Importance of lipids in organism

- Lipids serve as metabolic fuels alternative to glucose
- Lipids are a component of cell membranes
- They are very good insulators (subcutaneous fat, tunics of nerve conductions)

Cholesterol:

- it is generally present in the plasma as esters with linoleic acid and linolenic acid
- intracellular (depot pool of cholesterol): esters of cholesterol with oleic acid and palmitic acid
- free cholesterol is a component of cell membranes
- a precursor for the synthesis of steroid hormones and bile acids

Triacylglycerols and phospholipids:

- The most important source of energy
- Short halftime in plasma - 12 h
- Intake by food, synthesis in liver, fat tissue and small intestine

- phosphatidylcholine takes part in structure of biomembranes
- sphingomyelin is present in central nervous system and myelinic sheaths of peripheral nerves

Fatty acids:

- Essential FA = linoleic acid, linolenic acid, arachidonic acid
- They occur in plasma either as esters or in a free form
- Depot pool in fat tissue in a form of TAG
- After lipolysis they are transported into liver, heart and muscles as a powerful source of energy
- The major part is esterified again under formation of TAG and phospholipids

Transport of lipids:

- Albumin ⇨ unesterified FA
- Prealbumin ⇨ retinol
- **Lipoproteins** ⇨ non-polar lipids

Determination of lipoproteins:

- **An ultracentrifugation** (to distinguish various classes according to the hydrated density):

  VLDL, IDL, LDL, HDL

- **Electrophoretically**: α-lipoproteins,
  pre-β-lipoproteins,
  β-lipoproteins,
  chylomicrons

- **Immunochemical methods**:
  Apo A, Apo B, Apo C, Apo D, Apo E, ...

Chylomicrons:

- They are formed in enterocytes
- **Apo B-48,** apo A, apo C, apo E are dominant apolipoproteins
- TAG are principal components (halftime 5 min, TAG are hydrolyzed by lipoprotein lipase to form FFA and monoacylglycerols)
- Chylomicron remnants are removed by liver

VLDL:

- **Apo B100**, apo C (handed on HDL), apo E, apo D are dominant apolipoproteins
- TAG in the core
- phospholipids and cholesterol on the surface
- VLDL
  - ⇨ arise on structures of endoplasmic reticulum and Golgi complex in hepatocytes and enterocytes
  - ⇨ pass by means of exocytosis into blood
- Lipoprotein lipase

LDL:

- **Apo B100** is one of the principal apolipoproteins (always one molecule only)
- Esterified cholesterol a phospholipids
- The LDL particle is internalized and broken down after binding on a membrane receptor
- Released free cholesterol inhibits the activity of 3-hydroxy-3-methylglutaryl- CoA reductase (key enzyme in synthesis *de novo* in cell)

HDL:

- **Apo AI, apo AII**, apo C and apo E are dominant apolipoproteins
- They are sythesized in hepatocytes and enterocytes
- **Nascent HDL**
  - ⇨ contains apolipoproteins and a bilayer of phospholipids
  - ⇨ has a discoidal shape
  - ⇨ admits free cholesterol from the surface of different tissues cell membranes and from other blood lipoproteins
- Esterification of cholesterol by means of LCAT (lecithin-cholesterol acyltransferase)
- **HDL2** (larger)**, HDL3** – spherical shape
- *CETP (cholesterol-ester-transfer-protein*)
- An exchange of cholesterol and TAG among HDL, VLDL and chylomicrons
- Lipoprotein lipase

Basic investigations of lipid metabolism

- **Cholesterol** 3.8 - 5.2 mmol/l
- **TAG** 0.9 - 1.7 mmol/l
- **HDL** > 0.9 mmol/l
- **LDL** < 4.5 mmol/l

Hyperlipoproteinemias

- Hypercholesterolemia
- Combined hyperlipidemia
- Hypertriglyceridemia

Primary hypercholesterolemias

- **Familial hypercholesterolemia**
  - a disorder of LDL receptors
  - cholesterol:
    - heterozygotes 7-15 mmol/l (ICD 30-50 years)
    - homozygotes 15-30 mmol/l (MI to 20 years)
  - increased concentration of LDL cholesterol and Apo B

Primary hypercholesterolemias

- **Familial defective Apo B100**
- a point mutation and a replacement of one amino acid in the position 3500 on the huge Apo B100 molecule
- cholesterol: 7-10 mmol/l

- **Polygenic hypercholesterolemia**
- a combination of adverse genetic and external factors
- cholesterol: 8 mmol/l approximately

Combined hyperlipidemias

- **Familial combined hyperlipidemia**
  - an intensive Apo B synthesis in liver with a concomitant increased production of VLDL and LDL (high atherogenic particles)
  - a frequent cause of ICD and MI to 60 years
  - cholesterol 10 - 15 mmol/l
    TAG 2.3 - 5.7 mmol/l

- **Familial dysbetalipoproteinemia**
  - a defective gene for ApoE - pathological lipoprotein β-VLDL
  - cholesterol 7.5 - 25 mmol/l
    TAG 2 - 10(20) mmol/l

Primary hypertriacylglycerolemias

- **Familial hyperlipoproteinemia type V**
  - rather uncommon disorder
  - more frequently in adults, obese, with DM and with hyperuricemia
  - an inductive factor: alcohol, drugs containing estrogens, renal insufficiency
  - increased in ELPHO: pre-β-lipoproteins and chylomicrons
  - cholesterol 7 - 13 mmol/l
    TAG 10 - 20 mmol/l

- **Familial hyperchylomicronemia**
  - a deficit of lipoprotein lipase or Apo CII
  - TAG 20 - 120 mmol/l
  - Treatment: fats containing FA with medium chains

Primary hyperlipoproteinemias

- **Familial hypertriacylglycerolemia**
- autosomal dominant transfer of disorder
- increased concentration of VLDL
- decreased concentration of HDL
- non-insulin-dependent diabetes mellitus adds at seniors
- cholesterol normal
- TAG to 6 mmol/l

Hyper-α-lipoproteinemias

- **Familial hyper-α-lipoproteinemia**

  - an occurrence of longevity
  - HDL cholesterol increased
  - total cholesterol slightly increased
  - TAG normal

Hypolipoproteinemias

- **Familial hypo-β-lipoproteinemia**
  - a longevity
  - low values of LDL cholesterol
  - a normal catabolism of LDL
  - a reduced production of apo B

- **A-β-lipoproteinemia**
  - a rare autosomal recessive disorder
  - heterozygotes have descreased LDL cholesterol
  - other lipids are in norm
  - homozygotes have a total deficit of lipoprotein particles containing apo B (malabsorption of fat, steatorrhea, retard grow, progressive degeneration of CNS, reduced visual sharpness, hemeralopia)

Hypolipoproteinemias

- **Hypo-α-lipoproteinemia**
  - lower HDL levels
  - a defective apo A-I (according to the location of the discribed case – Apo-A-I-Milano)
  - HDL cannot be produced without apo A-I
  - Apo C-II cannot be transported back into liver – relative deficiency of apo C-II
  - an increased level of VLDL

- **An-α-lipoproteinemia (Tangier disease)**
  - absence of HDL in plasma
  - extremely low levels of apo A-I and apo A-II
  - abnormally fast catabolism of HDL and apo A-I

Cholesterol storage disorders

- **Wolman´s disease**
  - deficit of lysosomal acid lipase
  - storage of cholesteryl esters and TAG into cells of liver, kidneys, suprarenal glands, hematopoietic system and small intestine
  - a fatal progress
- **Cholesteryl ester storage disease**
  - a milder form of previous disorder
- **Familial deficiency of lecithin cholesterol acyltransferase**
  - cholesteryl esters are missing
  - TAG are increased, but cholesterol is variable

Secondary hyperlipoproteinemias

1. **Diabetes mellitus type I**

- insulin is an activator of lipoprotein lipase
- if DM is decompensated
  - ⇨ ketoacidosis, hypertriglyceridemia and sometimes increased cholesterol as well

2. **Diabetes mellitus type II**

- a more intensive synthesis of VLDL in liver, insulin resistance, HDL reduction, TAG rise
- if DM is decompensated
  - ⇨ glycosylation of apo B

Secondary hyperlipoproteinemias

❸ **Hypothyreoidism**

- thyroxine increases the biosynthesis of LDL receptors in liver and an activity of lipoprotein lipase in adipocytes (by action of cAMP) as well

❹ **Nephrotic syndrome**

- hypoalbuminemia
- a stimulation of lipoprotein synthesis.
- increased cholesterol and TAG

Secondary hyperlipoproteinemias

5. **Chronic renal failure**
   - an inhibition of lipoprotein lipase in the plasma of uremic patients
   - elevated TAG
6. **Primary biliary cirrhosis**
   - hypercholesterolemia
7. **Obesity - TAG**
8. **Alcoholism - TAG**
9. **Treatment with hormones and diuretic drugs**
10. **Mental anorexia**

Treatment of lipid metabolism disorders

- **Isolated hypercholesterolemia**

  ⇨statins or statins + resins

- **Hypertriacylglycerolemia:**

  ⇨ fibrates or nicotinic acid

- **Combined hyperlipidemias**:

  ⇨ fibrates, resins + fibrates, statins + resins

Atherosclerosis

1. a damage of endothelial cells
   - monocytes and T-lymphocytes are adhered on them
2. endothelial cells diffuse into intima
3. endothelial cells turn into macrophages
   - principal cells of atherosclerotic process
4. lipoprotein particles are absorbed into macrophages
   - β-VLDL, LDL
   - LDL absorption is accelerated by lipoperoxidation:

a number of scavenger receptors on the cell surface isn´t regulated according to its cholesterol requirement

⇨ a massive accumulation of lipoprotein particles inside macrophages ⇨ transformation into foam cells

Risk factors

Atherogenic indexes

$\frac{\text{Total Chol} - \text{HDL Chol}}{\text{HDL Chol}}$	Upper limit: females < 3.0 males < 4.2
$\frac{\text{LDL Chol}}{\text{HDL Chol}}$	Upper limit: females to 2.3 males to 2.8
$\frac{\text{Total Chol}}{\text{HDL Chol}}$	Upper limit: females to 4.0 males to 4.8

Positive risk factors

- males > 45 years, females > 55 years
- an incidence of early ICD in familial history
- smoking
- hypertension 140/90 mm Hg
- HDL cholesterol < 0.9 mmol/l
- diabetes mellitus

Negative risk factor

- HDL Chol > 1.6 mmol/l

Description of optimal cardiac marker

- sensitivity assumes:
  - high concentration in the myocardium
  - rapid release for an early diagnosis
  - extended halftime in blood for a late diagnosis

- specificity assumes:
  - absence of marker in the other tissues except the myocardium
  - a marker cannot be proved in blood of individuals with intact myocardium

Recent recommendation of biochemical markers to AMI diagnosis

myoglobin and troponins

➔ **myoglobin** – an early marker

- ✓ high sensitivity
- ✓ low specificity
- ✓ recommended **0 - 4 h** after the onset of pain
- ✓ **diagnostic window 2 - 12 h** after the onset of symptoms
  - the double value after 2 h
  - the peak after 4 h
  - the application is limited to 8 – 12 h

◆ **two decision thresholds ? ACS vs. AMI**

- precision of the measurement is derived from biological variability (CV = 6 %)

Definitive markers cTnT and cTnI

- high specificity and sensitivity
- intervals of bleeding
  - **at admission and 4, 8, 12 h after admission**
  - **diagnostic window from 4 h to 7 days**
- required precision of measurement - consensually

  CV = 10 %

cTnT versus cTnI

◆cTnT

- ✓ one manufacturer
- ✓ elevated within 6 - 10days
- ✓ POCT qualitative
- ✓ 10 - 20 percents of results are positive in renal failure

◆cTnI

- ✓ a lot of manufacturers
  - up to fifteen-fold differences among results
- ✓ elevated within 4 – 7 days
- ✓ POCT qualitative
  quantitative
- ✓ 5 - 8 percents of results are positive in renal failure

IFCC

Recent recommendation of biochemical markers for diagnosis of acute coronary syndrome

- diagnostics of acute coronary syndrome (ACS), not AMI only
- it is essential in asymptomatic myocardial damages (without an ST-segment elevation of ECG)
- it is beneficial but not inevitable in symptomatic AMI with an ST-segment elevation