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Post-Cholecystectomy diarrhoea rate and predictive factors – a systematic review of the literature

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Abstract

Objectives

Cholecystectomy is one of the most common surgical procedure performed worldwide to treat gallstone-related disease. Post-cholecystectomy diarrhoea is a well-reported phenomenon, however the actual rate, predictive factors and mechanism of action have not been well determined.

Outcome measures

A systematic review was undertaken to determine the rate and predictive factors associated with diarrhoea in the post-cholecystectomy setting.

Method

The review was conducted according to the PRISMA protocol. It was registered on PROSPERO (CRD42019140444). Databases searched included Medline, Embase, Pubmed, Cochrane and Google Scholar. Out of the 1204 papers obtained, 21 were found to contain relevant information about post cholecystectomy diarrhoea, including the number of patients developing diarrhoea, method of symptom assessment, and time of onset post-cholecystectomy. Papers that did not include PCD as a separate entity were excluded.

Results

A pooled total of 3476 patients were included across the identified studies with 462 (13.3%) patients developing PCD. Possible predictive factors varied across all studies, with characteristics such as gender, age and weight of patients postulated as being predictive of PCD, with no agreement across studies.

Conclusions

PCD is therefore relatively common (13.3%). This has important implications for patient consent. Patients ought to be investigated early for bile acid diarrhoea in suspected PCD. More studies are required to determine the possible predictive factors for PCD.

Article Summary – Strengths and limitations of this study

- Able to inform the consent process prior to surgery
- A thorough literature review
- However, most studies not specifically powered to investigate post-cholecystectomy diarrhoea

Keywords: cholecystectomy, diarrhoea, post-operative

Introduction

Cholecystectomy is the gold standard treatment for symptomatic gallstone disease, which occurs in up to 22% of adults (1).. The laparoscopic approach to this surgery is now well-documented and accepted as standard practice, due to the significantly lower morbidity and mortality when compared with to open surgery (2). As a result, its adaptation into a laparoscopic procedure has increased the frequency with which cholecystectomy is performed (3, 4). Despite the notable benefits of cholecystectomy in treating gallstone-related disease, the postoperative course for a proportion of patients may be plagued by persistent or even new symptoms, including new-onset diarrhoea (5). This may be distressing for patients and have a significant impact on their quality of life (6). While it may be just a minor annoyance for some, others may well consider post-cholecystectomy diarrhoea to be a social disability (7, 8).

The actual incidence of post-cholecystectomy diarrhoea is unknown. Furthermore, implicated mechanisms in the onset of this condition remain significantly under-investigated.

At present, there are two main theories regarding the mechanism. The first suggests changes in the oro-caecal and colonic transit times secondary to increased enterohepatic circulation brought on by removal of the gallbladder (7). The second mechanism is less well-defined and involves the potential role of bile acids in causing diarrhoea (9). This mechanism has been proposed in idiopathic bile acid diarrhoea, where there is interruption of a negative feedback loop which controls bile acid synthesis. The working theory is that removal of the gallbladder, thus removing a bile storage system, will lead to over synthesis of bile acids by interrupting the same negative feedback loop, thus causing diarrhoea by overloading the uptake mechanisms in the terminal ileum (10).

The aim of this systematic review is to analyse published literature in order to assess the prevalence of post-cholecystectomy diarrhoea and possible pathophysiological mechanisms implicated in its development. Potential pre-operative factors which may help to predict the development of post-cholecystectomy diarrhoea, will also be examined. Recommendations for future direction of research shall be made, if appropriate.

Methods

The review was registered on PROSPERO (CRD42019140444). A literature search was performed on PUBMED, EMBASE and MEDLINE, Cochrane, google scholar using the keywords ‘post-cholecystectomy’ ‘postoperative’ ‘cholecystectomy’ ‘diarrhoea’ and ‘predictive factors’. There were no language limitations. The search strategy is outlined in figure 1.

The inclusion criteria were cohort studies or randomised trials which investigated the rate of post-cholecystectomy diarrhoea and predictive factors for this condition. Case reports, case series, conference abstracts and expert opinion pieces were also excluded. Systematic reviews were also excluded as all the original articles from those reviews were included in this review. Studies pertaining to persistent symptoms after laparoscopic cholecystectomy, that is symptoms present pre-operatively, rather than new symptoms were also excluded.

Data was extracted from the studies independently and entered into an electronic database. The results were subsequently collated. Data extracted included: patient numbers, age, gender, type of study, indication for surgery, preoperative symptoms, postoperative symptoms, predictive factors. The outcomes of the review were to identify the prevalence of post-cholecystectomy diarrhoea, potential predictive factors and possible pathophysiological mechanisms.

The systematic review was written according to preferred reporting systems for systematic reviews (PRISMA) guidelines (11). Risk of bias assessment was performed using the Newcastle-Ottawa scale for cohort studies and the Cochrane risk of bias tool for randomised controlled trials as appropriate (12, 13). The papers were classified according to the Oxford OCEBM levels of evidence (14).

Two independent reviewers (AF and JAA) performed the literature search and reviewed papers for inclusion to ensure the criteria were met. Any differences were resolved by mutual consent. All data extraction was also performed independently by the same two authors.

Patient and public involvement

There was no patient or public involvement in this study.

Results

Selected studies

A total of 1204 papers were identified in the initial search which was reduced to 947 after removal of duplicates. After screening by title and abstract 45 papers were initially considered. Full-text review of these papers revealed that 17 were relevant, that is describing new-onset post-cholecystectomy diarrhoea. The reference lists of the chosen articles were also screened, and a further 4 papers were found to fit the inclusion criteria. This is shown in Figure 1. Two articles had to be excluded as full text could not be obtained despite contacting the authors.

Characteristics of included studies

Most of the studies included were cohort, longitudinal, case-control or cross-sectional studies, of which 11 were prospective and 8 were retrospective. Two studies were randomised controlled trials, one of which was an RCT comparing laparoscopic cholecystectomy and cholecystectomy via minilaparotomy, however one of the reported outcomes was diarrhoea and therefore merited inclusion into this review. The other RCT was to investigate the effect of Rowachol on post-LC pain however the authors also assess symptom clusters including diarrhoea, once again meriting including into the study.

Quality assessment and risk of bias

The Newcastle-Ottawa assessment scale for cohort studies was selected for a risk of bias assessment and adapted to included observational studies. An adaptation of the tool is provided in *Supplementary Table 1*. Patients who underwent laparoscopic cholecystectomy were assessed via a combination of structured interviews and self-reporting. However, as shown in *Table 1,* patient follow-up in a number of studies was not adequate as several patients were not followed up for longer than 3 months. Consequently, this may introduce high levels of bias. Furthermore, lack of a control group in the majority of studies also predisposes to bias in the results. The full risk of bias assessment can be found in the supplementary information section. It was not

possible to check the heterogeneity of studies due to lack of data, as confidence intervals were not available.

Level of evidence

The level of evidence was assessed as per the Oxford criteria for Evidence Based medicine. As most of the studies were cohort studies, and a large number of them were retrospective in nature, the general level of evidence was low, classed at 3 or 4. More detail is shown in supplementary table 1.

Rate of PCD

A total of 3476 patients were included across all the studies with 462 (13.3%) patients developing post-cholecystectomy diarrhoea, though the rates in the studies vary between 2.1% and 57.2%. The greater majority of patients were assessed in the first three to six months postoperatively, though there is also a large amount of variation in the timing of PCD as patients were assessed between 6 weeks up to 4 years postoperatively. These are outlined in table 1 below. There was not enough data to be able to calculate median time to development of PCD post-cholecystectomy.

Predictive factors for PCD

Several potential risk factors for PCD were identified. Age less than 45 or 50 was mentioned in 2 studies, as was a high BMI. One study suggested that it was commoner in males while two others suggested it was commoner in females. A further two studies associated PCD development with preoperative heartburn or gastritis, while two others still related this to high fat intake. There is lack of consistency in the predictive factors identified in all studies, some studies found no potential predictive factors including sex, age and preoperative symptoms.

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Author	Year	Study type	PCD rate (%)	Investigative method	Predictive factors	Time post-op	Level of evidence
Ros and Zambon	1987	Prospective Cohort Study	8/93 (8.6)	Interview + own questionnaire	Not assessed	2 years	3
Wilson et al	1993	Retrospective case-controlled study	6/100 (6)	Own questionnaire	Not assessed	0-31 months	4
Heaton et al	1993	Retrospective cohort study	3/37 (9)	Questionnaire	Not assessed	3 months-26 years	4
McMahon et al	1995	Randomised controlled trial	62/233 (26.6)	Own Questionnaire; SF-36 and HADS	Not assessed	1 year	2
Fort et al	1996	Prospective Cohort Study	18/148 (12)	Own Questionnaire	Not assessed	4 years	3
Luman et al	1996	Prospective Cohort Study	2/97 (2.1)	Own Questionnaire	Not assessed	6 months	3
Gui et al	1998	Retrospective case control study	5/92 (5.4)	Questionnaire	Not assessed	12 months	4
Hearing et al	1999	Prospective cohort study	6/106 (5.7)	Telephone questionnaire +stool record form	Not assessed	2-6 months	3
Sauter et al	2002	Prospective cohort study	3/51 (5.9)	Interview	Not assessed	3 months	3
Topcu et al	2003	Retrospective case control study	8/200 (4)	SF36 and GIQLI	Not assessed	3-4 years	4
Finan et al	2006	Prospective cohort study	12/55 (21.8)	SF36	Not assessed	2-32 months	3
Fisher et al	2008	Prospective Cohort study	17/100 (17)	Telephone survey	High BMI, male, <50 years old	6-12 months	3
Mertens et al	2009	Prospective cohort study	17/129 (3.5)	Questionnaire	Preoperative flatulence and heartburn	6 weeks	3

Kim et al	2014	Prospective cohort study	13/65 (20)	SCL 90 R	Gastritis	3-6 months	3
Yueh et al	2014	Prospective longitudinal study	7/125 (5.7)	Questionnaire (internally validated)	High fat diet, age <45	3 months	3
Wanjura et al	2016	Retrospective cohort study	54/451 (12)	EQ-5D and GIQLI	Female, gallstone pain and pancreatitis/CBD stones	37-49 months	4
Talseth et al	2017	Retrospective cohort study	51/931 (5.47)	Questionnaire - HADS	women		3
Manriquez et al (SPANISH)	2017	Retrospective cohort study	8/100 (8)	Telephone survey		4-6 months	3
Del Grande	2017	Retrospective cross-sectional study	39/111 (35.1)	Own questionnaire	Prior gastrointestinal symptoms	N/A	3
Kim et al	2018	Randomised controlled trial	79/138 (57.2)	EORTC-QLQ C-30	None found	3 months	2-3
Jasim et al	2018	Prospective cohort study	44/114 (38.59%)	Bristol stool chart	Age <40; increased BMI, fatty meals	10 days, 3 months, 6 months	3

PCD: post-cholecystectomy diarrhoea; SF-36: Short form 36 ; HADS: hospital anxiety and depression score; GIQLI: Gastrointestinal quality of life; MPQ: McGill pain questionnaire

Discussion

Diarrhoea is one of the most reported postoperative symptoms after cholecystectomy, whether this is persistent or new postoperatively, though it varies significantly between studies (1). The first mention of this in the literature as a common postoperative sequela is due to Ros and Zambon (1987) who conducted a prospective cohort study to assess postcholecystectomy symptoms. The post-operative assessment took place two years after surgery and only 93 of the original 124 patients were available. Eight of these patients reported postoperative loose stools and watery diarrhoea (15). In subsequent studies, post-cholecystectomy patients were compared to patients having other surgeries such as inguinal hernia , laparoscopic sterilisation and hysterectomy, and bowel habit assessed and compared (5, 16, 17). In some cases a proportion of patients who developed diarrhoea resolved after a few weeks or months (18, 19).

The question of whether laparoscopic or open cholecystectomy affected the postoperative symptoms was explored. McMahon et al (1995) performed a multicentre randomised controlled trial to assess the symptomatic outcome between minilaparotomy and laparoscopic cholecystectomy. However, no difference between open or laparoscopic surgery was found(20). Topcu et al (2003) also evaluated gastrointestinal symptoms and quality of life after open and laparoscopic cholecystectomy using the SF36 and GIQLI questionnaires, and once again found no difference in the PCD rate(21).

Investigation of PCD

A variety of investigative tools including questionnaires (whether previously validated or designed by the researchers), telephone interviews, the Bristol stool chart and stool record forms, from six weeks up to four years postoperatively (17, 22-24) have been used to assess post cholecystectomy symptoms including diarrhoea. However, this wide range of investigative tools makes study comparison very difficult. In most cases validated questionnaires were used such as SF36, GIQLI and GSRS. However, in some studies these were administered retrospectively which limits their objectivity. Some of the questionnaires were also aimed towards general quality of life rather than specific to gastrointestinal symptoms. Other studies used non-validated questionnaires thus limiting their reproducibility. There is also a lot of dependence on patient recall especially in the retrospective studies, as well as differences in describing stool function and what is considered 'diarrhoea' if a standardised tool such as the Bristol stool chart is not used. The main issue with patient recall is the perception of change when change is not always present.

Pathophysiology of PCD and future work for understanding the mechanism

The concept of post-cholecystectomy diarrhoea and its relationship to bile acids was first mentioned in 1979, where a case series of three patients developing diarrhoea after cholecystectomy showed that two of them had elevated faecal bile acids and in all patients diarrhoea resolved with cholestyramine, thus implying bile-acid mediation of such diarrhoea (25). Arlow et al. (1987) posited a 'choleric enteropathy' theory when they investigated eight patients with post-cholecystectomy diarrhoea, of whom six had elevated faecal bile acids. They put forward the suggestion that this diarrhoea may be due to the increased production of dihydroxy bile acids and increased daily turnover of primary bile acids due to increase in the

enterohepatic cycles as well as continuous bile flux due to a lack of gallbladder(5). These patients also responded to cholestyramine therapy (26).

Fort et al were the first to investigate the prevalence and physiology of post-cholecystectomy diarrhoea(7). While cholecystectomy removes the storage area for the bile acid pool, studies have demonstrated that the major effect of this on the enterohepatic cycle is that there is more bacterial dehydroxylation due to bile acid spending more time in the gut between meals (27, 28). As an endogenous source of intestinal secretagogues, the theory that increased dehydroxylation of bile acids causes diarrhoea has been put forward, however it has been shown that the amount of secretion they cause is not enough to cause diarrhoea (29). This was shown by Fromm et al. who investigated 25 patients with post-cholecystectomy diarrhoea, though the group was heterogenous and characterised by patients with other conditions that could cause diarrhoea. In fact, in most of their group patients failed to respond to cholestyramine therapy (29).

Studies investigating bile acid metabolism after cholecystectomy have shown that there is an increase of secondary bile acids in the enterohepatic circulation. Post-cholecystectomy patients have a higher total bile acid faecal excretion than patients with a gallbladder. Deoxycholic acid (DCA), a secondary bile acid, concentrations is higher post-cholecystectomy (30). Deoxycholic acid induces net secretion of salt and water in the colon and thus this may be a factor in development of post-cholecystectomy diarrhoea, though this had been shown in studies using concentrations of DCA that are much higher than those found in the stool of normal patients (though not higher than DCA concentrations of patients with BAD). DCA was not found to increase basal rectal motility in a study by Edwards et al, though it was found to increase the sensitivity of the rectum by reducing the volume required to produce a desire to defecate, which may be another way in which DCA can effect postoperative diarrhoea (31).

Intestinal transit after cholecystectomy has been another aspect implicated in post-cholecystectomy diarrhoea. Orocaecal transit has been shown to increase after cholecystectomy (7, 32), as is colonic transit though this remains technically within normal limits (7). In some cases, though patients did not report diarrhoea after cholecystectomy, they did report an increase in bowel movements and fewer formed stools (33, 34). The investigators did not always define what they meant by diarrhoea in a standardised manner (such as number of episodes per day and the use of the Bristol stool chart) and some divided it into 'mild' and 'severe', again without defining what classifies patients into these divisions(19). Some papers talk about decrease in stool consistency and increase in bowel motions rather than diarrhoea (35).

Levels of C4, which is a marker of bile acid synthesis, tend to increase after cholecystectomy thus reflecting increased synthesis postoperatively (34, 36). FGF19 and C4 levels show significant daily changes and peak at noon, however, after cholecystectomy, this diurnal rhythm changes and FGF19 levels are significantly less at noon, declining at three months after surgery. FGF19 levels were shown to correlate to BA synthesis as measured by C4 levels prior to surgery, but this correlation was lost after cholecystectomy (36). Sauter et al, investigated bile acid malabsorption after cholecystectomy by measuring C4 levels and investigating changes in bowel habit and found that while most patients describe an increase in bowel motions after

cholecystectomy, however there was no correlation with C4 levels and the described changes in bowel habit, despite an overall increase in C4 levels after cholecystectomy (33).

Thus is can be seen that he mechanism behind the development of PCD is still not clearly defined despite several avenues being investigated

Predictive factors for PCD

Predictive factors identified for post-cholecystectomy diarrhoea varied widely across studies that assessed such factors. Fisher et al (2008) concluded that it was associated with being male, younger than 50 and having a high BMI, also confirmed by Yueh et al (2014) and Jasim et al (2018) (though in this case the age limit was less than 40 years old) while Del Grande et al (2017) associated this with prior gastrointestinal symptoms, though they did not define which ones(35, 37-39). Mertens et al (2009) clarified this further by stating that it was preoperative flatulence and heartburn which predicted postoperative symptoms including diarrhoea. Yueh et al (2014)also found that not following a low-fat diet could be associated with PCD (38). Talseth et al's (2017) study found that PCD was more common in patients having cholecystectomy for biliary colic, while Manriquez et al (2017) asserted that it was more common in patients having cholecystectomy for asymptomatic cholelithiasis (18, 40). On the other hand, Kim et al (2018) identified no predictive factors including age, BMI, sex, ASA score, pre-operative ERCP, comorbidities, difficult laparoscopic cholecystectomy, open conversion or pathology(41). Wanjura et al (2016) found that several factors were predictive of worse gastrointestinal symptoms after cholecystectomy, including female gender, CBD stones or pancreatitis and gallstone pain as an indication for surgery, however did not particularly relate this to diarrhoea (42). Kim et al (2014) also said that gastritis was a preoperative predictive factor for developing post cholecystectomy symptoms however once again did not specifically relate this to diarrhoea (19).

Definition and recommendations for consent and investigation

The difference in prevalence of diarrhoea across the studies could be attributed to factors such as study design, follow up length, questionnaire wording (as some studies used non-validated questionnaires), issues with patient recall and definitions of diarrhoea. Unfortunately, most of the studies in this review are not powered specifically to find the rate of post-cholecystectomy diarrhoea, but investigate post-cholecystectomy symptoms in general, and in fact most studies focused on dyspeptic symptoms and pain. Some studies were also excluded as they did not specify whether the diarrhoea reported was new onset after cholecystectomy.

From the above we can attempt to define PCD as 'the development of diarrhoea, more than three times a day for more than four weeks, post-cholecystectomy'. Investigations for PCD should include basic blood and stool tests, followed by endoscopic examination and ^{75}SeHCAT tests to investigate for inflammatory bowel disease and bile acid diarrhoea respectively (43).

The major strength of this review is that we considered the possible predictive factors for the development of post-cholecystectomy diarrhoea. It should also inform the consent process prior

to surgery, as currently patients are not always informed that this is a possibility, and may significantly affect their quality of life (44).

Implications for future research

Larger prospective studies are required to determine the exact rate of post-cholecystectomy diarrhoea and possible predictive factors. It would also be interesting to see how many patients are investigated for PCD using real time clinical data, to investigate how this issue is being handled outside of study protocols. A useful method of keeping better track of such patients is setting up a national registry which could be run by trainees. Further work is also required to determine the exact mechanism behind its development, potentially looking further into the role of FGF19 and C4 levels, and their relationship to bile acid synthesis after cholecystectomy.

Conclusion

Post-cholecystectomy diarrhoea is becoming an increasingly recognised issue with an overall prevalence of around 13.1%. However, no well-defined predictive factors can be elucidated. It is often not recognised as a problem as patients are not routinely followed up. It is also a significant burden on patients. The mechanism behind its development also need to be investigated further, though the role of bile acids in this is also becoming more defined. Patients need to be more informed about the possibility of this occurring as part of the consent process pre-operatively and in the postoperative period more support needs to be offered to patients in the investigation and diagnosis process.

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Figure legends

Figure 1: PRISMA Flowchart for study selection

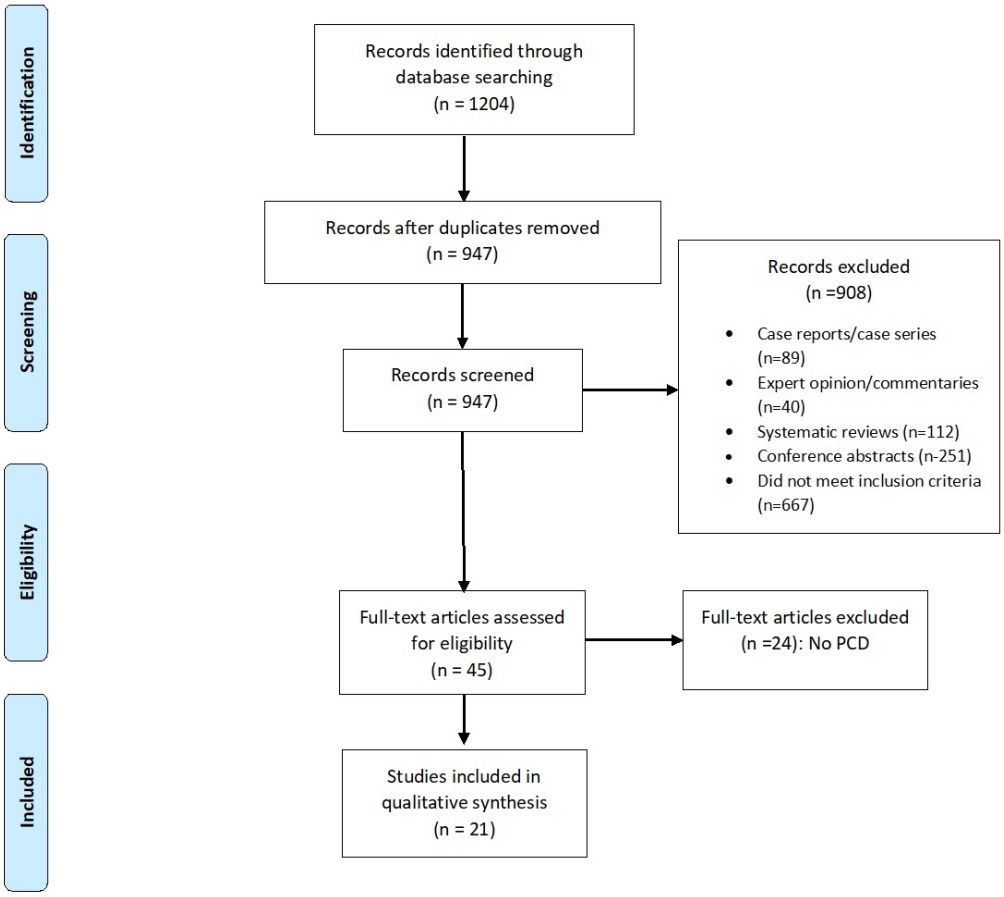

Figure 1: PRISMA Flowchart for study selection

Figure 1: PRISMA Flowchart for study selection

229x265mm (120 x 120 DPI)

	Representativeness of cohort	Selection of non-exposed cohort	Assessment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability	Assessment of outcome	Follow up long enough	Adequacy of follow up	Overall
Ros et al. 1987	Somewhat representative*	N/A	Structured interview*	Yes*	No controls applied	Record linkage*	Yes*	Subjects lost to follow up unlikely to introduce bias *	low
Heaton et al. 1993	Somewhat representative*	Same community*	Structured interview*	N/A	Study controls for laparoscopic cholecystectomy*	Self report	Yes*	Complete follow up *	low
Wilson et al. 1993	Somewhat representative*	Same community*	Structured interview*	Yes*	Study controls for laparoscopic cholecystectomy*	Record linkage* and self report	No for all patients	Not adequate for all patients	`high
Fort et al. 1996	Somewhat representative*	Same community*	Surgical record and Structured interview*	Yes*	Study controls for laparoscopic cholecystectomy*	Record linkage* and self report	Yes*	Complete follow up *	low
Luman et al. 1996	Truly representative*	N/A	Surgical record and structured interview*	Yes *	No controls applied	Record linkage* and self report	Yes*	Complete follow up*	low
Gui et al. 1998	Truly representative*	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage* and self report	Yes*	Complete follow up*	low
Hearing et al. 1999	Somewhat representative*	Same community*	Surgical record and structured interview*	Yes*	Study controls for laparoscopic cholecystectomy*	Record linkage* and self report	Yes*	Subjects lost to follow up unlikely to introduce bias *	low
Sauter et al. 2002	Truly representative*	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage and self report *	No	Complete follow up*	high
Finan et al. 2006	Truly representative*	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage* and self report	Not for all patients	Subjects lost to follow up unlikely to introduce bias *	high
Fisher et al. 2008	Truly representative*	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage* and self report	Yes*	Complete follow up*	low
Mertens et al. 2009	Truly representative*	N/A	Self report*	Yes *	No controls applied	Self report *	No	Subjects lost to follow up unlikely to introduce bias *	high
Kim et al. 2014	Somewhat representative*	N/A	Surgical record*	Yes*	No controls applied	Record linkage*	No for all patients	Complete follow up*	high
Yueh et al. 2014	Somewhat representative *	N/A	Surgical record and structured interview*	No	No controls applied	Record linkage* and self report	Yes*	Complete follow up*	high

Lamberts et al. 2015	Truly representative *	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage* and self report	No	Subjects lost to follow up could introduce bias	high
Wanjura et al. 2016	Truly representative*	Same community*	Surgical record and structured interview*	Yes*	Study controls for laparoscopic cholecystectomy*	Record linkage* and self report	Yes*	Complete follow up*	low
Del Grande et al. 2017	Somewhat representative *	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage* and self report	Yes*	Complete follow up*	low
Manriquez et al. 2017	Truly representative *	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage* and self report	Yes*	Complete follow up*	low
Talseth et al. 2017	Somewhat representative *	Same community*	Surgical record and structured interview*	Yes*	Study controls for laparoscopic cholecystectomy*	Record linkage* and self report	No	Subjects lost to follow up could introduce bias	high
Jasim et al. 2018	Somewhat representative *	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage* and self report	No	Complete follow up*	high

Supp. Table 1: Newcastle – Ottawa Quality assessment scale: Cohort studies

- * = low bias

Study	Randomisation	Allocation concealment	Blinding	Outcome data	Analysis	Follow up	Risk of bias
McMahon et al. 1995	Randomisation method not adequately described	Allocation concealment unknown	Blinding unknown	Outcome data reported	ITT analysis	Adequate follow	high
Kim et al. 2018	Randomization described	Allocation concealment unknown	Blinding unknown	Outcome data reported	Cluster analysis	Inadequate follow	moderate

Supp. Table 2: Cochrane handbook assessment scale for risk of bias: R

Protocol: Post-Cholecystectomy diarrhoea rate and predictive factors – a systematic review of the literature

Farrugia A, Attard JA, Williams N, Arasaradnam RP

Introduction

Cholecystectomy is one of the most common procedures performed worldwide and is the gold standard of treatment for symptomatic gallstone disease, which is present in up to 22% of adults (1). The laparoscopic approach to this surgery is now well-documented and accepted as a standard method of treatment, with low morbidity and mortality, and indeed this approach has increased the frequency with which cholecystectomy is performed (2, 3). Despite the use of cholecystectomy in treating gallstone-related disease such as cholecystitis or gallstone pancreatitis, at times there are persistent or even new symptoms postoperatively, including new onset diarrhoea (4). This may be distressing for patients and may affect their daily life considerably (5). This can be a minor annoyance, but in some cases people consider post cholecystectomy diarrhoea to be a social disability (6).

The actual rate of post-cholecystectomy diarrhoea is unknown as is the mechanism. There are two main theories regarding the mechanism, the first being changes in the orocaecal and colonic transit times secondary to increased enterohepatic circulation after the removal of the gallbladder (6). The second mechanism is less well-defined and involves the potential role of bile acids in causing diarrhoea (7). There is also a lack of knowledge surrounding any pre-operative predictive factors that may indicate the possibility that a patient may develop post cholecystectomy diarrhoea. This systematic review aims to assess the prevalence of post-cholecystectomy diarrhoea and discuss possible mechanisms behind its development, as well as any predictive factors.

Methods

A literature search will be performed on PUBMED, EMBASE and Ovid MEDLINE using the keywords 'post-cholecystectomy' 'postoperative' 'cholecystectomy' 'diarrhoea' and 'predictive factors'. The search will be performed in the manner outlined in table 1.

Search (DD/MM/YYYY)	Hits Pubmed	Hits EMBASE	Hits Ovid MEDLINE
1. Cholecystectomy			
2. Cholecystectomies			
3. 1 OR 2			
4. Diarrh*			
5. Bowel habit			
6. 4 OR 5			
7. Postoperative			
8. Post-operative			
9. Post-cholecystectomy			
10. Postcholecystectomy			
11. 7 OR 8 OR 9 OR 10			
12. Predict*			
13. 3 AND 6 AND 11			
14. 3 AND 6 AND 12			
15. 3 AND 6 AND 11 AND 12			

Table 1: Search strategy

Inclusion criteria

Studies included will be randomised trials, cohort studies or observational studies in which the postcholecystectomy diarrhoea rate can be elicited. Studies including predictive factors for postcholecystectomy diarrhoea will be included. There will be no language exclusions

Exclusion criteria

Conference abstracts, case series or case reports and expert opinion papers will be excluded from the study. Studies where we are not able to elicit post-cholecystectomy diarrhoea rate or distinguish between new-onset symptoms postoperatively or continuing symptoms will also be excluded.

Data extraction from each paper

- Number of patients
- Age
- Gender
- Type of study
- Indication for surgery
- Preoperative symptoms
- Postoperative symptoms
- Predictive factors
- Time to diagnosis

Also papers will be reviewed separately by two individuals and if there is any discrepancy will be reviewed by third individual who will act as final arbitor.

The PRISMA statement will be followed.

Results

A PRISMA low chart will be used to show the method of study selection. Results will be reported as characteristics of selected studies including whether the study is a randomised controlled trial, a cohort or observational study, and whether it is prospective or retrospective. The number of patients in each study and postcholecystectomy diarrhoea rate will be reported as well as the predictive factors.

A statistician will be consulted to assess heterogeneity and the relevance of predictive factors elicited on the prevalence of postcholecystectomy diarrhoea.

Primary Outcomes

- Predictive factors for diarrhoea after cholecystectomy

Secondary Outcomes

- Rate of bile acid diarrhoea after cholecystectomy
- Mean time to diagnosis

References

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Fig 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3,4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3,4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4, fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supp tables 1 and 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	5
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

BMJ Open

Post-Cholecystectomy diarrhoea rate and predictive factors – a systematic review of the literature

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	SURGERY, Adult gastroenterology < GASTROENTEROLOGY, Malabsorption < GASTROENTEROLOGY

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Post-Cholecystectomy diarrhoea rate and predictive factors – a systematic review of the literature

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Word count: 2989

Abstract

Objectives

Cholecystectomy is one of the most common surgical procedure performed worldwide to treat gallstone-related disease. Post-cholecystectomy diarrhoea is a well-reported phenomenon, however the actual rate, predictive factors and mechanism of action have not been well determined. A systematic review was undertaken to determine the rate and predictive factors associated with diarrhoea in the post-cholecystectomy setting.

Methods

The review was conducted according to the PRISMA protocol. Databases searched included Medline, Embase, Pubmed, Cochrane and Google Scholar up to 29th September 2020 The inclusion criteria consisted of cohort studies or randomised trials which investigated the rate of post-cholecystectomy diarrhoea and predictive factors. Case reports, case series, conference abstracts and expert opinion pieces were excluded as were other systematic reviews as all the original articles from those reviews were included in this review. Papers that did not include PCD as a separate entity were excluded. Bias assessment was performed using the Newcastle-Ottawa scale for cohort studies and the Cochrane risk of bias tool for randomised controlled trials as appropriate. Data was extracted by two authors (AF and JAA) and an overall rate of PCD was calculated. Predictive factors were also extracted and compared between studies.

Results

1204 papers were obtained and 21 were found to contain relevant information about post cholecystectomy diarrhoea, including the number of patients developing diarrhoea, method of symptom assessment, and time of onset post-cholecystectomy. A pooled total of 3476 patients were included across the identified studies with 462 (13.3%) patients developing PCD. Possible predictive factors varied across all studies, with characteristics such as gender, age and weight of patients postulated as being predictive of PCD, with no agreement across studies.

Discussion

PCD is therefore relatively common (13.3%). This has important implications for patient consent. Patients ought to be investigated early for bile acid diarrhoea in suspected PCD. More studies are required to determine the possible predictive factors for PCD. Limitations of the study included that most studies were not powered for calculation of PCD, and assessment methods between studies varied.

Other

This systematic review was registered on PROSPERO (CRD42019140444). This research received funding from Bowel Research UK.

Strengths and Limitations

- This review focused on post-cholecystectomy diarrhoea and all studies relating to post-cholecystectomy symptoms were extensively investigated to extract all possible data.
- Possible predictive factors for post-cholecystectomy diarrhoea were assessed which has not been extensively investigated.
- A wide variety of questionnaires was used to assess symptoms making it difficult to standardise postoperative symptoms between studies, and this relied heavily on patient recall thus opening up all the studies to recall bias.
- There was a generally low level of evidence as most studies were cohort studies.
- Patients were followed up for a variety of timeframes across the studies and thus it was difficult to standardise.

Keywords: cholecystectomy, diarrhoea, post-operative

Introduction

Cholecystectomy is the gold standard treatment for symptomatic gallstone disease, which occurs in up to 22% of adults (1). The laparoscopic approach to this surgery is now well-documented and accepted as standard practice, due to the significantly lower morbidity and mortality when compared with to open surgery (2). As a result, its adaptation into a laparoscopic procedure has increased the frequency with which cholecystectomy is performed (3, 4). Despite the notable benefits of cholecystectomy in treating gallstone-related disease, the postoperative course for a proportion of patients may be plagued by persistent or even new symptoms, including new-onset diarrhoea (5). This may be distressing for patients and have a significant impact on their quality of life (6). While it may be just a minor annoyance for some, others may well consider post-cholecystectomy diarrhoea to be a social disability (7, 8).

The actual incidence of post-cholecystectomy diarrhoea is unknown, though there is a wide range reported in the literature (2.1% to 57.2%)(9, 10). Furthermore, implicated mechanisms in the onset of this condition remain significantly under-investigated.

At present, there are two main theories regarding the mechanism. The first suggests changes in the oro-caecal and colonic transit times secondary to increased enterohepatic circulation brought on by removal of the gallbladder (7). The second mechanism is less well-defined and involves the potential role of bile acids in causing diarrhoea (11). This mechanism has been proposed in idiopathic bile acid diarrhoea, where there is interruption of a negative feedback loop which controls bile acid synthesis. The working theory is that removal of the gallbladder, thus removing a bile storage system, will lead to over synthesis of bile acids by interrupting the same negative feedback loop, thus causing diarrhoea by overloading the uptake mechanisms in

the terminal ileum (12). 63.5% of patients who develop diarrhoea after cholecystectomy develop bile acid diarrhoea (13).

The aim of this systematic review is to analyse published literature in order to assess the incidence of post-cholecystectomy.Potential pre-operative factors which may help to predict the development of post-cholecystectomy diarrhoea, will also be examined. Recommendations for future direction of research shall be made, if appropriate.

Methods

The review was registered on PROSPERO (CRD42019140444). A literature search was performed on PUBMED, EMBASE and MEDLINE, Cochrane, google scholar using the keywords 'post-cholecystectomy' 'postoperative' 'cholecystectomy' 'diarrhoea' and 'predictive factors'. There were no language limitations. The last search date was 29th September 2020. There were no restrictions to the year of publication. The search strategy is outlined in figure 1.

The inclusion criteria were cohort studies or randomised trials which investigated the rate of post-cholecystectomy diarrhoea and predictive factors for this condition. Case reports, case series, conference abstracts and expert opinion pieces were also excluded. Systematic reviews were also excluded as all the original articles from those reviews were included in this review. Studies pertaining to persistent symptoms after laparoscopic cholecystectomy, that is symptoms present pre-operatively, rather than new symptoms were also excluded.

Data was extracted from the studies independently and entered into an electronic database. The results were subsequently collated. Data extracted included: patient numbers, age, gender, type of study, indication for surgery, preoperative symptoms, postoperative symptoms, predictive factors. The primary endpoint was to identify the rate of post-cholecystectomy diarrhoea and the secondary endopoint was to identifypotential predictive factors.

The systematic review was written according to preferred reporting systems for systematic reviews (PRISMA) guidelines (14). Risk of bias assessment was performed using the Newcastle-Ottawa scale for cohort studies and the Cochrane risk of bias tool for randomised controlled trials as appropriate (15, 16). The papers were classified according to the Oxford OCEBM levels of evidence (17).

Two independent reviewers (AF and JAA) performed the literature search and reviewed papers for inclusion to ensure the criteria were met. Any differences were resolved by mutual consent. All data extraction was also performed independently by the same two authors.

Patient and public involvement

There was no patient or public involvement in this study.

Results

Selected studies

A total of 1204 papers were identified in the initial search which was reduced to 947 after removal of duplicates. After screening by title and abstract 45 papers were initially considered. Full-text review of these papers revealed that 17 were relevant, that is describing new-onset post-cholecystectomy diarrhoea. The reference lists of the chosen articles were also screened, and a further 4 papers were found to fit the inclusion criteria. This is shown in Figure 1. Two articles had to be excluded as full text could not be obtained despite contacting the authors.

Characteristics of included studies

Most of the studies included were cohort, longitudinal, case-control or cross-sectional studies, of which 11 were prospective and 8 were retrospective. Two studies were randomised controlled trials, one of which was an RCT comparing laparoscopic cholecystectomy and cholecystectomy via minilaparotomy, however one of the reported outcomes was diarrhoea and therefore merited inclusion into this review (18). The other RCT was to investigate the effect of Rowachol on post-LC pain however the authors also assess symptom clusters including diarrhoea, once again meriting including into the study (10). The studies and data obtained are shown in *Table 1*.

Quality assessment and risk of bias

The Newcastle-Ottawa assessment scale for cohort studies was selected for a risk of bias assessment and adapted to included observational studies. An adaptation of the tool is provided in *Supplementary Table 1*. Patients who underwent laparoscopic cholecystectomy were assessed via a combination of structured interviews and self-reporting. However, as shown in *Table 1,* patient follow-up in a number of studies was not adequate as several patients were not followed up for longer than 3 months. Consequently, this may introduce high levels of bias. Furthermore, lack of a control group in the majority of studies also predisposes to bias in the results. The full risk of bias assessment can be found in the supplementary information section. It was not possible to check the heterogeneity of studies due to lack of data, as confidence intervals were not available.

Level of evidence

The level of evidence was assessed as per the Oxford criteria for Evidence Based medicine. As most of the studies were cohort studies, and a large number of them were retrospective in nature, the general level of evidence was low, classed at 3 or 4. More detail is shown in supplementary tables 1 and 2.

Demographics

Demographic data was not routinely available in all studies. However, from those that reported it there were 2250 women and 787 men. Five of the included studies did not provide this information. The age range of patients across the studies was 18 to 85. 1855 cholecystectomies were performed laparoscopically and 378 were open, though once again there were 5 studies were this information was not provided.

Rate of PCD

A total of 3476 patients were included across all the studies with 462 (13.3%) patients developing post-cholecystectomy diarrhoea, though the rates in the studies vary between 2.1% and 57.2%. The greater majority of patients were assessed in the first three to six months postoperatively, though there is also a large amount of variation in the timing of PCD as patients were assessed between 6 weeks up to 4 years postoperatively. These are outlined in table 1

below. There was not enough data to be able to calculate median time to development of PCD post-cholecystectomy.

Predictive factors for PCD

Several potential risk factors for PCD were identified. Age less than 45 or 50 was mentioned in 2 studies, as was a high BMI. One study suggested that it was commoner in males while two others suggested it was commoner in females. A further two studies associated PCD development with preoperative heartburn or gastritis, while two others still related this to high fat intake. There is lack of consistency in the predictive factors identified in all studies, some studies found no potential predictive factors including sex, age and preoperative symptoms.

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Author	Year	Study type	PCD rate (%)	Investigative method	Predictive factors	Time post-op	Level of evidence
Ros and Zambon	1987	Prospective Cohort Study	8/93 (8.6)	Interview + own questionnaire	Not assessed	2 years	3
Wilson et al	1993	Retrospective case-controlled study	6/100 (6)	Own questionnaire	Not assessed	0-31 months	4
Heaton et al	1993	Retrospective cohort study	3/37 (9)	Questionnaire	Not assessed	3 months-26 years	4
McMahon et al	1995	Randomised controlled trial	62/233 (26.6)	Own Questionnaire; SF-36 and HADS	Not assessed	1 year	2
Fort et al	1996	Prospective Cohort Study	18/148 (12)	Own Questionnaire	Not assessed	4 years	3
Luman et al	1996	Prospective Cohort Study	2/97 (2.1)	Own Questionnaire	Not assessed	6 months	3
Gui et al	1998	Retrospective case control study	5/92 (5.4)	Questionnaire	Not assessed	12 months	4
Hearing et al	1999	Prospective cohort study	6/106 (5.7)	Telephone questionnaire +stool record form	Not assessed	2-6 months	3
Sauter et al	2002	Prospective cohort study	3/51 (5.9)	Interview	Not assessed	3 months	3
Topcu et al	2003	Retrospective case control study	8/200 (4)	SF36 and GIQLI	Not assessed	3-4 years	4
Finan et al	2006	Prospective cohort study	12/55 (21.8)	SF36	Not assessed	2-32 months	3
Fisher et al	2008	Prospective Cohort study	17/100 (17)	Telephone survey	High BMI, male, <50 years old	6-12 months	3
Mertens et al	2009	Prospective cohort study	17/129 (3.5)	Questionnaire	Preoperative flatulence and heartburn	6 weeks	3

Kim et al	2014	Prospective cohort study	13/65 (20)	SCL 90 R	Gastritis	3-6 months	3
Yueh et al	2014	Prospective longitudinal study	7/125 (5.7)	Questionnaire (internally validated)	High fat diet, age <45	3 months	3
Wanjura et al	2016	Retrospective cohort study	54/451 (12)	EQ-5D and GIQLI	Female, gallstone pain and pancreatitis/CBD stones	37-49 months	4
Talseth et al	2017	Retrospective cohort study	51/931 (5.47)	Questionnaire - HADS	women		3
Manriquez et al	2017	Retrospective cohort study	8/100 (8)	Telephone survey		4-6 months	3
Del Grande	2017	Retrospective cross-sectional study	39/111 (35.1)	Own questionnaire	Prior gastrointestinal symptoms	N/A	3
Kim et al	2018	Randomised controlled trial	79/138 (57.2)	EORTC-QLQ C-30	None found	3 months	2-3
Jasim et al	2018	Prospective cohort study	44/114 (38.59%)	Bristol stool chart	Age <40; increased BMI, fatty meals	10 days, 3 months, 6 months	3

Table1: Included studies. PCD: post-cholecystectomy diarrhoea; SF-36: Short form 36 ; HADS: hospital anxiety and depression score; GIQLI: Gastrointestinal quality of life; MPQ: McGill pain questionnaire

Discussion

Diarrhoea is one of the most reported postoperative symptoms after cholecystectomy, whether this is persistent or new postoperatively, though it varies significantly between studies (1). The first mention of this in the literature as a common postoperative sequela is due to Ros and Zambon (1987) who conducted a prospective cohort study to assess postcholecystectomy symptoms. The post-operative assessment took place two years after surgery and only 93 of the original 124 patients were available. Eight of these patients reported postoperative loose stools and watery diarrhoea (19). In subsequent studies, post-cholecystectomy patients were compared to patients having other surgeries such as inguinal hernia , laparoscopic sterilisation and hysterectomy, and bowel habit assessed and compared (5, 20, 21). In some cases a proportion of patients who developed diarrhoea resolved after a few weeks or months (22, 23).

The question of whether laparoscopic or open cholecystectomy affected the postoperative symptoms was explored. McMahon et al (1995) performed a multicentre randomised controlled trial to assess the symptomatic outcome between minilaparotomy and laparoscopic cholecystectomy. However, no difference between open or laparoscopic surgery was found(18). Topcu et al (2003) also evaluated gastrointestinal symptoms and quality of life after open and laparoscopic cholecystectomy using the SF36 and GIQLI questionnaires, and once again found no difference in the PCD rate(24).

Investigation of PCD

A variety of investigative tools including questionnaires (whether previously validated or designed by the researchers), telephone interviews, the Bristol stool chart and stool record forms, from six weeks up to four years postoperatively (9, 21, 25, 26) have been used to assess post cholecystectomy symptoms including diarrhoea. However, this wide range of investigative tools makes study comparison very difficult. In most cases validated questionnaires were used such as SF36, GIQLI and GSRS. However, in some studies these were administered retrospectively which limits their objectivity. Some of the questionnaires were also aimed towards general quality of life rather than specific to gastrointestinal symptoms. Other studies used non-validated questionnaires thus limiting their reproducibility. There is also a lot of dependence on patient recall especially in the retrospective studies, as well as differences in describing stool function and what is considered 'diarrhoea' if a standardised tool such as the Bristol stool chart is not used. The main issue with patient recall is the perception of change when change is not always present.

Pathophysiology of PCD and future work for understanding the mechanism

The concept of post-cholecystectomy diarrhoea and its relationship to bile acids was first mentioned in 1979, where a case series of three patients developing diarrhoea after cholecystectomy showed that two of them had elevated faecal bile acids and in all patients diarrhoea resolved with cholestyramine, thus implying bile-acid mediation of such diarrhoea (27). Arlow et al. (1987) posited a 'choleric enteropathy' theory when they investigated eight patients with post-cholecystectomy diarrhoea, of whom six had elevated faecal bile acids. They put forward the suggestion that this diarrhoea may be due to the increased production of dihydroxy bile acids and increased daily turnover of primary bile acids due to increase in the

enterohepatic cycles as well as continuous bile flux due to a lack of gallbladder(5). These patients also responded to cholestyramine therapy (28). Fort et also investigated the prevalence and physiology of post-cholecystectomy diarrhoea(7). There is increased bacterial dehydroxylation due to bile acid spending more time in the gut between meals after cholecystectomy (29, 30) andthe theory that this causes diarrhoea has been put forward, however it has been shown that the amount of secretion they cause is not enough to cause diarrhoea by Fromm et al (31).

Intestinal transit after cholecystectomy has been another aspect implicated in post-cholecystectomy diarrhoea. Orocaecal transit has been shown to increase after cholecystectomy (7, 32), as is colonic transit though this remains technically within normal limits (7). In some cases, though patients did not report diarrhoea after cholecystectomy, they did report an increase in bowel movements and fewer formed stools (33, 34). The investigators did not always define what they meant by diarrhoea in a standardised manner (such as number of episodes per day and the use of the Bristol stool chart) and some divided it into 'mild' and 'severe', again without defining what classifies patients into these divisions(23). Some papers talk about decrease in stool consistency and increase in bowel motions rather than diarrhoea (35). This may tie in with increased DCA concentrations after cholecystectomy, however it was not found to increase basal rectal motility in a study by Edwards et al, though it was found to increase the sensitivity of the rectum by reducing the volume required to produce a desire to defecate, which may be another way in which DCA can effect postoperative diarrhoea (36).

Levels of C4, which is a marker of bile acid synthesis, tend to increase after cholecystectomy thus reflecting increased synthesis postoperatively (34, 37). FGF19 and C4 levels show significant daily changes and peak at noon, however, after cholecystectomy, this diurnal rhythm changes and FGF19 levels are significantly less at noon, declining at three months after surgery. FGF19 levels were shown to correlate to BA synthesis as measured by C4 levels prior to surgery, but this correlation was lost after cholecystectomy (37). Sauter et al, investigated bile acid malabsorption after cholecystectomy by measuring C4 levels and investigating changes in bowel habit and found that while most patients describe an increase in bowel motions after cholecystectomy, however there was no correlation with C4 levels and the described changes in bowel habit, despite an overall increase in C4 levels after cholecystectomy (33).

Thus, it can be seen that he mechanism behind the development of PCD is still not clearly defined despite several avenues being investigated

Predictive factors for PCD

Predictive factors identified for post-cholecystectomy diarrhoea varied widely across studies that assessed such factors. Fisher et al (2008) concluded that it was associated with being male, younger than 50 and having a high BMI, also confirmed by Yueh et al (2014) and Jasim et al (2018) (though in this case the age limit was less than 40 years old) while Del Grande et al

(2017) associated this with prior gastrointestinal symptoms, though they did not define which ones(35, 38-40). Mertens et al (2009) clarified this further by stating that it was preoperative flatulence and heartburn which predicted postoperative symptoms including diarrhoea. Yueh et al (2014)also found that not following a low-fat diet could be associated with PCD (39). Talseth et al's (2017) study found that PCD was more common in patients having cholecystectomy for biliary colic, while Manriquez et al (2017) asserted that it was more common in patients having cholecystectomy for asymptomatic cholelithiasis (22, 41). On the other hand, Kim et al (2018) identified no predictive factors including age, BMI, sex, ASA score, pre-operative ERCP, comorbidities, difficult laparoscopic cholecystectomy, open conversion or pathology(10). Wanjura et al (2016) found that several factors were predictive of worse gastrointestinal symptoms after cholecystectomy, including female gender, CBD stones or pancreatitis and gallstone pain as an indication for surgery, however did not particularly relate this to diarrhoea (42). Kim et al (2014) also said that gastritis was a preoperative predictive factor for developing post cholecystectomy symptoms however once again did not specifically relate this to diarrhoea (23).

Definition and recommendations for consent and investigation

The difference in prevalence of diarrhoea across the studies could be attributed to factors such as study design, follow up length, questionnaire wording (as some studies used non-validated questionnaires), issues with patient recall and definitions of diarrhoea. Unfortunately, most of the studies in this review are not powered specifically to find the rate of post-cholecystectomy diarrhoea, but investigate post-cholecystectomy symptoms in general, and in fact most studies focused on dyspeptic symptoms and pain. Some studies were also excluded as they did not specify whether the diarrhoea reported was new onset after cholecystectomy.

There has been no standardised definition of PCD and indeed most of the studies do not specify how they defined 'diarrhoea' in the postoperative period. We feel that a standard definition would be helpful in the investigation of PCD. From the above we can attempt to define PCD as 'the development of diarrhoea, more than three times a day for more than four weeks, post-cholecystectomy'. Investigations for PCD should include basic blood and stool tests, followed by endoscopic examination and ^{75}SeHCAT tests to investigate for inflammatory bowel disease and bile acid diarrhoea respectively (43).

Possible therapies for PCD

If it is indeed bile acid diarrhoea, a bile acid sequestrant such as colestyramine could help symptoms (13). However, in other patients once other causes have been excluded including inflammatory bowel disease, other symptomatic treamtents are required such as loperamide or dietary modifications (44).

Strengths and limitations

The major strength of this review is that we considered the possible predictive factors for the development of post-cholecystectomy diarrhoea. We also looked at all studies involving post-cholecystectomy symptoms and if data could be extracted regarding PCD this was also done,

thus adding more numbers to the study and providing a more accurate picture of the actual PCD rate. It should also inform the consent process prior to surgery, as currently patients are not always informed that this is a possibility, and may significantly affect their quality of life (45).

However, there were some methodological limitations. There was no standardisation between studies in terms of follow up times, as well as questionnaire use. Some authors also used non-validated questionnaires thus making reproducibility difficult. Questionnaires are heavily based on patient recall and there is therefore an element of recall bias in all these studies. Almost all the studies were cohort studies, thus the lack of control group contributed to a low general level of evidence. These limitations could be the reason behind the wide variation of PCD rates across the studies.

Implications for future research

Larger prospective studies are required to determine the exact rate of post-cholecystectomy diarrhoea and possible predictive factors. It would also be interesting to see how many patients are investigated for PCD using real time clinical data, to investigate how this issue is being handled outside of study protocols. A useful method of keeping better track of such patients is setting up a national registry which could be run by trainees. Another potential method of investigating this would be to set up a large, prospective, national study of patients having cholecystectomy for various reasons, including cholelithiasis, polyps and cancer, and investigate possible predictive factors such as BMI, smoking, sex, age, and co-morbidities. The quality of life (QOL) pre- and post-operatively could also be assessed, especially the difference in QOL between those who develop PCD and those who do not. Further work is also required to determine the exact mechanism behind its development, potentially looking further into the role of FGF19 and C4 levels, and their relationship to bile acid synthesis after cholecystectomy.

Conclusion

Post-cholecystectomy diarrhoea is becoming an increasingly recognised issue with an overall incidenceof around 13.1%. However, no well-defined predictive factors can be elucidated. It is often not recognised as a problem as patients are not routinely followed up. It is also a significant burden on patients. The mechanism behind its development also need to be investigated further, though the role of bile acids in this is also becoming more defined. Patients need to be more informed about the possibility of this occurring as part of the consent process pre-operatively and in the postoperative period more support needs to be offered to patients in the investigation and diagnosis process.

Ethics Statement

Ethical approval was not applicable for this study.

Contributorship statement

AF and JA performed the literature search and wrote the manuscript

SK NW and RA supervised the writing, helped with analysis and led the research project

Competing interests

There are no competing interests to declare for any author

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Data Sharing

No additional data available.

Data availability

All data relevant to the study are included in the article or uploaded as supplementary information.

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Figure legends

Figure 1: PRISMA Flowchart for study selection

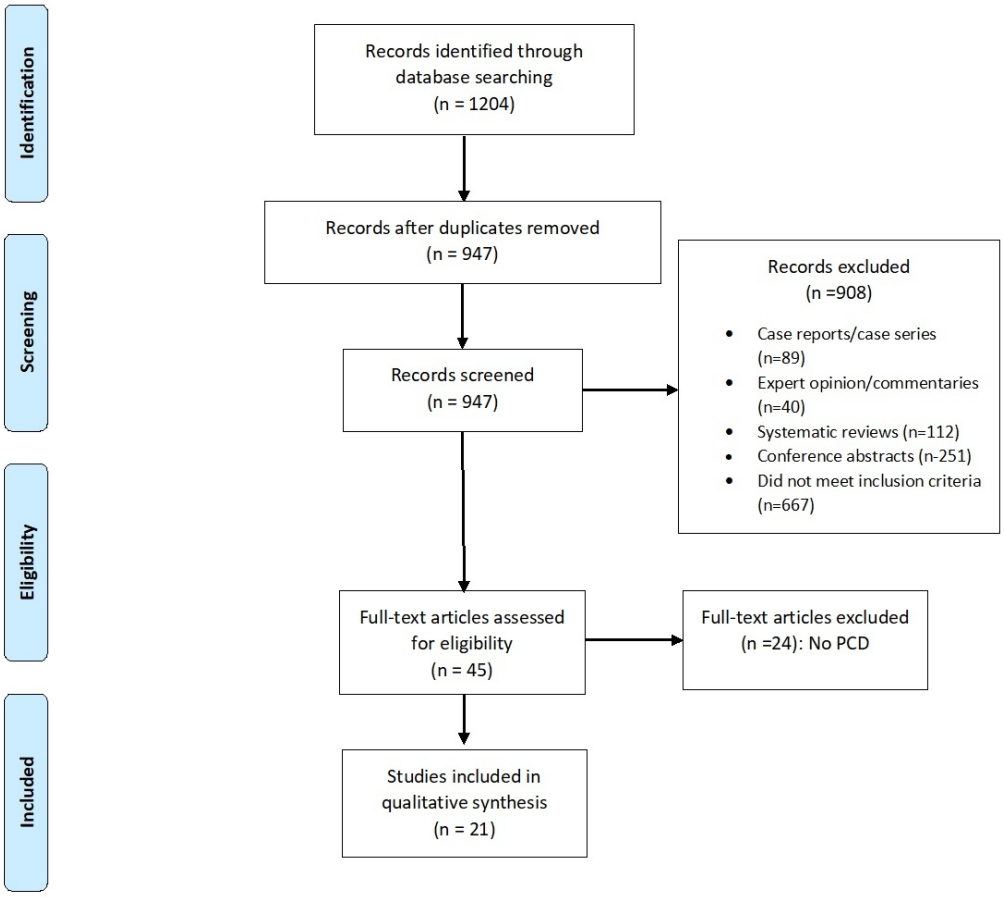

Figure 1: PRISMA Flowchart for study selection

Figure 1: PRISMA Flowchart for study selection

229x265mm (120 x 120 DPI)

	Representativeness of cohort	Selection of non-exposed cohort	Assessment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability	Assessment of outcome	Follow up long enough	Adequacy of follow up	Overall
Ros et al. 1987	Somewhat representative*	N/A	Structured interview*	Yes*	No controls applied	Record linkage*	Yes*	Subjects lost to follow up unlikely to introduce bias *	low
Heaton et al. 1993	Somewhat representative*	Same community*	Structured interview*	N/A	Study controls for laparoscopic cholecystectomy*	Self report	Yes*	Complete follow up *	low
Wilson et al. 1993	Somewhat representative*	Same community*	Structured interview*	Yes*	Study controls for laparoscopic cholecystectomy*	Record linkage* and self report	No for all patients	Not adequate for all patients	`high
Fort et al. 1996	Somewhat representative*	Same community*	Surgical record and Structured interview*	Yes*	Study controls for laparoscopic cholecystectomy*	Record linkage* and self report	Yes*	Complete follow up *	low
Luman et al. 1996	Truly representative*	N/A	Surgical record and structured interview*	Yes *	No controls applied	Record linkage* and self report	Yes*	Complete follow up*	low
Gui et al. 1998	Truly representative*	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage* and self report	Yes*	Complete follow up*	low
Hearing et al. 1999	Somewhat representative*	Same community*	Surgical record and structured interview*	Yes*	Study controls for laparoscopic cholecystectomy*	Record linkage* and self report	Yes*	Subjects lost to follow up unlikely to introduce bias *	low
Sauter et al. 2002	Truly representative*	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage and self report *	No	Complete follow up*	high
Finan et al. 2006	Truly representative*	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage* and self report	No for all patients	Subjects lost to follow up unlikely to introduce bias *	high
Fisher et al. 2008	Truly representative*	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage* and self report	Yes*	Complete follow up*	low
Mertens et al. 2009	Truly representative*	N/A	Self report*	Yes *	No controls applied	Self report *	No	Subjects lost to follow up unlikely to introduce bias *	high
Kim et al. 2014	Somewhat representative*	N/A	Surgical record*	Yes*	No controls applied	Record linkage*	No for all patients	Complete follow up*	high
Yueh et al. 2014	Somewhat representative *	N/A	Surgical record and structured interview*	No	No controls applied	Record linkage* and self report	Yes*	Complete follow up*	high

Lamberts et al. 2015	Truly representative *	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage* and self report	No	Subjects lost to follow up could introduce bias	high
Wanjura et al. 2016	Truly representative*	Same community*	Surgical record and structured interview*	Yes*	Study controls for laparoscopic cholecystectomy*	Record linkage* and self report	Yes*	Complete follow up*	low
Del Grande et al. 2017	Somewhat representative *	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage* and self report	Yes*	Complete follow up*	low
Manriquez et al. 2017	Truly representative *	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage* and self report	Yes*	Complete follow up*	low
Talseth et al. 2017	Somewhat representative *	Same community*	Surgical record and structured interview*	Yes*	Study controls for laparoscopic cholecystectomy*	Record linkage* and self report	No	Subjects lost to follow up could introduce bias	high
Jasim et al. 2018	Somewhat representative *	N/A	Surgical record and structured interview*	Yes*	No controls applied	Record linkage* and self report	No	Complete follow up*	high

Supp. Table 1: Newcastle – Ottawa Quality assessment scale: Cohort studies

- * = low bias

Study	Randomisation	Allocation concealment	Blinding	Outcome data	Analysis	Follow up	Risk of bias
McMahon et al. 1995	Randomisation method not adequately described	Allocation concealment unknown	Blinding unknown	Outcome data reported	ITT analysis	Adequate follow	high
Kim et al. 2018	Randomization described	Allocation concealment unknown	Blinding unknown	Outcome data reported	Cluster analysis	Inadequate follow	moderate

Supp. Table 2: Cochrane handbook assessment scale for risk of bias: R

PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Fig 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3,4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3,4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4, fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supp tables 1 and 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	5
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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