

Class 13:

Plasma proteins:

types, functions and variation in different diseases.

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Objectives for this lecture

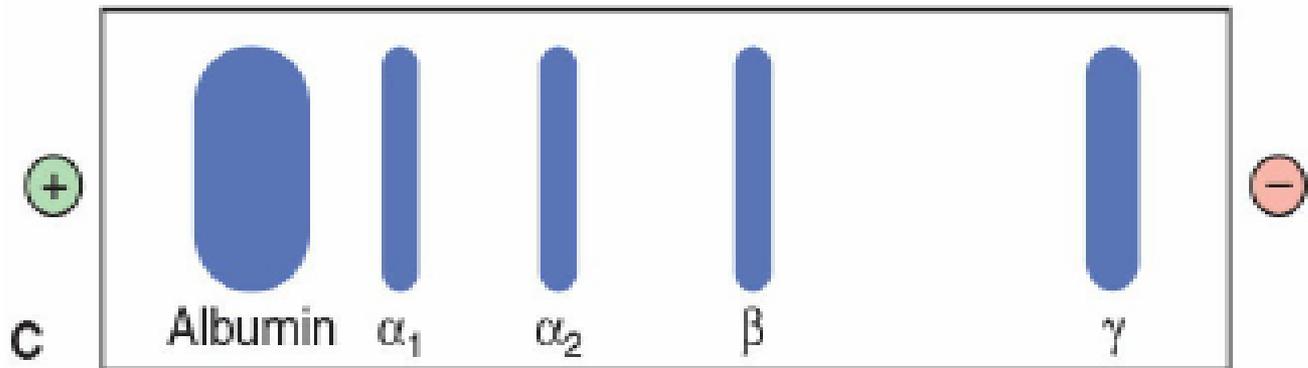
- Discuss the different type of plasma proteins.
- understand the effect of liver and kidney disease on the level of plasma proteins.

Plasma contains a complex mixture of proteins

- Concentration **65 –80 g/L**
 - groups on the basis *solubility* (ethanol):
 - Fibrinogen 4%
 - Albumin 60%
 - Globulins 35%
 - *Other plasma proteins* : 1%
 - rich in disulfide bonds
 - contain carbohydrate (glycoprotein) or lipid (Lipoprotein).

Plasma proteins

- electrophoresis within a **cellulose acetate** for serum protein give:
 - ✓ *Albumin*
 - ✓ *α_1 -, α_2 -, β -, and γ - globulins.*



Plasma

65-80 g/L
Proteins (100%)

Albumin

60%

Globulins

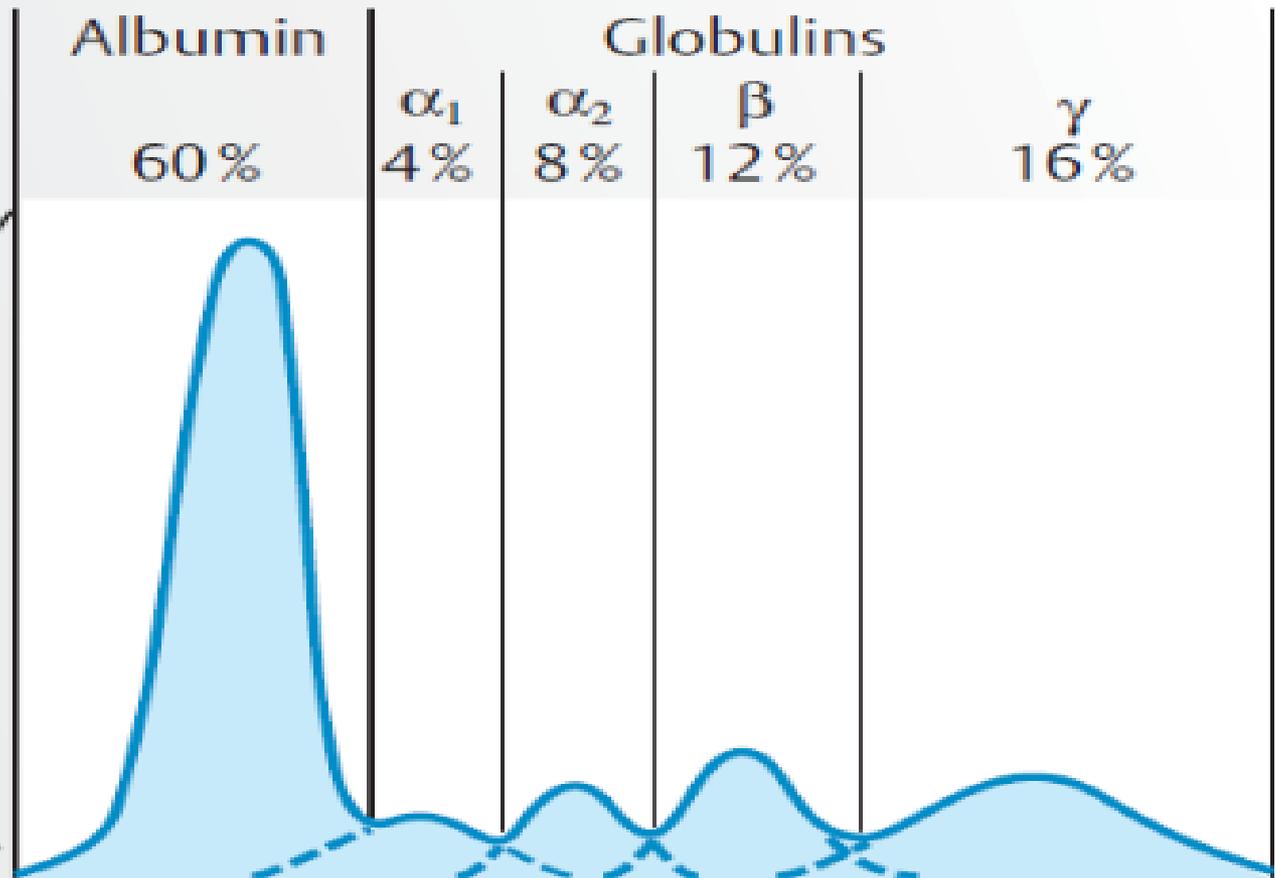
α_1
4%

α_2
8%

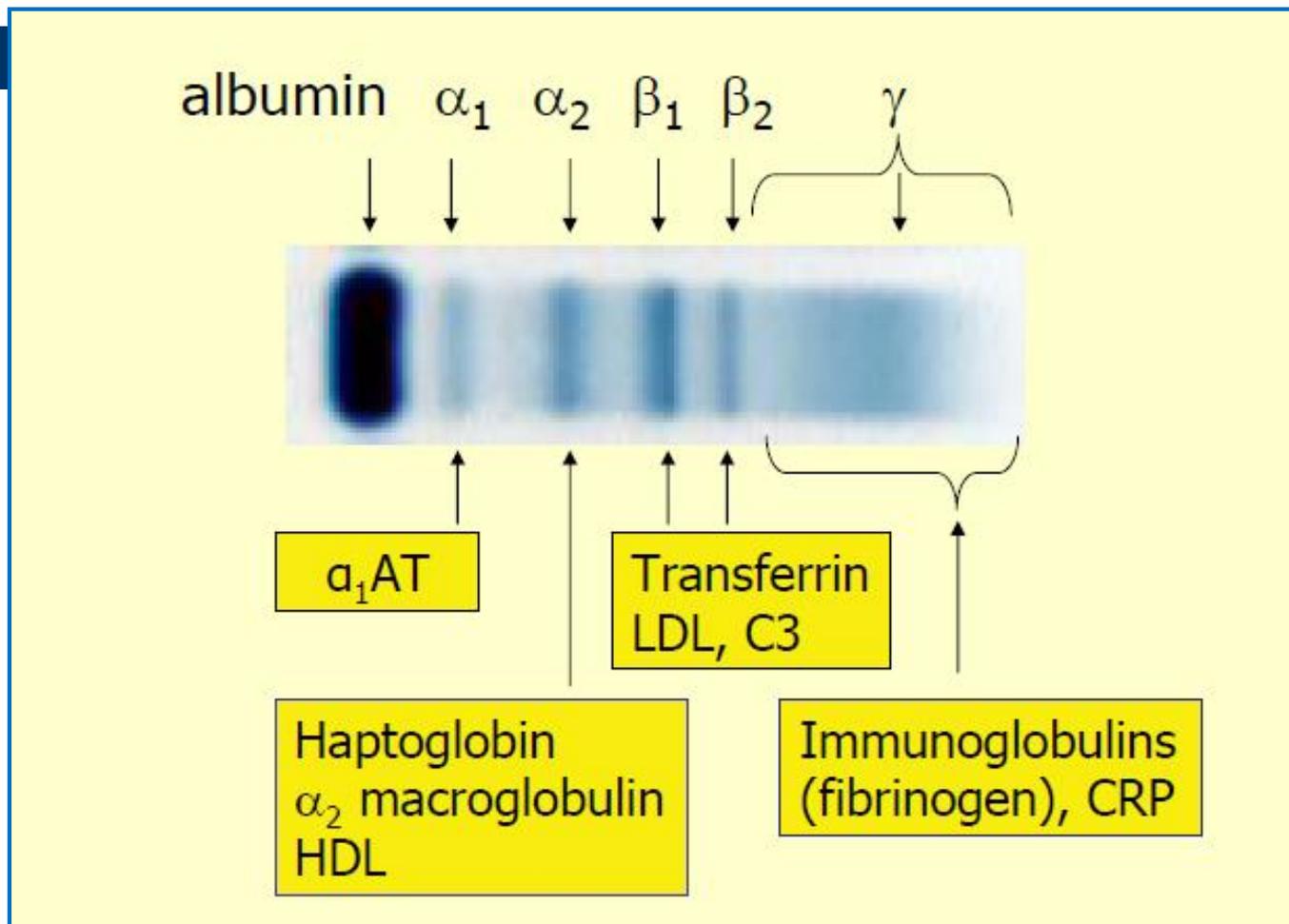
β
12%

γ
16%

Electrophoretic protein fractions



Major Components of globulin bands



Plasma proteins participate in:

1. Blood coagulation
2. Maintenance of homeostasis (pH, osmotic pressure)
3. Defence against infection
4. Transport of:
 - *nutrients*
 - *hormones*
 - *Metabolites*
 - *drugs*
 - *metabolic waste*

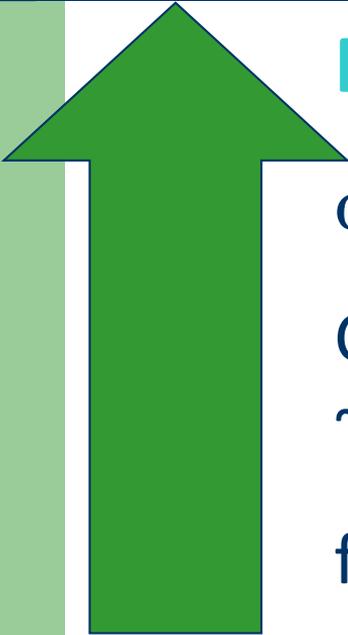
properties of plasma proteins

- Synthesized in the *liver*.
(Exception: γ -globulins – synthesized in plasma cells).
- have characteristic half-life in the circulation
(albumin – 20 days)

Acute phase reactants (APRs)

- Class of proteins whose plasma levels change (increase or decrease) during acute inflammatory response
1. APRs concentration changes in:
 1. infection
 2. surgery
 3. injury
 4. cancer

Types of APRs



Positive

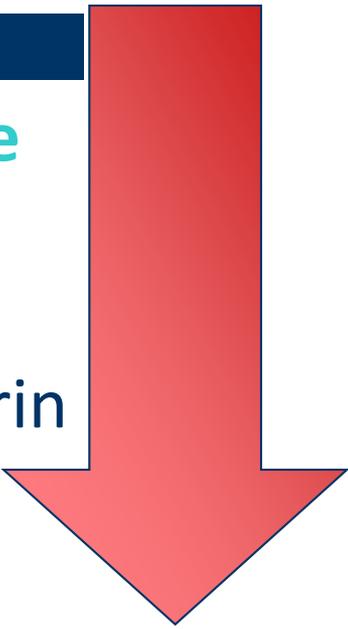
α 1-antitrypsin

C-reactive protein (CRP):
~1000-fold increase!

fibrinogen

haptoglobin (HP)

C3, C4



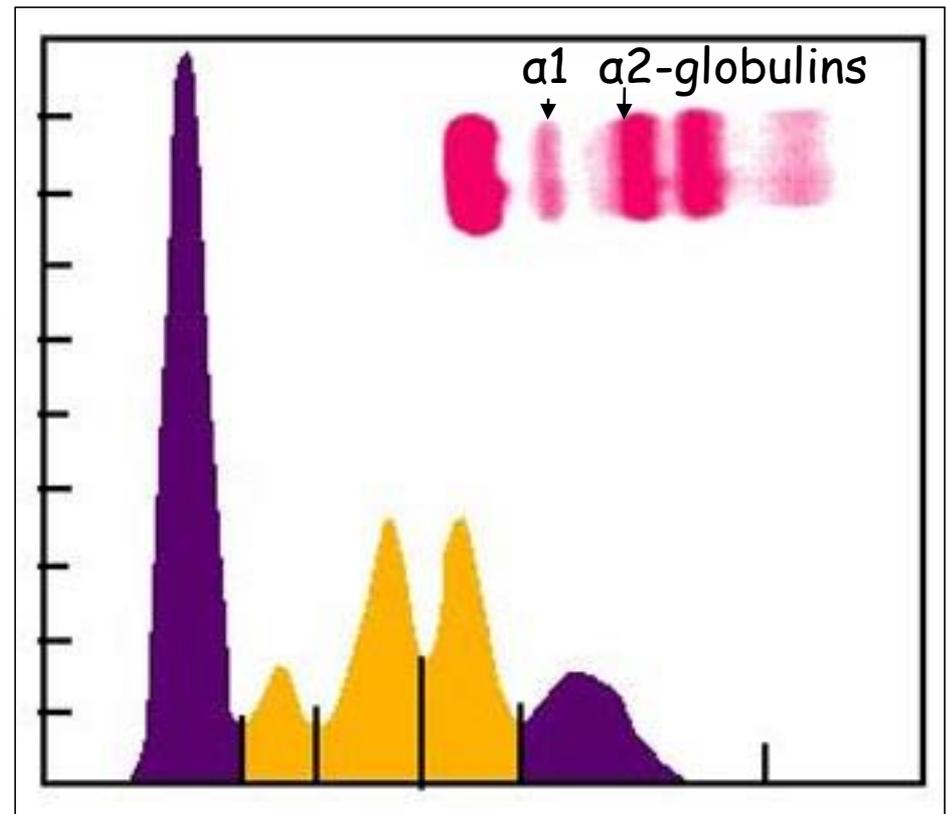
Negative

albumin

transferrin

Acute inflammatory response

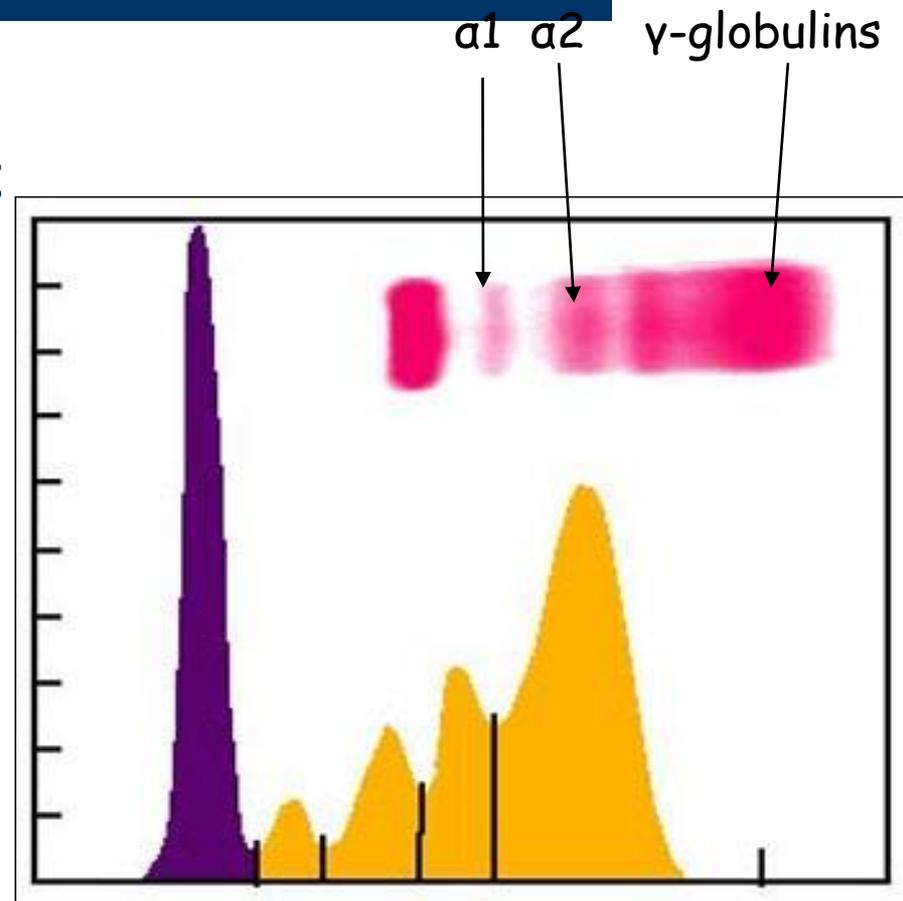
- Immediate response occurs with stress or inflammation caused by infection, injury or surgical trauma
 - Normal or ↓ albumin
 - ↑ α 1 and α 2 globulins



Chronic inflammatory response

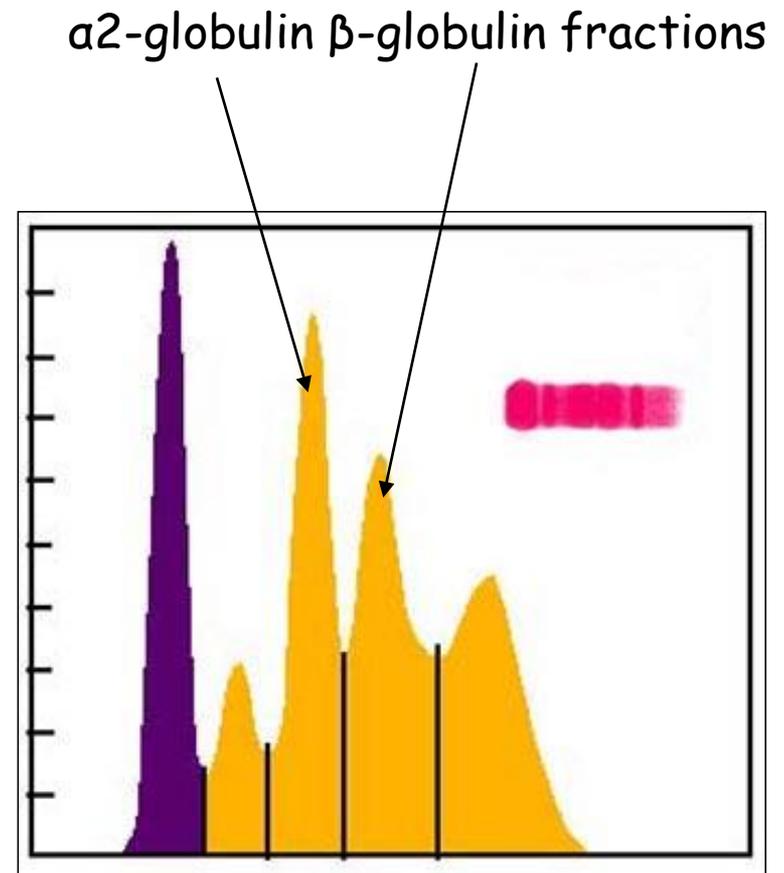
- Late response is correlated with chronic infection (autoimmune diseases, chronic liver disease, chronic infection, cancer)

- Normal or ↓ albumin
- ↑ α 1 or α 2 globulins
- ↑↑ γ globulins



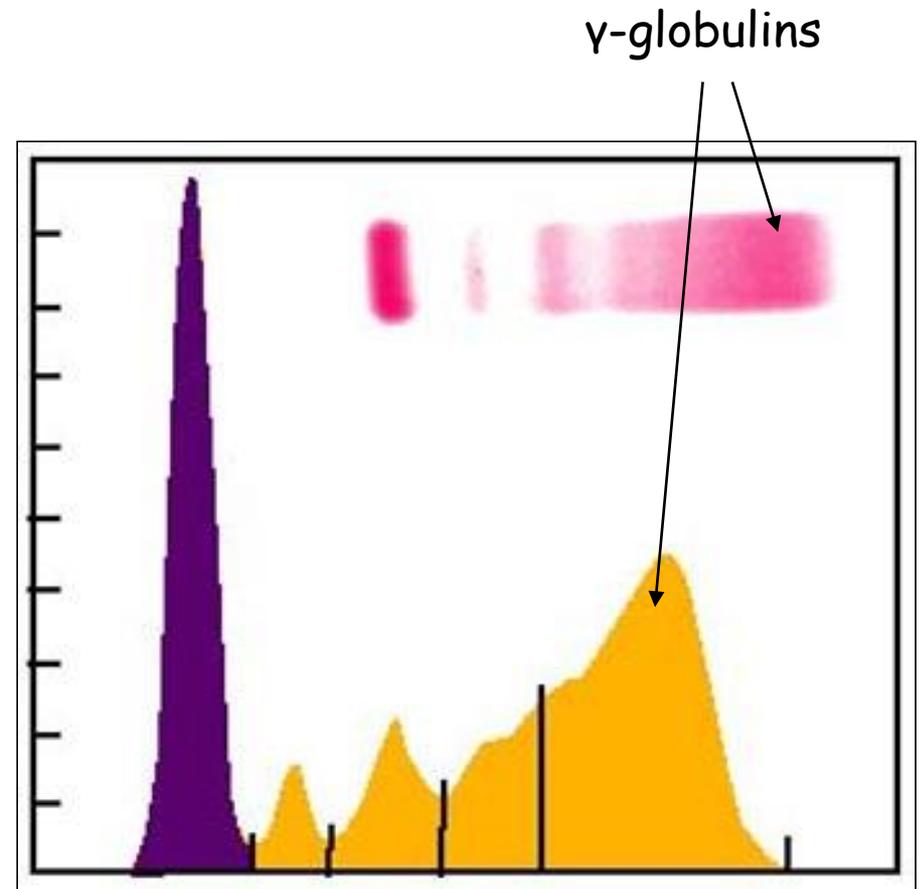
Nephrotic syndrome

- The kidney damage illustrates the long term loss of lower molecular weight proteins
 - ↓ albumin and IgG – they are filtered in kidney
- Retention of higher molecular weight proteins
 - ↑↑ α₂-macroglobulin and ↑β-globulin)



Liver damage - Cirrhosis

- Cirrhosis can be caused by chronic alcohol abuse or viral hepatitis
 - ↓ albumin
 - ↓ α 1, α 2 and β globulins
 - ↑ Ig A in γ -fraction



Albumin

- Not a glycoprotein
- has lowest molecular weight of plasma proteins
- Liver produces 12g /day (25% of total hepatic protein synthesis and 50% of secreted protein)
- Half-life: 20 days
 - For this reason, measurement of serum albumin concentration is used to assays liver function test

Albumin Functions

- 1. Maintenance of the osmotic pressure of plasma**
 - gives greater osmotic effect at the pH 7.4 of blood
 - responsible for about 75- 80 % of the osmotic effect of plasma because:
 - It constitutes slightly > half the plasma proteins by weight
 - It has the lower molecular weight of the major plasma proteins.

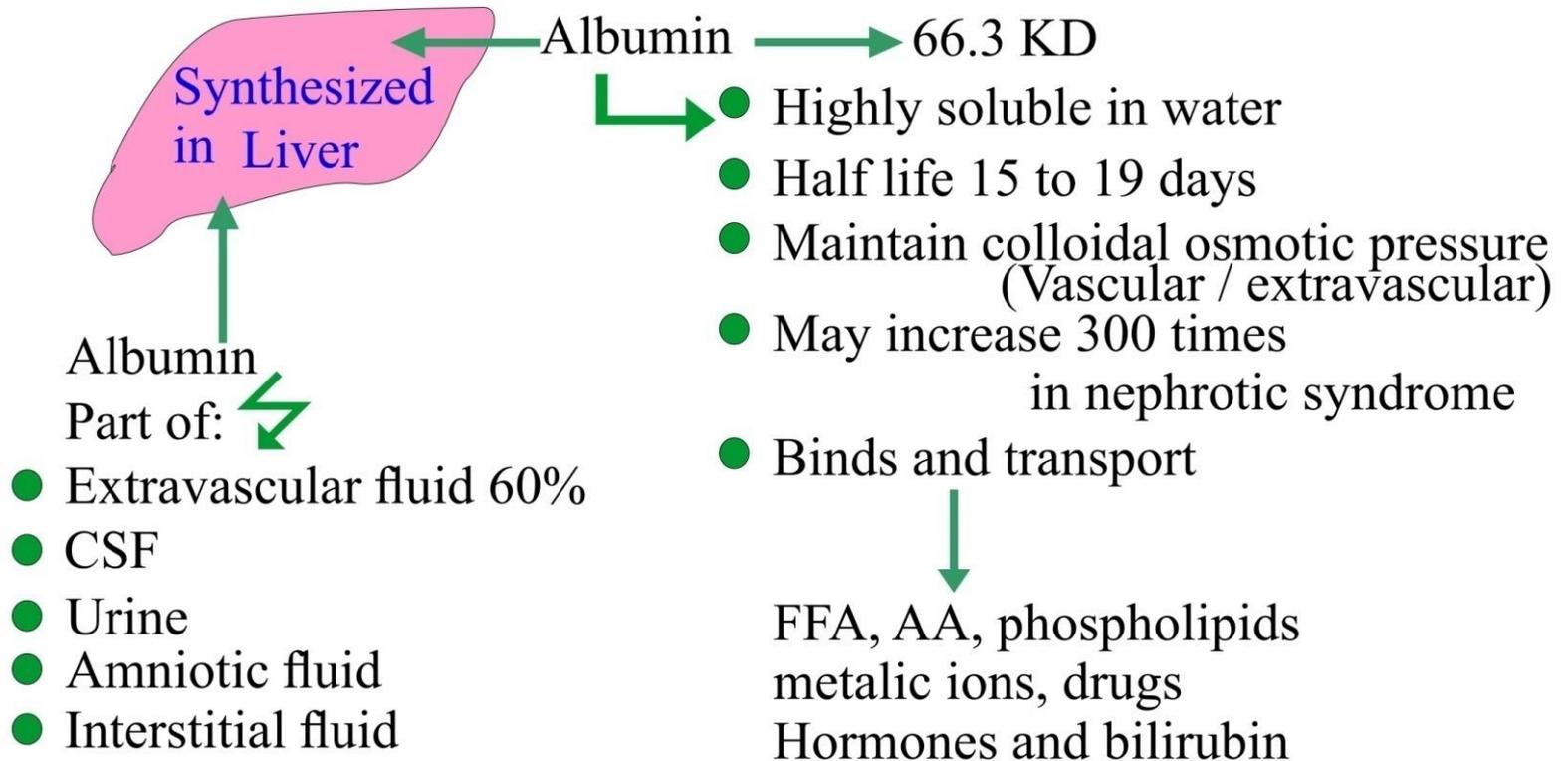
Albumin Functions

2. **Transport:** It can bind and transport many diverse molecules and serve as low-specificity transport protein, which include:
 - free fatty acids
 - steroid hormones
 - bilirubin
 - drugs (sulfonamides, aspirin)
 - Ca^{2+} , Cu^{2+}

Causes of Albumin Deficiency

- Liver diseases (cirrhosis) – decrease in the ratio of albumin to globulins
- Protein malnutrition
- Excessive excretion by kidneys (renal disease) (**proteinuria**)
- Mutation causing **analbuminemia** (little or no circulating albumin)
 - There will be a reduction in osmotic pressure, leading to enhanced fluid retention in tissue spaces (edema)

Albumin Properties



Transferrin

- Beta globulin
- Concentration in plasma: 3 g/l
- **Functions:**
 1. **Transport of iron:** from catabolism of heme and from food (gut) to the sites where iron is required, i.e. to the bone marrow and other organs
 2. 2 moles of **Fe³⁺** per 1 mole of transferrin

Causes of transferrin deficiency:

- Burns
- Infections
- Malignancies
- Liver and kidney diseases
- Pregnancy

Ferritin

- Intracellular protein; only small portion in plasma
- **Function:**
 - Stores iron that can be called upon for use when needed
- **Primary hemochromatosis:**
 - genetic disorder
 - characterized by increased absorption of iron from the intestine \Rightarrow accumulated iron damages organs such as the liver, skin, heart, and pancreas.
 - concentration of ferritin is elevated.

Ceruloplasmin

- α 2-globulins
- Conc. in plasma: 300 mg/l
- **Functions:**
 - Carries 90% of copper in plasma (copper – cofactor for a variety of enzymes);
 - 1 molecule binds 6 atoms of copper;
 - binds copper more tightly than albumin that carries other 10% of copper
 - ⇒ Albumin may be more important in copper transport (donates copper to tissues more readily)

Causes of ceruloplasmin decrease

- **Liver diseases**, in particular **Wilson's disease**:
 - **Genetic disease** in which copper fails to be excreted into the bile and accumulates in liver, brain, kidney, and red blood cells
 - **Cause**: mutations in the gene encoding for copper-binding ATPase
 - **Consequences**: accumulation of copper in liver, brain, kidneys... \Rightarrow liver disease, neurologic symptoms

Causes of ceruloplasmin increase

- Inflammatory states
- Carcinomas, leukaemia
- Rheumatoid arthritis

Haptoglobin

- α_2 - globulin, tetrameric

- **Functions:**

- **binds free hemoglobin** and delivers it to the reticuloendothelial cells
- **complex Hb-Hp** is too large to pass through glomerulus

⇒ prevention of loss of free Hb in the urine

⇒ kidney damage

Causes of Hp increase

- Inflammation, infection
- Injury
- Malignancies

Causes of Hp decrease

- **Haemolytic anaemia**

half-life of Hp = 5 days x of complex Hp-Hb = 90 min (the complex is being rapidly removed from plasma)

⇒ Hp levels fall when Hb is constantly being released from red blood cells (as in haemolytic anaemia)

Hemopexin

- β -globulins
- Binds free heme and transfers it to the liver

⇒ prevent its urinary excretion

transferrin

ferritin

ceruloplasmin

haptoglobin

hemopexin

act as antioxidants: remove Fe^{2+} (iron) and thus **prevent the Fenton reaction:**



Free radicals



*Oxidative stress
cellular damage
eventual cellular death*

α 1- Antitrypsin

- A glycoprotein with 394 a.a (52 kDa)
- Synthesized by hepatocytes and macrophages
- Major component (>90 %) of the α_1 -fraction
- Highly polymorphic, the most common is M type
- **Function:** principal **plasma inhibitor of serine protease** (inhibits trypsin, elastase)

α 1- Antitrypsin

- Genetic deficiency of α 1-Antitrypsin
 - Synthesis of the defective α 1-Antitrypsin occurs in the liver but it cannot secrete the protein
 - α 1-Antitrypsin accumulates in hepatocytes and is deficient in plasma

α 1- Antitrypsin

- Deficiency has a role in **emphysema** –proteolytic damage of the lung
- Methionine involved in antitrypsin (AT) binding to proteases is oxidized by smoking
 - ⇒ *AT no longer inhibits proteases*
 - ⇒ *increased proteolytic damage of the lung, devastating in patients with AT-deficiency*

α 1 Fetoglobulin (AFP)

- Major protein in the human fetal plasma and amniotic fluid (glycoprotein)
- AFP levels decrease gradually during intra-uterine life and reach adult levels at birth
- Very low amounts in adults
- Function is unknown but it may protect fetus from immunologic attack by the mother or has same function of albumin in adult
- Sequences of fetoglobulin and albumin are homologous

α 1 Fetoglobulin(AFP)

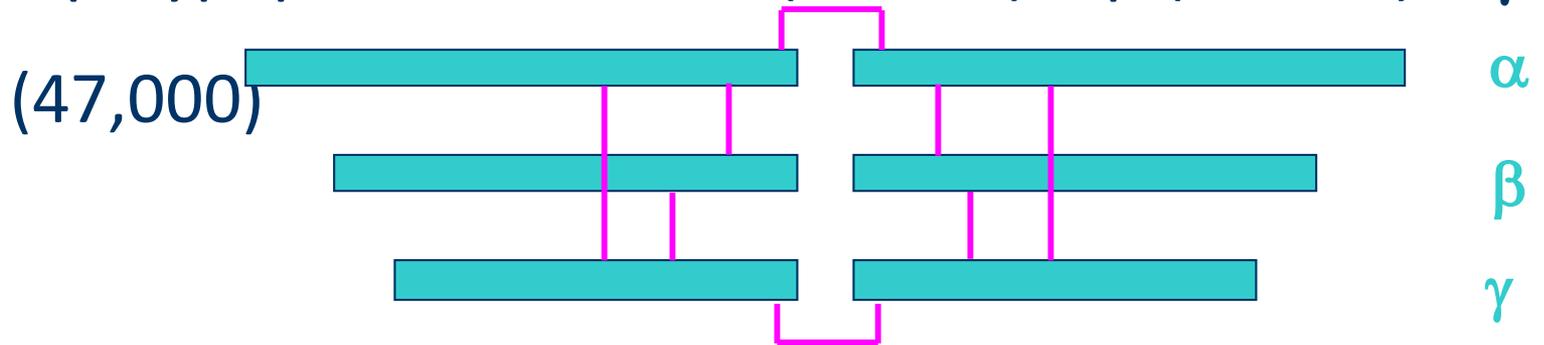
- Elevated maternal AFP levels associated with:
 - Neural tube defect, anencephaly
- Decreased maternal AFP levels associated with:
 - Increased risk of Down's syndrome
- AFP is a tumor marker for:
 - Hepatoma and testicular cancer

Fibrinogen

- Structure

- MW 340 000

- 6 polypeptide chains, 2 α (67,000), 2 β (56,000), 2 γ



— Disulfide bond

Fibrinogen

- **Function**

- Blood coagulation (clotting)

Fibrinogen $\xrightarrow{\text{Thrombin}}$ Fibrin

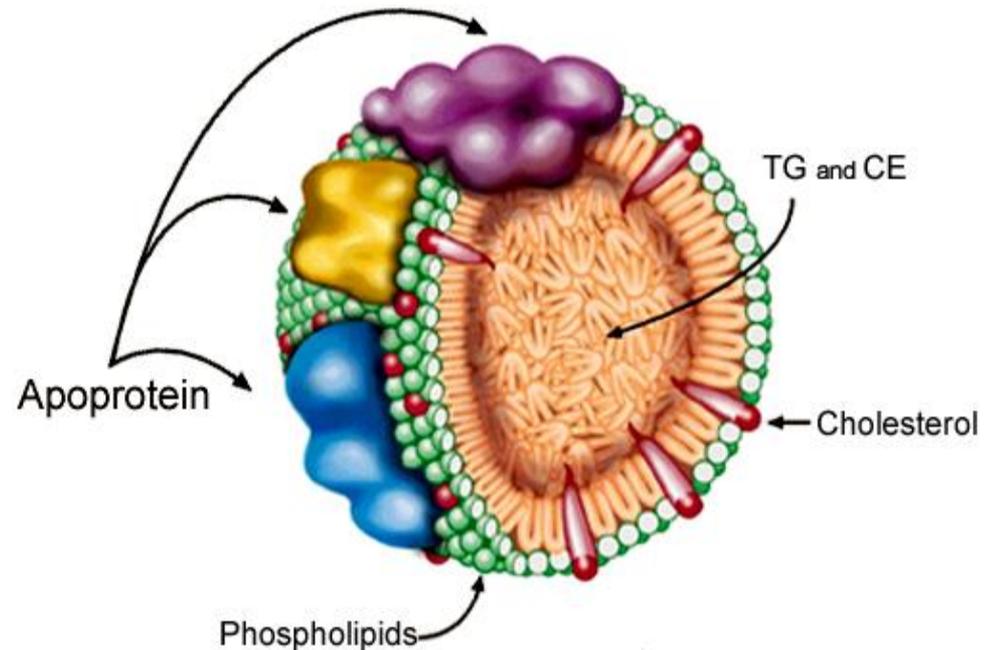
Fibrin $\xrightarrow{\text{Plasmin}}$ Degradation

Lipid transport in blood

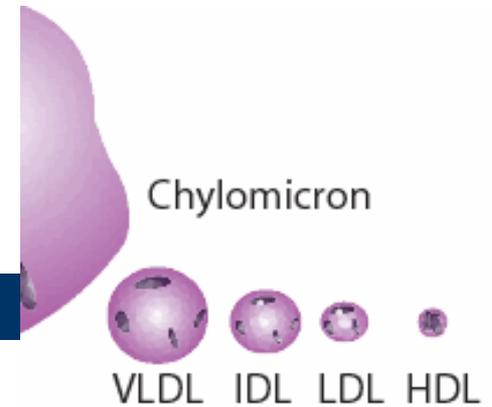
- The plasma lipoproteins are spherical macromolecular complexes of lipids and specific proteins (apolipoproteins)
- Lipoproteins function both to keep their component lipids soluble as they transport them in the plasma (to and from the tissues)

Plasma Lipoproteins Structure

- **LP core**
 - Triglycerides
 - Cholesterol esters
- **LP surface**
 - Phospholipids
 - Proteins
 - cholesterol



Lipoprotein classes



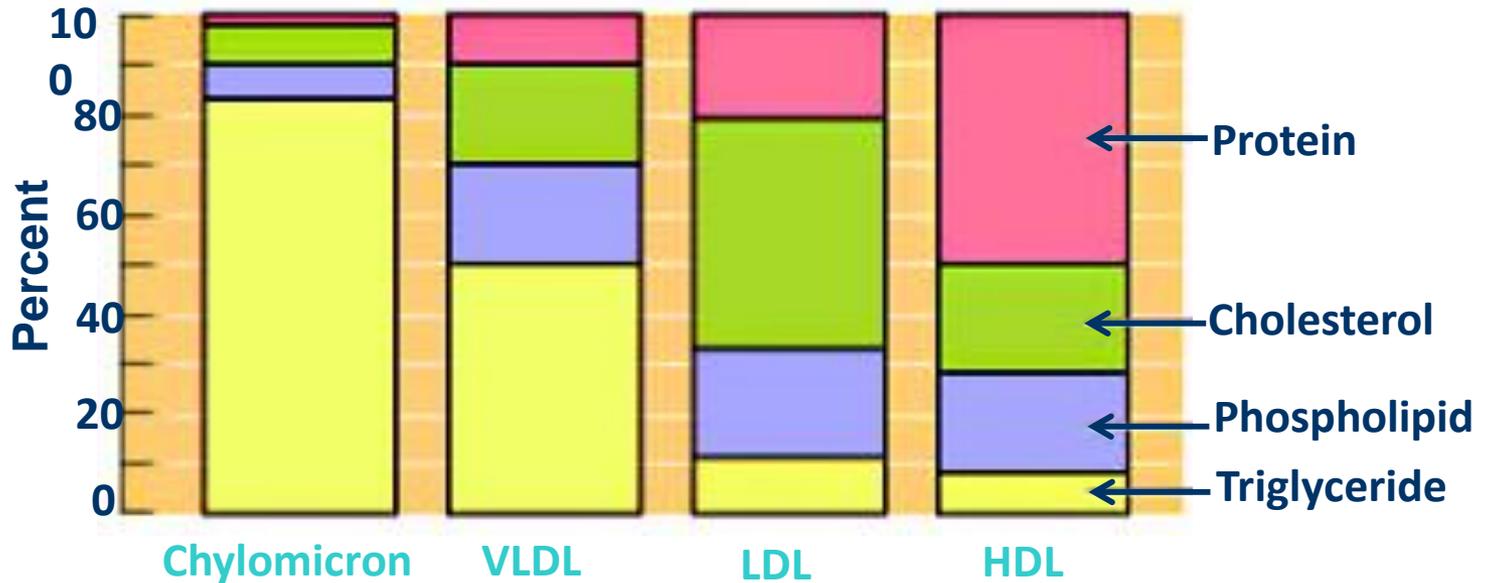
1. Chylomicrons
2. very low density lipoproteins (VLDL)
3. intermediate density lipoproteins (IDL)
4. low density lipoproteins (LDL)
5. high density lipoproteins (HDL)

They are identified and classified on basis of:

- Chemical composition
- Physical properties including density and floatation characteristics
- Mobility upon electrophoresis

Chemical composition

Lipoprotein	Chylomicron	VLDL	LDL	HDL
Triglyceride	90	65	10	2
Cholesterol	5	13	43	18
Phospholipid	4	12	22	30
Protein	1	10	25	50



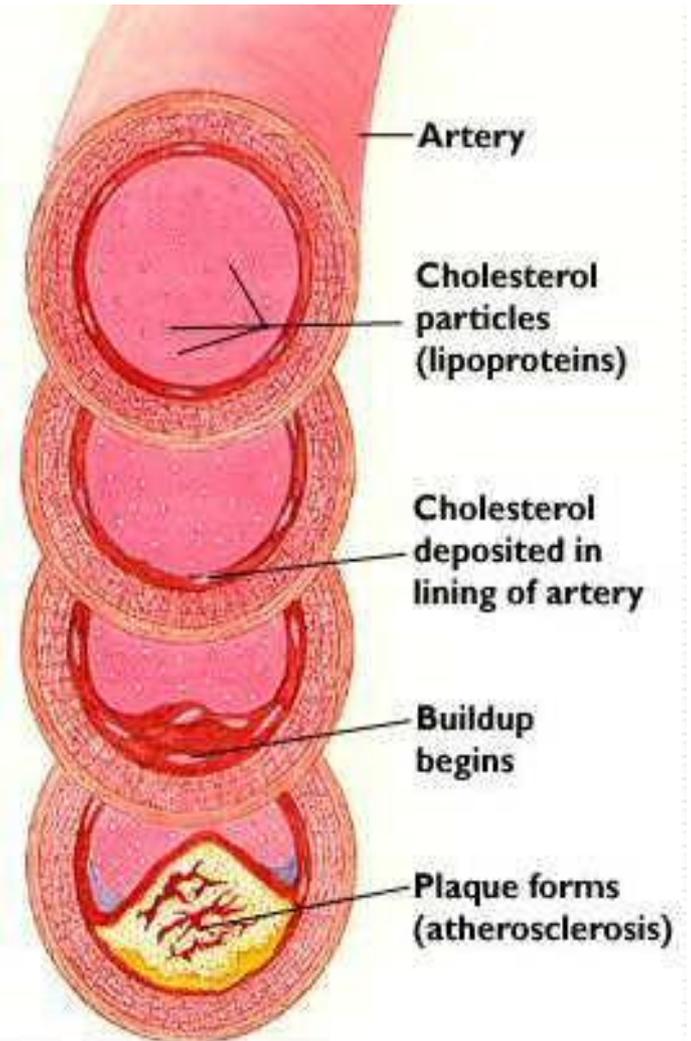
Properties and functions of lipoproteins

Increasing density

Lipoprotein class	Density (g/mL)	Diameter (nm)	Source and function
HDL α -lipoprotein	1.063-1.21	5 – 15	Liver Removes “used” cholesterol from tissues and takes it to liver → good cholesterol
LDL β -lipoprotein	1.019 – 1.063	18 – 28	Formed in circulation by partial breakdown of IDL. Delivers cholesterol to peripheral tissues
IDL	1.006-1.019	25 - 50	Synthesized from VLDL during VLDL degradation Triglyceride transport and precursor to LDL
VLDL pre- β lipoprotein	0.95 – 1.006	30 - 80	Liver transport mainly TG from liver to peripheral tissues
Chylomicron	< 0.95 Least dense	100 – 500 Large sized	Intestine Transport of dietary TG from intestine to liver

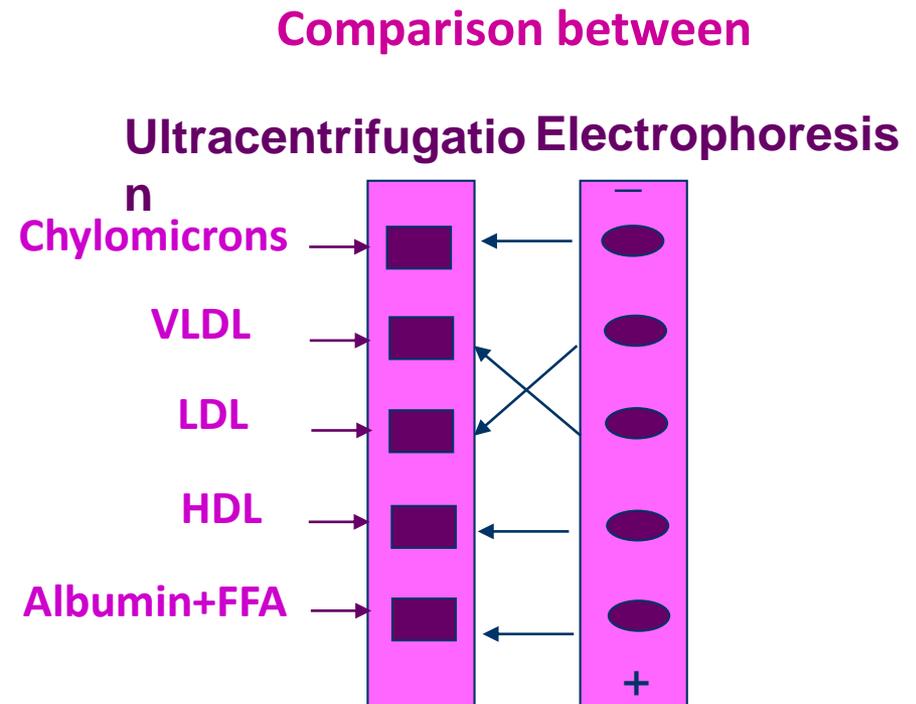
- Note that
 - **high LDL** values are **bad**
 - **high HDL** values are **good**
- High LDL Cholesterol and Low HDL Cholesterol

→ **Atherosclerosis**



Separation of lipoproteins

- Plasma lipoproteins are separated by 2 methods (ultracentrifugation, electrophoresis) into different fractions



References

- Victor A Hoffbrand, Paul Moss, J Pettit; ***Essential Haematology***. Essentials Series Blackwell Science, New York; 2008.
- Victor W. Rodwell, David A. Bender, Kathleen M. Botham, Peter J. Kennelly, P. Anthony Weil. ***Harper's Illustrated Biochemistry***. McGraw-Hill Ed, 31 ed, 2018.