

Gallstone Disease

Subjects: Gastroenterology & Hepatology

Contributor: Tatyana Romanova

Gallstone disease (GSD) has, for many years, remained a high-cost, socially significant public health problem. Over the past decade, a number of studies have been carried out—both in humans and in animal models—confirming the role of the microbiota in various sections of the gastrointestinal tract as a new link in the etiopathogenesis of GSD. The microbiome of bile correlates with the bacterial composition of saliva, and the microbiome of the biliary tract has a high similarity with the microbiota of the duodenum. Pathogenic microflora of the oral cavity, through mechanisms of immunomodulation, can affect the motility of the gallbladder and the expression of mucin genes (*Muc3*, *MUC4*), and represent one of the promoters of stone formation in the gallbladder. The presence of *H. pylori* infection contributes to the formation of gallstones and affects the occurrence of complications of GSD, including acute and chronic cholecystitis, cholangitis, pancreatitis. Intestinal bacteria (*Clostridium*, *Bifidobacterium*, *Peptostreptococcus*, *Bacteroides*, *Eubacterium*, and *Escherichia coli*) participating in the oxidation and epimerization of bile acids can disrupt enterohepatic circulation and lead to the formation of gallstones. At the same time, cholecystectomy due to GSD leads to the further transformation of the composition of the microbiota in various parts of the gastrointestinal tract, increasing the risk of developing stomach cancer and colorectal cancer. Further research is required to determine the possibility of using the evaluation of the composition of the microbiota of the gastrointestinal and biliary tracts as an early diagnostic marker of various gastroenterological diseases.

Keywords: Gallstone disease ; microbiota ; gut ; bile acids ; oral cavity ; cholecystectomy

1. Introduction

The presence of live bacteria in gallstones has been proven by electron microscopy, bacteriological cultivation and molecular genetic methods.^{[1][2][3][4]}

In a study by Hazrah et al.^[1], microorganisms were cultured from gallstone nuclei in 81% of cases of GSD and in 77% of cases of gallbladder cancer, regardless of the type and size of the stones. Bacteria were present in 75% of pigmented, 76% mixed and 20% cholesterol stones.^[5]

According to Kose et al.^[6] the composition of the intestinal microbiota can also affect the formation of the type of stones in the gallbladder (cholesterol, pigment, mixed). Under the action of a deconjugating factor, β -glucuronidase produced by bacteria, precipitation of calcium bilirubinate crystals occurs, which are conjugated with anionic glycoprotein, which leads to agglomeration of calcium bilirubinate crystals into macroscopic stones^[7].

In studies of Stuart L. et al., the effect of bacterial factors on the composition and morphology of gallstones (beta-glucuronidase and phospholipase) and mucus, as well as their effect on the severity of infection, was studied^{[8][9]}. Two hundred ninety-two patients were examined and 382 gallstones were cultured. The stones were examined using scanning electron microscopy and infrared spectroscopy. Bacteria were tested for production of β -glucuronidase / phospholipase and quantitative production of mucus^{[8][9]}. It has been proven that bacterial characteristics can control the formation of gallstones. There was more pigment in gallstones with phospholipase / glucuronidase producing bacteria (71% versus 26%, $p < 0.0001$), while mucus (or its absence) was associated (67%) with cholesterol stones ($p < 0.031$, all comparisons)^[5]. Severe infections directly correlated with β -glucuronidase / phospholipase, creating a surface for colonization (55% versus 13% without, $p < 0.0001$); however, with regard to the formation of mucus (55% versus 8%, mucus < 75 or > 75 , $p = 0.008$), bacteria producing only mucus were most often found in the centers of cholesterol stones^[8].

In a study by Peng Y. et al. When studying the microbiome of gallstones and bile in patients with gallstone disease, it was found that 30% of cultured strains of cholesterol gallstones secrete β -glucuronidase and phospholipase A2. In total, 14 genera of bacteria were identified in cholesterol gallstones, and eight genera in bile. *Pseudomonas spp.* were the dominant bacteria in the gallstones of cholesterol and bile. *Pseudomonas aeruginosa* strains had the highest β -glucuronidase activity and produced the highest concentration of phospholipase A2^[10].

There is another alternative mechanism for the formation of stones in the biliary tract: the formation of biofilms during the formation of pigment stones^[11]. The agglomerating factor in this case is glycocalyx (anionic glycoprotein). Differences in the functional metagenomes of microbial communities in pigmented and cholesterol gallstones were revealed^[6]. The genes involved in biofilm formation were mainly isolated from *Klebsiella* and *Enterococci* found in pigment stones, and bile resistance genes were present in *Escherichia*, *Shigella*, *Serratia*, *Bacillus* and *Klebsiella*. Isolated from cholesterol stones. In addition, most positive cholesterol gallstones examined were dominated by gram-positive bacteria that were not identified in pigment stones. In pigment stones, a high proportion of genes involved in carbohydrate metabolism was revealed, and in cholesterol stones, the profile in which protein metabolism predominates was more active^[6].

2. Intestinal microbiome and cholecystectomy

The composition of the microbiome of the intestine and biliary tract varies significantly in patients with GSD and in healthy people^{[12][13][14]}. In patients with GSD, microbial diversity decreases, which is accompanied by a decrease in the beneficial genus *Roseburia*^[12], with an overgrowth of bacteria such as *Proteobacteria*, including a wide range of pathogenic microorganisms, such as *Escherichia*, *Salmonella*, *Vibrio*, and *Helicobacter* ^[15]. In patients with GSD, enrichment of *Anaerotruncus*, *Parabacteroides*, and *Paraprevotella* is noted at the age of over 60, while in individuals without GSD this increase was not detected^[16].

Cholecystectomy leads to a significant change in the composition of the intestinal microbiota^{[17][15]}. After cholecystectomy, an even more pronounced decrease in the actual number of taxa occurs compared with individuals without GSD^{[16][17]} and an increase in the number of *Bifidobacterium* and *Anaerostipes Dorea*^[16]. In some individuals, an increase in the species *B. obeum* and *V. Parvula* (type *Firmicutes*)^{[16][17]} and *Bacteroidetes*^[12] was noted.

In patients with cholecystectomy, the number of *Anaerotruncus*, *Parabacteroides*, and *Paraprevotella* is also significantly reduced, and no increase is observed with age compared with individuals without GSD^[16]. A decrease in the number of bacteroids negatively associated with secondary bile acids is probably one of the main reasons for the increase in the incidence of colorectal cancer in patients with cholecystectomy.

Changes in the microbiome that occur after cholecystectomy persist for a long time^[16]. Such changes are probably mediated by an abnormal transintestinal flow of bile acids, which begin to act without the rhythmic function of the gallbladder, increase the loss of bile acids from the intestine^[18] and alter intestinal immune homeostasis^[19]. Symptomatic gallstones and cholecystectomy have been shown to be associated with an increased risk of developing stomach cancer^{[20][21]}, small intestine cancer^[22], and colon cancer^{[23][19]}.

References

1. P. Hazrah; K.T.H. Oahn; M. Tewari; A.K. Pandey; K. Kumar; T.M. Mohapatra; H. S. Shukla; The frequency of live bacteria in gallstones. *HPB* **2004**, 6, 28-32, [10.1080/13651820310025192](https://doi.org/10.1080/13651820310025192).
2. J. Ramana Ramya; K. Thanigai Arul; M. Epple; U. Giebel; J. Guendel-Graber; V. Jayanthi; M. Sharma; M. Rela; S. Narayana Kalkura; Chemical and structural analysis of gallstones from the Indian subcontinent. *Materials Science and Engineering: C* **2017**, 78, 878-885, [10.1016/j.msec.2017.04.004](https://doi.org/10.1016/j.msec.2017.04.004).
3. Alexander Swidsinski; Wolfgang Ludwig; Hartmut Pahlig; Friedrich Priem; Molecular genetic evidence of bacterial colonization of cholesterol gallstones. *Gastroenterology* **1995**, 108, 860-864, [10.1016/0016-5085\(95\)90461-1](https://doi.org/10.1016/0016-5085(95)90461-1).
4. Dong Ki Lee; Phillip I. Tarr; Geoffrey W Haigh; Sum P. Lee; W. Geoffrey Haigh; Bacterial Dna in Mixed Cholesterol Gallstones. *American Journal of Gastroenterology* **1999**, 94, 3502-3506, [10.1111/j.1572-0241.1999.01614.x](https://doi.org/10.1111/j.1572-0241.1999.01614.x).
5. Vijay C. Antharam; Daniel C. McEwen; Timothy J. Garrett; Aaron T. Dossey; Eric C. Li; Andrew N. Kozlov; Zhubene Mesbah; Gary P. Wang; An Integrated Metabolomic and Microbiome Analysis Identified Specific Gut Microbiota Associated with Fecal Cholesterol and Coprostanol in *Clostridium difficile* Infection. *PLOS ONE* **2016**, 11, e0148824, [10.1371/journal.pone.0148824](https://doi.org/10.1371/journal.pone.0148824).
6. S. H. Kose; K. Grice; W. D. Orsi; M. Ballal; Marco J. L. Coolen; Metagenomics of pigmented and cholesterol gallstones: the putative role of bacteria. *Scientific Reports* **2018**, 8, 11218, [10.1038/s41598-018-29571-8](https://doi.org/10.1038/s41598-018-29571-8).
7. Manabu Kawai; Makoto Iwahashi; Kazuhisa Uchiyama; Minoru Ochiai; Hiroshi Tanimura; Hiroki Yamaue; Gram-positive cocci are associated with the formation of completely pure cholesterol stones. *American Journal of Gastroenterology* **2002**, 97, 83-88, [10.1111/j.1572-0241.2002.05425.x](https://doi.org/10.1111/j.1572-0241.2002.05425.x).

8. Lygia Stewart; J. McLeod Griffiss; Gary A. Jarvis; Lawrence W. Way; Gallstones Containing Bacteria are Biofilms: Bacterial Slime Production and Ability to Form Pigment Solids Determines Infection Severity and Bacteremia. *Journal of Gastrointestinal Surgery* **2007**, 11, 977-984, [10.1007/s11605-007-0168-1](https://doi.org/10.1007/s11605-007-0168-1).
9. Lygia Stewart; J. McLeod Griffiss; Gary A. Jarvis; Lawrence W. Way; Biliary bacterial factors determine the path of gallstone formation. *The American Journal of Surgery* **2006**, 192, 598-603, [10.1016/j.amjsurg.2006.08.001](https://doi.org/10.1016/j.amjsurg.2006.08.001).
10. Yuhong Peng; Yang Yang; Yongkang Liu; Yuanyang Nie; Peilun Xu; Baixue Xia; Fuzhou Tian; Qun Sun; Cholesterol gallstones and bile host diverse bacterial communities with potential to promote the formation of gallstones. *Microbial Pathogenesis* **2015**, 83, 57-63, [10.1016/j.micpath.2015.05.002](https://doi.org/10.1016/j.micpath.2015.05.002).
11. Lygia Stewart; Alison L. Smith; Carlos A. Pellegrini; Roger W. Motson; L W Way; Pigment Gallstones Form as a Composite of Bacterial Microcolonies and Pigment Solids. *Annals of Surgery* **1987**, 206, 242-250, [10.1097/00000658-198709000-00002](https://doi.org/10.1097/00000658-198709000-00002).
12. Nirit Keren; Fred M. Konikoff; Yossi Paitan; Gila Gabay; Leah Reshef; Timna Naftali; Uri Gophna; Interactions between the intestinal microbiota and bile acids in gallstones patients. *Environmental Microbiology Reports* **2015**, 7, 874-880, [10.1111/1758-2229.12319](https://doi.org/10.1111/1758-2229.12319).
13. Natalia Molinero; Lorena Ruiz; Christian Milani; Isabel Gutiérrez-Díaz; Borja Sánchez; Marta Mangifesta; José Segura; Isabel Cambero; Ana Belén Campelo; Jose Ignacio Rodriguez Garcia; et al. The human gallbladder microbiome is related to the physiological state and the biliary metabolic profile.. *Microbiome* **2019**, 7, 100, [10.1186/s40168-019-0712-8](https://doi.org/10.1186/s40168-019-0712-8).
14. Natalia Molinero; Lorena Ruiz; Borja Sánchez; Abelardo Margolles; Susana Delgado; Intestinal Bacteria Interplay With Bile and Cholesterol Metabolism: Implications on Host Physiology.. *Frontiers in Physiology* **2019**, 10, 185, [10.3389/fphys.2019.00185](https://doi.org/10.3389/fphys.2019.00185).
15. Tao Wu; Zhigang Zhang; Bin Liu; Dezhi Hou; Yun Liang; Jie Zhang; Peng Shi; Gut microbiota dysbiosis and bacterial community assembly associated with cholesterol gallstones in large-scale study. *BMC Genomics* **2013**, 14, 669-669, [10.1186/1471-2164-14-669](https://doi.org/10.1186/1471-2164-14-669).
16. Wenxue Wang; Junfeng Wang; Julian Li; Pingping Yan; Yun Jin; Ruyi Zhang; Wei Yue; Qiang Guo; Jiawei Geng; Cholecystectomy Damages Aging-Associated Intestinal Microbiota Construction. *Frontiers in Microbiology* **2018**, 9, 1402, [10.3389/fmicb.2018.01402](https://doi.org/10.3389/fmicb.2018.01402).
17. Won Jae Yoon; Han-Na Kim; Eunhyo Park; Seungho Ryu; Yoosoo Chang; Hocheol Shin; Hyung-Lae Kim; Sun Young Yi; The Impact of Cholecystectomy on the Gut Microbiota: A Case-Control Study. *Journal of Clinical Medicine* **2019**, 8, 79, [10.3390/jcm8010079](https://doi.org/10.3390/jcm8010079).
18. Gerd H. Sauter; Ahmed C. Moussavian; Guenther Meyer; Heinrich O. Steitz; Klaus G. Parhofer; Dieter Jüngst; Bowel habits and bile acid malabsorption in the months after cholecystectomy. *American Journal of Gastroenterology* **2002**, 97, 1732-1735, [10.1111/j.1572-0241.2002.05779.x](https://doi.org/10.1111/j.1572-0241.2002.05779.x).
19. Hana Sarashina-Kida; Hideo Negishi; Junko Nishio; Wataru Suda; Yuki Nakajima; Mika Yasui-Kato; Keiko Iwaisako; Sujin Kang; Nobuyasu Endo; Hideyuki Yanai; et al. Gallbladder-derived surfactant protein D regulates gut commensal bacteria for maintaining intestinal homeostasis. *Proceedings of the National Academy of Sciences* **2017**, 114, 10178-10183, [10.1073/pnas.1712837114](https://doi.org/10.1073/pnas.1712837114).
20. Katja Fall; Weimin Ye; Olof Nyrén; Risk for Gastric Cancer After Cholecystectomy. *American Journal of Gastroenterology* **2007**, 102, 1180-1184, [10.1111/j.1572-0241.2007.01169.x](https://doi.org/10.1111/j.1572-0241.2007.01169.x).
21. Yen-Kung Chen; Jiann-Horng Yeh; Cheng-Li Lin; Chiao-Ling Peng; Fung-Chang Sung; Ing-Ming Hwang; Chia-Hung Kao; Cancer risk in patients with cholelithiasis and after cholecystectomy: a nationwide cohort study. *Journal of Gastroenterology* **2014**, 49, 923-931, [10.1007/s00535-013-0846-6](https://doi.org/10.1007/s00535-013-0846-6).
22. Michael J Goldacre; Clare J Wotton; Julie Abisgold; David G. R. Yeates; John Collins; Association Between Cholecystectomy and Intestinal Cancer. *Annals of Surgery* **2012**, 256, 1068-1072, [10.1097/sla.0b013e3182759efb](https://doi.org/10.1097/sla.0b013e3182759efb).
23. James J. Farrell; Lei Zhang; Hui Zhou; David Chia; David Elashoff; David Akin; Bruce J Paster; Kaumudi Joshipura; David T W Wong; Variations of oral microbiota are associated with pancreatic diseases including pancreatic cancer.. *Gut* **2012**, 61, 582-8, [10.1136/gutjnl-2011-300784](https://doi.org/10.1136/gutjnl-2011-300784).