

Original Research Article

Effect of micropancreatic enzyme on biochemical profile in patients who have undergone cholecystectomy

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Abstract

Purpose: To determine the effectiveness of micropancreatic enzymes on biochemical profiles in patients who have undergone cholecystectomy.

Method: A total of 122 patients with pancreatic exocrine insufficiency who visited the outpatient clinic of Sorgun State Hospital, Yozgat, Turkey and had undergone cholecystectomy in the last three months were assigned to study and control groups. Study group (n = 72) received micro pancreatic enzyme mixture for at least 4 weeks within 3 months of cholecystectomy. Control group (n = 50) with a history of cholecystectomy did not use any digestive aids or micro pancreatic enzyme mixture during the same period. Pancreatic insufficiency, water consumption, Vit D, B12, calcium, and lipid profiles were compared in both groups.

Results: Severity of pancreatic exocrine insufficiency was significantly mild in study group compared to control group (p < 0.05). In patients who had undergone cholecystectomy, total cholesterol, triglyceride, high-density lipoprotein and low-density lipoprotein levels after at least 6 weeks were significantly lower in study group compared to control group (p < 0.05).

Conclusion: Micropancreatic enzyme improves pancreatic function, and lowers lipid levels in patients who have undergone cholecystectomy. A prospective, randomized controlled study will be useful in determining the appropriate dosage and duration of use which provides symptomatic relief and biochemical improvement in patients who have undergone cholecystectomy.

Keywords: Cholecystectomy, Pancreatic exocrine insufficiency, Pancreatic exocrine replacement therapy (PERT)

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INTRODUCTION

The gallbladder is a digestive organ adjacent to the liver that contains secretions from the liver. Bile synthesized in the liver is transmitted through the main hepatic duct to ductus choledochus and from there to the duodenum. If needed, additional bile support is transmitted from the gallbladder to the ductus choledochus via the cystic duct [1].

Bile is mainly composed of water (80 %), electrolytes, bile salts (10 %), proteins (4 - 5 %), lipids (1 %), and bile pigments. Sodium, potassium, calcium and chlorine are in the same concentration in bile as plasma or extracellular fluid. In the intestines, approximately 80 % of conjugated bile acids are absorbed in the terminal ileum. The remainder is dehydroxylated (deconjugated) by intestinal bacteria to form

secondary bile acids, deoxycholate and lithocholate. These are absorbed in the colon, transported to the liver, conjugated and secreted into bile. Cholesterol and phospholipids synthesized in the liver are the main lipids found in bile. Synthesis of phospholipids and cholesterol by the liver is partially regulated by bile acids. Thus, bile plays a role both in the digestion of existing fats and re-synthesis [2,3].

Major enzymes involved in digestion are mainly amylase, lipase, cholesterol ester hydrolase, phospholipase A2, phosphatase, colipase, trypsin, chymotrypsin, elastase, aminopeptidase and carboxypeptidase. They are mostly synthesized as pro-enzymes and are inactive. The Lipids are further broken down into fatty acids and 2-monoglyceride in the duodenum by pancreatic lipase. In addition, bile salts form the necessary micellar form for digestion. Therefore, digestion of fats is done by pancreatic lipase, and bile secretion is of great importance. When there is a problem in bile secretion, it is possible to encounter signs of pancreatic insufficiency. With the deterioration of fat digestion, fat-soluble vitamins which include A, D, E, and K deficiency are encountered. For example, in the absence of pancreatic protease, vitamin B12 (released from the R factor by action of pancreatic protease) malabsorption develops [4].

Pancreatic exocrine insufficiency develops as a result of deficiency of pancreatic secretions or additional pathologies in its secretion. Although the most common cause is chronic pancreatitis, lesions obstructing secretory ducts and previous upper gastrointestinal surgeries contribute. In patients who have undergone cholecystectomy, lipid digestion is affected, and signs of pancreatic exocrine insufficiency may be observed [5,6]. While pancreatic exocrine insufficiency may present with nonspecific digestive complaints such as abdominal pain, indigestion, bloating, flatulence, and diarrhea, it also comes with more specific symptoms such as steatorrhea, vitamin deficiency and severe weight loss. Because of these non-specific symptoms, it is often difficult to diagnose patients [7]. Diagnosis includes first-line fecal elastase test. However, evaluation of symptoms following treatment as specified by guidelines leaves the path from treatment to diagnosis open [8].

The pancreatic exocrine insufficiency questionnaire was developed to define and regulate treatment dose, thus aiding in diagnosis and treatment follow-up [9]. After postprandial cholecystectomy, bolus flow of bile secretion into the duodenum is lost. Therefore, it becomes difficult for pancreatic enzymes to act, and signs

of pancreatic exocrine insufficiency are observed. Pancreatic enzyme mixtures are used in the treatment of pancreatic exocrine insufficiency [10]. Therefore, this study investigated the effect of micropancreatic enzymes on biochemical profiles following cholecystectomy.

METHODS

Patient groups

A total of 122 patients with pancreatic exocrine insufficiency who visited the outpatient clinic of Sorgun State Hospital, Yozgat, Turkey and had undergone cholecystectomy in the last three months were assigned to study and control groups. Required ethical approval was obtained from the Ethics Committee of T.C. Bozok University (approval no. 2017-KAEK-189_2022.12.15_19) and conducted in accordance with the guidelines of Declaration of Helsinki [11].

Inclusion criteria

Patients who had undergone cholecystectomy within the last 3 months and received pancreatic enzyme replacement therapy in other health centers due to digestive complaints.

Exclusion criteria

Presence of known pancreatic enzyme synthesis disorders such as acute and chronic pancreatitis, cystic fibrosis, patients using drugs that affect lipid profile, diabetes mellitus, gastrointestinal system surgery other than cholecystectomy, patients with a body mass index < 18.5 and > 30 kg/m².

Treatment protocol

Study group (n = 72) received micro pancreatic enzyme mixture (25000 IU pancreatin, three times daily with meal for at least 4 weeks within 3 months of cholecystectomy). Control group (n = 50) with a history of cholecystectomy did not use any digestive aids or micro pancreatic enzyme mixture during the same period. All patients were prescribed non-steroid anti-inflammatory for analgesia (25 mg dexketoprofen orally twice daily for 7 days), proton pump inhibitor (40 mg esomeprazole once a day, for 30 days) and 2nd generation cephalosporin for prophylaxis (500 mg cefuroxime twice daily for 7 days) on postoperative period. All the patients included in the study used all prescribed medicine as indicated. No perioperative complication was observed. All patients were discharged on

postoperative day 1. After discharge, patients were advised to have fluid or mash nutrition for the first 3 days. Dietary compliance was verified verbally.

Evaluation of parameters/indices

Baseline characteristics

Detailed anamnesis including personal information, water consumption, age, sex, height, weight and all system symptoms such as gastrointestinal, neurological, and pulmonary function including post-surgical symptoms and medications were recorded and compared.

Biochemical evaluation

Daily water ingestion, hemogram and biochemistry tests, vitamin D and vitamin B12 levels were recorded and compared after treatment.

Pancreatic insufficiency

A pancreatic exocrine insufficiency (PEI) questionnaire was administered to patients who had undergone cholecystectomy. The questionnaire consists of 18 questions in 3 parts. In the first two sections, symptoms were evaluated, while the last section evaluated patient behaviors. Symptom query consisted of 7 questions on abdominal complaints, 5 questions on bowel complaints, and 6 questions on behaviors. Patients were asked to answer questions about their digestive systems in the last 7 days. A score of 0, 1, 2, 3, and 4 indicated none, less, medium, more, and very much respectively. Higher scores indicated higher severity of pancreatic exocrine insufficiency. The result was obtained by taking the average of each section within itself and the average of the total score. Mean score > 0.6 indicated pancreatic exocrine insufficiency diagnosis. According to the score, mild PEI symptoms (0.6 - 1.4), moderate PEI symptoms (1.5 - 1.7) and

severe PEI symptoms (> 1.8) were compared. Consistency of the scale (Cronbach's alpha = 0.77 - 0.82) and reliability (Cronbach's alpha = 0.73 - 0.87) were high [12].

Data analysis

Data was analyzed using Statistical Packages for Social Sciences (SPSS, version 22.0; Inc., Chicago, USA). Categorical data were expressed as frequency and percentages and compared using Chi-square test. Continuous data were expressed as mean ± standard deviation (SD) with minimum and maximum values indicated where appropriate. *P* < 0.05 was considered statistically significant.

RESULTS

A total of 100 (82 %) were females, and 22 (18 %) were males. Mean age was 47.36 ± 11.16 (22 – 68 years). There was no significant difference in age and gender between the two groups (*p* > 0.05). Amylase and lipase values were within reference range. Pancreatic exocrine insufficiency was significantly milder in study groups compared to control group (Table 1).

Table 1: Pancreatic exocrine insufficiency in study and control groups (n, %)

Group	Mild*	Moderate	Severe	Total
Study (n=72)	40(55.6)	18(25)	14(19.4)	72(100)
Control (n=50)	12(24.0)	10(20.0)	28(56.0)	50(100)
Total	52(42.6)	28(23.0)	42(34.4)	122(100)

**P* < 0.05

Water consumption

There was no significant difference in the amount of water consumed per day after cholecystectomy and the severity of pancreatic exocrine insufficiency (*p* > 0.05; Table 2).

Table 2: Water consumption and pancreatic exocrine insufficiency (n, %)

Group	PEI severity	Water intake			Total
		1 L/day	2 L/day	3 L/day	
Study (n = 72)	Mild	18(45.0)	12(30.0)	10(25.0)	40(100)
	Moderate	10(55.)	4(22.2)	4(22.2)	18(100)
	Severe	10(71.4)	0(0)	4(28.6)	14(100)
	Toplam	38(52.8)	16(22.2)	18(25.0)	72(100)
Control (n = 50)	Mild	6(50.0)	4(33.3)	2(16.7)	12(100)
	Moderate	8(80.0)	2(20.0)	0(0)	10(100)
	Severe	14(50.0)	10(35.7)	4(14.3)	28(100)
	Total	28(56.0)	16(32.0)	6(12.0)	50(100)

Table 3: Micro-pancreatic enzyme mixture, vitamin D, calcium and vitamin B12 levels

Parameter	Group	Mean ± SD	P-value
Vitamin D	Study (n = 50)	10.83±5.82 ng/mL	0.096
	Control (n = 50)	9.21±3.0 ng/mL	
Calcium	Study (n = 72)	9.73±0.41mg/dL	0.315
	Control (n = 50)	9.51±0.3mg/dL	
B12	Study (n = 37)	315.38±75.54 pg/mL	0.531
	Control (n = 22)	295.17±88.07 pg/mL	

Table 4: Lipid profiles of study and control groups

Parameter	Group	N	Mean (mg/dL)	Results
Total Cholesterol	Study	68	195.80±40.24	0.001*
	Control	50	219.92±28.00	
Triglyceride	Study	68	136.94±80.93	0.001*
	Control	50	220.44±81.21	
HDL	Study	68	48.30±10.14	0.011*
	Control	50	54.56±16.25	
LDL	Study	68	112.12±27.62	0.003*
	Control	50	126.12±21.21	

*P < 0.05

Vitamin D, Calcium and B12 levels

There was no significant difference in levels of vitamin D, calcium and vitamin B12 between both groups ($p > 0.05$). There was no decrease in vitamin and calcium values due to compensatory mechanisms and storage form in the body (Table 3).

Lipid profile

Study group showed significantly lower lipid profiles compared to control group ($p < 0.05$; Table 4).

DISCUSSION

Since symptoms due to pancreatic exocrine failure are not specific, it is quite difficult to define these symptoms for proper diagnosis. In addition to the direct tests used in diagnosis such as the Secretin-CCK and Lundha test, trypsinogen level, fat measurement in the feces, fecal chymotrypsin activity and fecal elastase-1 level are also indirect tests used to measure pancreatic function [13]. Direct tests are not always accessible in addition to the high cost incurred. Previous study revealed that the pancreatic exocrine insufficiency questionnaire (PEIQ) may be a reliable diagnostic tool [12]. In another study, symptoms, lifestyle and behavioral tendencies of patients were examined as a standardized diagnostic tool [14]. The most common symptoms included are weakness, fatigue, weight loss, abdominal pain, nausea, bloating and gas, intense flatulence and diarrhea. Fatty defecation, which is a sign of pancreatic exocrine insufficiency, was present in 49 %, and foul-smelling defecation was present in 42 % in a wide range of populations (Germany, England, France, and the United Kingdom). The

international similarity and significance of these symptoms showed that PEIQ is a tool that may be used in diagnosis [14]. Patients with complaints of pancreatic exocrine insufficiency avoid certain foods such as fatty foods. Also, pancreatic exocrine insufficiency affects social lives, and treatment has to be initiated for these individuals. Water is one of the basic elements that aid digestion. The main component of bile is water, and of course it plays a role in the digestion of fats. This study revealed that daily water consumption does not affect the efficacy of bile on fat digestion. No relationship was established between the amount of water consumed and symptomatic relief from pancreatic exocrine insufficiency. Since the main digestion of lipids is by pancreatic lipase, evaluation of exocrine enzyme replacement therapies in fat malabsorption is required. It has been shown that pancreatic exocrine enzyme replacement (PERT) therapy improves malabsorption and digestive problems.

A study conducted by Whitcomb *et al* [15] revealed PERT improved symptomatic relief and absorption compared to placebo. Since diagnosis of pancreatic enzyme insufficiency is difficult, applications such as diet or medications from treatment to diagnosis are used. In practice, pancreatic enzyme extracts are used for pancreatic enzyme deficiency symptoms [15]. This study utilized the PEYQ scale on patients who had undergone cholecystectomy in the last 3 months. Severity of PEI was significantly higher in control group compared to study group. Normally, during postprandial period, the gallbladder contracts with the help of cholecystokinin, and empties bolus bile secretion onto the chymus which aids digestion both by physical digestion of the bile itself and by activation of pancreatic pre-enzymes. There are

studies in which pancreatic exocrine function defect is caused by impaired working stability of lipase colipase affected by bile acids [16]. In early post-cholecystectomy period, postprandial bolus bile secretion is impaired, and the inability to inhibit lipase degradation by colipase may lead to PEI development. Thus, symptomatic relief may be obtained by oral replacement of early degraded lipase. Malfunction in lipid digestive metabolism is observed in patients who have undergone cholecystectomy. While digested lipids complete their cycle through oxidation, those that are not digested increase the risk of cardiovascular disease by causing atherosclerosis at high serum levels. Findings from this study revealed that serum lipid levels were significantly lower in study group compared to control group. As a result, micro pancreatic enzyme mixture reduced cardiovascular risk in patients who have undergone cholecystectomy. Furthermore, the role of cholecystectomy in cardiovascular deaths and pancreatic enzyme therapy as a cardioprotective treatment agent would require further investigation.

Limitations of this study

There are some limitations of the study. The lack of long-term follow-up may limit the validity of the results. Therefore, it is not appropriate to extrapolate the results obtained during the early postoperative period to the entire post-cholecystectomy process. This study enrolled patients who used micro pancreatic enzyme mixture for 30 days or more. Thus, the data are insufficient to reach a clear conclusion on the appropriate duration of use in post-cholecystectomy period.

CONCLUSION

Treatment with micropancreatic enzyme mixture significantly improves symptoms, and digestion, and lowers serum lipid levels. A prospective, randomized controlled study will be useful in determining the appropriate dosage and duration of use which provides symptomatic relief and biochemical improvement in patients who have undergone cholecystectomy.

DECLARATIONS

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Ethical approval

It was obtained from the Ethics Committee of T.C. Bozok University (approval no. 2017-KAEK-189_2022.12.15_19).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Duygu Felek designed and wrote the article while Onur İlkey Dinçer and Duygu Felek collected and analyzed the data.

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