Chapter

# Cholestasis: The Close Relationship between Bile Acids and Coenzyme Q10

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## Abstract

Cholestasis is defined as the impairment in formation or excretion of bile from the liver to the intestine. It may result from defects in intrahepatic production of bile, impairment of hepatic transmembrane transporters, or mechanical obstruction to bile flow. In cholestasis, hepatocytes are exposed to high levels of bile acids, particularly those bearing hydrophobic properties. The increase in bile acids induces oxidative stress, leading to an imbalance in the prooxidant:antioxidant ratio which determines the final cellular redox status. This chapter will focus on the close relationship between bile acids and the most powerful endogenous antioxidant, coenzyme Q10 in cholestasis, and the eventual alternative therapeutic option of CoQ10 supplementation to current traditional therapies.

**Keywords:** cholestasis, coenzyme Q10, bile acids

## 1. Cholestasis: types, clinical presentation, diagnosis and current therapeutic approaches

Bile is a nonenzymatic secretion produced by hepatocytes. The main components of bile include bile salts necessary for enzymatic fat digestion and absorption, bilirubin, and cholesterol. Drugs and other xenobiotics are also excreted into bile following hepatic metabolization. Bile flow is dependent on the active canalicular transport of bile acids and other substrates mediated by the bile salt export pump (Bsep), which transports osmotically active monoanionic bile salts into the bile canaliculus and multidrug resistance-associated protein 2 (Mrp2), which exports oxidized and reduced glutathione. Bile secreted by the hepatocytes is stored and concentrated in the gallbladder, which contracts in the presence of the hormone cholecystokinin resulting in bile release into the duodenum through the cystic and common bile duct.

Cholestasis is defined as the decrease or suppression of bile flow due to impaired secretion by hepatocytes or to obstruction of bile at any level of the excretory pathway, from the hepatocyte canalicular membrane to the ampulla of Vater in the duodenum. Cholestasis leads to the retention of the major constituents of bile, bilirubin, and bile acids, in blood. By convention, cholestasis is chronic when it lasts more than 6 months. Prevalence of cholestasis is not significantly different between males and females. Nevertheless, women are at lighter risk of developing drug-induced cholestasis and intrahepatic cholestasis of pregnancy. Despite that, cholestasis may affect people of every age group, newborns and infants are more prone due to the immaturity of the liver.

The morphologic features of cholestasis are dependent on the severity, duration, and the underlying cause. Cholestasis is classified as intrahepatic or extrahepatic cholestasis depending on the cause that leads to impaired bile flow. Intrahepatic cholestasis is due to a disease affecting the hepatocytes and/or the intrahepatic bile ducts, whereas extrahepatic cholestasis or obstructive cholestasis results from the obstruction of the extrahepatic biliary ducts.

Obstruction of bile ducts can be caused by gallstones, cysts, stenosis, or tumors. The most frequent causes of extrahepatic cholestasis in adults include cholelithiasis and malignancies of the biliary tree or the head of the pancreas. However, in children, biliary atresia and cystic fibrosis are the main causes. Intermittent or partial obstruction may lead to ascending cholangitis, a secondary bacterial infection of the biliary tree. The typical morphological changes are reversible if the obstruction is corrected, but if it persists it can lead to biliary cirrhosis.

Causes of intrahepatic or hepatocellular cholestasis include viral and autoimmune hepatitis, inborn errors of bile acid synthesis, primary biliary cirrhosis, progressive familial intrahepatic cholestasis, primary sclerosing cholangitis, total parenteral nutrition, and drug toxicity. The drug class mostly implicated in cholestasis is antibiotics. However, anti-inflammatory drugs, highly active antiretroviral therapy, psychotropes, some chemotherapy agents, oral contraceptives, and anabolic steroids have also been reported to cause cholestasis [1]. Although primary sclerosing cholangitis affects intrahepatic bile ducts, it can also affect extrahepatic bile ducts.

Clinical presentation of cholestasis includes jaundice, pruritus, skin xanthomas, or symptoms associated with intestinal malabsorption. Jaundice and pruritus are present in all types of cholestasis whether acute or chronic, whereas the other clinical features are more associated with chronic cholestasis.

Jaundice is the clinical expression of bilirubin retention. Excretion of conjugated bilirubin is the rate-limiting step of bilirubin clearance. During cholestasis, conjugation of bilirubin continues but the excretion is significantly reduced. Jaundice is observed by scleral icterus at a concentration as low as 2 mg/dL accompanied by dark urine. The concentration of conjugated bilirubin in blood depends on its production rate and excretion pathways, as well as cholestasis degree. Non conjugated bilirubin is also increased in patients with cholestasis. The magnitude of the increase in serum bilirubin concentration does not correlated with the type or severity of cholestasis. Pruritus is a frequent clinical manifestation of cholestasis, which has been long associated with increased serum bile acids. However, its origin is multifactorial and diverse studies show that not only bile acids but also lysophosphatidic acid, and bilirubin are potential mediators of cholestatic itch [2]. Retention of bile acids and their conjugated salts results in biological membrane injury, particularly in the liver due to their detergent properties. Increased hydrophobic bile salts favor their incorporation into membranes, altering membrane fluidity and function. Enhanced secondary bile acids like lithocholic acid result in further membrane injury. The transport of bile salts from plasma to bile is the principal driving force for bile formation and it is mediated by several hepatic transporters, mostly belonging to the ABC family of transporters. Numerous studies support that the failure to excrete bile salts into the canaliculus is the main mechanism underlying cholestasis. In this sense retrieval of the canalicular transporters Bsep and Mrp2 from hepatocyte plasma membrane to endosomal compartments in different types of cholestasis has been well documented [3, 4]. However, other works consider that the endocytic retrieval of canalicular transporter is the result of cholestasis on the hepatocyte function. In either case, the retention of bile salts in the liver induces down-regulation of bile acid synthesis, overall reduction in the total pool size and damage to hepatocytes.

Skin xanthomas and signs of malabsorption are associated with chronic cholestasis. Skin xanthomas result from focal accumulation of cholesterol in the dermis and usually appear around the eyes, but may be present in other parts of the body. Malabsorption occurs due to the failure of enough bile salts to reach the duodenum, so the digestion and absorption of dietary fat is impaired. Fat soluble vitamins like A, E, D, and K are poorly absorbed in cholestasis leading to clinical symptoms and signs of their deficiency.

In all types of cholestasis, characteristic laboratory findings are elevated serum alkaline phosphatase and γ-glutamyltranspeptidase, enzymes present on the canalicular membranes of hepatocytes, and bile duct epithelial cells. Alkaline phosphatase is also elevated in bone growth or disease, pregnancy, or intestinal diseases. λ-Glutamyltranspeptidase is a sensitive marker of cholestasis [5], although no specific since it can be elevated in other liver diseases [6]. Furthermore, its elevation may reflect enzyme induction by drugs or alcohol. Serum 5′-nucleotidase, an enzyme located in canalicular membranes and lining the sinusoids is also elevated in cholestasis, although it appears to be less sensitive than alkaline phosphatase. Serum elevation of hepatic enzymes is accompanied by increased serum bilirubin and bile acids. An increase in serum bile acids is an early marker of cholestasis.

In the diagnosis of cholestasis, the first key step is to identify whether it is intrahepatic, extrahepatic, or both. The patient history and physical examination usually provide useful information. Elevation of both hepatic enzymes (alkaline phosphatase and λ-glutamyl transpeptidase) is a hallmark of cholestasis although the identification of the type of cholestasis requires imaging studies and additional biochemical studies. Imaging studies include first an abdominal ultrasonography to exclude dilated intra and extrahepatic ducts. When bile duct alterations are observed, further imaging studies like magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography should be performed. A diagnostic of intrahepatic cholestasis can be made when imaging studies exclude mechanical obstruction. Then, further biochemical studies are necessary to identify the intrahepatic cause of cholestasis, including liver biopsies when the diagnosis is unclear.

The therapeutic intervention for cholestasis may differ depending on the etiology [7]. Based on controlled clinical trials, ursodeoxycholic acid (UDCA) is the treatment of choice for diverse cholestatic disorders like primary biliary cirrhosis and intrahepatic cholestasis of pregnancy due to its anticholestatic properties. However, UDCA treatment is not so effective in other cholestatic disorders like in primary sclerosing cholangitis. No therapy of proven benefit for the long-term prognosis of genetic cholestatic liver disease exists. In drug-induced cholestasis, withdrawal of the drug is the only effective treatment [8]. Pruritus is a common manifestation of cholestasis, which can be of serious severity. Management of pruritus includes cholestyramine as first line-treatment and then rifampicin, and opiate antagonists [9].

## 2. Bile acids: physicochemical properties, synthesis, and therapeutics

### 2.1 Bile acids physicochemical properties

Bile acids (BA) are steroid compounds, hydroxyl derivatives of 5β-cholan-24 oic acid. Primary BA are cholic acid (CA) and chenodeoxycholic acid (CDCA);

secondary BA such as deoxycholic acid (DCA) and lithocholic acid (LCA), all of them in 3α-position, and ursodeoxycholic acid (UDCA) is a hydroxyl derivative in 3β-position (**Figure 1**) [10].

BA have different physicochemical properties according to the number, position, and orientation of their hydroxy groups and the conjugation with glycine and taurine (**Figure 1**). In this sense, this characteristic influence their solubility, detergency, and hydrophobicity [11].

BA have an important role in biological systems under physiological and pathological conditions [12]. Their functions are associated with lipid digestion and absorption, solubilization of cholesterol and bile formation. In this case, BA influence in volume and composition of the bile.

The number, position, and orientation of the hydroxy groups of the BA impact directly on the hydrophobicity and detergency property and the relationship to the toxicity. In the case of BA with hydroxy groups in 3-α position, the higher the number of hydroxy groups, less hydrophobicity and lower detergency and, as a result, lower toxicity.

It must be pointed out that the orientation of the hydroxy group rules over the properties in the molecule. This can be seen on the CDCA (7α) and its epimer, the UDCA (7β), where the UDCA showed a strong reduction of detergency and hydrophobicity. Also, the BA toxicity is directly related to its hydrophobicity and detergency, because those interact with the cellular membranes in different ways, including the union, the insertion in the lipidic bilayer and its solubilization increasing its fluidity [10].

Therefore, UDCA is administered as therapeutic agent for the treatment of hepatobiliary disorders such as cholestasis, biliary dyspepsia, primary biliary cirrhosis, and different cholestatic conditions.

### 2.2 Bile acids synthesis

The synthesis of BA is produced exclusively in the liver, based on a series of enzymatic reactions in the hepatocyte, in which 17 enzymes are involved. The cholesterol (hydrophobic compound) turns into the primary BA, also known as colic acid (CA) and chenodeoxycholic (CDCA), through the first step and limiting of the called "classic" or "neutral" way of the BA biosynthesis, where the hydroxylation of the cholesterol is produced, catalyzed by the enzyme cytochrome P450

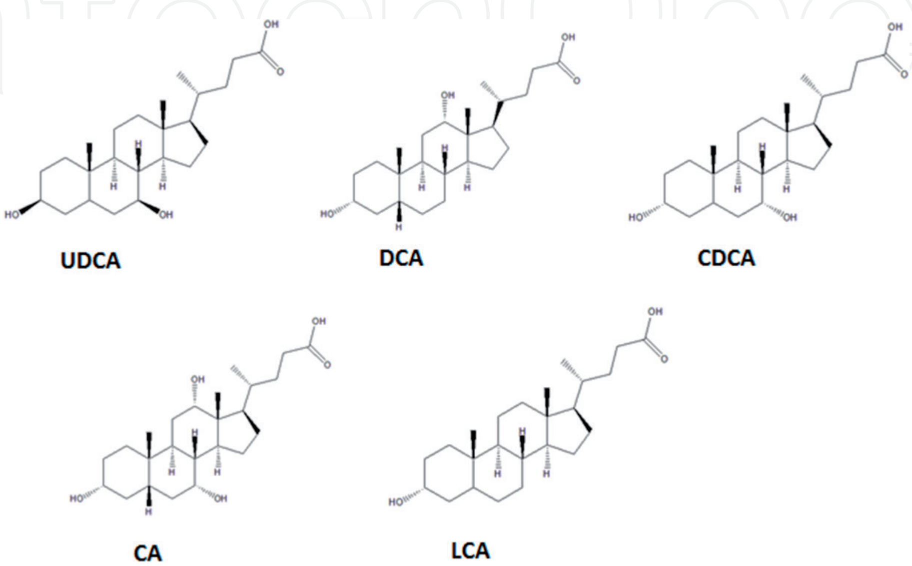


**Figure 1.**
*Bile acids: chemical structure.*

cholesterol 7a-hydroxylasa (CYP7A1). The BA synthesis can also occur through an "alternative" or "acidic" way, where the CYP27A1 intervenes and changes the BA oxysterols. Unlike the CYP7A1, the CYP27A1 is not regulated by the BA and is estimated only the 6% of the synthesis of BA is produced through this way. Before its secretion in the canalicular biliary light for the storage in the biliary gold bladder as mixed micelles with phospholipids and cholesterol, the primary BA are mainly conjugated with taurine and glycine, forming the conjugated BA, that with the $Na^+$ and $K^+$ form the biliary salts. When ingesting a food, the contraction of biliary gold bladder expels the micellar BA to the intestinal light to help digestion. In the gut, the intestinal bacteria deconjugate and dehydroxylate the primary BA, resulting in other species, denominated secondary BA: deoxycholic acid (DCA), a CA derivative, and ursodeoxycholic acid (UDCA), a CDCA derivative. The enterohepatic circulation allows the 95% of the BA to be reabsorbed from the distal ileum and transported back to the liver through portal circulation. Only 5% of the BA are not reabsorbed and are eliminated through feces. This small amount of loss is recovered through the novo synthesis of the BA in the liver. The size of the BA reserve is strictly regulated by the liver and gut to avoid a cytotoxic accumulation. When the reserve of BA increases, a feedback mechanism is activated, ruled by the interaction of several nuclear receptors, mainly the farnesoid X nuclear receptor (FXR) to inhibit the novo synthesis of BA. Therefore, the FXR is a "BA sensor," when the BA are joined to this receptor, they mediate their own synthesis control to provide a strict regulation of its reserve [13–15].

### 2.3 Bile acid therapy in hepatobiliary disease: role of UDCA

BA as therapeutic agent are appropriated in the chronic cholestasis deceases. BA can be orally administered following two strategies, the "displacement therapy" and/or "replacement therapy." UDCA may be used to displace endogenous BA to decrease the intrahepatic concentration of potentially cytotoxic BA accumulated in cholestasis. On the other hand, primary BA such as cholic acid (CA) might be used to replace a depleted BA pool resulted from defective biosynthesis on consequence to restore the physiological function of BA [16, 17].

UDCA (3α-7β-hydroxy-5β-cholan-24-oic acid) is naturally occurring BA, that normally constitutes 1–2% of the BA in human bile. UDCA is obtained by 7α-epimerization of the primary BA chenodeoxycholic acid (CDCA), by intestinal bacteria. [18] UDCA and CDCA differ in the hydroxyl group orientation at seventh position, allowing higher hydrophilicity of UDCA in comparison to CDCA.

UDCA is a weak acid (pKa = 5), and poorly water soluble, however, its solubility increases directly to the increase of the solution pH. After orally administrations, UDCA must be solubilized in mixed micelles present in small intestinal content in order to allow absorption [19, 20]. During the cholestasis disease, the UDCA bioavailability is limited due to the reduction of endogenous BA micelles in the duodenal lumen. Unconjugated UDCA is absorbed by passive diffusion in the proximal jejunum and in the ileum, thus extracted from portal venous blood by the liver and conjugated with glycine or taurine. Conjugated UDCA is secreted into the bile.

It is worth mentioning that in the UDCA oral administration, the half-life of the UDCA in the portal circulation is short, thus the maximum concentrations in liver/bile achieved by dividing the dose equally over 24 h are adequate.

UDCA is the BA of choice in view of the proven efficacy and lack of side effects in the treatment of cholestasis diseases. In the case of CDCA, its inherent toxicity is related to the fact that CDCA undergoes bacterial conversion dihydroxylation to a toxic, monohydroxy BA, like lithocholic acid (LCA), unlike UDCA, which is more resistant to bacterial dihydroxylation [21, 22].

The versatility presented by UDCA in the treatment of cholestatic diseases is due to its multiple action mechanisms:

- Biliary stones dilution
- Changes in the BA reserve hydrophobicity level
- Protection against the cellular death induced by cytotoxic BA
- Modulation of the expression of the transporters and the liver's enzymatic systems
- Normalization of the altered cellular location of hepatocellular transporters
- Immunoregulatory effects

#### *2.3.1 Biliary stones dissolution*

UDCA reduces the content of cholesterol in the bile by reducing the hepatic synthesis of cholesterol and its absorption by the gut itself. In addition to solubilizing the cholesterol into micelles, it causes the cholesterol to scatter into liquid crystals in an aqueous medium causing a favorable environment for the dissolution of biliary stones. In addition to this, reduces the viscosity and improves the bile flow.

#### *2.3.2 Changes in the BA reserve levels of hydrophobicity*

In the cholestasis, the increase of hydrophobic BA produces the cytolysis of plasmatic membrane. In normal individuals, the UDCA represents not more than 4% of the complete endogenous BA reserve. Under a treatment with UDCA, this percentage increases to 40–60% under a conventional dosage of 13–15 mg/kg/day, becoming the UDCA the predominant BA, which shifts the more hydrophobic endogenous BA. Therefore, the substitution of the potentially toxic hydrophobic endogenous BA in the total BA group to a hydrophilic turns the bile more hydrophilic and less cytotoxic, reducing the hepatic lesion.

### 2.4 UDCA and oxidative stress

It has been proposed that UDCA antioxidative action is due to the induction of glutathione (GSH) synthesis and in this way, mitochondrial injury apoptosis is prevented [23]. UDCA activates the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway and induces the translocation of nuclear factor-E2-related factor 2 (Nrf2) into the nucleus. Hence, it could be hypothesized that UDCA increases the gene expression of enzymes associated with GSH synthesis and induces the down-regulation of intracellular ROS levels [24]. In a similar fashion, insulin reduces oxidative stress by the activation of PI3K and extracellular signal-regulated protein kinase in HepG2 cells [25]. Therefore, both UDCA and insulin may exert a cytoprotective effects against oxidative stress and. Noteworthy, UDCA may reduce fatty acids-induced insulin resistance.

## 3. Coenzyme Q10: generalities, clinical approaches and its relation to intrahepatic cholestasis of pregnancy

Coenzyme Q (CoQ) is an endogenous lipophilic compound synthetized in all tissues and cells. The biosynthetic pathway of CoQ in eukaryotes has been characterized by studies of mutants deficient in CoQ in *Saccharomyces cerevisiae*. The biosynthesis of CoQ initiates with the hydroxybenzoic acid to which a polyisoprenoid lipid tail is attached. Thus, CoQ is the product of two different converging biosynthetic pathways: the synthesis of 4-hydroxybenzoate, derived from the metabolism of tyrosine and the synthesis of the isoprene side chain that begins with the conversion of acetyl-coenzyme A (CoA) through the mevalonate route and regulated by the HMG CoA reductase. Formerly, the trans-prenyl transferase catalyzes the condensation of farnesyl pyrophosphate with numerous trans isopentenyl pyrophosphates, to form the long isoprenoid chain. Finally, these two pathways converge in a terminal step, where 4-hydroxybenzoate and polyprenyl pyrophosphate are linked by a condensation reaction catalyzed by the enzyme polyprenyl 4-hydroxybenzoate transferase [26].

Due to its ubiquitous distribution, CoQ is also called ubiquinone. In mammals, ubiquinone contains a 2,3-dimethoxy-5-methylbenzoquinone core with, predominantly, a hydrophobic 10 isoprenyl units, so it is designated as coenzyme Q10 (CoQ10, **Figure 2**).

CoQ10, mainly placed in the inner mitochondrial membrane, plays its principal role in promoting the electron transfer from complexes I and II to complex III within the mitochondrial respiratory chain to finally obtain cellular energy [27]. Taking into account its redox properties, CoQ10 also acts as a potent lipophilic antioxidant, scavenging oxygen reactive species, protecting lipids, protein, and cellular DNA and being involved in multiple steps of vital cellular metabolism such as the electron transfer in plasmatic membranes [28] and lysosomes [29], modulation of apoptosis [30, 31] and proton transport between uncoupled proteins [32]. CoQ10 also has an important intracellular signaling role in modulating the mitochondrial permeability transition pore [33].

Although its biosynthesis is not completely dilucidated, it is well known that different mutations in some genes which codify for proteins within its biosynthetic pathway have been identified. These mutations define the primary CoQ10 deficiencies [34–40]. At this time, from the 13 known CoQ genes direct or indirect related to CoQ biosynthesis, it is recognize that eight of them can cause CoQ10 deficiency and disease [41]. Primary CoQ10 deficiencies are a group of rare diseases of clinically heterogeneous appearance suggesting an autosomal recessive inheritance, because relatives are often affected, whereas parents are characteristically unaffected. The four most frequent clinical phenotypes associated with primary CoQ10 deficiencies are encephalomiophaty, cerebellar ataxia, multisystemic infantile form, and glomerulophaty and myophaty, all of them having a muscular and neurologic compromise [27]. Patients affected with primary CoQ10 deficiency, although its clinical severity, highly respond to CoQ10 supplementation being most effective the sooner the treatment begins [35, 42].

On the contrary, secondary CoQ10 deficiency is more frequent and of less severe clinical presentation. However, its treatment only ameliorates the symptoms although improve life quality. Secondary CoQ10 deficiency is associated to different pathologies such as neuro-muscular degenerative pathologies, cardiovascular, thyroid

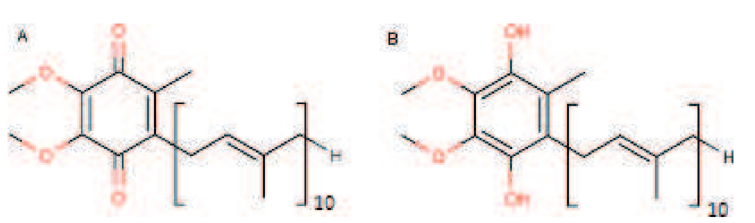


**Figure 2.**
*Coenzyme Q10: (A) oxidized form and (B) reduced form.*

and reproductive diseases as well as cancer among others [43–46]. Coenzyme Q10 deficiency is commonly found associated to mitochondrial oxidative phosphorylation impairment, probably as an adaptive mechanism to maintain a balance in mitochondrial redox status. However, in spite of the high incidence of secondary CoQ deficiencies, the precise mechanisms underlying these secondary deficiencies remain unidentified specially in non-mitochondrial oxidative phosphorylation disorders [47].

What is certain is that final cellular CoQ10 concentration is related to the balance existing between biosynthetic and dietary supply on one side and energetic consumption on the other [48].

In a previous work, we have demonstrated a reduced plasmatic level of CoQ10 in mothers with intrahepatic cholestasis of pregnancy (ICP) as well as in an animal model, being the first report connecting CoQ10 deficiency to this disorder [49]. Later, it was confirmed in another study, which analyzed fetal CoQ10 levels in cord blood from ICP mothers [50]. It is well known that ICP is a high-risk pregnancy disease characterized by the accumulation of total serum bile acids, with an enhanced proportion of the hydrophobic bile acids which are highly cytotoxic. During the last decade, it was found many evidences suggesting that hydrophobic bile acids increase is responsible for the higher oxidative stress observed in ICP [51–53]. Thus, it was reasonable to suspect that CoQ10 levels could be diminished, secondary to the oxidative stress and/or mediated by a metabolic feedback [50]. Furthermore, a depleted CoQ9 levels (the predominant form of ubiquinone in rodents) was also observed in plasma, brain and muscle in a cholestatic rat model together with a positive correlation between CoQ9 and ursodeoxycholic/lithocholic acid ratio (UDCA/LCA). The latter suggests that increased plasma LCA may be closely related to CoQ9 decrease in blood and tissues [49].

CoQ10 decrease in ICP possibly reveals a disturbance on the delicate balance between oxidative stress and antioxidant defenses, thus accumulating large amounts of free radicals, imparing energy production, and increasing risk for the fetus. Although the relationship between CoQ10 and serum bile acids is not well established, it is possible that reduced CoQ10 levels result from enhanced ubiquinone extraction from blood because of higher cellular demand. As it was previously mentioned, it is also probable that CoQ10 depletion may be caused by increased proportion of circulating and intracellular hydrophobic bile acids and enhanced consumption of the CoQ10 by free radicals and/or a metabolic down regulation. The relationship between CoQ and bile acids will be discussed in the next section.

Since CoQ10 is a potent antioxidant and is even proposed as the first line of defense against oxidative insult [54], its tissue distribution and plasma levels will be dependent on its susceptibility to the oxidative stress induced by cholestasis.

## 4. Bile acids and coenzyme Q10: possible relationship

Several studies have provided evidence that oxidative stress may play an important role in the pathogenesis of hepatic injury in animal models of cholestasis [52, 55–58] and in humans [59–61].

Hepatic mitochondria have been proposed as the most important cellular source of reactive oxygen species (ROS) induced by bile acids (BA). Hydrophobic BA impair respiration and electron transport in hepatic mitochondria. Krähenbühl et al. reported that hydrophobic BA decrease the activities of several enzyme complexes involved in the electron transport chain, such as complexes I, III, and IV but not affected complex II in isolated rat liver mitochondria. Furthermore, hydrophobic BA decrease the mitochondrial membrane potential developed upon succinate energization and decrease state three and enhance state four in mitochondria [62].

Yerushalmi et al. [63] proposed that ROS are generated at the ubiquinone-complex III interaction of the respiratory chain in hepatic mitochondria upon exposure to BA. Additionally, Botla et al. [64] reported that hydrophobic BA initiates the membrane permeability transition in hepatic mitochondria. In this context, oxidative stress results from an imbalance between increased free radical and impairment of antioxidant systems.

Therefore, the link between BA and CoQ has recently achieved clinical relevance and open to potential therapeutics challenges. As it was aforementioned, a study with a validated animal model of ICP, which shows similar biochemical hepatic alterations as observed in ICP patients, showed a significant decrease in CoQ9 and α-tocopherol in plasma that correlated negatively with the increase in LCA levels in the animal model of ICP [49]. Stocker and Bowry reported that CoQ acts earlier than α-tocopherol in the antioxidant system, thus the reduction of plasmic CoQ could be considered as an early marker of oxidative insult [54]. The decrease in these antioxidants may contribute to increase oxidative stress in ICP [49]. CoQ plasmatic levels more likely reflect the degree of metabolic request; in this case decreased levels may be related to consumption by free radicals or by increasing cellular demand. On the other hand, tissue CoQ levels are related to the balance between biosynthesis, dietary supply and energetic consumption [48]. The increase in BA has different effect over CoQ tissue levels. It was observed that skeletal muscle and brain were more susceptible to oxidative stress and showed a decrease in CoQ levels in ICP animals, whereas liver and heart content of CoQ remained unchanged. An hepatic paradox described in animal model of cholestasis including EE cholestasis, where the activity of HMG-CoA reductase and 7 alpha hydroxylase is increased despite the increase of BA, could possible explain this finding [65–68]. Thus, taking into account, that CoQ is synthesized via HMG-CoA reductase, it is possible that levels were maintained by an increase in its synthesis [49].

In accordance with those results, a significant decrease in CoQ10 and vitamin E levels was also observed in ICP patients respect to control pregnancies, coupled to an increase in total serum BA with a more hydrophobic profile [49]. It is worth mentioning that neonates are highly susceptible to oxidative damage caused by ROS, since the extrauterine environment is richer in oxygen than the intrauterine environment [69]. This problem is further aggravated by the low efficiency of natural antioxidant systems in the neonate that could be worsened if the antioxidant capacity of mother is deficient [48]. In addition, the direction of placental BA gradient, in normal pregnancy occurs from the fetus to the mother in order to promote toxic compounds elimination from the fetal compartment, while in ICP, this gradient is inverted allowing to accumulate BA in the fetal compartment [70, 71]. Thus, decreased CoQ10 levels in mothers with ICP may pose a risk for the newborn.

Recently, another study which evaluates umbilical cord blood of newborn from ICP mothers showed a decrease in cholesterol normalized CoQ10 content and an increase in total serum BA respect to normal pregnancy [50]. The results obtained by Martinefski et al. demonstrated a highly prooxidant environment.

Nowadays, since the relationship between CoQ and BA is not well established, two explanations have been hypothesized. On one hand, during ICP, cholesterol levels could possibly be maintained due to a mevalonate pathway deviation flow that absorbs another branch of the metabolic flow including those required to support CoQ synthesis [72].

On the other hand, hydrophobic BA stimulate the generation of ROS leading to a consumption of different antioxidants, including CoQ. Both scenarios led to a secondary CoQ deficiency.

In the field of cholestasis therapeutics, CoQ10 synthetic analog (idebenone) has shown to prevent BA stimulation of ROS from hepatic mitochondria and isolated hepatocytes [63]. Therefore, taking into account the deficiency of CoQ found in ICP, supplementation with CoQ10 could represent a new complementary therapeutic proposal for ICP in order to protect both the mother and the newborn. However, further studies are required to obtain a deeper conclusion.





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