World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-21, April 2023
ISSN: 2749-3644

MAIN CAUSES, DIAGNOSIS, AND EFFECTIVE TREATMENT OF POSTCHOLECYSTECTOMY SYNDROME

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Article history:

Received: February 20th 2023
Accepted: March 20th 2023
Published: April 28th 2023

Abstract:

The paper presents the frequency and differences of opinions on the definition of postcholecystectomy syndrome. Four groups of the main causes responsible for the development of different clinical symptoms after cholecystectomy are distinguished. It is proved that pathogenesis of digestive disorders in postcholecystectomy syndrome is complex and multicomponent, includes the number of "crossing" closely connected pathogenic "rings". It is shown that in the absence of indications for surgical correction of the syndrome the optimal way to break the above described "vicious circles" is the prescription of pancreatin combination in the form of enterosolubilic minimicrospheres and selective myotropic antispasmodic agent mebeverine.

Keywords: cholecystectomy, postcholecystectomy syndrome, common bile duct

INTRODUCTION. In 1882 Langenduchuch performed the first cholecystectomy, in Russia it was first performed in 1889 by Y.F. Kosinski, therefore the history of cholecystectomy counts 130 years, however surgical intervention does not always lead to a complete recovery. A significant number of patients have persisting clinical symptoms, developing various alterations of digestive organs, combined by the term "postcholecystectomy syndrome" (PCES), which corresponds to the category K 91 in the International Classification of Diseases and Causes of Death, Revision 10 (ICD-10). And if previously it was considered that PCES was revealed in 5-40% of patients who had undergone cholecystectomy [1-3], nowadays there are indications that PCES rate reaches 40-50% [4]. The name PCES first appeared in American literature in 1930s. It is a collective term meaning diseases related directly or indirectly to the surgery itself, as well as diseases progressing as a result of the surgery. By the way, most clinicians consider the term "postcholecystectomy syndrome" to be unhelpful and even inappropriate, because it does not reflect the essence of suffering, the causes of occurrence and the essence of pathological processes observed in this category of patients. Despite the fact that PCES is included in ICD-10, there is still no exact understanding of the essence of this syndrome. Nevertheless, due to its simplicity and capacity, the term is widely used in clinical practice [1-3, 5]. Some authors suggest to distinguish "true" PCES, putting into this concept only disorders of Oddi sphincter motility and duodenal motility function, recurrent hepatic colic resulting from incompletely performed cholecystectomy [1-4, 6]. PCES also includes conditions the causes of which were not eliminated during the operation and/or developed as a result of past manipulations on the biliary tract. These are residual stones of common bile duct, pathologically changed stump of bladder duct, stenotic papillitis, posttraumatic scar stricture of common bile duct, leftover part of gallbladder, stone of bladder duct, long bladder duct, neurinoma in scar area, granuloma of foreign body, bile duct cysts and other mechanical obstacles in bile ducts, which could be removed during operation, but for different reasons remained unnoticed. Biliary tract damage, narrowing and scarring of the bile ducts could have occurred due to the surgical intervention [1, 6]. Many clinicians advocate a broader interpretation of this term, including in this syndrome both functional disorders developed after gallbladder removal and pre-existing organic diseases of hepatopancreatobiliary zone, aggravation and progression of which are provoked by cholecystectomy [1-4, 6]. This fact is the basis for such estimation, because the course of cholelithiasis in 60-80% is accompanied by other digestive organs diseases, which are closely connected with biliary system in the first place [2, 3, 6]. On the basis of these data at least 4 groups of basic causes of different clinical symptoms after cholecystectomy can be distinguished [6]:

1) diagnostic errors made at the preoperative stage during the examination of the patient and/or during surgery;

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Volume-21, April 2023
ISSN: 2749-3644

2) technical errors and tactical mistakes made during surgery;

3) functional disorders associated with gallbladder removal

4) exacerbation or progression of pre-operative diseases, especially of hepatopancreatobiliary zone, and development of new pathological conditions, conditioned by adaptive restructuring of digestive organs due to cholecystectomy.

The first two groups of causes require, mainly, surgical solution of the problem, which is reflected in the relevant literature. For gastroenterologists, therapists, who encounter a patient who has undergone cholecystectomy, it is important to understand the nature of pathophysiological disorders caused by surgery, which allows to properly assess the nature of clinical symptoms and choose the most optimal therapy to correct the identified disorders [2, 3]. Most researchers believe that after cholecystectomy there develops sphincter Oddi hypertonicity, and in the first month after the operation it is revealed in 86% of cases, in a year - in 63%, in 2 years - in 30% of cases [7]. This effect is explained by switching off the regulating role of Lutkens sphincter and muscle activity of the gallbladder, because the tone of Oddi sphincter reflexively decreases during gallbladder contraction, which ensures coordinated activity of all biliary tract sphincter apparatus [2, 3]. Common bile duct sphincter dysfunction leads to biliary hypertension, cholestasis and is accompanied by right subcostal or epigastric pain. When pancreatic duct sphincter dysfunction prevails the clinical picture typical for pancreatic pathology develops [2, 3]. Many clinicians advocate a broader interpretation of this term, including in this syndrome both functional disorders developed after gallbladder removal and pre-existing organic diseases of hepatopancreatobiliary zone, aggravation and progression of which are provoked by cholecystectomy [1-4, 6]. This fact is the basis for such estimation, because the course of cholelithiasis in 60-80% is accompanied by other digestive organs diseases, which are closely connected with biliary system in the first place [2, 3, 6]. On the basis of these data at least 4 groups of basic causes of different clinical symptoms after cholecystectomy can be distinguished [6]:

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- Symptoms associated with damage to hepatocytes and biliary tubules:

- The development of hepatitis as such, i.e., an inflammatory-necrotic process in the liver with subsequent progression of fibrosis (although, of course, hepatitis itself may not be a consequence of cholestasis, but, on the contrary, its cause);

- symptoms associated with cholemia:

- Biochemical changes characteristic of cholestasis (increased bile acids, total and conjugated bilirubin, cholesterol, increased alkaline phosphatase activity, in some cases

- ▪ -glutamyltranspeptidase);

- endotoxemia;

- increased risk of acute renal failure and bacterial complications, bleeding;

- symptoms associated with accumulation of bile elements in soft tissues, organs, central nervous system:

-jaundice;
- skin itching;
- xanthomas;
- acute ulcers;

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-21, April 2023
ISSN: 2749-3644

- encephalopathy;
- Symptoms associated with decreased intake of bile acids into the intestinal lumen due to cholestasis and biliary insufficiency:
- steatorrhea;
- malabsorption;
- deficiency of fat-soluble vitamins;
- disorders of bone mineralization (osteoporosis). Let us elaborate on the pathogenesis of symptoms of cholestasis and biliary insufficiency associated with the reduction of bile acids in the intestinal lumen, as this is the reason why hepatogenic pancreatic insufficiency develops.

There can be 3 types of pathogenetic relationships: first cholestasis and biliary insufficiency develop, and pancreatic insufficiency is its consequence (primary biliary cirrhosis, gallstone disease, PCES, mechanical jaundice, etc.); less often cholestasis and biliary insufficiency develop first.); more rarely, initially, pancreatic disease with primary pancreatic insufficiency develops, which leads to liver pathology (pancreatic tumor, pseudo-tumor-like pancreatitis, large pancreatic cysts, leading to compression of the intrapancreatic part of the choledocha and mechanical jaundice); even rarer liver disease with cholestasis and BP pathology develop simultaneously, usually as a result of single etiologic factor (primary sclerosing pancreatocholangitis, stenotic papillitis, duodenal tumor, phateroviscus). To understand the pathogenesis of hepatogenic pancreatic insufficiency it is necessary to enumerate bile acids functions [9, 11, 12]:

- participation in the process of fat digestion;
- stimulation of synthesis of regulatory peptides (cholecystokinin-pancreozymin, etc.);
- Providing absorption of fat-soluble vitamins;
- Maintaining the total pool of bile acids (enterohepatic circulation);
- regulation of bile formation;
- regulation of surface tension in the enteric medium;
- participation in the regulation of the peristalsis of the digestive tract;
- bacteriostatic;
- regulation of cholesterol synthesis;
- secretory. The main significance in the pathogenesis of hepatogenic (chologenic) pancreatic failure in cholestasis and biliary insufficiency is a decrease in the participation of bile acids in fat digestion. The role of bile acids in fat digestion is manifold [5]:
- bile contains bile acid conjugates, which participate in the process of micelle formation (cholesterol and phospholipids dissolve in them); mixed micelles are the main structure of bile and stabilize it;
- bile acids conjugates play an important role in emulsification of fats, i.e. in their preparation for the action of pancreatic lipase;
- bile acids activate pancreatic enzymes (primarily lipase), participate in activation of cholecystokinin-pancreozymin;
- bile acids not only emulsify fats, but also accelerate absorption in the jejunum of fatty acids and monoglycerides. Due to the reduced involvement of bile acids in the intestinal digestion process, processes and symptoms develop. It is when the concentration of bile acids in the intestine is reduced that the likelihood of steatorrhea increases significantly [9]. In severe cholestasis, secondary pancreatic insufficiency has distinct, sometimes severe clinical manifestations. In other diseases, in particular in PCES, pancreatic insufficiency manifestations are not always clinically significant, in some patients they are revealed only by coproscopy; and finally, in other liver and biliary diseases steatorrhea is minimal and determined only coprologically, not realized in clinical manifestations. Let us consider the pathogenesis of the eating disorder inherent in PCES . Due to Oddi sphincter dysfunction, less often due to development of choledochal scarring, which develops in most patients after cholecystectomy, as well as due to asynchronism of bile and chyme inflow in duodenum in absence of bile reservoir, chogenic secondary pancreatic insufficiency is formed. In addition, the same asynchronism is the cause of an increase in free bile acids, which leads to predominantly secretory diarrhea and further to enteric pancreatic insufficiency. If the patient underwent cholecystectomy already on the background of a long history of cholelithiasis, the probability of secondary biliary cirrhosis and, hence, hepatogenic pancreatic insufficiency cannot be excluded. Formation of biliary pancreatitis before or after cholecystectomy is the cause of development of not only secondary pancreatic insufficiency after cholecystectomy, but also primary pancreatic insufficiency, i.e. arising as a result of pancreatic parenchyma damage itself. Secondary pancreatic insufficiency can also form due to disorder of bile acids participation in maintenance of their common pool, i.e. when enterohepatic circulation of bile acids is disturbed. In this case, a pronounced disturbance of the intestinal flora develops, leading to increased deconjugation of bile acids in the small intestine by bacterial enzymes. In disease or after resection of the small intestine, on the contrary, the flow of bile acids in the blood from the intestine decreases. In these patients, the bile acid content in the intestinal lumen

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Available Online at: https://www.scholarexpress.net
Volume-21, April 2023
ISSN: 2749-3644

usually increases, leading to diarrhea and further to enteric pancreatic insufficiency. When the enterohepatic circulation of bile acids is disturbed and their return to the liver is reduced, such a function as participation of these acids in bile formation is also disturbed. There is also a violation of such function of bile acids as regulation of surface tension in the enteric environment. Foam covering a thin layer of the surface of the mucosa of the digestive canal, obstructs parietal digestion, reduces the activity of pancreatic enzymes and aggravates nutrient malabsorption. Due to reduction of bile acids inflow after cholecystectomy into duodenal lumen, motility activity of small and large intestine and, more specifically, duodenum is inhibited. Duodenostasis develops in patients, leading to disturbance of pancreatic secretion outflow, intraductal hypertension and finally - to chronic pancreatitis and primary pancreatic insufficiency. "Loss" or reduction of bacteriostatic function of bile acids also plays an essential role in development of secondary pancreatic insufficiency both hepatogenic (chologenic), and enterogenic. Taking into account the bacteriostatic function of bile acids, their decreased intestinal supply aggravates the so-called "enteropancreatic syndrome" initially caused by primary pancreatic insufficiency in patients with biliary pancreatitis. With pancreatic enzyme deficiency in the intestinal lumen, a certain part of the food nutrients is underdigested, i.e. not reaching the degree of hydrolysis necessary for absorption and passage through the intestinal barrier into the blood. In this case, the pool of primary nutrients decreases. As a result, the bacterial pool in the intestine inevitably increases, because, first, the bactericidal role of pancreatic enzymes decreases (there are simply fewer of them than necessary in the intestinal lumen) and, second, the undigested nutrients serve as a breeding ground for intestinal flora. Intestinal flora are involved in the hydrolysis of nutrients, and the pool of secondary nutrients finally prepared for absorption in the intestine is greater in PCEC patients with pancreatitis phenomena than in healthy individuals. In parallel, the pool of bacterial metabolites entering the blood increases. However, bacterial enzymes still do not hydrolyze nutrients to the extent that they do when sufficient pancreatic and intestinal enzymes are present in the intestines of healthy individuals. Thus, the volume of ballast increases, which is clinically realized in an increase in the volume of feces, in the appearance of lyentery, steatorrhea, creatorrhea, amylorrhea. With bile acid deficiency in the intestinal lumen, not only pancreatic enzymes are not sufficiently activated (hepatogenic or chologenic pancreatic insufficiency joins), but also the reduced bacteriostatic function of bile acids leads to even greater growth of intestinal bacterial pool, progression of excessive bacterial growth syndrome, maldigestion and malabsorption. Thus, the pathogenesis of digestive disorders in PCES turns out to be complex and multicomponent, involving a number of "overlapping", closely related pathogenetic "rings". [2]. In cholestasis the activity of pancreatic lipase is reduced, steatorrhea and other clinical manifestations of pancreatic insufficiency develop. Accumulation of undigested nutrients in the intestinal lumen enhances propulsion, i.e., peristalsis with spasm of intestinal smooth muscles and pain [2]. In addition, the accumulation of undigested nutrients in the intestine leads to excessive bacterial growth. Microbial contamination of the small intestine is also promoted by the reduced bacteriostatic action of bile acids (Fig. 3). Excessive bacterial growth in the intestine, in turn, causes damage to membrane enzymes by microbial toxins and impaired membrane digestion. Malabsorption aggravates the accumulation of undigested nutrients in the intestine, translocation of intestinal flora and increases the risk of bacterial complications [1,6]. On the other hand, microbial contamination of the intestine leads to early deconjugation of bile acids and hence to an even greater reduction of their role in fat digestion. Decrease of surface tension on liquid-gas border contributes to excessive gas formation, i.e. flatulence, increase of pain [9]. Entering the large intestine with insufficiently digested food remains stimulates proliferation of bacterial flora in it, due to which they are broken down (dysbiosis of the large intestine) with possible subsequent retrograde penetration of appropriate bacterial flora into the small intestine (normally containing a small number of microorganisms) through the baulking flap. Formation of cecoileal reflux is promoted by increased pressure in the colon cavity due to accumulation of gaseous products of insufficiently digested food in it. Products of bacterial decomposition of insufficiently digested food (indole, scatole, phenol, cresol, hydrogen sulfide, carbon dioxide, hydrogen, ammonia, etc.) and endotoxins of bacteria can increase the peristaltic activity of the intestine and accelerate the passage of food through it, which reduces the contact time of pancreatic and intestinal enzymes with food substances in the cavitary and membrane digestion. As a result, their digestion is impaired (enteric pancreatic insufficiency). An important role in the pathogenesis of this deficiency is played by a decrease in pH in the intestinal lumen in bacterial overgrowth syndrome, due to which the available enzymes in this lumen are partially or even completely inactivated. The products of bacterial food breakdown in the intestine can lead to

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Available Online at: https://www.scholarexpress.net
Volume-21, April 2023
ISSN: 2749-3644

organic changes in the intestinal mucosa (dystrophy, inflammation), which may result in poor absorption of the end products of food breakdown. Deconjugated bile acids formed in excess during bacterial infestation of the initial sections of the small intestine, which have a damaging effect on its mucous membrane, also contribute to this [9]. Due to impaired hydrolysis of fats, absorption of fat-soluble vitamins (A, D, E, K) suffers. On the basis of vitamin D deficiency and excessive calcium excretion, osteoporosis may develop, the appearance of bone pain [1, 4]. How to break these pathological links, what is the strategy of digestive disorders management in PCES patients. It is postulated that polyenzyme replacement therapy is the leading method of reducing not only maldigestion and malabsorption (increased stool frequency, lenteria, steatorrhea, flatulence, abdominal pain), but also numerous manifestations caused by a lack of intake of plastic substances, vitamins, electrolytes. Moreover, a positive effect on the course of PCES is not only due to the reduction of manifestations of maldigestion and malabsorption, but also the possibility of expanding the diet, reducing sytophobia due to the relief of abdominal pain syndrome. However, there are differences in recommendations on the tactics of polyenzyme therapy. At first glance, there is no doubt that it is necessary to prescribe the 4th generation drugs (enterosolubilic minimicrospheres). If we rely on experimental studies showing the dependence of particle size on the rate of their evacuation from the stomach, especially simultaneously with food, it becomes clear - large pills (more than 2 mm in diameter) pass through the pyloric canal rather slowly, often do not pass completely at all. Most of them are destroyed and only in the form of fragments pass into the duodenum. The enterosolubilic coating covering large-sized tablets further delays the presence of the tablets in the stomach, since fragmentation of the tablets is possible only at pH higher than 5, and more often 6. Under these conditions, there is no talk of simultaneous evacuation of tablets and food at all. Delay of tablets in the stomach, their late fragmentation contribute to partial inactivation of drug components (pancreatic lipase and proteases are irreversibly inactivated at pH below 3 and 4, respectively), reaching 80% [5,8]. Another reason explaining their practical unsuitability is the low content of lipase in 1 tablet, which determines the need to use at least 5-7 tablets per meal, and this without taking into account the fact that the drug is partially inactivated in the stomach when "crumbling" a large tablet, so that the potential dose is even 2 times higher. Therefore, only modern polyenzyme preparations with lipase activity of 25000-40000 IU (Creon) can fully replace exocrine pancreatic function also in CP with external secretory insufficiency (Table 3). When choosing a dose of pancreatin it is necessary to be guided by the data of fecal elastase activity, the dose is adjusted according to clinical data (relief of diarrhea and steatorrhea, flatulence, stabilization and weight gain), laboratory data (reduction of fat in stool, reduction of fecal volume, disappearance of neutral fat in microscopy), results of isotope breath tests with labeled triglycerides or starch [5, 9]. In order to obtain the most effective response, when choosing a myotropic antispasmodic to resolve Oddi sphincter spasm, the attending physician should consider the following requirements for the ideal antispasmodic: 1) high antispasmodic activity, 2) high rate of onset of action, 3) high selectivity of action, 4) long-term effect, 5) high safety, 6) extensive experience of use, 7) accessibility to the population, 8) availability of oral forms. Systemic antispasmodics do not meet most of these requirements. They reduce the tone of internal organs, dilate blood vessels, can cause "bypass syndrome" in patients with atherosclerotic arterial disease, lower blood pressure. Some patients may have palpitations, fever, visual disturbances, dizziness, bowel atony, and difficulty in urination. These drugs are not selective for the Oddi sphincter. An alternative is the use of selective antispasmodics, of which Duspatalin (Mebeverine hydrochloride), which is a classic myotropic antispasmodic - sodium channel blocker, meets the requirements for an ideal antispasmodic. The peculiarity of the drug is that its use preserves normal peristalsis after suppressing hypermotility. And there is no dose of mebeverine that would completely inhibit peristalsis, i.e. cause hypotension. Mebeverine has two effects: 1) the drug has an antispastic effect by reducing the permeability of smooth muscle cells to sodium ions. In therapeutic doses, mebeverine has a direct blocking effect on sodium channels which helps to limit sodium influx and prevent subsequent muscle spasm; 2) mebeverine indirectly decreases outflow of potassium ions and therefore does not cause hypotension. The second side of the action of mebeverine is as follows. There are b1-adrenoreceptors in the wall of the digestive tract associated with calcium ion depots. These depots constantly restore calcium levels from the extracellular environment. Stimulation of these receptors promotes the mobilization of calcium ions from the depot into the cell and the opening of channels for potassium ions and, consequently, a decrease in smooth muscle cell tone. Mebeverine blocks the filling of the depot with extracellular calcium, and when b1-adrenoreceptors are activated in the presence of the drug, the depot cannot recharge after emptying. As a result, the outflow of potassium ions from the cell stops,

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Available Online at: https://www.scholarexpress.net
Volume-21, April 2023
ISSN: 2749-3644

and hypotension or relaxation does not occur. This effect is the basis of the most important benefit of the drug Duspatalin, which is the normalization of the tone of the Oddi sphincter [15, 16, 18, 20, 21]. The efficacy and optimal dose of the drug have been established in randomized controlled trials. When administered orally, more than 90% of the dose of mebeverine is absorbed in the intestine, but the drug is not detected in the blood in unchanged form, because it is metabolized to inactive products in the intestinal wall and the liver, so it acts only on the digestive tract. The drug is registered in 74 countries and has been widely used since 1965 and as an effective antispasmodic is prescribed to 6.5 million patients each year. The safety of mebeverine is confirmed by long experience of its use in wide practice, as well as by the results of clinical trials in more than 3,500 patients, which did not reveal any serious undesirable side effects, including studies conducted in Russia [1,5]. The drug can be prescribed for glaucoma and prostatic hyperplasia when cholinolytic agents are contraindicated. Slow release from capsules during intestinal passage (prolonged action is very important to ensure a stable effect), i.e. a single intake of the drug capsule ensures absence of spasms and hypotension of the biliary tract for at least 12 hours and allows taking it only 2 times a day. Course duration is determined by the severity of the underlying disease and varies from 2-3 to 12 weeks to 6 months in patients with biliary dependent pancreatitis. The number of treatment courses per year is determined by attending physician taking into account the severity of the disease, it is also possible to use the drug "on demand", because the drug starts to have an effect after only 20-30 minutes of intake [6].

CONCLUSIONS: Thus, we can conclude that pathogenesis of digestive disorders in PCES is complex and multicomponent, includes a number of "crossed", closely related pathogenetic "rings", in the absence of indications for surgical correction of the syndrome, the optimal way to break the above "vicious circles" is prescription of pancreatin combination in form of enterosolic minimicrospheres and selective myotropic spasmolytic mebeverine.

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