Hepatology

Case reports

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Biochemical methods in hepatology

- Part of a complex of laboratory methods, such as
  - microbiology, serology, immunology, molecular biology, function tests
- Static (classical LFT´s) vs. Dynamic tests (breath and farmacokinetic tests)

Biochemical exams

- Tests reflecting hepatocellular damage (ALT, AST)
- Tests reflecting damage of bile ducts and canalicular pole of hepatocytes (ALP, GGT)
- Tests measuring synthetic function of the liver (albumin, prealbumin, cholinesterase, prothrombin complex/factors)
- Tests measuring liver capacity for transport of organic anions (bilirubin, bile acids)
- Tests measuring liver capacity to metabolize endogeneous and exogeneous substances (amonnia, CDT, lidocain, aminopyrine, etc.)
- Accessory tests enabling to determine right diagnosis of a disease primarily of other than liver origin (e.g. dg of metabolic syndrome in NASH/NAFLD or right heart failure)
- Specific tests for accurate diagnosis in specific liver diseases (serological tests for infectious hepatitis, specific antibodies, targeted genetic exams, metabolic diseases…)

LFT´s

- Liver function tests (LFT´s) do not assess hepatic functions, they are just surrogate markers
- In broad context, they cover a wide range of not very specific markers
- Specific LFT´s consists of not routinely used exams, such as breath tests (aminopyrine, galactose, chromexcretory tests…)

LFT´s

Hepatocellular damage	AST
	ALT
	LD
	GST (glutathion-S-transferáza B)
Obstruction of bile ducts	ALP
	GGT
	Conjugated bilirubin, bile acids,
Met. of organic anions	S-, U-bilirubin (direct, indirect, delta)
	U-urobilogen
	S-bile acids
Protein synthesis	albumin
	prealbumin
	Cholinesterase
	prothrombin time

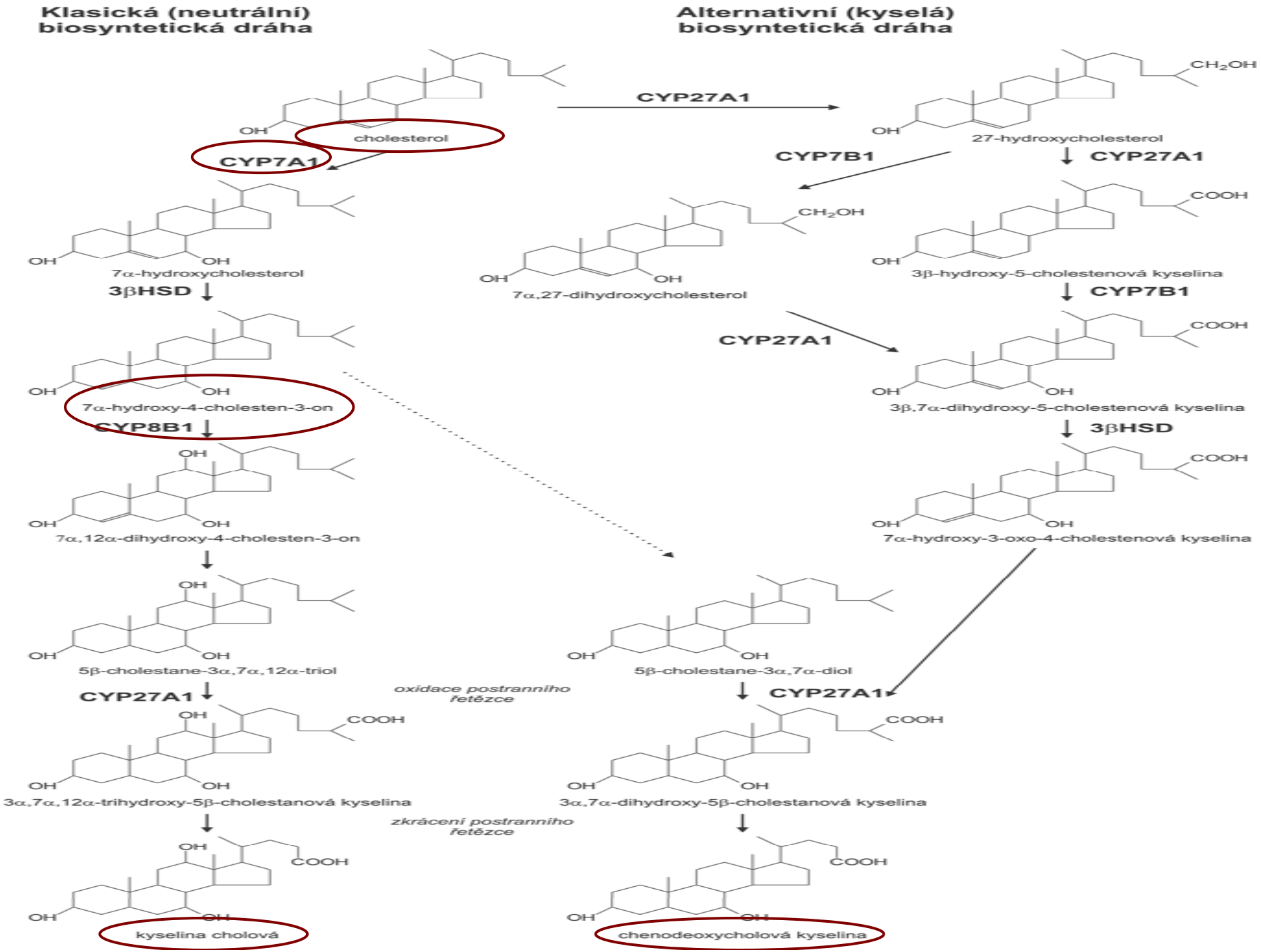
LFT - use

- Screening of liver diseases
- Confirmation of clinical suspicion
- Differential diagnosis of liver diseases
- Prognosis
- Assessment of treatment response

Factors affecting biliary cholesterol saturation

5F rule

- **Age: decline of cholesterol 7α hydroxylase activity – CYP7A1 (FORTY)**


Klasická (neutrální) biosyntetická dráha
Alternativní (kyselá) biosyntetická dráha
cholesterol
CYP27A1
CYP7A1
27-hydroxycholesterol
CYP7B1
CYP27A1
7α-hydroxycholesterol
7α,27-dihydroxycholesterol
3β-hydroxy-5-cholestenová kyselina
3βHSD
CYP7B1
CYP27A1
7α-hydroxy-4-cholesten-3-on
3β,7α-dihydroxy-5-cholestenová kyselina
CYP8B1
3βHSD
7α,12α-dihydroxy-4-cholesten-3-on
7α-hydroxy-3-oxo-4-cholestenová kyselina
5β-cholestane-3α,7α,12α-triol
5β-cholestane-3α,7α-diol
CYP27A1
oxidace postranního řetězce
CYP27A1
3α,7α,12α-trihydroxy-5β-cholestanová kyselina
3α,7α-dihydroxy-5β-cholestanová kyselina
zkrácení postranního řetězce
kyselina cholová
chenodeoxycholová kyselina

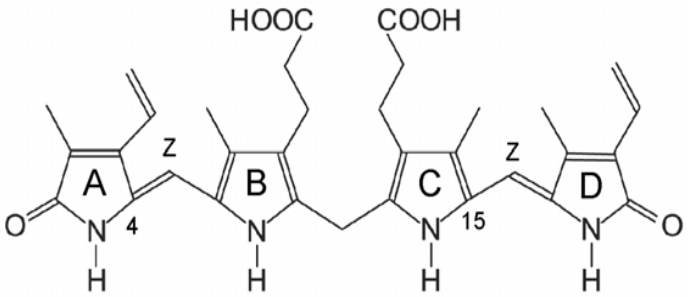
Factors affecting biliary cholesterol saturation

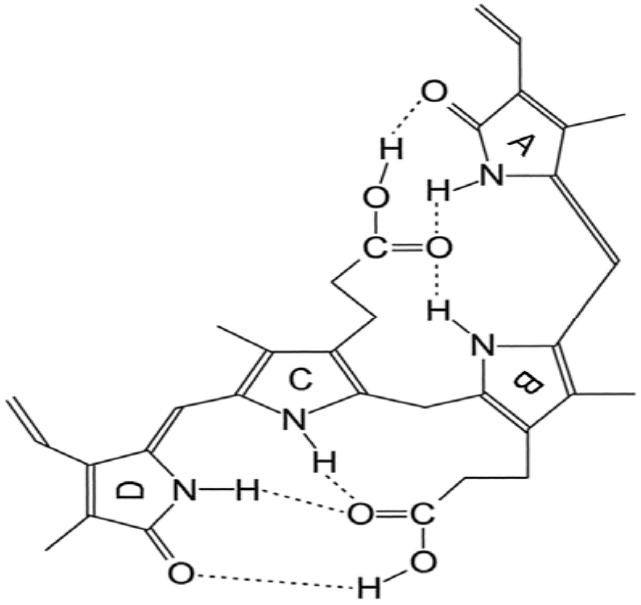
5F rule

- **Age: decline of cholesterol 7a hydroxylase activity – CYP7A1 (FORTY)**
- **Sex: CSI higher by 15 - 20% in women (FEMALE)**
- **Hormonal influences: estrogens increase biliary cholesterol secretion (FERTILE)**
- **Obesity, rapid weight loss (FATTY)**
- **White population (FAIR)**
- **Diet and drugs (fiber, fibrates, statins…)**

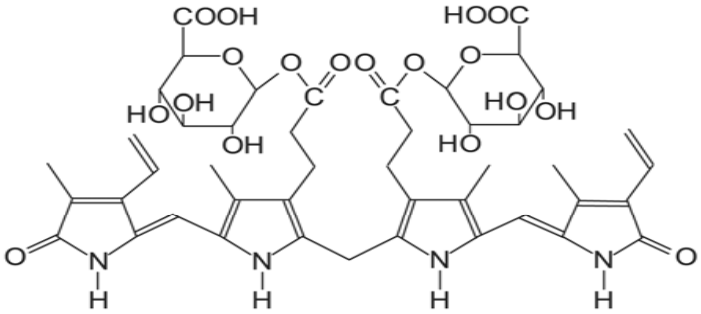
Bilirubin

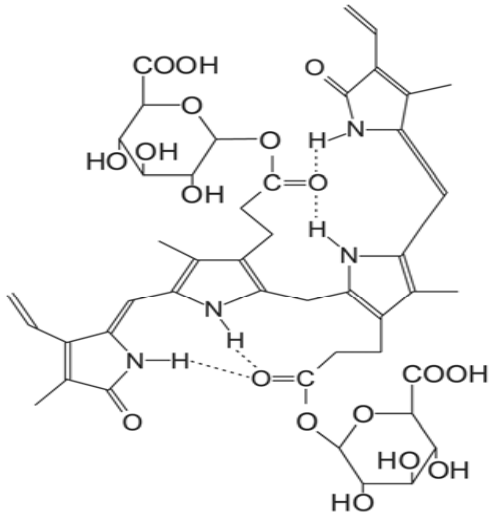
- Thanks to its conformation, unconjugated bilirubin is non-polar and reacts in diazo reaction ¨indirectly¨,
- whereas conjugated bilirubin is polar and reacts ¨directly¨



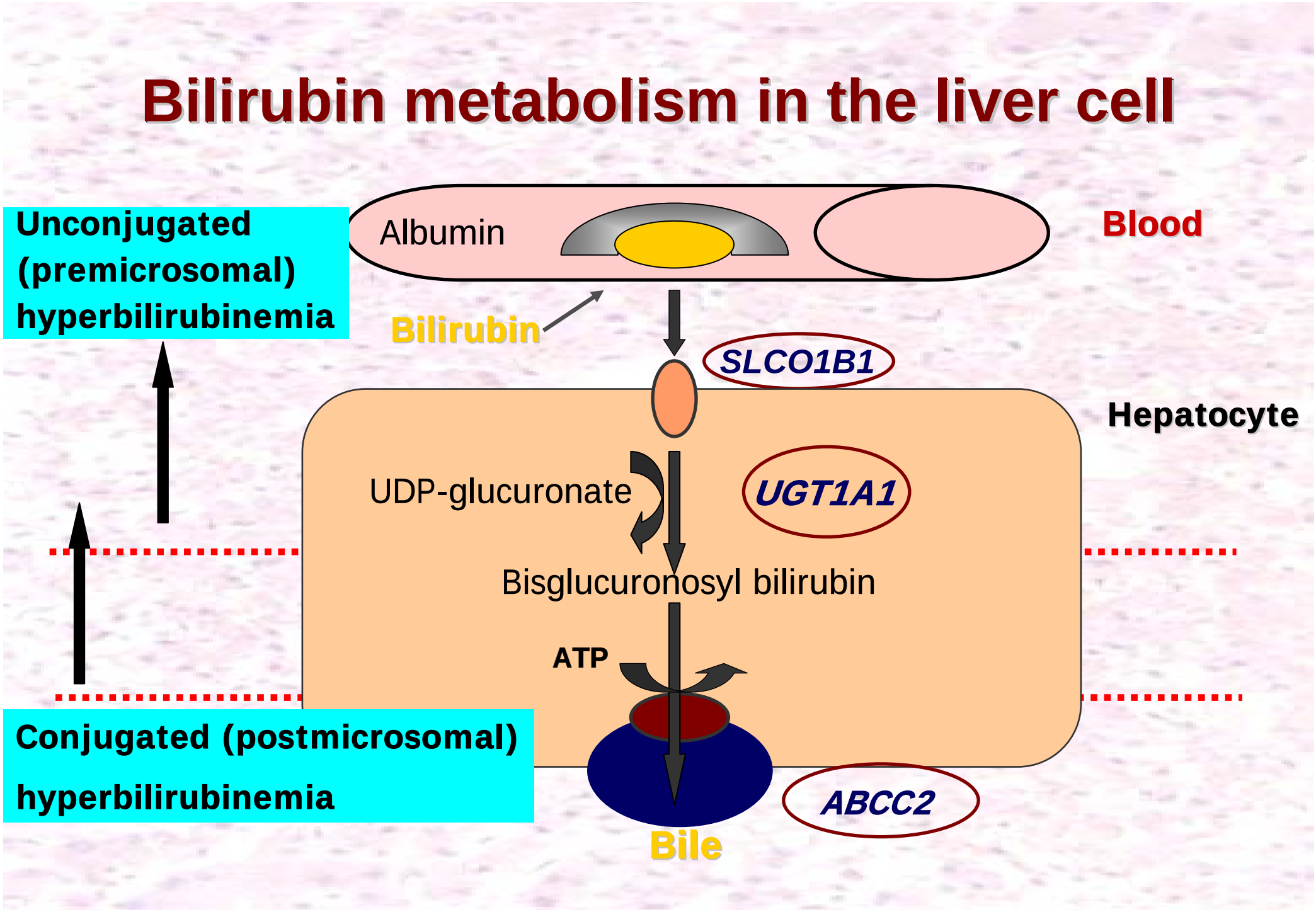


- Division of hyperbilirubinemias on:
  - Premicrosomal
  - Postmicrosomal
  - Mixed



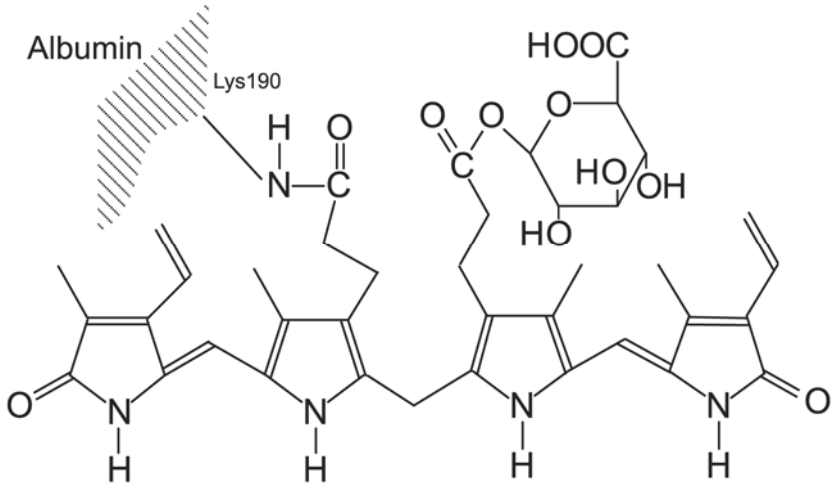


Bilirubin metabolism in the liver cell

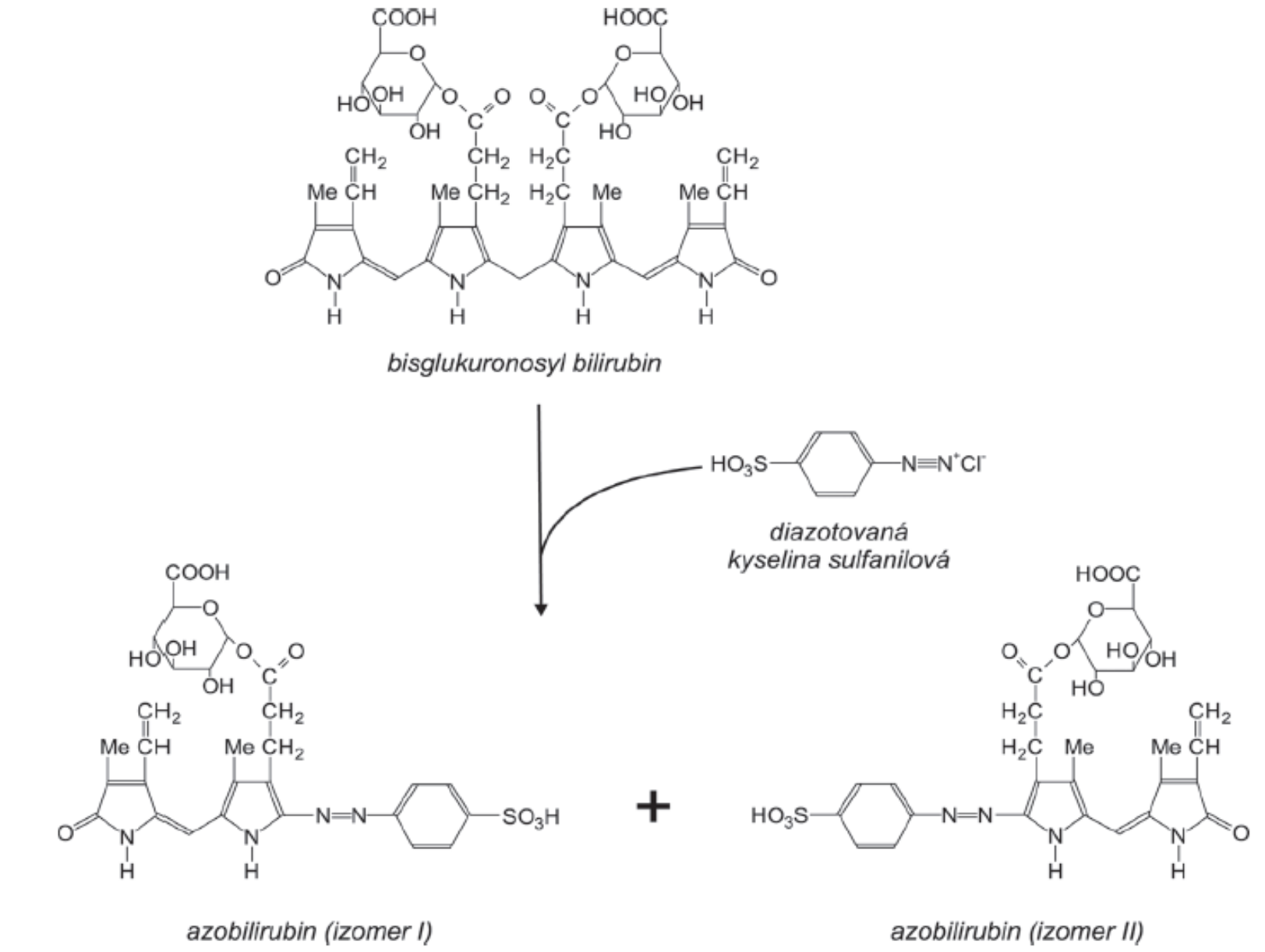


Delta bilirubin

- Is formed by transesterification of glucuronosyl bilirubin in long-term conjugated hyperbilirubinemias
- Is not secreted to urine
- Reacts ¨directly¨ with diazo reagent
- Albumin half-life determines half-life of delta-bilirubinemia



Principle of bilirubin diazo-reaction



Can UDCA be administered in breast-feeding mothers?

¨It is not known, whether UDCA is transported to breast milk, it is thus not recommended to administer drug during breast-feeding.¨

SPC Ursofalk® 8.9. 2004

¨It is not known, whether UDCA is transported to breast milk. Plasma levels in mothers are minimal. UDCA administration during breast-feeding, especiall risks and potential benefits must be assessed by a medical doctor.

SPC Ursosan® 1.1. 2007

Hepatocellular damage markers I

- AST – low specificity
  - liver
  - myocardium
  - sceletal muscles
  - kidney
  - pancreas
  - erythrocytes

  - mitochondrial (70%) a cytoplasmatic (30%) isoenzyme

Hepatocellular damage markers II

- ALT
  - relative specificity
  - in cytosol of hepatocytes
  - Elevation of ALT and cytoplasmic isoenzyme of AST – increased membrane permeability (1 damaged hepatocyte out of 2000)
  - Elevation of mitochondrial AST – hepatocellular necrosis.
  - Ratio AST/ALT (de Ritis index) – values above 1: worse prognosis

Hepatocellular damage markers III

- Extreme values of aminotransferases (more than 20x)
- Acute toxic damage of the liver
- Fulminant hepatitis
- Liver hypoperfusion (shock, acute heart failure)

Cholestatic markers I

- S-alkaline phosphatase (ALP)
  - Several isoenzymes, mainly bone, hepatic, intestinal and placental
  - Intestinal isoenzyme- elevation when hepatic uptake is decreased. Only in subjects with ABO blood group 0 and B (Intestinal ALP is bound to RBC of blood group A)
  - Odysseus syndrome
  - Electrofocusation: 19 isoenzymes (Griffith)
  - Liver: 7 different forms, „biochemical biopsy of the liver“
  - macro ALP

Cholestatic markers II

- S-gammaglutamyltransferase (GGT)
  - In tissues with excretory or absorption function
  - Also in prostate (increase by 50% in men) and in placenta (higher c in newborns)
  - Liver: in microsomal fraction and in cell membranes of bile duct lining
  - Sensitive, but non-specific marker of liver diseases
- S- Bile acids

Synthetic function markers I

- S-albumin
  - Half-life 18-21 days
  - hypoalbuminaemia:
  - Decreased synthesis
  - Sequestration in EV space (ascites)
  - Increased catabolism in fever or trauma
  - Decreased intake of protein
  - Malabsorption
  - Loss in kidney disease, burns or protein-loosing enteropathy

Synthetic function markers II

- S-prealbumin
  - Half-life 1,9 days
- S-cholinesterase (CHE)
  - Activity in many organs, several isoenzymes
  - total CHE- predominantly of hepatic origin
  - Decrease also in organophosphate poisoning
  - Increase in Gilbert syndrome and alcohol abuse
- S-coagulation factors, routinely PT, protein C and f VII: the shortest half-life