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РОЛЬ МИКРОФЛОРЫ КИШЕЧНИКА В РАЗВИТИИ ЖЕЛЧНОКАМЕННОЙ БОЛЕЗНИ (ОБЗОР ЛИТЕРАТУРЫ)

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АННОТАЦИЯ

Желчнокаменная болезнь — одно из самых распространенных заболеваний органов пищеварения, поражающее все слои населения. В настоящее время желчнокаменная болезнь рассматривается как длительный, многоэтапный процесс, в котором периоду камнеобразования предшествуют изменения метаболизма и физико-химических свойств желчи. Однако среди множества способствующих факторов недостаточно внимания уделяется роли инфекционного фактора в развитии желчнокаменной болезни. Анализ данных литературы показал, что на сегодняшний день существуют различные механизмы, способствующие развитию желчнокаменной болезни избыточным энтеральным бактериальным ростом. Во-первых, при избыточном бактериальном росте дуодено-билиарный рефлюкс приводит к инфицированию желчных путей и развитию воспаления в желчном пузыре. Вещества, возникающие при воспалительном процессе (белки, слизь, слущенный эпителий), являются матрицей, на которой формируется желчный камень. Во-вторых, существенна роль дисбактериоза в нарушении энтерогепатической циркуляции желчных кислот. Изменение соотношения конъюгированных и деконъюгированных желчных кислот способствует образованию литогенной желчи. В-третьих, избыточный бактериальный рост приводит к эндотоксемии, которая оказывает повреждающее действие на метаболизм желчных кислот в печени. Наконец, пищеварительная и всасывательная функции тонкого кишечника находятся в определенной зависимости от микробиоты, но участие этого канала в желчнокаменной болезни требует дальнейшего изучения.

Ключевые слова: желчнокаменная болезнь, энтерогепатическая циркуляция желчных кислот, эндотоксинемия, избыточный бактериальный рост, кишечная аритмия.

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THE ROLE OF INTESTINAL MICROFLORA IN THE DEVELOPMENT OF GALLSTONE DISEASE
(LITERATURE REVIEW)

ANNOTATION

Cholelithiasis is one of the most common diseases of the digestive system, which affects all segments of the population. Currently, cholelithiasis is seen 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 development of cholelithiasis by excess enteral bacterial growth. First, with excessive bacterial growth, duodena-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. Thirdly, excessive bacterial growth leads to endotoxemia, which has a damaging effect on 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: cholelithiasis, enterohepatic circulation of bile acids, endotoxemia, excessive bacterial growth, gallstone disease, intestinal arrhythmia.

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O'T-TOSH KASALLIGI RIVOJLANISHIDA ICHAK MIKROFLORASINING O'RNI (ADABIYOTLAR SHARHI)

ANNOTATSIYA

Xolelitiaz ovqat hazm qilish tizimining eng keng tarqalgan kasalliklaridan biri bo'lib, aholining barcha qatlamlariga ta'sir ko'rsatadi. Hozirgi kunda xolelitiaz uzoq davom etadigan, ko'p bosqichli jarayon sifatida qaralmoqda. Bunda tosh hosil bo'lishidan oldin moddalar almashinuvi va o't suyuqligining fizik-kimyoviy xossalari o'zgaradi. Biroq, xolelitiaz rivojlanishiga olib keluvchi ko'plab omillar orasida infeksiyon omilining roliga yetarlicha e'tibor qaratilmagan. Adabiyotlar tahlili shuni ko'rsatdiki, bugungi kunda ichakdagi bakteriyalarning ortiqcha o'sishi orqali xolelitiaz rivojlanishiga yordam beradigan turli mexanizmlar mavjud. Birinchidan, bakteriyalarning haddan tashqari ko'payishi bilan o'n ikki barmoqli ichak-o't yo'llari refluksi o't yo'llarining infeksiyalanishiga va o't pufagida yallig'lanish rivojlanishiga olib keladi. Yallig'lanish jarayonida paydo bo'ladigan moddalar (oqsillar, shilimshiq, ko'chib tushgan epiteliy) o't toshi hosil bo'ladigan matritsa vazifasini bajaradi. Ikkinchidan, o't kislotalari enterogepatik aylanishining buzilishida disbakteriozning roli muhimdir. Konyugatsiyalangan va dekonyugatsiyalangan o't kislotalari nisbatining o'zgarishi litogen o't hosil bo'lishiga yordam beradi. Uchinchidan, bakteriyalarning haddan tashqari ko'payib ketishi jigardagi o't kislotalari almashinuviga zararli ta'sir ko'rsatadigan endotoksemiyaga olib keladi. Nihoyat, ingichka ichakning hazm qilish va so'rish funksiyalari mikrobiotaga ma'lum darajada bog'liq, ammo bu omilning xolelitiazda ishtiroki qo'shimcha tadqiqotlarni talab etadi.

Kalit so'zlar: xolelitiaz, o't kislotalarining enterogepatik aylanishi, endotoksemiya, bakteriyalarning ortiqcha o'sishi, o't-tosh kasalligi, ichak diskineziyasi.

Cholelithiasis is a widespread disease of the digestive organs affecting all segments of the population [6, 18]. The frequency of cholelithiasis occurrence in different countries is 10-15%, in Russia it varies within 3-12%, with notable differences in gender and age [19]. Cholelithiasis is a long, multi-stage process characterized by a violation of the physicochemical properties of bile initially, and only later leads to the formation of stones in the gallbladder and/or bile ducts. However, among the many factors contributing to the development of cholelithiasis, insufficient attention is paid to the role of the infectious component.

Data from biliary microflora contamination studies in patients with cholelithiasis

Biliary tract infection most often occurs due to insufficiency of the sphincter structures of the bile ducts, on the one hand, and

excessive bacterial growth in the small intestine, on the other [14].

Excessive bacterial growth in the small intestine during barrier function disruption promotes bacterial translocation in the body, which ensures the penetration of microorganisms into the biliary system and the development of inflammation in it [15]. Conditionally pathogenic flora can penetrate the bile ducts retrograde from the large intestine if there is dysbiosis [3, 19]. In this case, microorganisms sensitive to bile die, while resistant microorganisms acquire the ability to colonize the corresponding biotope with the development of an infectious-inflammatory process [14].

It has been established that bile, gallbladder wall, and gallstones in patients with various clinical forms of cholelithiasis are primarily infected with intestinal microflora. Among the

microorganisms secreted from the gallbladder of patients with cholecystitis and cholelithiasis, the leading place is occupied by opportunistic enterobacteria, *E. coli*, streptococci, staphylococci, klebsiella, and protozoa (lamblia) [13]. At the same time, a significant predominance of aerobic flora over anaerobic is observed. The most pronounced antibacterial activity of bile and bile acids belongs to anaerobes (bacteroids, clostridia, lactobacilli), as well as gram-positive cocci (pneumococci, staphylococci). Gram-negative microorganisms are less susceptible to their effects (salmonella, shigella, *E. coli*) [14].

The results of studying feces for the content of short-chain fatty acids in patients with cholelithiasis risk factors, as well as in patients with cholelithiasis, showed the presence of dysbiosis characterized by an increase in the concentration of microorganisms that carry out 7- α -dehydroxylation of bile acids, especially *E. coli* and clostridia, eubacteria, bacteroids [2].

V.A. Gritsenko [13], studying the problem of extraintestinal escherichiosis, indicates that in various types of cholecystitis (phlegmonous, gangrenous, calculous), *E. coli* is isolated from bile and gallbladder in 30-60% of cases. It is *Escherichia* that often provoke the development of purulent-inflammatory complications after cholecystectomy. *E. coli* spreads throughout the body and enters the biliary system mainly through translocation into the intestinal lymphatic and circulatory systems. Literature data suggest that a similar bacterial translocation process is possible for other intestinal microorganisms: enterobacteria (*Klebsiella*, *Serratia*), pseudomonads, enterococci, etc. [14].

The pronounced resistance to bile in *E. coli* strains isolated in cholecystitis is an adaptive reaction that develops as a result of prolonged contact with bile. Strains of *E. coli* obtained in intestinal dysbiosis showed a relatively high level of stability due to the functioning of a "vicious circle," when bacteria migrate from the intestines to the portal vein, enter the liver, then the bile ducts, interact with bile, and return with it to the intestines [13].

Most literature sources indicate that in cholecystitis, regardless of the nature of the lesion, bacteriocholia is mainly caused by enterobacteria, among which *E. coli* accounts for 30-57%. In addition to *Escherichia*, biliary cultures can be represented by other members of the Enterobacteriaceae family: *Klebsiella* (1-10%), *Proteus* (7-8%), *Enterobacter* (9.2%), and others, in quantities up to 75%. Enterococci constitute on average from 10 to 27%, staphylococci - from 9.7 to 16.25%, streptococci - from 7.3 to 12.5%. Pseudomonads and yeast-like fungi are less common [18].

Most literature sources [15, 18] indicate the predominance of intestinal group bacteria in bile of patients with hepatobiliary pathology, although there are other results. For example, in the work of K.I. Savitskaya et al. (2003) [17], data are presented on the isolation of gram-positive coccal flora in 70% of patients with chronic pancreatitis.

According to bacteriological analyses of bile conducted for cholelithiasis, microbes of the genus *Enterococcus* [21] are found in second place, which are representatives of normal digestive tract microflora.

Among cultures of strict anaerobes obtained from bile, non-spore-forming species predominated (89%), and in 11% of cases - clostridia [15]. Among anaerobic biliary cultures, representatives of the Bacteroidaceae family predominate, with *B. fragilis* present in 25% of cases. The proportion of anaerobic cocci (peptococci, peptostreptococci, and anaerobic streptococci) can also be significant in this pathology and constitutes 21.4% of all anaerobic strains.

Bile can be one of the factors regulating the microbial composition in the gallbladder, bile ducts, intestines, and thus forming a specific microecology of the digestive tract [19]. A.V. Valyshev et al. [3] identified the identity of pathogens isolated from feces and bile in 74% of cases and the presence of persistence factors (anti-lysozyme, anti-interferon, anti-complementary activity) in isolated bacterial strains in intestinal dysbiosis and bile duct diseases. This confirms the leading role of intestinal microbiocenosis in the occurrence of inflammatory processes in the hepatobiliary system and, consequently, in the formation of lithogenic bile [14].

Microflora involvement in enterohepatic disorders circulation of bile acids

The main components of bile are formed in liver cells from cholesterol with the participation of the cholesterol-7 α -hydroxylase enzyme. These include cholic and chenodeoxycholic bile acids. The next stage is their conjugation with amino acids and subsequent excretion through the bile ducts into the small intestine, where the majority (85-90%) is deconjugated by intestinal microflora. Then, bile acids are absorbed in the terminal part of the ileum and enter the liver via the portal vein system, where their repeated conjugation and incorporation into bile occur [6, 21]. It has been established that bacteroides and lactobacilli participate in this process [4]. Approximately 5-10% of the unabsorbed primary bile acids enter the large intestine, where under the influence of bacterial 7 α -dehydroxylase of gram-positive anaerobic bacteria (eubacteria and clostridia), secondary hydrophobic bile acids (deoxycholic and lithocholic) are formed, which are absorbed and re-conjugated in hepatocytes. In patients with cholelithiasis, the intestinal transit time increases, which enhances the formation of deoxycholic acid as a result of bacterial metabolism. Increased concentration of secondary bile acids in the gallbladder has a lithogenic effect.

In the pathogenesis of cholelithiasis, disruptions in the enterohepatic circulation of bile acids play a significant role [20, 21]. Literature reports indicate impaired metabolism of primary bile acids and cholesterol in patients with various gallbladder diseases. These changes are attributed to an increase in microorganisms involved in bile acid metabolism [16]. Patients with cholelithiasis exhibited increased activity of pathogenic bacteria in ileal aspirates, combined with elevated pH in the large intestine and slowed transit through both small and large intestines. Among the known causes of bile acid absorption disorders, prolonged intestinal transit is particularly important, as it leads to increased bacterial conjugation time even with a constant quantitative and qualitative composition of the microbiota [16, 22]. Shortened intestinal transit also plays a crucial role in disrupting the enterohepatic circulation of bile acids, contributing to accelerated fecal excretion of bile acids and decreased absorption [4, 14].

Conversely, evidence suggests that low concentrations of bile acids result in insufficient antibacterial properties of bile [17]. This promotes the activation of opportunistic flora and the development of small intestinal bacterial overgrowth syndrome. However, the frequency and characteristics of bacterial overgrowth and intestinal dysbiosis in cholelithiasis remain understudied. Current data indicates that intestinal microflora can biotransform bile acids, cholesterol, and steroid hormones into various metabolites during enterohepatic circulation [20].

Chronic biliary insufficiency significantly impacts the course of cholelithiasis, leading to bacterial overgrowth and premature deconjugation of bile acids, which damage the mucosa of both

small and large intestines. The inflammatory process in the small intestinal mucosa disrupts the enterohepatic circulation of bile acids, further exacerbating biliary insufficiency. Under normal physiological conditions, bile sterility is maintained by the antibacterial action of bile acids [22]. In chronic biliary insufficiency, especially when combined with decreased concentrating and evacuating functions of the gallbladder and Oddi sphincter dysfunction, conditions arise that reduce the antibacterial properties of bile. During biliary sludge formation, biliary insufficiency is detected in 91.7% of cases (54.5% mild and 45.5% moderate) [22].

The reduction in bile's antibacterial properties inevitably creates a favorable environment for bacterial overgrowth. Cholelithiasis patients exhibit more pronounced disturbances in small intestinal microflora. Due to decreased protective properties of the gallbladder, manifested in the reduced bactericidal effect of bile, patients with cholelithiasis experience excessive bacterial growth in the intestines. The normal intestinal microflora decreases and is replaced by opportunistic bacteria. Duodenal mucosal biopsies from cholelithiasis patients show signs of opportunistic microflora activation, with up to 28 different genera of microorganisms identified. Hemolytic staphylococci (53%), Enterobacteriaceae family bacteria (69%), *Candida* fungi (49%), and bacteroids (47%) predominate, present in quantities of 3.3-5.2 log CFU/g in combinations of 2-7 groups [22].

As shown by the research of Ya.M. Vakhrushev et al. [7], when studying the biochemical properties of bile, a significant decrease in the concentration of bile acids in the "B" and "C" portions of bile in patients with cholelithiasis was revealed compared to the control. Also, in cholelithiasis, a tendency towards an increase in cholesterol concentration and a significant decrease in the cholesterol coefficient in both the "B" and "C" portions of bile were revealed. When studying individual fractions of bile acids, a decrease in free (cholic, chenodeoxycholic, deoxycholic) and an increase in conjugated (glycocholic, glycodeoxycholic, taurocholic, taurodeoxycholic, ursodeoxycholic) bile acids in the "B" and "C" portions of bile compared to the control is observed. Disruption of the balance between bile acids leads to the development of colloidal instability of bile, which is a prerequisite for the development of cholelithiasis. The same authors studied the total amount of bile acids in the blood of patients with cholelithiasis using mass spectrometry, showing a decrease compared to the control. At the same time, multidirectional disorders of the bile acid pool were noted - a decrease in chenodeoxycholic and deoxycholic acids, as well as an increase in ursodeoxycholic, glycocholic, glycodeoxycholic, taurocholic, and taurodeoxycholic acids.

The formation of bile acids in hepatocytes is a complex, multi-stage process involving 17 different enzymes in various structures of liver cells [12]. When analyzing bile acid content, it's important to remember that many factors, including the bile acids themselves, the condition of the liver and endocrine system, cholesterol concentration, and circadian rhythms, influence their synthesis and excretion [8, 12, 21]. In the metabolism of bile acids, an important role belongs to the small intestine, since fibroblast growth factor 15 is synthesized in enterocytes, which regulates a number of enzymes involved in the synthesis of bile acids [21].

Changes in the bile acid content in the blood can be related to increased bile acid absorption in the proximal part of the small intestine. In patients with biliary sludge, excessive bacterial growth leads to a disruption of normal bile acid absorption in the

distal part of the ileum. In this case, premature deconjugation and absorption of bile acids are characteristic [13, 18]. In excessive bacterial growth, a decrease in free bile acids and an increase in conjugated bile acids in bile are observed. Additionally, excessive bacterial growth can serve as the initial link in the bacterial translocation mechanism [16]. There are microorganisms that are more prone to translocation due to their better ability to adhere to intestinal epithelium (*E. coli*, *Klebsiella*, *Enterococci*). This bacterial flora is capable of penetrating even the histologically normal mucous membrane of the intestinal wall and then entering the hepatobiliary system. It can be assumed that the excessive bacterial growth found in most patients with biliary sludge can be a source of bacteriocholia, and bacterial colonization of extrahepatic bile ducts contributes to the formation of gallstones [17].

In the process of bile acid deconjugation in the distal and proximal parts of the colon, the enzymes of lactobacilli and bacteroids participate [22]. Practically in all patients with cholelithiasis, dysbiotic disorders are detected during fecal culture, which in 91% of cases are characterized by the combination of several forms of dysbiosis. In patients with biliary sludge, a decrease in the number of lactobacilli less than 107 CFU/g is observed in 40.9% of cases. An increase in the proportion of lactose-negative and hemolytic *E. coli* (28.6% and 18.2%, respectively) was revealed. Consequently, with excessive bacterial growth and colon dysbiosis, significant changes occur in the deconjugation of bile acids, consisting in a disruption of the ratio of conjugated and deconjugated bile acids in bile and blood. Disruption of enterohepatic circulation contributes to a decrease in bile acid content in the intestines. Malabsorption syndrome develops, the composition of intestinal microflora is disrupted, excess ethanol and organic acids are formed, the pH of the chyme decreases, and the deconjugation of bile acids increases. The consequence is the progression of excessive bacterial growth, the formation of an increased amount of endotoxins, their entry into the liver, and the development of systemic inflammation [22, 5]. Dysbiosis disrupts the enterohepatic circulation of bile acids, and a decrease in the amount of bile acids in the intestines exacerbates dysbiosis.

Thus, the small intestine is an important element in the disruption of enterohepatic circulation of bile acids. Increased absorption of prematurely decomposed bile acids in the proximal part of the small intestine increases the rate of bile acid return to the liver, which leads to a decrease in their synthesis in hepatocytes and excretion with bile. Due to excessive bacterial growth in the distal part of the ileum and dysbiosis, significant changes occur in the deconjugation of bile acids, which leads to a disruption in the ratio of bile acid fractions in the blood and bile.

Influence of microflora on the development of intestinal arrhythmias. According to literature data, intestinal brady arrhythmia is present in 90% of patients with gallstone disease [11, 15]. The frequent combination of cholelithiasis with intestinal pathology has even allowed some authors to consider gallstone disease as a "intestinal" pathology. Thanks to research, it is known that patients with gallstone disease have a regular intestinal rhythm characterized by daily stool 7 times a week, and intestinal brady arrhythmia occurs. This intestinal rhythm disorder in patients with gallstone disease occurs more frequently compared to obesity [19]. Bradiarrhythmia occurs against the background of intestinal dysbiosis, manifested by a decrease in the number of lactobacilli, bifidobacteria, enterococci, a full-fledged *E. coli*, with an increase in the

concentration of opportunistic flora, including klebsiella, enterobacteria, and others [9, 19].

According to modern literature, in most patients with gallstone disease, colon dysbiosis was detected through hydrogen respiratory tests with lactulose [22]. Dysbiosis contributes to the disruption of intestinal functions. With a decrease in the content of lactobacilli and bifidobacteria, a decrease in their enzymatic activity is noted, which contributes to a decrease in the utilization of biologically active substances by the human body and further activation of fermentation and putrefaction processes in the intestines. The increase in the number of representatives of the conditionally pathogenic flora causes impaired absorption of nutrients, leading to competitive interaction with normal microflora for participation in the processes of nutrient assimilation from food [10]. According to research results by Ya.M. Vakhrushev and N.V. Bakanova, the more pronounced the manifestations of dysbiosis, the more severely the motor function of the colon and ileocecal valve is impaired [9].

There is evidence that dysfunctional reactions of the gallbladder are characterized by impaired bile flow to the intestines and changes in bile composition, leading to a decrease in the bactericidal properties of the duodenal contents and the occurrence of excessive bacterial growth, which, in turn, contributes to the disruption of enterohepatic circulation of bile acids and an increase in pressure in the intestinal lumen [1].

The presence of excessive bacterial growth in the small intestine and colon dysbiosis leads to endotoxemia, which is the cause of liver and intestinal cell damage with impaired function [17, 20]. This manifests as a disruption of bile acid synthesis and the development of mucosal dystrophy, which contributes to changes in motor function and the processes of digestion and absorption [18].

The clinical manifestations of excessive bacterial growth are caused by premature deconjugation of bile acids. The results of studies by L. Bala et al. show that with excessive bacterial growth in patients, a significant increase in the concentration of decomposed bile acids is noted compared to patients without excessive bacterial growth, respectively, 500 and 10 $\mu\text{mol/l}$ [21]. An increase in the content of decomposed bile acids leads to damage to the epithelial layer of the small intestinal mucosa due to its detergent properties. As a result, patients develop steatorrhea, creatorrhea, and amyloorrhea [12]. There is also evidence that decomposed bile acids are capable of disrupting water-salt balance: they inhibit sodium absorption, increase the secretion of water and chlorides, activate small intestinal peristalsis, which intensifies diarrheal syndrome against the background of intestinal tachyarrhythmia [20].

Conclusion

Based on the analysis of literature data, we note that to date, various mechanisms of the influence of excessive bacterial growth on the development of gallstone disease are known. Firstly, with excessive bacterial growth, duodenal-biliary reflux leads to infection of the bile ducts and the development of an inflammatory process in the gallbladder. Substances formed during the inflammatory process (proteins, mucus, desquamated epithelium) are a matrix on which gallstones are formed. Secondly, the role of dysbiosis in violation of the enterohepatic circulation bile acids is significant. A change in the ratio of conjugated and deconditioned bile acids contributes to the formation of lithogenic bile. Thirdly, the bacterial overgrowth leads to endotoxemia, which has a damaging effect on the metabolism of the bile acids in the liver. Finally, there is a certain dependence of the digestive and absorption functions of the small intestine on microbiota, however, the participation of this channel in the cholelithiasis requires further research.

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