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Contents

Monthly Volume 16 Number 11 November 27, 2024

EDITORIAL

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

Contents

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 11 November 27, 2024

Contents

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 11 November 27, 2024

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 11 November 27, 2024

Contents

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EDITORIAL

Biliary microbiome and gallstones: A silent friendship

Tuhina Banerjee, Aakansha Giri Goswami, Somprakas Basu

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Abstract

With increasing evidence, the biliary tract and the gallbladder mucosa are no longer considered sterile environments devoid of bacteria. Rather a profound biofilm of resident bacterial flora is associated with the mucosal surface. The bile too harbors a resident flora. It is when a dysbiotic process ensues, that this bacterial flora either becomes opportunist or is replaced by a pathogenic one that has a strong ability to survive the challenges of the biliary environment. Although once believed a metabolic problem, recent evidence indicates a complex interaction between different species of bacteria and gallbladder mucosa and bile which may culminate in calculus formation. The resident microbiota and its several enzymes dictate the type of gallstone by the mere interplay of the constituting type of bacteria in the biofilm, even without any evidence of infection. Dysbiosis is often mediated by either intestinal dysbiosis or less probably by oral dysbiosis. The gallstones, in turn, provide a haven for the resident microbiota in which they can form their own defined niche enriched with the biofilm that can resist the biliary defense mechanisms and survive the hostile biliary environment in the background of biliary stasis and local infection. However, this process of silent friendship is more complex than said, and further research is needed to define the relationship between the two.

Key Words: Biliary microbiome; Resident flora; Dysbiosis; Gallstones; B-glucuronidase

Core Tip: The concept of the existence of a resident biliary microbiome has been emerging in recent times. There is a well-established association between this microbiome and gallstone formations. Dysbiosis in the biliary microbiome rather than infection is the key phenomenon responsible for gallstone formation as evident from the emerging metagenomics-based studies.

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INTRODUCTION

During the last few years, our understanding of the interactions between the microbiome and the host has experienced one of the greatest developments in health and disease. A significant move from the traditional microbiological culture to metagenomics-based techniques has revolutionized the concept of microorganisms and their habitat within the human body. Consequently, the concept of 'sterile sites' within the human body has been changing. In this context, emerging evidence from available studies on the biliary microbiome has largely associated biliary tract diseases with dysbiotic conditions in the biliary ecosystem[1,2]. This idea of dysbiosis has also been proposed for gallstone formation and gallstone disease, thus compelling the scientific community to contemplate whether dysbiosis in the gallbladder microbiome vis-à-vis ascending infection from the intestine is responsible for gallstones.

THE HOST FACTORS

The biliary microbiome constitutes not only the resident microflora in the bile but also that of the gallbladder mucosa[3]. For long, this microbiome was unidentified, and bacterial colonization in the gallbladder was not the accepted concept. This was not only due to the limitations of culture-based microbiological evidence but also due to the well-established biliary defense mechanisms, inhibiting bacterial colonization. Anatomical factors like higher basal tone of the Sphincter of Oddi as compared to the duodenal pressure and intact biliary epithelium prevent translocation of microorganisms from the gastrointestinal tract (GIT)[4,5]. Similarly, physiological factors like the washing effects of the high volume of bile per day from the gallbladder and mucus secreted by the biliary epithelium, prevent bacterial adherence to the mucosa and hence colonization[5,6]. Besides, the well-studied antimicrobial properties of bile supported by the fact of reduced bacterial colonization in the duodenum have also proved to be a potent defensive factor. Immunological factors like the innate receptors (TLRs) and defensins (1 and 2), the presence of macrophages, and Kupffer cells promote the killing and destruction of bacteria[6,7].

MICROBIOME FACTORS

With the concept of the resident biliary microbiome, came the important question of how these challenges are met by bacteria to survive and persist in the gallbladder. In this regard, properties of Proteobacteria have already revealed the extent of bile tolerance exhibited by certain organisms under specific conditions. Gram-negative bacteria are more bile tolerant including few inherently tolerant ones as compared to the Gram-positive organisms. Bacteria like *Salmonella* species, *Escherichia coli*, *Helicobacter bilis*, *H. hepaticus*, and *Campylobacter* are known for their bile tolerant property and have been isolated from the bile and the gallbladder[8]. Probiotic Gram-positive bacteria are more bile tolerant than other Gram-positive pathogens, a fact supported by the report of *Enterococcus faecalis* in the biliary microbiome[1]. Varying bile acid levels in the intestine as well as exposure to varying pH, temperatures, and growth conditions account for the increase in bile tolerance. Modifications in the lipid composition of the bacterial cell wall along with the regulation of several efflux pumps, porin channels, and expression of bile-induced genetic characters to regulate bacterial virulence aid in the survival of bacteria in the gallbladder[1,4]. It is interesting to note that bile tolerance is highly strain-specific and therefore cannot be generalized. Besides, the role of several bacterial enzymes in the pathogenesis of gallstone formation has also been analyzed. The β-glucuronidase enzyme along with other hydrolyzing enzymes like phospholipases and hydrolases, cause precipitation of calcium salts that agglomerate into gallstones[9,10].

GALLBLADDER MICROBIOME AND GALLSTONES

The ascending route of bacterial movement from the GIT has been widely proposed as the most common route to the gallbladder. Consequently, laxity of the Sphincter of Oddi or any cause of obstruction to bile flow, as seen in gallstone

disease, could account for the different sources of bacterial translocation. Microorganisms like *Salmonella* follow the hematogenous route for entering the gallbladder through the enterohepatic circulation[3]. Until the landmark study by Maki[11], it was presumed that the formation of gallstones can occur even without any infection. However, the said study introduced the concept of infection in the causation of pigment gallstone, which opened new vistas for a probable role of the biliary microbiome in gallstone formation.

There has been adequate data on the role of the intestinal microbiome in the establishment of the biliary microbiome [12-14]. Due to the anatomical location of the bile duct in connection with the duodenum, it has been hypothesized and demonstrated through several studies that the biliary microbiome closely resembles the intestinal microbiome, though the biliary microbiome is more diverse[13]. Interestingly, the microbiome of the bile and the gallbladder correlates with that of the oral and respiratory flora whereas the microbiome of the biliary tract correlates with that of the intestinal flora[14]. In this context, dysbiosis in oral flora could be one of the facilitators for gallstone formation, although the mechanisms are yet to be elucidated. On the other hand, microbiological culture of the bile and the gallbladder mucosa or gallstones as well as high throughput sequencing techniques have revealed the existence of several biofilm-forming enteric bacteria in varying combinations, thus indicating that the intestinal flora contributes to the dysbiosis in the gallbladder microbiome in gallstone disease[15]. At this juncture, it is noteworthy that the resident gallbladder microbiome in healthy persons is quite complex with the presence of various members of *Firmicutes*, *Actinobacteria*, *Proteobacteria* and less frequently Bacteroidetes[16,17]. Dysbiosis in this resident biliary flora mediated by either intestinal dysbiosis or less probably by oral dysbiosis predisposes to gallstone formation.

With the introduction of improved molecular-based technologies both for detection and bile sampling, it was established that bacterial colonization of bile, gallbladder and biliary mucosa, and the existence of a resident microflora rather than infection with any single bacteria, in an otherwise sterile biliary environment was the important contributing factor for gallstone formation[1]. Following this, metagenomics-based studies revealed the diversity of bacteria in gallstones, supporting this concept of constant colonization with multiple bacterial species instead of a single species of bacteria, which would have suggested infection[1,18]. Additionally, it could be asserted that if diverse microflora could exist in the hostile biliary environment, it is the dynamic change in bacterial colonization that plays the most important role in gallstone diseases. Thus, changes in dynamic equilibrium rather than infection of the bile and the gallbladder mucosa are accountable for the risk of cholelithiasis[19].

MICROBIOTA OF GALLSTONES

The involvement of bacteria in 77% of pigmented stones, 20% of cholesterol stones, and 76% of mixed stones has been documented in a metagenomics-based study[20]. In pigment stones, bacteria with hydrolytic enzymes like β-glucuronidase have been implicated in its pathogenesis. The ability of bacteria like *Klebsiella* and *Enterococcus* to form biofilms has also been implicated in the formation of pigment stones, in which the glycocalyx serves as the agglomerating factor for stone formation[21]. The presence of Gram-positive bacteria has not yet been reported in pigment stones though genes involved in carbohydrate metabolism have been detected in high numbers[22]. As against pigment stones, the formation of cholesterol stones was long considered as that associated with metabolic imbalances rather than having any infectious etiology[23]. Adding to this, studies based on basic molecular techniques did not reveal bacterial DNA in pure cholesterol stones. On the contrary, bacterial DNA of *Propionibacteria*, clostridia, and enterobacteria groups was detected in mixed stones with high cholesterol content[24]. When quantitative PCR-based studies were performed, surprisingly, it was inferred that even culture-negative cholesterol gallstones harbored a very low quantity of bacteria[25]. The spectrum of bacterial flora in these gallstones was highly diverse and mixed, with *Bacillus*, *Alcaligenes, etc.* as major constituents[25,26]. This finding conceptualized that in cholesterol gallstones, multiple bacterial species existed, suggesting their persistence and constant colonization. Another study on pure cholesterol stones reported that 57% of the gallstones contained Gram-positive bacterial DNA in the core of the stones[27]. This finding was quite unexpected as bacteria colonizing the gallbladder mucosa or bile are usually predicted to be bile-tolerant Gram-negative in nature. *Pseudomonas* species was the predominant organism in cholesterol gallstones and bile of patients with gallstones in a study by Peng *et al*[18]. Notably, *Pseudomonas aeruginosa* possesses the highest β-glucuronidase activity which also could suggest a similar mechanism of formation of cholesterol gallstones like pigment stones. Mixed stones have demonstrated higher bacterial numbers as compared to pure cholesterol stones, the organisms being present on the surfaces and core of such stones[28]. Therefore, the role of colonizing bacteria, secreted hydrolyzing enzymes, and subsequent infection could be proposed for the formation of mixed stones until further validation by metagenomics-based studies.

CONCLUSION

With further evidence, our understanding of the several interactions of the microbiome of the GIT and that of the gallbladder mucosa and bile in gallstone formation will improve. There is much heterogeneity in the existing limited literature focusing on gallbladder microbiome which would be overcome with more well-planned studies in this field. However, one important point to be noted here even with the existing level of evidence is that gallbladder microbiome is associated with gallstone diseases. In this regard, the diversity of bacterial communities and richness of the bacterial members have been reported to be higher in gallstones as compared to bile in a few studies[26,29]. This finding is very noteworthy as it suggests that gallstones provide a 'protective environment' for bacteria in which they can form their distinct niche within them with those organisms that can resist the biliary defense mechanisms and survive the hostile

biliary environment. Just like a true friend, the gallstone provides an effective platform for bacterial communities to build up their dominion, itself being an integral part of it. This 'silent friendship' provides a direct invitation to the researchers to decipher the hidden secrets of this existing long-term friendship for opening new vistas in diagnostics, therapeutics, and above all in our understanding of host-microbiome interactions.

FOOTNOTES

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