Biochemistry team 436

Lactic acidosis lecture Summary

Metabolic acid base disorders

Metabolic acidosis:
Reduction in Bicarbonate concentration in ECF.

Causes:
- Impaired excretion of H+
- Increased production of H+
- Ingestion of H+ or drugs metabolized to acids.

High anion gap: > 11 mEq/L

Clinical effects:
- Hyperventilation
-Arrythmia, cardiac arrest
- Increased H+ conc stimulates respiratory response.

Metabolic alkalosis:
Increase in Bicarbonate concentration in ECF.

Causes:
- Loss of H+ due to vomiting.
- Potassium deficiency due to diuretics.
- Ingestion of sodium bicarbonate.

Low anion gap: < 3 mEq/L

Clinical effects:
- Hypoventilation.
- Increased PCO2 to compensate.
- Respiratory arrest.
-Confusion, coma, death.

Lactate metabolism in tissue:

- Body produces 1500 mmoles of lactate daily.
- All tissues produce lactate in anaerobic conditions.
- Skeletal muscles produce a lot of lactate during intense exercise.
- Lactate enters blood & is metabolized by Cori cycle in liver.
- Lactate is metabolized in 60% liver and 30% kidney.
- Some is metabolized to CO2 and H2O in Krebs cycle.
- Pyruvate is converted to lactate by lactate dehydrogenase.

Lactic acidosis can occur due to:

- Excessive tissue lactate production.
- Impaired hepatic metabolism of lactate.

Diagnosis of lactic acidosis:

- Hyperlactemia: 2 to 5 mmols/L
- Severe lactic acidosis: > 5 mmols/L

Treatmentof lactic acidosis:

- Correcting the underlying condition.
- Restoring adequate tissue oxygenation.
- Avoiding sodium bicarbonate.

Lactic acidosis:
Elevated conc. Of plasma lactate.
It has two types.

Type A:
Due to hypoxia in the tissue.

In cases of:
- M.I
- Pulmonary embolism.
- Hemorrhage.
- Tissue hypoperfusion (shock, cardiac arrest, heart failure)
- Anaerobic exercise.

Type B:
Due to disorders in carbohydrate metabolism.

In cases of:
- Liver failure
- Drug intoxication
- Chronic hepatic disease accompanied by bleeding or shock.
- Congenital lactic acidosis due to deficiency of pyruvate dehydrogenase enzyme.

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Cholesterol metabolism lecture Summary

Cholesterol

1) Structure:
Sterol: 4 rings with a hydrocarbon tail and a hydroxyl group.
Cholesteryl ester: have a fatty acid tail

2) Function:
- Most important animal steroid.
- Maintains membrane fluidity.
- Insulating nerve fibers.
- Parent molecule for bile acids, bile salt, steroid hormones, vitamin D3.

3) Synthesis:
- In all tissues mainly in liver, intestines, adrenal cortex, testes, ovaries.
- Carbon atoms are derived from acetyl CoA.
- Biosynthesis enzymes are located in ER and cytoplasm.

HMG CoA Synthase enzyme:
In cytosol: cholesterol synthesis
In mitochondria of liver: ketogenesis
1) It makes HMG CoA from acetyl coA.

Mevalonic acid synthesis: in cytosol. Rate limiting step.
2) HMG CoA is reduced into mevalonic acid by **HMG CoA Reductase.**

HMG CoA Reductase: ER membrane enzyme with catalytic unit hanging in cytosol.
3) Synthesis of IPP (5C unit) from mevalonic acid.
4) Synthesis of FPP by putting 3 IPPs together.
5) Condensing to squalene, a 30C compound by squalene synthase.
6) Cyclization of squalene to 30C lanosterol.
7) Synthesis of 27 C Cholesterol (defect leads to Smith Lemli Oplitz syndrome)

4) HMG CoA Reductase Regulation:
It is the rate limiting enzyme of cholesterol synthesis.

1) Sterol dependent regulation of HMG CoA gene expression
Important molecules:
- SRE –SREBP – SCAP –Insig
Know what happens to SCAP when cholesterol is high or low.

2) Hormonal regulation
Important molecules:
Insulin, thyroxine, cortisol, glucagon.

3) Sterol accelerated enzyme degradation
Important molecule: Insigs

4) Sterol independent phosphorylation/dephosphoryltion
Important molecule:
ATP levels, AMP Kinase

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Lipoprotein metabolism lecture Summary

Lipids are hydrophobic molecules, to become soluble and transported in plasma, they become Lipoproteins, made of lipids and proteins.

Types of Lipoproteins:
1- Chylomicrons
2- VLDL
3- LDL
4- HDL

- ✧ Assembled in the intestinal mucosal cells
- ✧ Transport to peripheral tissue:
  - ✧ Dietary TAGs (90%)
  - ✧ Cholesterol
  - ✧ Fat-soluble vitamins
  - ✧ Cholesteryl esters
- ✧ The milky appearance of plasma after a meal is due to chylomicrons

Lipoproteins differ based on:
1- Lipid and protein composition
2- Size
3- Density
4- Site of origin

Composition of Lipoproteins:

A- Neutral lipid core:
1- Triacylglecerols: mainly transported by Chylomicrons (90%) and VLDL (60%)
2- Cholesteryl esters

B- Hydrophobic shell:
1- Amphipathic apolipoproteins
2- Phospholipids
3- Free cholesterol: mainly transported by LDL (50%) and HDL (25%)

Types:
- ✧Apo A
- ✧Apo B48 and Apo B 100
- ✧Apo C-I, C-II, C-III
- ✧Apo E

Functions:
- ✧Provide structure to lipoprotein particles
- ✧Provide recognition sites for cell-surface receptors
- ✧Activators or coenzymes for the enzymes involved in lipoprotein metabolism

VLDL Metabolism

1. Release from the liver

- ✧ As nascent particles containing:
  - ✧ TAGs and cholesterol
  - ✧ Apo B-100
- ✧ Obtain apo C-II and apo E from circulating HDL particles
- ✧ Apo C-II is required for activation of LPL

2. Modification in the circulation

- ✧ TAGs in VLDL are degraded by lipoprotein lipase (LPL)
- ✧ VLDL becomes smaller and denser
- ✧ Surface components (apo C and E) are returned to HDL
- ✧ VLDL transfers TAGs to HDL in exchange for cholesteryl esters
- ✧ This exchange is catalyzed by cholesteryl ester transfer protein (CETP)

3. Conversion to LDL

- ✧ After modifications, VLDL is converted to:
  - ✧ LDL
  - ✧ IDL (taken up by liver cells thru apo E)
  - ✧ VLDL remnants
- ✧ Apo E exists in three isoforms:
  - ✧ Apo E-2 (Poorly binds to receptors)
  - ✧ Apo E-3
  - ✧ Apo E-4

Lipoprotein Lipase

- ✧ Extracellular enzyme that degrades lipids
- ✧ Anchored by heparin sulfate to the capillary walls of most tissues
- ✧ Manly present in adipose tissue, cardiac and skeletal muscle
- ✧ Requires ApoC-II for activation
- ✧ Degrades TAGs into free fatty acids and glycerol
- ✧ Insulin stimulates LPL synthesis
- ✧ Deficiency of LPL or apo C-II causes: Type 1 hyperlipoproteinemia (familial LPL deficiency)

VLDL Diseases

1- Hypo-lipoprotein-emia

✧Abetalipoproteinemia is due to inability to load apo B with lipids
✧Few VLDLs and chylomicrons are formed
✧TAGs accumulate in liver and intestine

2- Steatohepatitis (Fatty liver disease)

✧Imbalance between:
  ✧TAG synthesis in the liver and
  ✧Secretion from the liver
✧Leads to accumulation of TAGs in the liver (fatty liver)

3- Type I hyperlipoproteinemia

✧A rare, autosomal recessive disease
✧Due to familial deficiency of LPL or its coenzyme (Apo C-II)
✧Causes excessive accumulation of chylomicrons in plasma (≥1000 mg/dl) (hyperchylomicronemia)
✧High fasting plasma TAGs are observed in these patients

4- Type III hyperlipoproteinemia

✧Also called familial dysbetalipoproteinemia, or broad beta disease
✧Individuals homozygous for apo E-2 are deficient in clearing:
  ✧Chylomicron remnants and
  ✧IDL from the circulation
✧Leads to hypercholesterolemia and premature atherosclerosis

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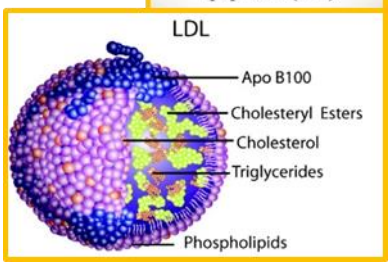
Lipoprotein and atherosclerosis lecture Summary



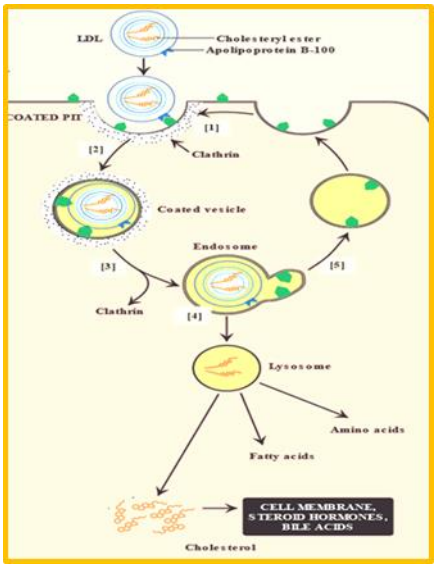
- LDL particles mainly contain cholesterol and cholesteryl esters
- Produced from VLDL particles
- Contain Apo B-100 lipoprotein
- Provides cholesterol to peripheral tissue
- LDL binds to cell surface receptors thru Apo B-100
- Called receptor-mediated endocytosis

How are LDL molecules taken up by the liver?

By Receptor-mediated endocytosis:

- Binding of Apo B-100 to LDL receptor glycoprotein
- Endocytosis
- Endosome formation (LDL vesicle fuses with other vesicles)
- Separation of LDL from its receptor
- Receptor is recycled
- LDL degraded by lysosomes releasing:

  Free cholesterol, fatty acids, amino acids, phospholipids



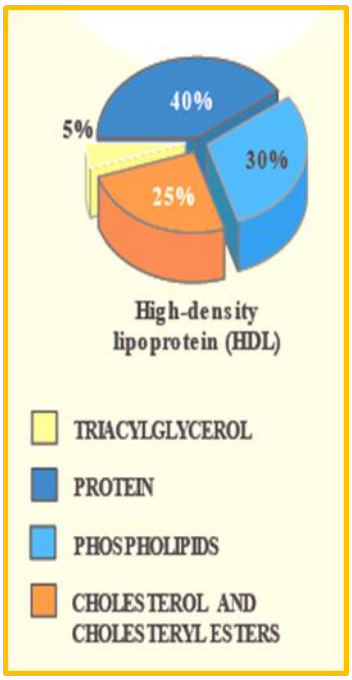
LDL is bad cholesterol

- Transports cholesterol to peripheral tissues
- Elevated LDL levels → increased risk for atherosclerosis / heart disease
- Deficiency or defects in LDL receptors results in:
  - Decreased uptake of cholesterol by cells
  - Increased accumulation of cholesterol in blood vessels
- Familial hypercholesterolemia
  - Patients are unable to clear LDL from blood
  - Premature atherosclerosis and heart disease

Up regulation:	Low intracellular cholesterol level causes:	Recycling	Increased	Increase	Increased	Increased
Down regulation:	High intracellular cholesterol level causes:	Degradation	Inhibition	Reduction	Decreased	Decreased
		LDL receptors:	Receptor synthesis at gene level	cell surface receptors	uptake of LDL by cells	de novo synthesis of cholesterol

High density lipoprotein (HDL):

- HDL particles mainly <u>contain</u>:
  - Protein, phospholipids, cholesterol, cholesteryl esters
- <u>Produced in</u> the liver and intestine
- <u>Contains</u> Apo A-1, C-2 and E lipoproteins
- Take up cholesterol <u>from</u> peripheral tissues to the liver



<u>Nascent HDL</u>:

Disk-shaped
Contains apo A-I, C-II and E lipoproteins
Mainly contains phospholipids

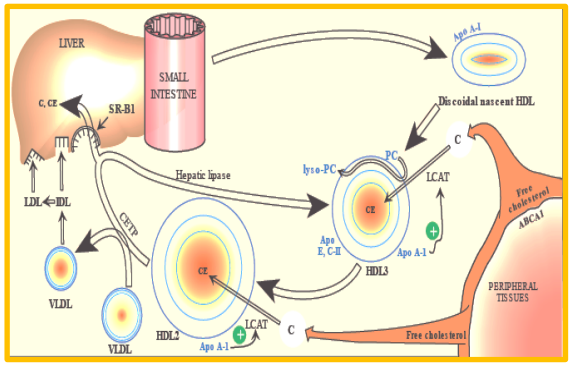
<u>Mature HDL:</u>

Nascent HDL + cholesteryl esters → HDL_3

HDL_3 + more cholesteryl esters → spherical HDL_2

HDL_2 transfers cholesterol to the liver

Functions of HDL:



- Reservoir of apoproteins (Apo C-II and E)
- Transports cholesterol to liver from:
  - Peripheral tissues
  - Other lipoproteins
  - Cell membranes
- Suitable for cholesterol uptake due to:
  - High content of phospholipids
  - Phospholipids solubilize cholesterol and provide fatty acids for cholesterol esterification

HDL is a good cholesterol:

- HDL transports cholesterol from peripheral tissues to the liver for degradation
- Reduces cholesterol level in tissues and circulation (reverse cholesterol transport)
- High HDL levels have inverse correlation with atherosclerosis
- Reverse cholesterol transport includes:
  - Cholesterol efflux from peripheral tissues to HDL
  - Cholesterol esterification
  - Binding and transfer of cholesteryl ester-rich HDL_2 to liver
  - Release of lipid-depleted HDL_3

Atherosclerosis:

- LDL uptake by cells is receptor mediated
- Additionally, macrophages possess scavenger receptors called scavenger receptor class A (SR-A)
- The macrophages take up chemically-modified LDL by endocytosis
- Chemically-modified LDL contains oxidized lipids and Apo B
- Unlike LDL receptors, the SR-A is not down-regulated in response to high intracellular cholesterol
- Cholesteryl esters accumulate in macrophages converting to foam cells
- Foam cells contribute to plaque formation and atherosclerosis

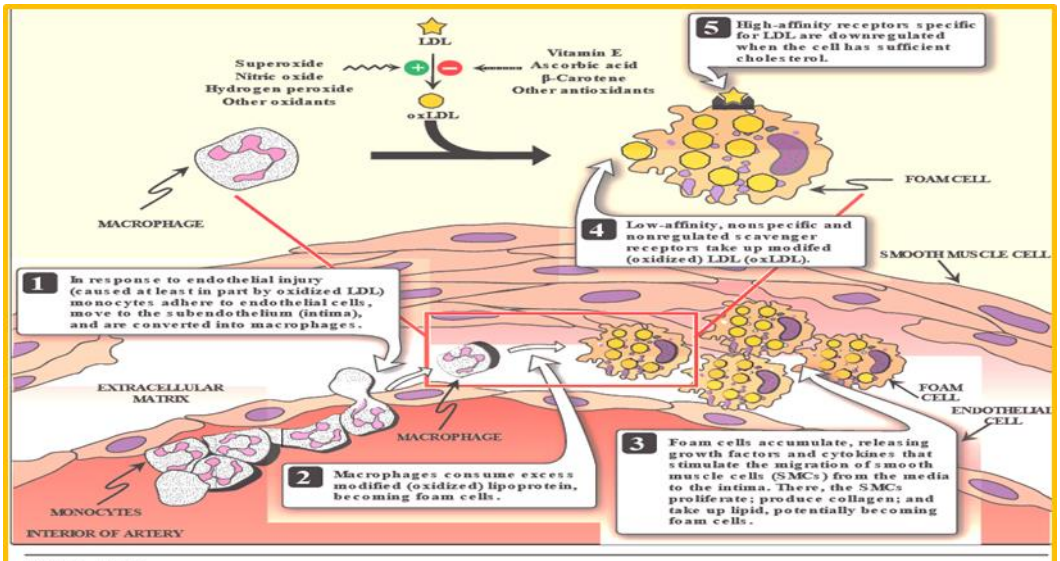


Figure 18.22
Role of oxidized lipoproteins in plaque formation in an arterial wall. LDL = low-density lipoprotein.

Lab investigations of atherosclerosis:

- Fasting serum lipid profile:
  - TAG level (reflects chylomicron and VLDL levels)
  - LDL, HDL levels
  - Total cholesterol level (reflects LDL, HDL and cholesterol levels)
- Other tests:
  - Serum lipoprotein electrophoresis
  - Serum apoprotein levels (e.g., apo-B)

Lipoprotein (a):

- Lp(a) is identical in structure to LDL particle
- Contains apo(a) in addition to apo B-100
- High plasma Lp(a) level is associated with increased risk of coronary heart disease
- Circulating levels of Lp(a) are determined by:
  - Genetics (mainly)
  - Diet (trans FAs increase Lp(a) levels)
  - Estrogen (decreases Lp(a) levels)
- The apo(a) protein is structurally similar to plasminogen
  - Competes with plasminogen
  - Slows the breakdown of blood clots
  - Triggering heart attack
    - A risk factor for CAD

Take home message:

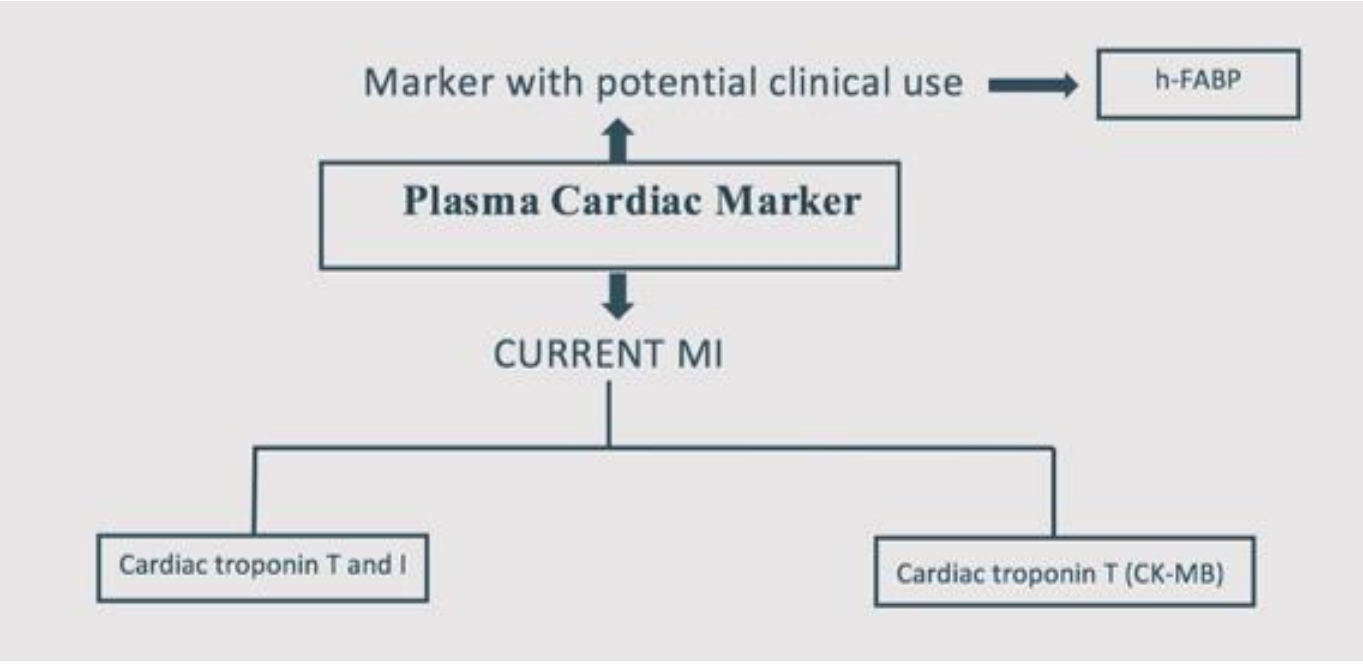
- Imbalance in the LDL and HDL metabolism causes increased accumulation of lipids in the body
- LDL is bad cholesterol whereas HDL is good cholesterol
- The pathogenesis of atherosclerosis includes the uptake of oxidized LDL by macrophages through scavenger receptor class A (SR-A) producing foam cells and atherosclerotic plaque

Biochemistry team 436

MI Biomarkers lecture Summary

Criteria of diagnosing MI	Features of an ideal marker

Requires presence of at least two of the following characteristics:
• Typical heart attack symptoms
• Characteristic rise and fall pattern of a cardiac marker in plasma
  • Rise and gradual fall of cardiac troponins
  • More rapid rise and fall of CK-MB
• Typical ECG pattern
	• High sensitivity (detected even in low concentration at early stages)
	• High specificity (specifically detecting damage of cardiac tissue, and is absent in non-myocardial tissue injury)
	• Rapid release into plasma
	• Easily measured
	• Good prognostic value (strong correlation between plasma level and extent of myocardial injury)



Enzyme	Abnormal activity detectable (Hours)	Peak value of abnormality (Hours)	Duration of abnormality (Days)
Troponin T , I	4 – 6	12 – 24	3 – 10
CK-MB	3 – 10	12 – 24	1,5 – 3
Total CK	5 – 12	18 – 30	2 – 5

Blood samples collected after MI ⇨

- Baseline (upon admission).
- Between 12 and 24 hours after the onset of symptoms.

Troponins	CK-MB	h-FABP	BNP
• Troponins are structural proteins in cardiac myocytes and in skeletal muscle. • Cardiac troponins (cTn) are structurally different from muscle troponins.	• Three main CK isoenzymes with two polypeptide chains B or M • It rises and falls transiently after MI	• cytosolic protein involved in fatty acid transport and metabolism .	• peptide produced by the ventricles of the heart in response to: ***Myocardial stretching and ventricular dysfunction after MI***
• cTn (cardiac troponins) are mainly bound to proteins, with small amount soluble in the cytosol. • ***Highly specific markers for detecting MI.***	• ***CK-MB is more sensitive and specific for MI than total CK*** • More than 5 % is indicative for MI	• A promising marker to be used in combination with troponins .	• ***marker for detecting Congestive heart failure***
• Detectable in plasma in ***4-6 h.*** after MI. • Level peaks in ***12-24 h*** • Remain elevated for up ***to 10 days.***	• Detectable in plasma in ***3-10 h***. after MI • Level Peaks in ***12–24 h.*** • Returns to normal in ***1.5-3 days***	• Detectable in plasma as early as ***30 min.*** • Level Peaks in ***6-8 h.*** • Returns to normal levels in ***24-30 h.***	• **Its *serum levels* in pulmonary diseases .** But **in heart failure** its ***levels are markedly high***
• After MI, cytosolic troponins are released rapidly into the blood (first few hours). • Structurally bound troponins are released later for several days.	• Useful for early diagnosis of MI or re-infarction • Not significant if measured after 2 days of MI • Not highly specific elevated in skeletal muscle damage	• Higher amounts in myocardium than in brain, kidney and skeletal muscle	• ***An important marker for differential diagnosis of pulmonary diseases and congestive heart failure .***

Biochemistry team 436

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Good Luck ..