

Bilirubin 01

Bilirubin	
Identifiers	
PubChem	250
Chemical data	
Formula	$C_{33}H_{36}N_4O_6$
Molar mass	584.662
Complete data	

Bilirubin is a yellow breakdown product of normal heme catabolism. Its levels are elevated in certain diseases and it is responsible for the yellow colour of bruises and the brown colour of feces. Bilirubin reduction in the gut leads to a product called urobilinogen. Urobilinogen is then oxidized to urobilin which is excreted in the urine.

Chemistry

Bilirubin consists of an open chain of four pyrrole-like rings (*tetrapyrrole*). In heme, by contrast, these four rings are connected into a larger ring, called a porphyrin.

Bilirubin is very similar to the pigment phycobilin used by certain algae to capture light energy, and to the pigment phytochrome used by plants to sense light. All of these contain an open chain of four pyrrolic rings.

Like these other pigments, bilirubin changes its conformation when exposed to light. This is used in the phototherapy of jaundiced

newborns: the isomer of bilirubin formed upon light exposure is more soluble than the unilluminated isomer.

Several textbooks and research articles show incorrect chemical structures for the two isoforms of bilirubin.^[1]

Function

Bilirubin is created by the activity of biliverdin reductase on biliverdin. Bilirubin, when oxidized, reverts to become biliverdin once again. This cycle, in addition to the demonstration of the potent antioxidant activity of bilirubin, has led to the hypothesis that bilirubin's main physiologic role is as a cellular antioxidant.^[2]

Metabolism

Erythrocytes (red blood cells) generated in the bone marrow are destroyed in the spleen when they get old or damaged. This releases hemoglobin, which is broken down to heme, as the globin parts are turned into amino acids. The heme is then turned into unconjugated bilirubin in the macrophages of the spleen. It is then bound to albumin and sent to the liver.

In the liver it is conjugated with glucuronic acid, making it soluble in water. Much of it goes into the bile and thus out into the small intestine. Some of the conjugated bilirubin remains in the large intestine and is metabolised by colonic bacteria to stercobilinogen and then oxidised to stercobilin.

Some is reabsorbed, and excreted in the urine as urobilinogen and the oxidised form, urobilin. If the liver's function is impaired, or when there is a hemolytic anemia (increased destruction of red blood cells), or biliary drainage blocked, some of the conjugated bilirubin appears in the urine, turning it dark amber.

Toxicity

Unconjugated hyperbilirubinaemia in the neonate can lead to accumulation of bilirubin in certain brain regions, a phenomenon known as kernicterus, with consequent irreversible damage to these areas manifesting as various neurological deficits, seizures, abnormal reflexes and eye movements. Aside from specific chronic medical conditions that may lead to hyperbilirubinaemia, neonates in general are at increased risk since they lack the intestinal bacteria that facilitate the breakdown and excretion of conjugated bilirubin in the feces (this is largely why the feces of a neonate are paler than those of an adult). Instead the conjugated bilirubin is converted back into the unconjugated form by the enzyme b-glucuronidase and a large proportion is reabsorbed through the enterohepatic circulation.

Benefits

Reasonable levels of bilirubin can be beneficial to the organism. Evidence is accumulating that suggests bilirubin can protect tissues against oxidative damage caused by free radicals and other reactive oxygen species. Statistical analysis of people with high normal or slightly elevated bilirubin levels in blood shows that they have a lower risk of developing cardiovascular diseases.

Blood tests

Bilirubin is in one of two forms:

Abb. Name	Soluble?	Reaction
"BC" <i>conjugated</i> or <i>direct</i>	Yes (bound to glucuronic acid)	Reacts <i>directly</i> when dyes are added to the blood specimen.
"BU" <i>unconjugated</i> or <i>indirect</i>	No	Free bilirubin does not react to the reagents until alcohol (methanol) or caffeine is added to the solution. Therefore, the measurement of this type of bilirubin is <i>indirect</i> . (It is

transformed into a soluble or direct form, in the liver.)

Total bilirubin measures both BU and BC. Total and direct bilirubin levels can be measured from the blood, but indirect bilirubin is calculated from the total and direct bilirubin.

To further elucidate the causes of jaundice or increased bilirubin, it is usually simpler to look at other liver function tests (especially the enzymes ALT, AST, GGT, Alk Phos), blood film examination (hemolysis, etc.) or evidence of infective hepatitis (e.g., Hepatitis A, B, C, delta, E, etc).

Bilirubin is an excretion product, and the body does not control levels. Bilirubin levels reflect the balance between production and excretion. Thus, there is no "normal" level of bilirubin.

Bilirubin is broken down by light, and therefore blood collection tubes (especially serum tubes) should be protected from such exposure.

Interpretation

Different sources provide reference ranges which are similar but not identical. Some examples for adults are provided below (different reference ranges are often used for newborns):

	μmol/L	mg/dL			
total bilirubin	5.1–17.0 ^[3]	0.2-1.9, ^[4]	0.3–1.0, ^[3]	0.1-1.2 ^[5]	
direct bilirubin	1.0–5.1 ^[3]	0-0.3, ^[4]	0.1–0.3, ^[3]	0.1-0.4 ^[5]	

Mild rises in bilirubin may be caused by

- Hemolysis or increased breakdown of red blood cells.

- Gilbert's syndrome - a genetic disorder of bilirubin metabolism which can result in mild jaundice, found in about 5% of the population.

Moderate rise in bilirubin may be caused by

- Drugs (especially anti-psychotic, some sex hormones, and a wide range of other drugs).
- Hepatitis (levels may be moderate or high).
- Biliary stricture (benign or malignant)

Very high levels of bilirubin may be caused by

- Neonatal hyperbilirubinaemia, where the newborn's liver is not able to properly conjugate the bilirubin (see jaundice).
- Unusually large bile duct obstruction, eg stone in common bile duct, tumour obstructing common bile duct etc.
- Severe liver failure with cirrhosis.
- Severe hepatitis.
- Crigler-Najjar syndrome
- Dubin-Johnson syndrome
- Choledocholithiasis (chronic or acute)

Cirrhosis may cause normal, moderately high or high levels of bilirubin, depending on exact features of the cirrhosis

Indirect bilirubin is fat soluble and direct bilirubin is water soluble.

Jaundice

Jaundice may be noticeable in the sclera (white) of the eyes at levels of about 30-50 $\mu\text{mol/l}$, and in the skin at higher levels. Jaundice is classified depending upon whether the bilirubin is free or conjugated to glucuronic acid into:

- Conjugated jaundice
- Unconjugated jaundice

How to Prepare for the Test

Fast for at least 4 hours before the test. Your health care provider may instruct you to stop taking drugs that affect the test.

Drugs that can increase bilirubin measurements include allopurinol, anabolic steroids, some antibiotics, antimalaria medications, azathioprine, chlorpropamide, cholinergics, codeine, diuretics, epinephrine, meperidine, methotrexate, methyldopa, MAO inhibitors, morphine, nicotinic acid, oral contraceptives, phenothiazines, quinidine, rifampin, salicylates, steroids, sulfonamides, and theophylline.

Drugs that can decrease bilirubin measurements include barbiturates, caffeine, penicillin, and high-dose salicylates.

Why the Test is Performed

This test is useful in determining if a patient has liver disease or a blocked bile duct.

Bilirubin metabolism begins with the breakdown of red blood cells. Red blood cells contain hemoglobin, which is broken down to heme and globin. Heme is converted to bilirubin, which is then carried by albumin in the blood to the liver.

In the liver, most of the bilirubin is chemically attached to another molecule before it is released in the bile. This "conjugated" (attached) bilirubin is called direct bilirubin; unconjugated bilirubin is called indirect bilirubin. Total serum bilirubin equals direct bilirubin plus indirect bilirubin.

Conjugated bilirubin is released into the bile by the liver and stored in the gallbladder, or transferred directly to the small intestines. Bilirubin is further broken down by bacteria in the intestines, and those breakdown products contribute to the color of the feces. A

small percentage of these breakdown compounds are taken in again by the body, and eventually appear in the urine.

Normal Results

- Direct bilirubin: 0 to 0.3 mg/dL
- Total bilirubin: 0.3 to 1.9 mg/dL

Note: mg/dL = milligrams per deciliter

If the bile ducts are blocked, direct bilirubin will build up, escape from the liver, and end up in the blood. If the levels are high enough, some of it will appear in the urine. Only direct bilirubin appears in the urine. Increased direct bilirubin usually means that the biliary (liver secretion) ducts are obstructed.

Increased indirect or total bilirubin may indicate:

- Crigler-Najjar syndrome
- Erythroblastosis fetalis
- Gilbert's disease
- Healing of a large hematoma (bleeding under the skin)
- Hemolytic anemia
- Hemolytic disease of the newborn
- Physiological jaundice (normal in newborns)
- Sickle cell anemia
- Transfusion reaction
- Pernicious anemia

Increased direct bilirubin may indicate:

- Bile duct obstruction
- Cirrhosis
- Dubin-Johnson syndrome (very rare)
- Hepatitis
- Intrahepatic cholestasis (buildup of bile in the liver) of many causes

Additional conditions under which the test may be performed:

- Biliary stricture
- Cholangiocarcinoma
- Cholangitis
- Choledocholithiasis
- Hemolytic anemia due to G6PD deficiency
- Hepatic Encephalopathy
- Idiopathic aplastic anemia
- Idiopathic autoimmune hemolytic anemia
- Immune hemolytic anemia (including drug-induced immune hemolytic anemia)
- Secondary aplastic anemia
- Thrombotic thrombocytopenic purpura
- Wilson's disease

Considerations

Factors that interfere with bilirubin testing are:

- Hemolysis (breakdown) of blood will falsely increase bilirubin levels
- Lipids in the blood will falsely decrease bilirubin levels
- Bilirubin is light-sensitive; it breaks down in light