BILIRUBIN METABOLISM

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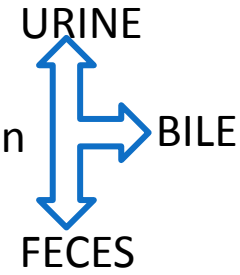
Bilirubin metabolism

Bilirubin pathway

Please check out this link before viewing the file to know if there are any additions/changes or corrections. The same link will be used for all of our work Physiology Edit

DEFINITION OF BILIRUBIN

- It is the water insoluble[1] breakdown product of normal heme catabolism has a greenish yellow color that excreted in
- It is toxic
- Serum bilirubin level is an important clinical marker of hepatobiliary excretory function.



BILIRUBIN METABOLISM

involves four discernible steps

The four steps are finely balanced.
Reduction at any step may cause→ hyperbilirubinemia.
Enhancement of the through put requires induction of multiple genes, probably coordinated by nuclear receptors

Formation
From [Heme : iron + porphyrin]
Heme source:
80% from hemoglobin,
20% other hemo-protein:
(cytochrome, catalase, peroxidas, myoglobin)

Plasma Transport

Hepatic Phase
1.Hepatic uptake
2.Conjugation
3.Biliary excretion

Intestine Excretion

1ST Step
BILIRUBIN FORMATION

RBCs in blood stream

Life span : 60-120 days.

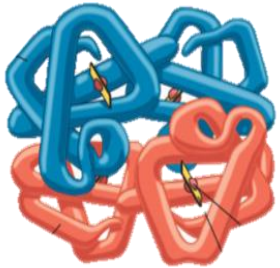
in

Old RBCs lysis by:

1) Extravascularly phagocytosed in the reticuloendothelial system or

2) intravascularly in blood stream

Give



Hemoglobin released (principal component of RBCs)

Split into

Heme

(By heme oxygenize)

Free Iron

Transported in the blood by transferrin

Stored

as a reservoir for erythropoiesis

Bile pigments

1st pigment is biliverdin

biliverdin reductase

FREE BILIRUBIN

into the plasma

Globin

breakdown and form

Amino acids

stored in the body

2ND Step

TRANSPORT OF BILIRUBIN IN PLASMA

Formed Bilirubin
in spleen

↓

free bilirubin in plasma
(hydrophobic)

↓

immediately combines with plasma proteins
(mainly albumin and globulin)
(give a water soluble compound)
(hydrophilic)

← **Called hemobilirubin, unconjugated, indirect bilirubin**
***still called free bilirubin**

↓

transported to hepatocytes for further metabolism and Conjugation process

Significance of bilirubin binding to albumin?!!

1)Increase the solubility of whole molecule.
2)Prevent unconjugated bilirubin freely come into other tissue, cause damage

drugs as sulfonamides and salicylates compete with bilirubin for albumin binding and displace bilirubin to enter into the brain in neonates → increase the risk of kernicterus
(a type of brain damage that can result from high levels of bilirubin in a baby's blood)→ can cause cerebral palsy and hearing loss

3rd Step HEPATIC PHASE (3 STEPS)

1- Hepatic Reuptake "1st Step" Bilirubin(without the albumin)is absorbed through the hepatic cell membrane, mediated by a carrier protein (receptor) & combined with Y & Z proteins that trap the bilirubin inside the cells.

2- Bilirubin-Albumin complex dissociate in plasma of liver into hemebilirubin & free albumin

3- Dissociation of hemebilirubin Inside hepatocytes into free bilirubin and free protein

4- Conjugation of bilirubin "2nd Step"

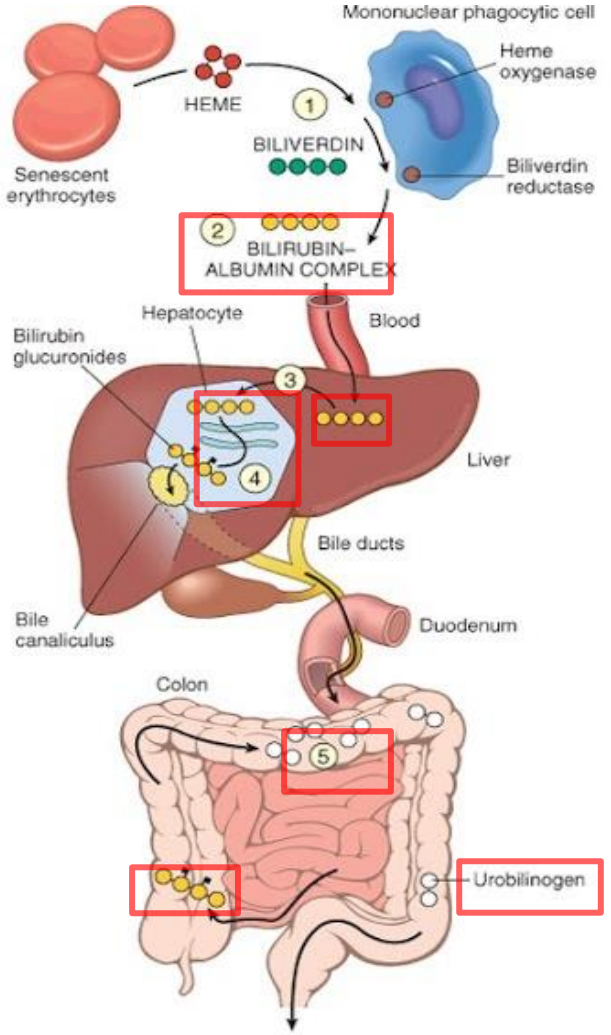
- 80% of free bilirubin conugate with 2 Uridine diphospho-glucuronic acid (UDPGA) catalyzed by the enzyme **glucuronyl transferase** in the smooth ER, forming the compound Bilirubin Diglucurnoide "Cholebilirubin, the conjugated form of bilirubin" that is water soluble
- 20% of the rest bilirubin conjugate with sulphate & other substances.

5- Secretion of conjugated bilirubin "Cholebilirubin" in the bile "3rd Step"

by liver hepatocytes by active transport " needs energy" into bile canaliculi, it's a **rate limiting step**, susceptible to impairment in liver disease

- Color of bile is due bilirubin
- Daily load of bilirubin: 250-300 mg in normal adults

6- Fate of conjugated bilirubin, majority of conjugated passes via bile ducts to intestine where it is transformed through bacterial action into **Urobilinogen**



FATE OF CONJUGATED BILIRUBIN

*Majority of conjugated blirubin passes via bile ducts to the intestine where it's transformed through bacterial action into **Urobilinogen** which is highly soluble

*Small portion returns to plasma and bound less tightly to albumin & is excreted in the urine. this causes a small portion of the bilirubin in the ECF to be of the conjugated type.

*Small amount is deconjugated and absorbed by the small intestine into the portal blood to the liver where it is extracted by the liver cells and conjugate again and excreted in the bile (enterohepatic circulation of bile pigments).

FATE OF UROBILINOGEN

70% of Urobilinogen

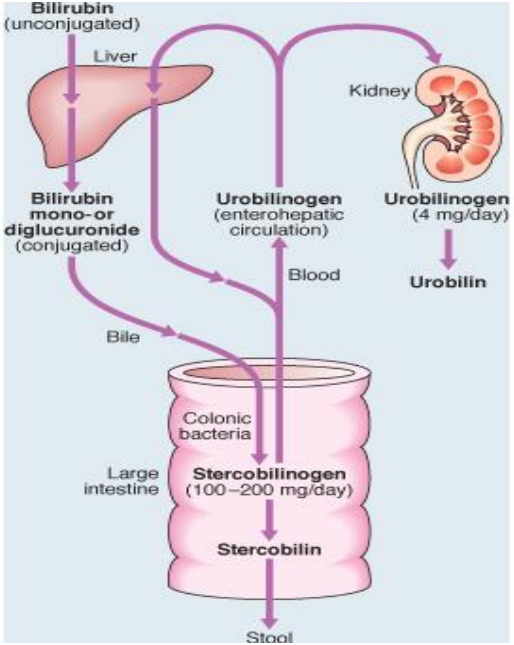
Converted in small intestine into **Stercobilinogen**, oxidized and excreted in the feces as **Stercobilin** that causes dark brown color of the feces.

20% of Urobilinogen

Reabsorbed through the intestinal mucosa into the portal vein and re-excreted by the hepatic cells in the bile (enterohepatic circulation).

10% of Urobilinogen

Escapes to the general circulation and excreted by the kidneys in the urine where it is oxidized to **Urobilin** when the urine is exposed to air.



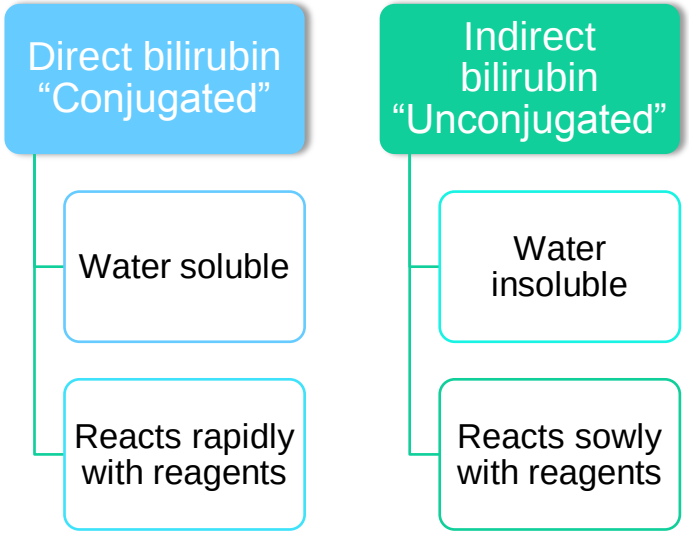
OTHER SUBSTANCES CONJUGATED BY GLUCOURONYL TRANSFERASE

- ✓ The glucuronyl transferase system in the smooth endoplasmic reticulum catalyzes the formation of the glucuronides of a variety of substances in addition to bilirubin.
- ✓ The list includes steroids & various drugs, these other compounds can compete with bilirubin for the enzyme system when they are present in appreciable amounts.

In addition several **barbiturates, antihistamines, anticonvulsants** and other compounds can cause marked proliferation of the smooth endoplasmic reticulum in the hepatic cells, with a concurrent **increase in hepatic glucuronyl transferase activity.**

Phenobarbital has been used successfully for the treatment of a congenital disease in which there is a relative deficiency of glucuronyl transferase (type 2 UDP-glucuronyl transferase deficiency).

TYPES OF BILIRUBIN IN SERUM



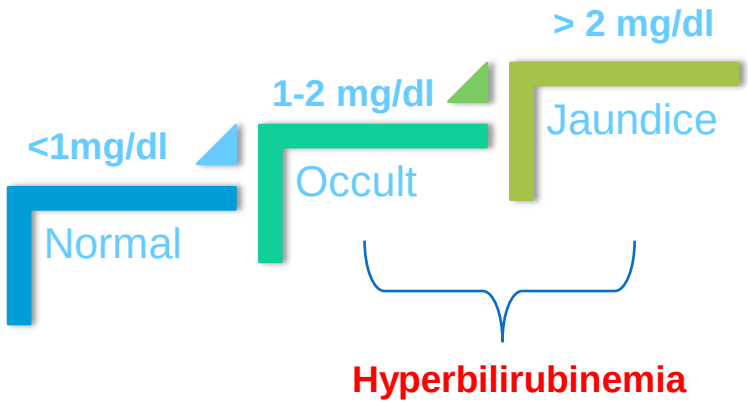
Total bilirubin = Direct bilirubin + Indirect bilirubin

Knowing level of each type of bilirubin has diagnostic importance

NORMAL RANGE OF BILIRUBIN

1~16 micromol/l (0.1~1mg/dl)

- 4/5 are unconjugated bilirubin,
- 1/5 are conjugated bilirubin.



OTHER SUBSTANCES EXCRETED IN THE BILE

Cholesterol & alkaline phosphatase

- In patients with jaundice due to intra or extra hepatic **obstruction** of the bile duct, the blood levels of these 2 substances usually rise.
- A much smaller rise is generally seen when the jaundice is due to **non obstructive** hepatocellular disease.

Adrenocortical, other steroid hormones & a number of drugs

- excreted in the bile and subsequently reabsorbed (enterohepatic circulation)

Summary

Bilirubin formation

RBCs lysis in spleen or blood strem →hemoglobin →bile pigment (biliverdin)--(by biliverdin reductase)→ free bilirubin (hydrophopic)

Transport of Bilirubin in Plasma

Bilirubin in spleen →go to bood strem → combines with(mainly albumin and globulin)→hemobilirubin, unconjugated bilirubin (hydrophilic)

Hepatic phase

Hepatic uptake

Bilirubin absorbed through the hepatiocytes membrane and traped inside the cell by Y & Z proteins

Conjugation

Bilirubin + 2 uridine diphospho-glucuronic acid– (by glucuronyl transferase) → bilirubin diglucuronide (cholebilirubin, direct, conjugated bilirubin) (highly hydrophilic)

glucuronyl transferase deficiency →jaundice *20% conjugate with sulphate

Bilirubin Secretion in Bile

Cholebilirubin secreted by the liver cells by an active transport process into the bile canaliculi

Unconjugated bilirubin normally not excreted in bile

energy-dependent, rate –limiting step →impairment in liver disease.

Fate of conjugated bilirubin

majority of conjugated bilirubin transformed through bacterial action into→urobilinogen→stercobilin→feces

Small amount deconjugated back by circulation→enterohepatic circulation

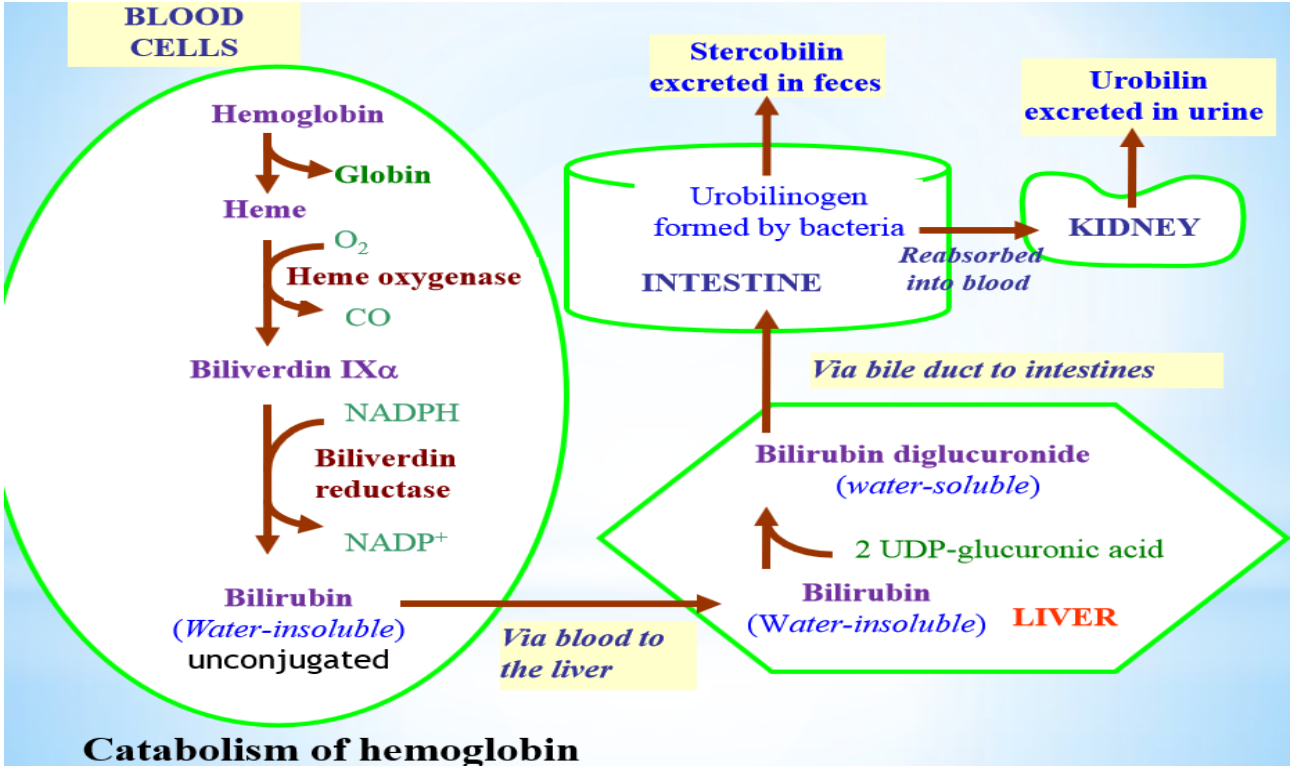
small amountof conjugated bilirubin returns to the plasma and bound less tightly to albumin→excreted in the urine

20 %of urobilinogen enter enterohepatic circulation & small amount → urobilin →excreted with ureine

Transport of bilirubin in plasma occurs in two forms

Unconjugated bilirubin (Hemobilirubin)	Conjugated bilirubin (Cholebilirubin)
Bound to albumin	Bound to glucuronicacid
The chief form of bilirubin in the blood	Present in low conc. in the blood
Lipid soluble (water insoluble) high affinity to lipid (hydrophopic)	Water soluble
Indirect reacting bilirubin-hemobilirubin	Direct reacting bilirubin-cholebilirubin
Not filtered through renal glomeruli →absent in urine	filtered through renal glomeruli → present in urine
Affinity to brain tissue (kernicterus), toxic	No Affinity to brain tissue less toxic

Summary 2



Cytochrome, catalase, peroxidas, myoglobin →other sources of heme

Sulfonamides and salicylates →drugs increase risk of kernicterus

Antihistamines, anticonvulsants →increase glucuronyl transferase activity

Phenobarbital→ treatment of a congenital deficiency of glucuronyl transferase

Steroids →can compete with bilirubin for glucuronyl transferase

MCQs

1-what would be the result from reduction of one step of bilirubin metabolism ?
A)hyperbilirubinemia
B)hypobilirubinemia
C)anemia
D)Increase bilirubin solubility

2- which one of the following are the main sites of old RBCs lysis ?
A. Pancreas and blood stream
B .Liver
C. reticuloendothelial system and blood stream
D. Only in blood stream

3- enzyme responsible to change biliverdin into free bilirubin ?
A. Bilirubin anhydrease
B. biliverdin reductase
C. Bilirubin
D. Biliverdin activator

4-which one of the following drugs may cause kernicterus in neonate ?
A. sulfonamides
B.Cephalocporin
C.amoxacilin
D.Asprine

5- Dark Color of feces is caused by
A. Bilirubin
B. Insetinal Bacteria
C. Hemebilirubin
D. Sterocobili

6- Enzyme responsible of conjugation reaction
A. Catalase
B. Glucuronyl tranferase
C. Bilirubin
D. Glucuronyl deaminase

7- Presence of 3 mg/dl bilirubin in the body is a condition called
A. Normal level
B. Occult
C. Jaundice
D. Anemia

Answer key:
1- A
2- C
3- B
4- A
5- D
6- B
7- C

SAQs

Q1what is the main importance of bilirubin albumin binding ?:

to increase bilirubin solubility and avoid its accumulation in the tissues because it's toxic

Q2:In brief explain the products of hemoglobin degradation ?

first will give globin , and heme (iron and bile pigment)→the globin will give amino acids that will stored in the body

Iron also will stored in the body ,bile pigment (biliverdin) converted to bilirubin by biliverdin reductase

Q3: Mention the steps of hepatic phase of bilirubin metabolism and explain each one briefly?

Step1: Hepatic reuptake

Step 2: Conjugation of bilirubin

Step3: Secretion of conjugated bilirubin in the bile

Q4: What are the types of bilirubin in the serum

1-Direct bilirubin "Conjugated" Cholebilirubin

2- Indirect bilirubin "Unconjugated" Hemobilirubin

Q5: What is the normal range of bilirubin in the body? And what happens in case of any increase of this amount?

Normal Range " 0.1 – 1 mg/dl"

Hyperbilirubenemia "increase" 1- Occult 1- 2 mg/dl or 2- Jaundice > 2 mg/dl

Thanks for checking our work

Good Luck

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