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Sphincter of Oddi Dysfunction: Updates from the Recent Literature

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Abstract Sphincter of Oddi dysfunction (SOD) has long been a controversial topic, starting with whether it even exists, as a sphincterotomy-responsive entity to treat, for either: (1) post-cholecystectomy abdominal pain and/or (2) idiopathic recurrent acute pancreatitis (IRAP). Many of its aspects had required further research to better prove or refute its existence and to provide proper recommendations for physicians to diagnose and treat this condition. Fortunately, there has been major advancement in our knowledge in several areas over the past few years. New studies on challenging the classification, exploring alternative diagnostic methods, and quantifying the role of sphincterotomy in treatment of SOD for post-cholecystectomy pain and for IRAP were recently published, including a randomized trial in each of the two areas. The goal of this paper is to review recent literature on selected important questions and to summarize the results of major trials in this field.

Keywords Sphincter of Oddi dysfunction · Review · Updates · Pancreatitis · Idiopathic · Post-cholecystectomy abdominal pain · Manometry

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Introduction

Sphincter of Oddi dysfunction (SOD) is defined based on typical biliary or pancreatic pain and is classified using Milwaukee criteria, or modified versions thereof, based on the presence or absence of ductal dilation or enzyme abnormalities. It is believed, more commonly in the USA, to be responsible for persistent or new episodic abdominal pain in patients following cholecystectomy. Sphincter of Oddi manometry (SOM) is considered the gold standard in diagnosing SOD. Like other functional gastrointestinal diseases, little is known about the etiology of the disease, and therefore, therapeutic modalities are not targeted toward a specific molecular pathway but rather on surgically or endoscopically ablating the sphincter. There has recently been significant advancement in our knowledge on treatment of SOD, and especially type III, particularly following completion of the Evaluating Predictors and Interventions in Sphincter of Oddi Dysfunction (EPISOD, sponsored by NIDDK) multicenter randomized sham-controlled trial [1••]. Here, we aim to highlight studies which answered important questions about SOD over the last 3 to 4 years in different categories.

Classification and Clinical Features

Definition of SOD: Does the Milwaukee Classification Cover It All?

The Milwaukee classification has been widely accepted as the classification system for SOD. Although arbitrary, it was helpful at grouping patients into three groups of descending perceived chance of benefit from sphincter intervention. Type 1 had dilated ducts and abnormal chemistry (highest benefit), type 2 had one or the other but not both, and type 3 had pain

alone (lowest benefit). Type Is likely had some type of fixed stenosis, and it was felt that it was "obvious" that they would respond, type IIs had two randomized trials supporting SOM-directed therapy, and type IIIs had only retrospective series showing modest benefits. Freeman et al. recently challenged this notion, showing that other characteristics (gender, gastroparesis, etc.) had more predictive value than the conventional "typing" [2]. However, in support of the traditional "typing," a few years later, in a smaller single-center Irish study, Heetun et al. included 72 patients in an endoscopic retrograde cholangiopancreatography (ERCP) database who had undergone a biliary sphincterotomy (without SOM) for a history of typical biliary pain [3], about half (55.6 %) of whom had previous cholecystectomy. At 1.5 years, type I patients reported complete pain relief in 91 %, compared with 75 and 50 % in type II and type III, respectively. The rate of complete response, interestingly, was not dependent on the gallbladder status (85 % in cholecystectomized patients and 81 % of the others). Lastly, for medical therapy, no difference in response was seen in type II and III groups (77 and 76 %), and type I patients had only a slightly lower response rate (62 %) to non-endoscopic therapy in a UK study [4].

Gong and colleagues suggested a modified Milwaukee classification and reported their experience in a cohort of 305 Chinese patients with SOD [5]. They suggested adding two groups to the current biliary and pancreatic type. They proposed a double-duct and a biliary-pancreatic reflux type. They defined the former (6.2 % of their cohort) as those with clinical, radiographical, and lab abnormalities seen in both biliary and pancreatic ducts, whereas the latter (13.4 % of their cohort) had similar abnormalities of both ducts but more pancreatic-type pain presentations. They did not present stratified response rates, however, and it is unclear how adding these would be helpful. In addition, these two groups may just represent chronic pancreatitis with secondary sphincter stenosis.

Is There a Validated Tool Available to Reliably Measure the Burden of SOD?

Thus far, there has been no validated tool to specifically measure the severity and burden of pain before and after treatment in patients with SOD. Most studies have used general tools such as the 36-item Short Form Health Survey (SF-36) or simply reported the frequency and intensity of pain to measure the outcome; however, it was felt that this may not work well for SOD-related pain which may be intermittent and severe, with normal quality of life in between attacks. Therefore, Durkalski and colleagues developed and validated a new measurement tool, based on a tool used to measure the pain burden of migraine headaches, to reliably assess outcomes of the treatment of SOD type III as part of an EPISOD trial [6]. They conducted two pilot studies to assess test-retest reliability of the recurrent abdominal pain intensity and disability (RAPID) instrument. This is a 90-day summation of number of days where productivity for various daily activities is decreased as a result of abdominal pain. Reduced activity was defined as missed days and days where productivity for paid work or school, household activities, and non-work activities are reduced by half as a result of abdominal pain episodes. The agreement of measurement using this instrument was demonstrated as being very good in both pre-sphincterotomy and post-sphincterotomy population and seemed to be responsive to sphincterotomy, improving significantly after intervention. Therefore, the authors suggested that RAPID is a reliable instrument for measuring disability resulting from abdominal pain in suspected SOD patients.

Can Clinical Features Predict Manometric Findings in Patients with SOD?

Except for type I SOD, wherein empiric sphincterotomy is considered acceptable, patients with suspected SOD are supposed to undergo ERCP and SOM for diagnostic purposes, followed by manometry-directed treatment. Given the high risk of complications in this group, finding a safer alternative to SOM is appealing and could avoid complications. Romagnuolo and colleagues performed a prospective cross-sectional study on 214 post-cholecystectomy patients, suspected for SOD and participating in the landmark EPISOD multicenter trial, to investigate if the patient and pain characteristics, such as more typical pain (esp. with trivially elevated biochemistry), less functional or psychological comorbidity, and more objective history (cholecystectomy for stones rather than dyskinesia), could predict the findings on SOM in patients with SOD [7•]. Patients with significant psychiatric history (severe untreated depression, suicidality, etc.) were excluded, but minor elevations in liver or pancreas enzymes were allowed in the trial (about 15 % of the cohort). Potential predictors that were investigated included age, sex, race, location of pain, narcotic use, characterization of pain, timing and pain-relief duration after cholecystectomy, pre-cholecystectomy gallbladder findings and pathology, psychological comorbidity, presence of functional disorders, Coping Strategies Questionnaire—Catastrophizing scale (CSQ-CAT), and quality of life (SF-36). Most patients (137; 64 %) had abnormal (including 34 % who had abnormal biliary and pancreatic SOM) pancreatic SOM and 77 patients (36 %) had normal pancreatic SOM. The study unfortunately showed that none of the demographical factors, pain patterns, functional disorders, gallbladder pathology, or increased pancreatobiliary enzymes predicted abnormal SOM findings. The authors found similar results when they explored different (60- and 100-mmHg) cutoffs for manometry. Therefore, this study showed that although some physicians perceive that they can pick out, based on some of the above features, which patients

are more likely to have manometric SOD, this large prospective study showed that the subjective findings in SOD are not reliable to predict objective measurements with SOM. These findings are perhaps not that surprising, since attempts at showing correlation between objective and subjective measures have failed in other functional GI diseases.

Diagnosis

Could SOM Be Replaced with Less Invasive Measurements in Diagnosing SOD?

SOM is still used as the gold standard for diagnosing SOD. However, it is an invasive procedure and the rate of complications is high. Thus, the idea of replacing SOM with a less invasive diagnostic test has been attractive to investigators, and many authors have unsuccessfully tried to study alternatives; we will focus on recent developments in this paper. Clinical predictors do not appear to be useful as an alternative, given the recent study summarized in the previous section. The following is a brief description of a few recently described methods and the corresponding studies.

Functional MRI

Corwin and colleagues conducted a study to test the hypothesis that delayed emptying in the duodenum indicated a disease state, by determining whether a biliary excreted contrast agent (similar to scintigraphy, but with higher resolution) is consistently visualized in the gallbladder and duodenum after a 30-min delay, using gadoxetate disodium-enhanced T1-weighted hepatobiliary phase MRI images, in 22 patients without evidence of liver or biliary disease [8]. They reported that only 13 patients demonstrated duodenal filling by 20 min and 16 by 30 min. Furthermore, 17 patients demonstrated gallbladder filling by 20 min and 21 filled by 30 min. Since a significant number of normal patients did not show duodenal filling by 30 min, while the majority fill the gallbladder by 30 min, the authors concluded that the lack of duodenal filling by 30 min is seen in normal individuals and cannot be used to diagnose SOD. The authors excluded patients with previous cholecystectomy, and so, the results may not be generalizable to post-cholecystectomy patients.

Optical Coherence Tomography (OCT)

OCT uses a low-power infrared light with a wavelength ranging from 750 to 1300 nm, using light scattering to highlight the details of the microstructure of the gastrointestinal wall layer in real time, in the same way that ultrasound uses sound back-scatter. The light interacts with the tissue layer interfaces and the image is formed based on changes in optical back-scattering properties of the different tissues. The higher frequency of light compared to sound allows much higher resolution, with a much lower depth of penetration, compared with ultrasound. Testoni and colleagues from Italy conducted a pilot study on five consecutive patients, without history of pancreatitis, with biliary type I SOD (although controversially, with intact gallbladders). The SOD diagnosis was only confirmed by secretin-enhanced magnetic resonance cholangiopancreatography (MRCP) (i.e., not SOM); five consecutive patients with body/tail pancreatic adenocarcinoma, i.e., without biliary or papillary involvement, were used as controls [9]. All patients underwent both endoscopic ultrasound of the papillary region and were investigated by intraductal probe-based OCT immediately before biliary sphincterotomy, apparently blinded to the diagnosis. The intermediate layer in patients with SOD type I was 2.3 times thicker than that in control patients ($p<0.0001$), and its infrared light back-scattering showed hyper-reflectivity of the fibromuscular layer of sphincter of Oddi (SO) as compared to controls. The lack of SOM use as the gold standard limits the validity of this study. Although interesting, at this stage, this is definitely still an experimental technique, and performing it requires time and expertise in selecting appropriate pictures in order to analyze them after the ERCP is completed and may not be practical. Furthermore, intraductal OCT is not really non-invasive; it still involves performing ERCP and cannulation of the ducts and is associated with the usual potential adverse events. In addition, patients with SOD type I are usually diagnosed based on simple imaging and laboratory data and may not need further investigations.

Measuring Distensibility of Sphincter of Oddi

In a promising European study, Kunwald and colleagues tried to measure the distensibility of the sphincter of Oddi as a new marker for SOD using a Functional Lumen Imaging Probe (FLIP) technique [10]. They constructed a probe to measure eight cross-sectional areas along a length of 25 mm inside a saline-filled bag. Inflation was used at a rate of 1 mL/min. They initially validated the technique and calibrated the probe. In the next stage of the study, they analyzed the sphincter profile and motility patterns of the sphincter during ERCP in four volunteers with biliary type pain and normal SOM. They were able to reconstruct a three-dimensional functional profile of the sphincter for each patient during the distention phase. The authors hypothesized that this new technique might be superior to SOM by allowing the clinician to image the "distensibility" and related proposed functional changes in the sphincter, as it is gently distended by a small balloon-like bag, and by configuring its functional anatomy. However, this procedure needs further investigation and validation and is potentially associated with an even higher adverse event rate than traditional SOM.

Trial of Botulinum Toxin

A diagnostic trial of something that would temporarily interfere with the sphincter, to help identify who would ultimately respond to ablation, has been theorized for some time now. Previous studies have shown that intrasphincteric Botox responders tend to also be sphincterotomy responders; however, it is not clear if this is just a repeated placebo effect. In a more recent study, Murray conducted an audit follow-up study on 25 patients who still had their gallbladder, with acalculous biliary pain and two gallbladder ejection fraction estimations less than 40 % on scintigraphy, to see if a partial response to botulinum toxin could identify patients with SOD [11]. Each patient received 100 units of botulinum toxin injected in four quadrants around the sphincter and was assessed for a pain-free interval of 4 weeks after the injection, followed by recurrence of their pain. Those with partial or complete relief were offered endoscopic biliary sphincterotomy, and patients who failed to benefit were assessed for laparoscopic cholecystectomy. All patients who experienced temporary biliary pain relief, and thus underwent endoscopic biliary sphincterotomy, reported relief of biliary pain (N=10). On the other hand, 8 out of 10 patients who had a negative initial response, and so underwent laparoscopic cholecystectomy instead, reported relief. The author concluded that the botulinum-toxin-induced relaxation of the SO might help to direct appropriate therapy for patients with acalculous biliary pain. Although this is a promising concept, randomized controlled trials, preferably with a saline injection control arm, are needed to confirm the result. We do not know the placebo response of sphincter injections (e.g., with saline), and it is reasonable to assume that placebo response from one intervention (e.g., Botox) may predict placebo response from another (sphincterotomy); in addition, surgical placebo responses are generally significantly higher than endoscopic ones. Also, some previous studies showed high post-Botox pancreatitis rates when pancreatic stents were not used. Lastly, patients would need to undergo two endoscopic procedures, one for the diagnosis and one for the treatment, both of which may have adverse events; this may make it less appealing for patients and endoscopists.

Could Using a Guidewire in SOM Change the Result?

Cannulation of the biliary and pancreatic ducts is essential for performing SOM and requires special skill and experience. Guidewires have been used to help in securing the catheter in the desired duct. The original published series that helped establish normal control values was done with a 5-Fr triple-lumen catheter without a wire [12], and studies since then have tried to mimic this technique. Blaut and colleagues investigated the effect of guidewires on manometry tracings, by enrolling 45 consecutive patients with suspected SOD [13], and performing biliary SOM with and without a guidewire (same cannulation). The SOM was done in the conventional retrograde fashion with a low-compliance infusion pump system, an aspirating catheter, and slow station pull-throughs. Biliary SOM performed with a guidewire in place revealed higher basal pressure than when repeated without a guidewire (52±33.4 mmHg vs. 34.4±20.5 mmHg; p=0.001). Leaving in a guidewire changed the results from normal to abnormal basal pressure in 11 cases; agreement between recordings with and without guidewire was seen in most (n=32) of the remaining patients (71 %). This study showed that leaving in guidewires may alter the basal biliary sphincter pressure, leading to incorrect diagnoses in approximately 1/3 of cases and hence should be discouraged. The authors suggested increased lateral pressure against the inner wall of the duct, consequently altering the degree of closure of the side ports, as a possible mechanism by which the guidewire affects the basal sphincter pressure measurements. This is an important finding and supports our current practice of avoiding guidewires to establish and maintain cannulation during SOM. Although unavoidable, for safety and feasibility reasons in a minority of patients, incorrect diagnoses caused by using guidewires during SOM may lead to unnecessary treatments including sphincterotomy and potentially complications. On a related note, Kakuyama et al. from Japan showed that a guidewire with the ability to measure pressure, used in coronary angiography, could be used to measure sphincter of Oddi pressure, without a catheter at all, in a pilot study of 22 patients, measuring area under the curve of contraction waves, but not the traditional basal pressures [14].

Are SOM Findings Reproducible?

Only a few studies have investigated the reproducibility of SOM [15–21]. In a study from the University of Indiana, Khashab and colleagues aimed at determining the frequency of SOD in persistently symptomatic patients who previously had normal SOM [15]. They prospectively included all patients who underwent ERCP for suspected SOD with an intact papilla and a previously normal SOM, if they had undergone a repeat ERCP for persistent symptoms and underwent repeat SOM. Thirty, out of 1037 patients with normal SOM, underwent repeat ERCP for persistent symptoms. The median duration between the two ERCPs was approximately 1.5 years. In these 30 patients, SOD classification prior to the initial ERCP was type I in one patient, type II in 17 patients, and type III in 12 patients. Of the 30 patients, 60 % (18) were diagnosed with SOD in the second ERCP. Among these 18 patients, 4/8 (50.0 %) in the subgroup with idiopathic recurrent pancreatitis had positive SOM, compared with 14/22 (63.6 %) in the subgroup with persistent abdominal pain. Based on these findings, repeated SOM may be justified in patients with persistent symptoms despite one previous

normal SOM; alternatively, it may point to problems with reliability and test-retest performance of SOM. The study fails to report the clinical outcome of the patients who received sphincterotomy after positive results in the second SOM, and therefore, whether repeated SOM changes the outcome of these patients could not be established from the reported findings. The authors also exclusively looked at the patients who developed or had persistent symptoms following normal initial SOM, who were a small fraction of the patients with normal SOM in this center. Lastly, most patients in the EPISOD trial, randomized to sham, who happened to have a second ERCP with manometry for persistent/recurrent pain, had concordant SOM (unpublished data), but some discrepant results did occur on retesting.

Psychosocial Factors in SOD

It is commonly believed that SOD is associated with psychosocial comorbidity, as it is seen in other functional GI diseases such as irritable bowel syndrome. However, the evidence is not very strong to support this hypothesis. Two previous studies suggested the effect of psychosocial factors in the pathogenesis of SOD [22, 23].

Sphincter of Oddi Dyskinesia Versus Stenosis

In a recent Australian cohort of 72 consecutive patients with suspected SOD, post-cholecystectomy patients were studied in three groups including SO dyskinesia (n=33), SO stenosis (n=18) (elevated basal pressures, which is the only feature in US centers that is used to define positive SOM), and normal SOM (n=21) [24]. Social and demographical status and the severity of stress-coping experiences were recorded for each patient. Logistic regression revealed that certain psychological, social, demographic, and clinical variables significantly predicted SO dyskinesia but not SO stenosis. Female sex, suppression of anger, use of coping strategies, higher education of the father, and higher proneness to stress could predict SO dyskinesia as compared to normal SOM. The authors concluded that for some patients with a diagnosis of SO dyskinesia, a stress-related motor dysfunction may explain the recurrence of the symptoms following cholecystectomy. Of note, SO dyskinesia was found not to predict pain response after sphincterotomy in the Australian randomized trial of SOD type II and had results similar to those with normal SOM; only SO "stenosis" (similar to the American definition of manometric SOD) predicted response above sham [25]. Perhaps, SO dyskinesia is a global duodenal functional dyskinesia, with duodenal and sphincter spasms causing right upper quadrant or epigastric pain. If true, this finding may be more related to irritable bowel syndrome (and its clinical features) and would not be responsive to sphincterotomy.

Psychosocial Factors in SOD Type III

As part of the EPISOD trial, Brawman et al. investigated 214 patients with post-cholecystectomy pain and suspected SOD type III in seven US centers enrolled in a multicenter-randomized trial [26]. Structured psychosocial assessments of anxiety, depression, coping, trauma, and health-related quality of life were performed. They reported anxiety in 9 %, depression in 8 %, past sexual trauma in 18 %, and physical abuse in 10 % of the study population (92 % female). Patients with greater pain burden were found to be significantly more depressed. Comparisons with age- and gender-adjusted US population norms indicated no statistically significant difference on SF-36 mental functioning (p=0.52), but physical functioning score was significantly worse than the population norm (p<0.0001). This study showed that, although the psychosocial comorbidity in SOD is high, it is still not significantly higher than that reported in surveys of age- and gender-matched general populations; it also seems that it may be lower than reported with other functional gastrointestinal disorders. This study is by far the largest trial reporting psychosocial characteristics of patients with suspected SOD and showed that there was a relatively low level of depression and anxiety despite high levels of disability due to pain, when compared with the prevalence of these issues in other chronic pain conditions. The findings of this study contradict the commonly held notion that SOD is associated with a higher rate of major psychosocial characteristics, similar to other functional GI diseases.

Treatment

Is Medical Therapy Effective in Treating Patients with SOD?

The role of medical therapy in patients with suspected or proven SOD has not been well investigated. Since the currently recommended diagnostic workup and therapeutic modalities are generally expensive and have high risk, developing medical treatment should be of interest.

A prospective study from the UK on 59 consecutive patients diagnosed with clinically suspected biliary SOD type I (14 %), II (51 %), and III (21 %) tried to understand the role of medical therapy in these patients [4]. None of the patients underwent SOM and the diagnosis was made based on clinical features, laboratory data, and imaging studies. Medical treatment consisted of the low-dose tricyclic antidepressant, amitryptiline (10–50 mg daily), followed by nifedipine (20 mg daily), and glyceril trinitrate spray as needed. Breakthrough pain medications were also allowed as needed, alone or in combination with the study treatments. Patients with SOD type I and type II with a dilated CBD who

failed medical treatment after 3–6 months were offered biliary sphincterotomy. Median follow-up duration was 15 months, and over that time, 51 % experienced symptom resolution/improvement on medical treatment only (62 % in type I, 77 % in type II, and 76 % in type III), 12 % after sphincterotomy, and 10 % after both medical treatment and sphincterotomy. Interestingly, all five patients with SOD type II (based on lab abnormalities, without dilated ducts) responded to medical therapy. Overall, 36 % of the patients experienced symptom resolution or improvement on low-dose tricyclic antidepressants.

Although the results of the above study were promising, there were a few weaknesses. First, this was not a controlled study, and therefore, it would be impossible to exclude the placebo effect. In addition, the definition of improvement or relief is not clear from the publication, and subjective outcomes are often prone to bias in an open-label study. Last but not least, a significant proportion of patients received opioids during the study; the high level of co-intervention makes attribution of the outcome to the study medications difficult. However, it does show that these medical interventions are associated with a reduction in symptoms in a majority of patients, whether SOD is what they are treating, or whether they are simply treating duodenal spasm or right colon spasm mimicking SOD; either way, medical therapy appears to be able to save consideration of ERCP in most people with these symptoms.

In another study, Vitton and colleagues studied 59 French patients with clinically suspected biliary SOD (11 type I, 34 type II, and 14 type III) who received medical treatment consisting of trimebutine 200 mg three times per day and/or nitrates as needed, taken sublingually [27]. In the event of intolerance or contraindication to one, the other medication was used. When the pain episodes occurred greater than one per week, a transdermal nitrate treatment (5 mg/day) was administered. After the average follow-up of 30 months (3–72), 54 % of patients with type I, 68 % of patients with type II, and 57 % of those with type III reported more than 50 % improvement in the frequency and intensity of pain with no statistical significance among the groups. Twenty-one patients showed less than 50 % improvement in their pain score, out of whom 14 underwent sphincterotomy. Sixty-four percent of these patients reported improvement in their pain following sphincterotomy (p=0.88 vs. relief with medical therapy). This study provides more evidence for medical treatment with trimebutine as an effective alternative to sphincterotomy in a relatively long follow-up. Again, the study is not controlled, and the medical failure group may not be the same as the all-comer group when comparing the two therapies. However, it does show a high rate of improvement with medical therapy, at a rate higher than the usual 30–40 % placebo rate seen in other medical-therapy-controlled studies, for suspected SOD. Again, some suspected SOD in this study may in fact be IBS.

Is Sphincterotomy Effective in Treatment of Patients with SOD Type III?

The EPISOD trial was a sham-controlled randomized trial designed to assess the effectiveness of endoscopic sphincterotomy as a treatment for abdominal pain in adult patients with suspected SOD type III, based on Rome III criteria, in seven US centers [1••]. Patients were included if they had typical abdominal pain for more than 3 months after cholecystectomy, with no evidence of past or present pancreatitis or prior sphincter intervention. They underwent SOM and were randomized to sphincterotomy (n=141) or sham (n=73), independent of the SOM results. Those allocated to sphincterotomy who had pancreatic sphincter hypertension (n=99) were randomized a second time to either biliary (n=52) or dual (n=49) sphincterotomy. Success of treatment was defined as improving to a level of less than 6 days of disability due to pain in the prior 90 days (using the RAPID tool) both at months 9 and 12 after randomization, with no narcotic use and no further sphincter intervention. At 1 year, 37 % of patients in the sham treatment group and 23 % in the sphincterotomy group experienced successful treatment (p=.01, in favor of sham). In patients with pancreatic sphincter hypertension randomized to sphincterotomy, the type of sphincterotomy did not influence the rate of success: 30 % experienced successful treatment following dual sphincterotomy and 20 % following biliary sphincterotomy alone (p=.22). Neither manometry results, age, reason for cholecystectomy (and response to it), pain characteristics, nor psychosocial comorbidities were predictors of outcome. The study demonstrated that sphincterotomy is not more effective than sham (perhaps harmful, in fact), regardless of the manometric findings; in addition, despite ERCPs done in expert hands with near-universal prophylactic pancreatic stenting, the post-ERCP pancreatitis rate was 13–14 %. The small subgroup (10–15 % of the cohort) who had mildly abnormal liver and/or pancreatic biochemistry (i.e., borderline type II SOD) had similarly disappointing results. This well-designed study provided strong evidence that performing sphincterotomy in patients with post-cholecystectomy pain, without marked enzyme or ductal abnormalities, is ineffective, perhaps mildly harmful, and should not be practiced, whether with or without SOM.

Risk of Post-ERCP Pancreatitis in Patients with SOD Type III?

Post-ERCP pancreatitis is a potentially life-threatening adverse event and is common after ERCP in patients with suspected SOD even with normal manometry [28]. Yaghoobi and colleagues studied the incidence and predictors of post-ERCP pancreatitis in patients with suspected SOD undergoing biliary or dual sphincterotomy in the EPISOD trial

[29•]. The methodology of the trial was discussed above. All but one patient received prophylactic pancreatic stents, but no pharmacological prophylaxis (e.g., rectal indomethacin) was given. Post-ERCP pancreatitis was defined as acute pancreatitis (pain, requiring >24-h admission, with pancreatic enzymes greater than three times the upper limit if normal) within 7 days after the procedure. Post-ERCP pancreatitis occurred in 26 randomized patients. The rate of post-ERCP pancreatitis was not significantly different in patients who received sphincterotomy (10.6 %) as compared to those undergoing sham or no treatment (15.1 %). In addition, the proportion was not statistically different in those who received biliary sphincterotomy alone (12.8 %) versus those undergoing dual sphincterotomy (6.4 %). In multivariate analysis, neither analgesic usage prior to the manometry, results of manometry, number of pancreatic injections, degree of difficulty of pancreatic cannulation, presence of ansa pancreatica, nor the type or length of the prophylactic pancreatic stents were found to be statistically significant predictors of PEP. However, it identified an interaction between duration and type of sedation ($p<0.01$). This study provided support for the concept that biliary sphincterotomy does not increase the high risk of post-ERCP pancreatitis in patients with suspected SOD regardless of manometric findings. The idea that pancreatic sphincterotomy may not increase the risk beyond a biliary sphincterotomy needs to be confirmed in other studies; it is not consistent with prior studies.

Does Size of Prophylactic Pancreatic Stent Impact Preventing Post-ERCP Pancreatitis?

Pancreatic stent placement has been shown to prevent post-ERCP pancreatitis in patients suspected with SOD with normal manometry in previous retrospective trial [28]. In the above-mentioned study by Yaghoobi et al., the size of the prophylactic stent was not shown to affect the rate of post-ERCP pancreatitis [29•].

In a randomized controlled trial, investigators compared different outcomes after using 5-Fr versus 3-Fr prophylactic pancreatic stent in 78 patients who were at high risk to develop post-ERCP pancreatitis including those with SOD type I or manometry-proven SOD type II or III. Post-ERCP pancreatitis, as one of the secondary outcomes, was not significantly different in two groups (10 versus 17 %, respectively, $p=0.51$) [30]. However, the 5-Fr stent was felt to be easier and faster to insert and required fewer wires for the procedure. There was no difference in spontaneous stent passage between the two stents.

Another retrospective study reported 243 patients with manometry-confirmed SOD and compared 133 patients who received a 3Fr stent with 110 who received a 5Fr stent [31]. The baseline characteristics of two groups were comparable. The authors found no difference in the rate of post-ERCP pancreatitis between the two groups (12 versus 12.7 %, respectively, $p=0.89$). These two studies are consistent with the multiple other studies that have shown no consistent difference among sizes of stents smaller than 6 Fr for pancreatitis prophylaxis. Larger than 5 Fr stents seem to have higher event rates.

SOD in Post-Roux-en-Y Gastric Bypass Patients

Diagnosis and treatment of suspected SOD in patients with abdominal pain and previous cholecystectomy following Roux-en-Y gastric bypass is challenging. ERCP, without going through a gastrostomy tube or without the assistance of balloon enteroscopy, is not feasible, given the surgically altered anatomy. Manometry is generally not feasible through an enteroscope as the SOM catheter is not compatible with its length. Pain syndromes from the altered anatomy are often multifactorial. Morgan and colleagues conducted a retrospective study on clinical outcomes of 16 patients who underwent transduodenal sphincteroplasty including biliary sphincteroplasty and pancreatic ductal septoplasty [32]. They were all diagnosed either clinically or by using magnetic resonance cholangiopancreatography with secretin stimulation. Out of 13 patients who responded to the survey follow-up, 11 (85 %) reported sustained pain improvement after surgery. The mean length of follow-up was 28 months (16–57). Most patients had types I and II and only three had type III. Three patients developed complications. The authors failed to report the proportion of response in each type of SOD. The authors concluded that if the clinical history is supported by laboratory and magnetic resonance cholangiopancreatography data, surgery could be performed relatively safely with low morbidity and good patient outcomes. The small sample size of the study and its retrospective nature and low availability of skill in surgical sphincteroplasty make it difficult to formulate a strong conclusion in this difficult population, with surgically altered anatomy.

SOD in Idiopathic Recurrent Acute Pancreatitis (IRAP)

Is Sphincterotomy Effective in Patients with IRAP and SOD?

There is no consensus definition of IRAP but, in general, is felt to be recurrent acute pancreatitis, in the absence of alcohol, gallstones, and obvious metabolic abnormalities or medications implicated as a cause. The role of SOM in the workup of patients with IRAP requires further evidence. To date, only one randomized trial of stenting (not sphincterotomy) and a few retrospective and prospective case series addressed the effect of endoscopic therapy in patients with SOD and IRAP; there is also controversy in the choice of the optimal

endoscopic treatment (biliary versus dual sphincterotomy) and method of outcome measurement. Previous studies showed reduction in the incidence of IRAP after pancreatic stenting, including one small, randomized trial of the latter [33]. It is not clear if biliary sphincterotomy, irrespective of the results of pancreatic manometry, is effective alone in patients with IRAP. It is also not clear if ERCP should only be offered in post-cholecystectomy patients, as is usually done for biliary pain. Lastly, the only randomized trial used long-term stenting of the pancreatic duct, and it is now felt that is not a safe alternative to pancreatic sphincterotomy.

Cote and colleagues aimed at assessing the effects of endoscopic sphincterotomy in patients with IRAP [34•]. All patients underwent SOM. Although written up as a single study, it really describes two randomized trials of patients with IRAP: (1) randomization of patients with pancreatic SOD (by SOM) (n=69) to receive either biliary sphincterotomy (BES) or a combination of biliary and pancreatic sphincterotomy (DES); 56 of these patients underwent biliary SOM (74 % in the BES group and 41 % in the DES group had abnormal biliary SOM); and (2) randomization of patients with normal pancreatic SOM (n=20) to biliary sphincterotomy or a sham procedure (19 of these patients underwent biliary SOM and none had biliary SOD).

They followed up the patients for a median of 78 months and compared the incidence of recurrent acute pancreatitis and chronic pancreatitis. In the first trial (positive pancreatic SOM), 48 % of patients who received biliary and 47 % of those who received dual sphincterotomy had at least one more episode of acute pancreatitis (p=1.0). In the second trial (normal pancreatic SOM), in patients with normal SOM (n=20), 27 % of those who received biliary sphincterotomy as compared to 11 % of those who received sham had recurrent acute pancreatitis (p=0.59). Combining both trials, 17 % of patients developed chronic pancreatitis during follow-up. The odds of recurrent acute pancreatitis during follow-up evaluation were significantly greater among patients with pancreatic SOD than those with normal pancreatic SOM (unadjusted hazard ratio, 3.5; p=0.04). This study showed the prognostic importance of pancreatic SOD and showed that biliary sphincterotomy in patients without pancreatic SOD does not help. There was no sham group in the pancreatic SOD group, so one cannot tell if sphincterotomy is more effective than sham here, but it seems that biliary and pancreatic sphincterotomy are not significantly more effective than one another.

It has been highlighted by other groups that many patients with IRAP and manometric SOD may have genetic abnormalities that predispose them to recurrent pancreatitis, perhaps made worse by the low-grade obstruction at the sphincter. Therefore, it is likely that even after successful endoscopic treatment, if one follows subjects long enough, many will have recurrence of pancreatitis because of this genetic problem. One hopes that endoscopic therapy reduces the frequency of attacks or extends the attack-free interval. In a recent retrospective German study by Wehrmann, 37 patients with IRAP and manometrically proven SOD (20 type I and 17 type II), who were originally enrolled in a prospective study, underwent sphincterotomy (24 dual and 13 pancreatic or biliary sphincterotomy) [35]. The authors then retrospectively assessed for the recurrence of acute pancreatitis over an average follow-up period of 11.5 years. Although 19 (51 %) out of 37 patients developed at least one episode of acute pancreatitis eventually, only two recurrences happened during the first 2.5 years of prospective follow-up; this rate is much lower than the natural history of recurrence in the first two to three years of follow-up in other studies, including in the control group of the small randomized trial of stenting by Jacob et al. [33]. The authors concluded that performing sphincterotomy seems to slow the natural course of IRAP. However, a conclusion is hard to achieve since there was no natural history control group to compare the frequency of episodes.

Conclusion

Recent studies have further clarified the clinical approach to SOD as follows:

Post-cholecystectomy abdominal pain:

- The Milwaukee classification of SOD, although useful, has had equivocal predictive power in outcome studies for stratifying patients into different chances of benefit from sphincter therapy.
- Multiple studies have explored new diagnostic modalities to replace SOM, such as clinical patient and pain features, functional MRI, Botox injection, and intraductal sphincter imaging such as OCT; however, there is no strong evidence to support any of these, and the risk of adverse events is not likely to be lower than that of manometry.
- Studies failed to show an association between psychosocial factors and suspected, or manometrically proven, SOD.
- Sphincterotomy is not what increases the risk in ERCP for type III SOD; the risk appears to lie in patient factors.
- Prophylactic pancreatic stent placement is effective in preventing post-ERCP pancreatitis in patients suspected of SOD.
- The landmark multicenter randomized sham-controlled EPISOD study provided strong evidence that neither biliary nor dual sphincterotomy for those suspected of having SOD type III (normal imaging, near-normal/normal labs) is effective for post-cholecystectomy abdominal pain; in fact, those interventions appeared harmful. This lack of effectiveness was seen overall, and in all clinical subgroups, regardless of the result of the manometry, and therefore, ERCP is not recommended. Based on these

findings, ERCP with or without SOM should not be used in these patients; it is both harmful and ineffective.
- Medical therapy (neuromodulators and nitrates/antispasmodics) appears to have promise with effectiveness in non-randomized series in a majority of patients suspected of having SOD.

IRAP:

- Based on a randomized trial, biliary and dual sphincterotomy in IRAP patients appears equally effective in preventing recurrent pancreatitis in patients with pancreatic sphincter hypertension.
- Pancreatic sphincter hypertension appears to predict a poor prognosis in IRAP.
- Biliary sphincterotomy in IRAP patients appears no better than sham in preventing recurrent pancreatitis, in patients with normal pancreatic sphincter pressures.

Despite significant advances in clinical knowledge in this field, the following topics need further investigation:

- developing new non-invasive methods to diagnose SOD type II, to prevent adverse events associated with ERCP and SOM;
- randomized trials of medical therapy for patients with biliopancreatic-type pains without objective findings;
- saline-controlled trials of Botox injection for biliopancreatic pain;
- controlled outcome studies of empiric cholecystectomy stratified by scintigraphy findings, in patients with unexplained biliary type pain but a normal gallbladder
- investigating the role of repeat manometry-driven therapy in symptomatic patients with prior diagnosis of SOD and previous sphincterotomy
- defining the role of pharmacological agents (esp. rectal indomethacin) in preventing post-ERCP pancreatitis, instead of, or in addition to, pancreatic stents, in patients suspected for SOD;
- randomized trial of biliary and/or pancreatic sphincterotomy versus sham in IRAP patients with positive pancreatic sphincter manometry; and
- randomized trial of minor papilla therapy in patients with pancreas divisum and IRAP.

Compliance with Ethics Guidelines

Conflict of Interest Mohammad Yaghoobi and Joseph Romagnuolo declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article contains studies with human or animal subjects performed by both authors [1••, 6, 7•, 26, 29•].

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- • Of importance
- •• Of major importance

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