primary and secondary
- Discuss the clinical significance of alterations in lipids and lipoproteins in plasma
- Request basic investigations and interpret results in common lipid disorders

Lipids

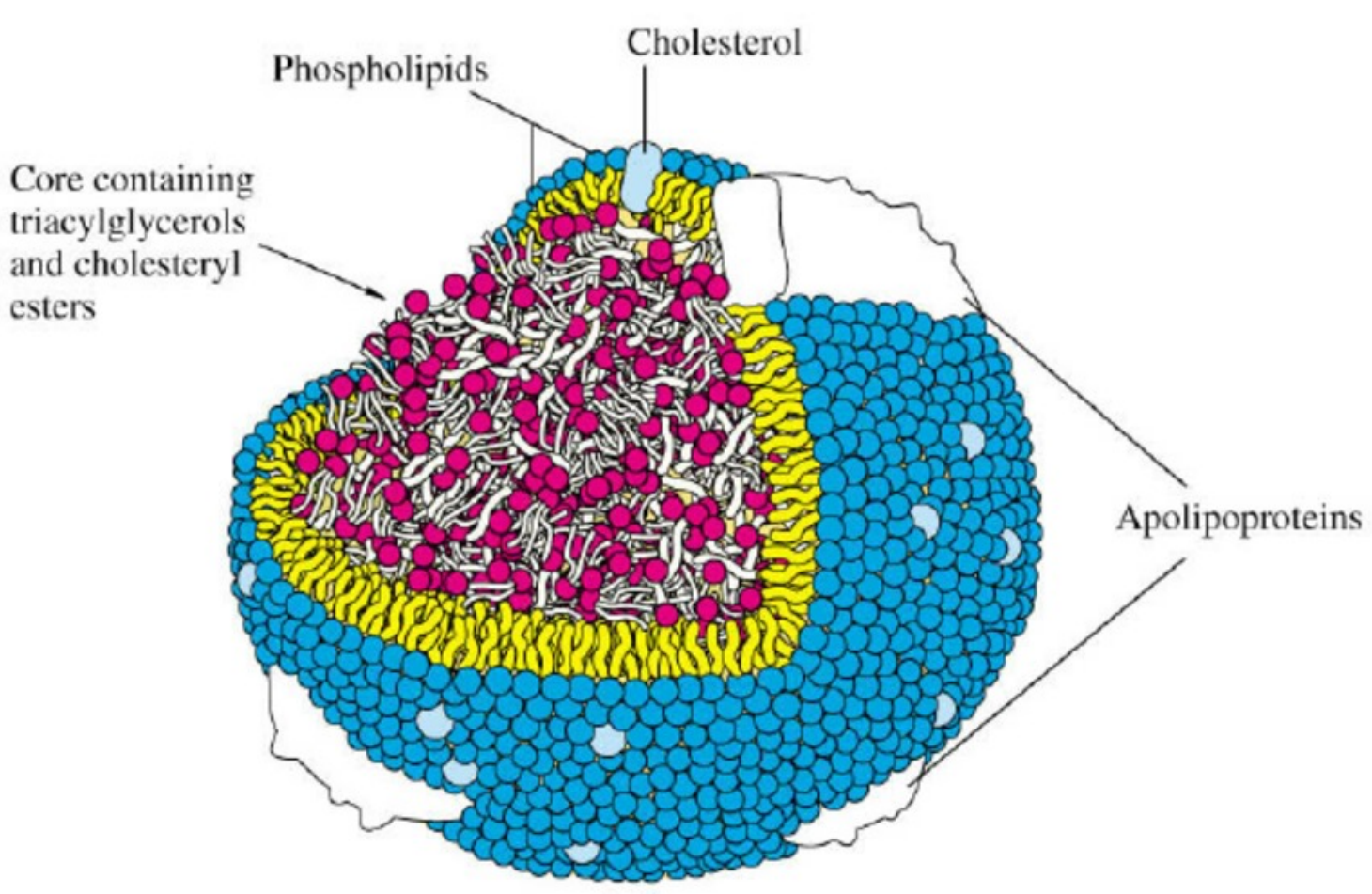
- Triglyceride
- Cholesterol
- Phospholipids
- Fatty acids

- Lipids are not water soluble (hydrophobic)
- Lipid is carried in lipoproteins that transport the lipid to various tissues for energy utilization, lipid deposition, steroid hormone production, and bile acid formation.
- The lipoprotein consists of esterified and unesterified cholesterol, triglycerides, and phospholipids, and protein.
- The protein components of the lipoprotein are known as apolipoproteins (apo) or apoproteins.
- The different apolipoproteins serve as cofactors for enzymes and ligands for receptors.

Lipoprotein structure

- Fat globule in water
- Central hydrophobic core (non-polar lipids)
  - Triglyceride
  - Esterified cholesterol
- Outer shell (polar lipids)
  - Apolipoproteins
  - Phospholipids
  - Unesterified/free cholesterol

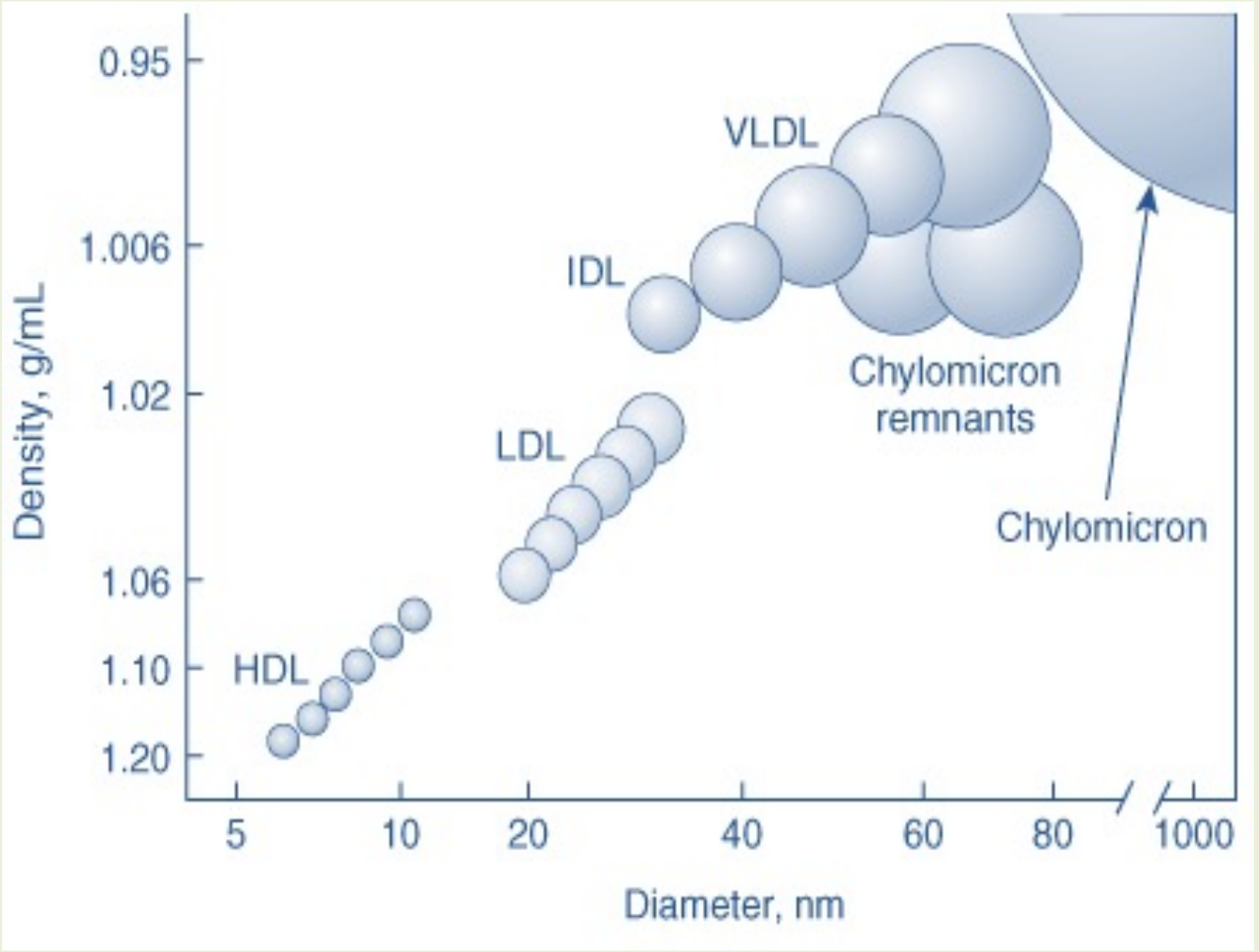
Composition of lipoprotein particle



Types of lipoprotein

- High density (HDL)
- Low density (LDL)
- Intermediate density (IDL)
- Very low density (VLDL)
- Chylomicrons

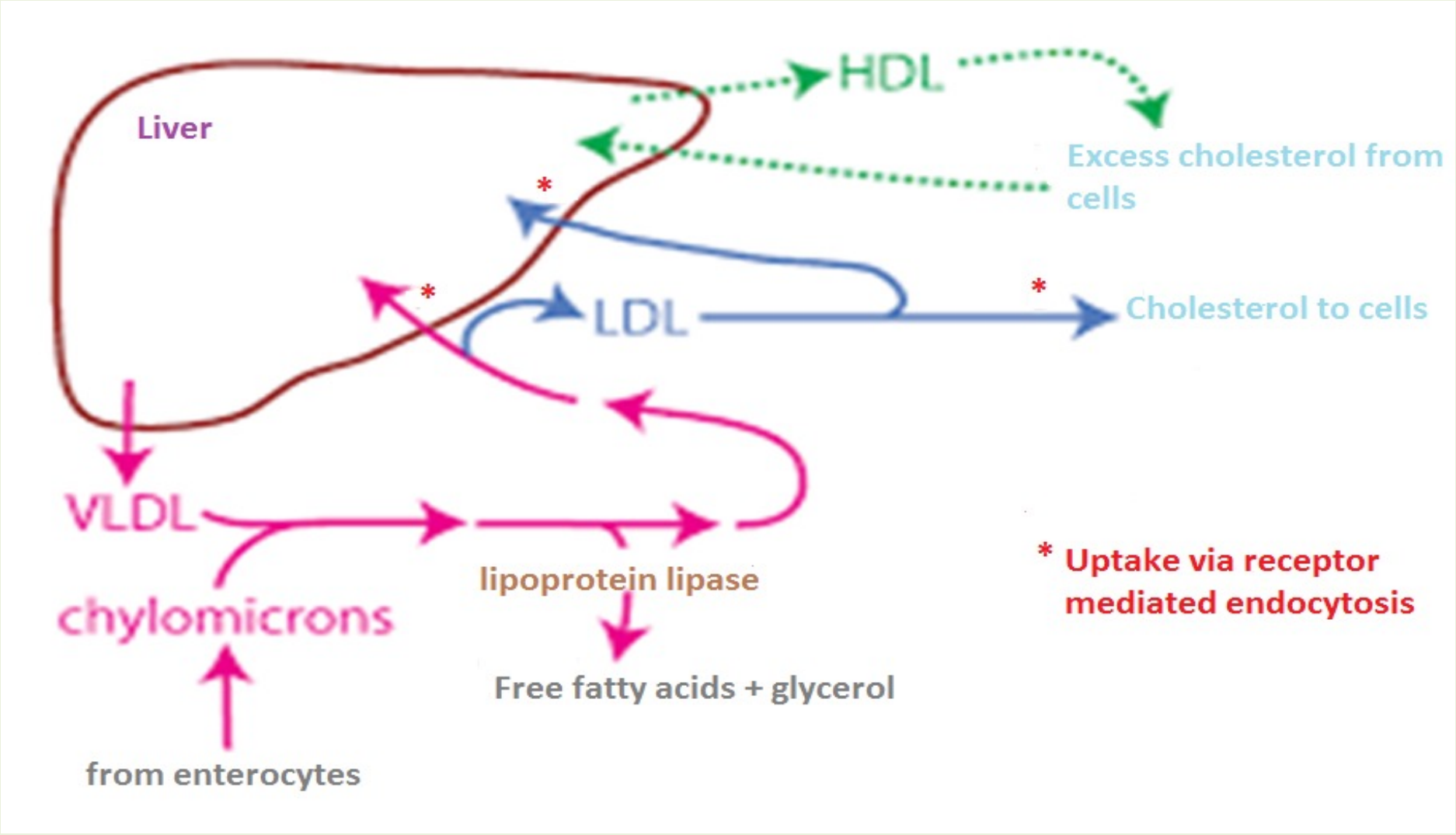
- Lipoproteins vary in size, density and electrophoretic mobility.
- Physicochemical properties are determined by their relative content of triglyceride, cholesterol, phospholipid and protein.
- Chylomicrons are large and scatter light and impart a milky appearance to plasma.


0.95
1.006
1.02
1.06
1.10
1.20
Density, g/mL
VLDL
IDL
LDL
HDL
Chylomicron remnants
Chylomicron
5
10
20
40
60
80
1000
Diameter, nm

Types of lipoprotein and their composition

Lipoprotein	Source	Protein (%)	Cholesterol (%)	Triglyceride (%)	Phospholipid (%)	Apolipoproteins
Chylomicron	Intestine	1	5	**90**	4	A,B-48,C,E
VLDL	Liver	5	20	**65**	10	B-100,C,E
IDL	VLDL	15	**35**	30	20	B-100,E
LDL	VLDL via IDL	20	**50**	10	20	B-100
HDL	Liver	**55**	15	5	25	A,C,E

Primary Functions of Lipoproteins



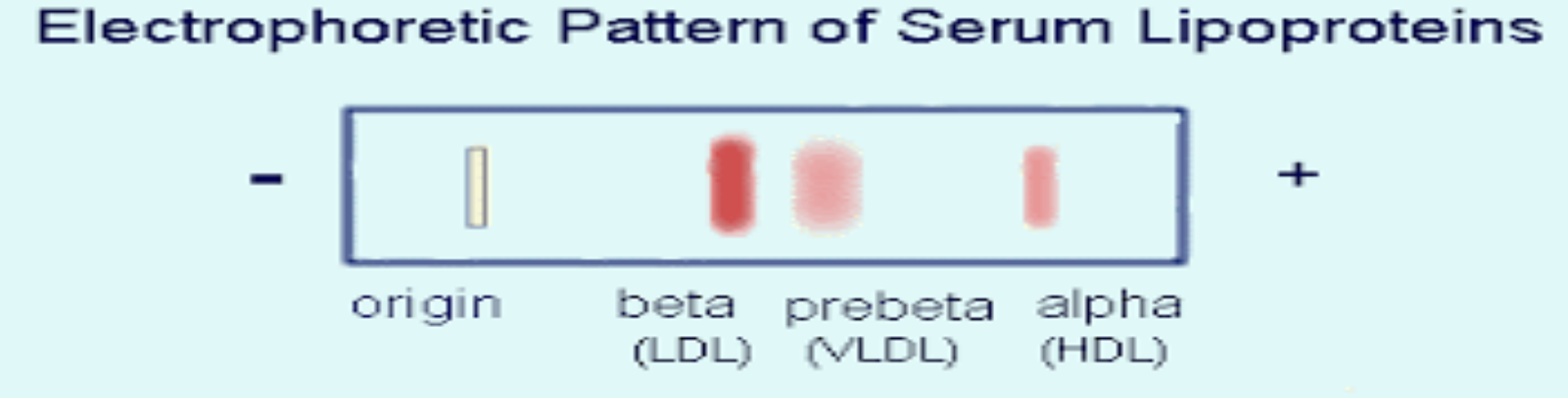
Broad basedly

- HDL – GOOD cholesterol
- LDL – BAD cholesterol

Methods of separation of lipoproteins

1. Ultracentrifugation
2. Electrophoresis

Electrophoretic mobility of lipoproteins



HDL	-	alpha
LDL	-	beta
VLDL	-	pre-beta
Chylomicrons	-	origin

Disorders of lipid metabolism

Primary hyperlipidaemias

- Hypercholesterolaemia
- Hypertriglyceridaemia
- Combined hyperlipidaemia

Secondary hyperlipidaemia

Hypercholesterolaemia	Hypertriglyceridaemia
Hypothyroidism	Diabetes
Obstructive jaundice	Alcoholism
Acute porphyria	Lipodystrophies
Growth hormone deficiency	Renal failure
Drugs : corticosteroids, chlorthalidone	Oestrogen (pregnancy,oral contraceptives)
	Glycogen storage disease
	Thiazides

Combined hyperlipidaemia

Nephrotic syndrome
Myelomatosis

Laboratory Investigations

- Serum total cholesterol
- Serum lipid profile
- Apolipoprotein levels
- Lipid electrophoresis
- Special tests – geno typing

- Screening, diagnosis, and treatment are based on the results of the measurement of serum lipids, which is generally accomplished by obtaining a lipid profile.

- On occasion, measurement of serum lipoproteins is necessary for one or more of these purposes.

Total cholesterol

- Usually fasting
- Non fasting acceptable for screening
- < 200 mg/dL (5.2 mmol/L) is desirable.
- > 200 mg/dL (5.2 mmol/L) proceed to a lipid profile.

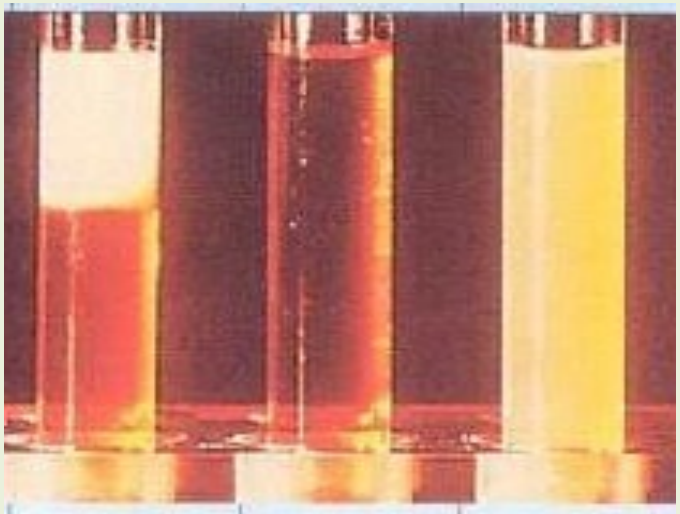
Lipid profile

- Fast for 9 – 12 hours (to remove chylomicrons).(Only water is allowed to drink)
- Collected to a plain tube without anticoagulant.
- Take a normal balanced diet for at least 3 weeks prior to test.
- Not on lipid lowering drugs unless being monitored.
- Refrain from alcohol 3 days before the test.
- No stress – absence of acute illnesses including stroke, trauma, myocardial infarction (MI).

  (Cholesterol level may be depressed after 24 hours to about 3 months after MI)

Observation of plasma appearance overnight

- Observe after keeping fasted plasma in a test tube at 4^0C for 18 hours.
- Milky layer on top - Chylomicrons
- Turbid - VLDL
- Clear - Normal/LDL



Lipid profile

- Measure
  - Total Cholesterol
  - HDL Cholesterol
  - Triglycerides
- Calculate
  - LDL Cholesterol
  - VLDL Cholesterol
  - Cardiac risk ratio

Friedewald formula

- Total cholesterol = HDL + LDL + VLDL
- LDL = Total cholesterol – (HDL + VLDL)
- VLDL = $\frac{\text{Triglyceride (mg/dL)}}{5}$

  = $\frac{\text{Triglyceride (mmol/L)}}{2.2}$
- Formula is not valid if triglycerides are > 400 mg/dL (4.5 mmol/L)
- In such instances LDL is measured using direct LDL assay.

Limitations of friedewald formula

- Non fasting samples
- Type 111 dysbetalipoproteinemia

Cardiac risk ratio

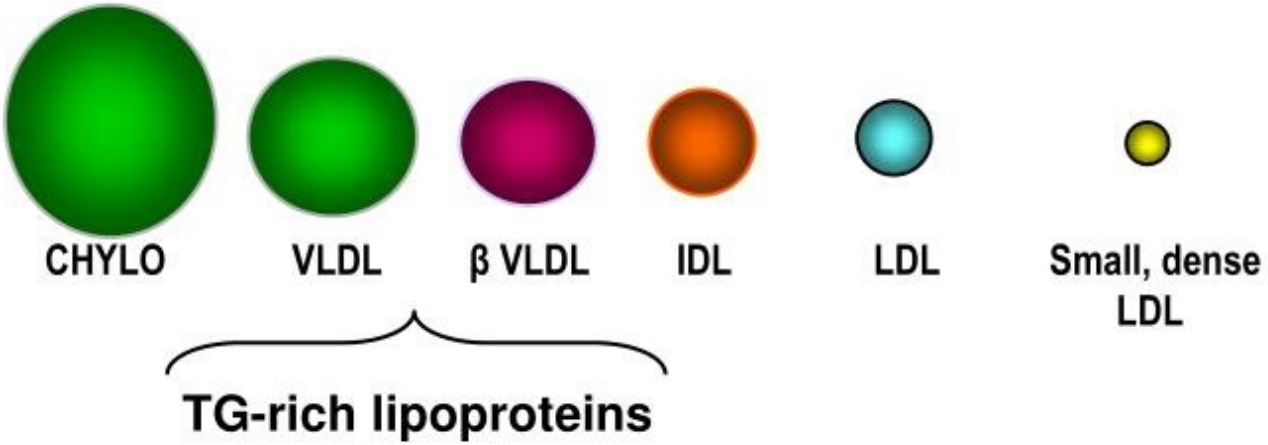
Total cholesterol / HDL Cholesterol

> 5 unfavourable

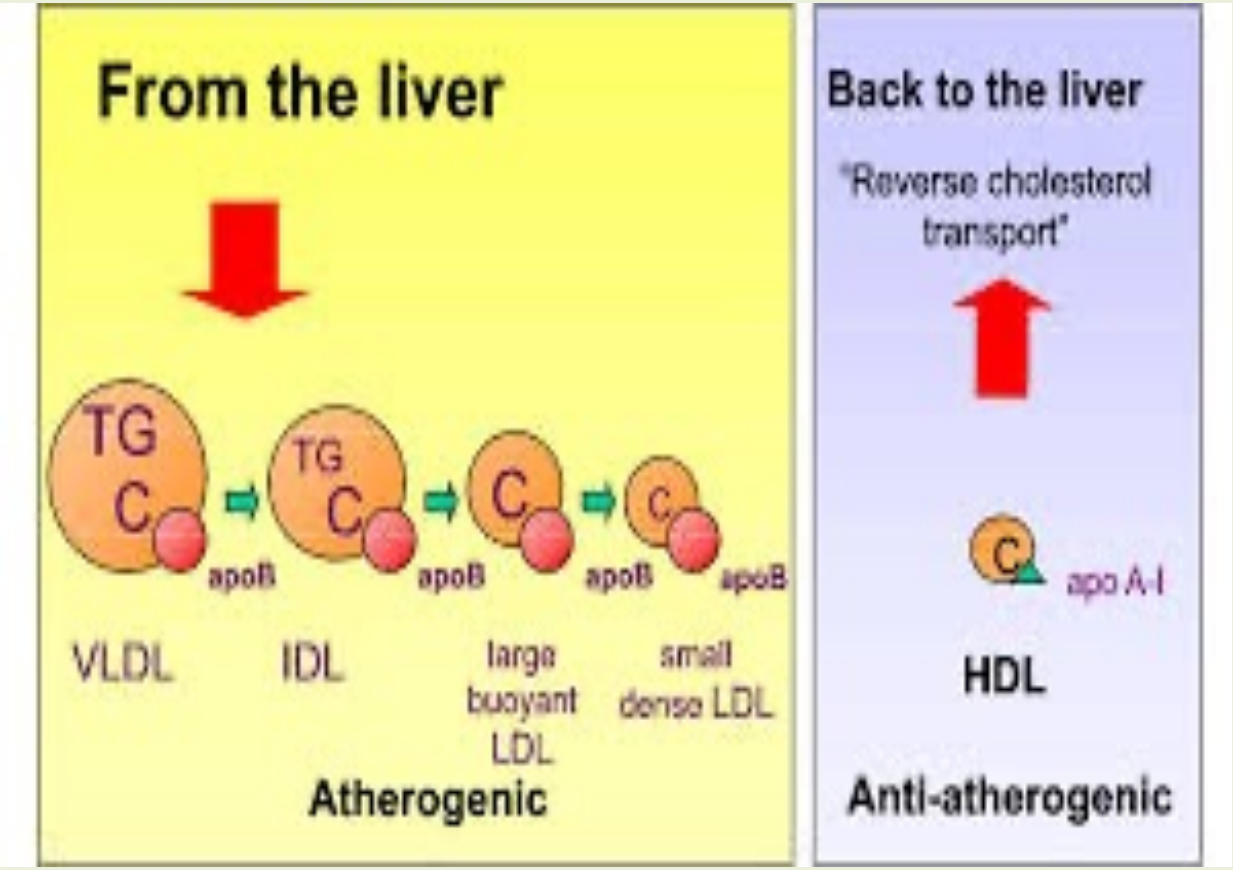
Apo B/Apo lipoprotein A1 ratio

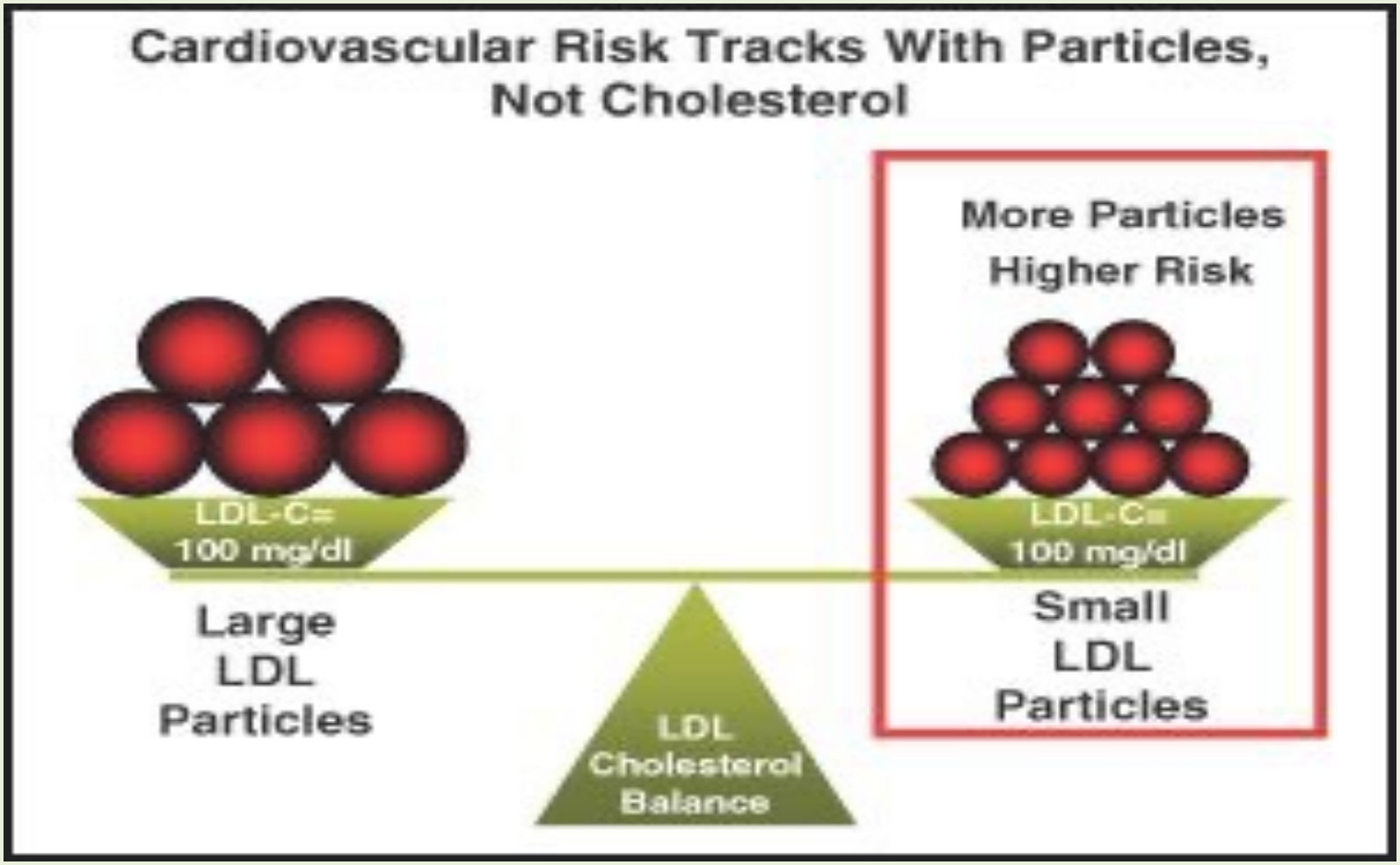
Atherogenic Particles

In people with the triade profile we should consider the quality of lipoproteins rather than the quantity of blood lipids



Consider « Non HDL Cholesterol » (equivalent to LDL + 30 mg/dl)


From the liver
TG
C
apoB
TG
C
apoB
C
apoB
C
apoB
VLDL
IDL
large buoyant LDL
small dense LDL
Atherogenic
Back to the liver
"Reverse cholesterol transport"
C
apo A-I
HDL
Anti-atherogenic


Cardiovascular Risk Tracks With Particles, Not Cholesterol
More Particles Higher Risk
LDL-C= 100 mg/dl
LDL-C= 100 mg/dl
Large LDL Particles
Small LDL Particles
LDL Cholesterol Balance

Classification

LDL cholesterol (mg/dL)	< 100	Optimum
	100 - 129	Near or above optimum
	130 - 159	Borderline high
	160 - 189	High
	⩾ 190	Very high
Total cholesterol (mg/dL)	< 200	Desirable
	200 - 239	Borderline high
	⩾ 240	High
HDL cholesterol (mg/dL)	< 40	Low
	⩾ 60	High

NCEP-ATP 111 – National Cholesterol Education Program Adult Treatment Panel 111

Classification of serum triglyceride (mg/dL)

< 150	**Normal**
150 – 199	**Borderline high**
200 – 499	**High**
> 500	**Very high**

Apoprotein levels

- Apoprotein A 1 – reflects HDL
- Apoprotein B – reflects LDL
- Apolipoprotein a – independent risk factor for myocardial infarction

Lipid electrophoresis

- Serum electrophoresis is done
- Stain with a lipid staining dye
- Fredrickson's classification of primary hyperlipidaemia's is based on this

Fredrickson's classification

Phenotype	Lipids	Electrophoresis picture	Lipoproteins	Diagnosis
1	↑TG	Origin	Chylomicrons	Familial Hyperchylomicronemia
11 a	↑TC	b-lipoprotein	LDL	Familial Hypercholesterolemia
11 b	↑TC, ↑TG	Pre b and b	VLDL + LDL	Familial Combined Hyperlipoproteinemia
111	↑TC, ↑TG	Broad b	IDL	Dysbetalipoproteinemia
1V	↑TG	Pre-b	VLDL	Primary Hypertriglyceridemia
V	↑TC, ↑TG	Origin & pre b	Chylo + VLDL	Mixed Hypertriglyceridemia

Special tests

- Apo E genotyping using PCR technique

  (Apo E shows polymorphism in familial dysbetalipoproteinaemia)

Conversion factor

- Cholesterol mg/dL /38.6 = mmol/L
- Triglyceride mg/dL /88.5 = mmol/L

Summary

- Screening test - Total cholesterol
- Confirming test - Lipid profile
- Phenotyping - Lipid electrophoresis
- Geno typing - PCR technology
- Monitoring tests - Lipid profile

References

- Marshall WJ, Bangert SK and Lapsley M. Lipids, lipoproteins and cardiovascular disease. In: Clinical Chemistry.7th ed.2012.p.239-258.

- Remaley AT, Rifai N & Warnick GR. Lipids, lipoproteins, apolipoproteins and other cardiovascular risk factors. In: Burtis C, Ashwood E & Bruns D. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics.5th ed. Publishing; 2012.p.731-805.

Thank you !