

Review Article

Understanding diarrhea in cholecystectomy patients: bibliographical review article*Compreensão da diarreia em pacientes colecistectomizados: artigo de revisão bibliográfica***Débora Gomes Junqueira Vilela¹, Andressa Morgenstern Santos², Thais Cristine Souza Silva³, Raimundo Celio Pedreira⁴, Vanessa Regina Maciel Uzan de Moraes⁵**

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ABSTRACT: Introduction: The present work covers the area of gastroenterology, the main condition being gallstones. One of the treatments used for this disease is cholecystectomy, which may have diarrhea as one of the symptoms in the postoperative period. This complication is the subject of investigation by health professionals and a reason for patients' doubts about its epidemiology, pathophysiology, associated clinical manifestations, diagnosis and treatment. Objectives: This study aims to systematically review the literature on aspects of post-cholecystectomy diarrhea and clarify doubts about the subject, contributing to the academic and medical society, in order to improve the quality of life of patients with this clinical manifestation. Methods: This is a literature review, in which the following databases were used: PubMed, SciELO and Google Scholar. Therefore, 124 articles were collected, of which 24 were selected according to the eligibility criteria. Conclusion: The present review allowed us to understand the pathophysiological mechanism, epidemiology, associated clinical manifestations, diagnosis and treatment of diarrhea in post-cholecystectomy patients. In the present study, we made this issue evident, which requires further study, as there are still many controversies about it, in addition to the prevalence of the symptom in post-cholecystectomy patients.

Keywords: Surgery; Cholelithiasis; Diarrhea.

RESUMO: Introdução: O presente trabalho contempla a área da gastroenterologia, sendo a principal afecção a litíase biliar. Um dos tratamentos utilizados para essa doença é a colecistectomia, a qual pode ter a diarreia como um dos sintomas no pós-operatório. Esta complicação é alvo de investigação dos profissionais da saúde e motivo de dúvidas dos pacientes acerca de sua epidemiologia, fisiopatologia, manifestações clínicas associadas, diagnóstico e de seu tratamento. Objetivos: Este estudo tem como objetivo rever sistematicamente a literatura acerca dos aspectos da diarreia pós-colecistectomia e esclarecer as dúvidas sobre o assunto, contribuindo com a sociedade acadêmica e médica, afim de melhorar a qualidade de vida dos pacientes com essa manifestação clínica. Métodos: Trata-se de uma revisão bibliográfica, em que foram utilizadas as bases de dados: PubMed, SciELO e Google Acadêmico. Para tanto, foram levantados 124 artigos, dos quais 24 foram selecionados de acordo com os critérios de elegibilidade. Conclusão: A presente revisão permitiu compreender como sucede o mecanismo fisiopatológico, a epidemiologia, manifestações clínicas associadas, o diagnóstico e o tratamento da diarreia nos pacientes pós-colecistectomia. No presente trabalho tornamos evidente esse assunto que requer mais estudo, pois ainda há muitas controversas acerca dele, além da prevalência do sintoma em pacientes pós-colecistectomia.

Palavras-chaves: Cirurgia; Colelitíase; Diarreia.

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INTRODUCTION

This work covers the area of gastroenterology, which is the specialty of medicine that studies and understands the diseases related to the digestive system. One of the main diseases of the gastrointestinal tract is cholelithiasis or also called gallbladder lithiasis, which corresponds to an imbalance in the amount of substances in the bile, such as: bile salts, water, cholesterol, bilirubin, and lectin. When there is an insufficient production of bile salts and lectin, or an excess production of cholesterol, there is a predisposition to gallstones. This is because lectin and bile salts make cholesterol a soluble substance, so when they are in short supply in the body the cholesterol remains insoluble, and can crystallize and form gallstones¹.

According to Zaterka and Eisig², gallstone cholecystopathy is an old disease that became known in the 6th century, and in the year 1882, the first gallbladder removal surgery was performed, which is now recognized as cholecystectomy. This surgery is considered the standard treatment for the resolution of cholelithiasis³, and one of the most used techniques is the laparoscopic cholecystectomy, which is considered preferable due to the several advantages for the patient: low risk of infection, low postoperative pain and morbidity, and less trauma to the abdominal wall⁴.

This surgical procedure is more frequent in patients between 18 and 44 years of age⁵. As patients who undergo this type of surgical procedure, the bile salts that used to be deposited in the gallbladder now flow in larger quantities and continuously into the intestine and consequently reach the colon, causing absorption, water secretion, and electrolyte disturbances⁶.

In addition, gastrointestinal symptoms such as bloating, flatulence, dyspepsia, and diarrhea may appear, the latter being the one that most affects the quality of life of postcholecystectomy patients. According to Farrugia and Arasaradnam⁷, the causes of diarrhea are classified into two types. The primary refers to idiopathic etiologies and the secondary is correlated to cholecystectomy. Postcholecystectomy diarrhea is characterized as increased frequency of bowel movements, which begins a few days after surgery⁸.

It was also observed the presence of several mechanisms that cause postcholecystectomy diarrhea, such as increased synthesis of bile acid, interruption of the negative feedback of its production and interference of the intestinal microbiota in the process of transformation of primary acids into secondary acids⁷. However, there are also several contradictions related to the low lipid diet recommended by some physicians. According to Yueh et al.⁹, there is a tendency of patients undergoing cholecystectomy to have low tolerance to foods rich in fat, thus patients who do not follow the recommendation of a low-fat diet are more likely to develop diarrhea.

OBJECTIVES

The objective of the present study was to systematically review the literature about the aspects of biliary diarrhea after cholecystectomy, in order to explain the epidemiology, pathophysiology, associated clinical manifestations, diagnosis, and treatment. This study is relevant because 30%-40% of patients after cholecystectomy develop some kind of symptom⁴, and 0.9%-35.6% of the manifestations are bile acid diarrhea⁹.

In summary, it is inferred that the study of diarrhea in postcholecystectomy patients is of great social and medical importance, because from a better understanding of the aspects of the subject it is possible to have several improvements for the quality of life of patients undergoing the surgical procedure.

MATERIAL AND METHODS

The present study was designed with the objective of performing a systematic review of the literature on aspects of diarrhea in postcholecystectomy patients. To this end, a bibliographic survey was carried out in the PubMed, SciELO, and Google Academic databases, as well as important books within the academic literature.

The variables of the research were epidemiology, pathophysiology of postcholecystectomy diarrhea, associated clinical manifestations, diagnosis and treatment of patients who underwent the surgical procedure and presented diarrhea as a symptom.

The search covers the area of gastroenterology, focusing on scientific collections that dealt with the theme: aspects of diarrhea in postcholecystectomy patients. 124 articles were found in the databases, and 24 articles were selected because they met the inclusion and exclusion criteria. In addition, 5 books that approached the theme were used.

The inclusion criteria used in the selection of articles were articles published between 2010 and 2021, in Portuguese, English or Spanish, which included the descriptors: Surgery; Colelithiasis; Diarrhea. As exclusion criteria, articles that were not related to the definition, pathophysiology, diagnosis, and treatment of cholelithiasis and biliary diarrhea were discarded.

RESULTS

After evaluation and selection of the articles that met the eligibility criteria (Flowchart 1), we constructed table 1 with the objective of contributing to the explanation of the results and discussion of the study. The table below (Table 1) was ordered according to the citation during the study and presents the year of publication, first author's name, abstract, and category.



Flowchart 1. Evaluation and selection of articles, according to eligibility criteria.

Table 1. Distribution of researched works according to the citation of articles during the work, presenting the year of publication, the name of the first author, abstract and category.

Author/Year	Abstract	Category
Castro 2021	It reports on the decrease in pain in the postoperative period of laparoscopic cholecystectomy when compared to the minilaparotomy technique. In the analysis of the text, the process is also considered the standard for the solution of cholelithiasis.	Laparoscopic versus minilaparotomy cholecystectomy in cholelithiasis: a systematic review and meta-analysis
Del Grande 2017	Discusses the advantages of laparoscopic surgery and the most common gastrointestinal symptoms after the surgical procedure. It presents a research that compares the consistency of stools in the pre and postoperative period of cholecystectomy, as well as analyzes possible variables for changing bowel habits, in addition to the surgical procedure.	Prevalence and predictors of changes in bowel habits after laparoscopic cholecystectomy.
Fingar 2015	It reports on the recurrence of procedures in young patients and young adults, exposing the most common age group.	Most frequent operating room procedures performed in US hospitals
León-Barúa 2013	Cholecystectomy is a determining factor for chronic diarrhea, this factor is little known by doctors and easily treated.	Chronic diarrhea after cholecystectomy.
Farrugia 2021	The article presents all the possible pathophysiological processes involved with post-cholecystectomy diarrhea, as well as the most effective diagnostic methods for its identification. It supports the theses related to the intestinal microbiota and the negative feedback of bile acids.	Bile acid diarrhoea: pathophysiology, diagnosis and management.
Manríquez 2017	The article also reports on post-cholecystectomy diarrhea being little known by doctors and presents important data related to the country of origin (Chile), where the prevalence of diarrhea after gallbladder surgery is 0.9% to 35.6%.	Post-cholecystectomy diarrhea: a frequent problem?
Yueh 2014	Article comprises the explanation of the pathological process concerning the formation of gallstones. Furthermore, it reports that the origin of post-cholecystectomy diarrhea is controversial and multifactorial and discusses the mechanisms that cause diarrhea.	Diarrhea after laparoscopic cholecystectomy: associated factors and predictors.
Pinto 2015	Laparoscopic cholecystectomy was described by Mouret, Dubois and Perissat, and has several advantages such as: smaller incision and reduced probability of complications, such as infection, bleeding, keloids and hematomas.	Videolaparoscopic cholecystectomy through single access: technique without the need for special materials and better ergonomics.
Andrade 2020	The research analyzes the determining factors for the hospital prevalence of patients who are candidates for videolaparoscopic cholecystectomy.	Identification of predictive factors of increased intra and postoperative hospital stay in candidates for laparoscopic cholecystectomy.
Sáltiel 2011	Cholecystectomy is the removal of the gallbladder, for resolution, there are two surgical techniques: open technique and videolaparoscopic. The article aims to evaluate the clinical profile of patients and, in addition, reports on the two techniques.	Profile of patients undergoing cholecystectomy at Hospital Regional de São José Dr. Homer by Miranda Gomes in the greater Florianópolis-SC.

Table 1. Distribution of researched works according to the citation of articles during the work, presenting the year of publication, the name of the first author, abstract and category. *Continuation*

Author/Year	Abstract	Category
Irigonhê 2020	The prevalent comorbidities are SAH, obesity and diabetes mellitus. Laparoscopic surgery demonstrates a low risk when performed under safe conditions	Analysis of the epidemiological clinical profile of patients undergoing laparoscopic cholecystectomy in a teaching hospital in Curitiba.
Villaba 2016	Chronic diarrhea is one of the most common symptoms in patients who underwent the cholecystectomy procedure, having a complex treatment due to a wide range of etiologies.	Resolution of post cholecystectomy chronic diarrhea using bile acid-binding resins: a case report.
Jaramillo 2017	The literature defines diarrhea as the presence of 3 or more watery deposits in more than 4 weeks in patients who underwent the surgical procedure.	Post-cholecystectomy diarrhea, diagnostic and therapeutic approach.
Michael 2015	It comprises the pathophysiological explanation of biliary diarrhea disorders related to FGF-19, FGFR4 or β -klotho genetic variations and other mechanisms that stimulate colonic motility.	Prevalence, Pathogenesis, and Therapy. Gut and liver
Brydon 2011	The diagnostic test for intestinal malabsorption performed using ⁷ HCO serum is preferable to SeHCAT due to its greater simplicity.	An evaluation of the use of serum 7-alpha-hydroxycholestenone as a diagnostic test of bile acid malabsorption causing watery diarrhea.
Walters 2014	Chronic diarrhea caused by bile acids has as its pathophysiological mechanism the homeostasis of bile acid production. Having several types of diagnostic test, such as SeHCAT (Selenium homocholelic taurine).	Bile acid diarrhea and FGF19: new views on diagnosis, pathogenesis and therapy.
Camilleri 2014	Elevated bile acids are demonstrated using the ⁷⁵ SeHCAT test and when it is not available for use, the surrogate for assessing the rate of bile acid synthesis is serum C4.	Effect of increased bile acid synthesis or fecal excretion in irritable bowel syndrome-diarrhea.
Wong 2012	C4 levels can be used to diagnose patients who have bile acid malabsorption.	Increased bile acid biosynthesis is associated with irritable bowel syndrome with diarrhea. Clinical gastroenterology and hepatology
Shin 2013	Primary bile acid levels are higher in individuals with poor IBS (irritable bowel syndrome) compared to people who do not have IBS.	Bowel functions, fecal unconjugated primary and secondary bile acids, and colonic transit in patients with irritable bowel syndrome. Clinical Gastroenterology and Hepatology
Covington 2013	Demonstrates the use of new non-invasive techniques for diagnosing chronic diarrhea. Current methods are expensive and require nuclear medicine, so the use of a cheaper and faster portable electronic nose becomes a paradigm shift.	Application of a novel tool for diagnosing bile acid diarrhoea. Sensors (Basel, Switzerland)
Orekova 2015	Although recognized as a cause of chronic diarrhea for over forty years, diagnostic tests and treatments for bile acid malabsorption (MAB) remain controversial.	Quantifying bile acid malabsorption helps predict response and tailor sequestrant therapy. Clinical Medicine
Menezes 2013	In the analyzed groups, regardless of the recommended diet (low fat or not), the patients had similar percentages of symptom prevalence, showing an insignificant difference and making the low fat diet in the postoperative period controversial.	Randomized study to evaluate low-fat diet in digestive symptoms in the immediate postoperative period of videolaparoscopy cholecystectomy.
Barreto 2010	The low availability of fat in the diet will depend on the tolerance of each patient towards the intake of fatty foods. With the return of the body's capacity, the patient will again secrete bile into the digestive tract by inferring lipids.	The need for patient information in the preoperative period of cholecystectomy.
Araújo 2020	Manual of oral diets of the University Hospital of the Federal University of Vale do São Francisco. The goal of a low-fat diet is to provide a low-fat diet to alleviate gastrointestinal symptoms and treat illness.	HU-UNIVASF hospital diet manual

Source: Produced by the authors of the article.

It was observed that, according to the publications^{4,6}, postcholecystectomy diarrhea is a subject little known by doctors and the academic community, despite the high recurrence of this manifestation in the post-surgical period of cholecystectomy, being around 0.9% to 35.6%. From this literature, it is evident the need for studies and research on the subject, in addition to its dissemination in the scientific

community.

According to Walters et al.²¹, biliary diarrhea is caused by increased flow of bile salts directly from the liver to the intestine, so that this increase causes hydroelectrolytic disorders in the gastrointestinal tract. Farrungia and Arasaradnam⁷ and Michael¹⁹ explain that the changes in the enterohepatic cycle are interrelated with

negative feedback and that the bile acids absorbed by the intestine activate the ileal FXR receptor, which activates the transcription of FGF-19, which acts on the liver and on the FGFR4 receptor reducing bile acid synthesis. It is concluded from these articles that cholecystectomized individuals do not have the functional negative feedback mechanism and therefore present the symptomatology of diarrhea.

Camillieri et al.²² and Wong et al.²³, states that the diagnostic methods for biliary diarrhea are 7 α -OH-4-cholesten-3-one, 75SeHCAT, analysis of the presence of 2-propanol and acetamine in urine, and the method considered the gold standard for diagnosis is stool analysis. This method is based on the analysis of the presence of primary acids in the feces, since in cholecystectomized patients, they are present in larger quantities.

Menezes et al.²⁷ argues that there is no need for a low lipid diet in the post-operative period of cholecystectomy and that the use of a low fat diet is based on the patients' fear of ingesting fat after surgery. However, Yueh et al.⁹ contradicts Menezes et al.²⁷, because in their studies, patients who ate such a diet had a lower degree of occurrence of postcholecystectomy biliary diarrhea.

Thus, it is inferred that the pathophysiological explanations for the cause of biliary diarrhea are known and clarified by the literature, however, the need for a hypolipid diet is controversial and requires research and analysis on such use.

DISCUSSION

Cholelithiasis is one of the most prevalent gastroenterological disorders in the world and is related to changes in the concentration of substances in the bile¹. According to Kumar et al.^{10,25} to 50 tons of gallstones are removed annually by surgery in the United States alone. This data highlights the high prevalence of this disease and also shows the importance of its treatment. Moreover, gallstones are divided into two types, according to the formation compounds, the most prevalent being cholesterol stones and the less common pigment stones.

Cholecystectomy is considered the standard procedure for the treatment of symptomatic cholelithiasis¹². There are two types of surgical procedures, the cholecystectomy in which the abdominal cavity is opened, known as "open", and the cholecystectomy called "closed", in which the surgical incision is minimal¹³. Laparoscopic cholecystectomy has several advantages compared to open cholecystectomy, among these benefits are: less likelihood of complications, less postoperative pain and morbidity and better healing in relation to keloids¹¹.

In this sense, despite the many benefits of laparoscopic surgery, there are also some possible complications of the procedure, such as bleeding, liver injury, postoperative complications, wound infections and

acute pancreatitis¹⁴. However, one of the most recurrent disadvantages is related to the symptoms present in the postoperative period. The most common clinical manifestations after cholecystectomy are increased bowel frequency, urgency, nocturnal defecation, excessive flatulence, abdominal pain, stool incontinence, and diarrhea⁷.

Moreover, the most recurrent symptom in postcholecystectomy cases is biliary diarrhea, being described in about 30% of the patients who undergo the surgical procedure for removal of the gallbladder¹⁵. Additionally, diarrhea is a symptom clinically defined as an increase in the frequency of bowel movements of softened stools; however, according to academia, to define a bowel frequency as diarrhea, it is necessary to research the daily weight of stools, which is not usually done in medical practice¹⁶.

Nevertheless, biliary-type diarrhea is conceptualized as chronic diarrhea because it lasts longer than four weeks and the presence of three or more diarrheal bowel movements in 24 hours. In addition, this symptomatology can appear in a few months or even years after surgery¹⁷. Biliary acid diarrhea is due to the fact that after cholecystectomy the drainage of bile salts is continuous from the liver to the gastrointestinal tract, causing water and electrolyte disturbances in the small intestine¹⁵.

Still on the trigger devices for postcholecystectomy biliary diarrhea, Michael¹⁹ notes the mechanism by G protein-coupled receptors. Excess bile acid concentration in the colon activates GPBAR1 (TGR5) receptors 1, which are found on ileal endocrine cells and function as a cell surface receptor for bile acids. The association between excess bile acid in the colon and genetic variation in this receptor interferes with the acceleration of colonic transit and motility in the intestine, causing increased fluid secretion.

From these pathophysiological mechanisms it is concluded that there are 3 types of intestinal malabsorption, type 1 caused by diseases in the ileum or ileal resection, type 2 of idiopathic cause, and finally type 3 due to bile acid malabsorption, which the postcholecystectomy diarrhea fits. Following this line of thought, there are some tests that can be performed in order to help diagnose postcholecystectomy diarrhea; among these tests, the SeHCAT 75 test (Selenium-75 homolic acid taurine test) is one of the methods used to establish the production, renewal, or replacement of bile acid²⁰.

It is a non-invasive diagnostic method and aims to calculate the accumulation of bile acid in the body over 7 days. This test has greater workability for diarrhea caused by idiopathic malabsorption, however, it can also be used in types 1 and 3. Bile acid loss is characterized in mild, moderate, or severe by the test, and many studies show positive test results for type 1 and 2 bile acid malabsorption²¹.

In agreement with Camillieri et al.²², another test

that can be used for the diagnosis of bile acid diarrhea is serum 7 α -OH-4-cholesten-3-one (C4), used in cases that 75SeHCAT is not available to be done. One of the validated methods for C4 analysis is high performance liquid chromatography and tandem mass spectrometry, the material used is a fasting blood sample. This is a test with a higher negative predictive value than positive predictive value, meaning that it is an exclusion test.

Stool analysis is considered according to Wong et al.²³ to be the gold standard method for analyzing bile acid diarrhea, although it is a more complicated method to perform and is not the most widely used in practice because of this. This test assesses the weight, fat, and the amount of bile acids in the stool (kenodeoxycholic, colic, deoxycholic, and lithocolic acids). Of these, colic and chenodeoxycholic acids are considered primary acids and are present in larger amounts in patients with bile acid diarrhea and are found in the fecal analysis²⁴.

Finally, according to Covington et al.²⁵ other diagnostic methods have been used and researched, among them the test using plain urine. This method using urine excreta evaluates the presence of propane-2-ol and acetamine. An electronic nose device can be used for the evaluation, which identifies chemical signatures in the urine specimens. However, therapeutic assays can also be performed for diagnosis; cholestyramine and colesevelam are the proposed drugs; however, there is no recommendation for the use of this method, and it is used only when no other type of diagnostic device is available^{7,26}.

Furthermore, according to Grande et al.⁴ there is no way to determine which patients will present with postoperative diarrhea, therefore, the tests combined with clinical medicine are important to establish the diagnosis and appropriate treatment. Certainly, the objective of the surgical treatment of cholecystectomy is the relief of symptoms and prevention of complications, as well as the dietary treatment aims to promote benefits to the quality of life and better recovery of the patient postoperatively²⁷. Barreto et al.²⁸ also describes that the patient should be oriented about the temporary changes in the body after surgery, as well as about the hypolipidic diet, which is one of the possible dietary treatments.

In this sense, to better understand which foods can be consumed after cholecystectomy, a Manual of Hospital Diets of HU-UNIVASF was prepared, which includes as one of the diets, the hypolipidic diet. Thus, this manual helps the physician when prescribing this diet, with a low rate of fats and oils, especially saturated fat. The foods it allows are: skimmed milk and yogurt, low-fat cheese, lean meats, eggs, honey, vegetables, and jam. The foods not allowed are yogurt and whole milk, heavy cream, yellow cheese, fried foods, and butter or margarine.

Despite being a common procedure in medical application, there is a contraposition of authors related to this theme of low-fat diet. According to Menezes et al.²⁷, some scholars believe that in the period after the cholecystectomy the restriction of fats is not necessary, since the gallbladder has the function of storing bile and not producing it. Finally, the author concludes that some physicians prefer the continuation of the preoperative established low-fat diet due to psychological factors of the patients, because some of these individuals are afraid of consuming fat even after surgery.

On the other hand, Yuch et al.⁹, infers a greater importance of the low-fat diet, since patients who did not follow the diet had a greater tendency to develop the pathophysiology of bile acid diarrhea compared to those who followed the low-fat diet. Thus, the recommendation of the low-fat diet is variable, depending on the practitioner's experience and the patient's clinical status.

CONCLUSION

The present review provided a better understanding of the aspects related to diarrhea in postcholecystectomy patients. The evidence points out that about 30% of patients who undergo cholecystectomy present biliary diarrhea, in addition to excessive flatulence, abdominal pain, stool incontinence, and nocturnal defecation. Moreover, there is no way to determine which patients will present with diarrhea postoperatively, since this symptomatology can appear in a few months or even years after surgery.

The pathophysiological mechanism of biliary diarrhea is intrinsically related to the process of synthesis and excretion of bile, involving the negative feedback mechanism, alteration of the intestinal microbiota, and genetic variation of the receptors for FGF-19 (fibroblast growth factor) and the receptor coupled to G protein. It is inferred that these mechanisms are modified after cholecystectomy surgery.

The relationship between a low-fat diet and a tendency to develop bile acid diarrhea is controversial among the literature reviewed. Studies suggest that patients who did not follow the diet were more prone to biliary diarrhea. On the other hand, there is evidence that does not relate the low-fat diet to diarrhea in postcholecystectomy patients.

It is believed that this work can contribute to bring improvements to the general health condition of the population. Since despite cholecystectomy being a common procedure in medical application, there is still little knowledge about the aspects of diarrhea in postcholecystectomy patients

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