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The Association between Gut Microbiome and Post-Cholecystectomy Syndrome and Diarrhoea: A Review

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ABSTRACT

Cholecystectomy is a common surgical gold-standard treatment for cholelithiasis and its complications. Generally, gallbladder removal has no long-term ramifications, and most patients recover quickly without impairment on daily living activities. Nonetheless, some patients are found to develop post-cholecystectomy syndrome (PCS) or diarrhoea (PCD), which can be uncomfortable, inconvenient and impair living quality. There is neither clear aetiology, nor clear solution for PCS/PCD.

The significance of gut microbiome in maintaining a healthy gastrointestinal system is well-established. Dysbiosis, an imbalance between commensal and pathogenic bacteria, can lead to multiple GIT disorders like IBS or functional dyspepsia and has a strong association with change in stool consistency [1-3]. Alteration in gut microbiota can easily occur with physical or chemical changes. An invasive procedure like cholecystectomy exposes the intestinal lumen to exogenous bacteria and causes inflammatory changes, while secretory pattern changes of bacteriostatic bile acid disrupt the pH and microbial composition of the intestinal lumen. As such, it is worth understanding GIT microbiota changes post-cholecystectomy.

While the concept of gut microbiome changes potentially causing PCS/PCD is not unknown, there is lack of literature reviewing research on what these microbial alterations are and establishing their association with PCS/PCD. In this review, we consolidate previous findings on post-cholecystectomy microbial alterations, effectiveness of diet on PCS/PCD based on gut microbiota and discuss the overall link between gut microbiome and PCS/PCD. This can deepen insight into aetiologies of idiopathic PCS/PCD, provide better management of PCS/PCD-associated comorbidities, and potentially offer a resolution for PCS/PCD through prescription of probiotics and prebiotics.

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Background of Post-Cholecystectomy Syndrome and Diarrhoea

Previous research studies have found that up to 45.5% of patients develop post-cholecystectomy syndrome (PCS), while up to 35.6% of patients reportedly develop persistent post-cholecystectomy diarrhoea (PCD) [4-6]. For both PCS and PCD, incidence is highest 1 week postoperatively, with decreasing prevalence over time as measured at 1 month, 3 months and beyond in multiple studies [5-8].

Post-Cholecystectomy Syndrome (PCS) refers to a group of recurring gastrointestinal symptoms developed after a cholecystectomy. It comprises of dyspepsia (epigastric pain, heartburn, bloating, postprandial fullness) and biliary-type pain (right upper quadrant pain) [9]. Symptoms may occur immediately postoperative, known as "early PCS", but may also persist up to months or years as "late PCS" [10]. Onset ranges from 2 days to 25 years after surgery.9 Early PCS is usually attributed to biliary causes linked back to operative complications causing bile leakage and obstruction, or incomplete surgery with retained gallstones in a long remnant cystic duct or in the common bile duct.10 The most common cause of PCS within <3 years postoperatively is an underlying extra-biliary gastrointestinal condition. This includes GERD, peptic ulcer disease (PUD), chronic pancreatitis and irritable bowel syndrome (IBS) [9,11]. On the other hand, aetiology of PCS lasting >3 years postoperatively most commonly involves biliary conditions like recurrent or dropped gallstones, biliary strictures and fibrosis, cystic duct remnants and sphincter of Oddi dysfunction [9,11]. Identifying these comorbidities and

complications involve investigations through endoscopies, MRCP and manometry, so as to manage underlying causes of PCS [10,11]. Notwithstanding these aetiologies, PCS can also be idiopathic as found in multiple studies [11,12].

Adjunct to PCS is post-cholecystectomy diarrhoea (PCD), whereby patients often present with increased frequency of liquid diarrhoea, associated with food intolerance and bloating.6 such change in bowel habits is attributed to multiple mechanisms, although none of them are unanimously proven to date. The most common hypothesis is bile acid malabsorption (BAM), whereby continuous bile acid flow into the duodenum leads to increased enterohepatic cycling and thus secretory bile acid diarrhoea. Adaptation to such change in bile acid delivery would explain subsequent alleviation of PCD in some patients. This theory is supported by increased serum BAM biomarker 7α-hydroxy-4-cholesten-3-one (7α-HCO) in patients with PCD, as well as successful and reversible suppression of PCD with cholestyramine [13]. However, other studies have also shown such increased biomarkers to be clinically insignificant to explain secretory PCD, whereas cholestyramine responses have been inconsistent between studies, disputing BAM as a definite cause of PCD [6,8,14]. Another potential cause of PCD is shortened colonic transit time as demonstrated in a study using modified radiopaque pallets which measured significant acceleration, however this has yet to be proven either with contrasting studies proving insignificance [6,15,16]. Other associated causes include psychosomatic factors like anxiety [17]. Nonetheless, in all, PCD and its aetiologies are still not well understood to date with no clinical guidelines to manage and prevent patients' discomfort and inconvenience.

Alterations in Gut Bacteria Post-Cholecystectomy

It is understood that the bacteriostatic properties of bile acid, in addition to pH changes brought about by continuous bile release into the duodenum after gallbladder removal, can lead to changes in the gut microbiome. The wipe out of previous microbial populations allows certain bacterial strains to proliferate over others and cause dysbiosis.

Previous studies have demonstrated changes in gut microflora composition after cholecystectomy by analysing the faecal microbiota of these patients through similar methods of bacterial 16S-rRNA gene sequencing:

A population cohort study in Germany compared the faecal microbiota of 1968 individuals split into 3 groups: (1) Post-cholecystectomy, (2) Asymptomatic gallstone carriers, and (3) Non-gallstone carriers – and found that only post-cholecystectomy patients demonstrated a significantly increased proportion of facultative *Escherichia coli* and *Shigella* and decreased beneficial *Faecalibacterium*, essential for colonocyte metabolism and anti-inflammatory mediation. Notably, there was a slight increase in beneficial *Clostridium XIVa*, which aids colonocyte metabolism, however this was insufficient to compensate for the former deficiency. There was also a general reduction in microbiota α-diversity [18].

Another study in China with 51 participants also studied 3 groups: (1) Post-cholecystectomy diarrhoea - PCD, (2) Post-cholecystectomy non-diarrhoea - PCND, and (3) Healthy controls - HC, and found significantly decreasing microbial α-diversity in the populations of HC, PCND and PCD accordingly. PCD also had a significantly decreased *Firmicutes/Bacteroidetes* ratio, decreased abundance of beneficial lipid metabolising bacteria, decreased probiotic *Bifidobacterium* and *Lactococcus*, and increased harmful *Prevotella* and *Sutterella*, as compared to PCND. Patients were recruited ≤1-year post-cholecystectomy [19].

Another Chinese study analysed the gut microbiome of 24 individuals split into 3 groups: (1) PCS/D patients, (2) Asymptomatic PCS/D patients, and (3) Healthy individuals. Significantly increased *Proteobacteria* and *Verrucomicrobia* and non-significantly decreased *Bacteroidetes* and *Firmicutes* were found in PCS patients versus healthy individuals. Stool samples were collected >2 years post-cholecystectomy [20].

Another study in China with 35 participants (15 healthy, 20 cholecystectomy patients) also demonstrated reduced intestinal microbiota diversity in post-cholecystectomy patients, with higher proportions of *Bifidobacterium*, *Anaerostipes*, *Dorea*, *E. coli*, *Bacteroidetes*, and decreased *Bacteroides*. Stool samples were collected 2 years post-cholecystectomy [21].

Diversity

From these studies, there is a clear trend of significantly decreased microbiota diversity in post-cholecystectomy (PC) patients. One of the above studies also distinguishes a larger reduction of α-diversity in PC patients with PCD against those asymptomatic. A diverse gut microbiome is essential for nutrient metabolism, immunomodulation and maintaining of stable bacterial proportions, preventing the dominance of specific species which might lead to GIT imbalance and thus dysfunction. Reduced microbiota diversity is associated with inflammatory bowel conditions, increased perturbation, abdominal infections and recurrent *C. difficile* associated diarrhoea [18,22]. In terms of the association of microbiota with PCD, a 2015 Belgium study affirms the strong association between gut microbial richness and stool firmness (Spearman's r = -0.45), with minimum diversity found in patients with diarrhoea.3 This renders decreased gut microbial diversity as demonstrated in PC patients a plausible explanation for PCD. Nonetheless, for PCS, while previous studies have demonstrated association between microbiota changes and functional disorders like dyspepsia and IBS, of which onset could be the cause of PCS, such symptoms are not clearly attributed to decreased microbiota diversity and richness, but rather alterations in proportion and composition of microbiota [1,2,23,24].

Composition

All the above studies demonstrate distinct changes in microbiota composition in PC patients. While there has yet to be consensus on which specific bacterial strains are dominant or suppressed, there is a general trend of increase in facultative and potentially pathogenic bacteria and decrease in beneficial commensal microbiota. Nonetheless, there are exceptions to this finding. One study showed an increase in *Clostridium XIVa*, a beneficial short chain fatty acid (SCFA) producer which helps regulate colonocyte regeneration and T-cells to reduce intestinal inflammation [25]. However, in this same study the beneficial effects of this increased strain was outweighed by the more significant loss of *Faecalibacterium* which plays similar roles [18,26]. Another study demonstrated an increase in *Bifidobacterium* in PC patients over healthy controls, which should be beneficial for lipid metabolism, reducing adiposity, suppressing inflammation, and immunoregulation [27].

PCS/PCD symptoms can be associated with chronic systemic inflammation, which is manifests in multiple functional GIT disorders like dyspepsia, IBD, IBS, metabolic syndromes, chronic infections and food intolerances [28,29]. Proinflammatory bacterial strains that were elevated in the above studies include *E. coli*, *Proteobacteria* and *Prevotella* [23,28,29]. Anti-inflammatory

bacteria strains like *Lactobacillus*, *Faecalibacterium* were all generally shown to decrease [29].

PCS symptoms can also be associated with functional dyspepsia (FD). One study has demonstrated a dominance in *Escherichia*/*Shigella* in patients with functional dyspepsia, a strain known to selectively proliferate in increased bile acid levels, corresponding to the increased *Escherichia*/*Shigella* proportion found our PC patients [2,18]. A dominance in *Bifidobacterium longum* was also found in FD patients, which could correlate with the unexpected finding of increased *Bifidobacterium* in PC patients. Other significant bacterial alterations in the study found increase in *Bacteroidetes* and *Bacteroides* and decrease in *Proteobacteria* and *Acidobacteria* [2]. While increase in *Bacteroidetes* were also found in one study of PC patients, there was in fact a decrease in *Bacteroides* and increase in *Proteobacteria* in our population.

PCS/D's potential association with new onset IBS might also be demonstrated by increased *Clostridium cluster XIVa* which was found to be associated with diarrhoea-predominant IBS.24 While such SCFA producing bacteria have shown beneficial effects on inflammation and oxidation, it has also been shown to promote non-inflammatory visceral colonic hypersensitivity in rats [30]. This would also correlate with our unexpected findings of slight increase of *Clostridium XIVa* in PC patients, although in that study there was an overall decrease in SFCA due to greater decrease in *Faecalibacterium*.

For PCD, a study has shown strong association between *Prevotella* and loose stools, which was replicated in our PCD patients with increased *Prevotella* counts [3]. One study also showed decreased *Firmicutes/Bacteroidetes* (F/B) ratio associated with IBD, which might be associated with PCD. As the 2 most dominant gut bacteria, with *Firmicutes* usually dominating in healthy adults, the F/B ratio is crucial for homeostasis and imbalance is linked to multiple pathologies p [31]. Nonetheless, previous reviews have demonstrated that F/B ratios vary widely across countries and populations, rendering the reliability in its values questionable [32].

Small Intestinal Bacterial Overgrowth (SIBO)

Other studies also measure the prevalence of SIBO, which occurs when abnormally high amounts of specific bacteria colonize the small intestine, leading to bloating, diarrhoea, malabsorption and inflammation, symptoms present in PCS and PCD. Relevant aetiologies of SIBO include change in bile quantity and composition or adhesions and strictures potentially caused by invasive cholecystectomy procedure [33]. SIBO is clinically significant with a bacterial count of >103 organisms/mL of jejunal aspirate culture and is measured in the following papers via non-invasive glucose-hydrogen breath tests (GBT):

A 2015 retrospective study in Korea involving 237 participants (62 post-cholecystectomy patients - PC, 145 functional GI diseased patients - FGID, 30 healthy controls - HC) found significantly increased frequency of positive GBT in PC patients (46.8%) as compared to FGID (26.2%) and HC (13.3%). SIBO measured by breath hydrogen H⁻2 was significantly increased in PC patients. PC patients were recruited at ≥6 months post-cholecystectomy [34].

Another 2016 Indian study followed 128 gallstone patients and found that presence of SIBO was significantly higher in late/2-15 years post-cholecystectomy gallstone patients (26.5%) as compared to similar rates in earlier/4-6 months post-cholecystectomy gallstone patients (13.9%) and pre-cholecystectomy patients (12.7%) [35].

Nonetheless, a 2018 Korean prospective study involving 304 participants (200 gallstones patients, 65 cholecystectomy patients, 39 healthy controls) found that SIBO was significantly higher in gallstones patients (40.5%) compared to cholecystectomy patients (24.6%) and healthy controls (20.5%). Increased incidence of SIBO in cholecystectomy patients over healthy controls was still significant. Cholecystectomy patients were recruited at ≥6 months post-cholecystectomy [36].

All the studies above demonstrated an increased incidence of SIBO measured by positive GBT in post-cholecystectomy patients. However, this association only applies to patients >6 months after cholecystectomy, as no significant association is found in earlier PC patients as found in one study. There are conflicting results between where presence of gallstones might be a confounder as while one study involved only gallstone patients and found significant difference with cholecystectomy, another study found significantly higher SIBO rates in gallstone patients than both cholecystectomy patients and healthy individuals. Despite that, all studies point to an association between SIBO and cholecystectomy. SIBO can directly present as PCS/PCD symptoms like abdominal pain, bloating, or watery diarrhoea, or lead to onset of GI disorders like IBS [1,33].

Effectiveness of Post-Cholecystectomy Dietary Modifications and Relation to Gut Microbiome

Dietary patterns have been found to largely influence gut microbiome, demonstrated in consistent associations with multiple GI disorders like IBD and IBS [37]. With large perturbations to gut microbiota during and after cholecystectomy due to physical invasion and acute change in bile acid secretion, the perioperative period is theoretically prime time to initiate reinstation of a healthy, well-balanced and diverse gut microbiome before chronic establishment of dysbiosis kicks in. While there is no standard guideline on nutrition recommendations post-cholecystectomy, previous studies have found varying associations between post-cholecystectomy dietary modifications and PCS and PCD development:

A Taiwanese study involving 125 PC patients found that adherence to a low-fat diet for 3 months after the operation was associated with decreased tendency for PCD at 1 week and 3 months, with low-fat diet being an important predictor of PCD only at week 1 [5].

Another Korean study involving 59 PC patients found that PCS at 3 months was associated with increased animal protein, cholesterol and eggs and decreased vegetables. Notably, PCS patients were also more likely to consume bread than rice for breakfast. Dietary habits were analysed by a food frequency questionnaire post-cholecystectomy and at 3 months [38].

However, one Brazilian study involving 40 PC patients found no significant effects of a low-fat diet on PCS development. A general decrease in dyspepsia was noticed over time, whereas colonic bloating and constipation were noticed to be more persistent. The post-operative period assessed was 15 days [39].

Another Spanish observational study involving 83 PC patients also found no significant association between low-fat diet and PCS improvement. Data was collected via a questionnaire on types of food consumed pre-cholecystectomy, 1 month and 6 months post-cholecystectomy [40].

From the limited literature, there appears to be divided consensus on the effectiveness of post-cholecystectomy dietary modifications, especially that of a low-fat diet. In the study where there is association between low-fat diet and reduced PCD risk, such association is found to be stronger at 1-week post-cholecystectomy, which coincides with the period of greatest adjustment should there be gut microbiome adaptation. Only one study explored the effects of other diet variations and obtained positive associations. The 2 studies that demonstrated associations were also noted to be on Asian populations, contrary to the other 2 non-Asian studies.

Dietary patterns are associated with alterations in the gut microbiome. With the understanding that dysbiosis is present with cholecystectomy, change in diet early post-cholecystectomy could shape a healthy microbiome to prevent PCS/PCD in the long run. Studies have found that diets high in animal-derived and plant-derived foods are associated with inverse microbiota taxonomy [37]. High animal protein and fat intake lead to increased abundance of *Firmicutes* and reduced *Bifidobacterium*, which are shown to be pro-inflammatory and associated with metabolic disorders [41]. High plant-based foods demonstrate an opposite effect to that. Increase in *Bifidobacterium* and other SCFA-producing bacteria is proven to have anti-inflammatory benefits and aid metabolism [37]. This finding coincides with the association between certain food groups and PCS as demonstrated in the Korean and Taiwanese study. However, there is insufficient evidence to prove such association at this point and more studies must be conducted to better understand the effectiveness of a dietary change post-cholecystectomy. Nonetheless, the relation to gut microbiome serves as a plausible hypothesis to guide further research on post-cholecystectomy dietary recommendations.

Conclusion

In all, this review consolidates evidence that cholecystectomy is associated with gut microbiome changes leading to PCS and PCD symptoms. These alterations include a decrease in gut microbiome alpha-diversity, changes in microbiota composition and possible post-cholecystectomy SIBO, which cause previously unexplained onset of bloating, dyspepsia, abdominal pain and diarrhoea as presented in PCS and PCD. Nonetheless, no bacterial-specific alteration has been identified to date and further research is required to narrow down patterns. As gut microbiome is highly variable between different populations due to influences of lifestyle and diets, demographically targeted research could be beneficial for understanding community specific changes and catering targeted treatments. With the factor of altered gut microbiome established, the hypothesis of effective dietary changes being supported by microbial mechanisms have supported limited findings of certain post-cholecystectomy diets reducing PCS/PCD. Nonetheless, there is insufficient research in the topic of post-cholecystectomy dietary recommendations and future studies can perhaps be designed based on diets that favour a healthy, non-inflammatory gut microbiome.

Additionally, in the topic of gut microbiota and PCS/PCD, with the understanding of antibiotic-induced dysbiosis, there is limited related research on post-cholecystectomy antibiotic use and PCS/PCD development. Studies on the effectiveness of post-cholecystectomy probiotics on preventing PCS/PCD development, or on eliminating PCS/PCD should also be explored in the future.

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