International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Bile Physiology and Pathophysiology: A Comprehensive Narrative Review

Alexandre Tavartkiladze[1, 2], Russel J. Reiter[3]

[1]Tbilisi State Medical University, Tbilisi, Georgia
[2]Institute for Personalized Medicine, Tbilisi, Georgia (Corresponding Author)

[3]Department of Cellular & Structural Biology, University of Texas Health Science Center, San Antonio, USA

Abstract: ***Bile is a complex biological fluid produced by the liver and delivered to the intestine through a highly regulated hepatobiliary network. Beyond its classical role in lipid emulsification and absorption, bile acids act as endocrine signals that integrate hepatic metabolism, intestinal barrier function, and the gut microbiome. This review summarizes key aspects of bile composition, cellular mechanisms of bile formation by hepatocytes and cholangiocytes, enterohepatic circulation, neuro-hormonal regulation, and clinically relevant consequences of dysregulation, including cholestasis, bile acid diarrhea, gallstone disease, malabsorption of fat-soluble vitamins, and post-cholecystectomy physiology. Special attention is given to the bidirectional crosstalk between bile acids and the intestinal microbiota and to age-, stress-, and inflammation-related modifiers of biliary homeostasis.***

Keywords: bile physiology; enterohepatic circulation; bile acids; cholestasis; microbiome interaction

1. Introduction: What Is Bile?

Bile (Latin: bilis) is a green–yellow fluid that plays an essential role in digestion, particularly in the emulsification and absorption of dietary lipids and fat-soluble vitamins. It is synthesized by hepatocytes, modified along the biliary tree by cholangiocytes, stored and concentrated in the gallbladder, and released into the duodenum after meals. In addition to its digestive functions, bile provides a major route for the excretion of cholesterol and bilirubin, and bile acids act as signaling molecules that influence metabolic homeostasis and inflammation [1,2,14,16,17].

The hepatobiliary system is typically conceptualized as having two main cellular components: (i) hepatocytes, which generate primary bile at the canalicular membrane, and (ii) cholangiocytes, the epithelial cells lining bile ducts, which modify bile through secretory and absorptive processes. These coordinated processes determine bile volume, pH, and solute composition and preserve duct integrity through protective mechanisms such as the bicarbonate-rich "umbrella" at the ductal surface [5,12,18].

A simplified overview of bile formation, storage, and delivery to the intestine is shown in Figure 1.

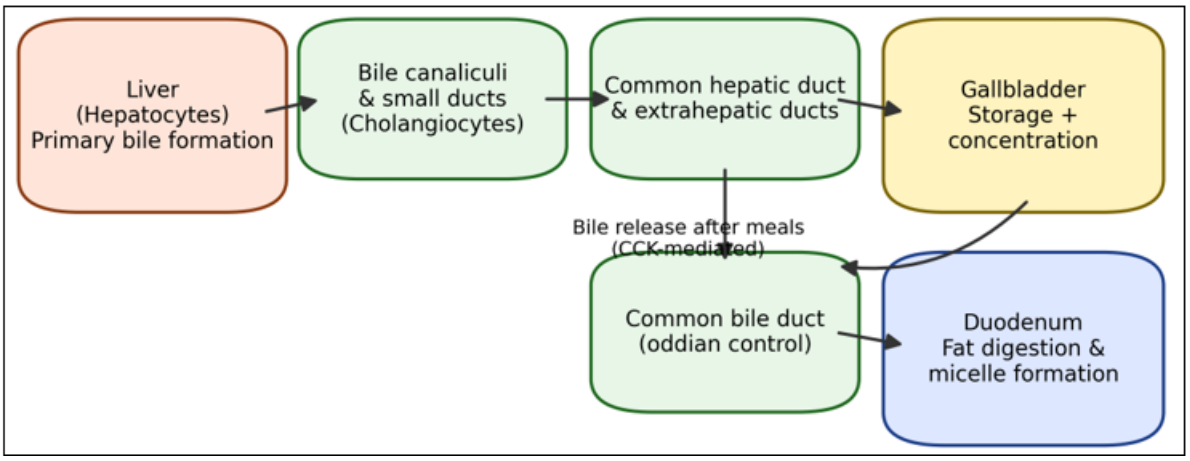

Figure 1: Schematic overview of bile formation in the liver, ductal modification, gallbladder storage, and release into the duodenum after meals (conceptual synthesis based on [1,14,16,17]).

2. Composition of Bile

Bile is a complex fluid containing water, bile acids, phospholipids, cholesterol, bile pigments (primarily bilirubin), electrolytes, and varying amounts of bicarbonate. Understanding the physicochemical organization of these components is central to explaining both normal digestive physiology and common biliary disorders such as cholestasis and gallstone disease [1,2,12,14,19].

2.1 Major Constituents

Bile acids: Bile acids account for approximately half of bile solids and represent its most important functional solutes. The primary bile acids- cholic acid and chenodeoxycholic

acid- are synthesized in hepatocytes from cholesterol through cytochrome P450-dependent pathways. In the intestine, microbial enzymes convert a fraction of primary bile acids to secondary bile acids (e.g., deoxycholic acid and lithocholic acid), including via 7α-dehydroxylation [2,3,7,8].

Phospholipids: Phosphatidylcholine (lecithin) contributes substantially to the lipid fraction of bile and is critical for the formation and stability of mixed micelles. In addition, phospholipids reduce the detergent toxicity of bile acids and protect the biliary epithelium [12,14,18].

Cholesterol: Bile represents the principal route for cholesterol elimination from the body. The relative proportions of cholesterol, bile acids, and phospholipids determine cholesterol solubility; disruption of this balance increases bile lithogenicity and promotes cholesterol gallstone formation [14,19,20].

Bilirubin: Conjugated bilirubin (bilirubin diglucuronide) is a final product of heme catabolism and contributes to bile color. In hepatocytes, bilirubin is conjugated with glucuronic acid via UDP-glucuronosyltransferase activity (UGT1A1), enabling biliary excretion [16,17].

Electrolytes, water, and bicarbonate: Bile contains sodium, potassium, calcium, chloride, and variable bicarbonate. Cholangiocytes secrete bicarbonate-rich fluid, contributing to an alkaline layer (the "bicarbonate umbrella") that helps shield the duct epithelium from bile-acid-mediated injury [5,12,18].

The approximate quantitative composition of bile is summarized in Table 1 and visualized in Figure 2.

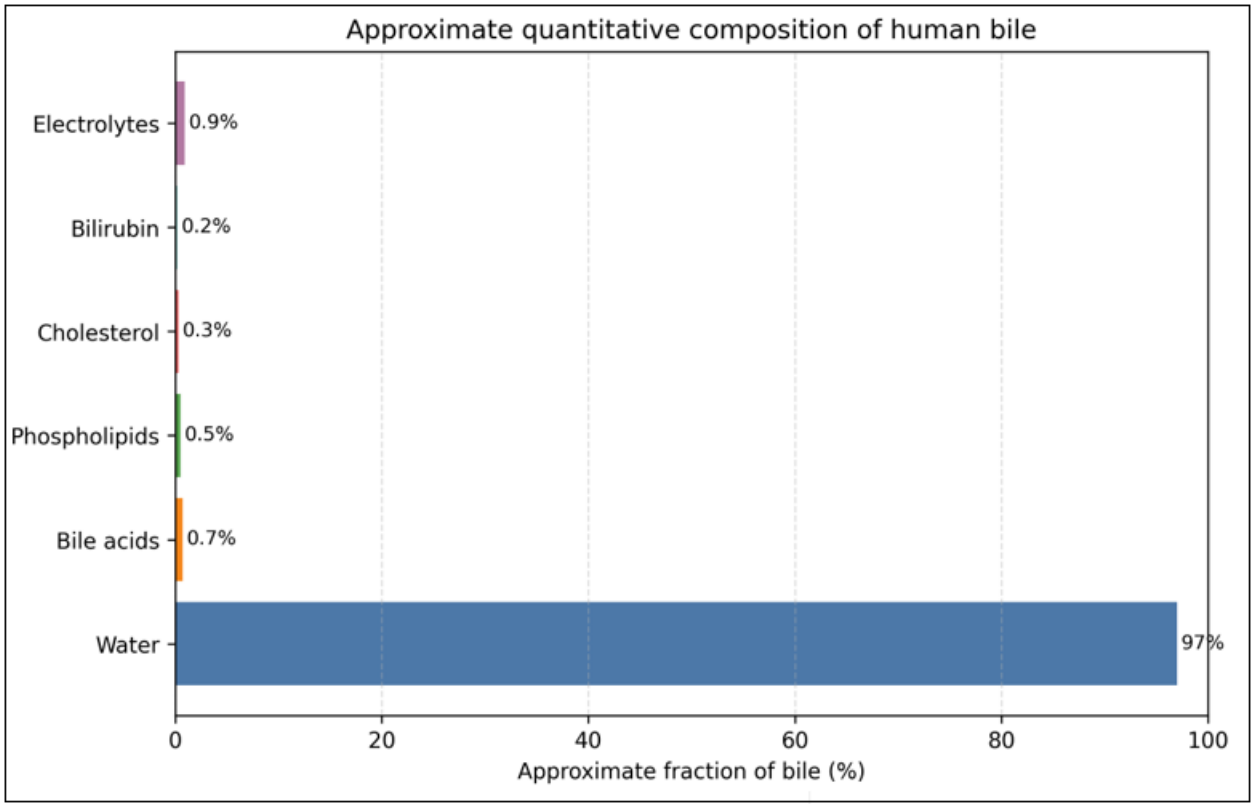

Figure 2: Approximate quantitative composition of human bile (percent fractions) (data summarized from classical physiology sources [1,12,14,16,17]).

2.2 Quantitative Composition

Table 1: Approximate quantitative composition of human bile and key functional roles

Component	Concentration	Primary function
Water	97%	Solvent; transport medium
Bile acids	0.7%	Lipid emulsification and micelle formation
Bilirubin	0.2%	Excretion of bile pigments
Phospholipids	0.5%	Mixed micelle stabilization; epithelial protection
Cholesterol	0.3%	Cholesterol excretion
Electrolytes	0.9%	Osmotic balance
Bicarbonate	Variable	pH regulation; ductal protection

3. Bile Formation at the Cellular Level

Bile formation is a multistep process that begins at the canalicular membrane of hepatocytes and continues along the biliary tree, where cholangiocytes modulate bile volume and composition. Two complementary flow components are commonly described: a bile-acid-dependent fraction and a bile-acid-independent fraction, reflecting distinct transporter-driven osmotic forces [1,12].

3.1 Hepatocytes: Primary Bile Formation

Hepatocytes constitute roughly 60% of the liver parenchyma and generate the majority of bile volume (often estimated at ~75%). Canalicular secretion is driven by active solute

transport into canaliculi, followed by osmotic water movement. The bile-acid-dependent fraction is typically considered to comprise about 60% of hepatocellular bile flow and is driven by active bile salt export via the bile salt export pump (BSEP/ABCB11). The bile-acid-independent fraction (approximately 40%) depends on secretion of glutathione, bicarbonate, and other organic anions, including via multidrug resistance-associated protein 2 (MRP2/ABCC2) [1,12].

3.2 Cholangiocytes: Ductal Modification of Bile

Cholangiocytes comprise only ~3–5% of hepatic cells yet contribute substantially to final bile volume (commonly estimated at 25–40%). These polarized epithelial cells have apical membranes exposed to bile and basolateral membranes facing the periductular circulation. Cholangiocytes perform three broad functions: (i) secretion, particularly of bicarbonate-rich fluid via channels and exchangers such as CFTR and AE2; (ii) selective reabsorption of solutes (e.g., glucose, amino acids, and bile acids under specific conditions); and (iii) sensory/signaling functions through receptors such as TGR5 that allow the duct epithelium to respond dynamically to luminal bile composition [5,18].

Key hepatocyte- and cholangiocyte-level mechanisms are summarized schematically in Figure 3.

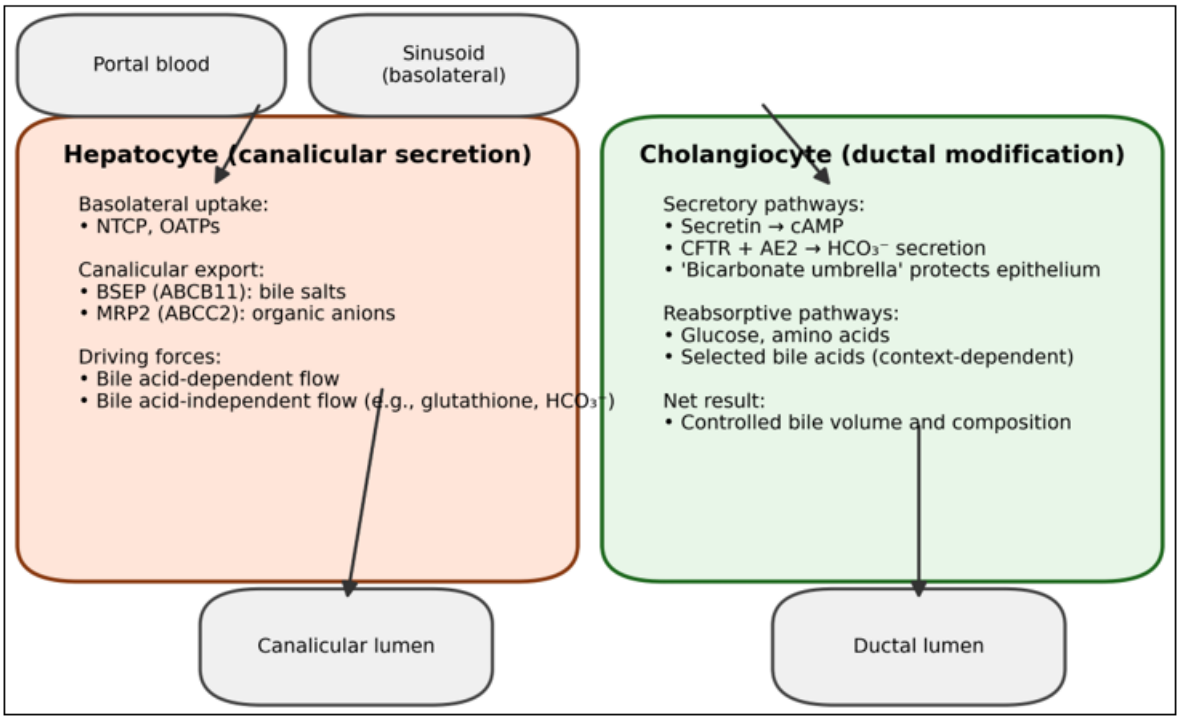

Figure 3: Conceptual schematic of major transporter-driven processes in hepatocytes (canalicular secretion) and cholangiocytes (ductal modification), including bile-acid-dependent and -independent bile flow and bicarbonate-rich secretion (conceptual synthesis based on [1,5,12,18]).

4. Enterohepatic Circulation

Enterohepatic circulation refers to the cyclical movement of bile acids between the liver and the intestine. This highly efficient system conserves the bile acid pool, with approximately 95% of bile acids being reclaimed and returned to the liver under normal conditions [2,3].

Key stages of the enterohepatic cycle include:

1) Synthesis and secretion: hepatocytes synthesize bile acids and secrete them into bile.
2) Storage: the gallbladder concentrates and stores bile between meals.
3) Release: cholecystokinin (CCK) stimulates gallbladder contraction and bile delivery into the duodenum after food intake.
4) Micellar solubilization: bile acids form mixed micelles with dietary lipids and fat-soluble vitamins, enabling efficient absorption.
5) Reabsorption: in the terminal ileum, the apical sodium-dependent bile acid transporter (ASBT) reclaims the majority of bile acids.
6) Return to the liver: bile acids return via the portal vein and are taken up by hepatocytes (e.g., via NTCP), completing the cycle.

A simplified map of the enterohepatic circulation is provided in Figure 4 [2,3,7,8].

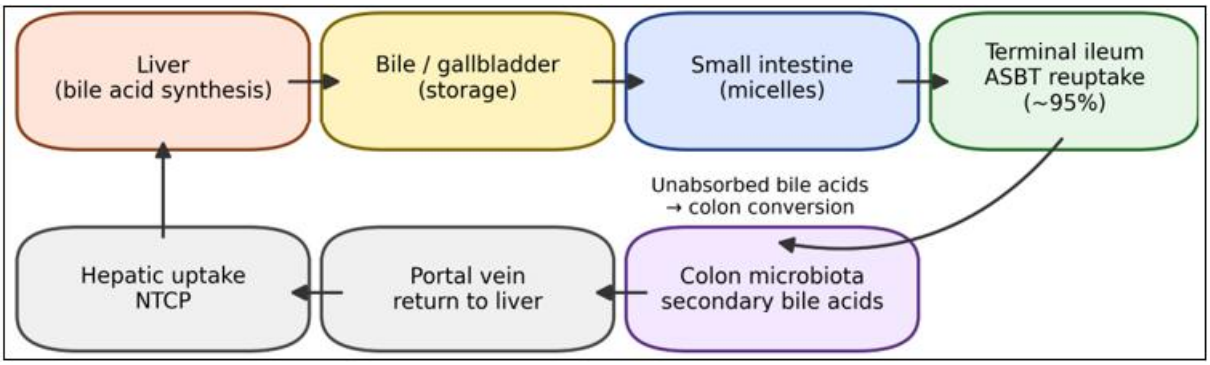

Figure 4: Enterohepatic circulation of bile acids, highlighting intestinal reuptake (ASBT), portal return, hepatic uptake (NTCP), and microbiome-driven conversion of primary to secondary bile acids (conceptual synthesis based on [2,3,7,8]).

5. Neural Regulation of the Biliary System

The gallbladder and bile ducts receive rich innervation from both parasympathetic and sympathetic divisions of the autonomic nervous system. This neural network provides rapid, context-dependent control of bile secretion, gallbladder motility, and sphincter tone, thereby coordinating bile delivery with feeding behavior and digestive demands [16,17].

5.1 Innervation

Parasympathetic innervation:
- Primary nerve: vagus nerve (cranial nerve X).
- Central origin: dorsal motor nucleus of the vagus (nucleus dorsalis nervi vagi) in the medulla.
- Major neurotransmitter: acetylcholine (ACh).
- Key receptor: muscarinic M3 receptors.
- Net effect: gallbladder contraction, relaxation of the sphincter of Oddi, and stimulation of bile delivery.

Sympathetic innervation:
- Pathway: greater splanchnic nerves from thoracic segments T5–T9.
- Relays: via the celiac ganglion (ganglion coeliacum) and associated plexuses.
- Major neurotransmitter: norepinephrine (NE).
- Key receptors: α- and β-adrenergic receptors.
- Net effect: gallbladder relaxation, contraction (increased tone) of the sphincter of Oddi, and inhibition of bile delivery.

5.2 Roles of Key Neurotransmitters

Multiple neurotransmitters and neuropeptides act on the biliary tract to fine-tune secretion and motility. Representative mediators, receptors, and signaling mechanisms are summarized in Table 2 [16,17].

Table 2: Selected neurotransmitters/neuropeptides involved in biliary regulation.

Neurotransmitter	Effect	Receptor	Mechanism
Acetylcholine	Stimulation	M3 muscarinic	Ca^{2+} mobilization
Norepinephrine	Inhibition	α/β adrenergic	cAMP modulation
VIP	Stimulation	VPAC receptor	Increase in cAMP
Somatostatin	Inhibition	SSTR2/5	Decrease in cAMP
Substance P	Stimulation	NK1 receptor	Ca^{2+} signaling
CGRP	Relaxation	CLR/RAMP1	Increase in cAMP

5.3 Cortical and Central Regulation

Higher-level brain centers can influence biliary physiology through a hypothalamus–liver axis that modulates autonomic outflow. Hypothalamic nuclei (including paraventricular and lateral regions) integrate metabolic and stress-related signals and coordinate downstream autonomic responses. In parallel, the prefrontal cortex and limbic structures (amygdala and hippocampus) modulate hypothalamic activity in relation to emotional and cognitive state, providing a mechanistic basis for stress-associated biliary dysfunction. The insular cortex participates in processing visceral sensations, whereas the anterior cingulate cortex is implicated in pain perception and affective regulation, which is clinically relevant for biliary pain syndromes [16,17].

6. Hormonal Regulation

Neural control is complemented by endocrine signaling from the gastrointestinal tract. Together, these systems coordinate bile flow with meal composition, intraluminal pH, and intestinal transit. Hormonal regulation is particularly important for gallbladder contraction and for ductal secretion of bicarbonate-rich fluid [14,16,17].

6.1 Cholecystokinin (CCK)

Cholecystokinin is the primary physiological stimulus for gallbladder contraction. It is released from I cells in the duodenum and jejunum in response to dietary fats and amino acids. Major effects of CCK include:
- Contraction of gallbladder smooth muscle (via CCK-A receptors).
- Relaxation of the sphincter of Oddi, facilitating bile entry into the duodenum.

- A modest stimulatory effect on hepatic bile secretion in some settings.

6.2 Secretin

Secretin is released from S cells in the duodenum in response to acidic chyme. It stimulates cholangiocytes to secrete bicarbonate-rich fluid, increasing bile volume (choleresis) and supporting neutralization of gastric acid in the proximal small intestine. Secretin signaling interacts with ductal channels and exchangers (including CFTR and AE2) to generate a protective alkaline layer at the epithelial surface [5,18].

6.3 Other Regulatory Molecules

Several additional hormones and mediators influence biliary function:

- Gastrin: a weak stimulant of gallbladder contraction.
- Motilin: modulates gallbladder tone during fasting and interdigestive phases.
- Somatostatin: inhibits gallbladder contraction and suppresses bile secretion.
- FGF19 (fibroblast growth factor 19): provides negative feedback inhibition of bile acid synthesis by repressing CYP7A1 expression downstream of intestinal FXR activation.

An integrated view of neural, hormonal, and microbiome-linked regulation is summarized in Figure 5 [3,7,8,10,11,16,17].

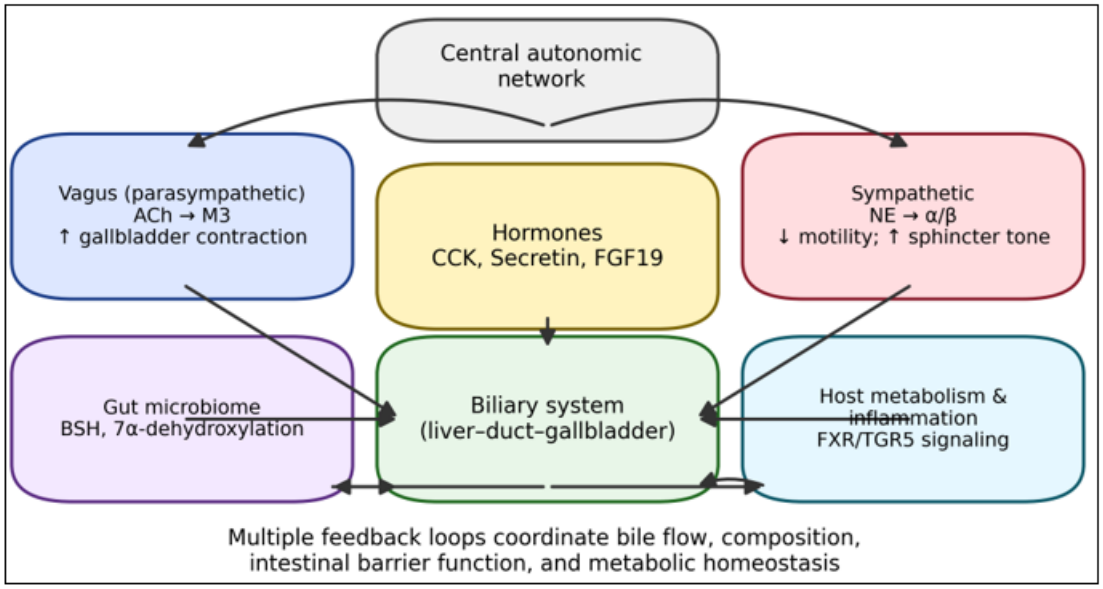

Figure 5: Integrated model of biliary regulation, illustrating central autonomic control, parasympathetic and sympathetic inputs, major gastrointestinal hormones, microbiome-mediated bile acid transformations, and host FXR/TGR5 signaling loops (conceptual synthesis based on [3,7,8,10,11,16,17]).

7. Age-Related Features of the Biliary System

Biliary physiology evolves across the lifespan. Developmental maturation, hormonal milieu, and age-related changes in motility and solute handling influence bile acid homeostasis and the risk of common biliary disorders [14,19].

7.1 Neonatal Period

In newborns, the biliary system is still maturing. Hepatocyte capacity for bile acid synthesis is limited, leading to a relatively small bile acid pool. UDP-glucuronosyltransferase (UGT1A1) activity is lower than in adults, contributing to physiologic neonatal jaundice. The gallbladder is relatively small, has limited concentrating capacity, and enterohepatic circulation is less efficient, in part due to lower expression of ileal ASBT transporters [16,17].

7.2 Pediatric Age

By approximately 1–2 years of age, biliary function approaches a mature state, with expansion of the bile acid pool and more efficient enterohepatic cycling. Gallstones are uncommon in children but can occur in the context of hemolytic disorders or total parenteral nutrition, among other risk factors [19].

7.3 Older Age

With aging, several clinically important changes are observed:

- Bile acid synthesis may decrease substantially (often reported on the order of ~50%).
- Gallbladder contractility and responsiveness to CCK weaken.
- Bile becomes more lithogenic (more cholesterol-supersaturated).

- The prevalence of gallstones rises with age, reaching approximately 30–40% in individuals older than 70 years in many populations.

These features contribute to increased susceptibility to gallstone disease, biliary sludge, and functional biliary disorders in older adults [13,14,19,20].

8. Impact of Chronic Stress and Inflammation

Chronic psychological stress and systemic inflammation can disrupt biliary physiology through neuroendocrine activation and cytokine-mediated alterations in transporter expression, ductal secretion, and epithelial barrier integrity. These influences help explain why functional biliary complaints and cholestatic patterns may accompany chronic stress states or inflammatory diseases [9,12,18].

8.1 Chronic Stress

Chronic stress can impair bile physiology via activation of the hypothalamic– pituitary– adrenal (HPA) axis and sustained shifts in autonomic tone. Major pathophysiological mechanisms include:

- Sympathetic hyperactivity: elevated norepinephrine promotes gallbladder hypokinesia and sphincter of Oddi spasm.
- Cortisol effects: chronically increased glucocorticoids can alter bile composition and increase cholesterol secretion, contributing to lithogenic bile.
- Parasympathetic suppression: reduced vagal tone diminishes gallbladder contractility and blunts CCK responsiveness.
- Bile stasis: incomplete gallbladder emptying can promote gallstone formation and predispose to cholestatic complications.

8.2 Chronic Inflammation

Pro-inflammatory cytokines and stress-responsive transcriptional programs substantially affect bile homeostasis. Notable mechanisms include:

- Cytokine-mediated cholestasis: TNF-α, IL-1β, and IL-6 can suppress expression and function of key bile transporters (e.g., BSEP, MRP2, NTCP).
- NF-κB activation: inflammatory signaling can reduce FXR activity, thereby disrupting bile acid homeostasis.
- Impaired bicarbonate secretion: inflammation may reduce AE2 expression and weaken the ductal bicarbonate umbrella.
- Increased duct permeability: disruption of tight junctions can allow back-diffusion of bile constituents and amplify epithelial injury.

These pathways link systemic inflammation to cholestatic patterns and may contribute to chronic cholangiopathies when sustained [9,10,18].

9. Bile Deficiency and Fat-Soluble Vitamins

Adequate bile acid delivery to the intestinal lumen is required for efficient digestion and absorption of dietary lipids and fat-soluble vitamins (A, D, E, and K). Bile acid deficiency- whether due to impaired hepatic secretion, duct obstruction, or altered enterohepatic cycling—can therefore lead to clinically significant malabsorption syndromes [16,17].

9.1 Mechanism of Absorption

Fat-soluble vitamins depend on mixed micelles formed by bile acids. Due to their amphipathic nature, bile acids emulsify dietary fats and solubilize lipophilic micronutrients into micelles that can approach the enterocyte apical membrane and support uptake.

9.2 Vitamin A (Retinol)

Clinical manifestations of vitamin A deficiency may include:

- Night blindness (nyctalopia), often an early symptom.
- Xerophthalmia (dryness of the conjunctiva and cornea).
- Keratomalacia and corneal ulceration in severe deficiency.
- Impaired immune function.
- Follicular hyperkeratosis and other skin changes.

9.3 Vitamin D (Calciferol)

Clinical manifestations of vitamin D deficiency may include:

- Hepatic osteodystrophy with osteomalacia and osteoporosis.
- Hypocalcemia and secondary hyperparathyroidism.
- Proximal muscle weakness and myopathy.
- Increased risk of fragility fractures.

9.4 Vitamin E (Tocopherol)

Clinical manifestations of vitamin E deficiency may include:

- Peripheral neuropathy due to axonal degeneration.
- Spinocerebellar ataxia.
- Myopathy and generalized muscle weakness.
- Retinopathy (sometimes resembling pigmentary retinopathy).
- Hemolytic anemia, particularly in premature infants.

9.5 Vitamin K (Phylloquinone/Menaquinone)

Clinical manifestations of vitamin K deficiency may include:

- Coagulopathy due to reduced activity of vitamin K-dependent clotting factors (II, VII, IX, X).
- Prolonged prothrombin time (PT) and elevated INR.
- Easy bruising and bleeding.
- Impaired bone mineralization due to defective osteocalcin carboxylation.

10. Disorders of Lipid Absorption

10.1 Steatorrhea

Bile deficiency can cause lipid malabsorption and steatorrhea. Under normal conditions, fecal fat excretion is generally ≤7 g/day. In steatorrhea, fecal fat can rise to ~20–

40 g/day or more, depending on the degree of malabsorption and dietary intake [16,17].

Common clinical features include:
- Bulky, greasy, foul-smelling stools.
- Stools that float or are difficult to flush/clean from the toilet bowl.
- Abdominal bloating, gas, and discomfort.
- Weight loss and caloric deficiency.

10.2 Essential Fatty Acid Deficiency

Impaired absorption of omega-3 and omega-6 fatty acids may lead to:
- Dermatitis, hair loss (alopecia), and other skin manifestations.
- Reduced immune resilience.
- Edema.
- Delayed wound healing.
- Neurologic symptoms in prolonged or severe cases.

11. Bile and the Gut Microbiome

Bile acids and the intestinal microbiome engage in complex bidirectional interactions. Bile acids shape microbial ecology through their detergent and signaling properties, while intestinal bacteria modify bile acids through deconjugation and other biotransformations, thereby altering host signaling and metabolic outcomes [7,8].

11.1 Bidirectional Crosstalk

This crosstalk is clinically relevant because it links hepatobiliary physiology to intestinal barrier integrity, systemic inflammation, and metabolic regulation. Changes in either bile flow/composition or the microbiome can propagate across this axis [7,8].

11.2 Effects of Bile Acids on the Microbiome

Bile acids can influence the microbiome through multiple mechanisms:
- Direct antimicrobial effects: bile acids can disrupt bacterial membranes, with particularly strong effects against many Gram-positive organisms.
- FXR-mediated effects: intestinal FXR activation can induce antimicrobial programs and contribute to mucosal defense.
- TGR5 signaling: bile acids can modulate immune responses and epithelial barrier function through membrane bile acid receptors.

11.3 Effects of the Microbiome on Bile Acids

Conversely, microbial enzymes diversify the bile acid pool and change the hydrophobicity and signaling potency of bile acids:
- Deconjugation: bacterial bile salt hydrolases (BSH) hydrolyze conjugated bile acids.
- 7α-dehydroxylation: anaerobes in the colon (e.g., some Clostridium and Eubacterium species) convert primary bile acids to secondary bile acids.
- Epimerization and oxidation: bacteria generate additional bile acid isomers and derivatives.

11.4 Dysbiosis in Bile Deficiency

Reduced bile delivery to the intestine may contribute to dysbiosis and downstream mucosal dysfunction. Reported patterns include:
- Small intestinal bacterial overgrowth (SIBO), facilitated by loss of bile's antimicrobial pressure.
- A pro-inflammatory shift with increased abundance of Gram-negative taxa (e.g., Proteobacteria).
- Reduced production of short-chain fatty acids (SCFAs) due to loss of fermentative commensals.
- Increased intestinal permeability ("leaky gut"), promoting endotoxemia and systemic inflammation.

These microbiome-linked mechanisms are now recognized as important modifiers of bile acid signaling and host metabolic phenotypes [7,8,11].

12. Homeostasis and Dysregulation

12.1 What Is Homeostasis?

Homeostasis refers to the ability of an organism to maintain relative constancy of its internal environment despite external perturbations. Canonical homeostatic systems regulate temperature, pH, electrolyte balance, blood glucose, and many other parameters through negative feedback loops that counteract deviation from set points [16,17].

12.2 Homeostasis of Bile Acids

Bile acid homeostasis is governed by tightly regulated feedback pathways. Key elements include:
- FXR (farnesoid X receptor): hepatic FXR activation by bile acids represses CYP7A1, the rate-limiting enzyme for bile acid synthesis.
- FGF19 signaling: intestinal FXR activation promotes FGF19 secretion, which provides additional negative feedback to the liver to suppress bile acid synthesis.
- TGR5 regulation: this membrane receptor participates in energy and immune homeostasis and modulates bile-acid-mediated signaling in several tissues.

12.3 Consequences of Dysregulation

Disruption of bile acid homeostasis can have broad systemic consequences:
- Metabolic syndrome: altered bile acid–FXR–FGF19 signaling has been linked to insulin resistance and dyslipidemia.
- Non-alcoholic fatty liver disease (NAFLD): dysregulated bile acid signaling can contribute to hepatic steatosis and inflammation.
- Systemic inflammation: impaired intestinal barrier function and endotoxemia can amplify inflammatory cascades.
- Cholestatic diseases: primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) involve progressive cholangiopathy and bile flow impairment.

These concepts motivate active drug development targeting bile acid receptors and transport pathways [10,11,15,18].

13. Post-Cholecystectomy Physiology

13.1 Physiological Adaptation

After cholecystectomy (surgical removal of the gallbladder), the biliary system undergoes adaptive changes:

- Continuous bile flow: bile enters the duodenum more continuously because the reservoir function is lost.
- Ductal dilation: the common bile duct may dilate modestly as a compensatory reservoir.
- Accelerated enterohepatic cycling: bile acids may circulate more frequently between liver and intestine.
- Loss of bile concentration: bile is no longer concentrated 5–10-fold between meals, as occurs in the gallbladder.

13.2 Post-Cholecystectomy Syndrome

Approximately 10–40% of patients report persistent or new symptoms after cholecystectomy. Common symptoms include:

- Bile acid diarrhea (BAD), often the most frequent manifestation.
- Dyspepsia and epigastric discomfort.
- Bloating and excessive gas.
- Reduced tolerance for fatty meals.

Proposed pathophysiological mechanisms include:

- Bile acid malabsorption: excess bile acids entering the colon stimulate water and electrolyte secretion, promoting diarrhea [4].
- Sphincter of Oddi dysfunction: spasm or stenosis may cause biliary-type pain.
- Bile reflux: retrograde bile flow into the stomach can cause bile gastritis.
- Altered intestinal motility: changes in transit time may contribute to symptoms.

13.3 Management Strategies

Management is guided by dominant symptoms and suspected mechanisms. Common strategies include:

- Bile acid sequestrants (e.g., cholestyramine, colesevelam) to bind excess bile acids in the colon.
- Diet modification: reduce saturated fat intake and consider smaller, more frequent meals.
- Ursodeoxycholic acid (UDCA): a hydrophilic bile acid that can partially replace more cytotoxic bile acids in selected contexts.
- Probiotics and microbiome-directed strategies (adjunctive), aiming to support intestinal ecosystem balance.

These approaches are consistent with broader clinical strategies for gallstone-related and bile-acid-mediated complications [4,14,20].

14. Nutrition and Practical Recommendations

14.1 General Principles

Dietary patterns influence bile composition, gallbladder motility, and intestinal microbiome ecology. Practical recommendations typically aim to maintain an optimal bile acid pool, prevent bile stasis, reduce lithogenicity, and support intestinal health [16,17].

14.2 Foods Commonly Recommended

Examples of dietary components that may support biliary and intestinal health include:

1) **Fiber-rich foods:**
- Whole grains (e.g., oats, barley, brown rice).
- Legumes (beans, lentils, chickpeas).
- Vegetables (e.g., broccoli, Brussels sprouts, spinach).
- Fruits (e.g., apples, pears, citrus).

2) **Healthy fats (in moderation):**
- Olive oil (rich in monounsaturated fatty acids).
- Fish oils (omega-3 fatty acids).
- Nuts and seeds (portion-controlled).
- Avocado.

3) **Foods with choleretic/cholagogue potential (context-dependent):**
- Artichoke (cynarin-containing preparations are traditionally associated with increased bile flow).
- Beets and beet greens.
- Radish and related cruciferous vegetables.
- Coriander and lemon juice as culinary adjuncts.

14.3 Foods to Limit

Common dietary elements that may worsen symptoms or increase lithogenic risk in susceptible individuals include:

- Saturated fats: fatty red meat, high-fat dairy, fried foods.
- Trans fats: margarine and many processed baked/cracker products.
- Refined carbohydrates: white bread, sweets, sugar-sweetened beverages.
- Alcohol: moderation or avoidance depending on clinical context.

14.4 Meal Timing and Pattern

Meal patterns can influence gallbladder emptying and bile stasis:

- Regular meals (3–5/day) may reduce bile stasis by promoting periodic gallbladder contraction.
- Smaller portions can reduce postprandial symptom burden in sensitive individuals.
- Adequate hydration (often ~1.5–2 L/day, adjusted for clinical context) supports overall digestive function.
- Avoiding prolonged fasting may reduce the risk of gallbladder stasis and stone formation.

15. Conclusions

Bile is a unique biological fluid central to digestion, lipid absorption, and metabolic regulation. The coordinated actions of hepatocytes and cholangiocytes determine bile flow, composition, and ductal protection, while enterohepatic circulation conserves the bile acid pool and enables systemic signaling through receptors such as FXR and TGR5. Neural and hormonal systems align bile delivery with feeding, and the gut microbiome both shapes and is shaped by bile acid chemistry. Disruption of these interconnected circuits contributes to a wide range of clinical problems, from cholestasis and gallstone disease to bile-acid-mediated diarrhea and vitamin malabsorption. A mechanistic understanding of bile physiology therefore supports rational diagnosis, prevention, and treatment of common hepatobiliary and gastrointestinal disorders [1,3,10,14,18,20].

References

[1] Boyer, J.L. Bile formation and secretion. Comprehensive Physiology 2013, 3(3), 1035–1078. https://doi.org/10.1002/cphy.c120027.
[2] Hofmann, A.F.; Hagey, L.R. Bile acids: chemistry, pathochemistry, biology, pathobiology, and therapeutics. Cellular and Molecular Life Sciences 2008, 65(16), 2461–2483. https://doi.org/10.1007/s00018-008-7568-6.
[3] Chiang, J.Y.L.; Ferrell, J.M. Bile acid metabolism in liver pathobiology. Gene Expression 2018, 18(2), 71–87. https://doi.org/10.3727/105221618X15156018385515.
[4] Keely, S.J.; Walters, J.R.F. The Farnesoid X receptor: good for BAD. Cellular and Molecular Gastroenterology and Hepatology 2016, 2(6), 725–732. https://doi.org/10.1016/j.jcmgh.2016.08.004.
[5] Tabibian, J.H.; Masyuk, A.I.; Masyuk, T.V.; O'Hara, S.P.; LaRusso, N.F. Physiology of cholangiocytes. Comprehensive Physiology 2013, 3(1), 541–565. https://doi.org/10.1002/cphy.c120019.
[6] Molinaro, A.; Wahlström, A.; Marschall, H.-U. Role of bile acids in metabolic control. Trends in Endocrinology & Metabolism 2018, 29(1), 31–41. https://doi.org/10.1016/j.tem.2017.11.002.
[7] Ridlon, J.M.; Kang, D.J.; Hylemon, P.B.; Bajaj, J.S. Bile acids and the gut microbiome. Current Opinion in Gastroenterology 2014, 30(3), 332–338. https://doi.org/10.1097/MOG.0000000000000057.
[8] Wahlström, A.; Sayin, S.I.; Marschall, H.-U.; Bäckhed, F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. Cell Metabolism 2016, 24(1), 41–50. https://doi.org/10.1016/j.cmet.2016.05.005.
[9] Trauner, M.; Meier, P.J.; Boyer, J.L. Molecular pathogenesis of cholestasis. The New England Journal of Medicine 1998, 339(17), 1217–1227. https://doi.org/10.1056/NEJM199810223391707.
[10] Schaap, F.G.; Trauner, M.; Jansen, P.L.M. Bile acid receptors as targets for drug development. Nature Reviews Gastroenterology & Hepatology 2014, 11(1), 55–67. https://doi.org/10.1038/nrgastro.2013.151.
[11] Vítek, L.; Haluzík, M. The role of bile acids in metabolic regulation. Journal of Endocrinology 2016, 228(3), R85–R96. https://doi.org/10.1530/JOE-15-0469.
[12] Reshetnyak, V.I. Physiological and molecular biochemical mechanisms of bile formation. World Journal of Gastroenterology 2013, 19(42), 7341–7360. https://doi.org/10.3748/wjg.v19.i42.7341.
[13] Shaffer, E.A. Gallbladder sludge: what is its clinical significance? Current Gastroenterology Reports 2001, 3(2), 166–173. https://doi.org/10.1007/s11894-001-0014-7.
[14] Housset, C.; Chrétien, Y.; Debray, D.; Chignard, N. Functions of the gallbladder. Comprehensive Physiology 2016, 6(3), 1549–1577. https://doi.org/10.1002/cphy.c150050.
[15] Arab, J.P.; Karpen, S.J.; Dawson, P.A.; Arrese, M.; Trauner, M. Bile acids and nonalcoholic fatty liver disease: molecular insights and therapeutic perspectives. Hepatology 2017, 65(1), 350–362. https://doi.org/10.1002/hep.28709.
[16] Guyton, A.C.; Hall, J.E. Secretory functions of the alimentary tract. In Guyton and Hall Textbook of Medical Physiology, 14th ed.; Elsevier: Philadelphia, PA, USA, 2020; pp. 823–835.
[17] Barrett, K.E.; Barman, S.M.; Brooks, H.L.; Yuan, J.X.-J. Hepatobiliary function. In Ganong's Review of Medical Physiology, 26th ed.; McGraw-Hill: New York, NY, USA, 2019; pp. 457–472.
[18] Banales, J.M.; Huebert, R.C.; Karlsen, T.; Strazzabosco, M.; LaRusso, N.F.; Gores, G.J. Cholangiocyte pathobiology. Nature Reviews Gastroenterology & Hepatology 2019, 16(5), 269–281. https://doi.org/10.1038/s41575-019-0125-y.
[19] Jungst, C.; Kullak-Ublick, G.A.; Jungst, D. Gallstone disease: microlithiasis and sludge. Best Practice & Research Clinical Gastroenterology 2006, 20(6), 1053–1062. https://doi.org/10.1016/j.bpg.2006.03.007.
[20] Portincasa, P.; Di Ciaula, A.; de Bari, O.; Garruti, G.; Palmieri, V.O.; Wang, D.Q.-H. Management of gallstones and its related complications. Expert Review of Gastroenterology & Hepatology 2016, 10(1), 93–112. https://doi.org/10.1586/17474124.2016.1109445.