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Metabolism of the Bilirubin and its Biochemistry Role

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Abstract. *Bilirubin is a tetrapyrrolic bile pigment that plays a crucial role in several vital metabolic pathways of the human body. It is a yellow-colored compound that circulates in the bloodstream and participates in various physiological processes. Bilirubin is predominantly generated through the catabolism of hemoglobin following the breakdown of erythrocytes, and its biosynthesis is primarily mediated by the liver. The homeostasis of bilirubin is intricately linked to multiple physiological and biochemical functions, and its precise regulation is essential for maintaining systemic health. Elevated serum bilirubin levels may serve as a clinical biomarker for a range of pathological conditions, including hepatic dysfunctions, hematological disorders, and cholestatic syndromes.*

Keywords: *bilirubin, free radicals, liver, Kupffer cells, cholesterol*

Introduction

Bilirubin metabolism affects various physiological and biochemical processes of the body, and its proper regulation is essential for maintaining health. Bilirubin exists in two major forms: conjugated and unconjugated bilirubin. Direct bilirubin is generated by the conjugation process in the liver and excreted from the body by being excreted as waste in the moist intestines. Conjugated bilirubin is formed in the liver through the conjugation process and is excreted into the intestines as a waste product, eventually being eliminated from the body. Unconjugated bilirubin, on the other hand, is produced as a result of erythrocyte degradation and is processed in the liver where it is converted into direct (conjugated) bilirubin. Disruptions in this metabolic pathway can lead to hyperbilirubinemia, a condition clinically manifested as jaundice. Notably, bilirubin is not merely a metabolic waste product; it also functions as a physiological antioxidant, helping to neutralize harmful free radicals in the body (Chen et al., 2018).

Materials and Methods

Thus, the liver serves as the central organ in the synthesis, excretion, and metabolism of bilirubin. Bilirubin originates from the degradation of erythrocytes, which have a lifespan of approximately 120 days, and its proper handling is essential for maintaining liver health. Hepatic metabolic processes—particularly the production and excretion of bilirubin—constitute key aspects of this function. The presence and concentration of bilirubin serve as important biomarkers for the early detection of liver and hematological disorders, providing a valuable basis for future clinical and molecular research (Agius, 2018).

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Hepatic Glucose Metabolism. Hepatocytes are the primary cell type involved in glucose metabolism within the liver. Circulating glucose enters hepatocytes via the GLUT2 transporter, which is embedded in the plasma membrane. The specific deletion of GLUT2 in hepatocytes abolishes hepatic glucose uptake. In addition, GLUT2 facilitates the release of glucose from the liver into the bloodstream. However, the absence of GLUT2 does not impair hepatic glucose production during fasting, suggesting that glucose may also be released via alternative transporters (e.g., GLUT1) or other mechanisms (Evans et al., 2013). Once inside the hepatocyte, glucose is phosphorylated by the enzyme glucokinase into glucose-6-phosphate (G6P). This reaction reduces intracellular free glucose concentrations, thereby facilitating continued glucose uptake. Since G6P cannot be transported out of the cell, it remains within hepatocytes. In the fed state, G6P serves as a key precursor for glycogen synthesis. Additionally, G6P is metabolized to pyruvate via glycolysis. Pyruvate then enters the mitochondria and is fully oxidized through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation, leading to ATP production (Fig. 1).

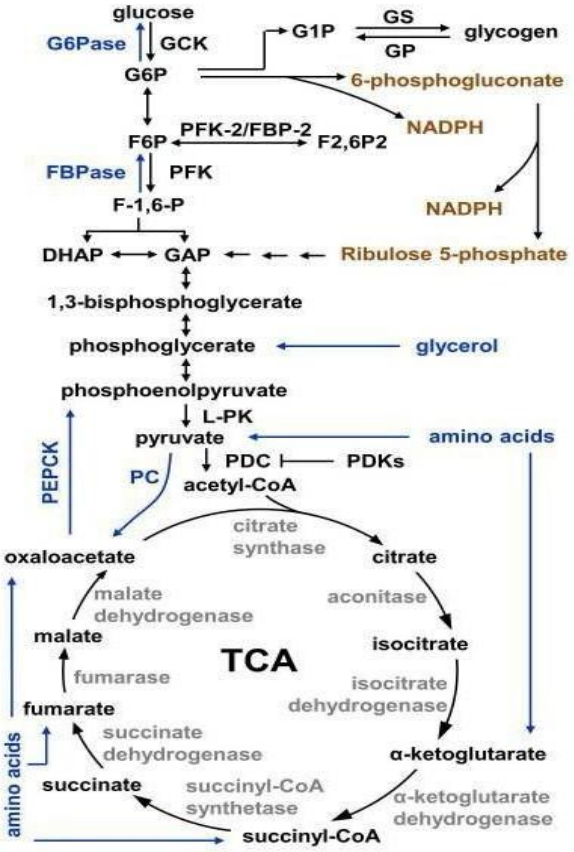


Figure 1. Glycogen metabolizm

In the fed state, glucose enters hepatocytes via GLUT2, is phosphorylated by glucokinase, and subsequently utilized by glycogen synthase for glycogen synthesis. During fasting, glycogen is hydrolyzed by glycogen phosphorylase to release glucose through glycogenolysis (Chew et al., 2023). The liver is considered the central regulatory organ responsible for maintaining whole-body cholesterol homeostasis (Fig. 2).

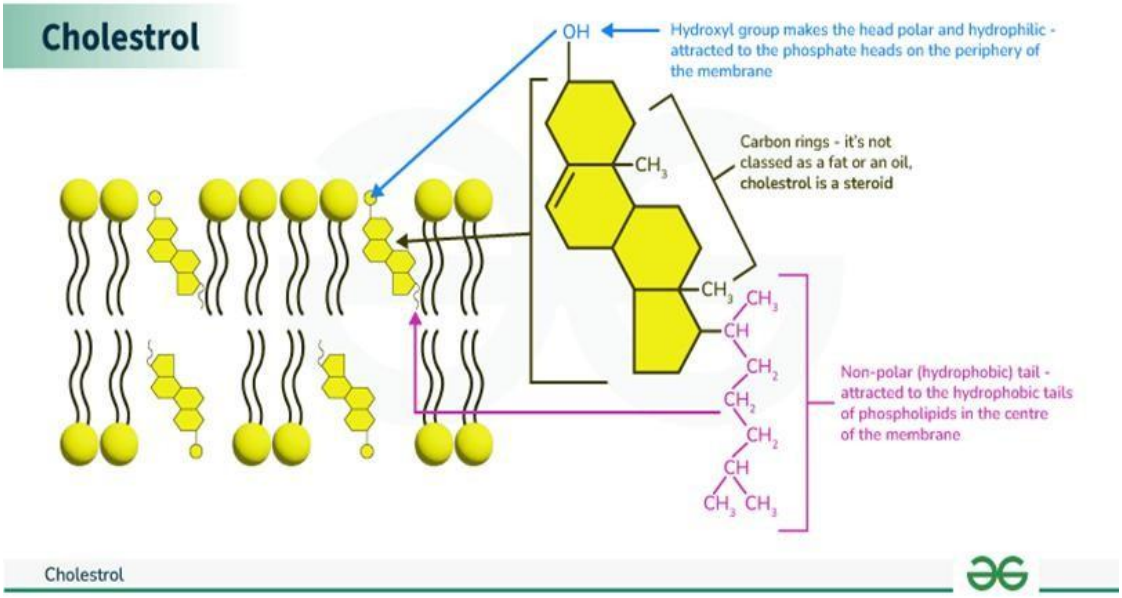


Figure 2. Structure of cholesterol

It serves as the primary site for de novo cholesterol biosynthesis, facilitates the clearance of cholesterol-containing chylomicron remnants and low-density lipoprotein (LDL) particles from the plasma, and makes a major contribution to the formation of high-density lipoproteins (HDL) (Zhang et al., 2023). Approximately 4 mg/kg of bilirubin is produced daily. Heme is a tetrapyrrolic macrocycle consisting of four pyrrole rings interconnected by carbon bridges, with a central iron atom. Bilirubin is primarily generated through a two-step sequential enzymatic degradation of heme within the reticuloendothelial system, particularly in the spleen. Other contributing cells include phagocytes and Kupffer cells of the liver. Once released into the plasma, bilirubin binds to albumin, the main transport protein in the bloodstream (Pirone et al., 2009).

The active transport of unconjugated bilirubin is mediated by carrier proteins, although the exact identity and mechanism of these transporters remain poorly understood (Fig. 3) (Blumgart et al., 2017). Albumin has a very high binding affinity for bilirubin, and under physiological conditions, unbound (free) unconjugated bilirubin is virtually undetectable in the plasma (Chew et al., 2023). Bilirubin is taken up by hepatocytes from the hepatic sinusoids via two distinct mechanisms: passive diffusion and receptor-mediated endocytosis. Passive diffusion does not require energy and occurs along the concentration gradient, resulting in a bidirectional flow.

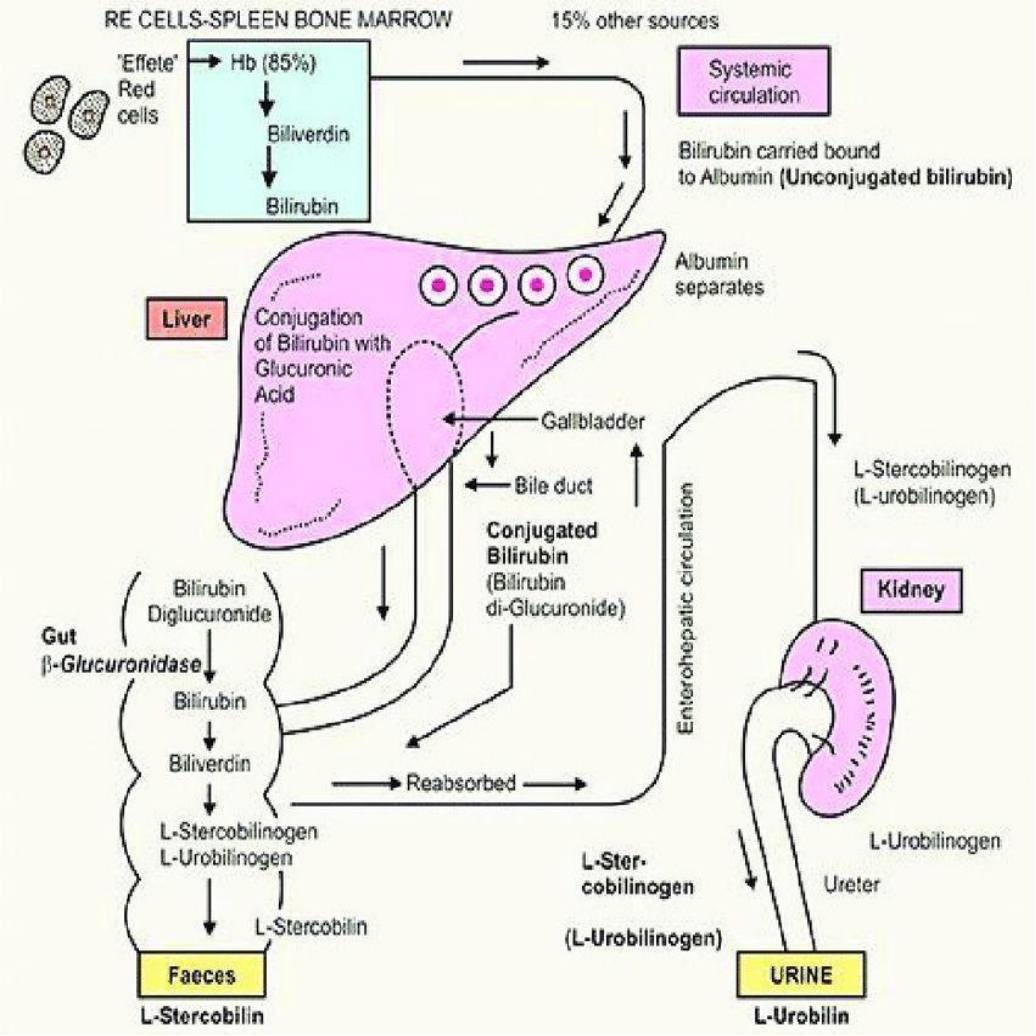


Figure 3. Bilirubin synthesis in the liver

Results and Discussion

The study demonstrated, that bilirubin is an important metabolite of heme (ferroprotoporphyrin IX), a coordination complex that links iron in various proteins. It is a potentially toxic substance. However, the body has developed mechanisms for its safe detoxification and excretion. Bilirubin and its metabolites also provide a distinctive yellow color of bile and feces and, to a lesser extent, urine. This topic summarizes the mechanism of heme metabolism and bilirubin synthesis (Bauer & Kämper, 2016). Bilirubin is formed by a 2-stage sequential catalytic degradation reaction that occurs primarily in the cells of the reticuloendothelial system, specifically in the spleen. Other cells include phagocytes and Kupfer cells of the liver. Receiving Heme these cells receive heme and the enzyme heme oxygenase acts on them. The enzyme releases chelated iron by catalyzing the oxidation of the alpha-carbon bridge. This reaction produces equimolar amounts of carbon monoxide, which is excreted by the lungs and leads to the formation of the green pigment biliverdin (Chisari & Ferrari, 2018). Bilirubin, insoluble in aqueous solution, binds in circulation to albumin, which is a reversible and covalent type of binding.

Metabolism of bilirubin. Albumin binding: after bilirubin is released into plasma, it is taken up by albumin, a carrier throughout the body. The binding affinity of albumin to bilirubin is quite high, and under ideal conditions, free (non-albumin-bound) unconjugated bilirubin does not appear in plasma. To a lesser extent, especially in cases of hypoalbuminemia, binding with high- density lipoproteins

also occurs. Albumin binding limits the outflow of bilirubin from the vascular cavity, minimizes glomerular filtration and prevents its deposition and deposition in tissues (de Sauvage et al., 2011). Bilirubin is taken from hepatic sinusoids into hepatocytes by two different mechanisms: passive diffusion and Receptor-Mediated Endocytosis. The passive diffusion process does not consume energy and, as a result, proceeds with a concentration gradient, making the flow bidirectional. Active transporter intake of unconjugated bilirubin from hepatic sinusoids is carried out through carrier proteins that are not well understood. Part of the conjugated and unconjugated bilirubin within the hepatocyte is transported back into the sinusoidal space, and this fraction is again transported downstream of the sinusoidal flow. Conjugation is mandatory to dissolve bilirubin in water and facilitate its secretion through the canalicular membrane and excretion with bile. Bilirubin binds to glucuronic acid in the hepatocyte by a family of enzymes called uridine-diphosphoglucuronic glucuronosyltransferase (UDPGT) (Sedlak et al., 2017). The process of glucuronidation is one of the many important detoxification mechanisms of the human body. Under normal conditions, bilirubin is the main molecule from which diglucuronide is synthesized. However, if the conjugation system fails under conditions of excessive bilirubin synthesis, most of the bilirubin may be conjugated as bilirubin monoglucuronide. The combination of bilirubin into a water-soluble form involves breaking hydrogen bonds, an important process for its excretion by the liver and kidneys. This is achieved by glucuronic acid, which binds the side chains of propionic acid of bilirubin (Liu et al., 2008).

Conclusion

In summary, the liver is the central organ involved in the synthesis, excretion, and metabolism of bilirubin. Bilirubin is generated from the degradation of erythrocytes, which have a lifespan of approximately 120 days, and its proper processing is essential for maintaining hepatic function. The metabolic activities of the liver – particularly those related to bilirubin production and elimination - constitute critical aspects of its physiological role. The plasma concentration of bilirubin serves as a valuable biomarker for the early detection of both hepatic and hematologic disorders. Bilirubin metabolism affects various biochemical processes, and its regulation is essential for maintaining health, and it provides a foundation for diagnostic research.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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