# Etiology and pathogenesis of sphincter of Oddi dysfunction. Hypothesis.

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## Abstract

**Introduction.** The sphincter of Oddi (SO) is responsible for the portioned release of bile and pancreatic juice into the duodenum and prevents reflux of duodenal chyme into the bile ducts. The etiology and pathogenesis of sphincter of Oddi dysfunction (SOD) is considered unknown. The normal anatomy of SO is described based on the results of examination of patients with SOD. The SOD is diagnosed, if SO pressure exceeds 40 mmHg, while the norm is defined as 10 mmHg. Both conservative and surgical treatment are aimed at reducing pressure, including with the intersection of SO, which inevitably damages its anti-reflux function. After examination and treatment, severe complications arise, which raises doubts among some authors about the advisability of their use. **Objective:** to isolate reliable scientific information from published materials and evaluate them from the point of view of the physiology of the digestive system. **Material and methods.** An analysis of the literature was carried out to determine the reliability of the results on which the diagnosis and treatment of SOD is based. Based on our own studies of normal and pathological physiology of the duodenum, a hypothesis of the occurrence of acquired diseases of the biliary system has been proposed. **Results.** It has been shown that hypersecretion of hydrochloric acid, which causes other acid-dependent diseases (ulcers, gastritis, duodenitis, gastroesophageal reflux), leads to dyskinesia and hypertrophy of the Ochsner and Kapandji sphincters, because of which in the duodenal segment, between these sphincters, where the SO opens, the pressure increases. This causes dysfunction of SO, increased pressure in the biliary and pancreatic tracts, duodeno-biliary reflux, stone formation, and inflammation in the gallbladder. **Conclusion.** A hypothesis has been proposed to understand the etiology and pathogenesis of sphincter of Oddi dysfunction as one of the clinical manifestations of hydrochloric acid hypersecretion. This hypothesis explains many scientific facts that were hitherto considered to be of unknown origin. Based on this hypothesis, diagnostic and treatment methods have been proposed that cannot cause the complications that are observed when using manometric study of the SO, ERCP, sphincterotomy and sphincteroplasty of the SO. However, studies are needed to confirm the effectiveness of this theoretically based treatment method.

**Keywords:** sphincter Oddi dysfunction; duodenal physiology; normal anatomy and function; hydrochloric acid hypersecretion; diagnosis and treatment SOD.

**1. Introduction.** All sphincters of the digestive tract play an important role in maintaining the normal function of this system, and the sphincter of Oddi (SO) is one of them. This sphincter is located on the border between the bile and pancreatic ducts on one side and the duodenum on the other. This explains the duality of its function. Firstly, it regulates the portioned flow of bile and pancreatic juice into the duodenum. Secondly, it prevents the reflux of duodenal contents into the ducts [1]. The sphincter of the common bile duct was first described in 1888 by Ruggero Oddi, who at that time was a medical student in Perugia (Italy). He not only discovered the sphincter, but also described the dilatation of the bile duct after cholecystectomy and was the first to perform manometry of the biliary tract [2].

## 2. Normal anatomy and physiology of the SO

In most cases, the common bile duct connects close to the duodenum with the large pancreatic duct, forming a common canal that flows into the duodenum. The terminal part of this canal, called the greater duodenal nipple or papilla Vateri, is in the lumen of the duodenum. Circular smooth muscle fibers of the SO surround the lower portion of the common bile duct, of the large pancreatic duct, and the common duct (Figure 1. a) [3]. Kune was the first to show that the zone of narrowing of the distal segment of the common duct, when studied with X-ray contrast agents, represents a zone of active contraction of the SO, which can be measured [4] **(Figure 1, b, c).**

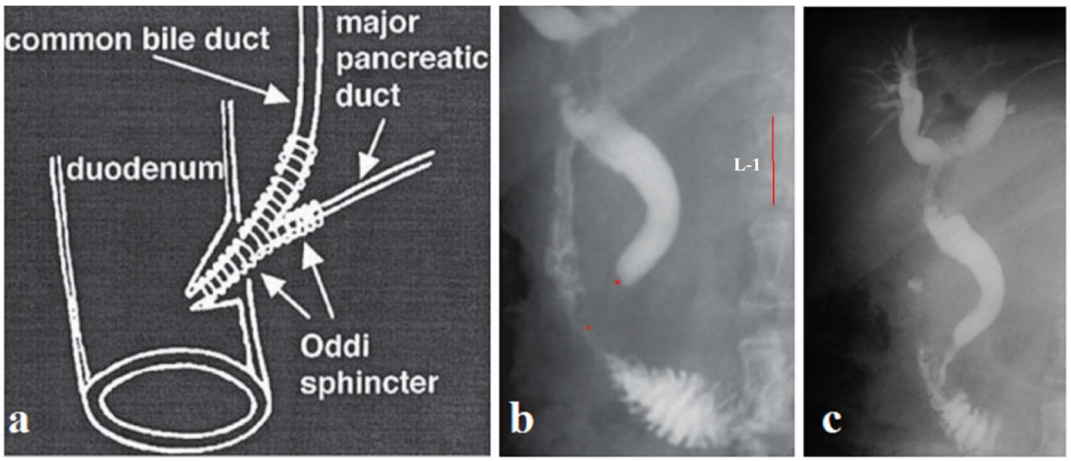


**Figure 1.** Towards the anatomy of SO. **(a)** Diagram from the article by Geenen et al [3]. **(b, c).** Stages of cholecysto-cholangiography in an elderly patient with SO dysfunction. **(b).** Since it is known that the height of the 1st lumbar vertebra in adults is approximately 2.2 cm, the distance between the two red dots, which is caused by the contraction of SO, is 1.1 cm. The width of the CBD in the proximal part is 1 cm, and above the SO - 0.5 cm. The straightened

contours of the 2nd part of the duodenum indicate duodenitis. **(c).** The contrast agent passes into the duodenum through the SO.

Since contrast studies are performed only on patients, the results of measuring SO length by this method should be treated with caution. In a manometric study, SO length was, in the control group, 9.5 ± 0.5 mm. No significant differences were found between controls and patients with common bile duct (CBD) stones [7]. Teilum measured the length of the SO in 148 autopsy specimens with adjacent structures obtained from adults. The median diameter of the common bile duct was 7 mm (range 4-13 mm). No associations were found between the length of the sphincter, and the diameter of the common bile duct, presence of stones in the gallbladder or the postcholecystectomy state [8]. Funch-Jensen et al during endoscopic manometry in healthy volunteers identified SO as a zone with elevated base-line pressure with an average length of 8 cm [9].

These studies of the SO anatomy were carried out in the 20th century. In all articles, SO is described as a narrow channel with a length of about 9.5 ± 0.5 mm [7]. This size is probably closer to the truth, since this was the only study performed among control subjects. SO generates a basal pressure that is higher than the pressure in the common bile duct and duodenum. In healthy volunteers, median values for amplitude were 102.9 mm Hg; base-line pressure, 10 mm Hg; wave duration, 4.8 sec; and frequency, 2.6/min. Most waves propagated antegrade or simultaneously, and in no individual were more than one third of the waves retrograde [9].

**2. 1. What is a SO ampulla?** In recent decades, a completely different picture has been described as normal SO anatomy. During cholangiography, in the area between the CBD and the papilla, two areas of contraction are identified, between which there is a wide cavity called the ampulla. When the peristaltic wave reaches SO, "first the upper part, the sphincter choledochus, opens from above downwards, the contrast enters the ampulla. Then the sphincter choledochus contacts, again from above downwards, isolating a small portion of contrast in the ampulla. The distal sphincter opens, and the systolic volume falls into the duodenum" [10]. The ampullae appear In all peristaltic systems, if sphincters function impaired. Normally, the last peristaltic creates the threshold pressure for sphincter opening. The ampulla represents the last peristaltic wave with a wide lumen, which reduces its ability to create a threshold pressure for SO opening. To create a threshold pressure, a functional sphincter arises, the contraction of

which allows the ampulla to create a higher pressure and inject a bolus into the lumen with a higher pressure than in the CBD (**Figure 2. a, b)** [11].

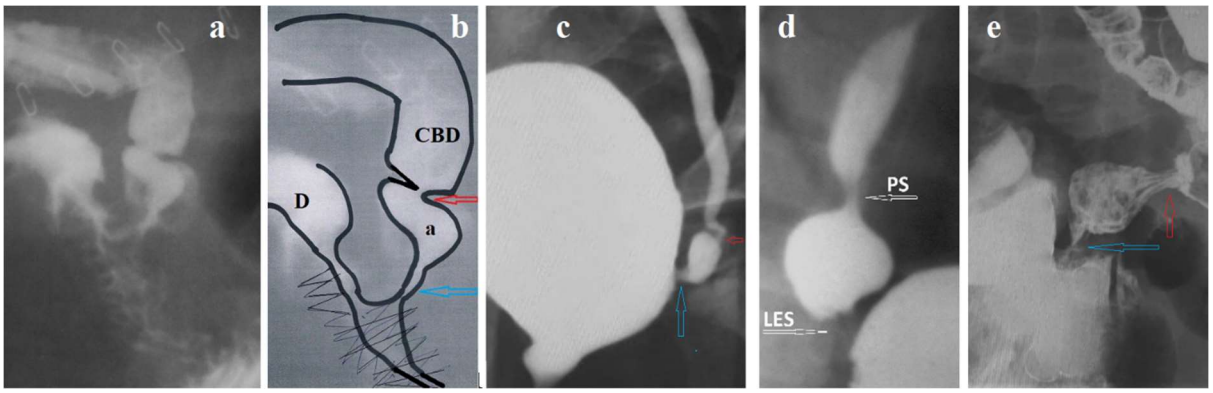


**Figure 2. (a).** Cholangiography for severe SO damage, and (b) a diagram for it. (d – duodenum; CBD – common bile duct; a – ampulla located between the shortened SO - blue arrow, and the functional sphincter - red arrow). (c). Vesicoureteral reflux. The ampulla is located between the vesicoureteral sphincter - blue arrow, and the functional sphincter - red arrow. (d). Gastroesophageal reflux. The phrenic ampulla is located between the LES and the functional (proximal) sphincter (PS). (e). A patient with enteritis. The ampulla is located between the ileocecal valve - blue arrow, and the functional sphincter - red arrow.

The cholangiography is performed on patients with severe symptoms of the disease. Therefore, the results obtained in patients with pathology of the pancreato-biliary system cannot be considered an anatomical norm. Secondly, it contradicts anatomical and radioligical studies conducted in control groups. It follows that the presence of an ampoule is evidence of severe SO damage.

Since the antireflux function of SO depends on the condition of the duodenum, below we will dwell on the normal anatomy and physiology of the duodenum.

**3. Duodenal motility**

In the duodenum, four sphincters function, which protects the small intestine from the aggressive effects of hydrochloric acid. If the bolus would pass through the duodenum as quickly as through the esophagus, then an extremely low pH bolus would cause damage of the jejunum. The post bulbar sphincter (PBS), together with the pyloric sphincter (PS), provides evacuation of the chyme from the stomach as portions of a certain volume (**Figure 3 A).** When the acid bolus reaches the Ochsner's sphincter, which is in the 3rd part of the duodenum, it causes of its contraction, which prevents entering aggressive chyme to the jejunum **(Figure 3 B).** As a result of the Ochsner's sphincter contraction, the bolus is thrown cranially, but

Kapanji's sphincter contraction, bolus is again thrown в towards the Ochsner's sphincter. This pendulum movement of the bolus between the Ochsner and Kapanji sphincters occurs several times. During this time, the chyme mixes with bile and pancreatic juice, which raise the pH of the chyme. When the pH reaches a level that is safe for the jejunum, Ochsner's sphincter opens, and bolus passes into the jejunum [12,13,14,15]. During gallbladder and stomach operations Ochsner found the duodenum is distended with gas to a point just below the entrance of the common duct, while below this it is contracted. In all histological specimens, there is also a marked thickening of the intestinal wall for 2 to 4 centimeters below the entrance of the common duct, with a marked increase in the circular muscle fibers. In his work, Ochsner not only described the sphincter in the third part of the duodenum, but also associated its function with the reaction to hydrochloric acid and its hypertrophy with such acid-related diseases as gastric ulcers, duodenal ulcers, and biliary tract pathology [12]. On a standard x-ray study, barium passes through the duodenum without delay because it has a high pH. When vitamin "C" was added to barium, we found a contraction of the Ochsner and Kapandji sphincters and were able to determine their sizes **(Figure 3 C)** [13].

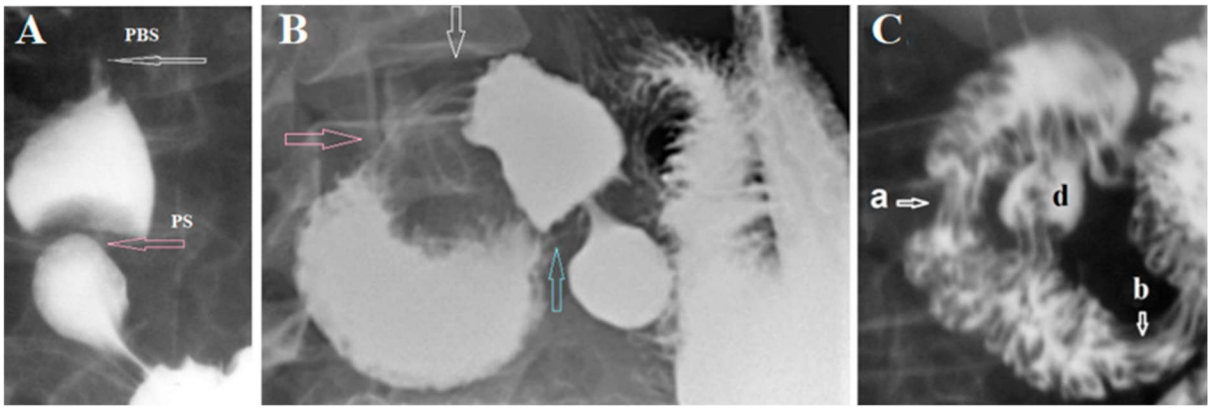


**Figure 3.** X-ray demonstration of the duodenal sphincters. (**A**). During antral contraction, the duodenal bulb fills to the limit, after which the pyloric sphincter (PS) contracts, stopping the flow of barium from the stomach into the bulb. Then, during the peristaltic contraction of the bulb between the PS and PBS, the pressure rises, which causes the PBS to relax, and the bolus penetrates the 2nd part of the duodenum. (**B**) In elderly patient with duodenal dyskinesia the white arrow shows PBS location. An expansion of the duodenum is determined between the Kapanji's sphincter (pink arrow) and the Ochsner's sphincter (blue arrow). (**C**) The duodenum was emptied, but the barium remained in deep folds because the barium-filled bowel was very wide. Two zones of contraction with longitudinal folds are visible: (a) the Kapanji's sphincter, and (b) the Ochsner's sphincter. The juxtapapillary diverticulum (d) is located between them.

These diverticula result from the extrusion of the mucosa between the muscular fibers. Thus, this diverticulum is evidence of high pressure that occurs between contracted sphincters Kapanji and Ochsner.

The above studies indicate that hypersecretion of hydrochloric acid, which causes acid-related diseases, leads to duodenal dyskinesia. This is accompanied by hypertrophy of the Ochsner and Kapandji sphincters and expansion of the duodenum between them, which is caused by an increase in pressure in this segment where the SO opens. This is confirmed by manometric studies by Zhang et al, which found that patients with SO pathology often (36%) have duodeno-biliary reflux. In some of them (80%), the pressure in the duodenum was higher than in the common bile duct [16].

**4. Criticism of the current state of the issue of etiology and pathogenesis of Oddi sphincter dysfunction**

**4.1.** All authors agree that the etiology of SOD is unknown. Some articles make assumptions that have no scientific basis.

**4. 2.** At present the SOD are mostly diagnosed by Rome IV criteria, which defined the biliary-type of pain, if it is localized in epigastric or right upper quadrant. These symptoms, however, are also common for other acid-related disorders (duodenitis, ulcers, GERD, etc.), that are more frequent than SO [17]. Thus, the clinical definition of SOD is erroneous and should not be used at all. This is an example of how decisions made by voting are not scientific and should not be used either in science or practice.

**4. 3.** Until now, all researchers refer to the Milwaukee classification of SOD, proposed by Hogan and Geenen in 1988 [18]. They subdivided sphincter of Oddi (SO) motor dysfunction into two broad categories: 1. SO stenosis: defined as a structural narrowing of part or all the SO segment, and 2) SO dyskinesia (SOD): defined as a primary disorder of SO tonic/phasic motor activity. They divided patients with SOD into three groups. SOD-I with biliary-type pain, abnormal liver function tests (SGOT; al PO4 greater than 2 x normal) documented on 2 or more occasions, delayed drainage of ERCP contrast greater than 45 min, and dilated CBD greater than 12 mm diameter; SOD-II with biliary-type pain but only 1 or 2 of the above criteria; SOD-III-patients with only biliary-type pain and no other abnormalities [18].

Firstly, as shown above, the so-called biliary-type pain is often a symptom of other acid-dependent diseases. Secondly, a review by Wilcox showed that type III SOD likely does not exist as a true pancreaticobiliary disease. In patients in whom SOD was diagnosed, approximately 50% in the sham group as compared to 36% in the sphincterotomy group had symptomatic improvement. This indicates about the placebo phenomenon [19]. Third, in the

article Ponchonin et al sixty-nine consecutive patients with SOD were treated with endoscopic sphincterotomy. No gallstones were found in the gallbladder or bile duct. Three patients (4.3%) were found to have adenocarcinoma in the ampulla of Vater. Thirty-six had normal results of biopsy analysis and 30 had inflammatory or fibrotic changes on biopsy specimens [20]. These studies suggest that type III SOD is not related to SOD, which is confirmed by other authors [17]. Therefore, this type should be excluded from the classification. It also turned out that the Milwaukee classification does not allow differentiating functional and organic lesions of SO, most likely because these are stages of the pathogenesis of the same disease.

**4.4.** According to Villavicencio Kim and Wu manometry is the gold standard for the diagnosis of SOD, although results vary with patient and operator experience. SOD is defined by manometry as a basal biliary or pancreatic sphincter pressure of >40 mmHg, which is greater than three standard deviations above average pressure. Other criteria are increased phasic wave frequency, or tachyoddia >8/min, an increase of >50% in the number of retrograde propagations of SO phasic contractions, and a paradoxical response to CCK [21]. However, this test is nonconfirmatory in 13–40% of patients with SOD type 1 [21]. Secondly, in almost 30% of patients it provokes pancreatitis, which served as a reason for Kegnæs et al not to recommend its use [17].

Geenen et al were probably the first to establish a pressure limit of 40 mmHg [22]. However, if SO normally creates a pressure of 10 mmHg [9], then 40 mmHg cannot be a diagnostic criterion for pathology, because patients with a pressure from 10 to 40 mmHg cannot be considered healthy if their pressure is higher than normal. And as a result, they fall out of the sight of doctors. This limit is used by surgeons to assess the effectiveness of sphincterotomy post-operatively. For example, it was shown that only patients with pressure >40 mmHg had more frequent and long-lasting pain relief [22,23].

**4.5.** The article by Walia et al no differences in outcome sphincteroplasty were found between type I, II, or III SOD patients [24]. If we consider that patients with SOD type III did not have SO lesions, this directly indicates, that the poor results (postoperative complications 27%; 33% of patients had subsequent biliary-pancreatic procedures, 22 patients undergoing subsequent ERCP and 4 patients progressing to pancreaticoduodenectomy) are due to the operation itself, and not to the pathology of SO.

**4.6.** The purpose of sphincterotomy and sphincteroplasty is to facilitate the outflow of bile and pancreatic juice. But the indicator of effectiveness is pain relief. What's really going on? All patients undergoing major ampullary sphincteroplasty had manometric pressures reduced to 0 mm Hg [24]. It follows from this that, in all patients led to a complete loss of the anti-relux

function of the SO. Dissection of the circular muscles of the SO leads to improved outflow of bile and pancreatic juice and pain relief. However, these procedures permanently destroy the antireflux function of SO and lead to the reflux of aggressive gastric juice into the bile ducts. Duodeno-biliary reflux causes an inflammatory process in the bile ducts, as well as pancreatitis (up to 30%). Healing of incised tissue often leads to restenosis. Over time, sclerotic changes and epithelial metaplasia occur in the ducts, with long-term carcinogenic effects in more than 4.3% of patients [17, 20]. We see an almost complete analogy of duodeno-biliary reflux with gastroesophageal reflux, where hydrochloric acid reflux causes esophagitis, dilatation of the esophagus and the formation of phrenic ampulla with metaplasia of the esophageal mucosa up to the appearance of a carcinoma [25]. Understanding the importance of sphincter preservation, Habib et al proposed partial sphincterotomy, which was tailored to the manometric findings and reduced sphincter length by only 46.7 ±10.3% [7].

**4.7.** Endoscopic sphincterotomy was reported to be effective in patients with abnormal SO manometry in many publications. However, the effect of sphincterotomy has subsequently been questioned even in those with positive SO manometry. Toouli et al. concluded that sphincterotomy was useful only in patients with SO stenosis [23]. Tanaka considers that biliary-type pain in SO dysfunction originates from increased biliary intraluminal pressure. They showed that the rise in the duodenal pressure during MMC phase III causes a transient elevation in biliary pressure, which is accompanied by biliary pain [26, 27]. Small bowel manometry found that disturbances of duodeno-jejunal motor activity were more pronounced in SOD I/II compared with SOD type III patients [28,29]. Zhang et al found that patients with SO pathology often (36%) have duodeno-biliary reflux. In some of them (80%), the pressure in the duodenum was higher than in the common bile duct [16]. Thus, they proved what Ochsner's work, and our x-ray studies suggested. Duodenal dyskinesia, caused by hypersecretion of hydrochloric acid, leads to an increase in pressure in the part where the SO opens. This may be the root cause of SOD and may also aggravate the disease after sphincterotomy. From this point of view, it is possible to understand a phenomenon that was considered inexplicable. Patients who have undergone Roux-en-Y gastric bypass surgery demonstrate better results with transduodenal sphincteroplasty than those with an unaltered alimentary stream [30,31]. This effect could be explained by the fact that in the Roux-en-Y duodenojejunal anastomosis significant part of the chyme passes past the duodenum, which reduces the pressure in it and the likelihood of penetration of chyme through SO.

**5. Etiology and pathogenesis of Oddi sphincter dysfunction**

Based on the analysis of the literature and our own research, the following conclusions can be drawn. (a). Hypersecretion of hydrochloric acid, which causes acid-related diseases (esophagus, stomach, and duodenum), leads to dyskinesia of the duodenum, including the Kapanji and Ochsner sphincters with hypertrophy of their walls; (b). In the duodenum between the Kapanji and Ochsner sphincters, where the SO opens, pressure increases. (c). An increase in pressure in the chamber into which the SO opens lead to a disruption of its function (dyskinesia), which causes to a delay in the outflow of bile and pancreatic juice, an increase in pressure in the ducts and contributes to the periodic reflux of an acidic bolus into the ducts. (d). With a significant expansion of the CBD, a shortening of the SO occurs with the formation of ampulla and a functional sphincter above it. (f). Duodeno-biliary reflux increases pressure in the biliary system, which leads to disruption of liver function tests, chronic pancreatitis, the formation of gallstones and acute cholecystitis, after contamination of microorganisms. (f). Pathology of the biliary system, including SOD, is an acid-dependent disease and therefore is always combined with other acid-dependent diseases. Their differential diagnosis can be difficult since many symptoms of different diseases are the same. The ontogenesis of the disease begins from the dyskinesia with the subsequent development of inflammatory, sclerotic, and anatomical changes, including the formation of ampulla, SO stenosis, metaplasia, which can lead to the tumor. Thus, SOD is one of the possible stages in the development of pathology caused by hypersecretion of hydrochloric acid. Wehrmann et al found that the lower esophageal sphincter pressure and anal sphincter resting pressure were significantly higher in patients with type I-SOD than in healthy subjects. These results provide evidence for a systemic involvement of the lower esophageal and the anal sphincter in patients with type I-SOD, which does not occur in patients with type III-SOD [32]. Knowledge of the etiology, pathogenesis and pathophysiology of the disease is necessary for prescribing pathogenetic treatment.

**6. Rationale for pathogenetic treatment of SOD**

Treatment of SOD assumed that pain was caused by SO spasm. Even though the results of the use of drug treatment in some patients suggested that nifedipine was effective, they were based on perception and tolerance toward pain intensity and were highly subjective [21]. The use of antispasmodics could not be successful in case of stenosis, and in case of dyskinesia, these drugs further disrupt the antirelux function of the SO. Since SOD is an acid-related disease, it is always combined with other similar problems, such as ulcers, inflammatory diseases of the esophagus, stomach, and GERD. From the point of view of the etiology and pathogenesis of SOD described above, pathogenetic treatment include:

**6.1.** Refusal to take provocateurs of hydrochloric acid hypersecretion (products containing lactose, honey, chocolate, citrus fruits). Without this, any treatment cannot be successful.

**6.2.** Taking drugs that suppress the secretion of hydrochloric acid (PPI) is of great importance but cannot be the only method of treatment.

**6.3.** The effectiveness of treatment by Carlsbad alkaline water (pH-8-9), including for diseases of the biliary tract [33], has been proven by its use over several centuries. It is known that hydrochloric acid hypersecretion, the tissues of the digestive tract are damaged not only by the acid, but also by pepsin, which requires acid for its activation. Unlike conventional drinking water, pH 8.8 alkaline water instantly denatures pepsin, rendering it permanently inactive. In addition, it has good acid-buffering capacity. Thus, the consumption of alkaline water may have therapeutic benefits for patients with gastrointestinal disease [34]. As shown by a study by Lazebnik et al, the use of natural mineral water "Borjomi" alleviates not only the symptoms of functional dyspepsia, but also constipation [35].

**6.4.** To prevent duodeno-biliary reflux, it is necessary to reduce pressure in the duodenum, which can be facilitated by mechanical stretching of the sphincters. Ingested dense tablets with a diameter of about 2 cm is pushed by a peristaltic wave through the hypertrophied Ochsner sphincter, which leads to a decrease in its tone. The procedure can be repeated several times **(Figure 4).** If there is no effect, it is advisable to expand the SO. Sphincterotomy and sphincteroplasty lead to the cessation of the antireflux function of SO - forever, and to severe complications. According to Hyun and Kozarek, the simplistic view that SOD, however it has been diagnosed, requires biliary or dual sphincterotomy is just that, simplistic and potentially misguided [36].

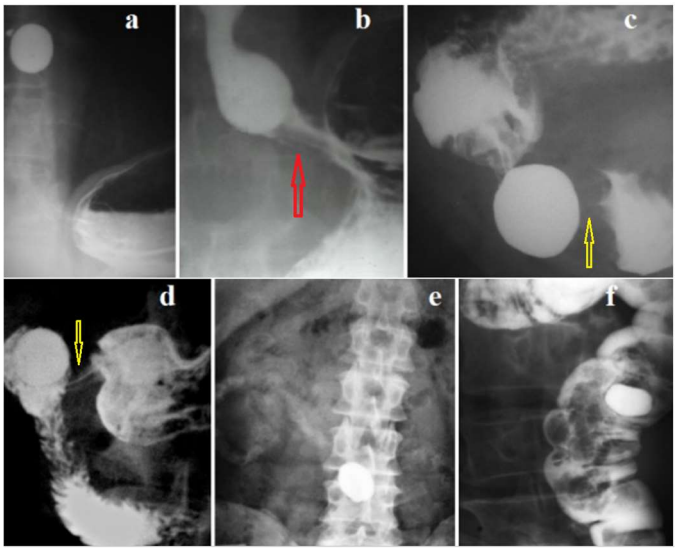

**Figure 4.** Radiographs from different studies demonstrating the movement of a contrast tablet through the digestive tract. (a). In the esophagus. (b). Above the lower esophageal sphincter (red arrow). (c). In the antrum of the stomach above the pyloric sphincter (yellow arrow). (d). In the duodenal bulb after passage through the pyloric sphincter (yellow arrow). (e). In the small intestine. (f). In the descending colon.

Tablets with a diameter of 1.9 to 2.5 cm, prepared from a mixture of barium and flour, passe through the entire digestive tract. In the small and large intestines, the tablets begin to decrease in size as they gradually dissolve under the influence of chyme. This way they can't get stuck for long periods of time and cause any damage. Using the example of the lower esophageal and pyloric sphincters, the diameter of which when opened normally does not exceed 4 mm, tablets with a diameter of up to 2.5 cm pass under the influence of a peristaltic wave. Patients do not feel the advancement of the tablet, except in very rare cases, if the tablet passed through the sphincter affected by the ulcerative process. Stretching the sphincters in patients with hypersecretion of hydrochloric acid improves their throughput and alleviates or completely relieves symptoms [37].

The complex of therapeutic measures described above is intended for the treatment of diseases of duodeno-biliary reflux, including SOD. However, with hypersecretion of hydrochloric acid, all organs of the digestive tract are affected, especially the esophagus, stomach, and duodenum. In this series, only the esophagus does not have any protection and requires additional treatment methods to those described above. This is very important because gastroesophageal reflux disease (GERD) progresses despite the absence of typical symptoms, often under the label of irritable bowel syndrome, functional dyspepsia, or other non-esophageal symptoms. Once a diagnosis of GERD has been made, the following should be added to the treatment described above:

**6.5. Additional recommendations when diagnosing GERD confirmed.**

**6.5.1.** Changing behavior (habits) on a permanent basis.

**A).** Need to go to bed with an empty stomach.

**B).** Cannot use a tight belt, bend over, or play sports after eating.

**C).** Need to reduce the volume of one feeding and reduce the weight if body mass index = or > 25.

**6.5.2.** During an exacerbation, along with taking PPI, antacids are recommended, as well as protectors of the esophageal mucosa 30 minutes after eating.

**Conclusion.** A hypothesis has been proposed to understand the etiology and pathogenesis of sphincter of Oddi dysfunction as one of the clinical manifestations of hydrochloric acid hypersecretion. This hypothesis explains many scientific facts that were hitherto considered to be of unknown origin. Based on this hypothesis, diagnostic and treatment methods have been proposed that cannot cause the complications that are observed when using manometric study of the SO, ERCP, sphincterotomy and sphincteroplasty of the SO. However, studies are needed to confirm the effectiveness of this theoretically based treatment method.

**References**


1. Horiguchi S, Kamisawa T. Major duodenal papilla and its normal anatomy. Dig Surg. 2010;27(2):90-3. doi: 10.1159/000288841.
2. Capodicasa, E. Ruggerro Oddi: 120 years after the description of the eponymous sphincter: a story to de remembered / E. Capodicasa // Gastroenterol. Hepatol. – 2008. – Vol. 23, N 8. – Pt. 1. – P. 1200-1203.
3. Geenen JE, Hogan WJ, Dodds WJ, et al. Intraluminal pressure recording from the human sphincter of Oddi. Gastroenterology. 1980 Feb;78(2):317-24.
4. KUNE GA. SURGICAL ANATOMY OF COMMON BILE DUCT. Arch Surg. 1964 Dec;89:995-1004. doi: 10.1001/archsurg.1964.01320060063012.
5. Kune GA. The influence of structure and function in the surgery of the biliary tract. Ann R Coll Surg Engl. 1970 Aug;47(2):78-91.
6. Kune, G. A. The practice of the surgery / G. A. Kune, A. Sali. – 2nd ed. – Oxford: Blackwell Scientific Pub., 1980. – 344 p.
7. Habib FI, Corazziari E, Biliotti D, Primerano L, Viscardi A, Speranza V, De Masi E, Fegiz G, Torsoli A. Manometric measurement of human sphincter of Oddi length. Gut. 1988 Jan;29(1):121-5. doi: 10.1136/gut.29.1.121.
8. Teilum D. In vitro measurement of the length of the sphincter of Oddi. Endoscopy. 1991 May;23(3):114-6. doi: 10.1055/s-2007-1010634.
9. Funch-Jensen P, Kruse A, Ravnsbaek J. Endoscopic sphincter of Oddi manometry in healthy volunteers. Scand J Gastroenterol. 1987 Mar;22(2):243-9. doi: 10.3109/00365528708991887
10. Horiguchi S, Kamisawa T. Major duodenal papilla and its normal anatomy. Dig Surg. 2010;27(2):90-3. doi: 10.1159/000288841.
11. Levin MD. Gastrointestinal Motility and Law of the Intestine. (Preprint), Posted Date: 26 December 2023 doi: 10.20944/preprints202312.2003.v1.

12. Ochsner AJ. VIII. Construction of the Duodenum Below the Entrance of the Common Duct and Its Relation to Disease. Ann Surg. 1906 Jan;43(1):80-7. doi: 10.1097/00000658-190601000-00009. (Open access).
13. Levin MD, Korshun Z, Mendelson G. [Duodenal motility in norm and in some diseases. Hypothesis]. Ter Arkh. 2016;88(4):68-74. doi: 10.17116/terarkh201688468-74.
14. Levin MD. Superior Mesenteric Artery Syndrome Results From Hypersecretion of Hydrochloric Acid. (Preprint), Posted Date: 8 January 2024 doi:10.20944/preprints202401.0605.v1.
15. Aldot G, Kapandji M, Ringendach J. Physiology of timed duodenal intubation. II. Role of Ochsner's sphincter in the mechanism of normal duodenal intubation and in that of certain prolongations of so-called Oddi's closed time. (1956) Arch Mal Appar Dig Mal Nutr. 1956 Dec;45(12):449-57.
16. Zhang ZH, Wu SD, Wang B, et al. Sphincter of Oddi hypomotility and its relationship with duodenal-biliary reflux, plasma motilin and serum gastrin. World J Gastroenterol. 2008 Jul 7;14(25):4077-81. doi: 10.3748/wjg.14.4077.
17. Kegnæs M, Novovic S, Shabanzadeh DM. Dysfunction of Biliary Sphincter of Oddi-Clinical, Diagnostic and Treatment Challenges. J Clin Med. 2023 Jul 20;12(14):4802. doi: 10.3390/jcm12144802.
18. Hogan WJ, Geenen JE. Biliary dyskinesia. Endoscopy. 1988 Aug;20 Suppl 1:179-83. doi: 10.1055/s-2007-1018172.
19. Wilcox CM. Sphincter of Oddi dysfunction Type III: New studies suggest new approaches are needed. World J Gastroenterol. 2015 May 21;21(19):5755-61. doi: 10.3748/wjg.v21.i19.5755.
20. Ponchon T, Aucia N, Mitchell R, et al. Biopsies of the ampullary region in patients suspected to have sphincter of Oddi dysfunction. Gastrointest Endosc. 1995 Oct;42(4):296-300. doi: 10.1016/s0016-5107(95)70125-7.
21. Villavicencio Kim J, Wu GY. Update on Sphincter of Oddi Dysfunction: A Review. J Clin Transl Hepatol. 2022 Jun 28;10(3):515-521. doi: 10.14218/JCTH.2021.00167.
22. Geenen JE, Hogan WJ, Dodds WJ, Toouli J, Venu RP. The efficacy of endoscopic sphincterotomy after cholecystectomy in patients with sphincter-of-Oddi dysfunction. N Engl J Med. 1989 Jan 12;320(2):82-7. doi: 10.1056/NEJM198901123200203.

23. Toouli J, Roberts-Thomson IC, Kellow J, Dowsett J, Saccone GT, Evans P, Jeans P, Cox M, Anderson P, Worthley C, Chan Y, Shanks N, Craig A. Manometry based randomised trial of endoscopic sphincterotomy for sphincter of Oddi dysfunction. Gut. 2000 Jan;46(1):98-102. doi: 10.1136/gut.46.1.98.
24. Walia S, Zaidi MY, McGuire S, Milam C, Fogel EL, Sherman S, Lehman G, Pitt HA, Nakeeb A, Schmidt CM, House MG, Ceppa EP, Timsina L, Zyromski NJ. Contemporary Outcomes of Transduodenal Sphincteroplasty: the Importance of Surgical Quality. J Gastrointest Surg. 2023 Dec;27(12):2885-2892. doi: 10.1007/s11605-022-05539-y.
25. Labenz J, Chandrasoma PT, Knapp LJ, DeMeester TR. Proposed approach to the challenging management of progressive gastroesophageal reflux disease. World J Gastrointest Endosc. 2018 Sep 16;10(9):175-183. doi: 10.4253/wjge.v10.i9.175.
26. Tanaka M, Ikeda S, Matsumoto S, Yoshimoto H, Nakayama F: Manometric diagnosis of sphincter of Oddi spasm as a cause of postcholecystectomy pain and the treatment by endoscopic sphincterotomy. Ann Surg 1985;202:712–719.
27. Utsunomiya N, Tanaka M, Ogawa Y, Konomi H, Takahata S, Nabae T, Yokohata K, Chijiiwa K: Pain associated with phase III of the duodenal migrating motor complex in patients with postcholecystectomy biliary dyskinesia. Gastrointest Endosc 2000;51:528–534.
28. Evans PR, Dowsett JF, Bak YT, Chan YK, Kellow JE. Abnormal sphincter of Oddi response to cholecystokinin in postcholecystectomy syndrome patients with irritable bowel syndrome. The irritable sphincter. Dig Dis Sci. 1995 May;40(5):1149-56. doi: 10.1007/BF02064214
29. Evans PR, Bak YT, Dowsett JF, Smith RC, Kellow JE. Small bowel dysmotility in patients with postcholecystectomy sphincter of Oddi dysfunction. Dig Dis Sci. 1997 Jul;42(7):1507-12. doi: 10.1023/a:1018879029855.
30. Madura JA, Madura JA 2nd, Sherman S, Lehman GA. Surgical sphincteroplasty in 446 patients. Arch Surg. 2005 May;140(5):504-11; discussion 511-3. doi: 10.1001/archsurg.140.5.504.
31. Giannopoulos GA, Digalakis MK. Surgical pancreatic sphincteroplasty. Historic or history? A review. Acta Chir Belg. 2010 Nov-Dec;110(6):569-74.
32. Wehrmann T, Wiemer K, Lembcke B. Osophagus- und anorektale Motilität bei Patienten mit Sphinkter-Oddi-Dysfunktion [Esophagus and anorectal motility in

patients with dysfunction of Oddi's sphincter]. Z Gastroenterol. 1996 Aug;34(8):483-9.

33. Benda J. Treatment of biliary diseases in Karlovy Vary. Rev Czech Med. 1967;13(1):1-15. PMID: 6044708.
34. Koufman JA, Johnston N. Potential benefits of pH 8.8 alkaline drinking water as an adjunct in the treatment of reflux disease. Ann Otol Rhinol Laryngol. 2012 Jul;121(7):431-4. doi: 10.1177/000348941212100702.
35. Lazebnik LB, Simanenkov VI, Tikhonov SV, Lishchuk NB. CLINICAL STUDY OF THE EFFICACY OF NATURAL MINERAL WATER "BORJOMI" IN PATIENTS WITH FUNCTIONAL DYSPEPSIA. Eksp Klin Gastroenterol. 2016;(11):26-30.
36. Hyun JJ, Kozarek RA. Sphincter of Oddi dysfunction: sphincter of Oddi dysfunction or discordance? What is the state of the art in 2018? Curr Opin Gastroenterol. 2018 Sep;34(5):282-287. doi: 10.1097/MOG.0000000000000455.
37. Levin MD. Examination and treatment of patients with gastroesophageal reflux disease in primary care. https://www.anorectalmalformations.com/_files/ugd/4d1c1d_81aa51b192f4488692f52f5ac6a3818d.pdf.