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The Role of Intestinal Microflora in the Development of Cholelithiasis (Literature Review)

Abstract

Cholelithiasis is one of the most common diseases of the digestive system, which affects all segments of the population. Currently, cholelithiasis is considered as a long, multi-stage process in which the period of stone formation is preceded by changes in metabolism and physical and chemical properties of bile. However, among the many contributing factors, insufficient attention is paid to the role of the infectious factor in the development of cholelithiasis. The analysis of the literature data showed that today there are various mechanisms for promoting of development of cholelithiasis by enteric bacterial overgrowth. First, with bacterial overgrowth, duodeno-biliary reflux leads to infection of the biliary tract and the development of inflammation in the gallbladder. Substances that occur during the inflammatory process (proteins, mucus, exfoliated epithelium) are the matrix on which the gallstone is formed. Secondly, the role of dysbiosis in violation of enterohepatic circulation of bile acids is essential. The change in the ratio of conjugated and deconjugated bile acids contributes to the formation of lithogenic bile. Third, bacterial overgrowth leads to endotoxemia, which damages the metabolism of bile acids in the liver. Finally, the digestive and suction functions of the small intestine are in a certain dependence on the microbiota, but the participation of this channel in cholelithiasis requires further research.

Key words: *gallstone disease, enterohepatic circulation of bile acids, bacterial overgrowth, intestinal dysrhythmia, endotoxinemia*

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GSD — gallstone disease, BA — biliary acids, EH BAC — enterohepatic biliary acids circulation, BaO — bacterial overgrowth

Gallstone disease (GSD) is one of the most widespread diseases of the digestive organs, to which all segments of the population are exposed [1, 2]. The incidence of GSD in different countries (regions of the world) is 10-15%, while in Russia it ranges from 3 to 12% with a marked gender and age difference [3]. Nowadays, GSD is considered as a long, multistage process in which the period of stone formation is preceded by changes in metabolism and physical and chemical properties of bile. However,

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among many contributing factors, insufficient attention is paid to the role of the infectious agent in the development of cholelithiasis.

Data from studies of bacterial contamination of the biliary tract in GSD

Infection of the biliary tract most often occurs via intestines due to sphincter insufficiency on the one hand, and bacterial overgrowth in the small intestine on the other hand [4].

Excessive growth of opportunistic bacteria in the intestine, their dissemination in the body in presence of a decrease in barrier and other protective factors lead to the ingress of agents into the biliary tract and the development of the inflammatory process. Opportunistic Enterobacteriaceae colonize the bile ducts due to translocation from the large intestine in the setting of dysbiosis [5]. At the same time, bile-sensitive microorganisms die, and resistant ones acquire the ability to colonize the corresponding biotope with the development of an infectious and inflammatory process [6].

It has been established that in patients with various clinical forms of GSD, bile, gallbladder wall, and biliary concretions are predominantly infected by microflora that are characteristic of the intestine. Among the microorganisms isolated from the gall bladder of patients with cholecystitis and GSD, opportunistic Enterobacteriaceae, Escherichia coli, Streptococci, Staphylococci, Salmonella typhi, and protozoans (lamblia) rank high [7]. At the same time, there is a significant prevalence of aerobic flora over anaerobic flora. The antibacterial activity of bile and biliary acids against anaerobes (Bacteroides, Clostridium, Lactobacilli), as well as gram-positive cocci (Pneumococci, Staphylococci) is most pronounced. Gram-negative microorganisms are less susceptible to their action (Salmonella, Shigella, Escherichia coli) [6].

In patients with an increased risk of stone formation in the gall bladder and with GSD, studies of short-chain fatty acids in feces revealed a change in the qualitative composition of the microbiota, which is manifested by an increase in the activity of those genera of microorganisms that are involved in the 7-alpha dehydroxylation of biliary acids, namely aerobic microorganisms (in particular, Escherichia coli, etc.) and anaerobes (some strains of Bacteroides, Clostridia, Eubacteria).

V. A. Gritsenko at al. (2002) [8], after studying the problem of extra-intestinal escherichiosis, point out that in various variants of cholecystitis (phlegmonous, gangrenous, calculous), Escherichia coli is isolated from bile and the gall bladder in 30–60% of cases. Escherichia often provokes the development of purulent and inflammatory complications after cholecystectomy. The main mechanism of E. coli dissemination in the body and infection of the liver and gall bladder is translocation from the intestine to the lymphatic and blood circulatory system. There is evidence in the literature that a similar process of bacterial translocation is possible for other intestinal microorganisms — Enterobacteriaceae (Klebsiella, Serratia), Pseudomonas, Staphylococci, Enterococci, etc. [6].

Expressed resistance to bile of strains of E. coli isolated from cholecystitis is an adaptive reaction resulting from prolonged contact with bile. A relatively high level of resistance was shown by fecal E. coli strains obtained in cases of intestinal dysbiosis, which is due to the functioning of a "vicious circle", when bacteria from the intestine migrate to the portal veins, enter the liver, then into the bile ducts, interact with bile and re-enter the intestine [8].

The overwhelming majority of literature sources cite data suggesting that in cholecystitis, regardless of its nature, mainly Enterobacteriaceae represent bacteria in bile, among which E. coli accounts for 30–57%. In addition to Escherichia, other members of the Enterobacteriaceae family may represent bile culture: Klebsiella (1–10%), Proteus (7–8%), Enterobacter (9.2%) and others, up to 75% in total. Enterococci account for an average of 10 to 27%, Staphylococci — from 9.70 to 16.25%, and Streptococci — from 7.3 to 12.5%. Pseudomonas and yeast-like fungi are less common [9].

Data from literature sources [9, 10] indicate the prevalence of intestinal bacteria in bile of patients with hepatobiliary disease, although other results are available. For example, the study by K. I. Savitskaya et al. (2003) [11], where the data on isolation in 70% of cases of gram-positive cocci from the bile of patients with chronic pancreatitis are presented. According to the results of most bile cultures carried out in connection with GSD, Enterococci, which are representatives of the microbiota of the

human digestive tract, are ranked second after Enterobacteriaceae [9].

Among cultures of strict anaerobes obtained from bile, asporogenous species predominate (89%), and 11% of cases are represented by Clostridium [6]. Among anaerobic biliary cultures, representatives of the Bacteroidaceae family are most often identified, and 25% of cases are represented by Bacteroides fragilis (B. Fragilis). The proportion of anaerobic cocci (Peptococci, Peptostreptococci and anaerobic Streptococci) can be also significant in this disease and accounts for 21.4% of all anaerobic strains.

Bile can be one of the factors that regulate microbial composition in the gall bladder, ducts, and intestine, and thus form a certain microecology of the digestive tract [3]. A. V. Valyshev et al. (1996) [5] revealed the uniformity of pathogens isolated from feces and bile in 74% of cases, and the presence of persistence factors (anti-lysozyme, anti-interferon and anti-complementary activity) in isolated bacterial strains in cases of intestinal dysbiosis and biliary duct disorders. This confirms the leading role of intestinal microbiota in the occurrence of inflammatory processes in the hepatobiliary system and, as a result, the formation of lithogenic bile [12].

Microbiota in the impairment of enterohepatic circulation of biliary acids

The main component of bile is primary biliary acids (BA) (cholic and chenodeoxycholic) that are synthesized in hepatocytes from cholesterol with participation of cholesterol-7α-hydroxylase. Upon entering the ileum, about 85–90% of primary BA are deconjugated with participation of the intestinal microbiota, absorbed and transported through the portal vein to hepatocytes, where they are conjugated again and included into the bile [1, 13]. It was found that this process involves Bacteroides and Lactobacilli [14]. Approximately 5–10% of non-absorbed primary BA enters the large intestine, where under the action of 7α-dehydroxylase of gram-positive anaerobic bacteria (Eubacteria and Clostridia), secondary hydrophobic BA (deoxycholic and lithocholic) are formed, which are absorbed, enter the liver, and again undergo conjugation in hepatocytes. In patients with GSD, intestinal transit time is increased, which enhances formation of deoxycholic acid as a result of bacterial metabolism. Increased concentration of secondary BA in the gall bladder induces a lithogenic effect.

Disturbance of enterohepatic circulation of biliary acids (EH BAC) is believed to be of great importance for the development of cholelithiasis [15, 16]. A disorder of EH BAC, which is manifested by changes in the metabolism of cholic acid, cholesterol and phospholipids has been observed in patients with GSD and chronic stone-free cholecystitis. This is due to increased activity of anaerobic microorganisms involved in 7-alpha-dehydroxylation of BA [17]. More bacteria and increased 7-dehydroxylase activity in intestinal aspirate from the iliac combined with higher pH in the large intestine and longer transit time in the small and large intestine are detected in patients with GSD. A longer period of intestinal transit, which promotes an increase in the time of bacterial conjugation even with a constant quantitative and qualitative composition of microbiota, is identified among the known reasons for abnormal absorption of BA [18–20]. Great importance of EH BAC disorders relates to the acceleration of the intestinal passage, resulting in increased BA excretion with feces and reduction of their absorption [21].

At the same time, there is evidence that a decrease in the BA level reduces the antibacterial properties of the bile [22]. This contributes to the activation of opportunistic microorganisms and bacterial overgrowth (BaO) in the intestine. However, the incidence and peculiarities of the occurrence of BaO, as well as an intestinal dysbiosis in case of GSD remain insufficiently studied. To date, evidence has been accumulated, showing that intestinal microbiota is capable of performing biotransformation of BA, cholesterol and steroid hormones into various metabolites in the process of EH BAC [23].

Chronic biliary insufficiency has special influence on the course of the GSD, which results in bacterial overgrowth and premature deconjugation of BA that damage the mucosa of the small and even large intestine. Inflammatory process in the mucosa of small intestine results in EH BAC disorders accompanied by worsening of biliary insufficiency. In physiological conditions, the sterility of bile is ensured by the antibacterial effect of BA. With chronic biliary insufficiency, especially when combined with reduced concentration and evacuation

function of the gallbladder and sphincter of Oddi dysfunction, conditions for the reduction of antibacterial properties of bile are created. At the stage of biliary sludge formation, biliary insufficiency is detected in 91.7% of cases (of which 54.5% are mild and 45.5% — moderate) [19].

Reduced antibacterial properties of bile inevitably create favorable conditions for the development of BaO in the small intestine. More pronounced changes in small intestine microbiota occur in case of cholecystolithiasis. Due to a decrease of the protective function of the gallbladder in the intestine of a patient with GSD, which function is realized in the bactericidal action of the bile, bacterial overgrowth develop, while a number of representatives of obligate intestinal flora is reduced and replacement of this flora by opportunistic bacteria occurs. In the duodenum mucosa sample, the signs of activation of opportunistic microflora with the secretion of up to 28 different genera of microorganisms are found in patients with GSD. In such a case, hemolytic Staphylococci (53%), bacteria of the Enterobacteriaceae family (69%), fungi of the genus Candida (49%), and Bacteroides (47%) in the amount of 3.3–5.2 log CFU/g in combination of 2–7 cultures dominate [19].

As it was demonstrated by Vakhrushev Ya. M. et al. (2017) [24], the biochemical study of bile revealed a significant decrease in the concentration of BA in cystic and hepatic bile of patients with GSD in comparison with the control. There was also a tendency of an increase in the concentration of cholesterol and a significant decrease in the cholate-cholesterol rate in both cystic and hepatic portions of bile from patients with GSD. When studying individual fractions of BA in patients with GSD, there was a decrease in free (cholic, henodeoxycholic, deoxycholic) and an increase in conjugated (glycocholic, glycodeoxycholic, tauroholic, taurodeoxycholic, ursodeoxycholic) BA in the "B" and "C" portions of bile in comparison with the control. Disruption of the balance of free and conjugated BA leads to the development of colloidal instability of bile, which is a prerequisite for the development of cholelithiasis. In the same authors' study of the total content of BA in blood based on the results of mass spectrometry assay, its decrease in patients with GSD in comparison with the control was noted. Omnidirectional BA spectrum disorders were also noted. Thus, levels of chenodeoxycholic and deoxycholic acids were decreased, while those of ursodeoxycholic, glycocholic, glycodeoxycholic, tauronic and taurodeoxycholic acids were increased.

The synthesis of BA from cholesterol occurs in the hepatocyte and includes 17 different enzymes that are located in the cytosol, endoplasmic reticulum, mitochondria, and peroxisomes [25]. It is necessary to take into account that the synthesis of BA is influenced not only by the state of the liver and the BA itself, which can contribute to an increase or decrease in their content according to the principle of negative feedback, but also by cholesterol, thyroid hormones, glucocorticoids, insulin, and circadian rhythms [13, 25, 26]. The small intestine actively participates in maintaining the homeostasis of BA by synthesizing of the fibroblast growth factor-15 by enterocytes, which regulates a number of enzymes responsible for the synthesis of BA [13]. Changes in the composition of BA in the blood may be associated with increased absorption of BA in the proximal part of the small intestine. In patients with pre-stone stage of GSD, BaO leads to disorders in the normal absorption of BA in the distal ileum. This is characterized by premature deconjugation and absorption of BA [27, 28]. With underlying BaO, there is a decrease in free and an increase in conjugated BA in bile. In addition, BaO can serve as an initial link in the mechanism of bacterial translocation [29]. There are microorganisms that are more prone to translocation due to their better ability to adhere to the intestinal epithelium (Escherichia coli, Klebsiella, Enterococci). These bacteria are able of penetrating even through the histologically normal mucous membrane of the wall of intestine, then getting into the hepatobiliary system. It can be assumed that the detected BaO in most patients with pre-stone stage of GSD can be a cause of bile contamination, while bacterial colonization of extrahepatic bile ducts contributes to bile stone formation [30].

The process of deconjugation of BA in the distal part of the iliac and proximal part of the colon involves Lactobacillus and Bacteroid enzymes [31]. Intestinal dysbiosis is detected in fecal culture of 100% of patients with GSD, while in the majority of patients (91%) various versions of combined disorders in the colon microbiota were noted. A decrease in the number of Lactobacilli to less than 10^7 CFU/g in 40.9% of patients with pre-stone stage of GSD was

noted to a greater extent. There was also an increase in the proportion of lactose negative and hemolytic Escherichia coli (up to 28.6% and 18.2%, respectively) against the background of a decrease in full-functional Escherichia coli (in 31.8% of patients). Consequently, with underlying BaO and colonic dysbiosis, significant changes occur in the deconjugation of BA, which leads to a disorder in the ratio of conjugated and deconjugated BA in bile and blood. Disorder in the EH BAC leads to a decrease in the content of BA in the intestine. Malabsorption syndrome develops, the composition of the intestinal microbiota is disrupted, ethanol and organic acids are formed in excess, the pH of chyme decreases and the deconjugation of BA increases. The consequence is the progression of BaO, the formation of an increased number of endotoxins, their entry into the liver, and the development of systemic inflammation [32]. In this way, dysbiosis leads to a disruption of EH BAC, while a decrease in the intake of BA in the intestine exacerbates the dysbiosis.

Thus, the small intestine is an important link in the disruption of EH BAC. The increase in the absorption of prematurely deconjugated BA in the proximal part of the small intestine accelerates the time of return of BA to the liver, which reduces their synthesis in hepatocytes and excretion into bile. As a result of BaO in the distal ileum and colonic dysbiosis, significant changes in the deconjugation of BA occur, which leads to an impaired ratio of BA fractions in the blood and bile.

Influence of microbiota on the development of intestinal rhythm decrease

According to literature data, intestinal rhythm decrease is present in 90% of patients with GSD [31]. Frequently revealed cholecystolithiasis in intestinal disorder even allowed some authors to consider GSD as an "intestinal" disease. Studies have shown that patients with gastrointestinal disorders have impaired bowel emptying in the form of intestinal rhythm decrease, in contrast to the regular intestinal rhythm corresponding to 7 days a week with daily stools. Intestinal rhythm decrease occurs 2 times more often than obesity [27]. Intestinal rhythm decrease occurs in the setting of impaired colon microbiota in the form of the reduction of the content of the anaerobic component (Bifidobacteria, Lactobacilli), Escherichia coli with normal enzymatic properties, Enterococci, and an increase in the content of opportunistic microorganisms (Klebsiella, Enterobacter) [30].

In studies with the use of hydrogen breath tests with lactulose, most patients with GSD were found to have colon dysbiosis [24]. Dysbiosis contributes to the disruption of intestinal functions. With a decrease in the quantity of Bifidobacteria and Lactobicilli, a decrease in their enzymatic activity is noted, which leads to the disturbance of processes of utilization of biologically active compounds by the human organism, activation of putrefactive and fermentation processes. The increase in the number of representatives of opportunistic flora causes disruption of nutrient absorption processes, promotes competitive interaction with representatives of normal microbiota for participation in the processes of fermentation and assimilation of food nutrients. When the severity of dysbiosis increases, motor activity of the colon and the function of the ileocecal valve are more seriously damaged [10].

Changes in the composition and decrease in the amount of bile in the intestinal lumen in the setting of gall bladder dysfunction are accompanied by a decrease in the bactericidal activity of the duodenal content with excessive reproduction of bacteria in the duodenum and jejunum, followed by premature deconjugation of BA and formation of duodenal hypertension [33].

The disorder of intestinal microbiota is a cause of endotoxinemia, which contributes to a toxic effect on the liver [30, 34] and intestinal function, which is manifested by a disorder of BA synthesis and dystrophic changes in mucosa, leading to the disorder of the motor function and disruption of the hydrolysis-resorption process [35].

An important pathogenetic component in BaO is the premature deconjugation of primary BA, which is carried out by the small intestine microbiota, which determines its clinical signs. According to L. Bala et al. (2006), in patients with BaO, the average level of deconjugated BA was significantly higher compared to those who did not have it: 500 μmol/L (within the range of 40–600) and 10 μmol/L (within the range of 0–300), respectively [36]. Deconjugated BA have detergent properties and can damage the epithelium of the small intestine mucosa. Clinical

signs of these disorders are creatorrhea, amylorrhea, and steatorrhea [36]. In addition, deconjugated BA together with bacterial toxins disrupt water-salt metabolism. BA induce the disruption of sodium absorption [23], an increase secretion of chlorides and water into the intestinal lumen, accelerate peristalsis of the small intestine, which aggravates diarrhea in the setting of intestinal rhythm increase.

Conclusion

Based on the performed analysis of the literature data, various mechanisms for promoting the development of cholelithiasis by BaO are known today. First, in BaO the duodenal biliary reflux leads to infection of the biliary tract and the inflammation in the gall bladder. Substances that occur during the inflammatory process (proteins, mucus, sloughed epithelium) are the matrix on which the gallstone is formed. Secondly, dysbiosis plays an essential role of the disruption of EH BAC. Changes in the ratio of conjugated and deconjugated BA contribute to the formation of lithogenic bile. Third, BaO leads to endotoxinemia, which has a damaging effect on the metabolism of BA in the liver. Finally, the digestive and absorption functions of the small intestine depend on the microbiota, but the involvement of this component in cholelithiasis requires further investigation.

Contribution of Authors

N. A. Khokhlacheva: development of the concept and design of the article, responsible for all aspects of the work.
A. P. Lukashevich: data collection, analysis and interpretation, justification and writing of the manuscript.
N. N. Glazyrina: data collection, analysis and interpretation, justification and writing of the manuscript.
Ya. M. Vakhrushev: verification of critical intellectual content, final approval of the manuscript for publication.
T. S. Kosareva: data collection, analysis and interpretation.

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