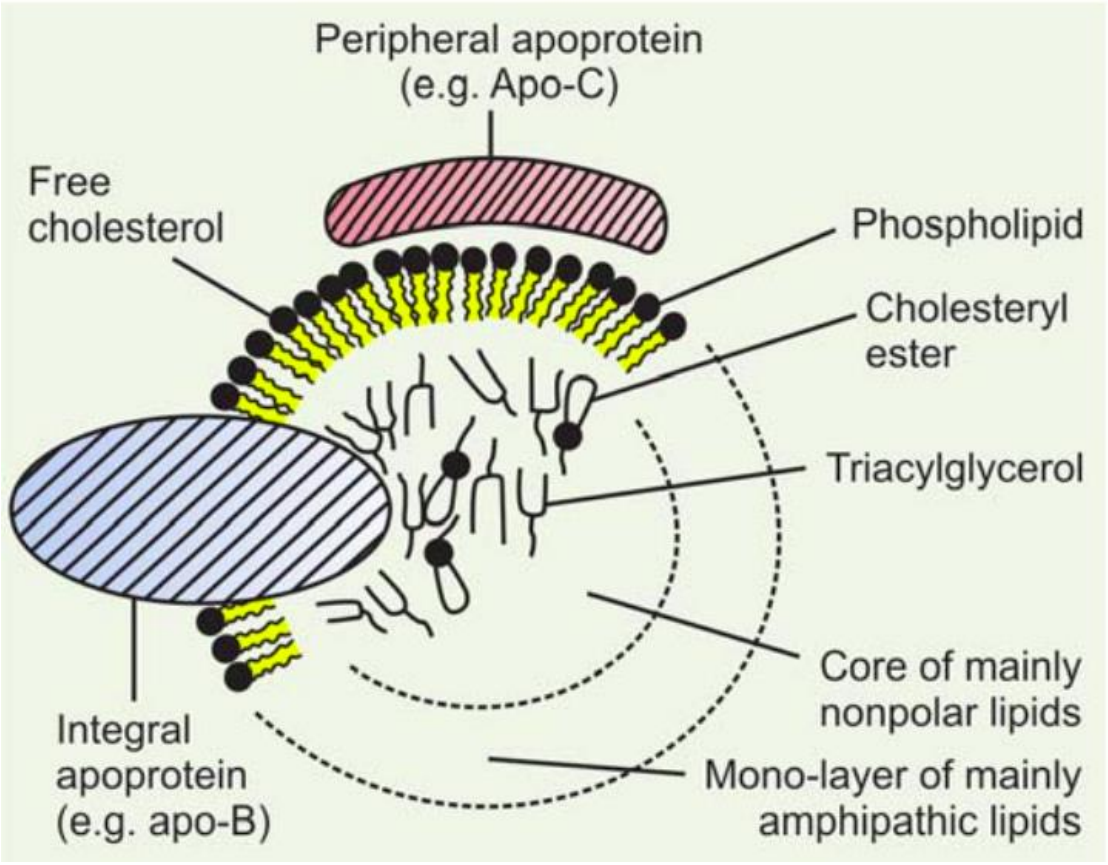
Plasma lipoproteins and metabolism

Introduction

- Total plasma lipid is 400—600 mg/dL.
- Lipids are insoluble in water
- Therefore, they are complexed with proteins to form lipoproteins.
- The protein part of lipoprotein is called apolipoprotein.
- The lipoproteins are usually abbreviated as Lp.
- In lipoproteins, more hydrophobic lipids, e.g. triglycerides and cholesteryl esters, are present in the interior and surrounded by amphipathic lipids e.g. phospholipids and free cholesterol
- Free fatty acids (FFA) or non-esterified fatty acids (NEFA) are complexed with albumin.



Classification of Lipoproteins

1- Depending on the density (by ultra-centrifugation)

2- On the electrophoretic mobility

- A sample of plasma is applied on a strip of cellulose acetate.
- The strip is put in buffer to make proteins acquire a negative charge.
- On application of an electric field, the plasma lipoproteins will separate on the strip into many bands according to their difference mainly in electric charge.
- The fastest is HDL (α – lipoprotein) which moves and appears closer to the anode followed by VLDL (pre-beta lipoprotein) and then LDL (β- lipoprotein).
- Chylomicrons should be absent in a fasting blood sample but if the sample was non-fasting then chylomicrons will remain at the site of application because chylomicrons are rich in TGs and the TGs are neutral and would not move in an electric field.

The lipoproteins in plasma are classified into five major types

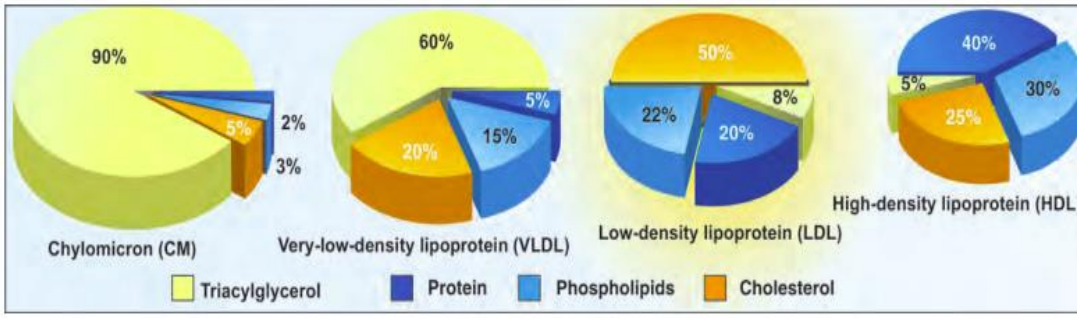
1. Chylomicrons—contains apoprotein B-48.

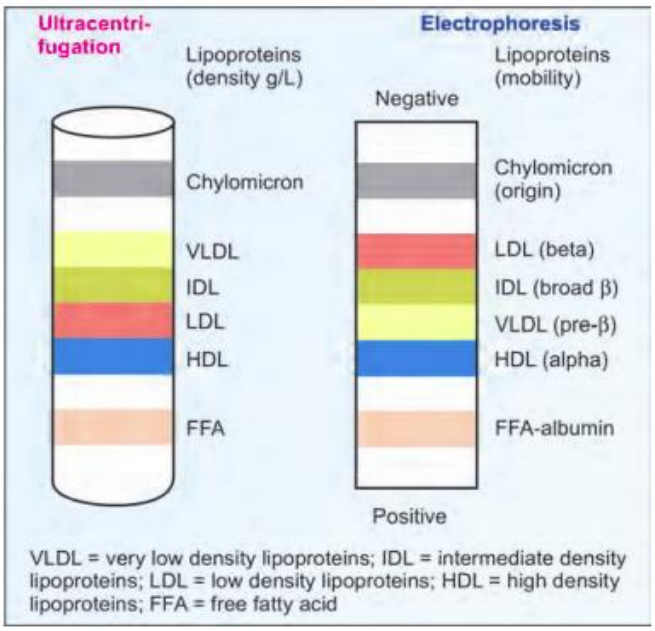
2. Very low density lipoproteins (VLDL) or pre-beta lipoproteins. Main apoprotein is B-100.

3. Intermediate density lipoproteins (IDL) or broadbeta lipoproteins

4. Low density lipoproteins (LDL) or beta-lipoproteins. Major apoprotein in LDL is B-100.

5. High density lipoproteins (HDL) or alpha-lipoproteins. Major apoprotein in HDL is apo-A.





Important Notes on composition of lipoproteins:

1) Chylomicrons: carry mainly exogenous TG. In a fasting state, normally there should be no chylomicrons but if they are found, this is abnormal. Chylomicrons cause turbidity of the plasma. After a meal we get chylomicrons but usually disappear after 6 hours. Complete disappearance may require 12 – 14 hours of fasting.

2) VLDL : carries mainly endogenous TG that is synthesized in the liver

3) LDL : carries cholesterol and its esters

4) HDL : carries large amount of phospholipids in addition to cholesterol.
- HDL carries cholesterol from peripheral tissues to the liver by a special process called reverse cholesterol transport; the process whereby excess cholesterol

	Chylomicron	*VLDL*	*IDL*	*LDL*	*HDL*	*FFA (*)*
Density g/L	<0.95	0.95–1.006	1.006–1.019	1.019–1.063	1.063–1.121	1.28–1.3
Diameter (nm)	500	70	30	25	15	-
Electrophoretic mobility	origin	pre-beta	broad beta	beta	alpha	albumin
% Composition						
Protein	2	10	20	20	30-60	99
TAG	80	50	30	10	10	0
Phospholipids	10	20	20	20	20-30	0
Cholesterol	10	20	30	50	10-30	0
FFA	0	0	0	0	0	1
Apoproteins	A,B-48,C-II,E	B-100, C-II,E	B-100, E	B-100	A-I, C, E	Albumin
Transport function	TAG from gut to muscle and adipose tissue	TAG from liver to muscle and adipose tissue		Cholesterol from liver to peripheral tissues	Cholesterol from peripheral tissues to liver	FFA from adipose T to muscle and liver

(*) Free fatty acids are not generally included in the lipoproteins. They are seen in circulation, weakly bound to albumin.

Apo-lipoproteins

- The protein part of lipoprotein is called apolipoprotein (apo-Lp) or apoprotein.
- All apoproteins are mainly synthesized in liver; but small quantities are produced from almost all organs.
- Intestinal cells produce small quantities of apo-A.
- The apoproteins present in lipoproteins are: Apo A-I , Apo A-II, Apo B-48, Apo B-10, Apo C-I, Apo C-II, Apo C-III, Apo D, Apo E
- apo A is an activator of LCAT enzyme while its Apo C will be taken by chylomicrons and VLDL and acts as an activator of LPL enzyme.

Apolipoproteins Functions:

1. Make the lipids water – soluble.

2. Activate the enzymes involved in lipoprotein metabolism

3. Are necessary for the binding of lipoproteins with tissue receptors.

4. Are necessary for secretion of lipoproteins from their sites of synthesis such as intestine and liver.

Examples of functions: Apo A is a cofactor for LCAT enzyme (lecithin cholesterol acyl transferase) which catalyzes the following reaction:

$$\text{Lecithin} + \text{Free cholesterol} \xrightarrow[\text{Apo A}]{\text{LCAT}} \text{C E} + \text{lysolecithin}$$

- Apo B - 48 is synthesized by intestine and combine chylomicrons.
- Apo B-100 is synthesized by liver and combines VLDL
- Apo C is a cofactor for lipoprotein lipase enzyme.

Chylomicrons

1- Synthesis of Chylomicrons

- Chylomicrons are formed in the intestinal mucosal cells, rich in triglyceride.
- Contain only apo-B-48 and apo-A but apo-C and apo-E are added from HDL in blood during transport.

2- Function of Chylomicrons

- Chylomicrons are the transport form of dietary triglycerides from intestines to the adipose tissue for storage; and to muscle or heart for their energy needs.
- The clearance of chylomicrons from the blood is rapid, the half-time of disappearance being under 1 hour in humans. Larger particles are catabolized more quickly than smaller ones.
- Fatty acids originating from chylomicron triacylglycerol are delivered mainly to adipose tissue, heart, and muscle (80%), while ~20% goes to the liver.

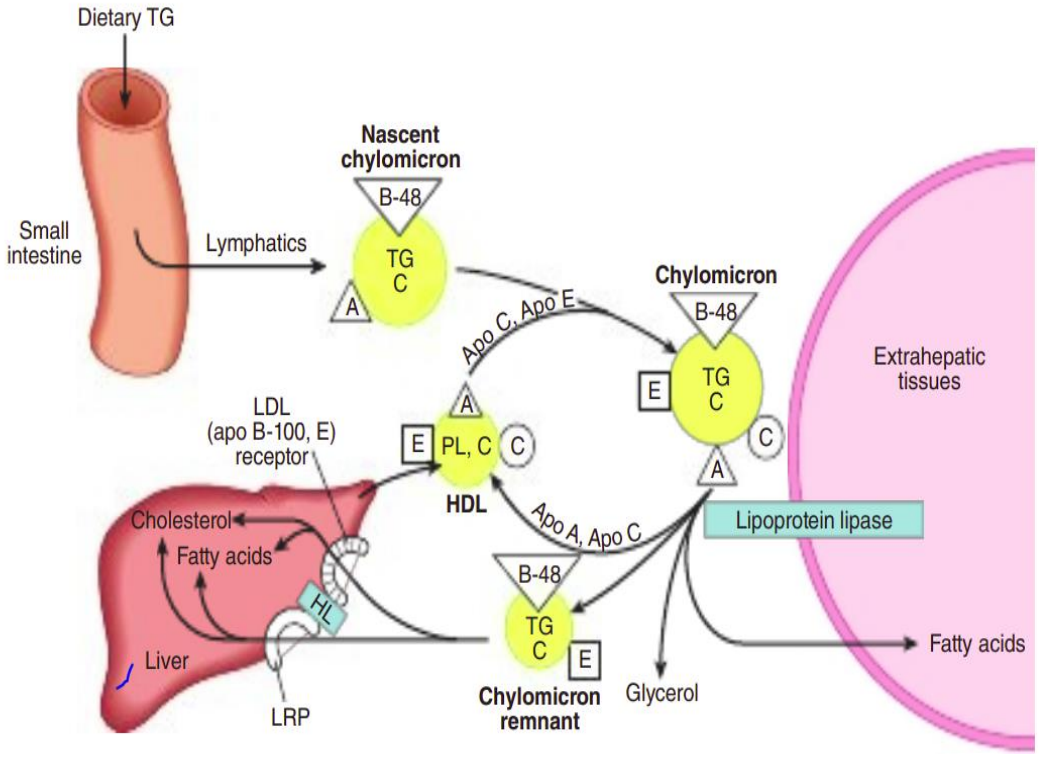
3- **Metabolism of Chylomicrons**

i. The dietary fat leaves the intestine mainly as nascent Chylomicrons

ii. Main sites of metabolism of chylomicrons are adipose tissue and skeletal muscle. The half-life of chylomicrons in blood is about 1 hour.

iii. The enzyme lipoprotein lipase (LpL) is located at the endothelial layer of capillaries of adipose tissue, muscles and heart; but not in liver.

- Apo C-II present in the chylomicrons activates the LpL. The LpL hydrolyzes triglycerides present in chylomicrons into fatty acids and glycerol.
- 90% of TG in chylomicrons will be hydrolyzed. F.As will be oxidized or re-esterified into TGs in such tissues. Apo C-II will return back to HDL. Chylomicrons will become smaller in size and called Chylomicron remnants. Chylomicron remnants will be taken by the liver through apo E receptors, delivering its content of cholesterol, apo B-48 and what remained of their TG.
- Apo E can recognize the apo E receptors.



Very low density lipoproteins

1- Synthesis of VLDL

- They are synthesized in the liver from glycerol and fatty acids and incorporated into VLDL along with hepatic cholesterol, apo-B-100, C-II and E.
- Apo-B-100 is the major lipoprotein present in VLDL when it is secreted. ApoE and C-II are obtained from HDL in plasma.

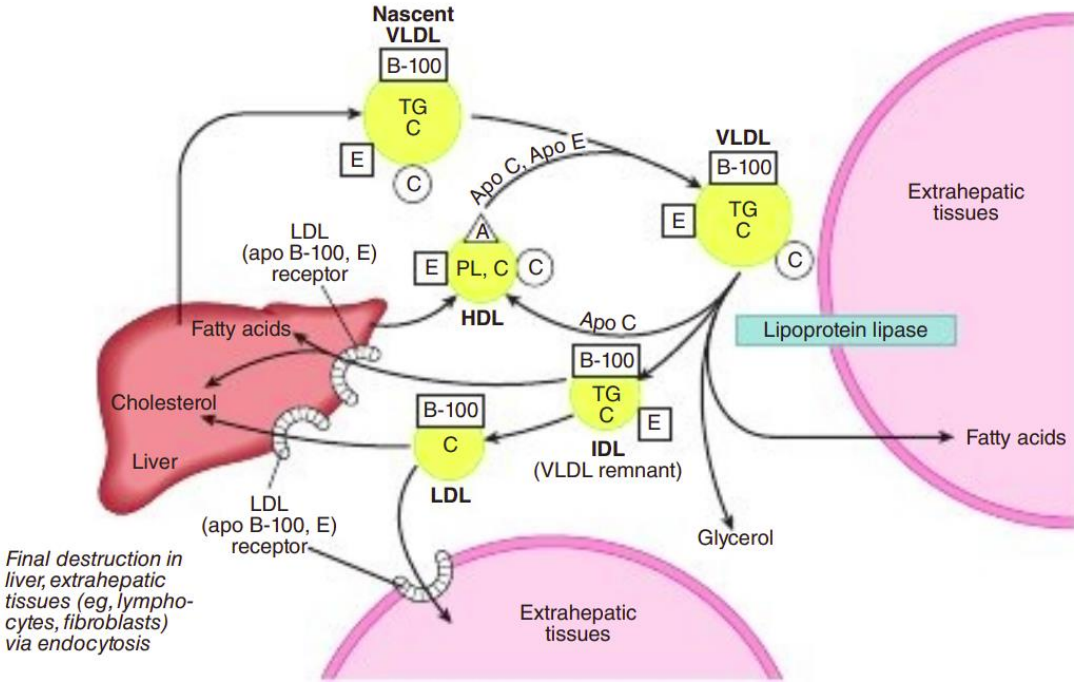
2- Function of VLDL

The VLDL carries triglycerols (endogenous triglycerols) from liver to peripheral tissues for energy needs

3- Metabolism of VLDL

- The half-life of VLDL in serum is only 1 to 3 hours.
- When they reach the peripheral tissues, apo C-II activates LpL which liberates fatty acids that are taken up by adipose tissue and muscle.
- The remnant is now designated as IDL (intermediate density lipoprotein) and contains less of TAG and more of cholesterol.
- The major fraction of IDL further loses triglyceride, so as to be converted to LDL (low density lipoprotein). This conversion of

VLDL to IDL and then to LDL is referred to as lipoprotein cascade pathway



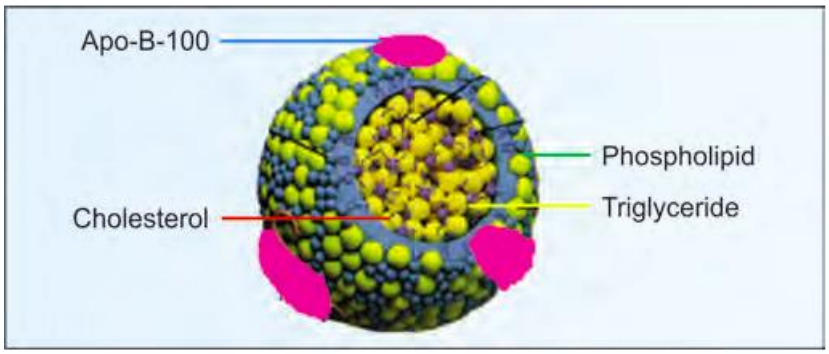
Low density lipoproteins

- Low density lipoproteins (LDL) transports cholesterol from liver to peripheral tissues.
- The only apoprotein present in LDL is apo B100.
- Most of the LDL particles are derived from VLDL, but a small part is directly released from liver.
- The half-life of LDL in blood is about 2 days.

Function of LDL

- About 75% of the plasma cholesterol is incorporated into the LDL particles.
- LDL transports cholesterol from liver to the peripheral tissues.
- The cholesterol thus liberated in the cell has three major fates:

i. It is used for the synthesis of other steroids like steroid hormones.
ii. Cholesterol may be incorporated into the membranes.
iii. Cholesterol may be esterified to a MUFA by acyl cholesterol acyl transferase (ACAT) for storage. The cellular content of cholesterol regulates further endogenous synthesis of cholesterol by regulating HMGCoA reductase.

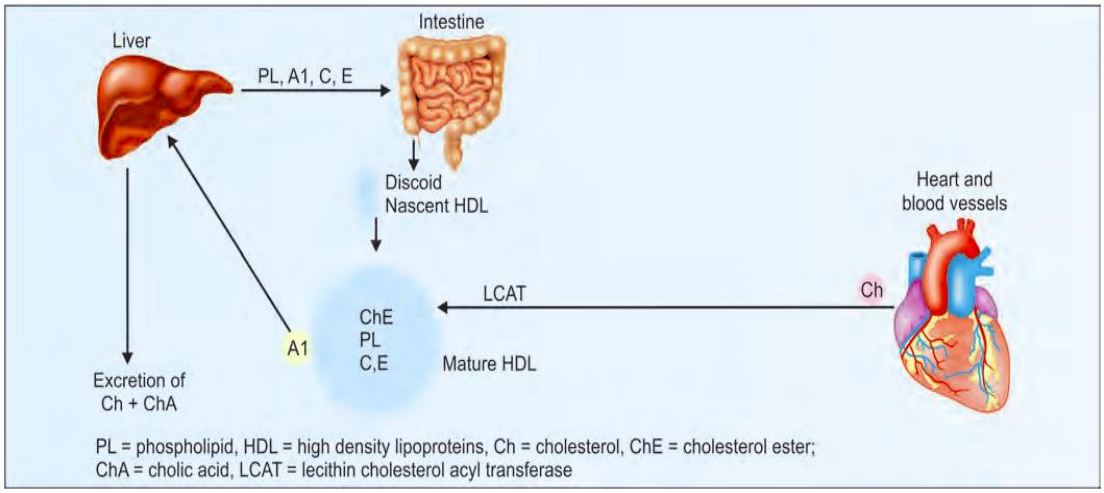


High density lipoprotein

- High density lipoproteins (HDL) transport cholesterol from peripheral tissues to the liver.
- The major apoproteins in HDL are Apo A1, with some Apo A2, Apo C and Apo E.
- HDL serves as a plasma reservoir of Apo C and Apo E which can be transferred to VLDL and chylomicrons and back.

Functions of HDL

i. HDL is the main transport form of cholesterol from peripheral tissue to liver, which is later excreted through bile. This is called reverse cholesterol transport by HDL.
ii. The only excretory route of cholesterol from the body is the bile.
iii. Excretion of cholesterol needs prior esterification with PUFA. Thus PUFA will help in lowering of cholesterol in the body, and so PUFA is anti-atherogenic.



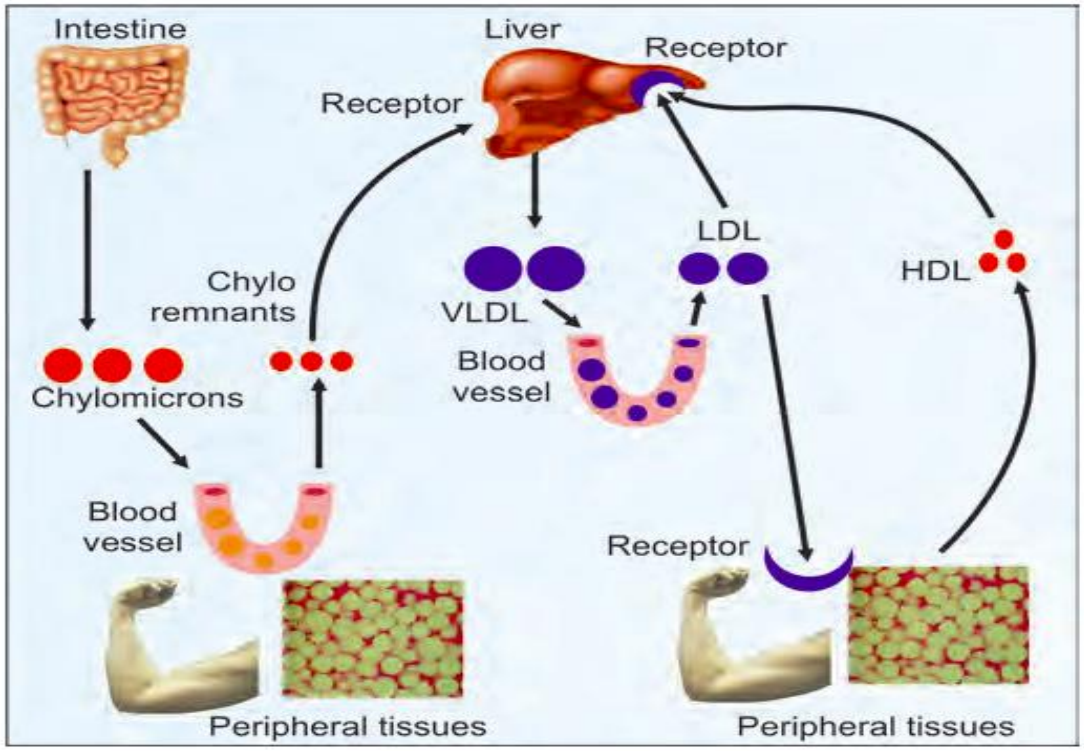


Fig. 13.18: Summary of lipoprotein metabolism

REFRANCES

1. Harper's Biochemistry. Lange, USA.

2. Lippincott Illustrated Reviews: Biochemistry, 7e. Denise R. Ferrier

3. Text book of medical biochemistry. Chtterjea MN. India. Latest edition.