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TOPIC HIGHLIGHT

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Sphincter of Oddi dysfunction and pancreatitis

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Abstract

Sphincter of Oddi dysfunction (SOD) is a term used to describe a group of heterogenous pain syndromes caused by abnormalities in sphincter contractility. Biliary and pancreatic SOD are each sub-classified as type Ⅰ, Ⅱ or Ⅲ, according to the Milwaukee classification. SOD appears to carry an increased risk of acute pancreatitis as well as rates of post ERCP pancreatitis of over 30%. Various mechanisms have been postulated but the exact role of SOD in the pathophysiology of acute pancreatitis is unknown. There is also an association between SOD and chronic pancreatitis but it is still unclear if this is a cause or effect relationship. Management of SOD is aimed at sphincter ablation, usually by endoscopic sphincterotomy (ES). Patients with type Ⅰ SOD will benefit from ES in 55%-95% of cases. Sphincter of Oddi manometry is not necessary before ES in type Ⅰ SOD. For patients with types Ⅱ and Ⅲ the benefit of ES is lower. These patients should be more thoroughly evaluated before performing ES. Some researchers have found that manometry and ablation of both the biliary and pancreatic sphincters is required to adequately assess and treat SOD. In pancreatic SOD up to 88% of patients will benefit from sphincterotomy. Therefore, there have been calls from some quarters for the current classification system to be scrapped in favour of an overall system encompassing both biliary and pancreatic types. Future work should be aimed at understanding the mechanisms underlying the relationship between SOD and pancreatitis and identifying patient factors that will help predict benefit from endoscopic therapy.

Key words: Sphincter of Oddi dysfunction; Pancreatitis, Post-ERCP pancreatitis; Sphincter of Oddi manometry; Endoscopic sphincterotomy

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INTRODUCTION

Sphincter of Oddi dysfunction (SOD) is the term used to describe a heterogenous group of clinical pain syndromes caused by abnormalities in sphincter contractility. The sphincter of Oddi (SO), a fibromuscular sheath encircling the distal common bile duct (CBD), pancreatic duct (PD) and common channel, controls the flow of bile and pancreatic secretions into the duodenum and prevents reflux of duodenal contents into the pancreaticobiliary system.

SOD describes SO dysmotility or stenosis leading to reduced transphincteric flow of bile or pancreatic juice[1]. SO stenosis is a structural abnormality where there is a physical alteration of the sphincter due to inflammation and fibrosis. SO dyskinesia results in a hypo- or hypertonic sphincter with altered motility causing an intermittent functional blockade of the sphincter[2]. As it is often difficult to distinguish SO stenosis from dyskinesia, the term Sphincter of Oddi dysfunction is used to cover both conditions.

Because of the anatomical position of the SO patients with SOD typically present with recurrent biliary or pancreatic type pain. The Rome Ⅱ diagnostic criteria for biliary pain are episodes of severe steady pain in the epigastrium and right upper quadrant, associated with all of the following: (1) Symptom episodes lasting at least 30 min with pain free episodes in between; (2) At least one attack of pain in the last 12 mo; (3) Pain that is steady and interrupts daily activities or requires consultation with a doctor; (4) No evidence of structural abnormalities to explain the symptoms.

Pancreatic pain is described as post-prandial, episodic, prolonged pain in the upper abdomen and/or back[3]. It is often presumed in the setting of acute recurrent pancreatitis in the absence of biliary stone disease or anatomical abnormalities. The true prevalence of SOD is not known but ongoing biliary type pain occurs in 10%-20% of patients who have had a cholecystectomy[4]. Sphincter ablation, usually by endoscopic sphincterotomy, is at the forefront in the management of SOD and one of the challenges of this condition is to identify which patients will benefit from it.

CLASSIFICATION OF SOD

The Milwaukee Classification, proposed by Hogan and Geenen[5,6], sub-classifies biliary and pancreatic SOD into three types on the basis of symptoms, laboratory tests and radiological imaging (Table 1). Abnormally high basal sphincter pressure identified during sphincter of Oddi manometry (SOM) confirms the presumed diagnosis. As biliary drainage time is difficult and somewhat impractical to measure and may increase the risk of an ERCP it is rarely performed in clinical practice. In any case, there may be little or no correlation between basal sphincter of Oddi pressures and drainage times[7]. Therefore, a contemporary modified version of the Milwaukee classification, which does not include duct drainage times, is generally used in practice[3]. Sub classification of SOD into types Ⅰ, Ⅱ and Ⅲ helps predict the underlying pathology and the likelihood of symptom relief after treatment. Type Ⅰ disease is thought to result from a fixed stenosis caused by chronic inflammation and fibrosis and has the highest response rate to therapy. An episodic dysmotility is the presumed underlying abnormality in the other types and often does not respond as well to treatment[8,9].

There are some potential problems with the Milwaukee classification. For example, the description of typical biliary or pancreatic pain may be interpreted differently between individuals and this may lead to inappropriate referral for SOM, particularly for patients with presumptive type Ⅲ SOD. Also, according to the Milwaukee criteria, LFTs should normalize between attacks but patients are often labeled with type Ⅱ SOD on the basis of pain and abnormal LFTs which do not normalize[10]. CBD diameter of at least 12 mm is one of the criteria in the diagnosis of SOD. Most patients being investigated for SOD have had their gallbladder removed and in the past it was accepted that it was normal for a post-cholecystectomy CBD to be 2-3 mm dilated. However, in a cohort of 59 patients, Majeed *et al*[11] found no difference between pre- and post-cholecystectomy CBD diameter. As the upper limit of normal for CBD diameter is 7 mm, a cut off of 12 mm potentially leaves a large number of patients misdiagnosed. Also, variations in basal pressure and response to sphincterotomy between the biliary and pancreatic portions of the SO have led to calls for this dual classification system to be scrapped in favor of a single, overall system.

Table 1 Milwaukee classification of sphincter of Oddi dysfunction

1 Biliary type:
Type Ⅰ:
Typical biliary type pain
Liver enzymes (AST, ALT or ALP) > 2 times normal limit documented on at least 2 occasions during episodes of pain
Dilated CBD > 12 mm in diameter
Prolonged biliary drainage time (> 45 min)
Type Ⅱ:
Biliary type pain and
One or two of the above criteria
Type Ⅲ:
Biliary type pain only
2 Pancreatic type SOD
Type Ⅰ:
Pancreatic type pain
Amylase and/or lipase > 2 times upper normal limit on at least 2 occasions during episodes of pain
Dilated pancreatic duct (head > 6 mm, body > 5 mm)
Prolonged pancreatic drainage time (> 9 min)
Type Ⅱ:
Pancreatic type pain, and
One or two of the above criteria
Type Ⅲ:
Pancreatic type pain only

SPHINCTER OF ODDI MANOMETRY

SOM remains the gold standard for the diagnosis of SOD. It is usually combined with a diagnostic ERCP examination and involves cannulating the ampulla with the manometry catheter. A triple lumen catheter allows continuous aspiration of PD fluid that may reduce the risk of post- procedural pancreatitis[12]. To determine which duct has been cannulated a small amount of contrast is injected or some fluid aspirated to determine its color. A catheter "pull-through" of the sphincter is performed to assess the pressure profile and to localize the point of peak basal pressure. Normal basal sphincter pressure is approximately 15 mmHg but ranges from 3 to 35 mmHg. It is generally accepted that a basal pressure greater than 40 mmHg (based on a threshold of 3 standard deviations above the median) is abnormal[13]. In patients with SO stenosis this recording is reproducible and does not respond to muscle relaxants[1]. In contrast, SO dyskinesia is characterized by a response to smooth muscle relaxants[5], an excess of retrograde contractions (> 50%), tachyoddia (rapid contraction frequency > 7/min) and a paradoxical contraction response of the SO following an intravenous dose of CCK[1,14].

In type I SOD SOM will be abnormal in 75%-95%[15]. However, the frequency of abnormal biliary manometry varies from 28% to 60% for type Ⅱ patients and from 7 to 55% in type Ⅲ patients[16]. Various factors may explain the differences in frequencies of SOD in published reports. For example, selection of patients with a typical biliary or pancreatic type pain rather than a non-specific pain will increase the yield of basal pressure abnormality. SOM measures a "snap shot" of sphincter pressure during the study period that may not always be reproducible. A study of 12 patients with previously normal SOM showed evidence of elevated SO pressures in 5 (42%) when re-tested after a median of 337 d[17]. Also, the pressure in the pancreatic and biliary portions of the SO can vary so assessment of only one sphincter component, rather than both, will reduce the frequency of SOD detection. Current data suggests a discordance rate of between 35% and 65%[16,18-22]. Therefore, both portions of the SO should be measured separately for a full assessment. This necessitates classifying each patient with respect to the pancreatic and biliary components of the SO and is one of the reasons some experts have called for a single overall classification system. When both sides of the sphincter are evaluated there is little difference between them in predicting

abnormal basal pressure[16].

Because SOM is technically difficult, invasive, has a variable diagnostic yield and has recognized complications, other indirect methods of evaluating SO function have been developed. These include the Morphine-Prostigmin provocative test (Nardi test; now obsolete), the ultrasound- or MRCP-secretin test, and quantitative hepatobiliary scintigraphy. However, current data suggests that non-invasive tests have a relatively low specificity and sensitivity[15], although there is some evidence that secretin stimulated MRCP may be useful in selecting patients with suspected type Ⅱ SOD who are most likely to benefit from sphincterotomy [23]. Therefore, despite the risk, and assuming careful patient selection, SOM remains the diagnostic tool of choice for most clinicians.

PANCREATITIS POST SOM

Acute pancreatitis is the main complication of SOM. Increased intraductal pressure, overfilling of the ductal system, difficult and repeated cannulation of the PD causing spasm and trauma have all been postulated as etiological factors, possibly by affecting pancreatic duct drainage[24]. This hypothesis is indirectly supported by the observation that PD stenting after biliary sphincterotomy[24] and needle knife sphincterotomy over a PD stent[25] have been found to reduce the incidence of pancreatitis in patients with SOD.

The rate of post-SOM pancreatitis in patients suspected of having SOD has been found to be as high as 31%[27-30]. Sherman *et al*[27] found a much lower rate of pancreatitis when an aspirating catheter was used (1 of 33 patients; 4%) compared with an infusion catheter (8 of 34 patients; 31%). Walters *et al*[31], however, found no difference in the incidence of pancreatitis when comparing the two types of manometry catheter (8% *vs* 13%). In a case series of 146 patients (207 SOM measurements), Rolny *et al*[28] reported a 6% incidence of pancreatitis when using the standard catheter. In addition, acute pancreatitis developed in 10 of 95 (11%) patients who had undergone pancreatic manometry alone, compared with 1 of 93 (1%) who had biliary manometry alone. Recommended methods of reducing the rate of pancreatitis from SOM include evaluating biliary SO alone in patients with suspected biliary disease[32], limiting SO perfusion to 1-2 min[33] and careful patient selection. For example, Scicchitano *et al*[29] found a significantly higher rate of pancreatitis when the indication for SOM was idiopathic acute recurrent pancreatitis (IARP) compared to unexplained abdominal pain (29% *vs* 6%). The incidence of pancreatitis was 50% in the patients with IARP and high SO basal pressure. Temporary prophylactic pancreatic duct stenting has been shown to reduce the incidence of pancreatitis in a variety of patient groups, including those undergoing SOM[25,26,34,35].

A retrospective review of 100 patients who had undergone SOM found an overall incidence of pancreatitis of 17%[30]. The incidence was significantly higher in patients who had undergone SOM and ERCP, compared to those who had only undergone SOM (26.1% *vs* 9.3%). Multiple regression analysis showed that sphincterotomy added no additional risk beyond that associated with ERCP. These results imply that other factors during ERCP, and not the manometry itself, predispose to pancreatitis. The authors recommended that ERCP should be performed at another session, possibly 24 h after SOM.

Results from other studies suggest that the risks of pancreatitis are intrinsic to the patient group undergoing the procedure and the therapy provided, rather than the SOM itself. Freeman *et al*[36] recorded complication rates for sphincterotomy in patients with suspected SOD and those in whom it was already confirmed. The complication rate was 21% for patients who underwent SOM and 25% when sphincterotomy was not preceded by SOM. Another study compared the pancreatitis rate from ERCP between patients with suspected SOD, some of whom also underwent SOM, and a control group of patients with biliary stones[37]. 27% of patients with suspected SOM developed post-procedural pancreatitis, compared with 3.2% of the control group ($P < 0.001$). However, there was no significant difference in the rate of acute pancreatitis in the first group between those who had SOM and those who did not (OR 0.72: 95% CI 0.08-9.2). Similarly, in a large trial of over 1000 patients who underwent ERCP with or without SOM, Cheng *et al*[38] found that SOM was not a risk factor for post-ERCP pancreatitis.

The variability in complication rates between studies is probably multifactorial and related to the timing and duration of the procedure, the number of passes with the manometry catheter and technique and skill of the operator. However, it is probable that, in skilled hands, SOM does not significantly increase the risks of post-ERCP pancreatitis and remains a useful tool in the diagnosis of SOD, particularly for types Ⅱ and Ⅲ.

SOD AND ACUTE PANCREATITIS

SOD may contribute to the risk of acute pancreatitis by causing abnormal biliary or pancreatic juice flow. In the Australian Bush opossum, which has a similar biliary and pancreatic anatomy to humans, the combination of pancreatic duct ligation and stimulation of pancreatic exocrine secretion with cholecystokinin/secretin uniformly causes acute pancreatitis[39]. In another group, reduced transphincteric flow was achieved by applying topical carbachol to the SO, causing PD pressures comparable with those opossums in which the PD was ligated. However, acute pancreatitis only occurred when carbachol application was combined with pancreatic secretory stimulation. Decompression of the PD negated the effects. Therefore, the combination of PD obstruction with increased exocrine secretion was needed to produce acute pancreatitis. Although it is a recognized complication of SOD, this study demonstrated that SOD might be a causative factor in the production of acute pancreatitis.

Kruszyna *et al*[40] carried out ERCP with pre- and post- sphincterotomy SOM in a group of 30 patients with mild acute biliary pancreatitis and compared results with a control group of 30 patients with no evidence of CBD stones or pancreatitis. The patients with pancreatitis had a significantly elevated CBD pressure, SO basal pressure and wave amplitude compared to controls.

There was a significant reduction in all parameters after sphincterotomy. They concluded that SO dysfunction, either primary or secondary to spasm caused by a gallstone migrating through the ampulla, may have a role in acute biliary pancreatitis.

Although there is very little direct evidence supporting the role of the SO in causing pancreatitis in humans, there is plenty of circumstantial evidence. Fazel *et al*[41] measured intrapancreatic ductal pressure blindly in 263 patients presenting with either recurrent abdominal pain, acute recurrent pancreatitis or chronic pancreatitis. Complete SOM was then performed and patients with SOD were found to have a significantly higher ductal pressure compared to those with normal SO motility. This difference was seen across all three groups ($P < 0.01$) and patients with acute and chronic pancreatitis did not have a significant elevation in intraductal pressure compared to individuals with abdominal pain only. The authors concluded that SOD leads to an increase in intrapancreatic ductal pressure but this rise in pressure is not the sole cause of pancreatitis.

Warshaw *et al*[42] showed that infusion of secretin caused PD dilatation of > 1 mm in 83% of patients with SO stenosis and 72% with accessory papilla stenosis, compared with controls. This dilatation response was abolished after surgical sphincteroplasty. A positive secretin test was associated with a good surgical outcome in 90% of cases. It has been shown that in patients undergoing surgery for idiopathic acute recurrent pancreatitis (IARP) the SO narrows at the opening of the PD, suggesting that this narrowing may play a role in its development[43].

An abnormality of SO function has also been implicated in the pathogenesis of acute pancreatitis attributed to other causes. An organophosphate insecticide is a recognized cause of acute pancreatitis in humans. It acts by irreversibly inhibiting cholinesterase resulting in delayed breakdown of synaptic acetylcholine[44], and has been shown to cause pancreatitis in animals[45], probably due to the combination of obstruction at the level of the SO and cholinergic stimulation of pancreatic secretions. Scorpion venom causes acetylcholine release, stimulating the pancreas and SO, and causes pancreatitis in a similar way to organophosphate poisoning[46].

Other rare causes of acute pancreatitis including hypercalcemia and hyperlipidemia may involve abnormalities of SO function. High extra-cellular calcium stimulates smooth muscle and stimulates pancreatic secretion in animal models and it is thought that abnormal calcium regulation of the SO may be an underlying factor in the pathophysiology[47]. A study of hypercholesterolemic rabbits showed a failure of SO relaxation again indirectly suggesting that SO dysfunction may contribute to the risk of pancreatitis[48]. Therefore, although its exact role is not known, the evidence, taken together, suggests that the SO at some level is an important factor in the development of acute pancreatitis, including pancreatitis that may be attributed to another aetiology.

SOD IN RECURRENT ACUTE PANCREATITIS

Clinical evaluation, blood testing and imaging will yield a cause of acute recurrent pancreatitis in 70%-90% of cases. In the remaining "idiopathic" acute recurrent pancreatitis (IARP) cases more extensive evaluation may be required, including assessment for SOD. Abnormal SOM in IARP ranges from 15%-72% with a mean of 30.5% (Table 2)[16,49-54]. The high incidence of abnormal SOM in IARP reflects the fact that a substantial proportion of these patients are likely to have SOD .

Table 2 Frequency of abnormal sphincter of Oddi manometry in idiopathic acute recurrent pancreatitis

Author	Year	Patient number, *n*	Abnormal SOM	Frequency (%)
Gregg *et al*[49]	1984	125	28	22
Toouli *et al*[50]	1985	28	14	50
Venu *et al*[51]	1989	116	17	15
Sherman *et al*[52]	1992	49	15	31
Eversman *et al*[16]	1999	47	34	72
Coyle *et al*[53]	2002	90	28	31
Kaw *et al*[54]	2002	126	41	33
Total		581	177	30.5

With the exception of a study by Eversman *et al*[16], the published studies measured sphincter pressure in only one duct, i.e., either pancreatic OR biliary, although in some cases it is not clear which duct was actually measured. Eversman *et al*, however, performed SOM of the biliary and pancreatic ducts in 593 patients, of whom 360 had intact sphincters. Of the 47 patients with idiopathic acute pancreatitis, 12 had increased pressure in the pancreatic portion of the SO, 3 had increased pressure in the biliary portion and 19 had it in both. The measurement of sphincter pressure in both ducts accounts for the much higher frequency of SOD in IARP that was found in this study. Choudari *et al*[55] also reported a higher frequency of basal sphincter abnormality of at least one duct in patients with chronic pancreatitis.

Of the 360 patients measured in the study by Eversman *et al*[16], 68 (18.9%) had abnormal pancreatic sphincter basal pressure alone, 41 (11.4%) had abnormal biliary basal sphincter pressure alone and in 113 (31.4%) the basal pressure was abnormal for both sphincters. Therefore, 219 (60.1%) of the patients had sphincter dysfunction. The authors concluded that assessment of both the pancreatic and biliary portions of the SO is necessary to accurately detect SOD. The frequency of SOD did not differ whether typed by biliary or pancreatic criteria (65% type Ⅱ and 59% type Ⅲ). As there was so little difference in the frequency of SOD according to the modified Geenen-Hogan criteria, the authors argued for an overall classification for SOD encompassing biliary and pancreatic types.

Guelrud *et al*[56] retrospectively reviewed ERCP studies from 64 children (> 1 year old) and adolescents with recurrent pancreatitis. SOM and sphincterotomy were performed in 9 patients, all of whom had SOD. Seven of these patients had a choledochal cyst and 2 had anomalous pancreaticobiliary union (APBU). After a mean follow up of 26.4 mo (range 18-38), 8 of these patients were symptom free and one had occasional pain but no further episodes of pancreatitis. They concluded that recurrent

pancreatitis and ABPU are associated with SOD in children and adolescents and that sphincterotomy was beneficial to these patients.

SOD AND CHRONIC PANCREATITIS

Early studies investigating the association of SOD and chronic pancreatitis were inconclusive. Some studies showed no difference in pancreatic sphincter pressures between patients with chronic pancreatitis and controls[57-61]. However, these studies involved patients with chronic pancreatitis due to alcohol and in two of the studies the controls were patients with unexplained abdominal pain[58] or suspected biliary dyskinesia[60]. Also, although one of these studies found no significant difference between SO basal pressure in patients with chronic pancreatitis and controls, the pancreatic duct pressure was significantly higher in the early stages of chronic pancreatitis than normal subjects[57]. Other trials have shown a correlation between elevated pancreatic sphincter pressures and chronic pancreatitis[19,62-64]. Many of these also used patients with chronic pancreatitis secondary to alcohol. However, in the only one of these studies that excluded alcoholic patients, basal pancreatic sphincter pressures were significantly higher in the early stages of chronic pancreatitis than controls[62]. Laugier[64] performed manometry of the SOD and main pancreatic duct before and after intravenous injection of secretin in chronic pancreatitis patients and controls. Secretin transiently increased pancreatic duct pressure in controls, but chronic pancreatitis patients had a persistently elevated pancreatic duct pressure and a manometric pattern of SOD. The secretin-induced elevation in ductal pressure was greater and more sustained in patients with chronic pancreatitis, particularly of recent onset (less than 4 years).

It has been shown that local installation of alcohol on the SO results in elevated SO pressures, suggesting a role in the pathogenesis of alcoholic pancreatitis[65]. Tarnasky *et al*[66] looked for evidence of chronic pancreatitis in patients undergoing manometry for investigation of unexplained upper abdominal pain (n = 104). Pancreatic ductography, EUS and pancreatic fluid bicarbonate concentration measurements were carried out. Patients with SOD were 4 times more likely to have evidence of chronic pancreatitis than those with normal sphincter pressure (P = 0.01). Of 68 patients with SOD, 20 (29%) had structural evidence of chronic pancreatitis and 20 of 23 patients (87%) with chronic pancreatitis had SOD. The authors concluded that SOD is associated with structural evidence of chronic pancreatitis in patients with unexplained pancreaticobiliary pain. Patients with chronic pancreatitis and SOD were significantly older than those with SOD but no chronic pancreatitis. This raises the possibility that SOD precedes the development of pancreatitis.

The available evidence certainly suggests a link between SOD and chronic pancreatitis. However, it is still not clear if this is a cause or effect relationship, i.e., does the generalized scarring associated with chronic pancreatitis also involve the sphincter or does the hypertensive sphincter cause elevated pressure and, hence, morphological changes? Further work is required to clarify this issue.

SPHINCTEROTOMY FOR SOD

Biliary type SOD

Management of SOD has traditionally been aimed at sphincter ablation by endoscopic sphincterotomy. Most data on sphincterotomy relates to biliary sphincter ablation alone and clinical improvement has been reported to occur in 55%-95% of patients[15] with the grade of SOD having a significant effect on outcome. Outcomes are generally measured using pain scores or quality of life measures[2], although a lack of standardization in characterizing the patients and assessing response make comparisons between trials problematic.

There are no randomized or controlled trials of therapy for type I SOD and the available evidence is derived from small retrospective trials. Rolny *et al*[67] carried out ERCP and SOM on 17 post-cholecystectomy patients with suspected type I SOD. All patients had a dilated CBD at ERCP and delayed contrast drainage and 11 had elevated SO pressure. Sphincterotomy resulted in symptom relief in all patients after a mean follow up of 28 mo. It was concluded that, in symptomatic post-cholecystectomy patients, the triad of abnormal LFTs, dilated CBD and delayed contrast drainage was sufficient to make a diagnosis of definitive SO abnormality and, as these patients invariably benefit from sphincterotomy, SOM was unnecessary.

Other studies have reported the effect of sphincterotomy for both type I and type Ⅱ patients. Thatcher *et al*[68] retrospectively reviewed 46 patients (31 with type I and 15 with type Ⅱ) who had undergone sphincterotomy for SOD. In the patients with type I SOD 87% had improved pain scores at 3 mo and 77% after a mean follow up of 12.5 mo. When evaluated along with the patients with type Ⅱ SOD, patients with a dilated bile duct and delayed contrast drainage at ERCP had a better response to therapy (P = 0.01) and reduced complication rate (P = 0.03) compared to those with normal ducts at ERCP. 29 patients underwent SOM but a favorable treatment outcome did not correlate with manometric assessment, particularly in patients with abnormal ducts. Therefore, patients suspected of having type I SOD benefited from sphincterotomy, irrespective of SOM results.

Lin *et al*[69] performed sphincterotomy on 24 patients based on clinical findings of post-cholecystectomy pain, biochemical abnormalities and/or dilated bile ducts. Enzyme abnormalities were a significant predictor of response to therapy (P = 0.018) whereas duct dilatation was not (P = 1.0).

These small studies suggest that endoscopic sphincterotomy without SOM is effective in suspected type I biliary SOD. However, patients with presumptive type Ⅱ SOD have, by definition, less concrete evidence for obstruction at the level of the sphincter so more extensive evaluation is necessary to predict those who would benefit from sphincterotomy.

Three randomized trials of endoscopic therapy for types Ⅱ and Ⅲ SOD have been reported. In one of these

47 patients with presumed type Ⅱ SOD were randomly assigned to endoscopic sphincterotomy (n = 23) or a sham procedure (n = 24) in a prospective double-blind study[6]. All patients had biliary type pain, clinical characteristics in keeping with biliary obstruction and had a previous cholecystectomy. Eleven patients in the treatment group had manometric evidence of elevated sphincter pressure and 10/11 described improved pain scores at 1 year. In contrast, only 3 out of 12 patients in the control group who had elevated pressure had an improved pain score over the same time period. Pain scores were unchanged in patients with normal sphincter pressures, irrespective of treatment. After one year sphincterotomy was performed in 12 symptomatic patients who had initially undergone the sham procedure, 7/12 with elevated sphincter pressure and 5/12 with normal pressure. A total of 40 patients were followed for 4 years and after that time 17 of the 18 patients (95%) with SOD verified by manometry had benefited from sphincterotomy. However, only 30%-40% of patients with an elevated sphincter pressure treated with sham sphincterotomy or with a normal pressure treated by sphincterotomy or sham benefited from therapy. The authors concluded that SOM predicted outcome from sphincterotomy and that sphincterotomy offers long-term pain relief in patients with verified SOD.

An Australian study of SOM in 81 post-cholecystectomy patients with biliary-type pain compared outcomes among a mixed group of patients with types Ⅰ (n = 9), Ⅰ-Ⅱ (n = 27), Ⅱ (n = 27) and Ⅲ (n = 18)[70]. The manometric records were categorized as SO stenosis, SO dyskinesia or normal, after which patients were randomized in each category to sphincterotomy or a sham procedure in a prospective double blind study. In the SO stenosis group symptoms improved in 11/13 patients treated with sphincterotomy compared to 5/13 who had a sham procedure (P = 0.041). Results from each treatment group did not differ for patients with SO dyskinesia and normal SOM. This trial provided further evidence that patients with presumed SO dysfunction, with subsequent manometrically diagnosed SOD, benefit from endoscopic sphincterotomy. The authors hypothesized a generalized motility disorder to account for the lack of benefit in patients with normotensive but dyskinetic sphincter function.

Sherman *et al*[71] reported results of a randomized trial comparing sphincterotomy, surgical biliary sphincteroplasty with pancreatic septoplasty (with or without cholecystectomy) to sham sphincterotomy for types Ⅱ and Ⅲ biliary patients with manometrically documented SOD (n = 52). After 3 years, 69% of patients undergoing endoscopic or surgical sphincterotomy had symptomatic improvement compared to 24% in the sham sphincterotomy group (P = 0.009). Type Ⅱ patients had an 81% response to sphincter ablation compared to 58% for type Ⅲ patients; double that of the sham sphincterotomy group.

These trials suggest that SOM is a useful guide in predicting benefit from sphincterotomy in type Ⅱ SOD. However, other (non-randomized) trials have suggested that manometric findings do not correlate with clinical outcome. For example, Botoman *et al*[72] included types Ⅱ (n = 35) and Ⅲ (n = 38) patients to assess response to sphincterotomy. There was no difference between the two groups with respect to sphincter hypertension (60% *vs* 55% respectively), symptomatic improvement at 3 years (60% *vs* 56%) or post-procedure pancreatitis rates (15% *vs* 16%). The authors suggested that current classifications are inadequate to define either incidence of SOD or response to sphincterotomy. In another trial SOM was performed in all but 3 patients from a total of 35 patients with suspected type Ⅱ SOD and 29 with type Ⅲ[73]. Sphincterotomy was performed in all patients with SO pressure greater than 40 mmHg, which included 62.5% of the type Ⅱ patients and 50% of the type Ⅲ patients. After 6 wk 70% of the patients with type Ⅱ SOD and 39% of the type Ⅲ SOD who had sphincterotomy reported benefit (P = 0.13, type Ⅱ *vs* type Ⅲ). None of the patients with normal manometry had symptomatic improvement. After long-term follow up (median 2.5 years) sustained improvement occurred in 60% of the type Ⅱ patients but only 8% of those with type Ⅲ (P < 0.01). The investigators felt that the current classification helps predict outcome after sphincterotomy but again acknowledged a lack of difference in the incidence of abnormal SO baseline pressure between type Ⅱ and type Ⅲ SOD.

Cicala *et al*[74] performed SOM and quantitative scintigraphy in 30 patients with suspected type Ⅰ or type Ⅱ SOD. Fourteen (6 type Ⅰ and 8 type Ⅱ) of the 22 patients were offered and underwent sphincterotomy. At long term follow up, all 14 patients were asymptomatic, biochemical abnormalities had resolved and hepatic hilum-duodenum transit time (HHDT) at scintigraphy had significantly decreased. The patients who had refused sphincterotomy had no change in symptoms or HHDT. Scintigraphy predicted favorable outcomes in 93% of cases compared to 57% for SOM. Two other studies found no correlation between response to sphincterotomy and sphincter pressure for either type Ⅰ or type Ⅱ patients[68,75].

The frequency of hypertension in either sphincter among patients with presumptive type Ⅲ SOD ranges from 25%-70%[76]. The previously cited trial by Sherman *et al*[71], which was published as an abstract, is the only randomized controlled trial that has dealt with outcomes post-sphincterotomy for patients with type Ⅲ SOD. 29 patients with presumed type Ⅲ SOD were randomized and after a 3-year follow up period symptoms had improved in 8/13 (62%) who had undergone endoscopic sphincterotomy, 3/10 (30%) who has sham sphincterotomy and 3/6 (50%) after surgery. A follow up study after dual sphincterotomy for biliary and pancreatic SOD, which included 166 patients with type Ⅲ SOD, found no significant difference in re-intervention rates between different classes of SOD (i.e., biliary *vs* pancreatic, type Ⅱ *vs* type Ⅲ)[77]. After a mean follow up of 44 mo, persistent symptoms prompted re-intervention in 28.3% of patients with type Ⅲ SOD, compared to 20.4% for combined type Ⅰ and Ⅱ (P = 0.105). Other studies report response rates between 8%-65% for type Ⅲ SOD[73,76].

It has been postulated that type Ⅲ SOD is part of a spectrum of functional GI disorders and many patients labeled with it may in fact have a diffuse gastrointestinal motility disturbance. Desautels *et al*[78], for example,

showed that patients with type Ⅲ SOD exhibit duodenal-specific visceral hyperalgesia and their symptoms are reproduced by duodenal distension. The challenge remains to identify which patients will most likely to benefit from a particular therapy. Varadarajulu *et al*[2] suggest that patients who present with discrete, self-limiting episodes of typical biliary or pancreatic type pain are the ones most likely to benefit from SOM and sphincterotomy. With the current evidence available it is reasonable to consider medical therapy as the first line of treatment for patients with suspected type Ⅲ SOD. ERCP with SOM should be considered in the event of failure of medical therapy with sphincterotomy if manometry is abnormal.

Pancreatic type SOD

Evidence that SOD may be a cause of IARP is supported by the resolution of pancreatitis after sphincterotomy, with up to 80% improvement in patients with IARP after biliary sphincterotomy[79]. Tarnasky *et al*[80] showed that biliary sphincterotomy reduced pancreatic basal pressure to within the normal range in 30% of patients immediately after the procedure and 20% after longer term follow up, presumably by ablation of the common channel sphincter, and hence a reduction in the length of the residual pancreatic portion. In a proportion of patients therefore, biliary sphincterotomy alone may resolve pancreatitis or pancreatic pain.

In the one controlled trial addressing response to therapy in patients with acute recurrent pancreatitis presumed to be secondary to SOD, Jacob *et al*[81] compared response to ERCP with or without stent insertion in patients with negative investigations including SOM. Stent insertion reduced the rate of recurrence of pancreatitis from 53% to 11% over a 3-year study period.

Kaw *et al*[54] assessed the relationship between microlithiasis and sphincter hypertension in 67 patients with IARP. After endoscopic biliary sphincterotomy, 88% of patients with type I SOD and 73% with type Ⅱ were asymptomatic, irrespective of microlithiasis or gallbladder status. In a study in which ERCP, SOM and endoscopic ultrasound (EUS) were carried out on 90 patients with acute recurrent pancreatitis, SOD was found to be the most common cause found ($n = 28$) [53]. Of the 22 of these patients who underwent biliary sphincterotomy 21 had reduced episodes of acute pancreatitis after 6 mo.

It has been suggested that inadequate pain relief after biliary sphincterotomy may be due to inadequate biliary sphincterotomy, recurrent biliary stenosis, chronic pancreatitis, other residual pancreaticobiliary disease or a non-pancreaticobiliary cause, e.g., irritable bowel syndrome or a persistent abnormality in pancreatic sphincter pressure[28,82,83]. In the latter case, dual biliary and pancreatic sphincterotomy may improve outcome. Eversman *et al*[84] reported long term outcome of biliary sphincterotomy alone in patients with SOD. Patients with SOD and an abnormal pancreatic sphincter pressure needed re-intervention more often than those with abnormal biliary sphincter pressure alone (39.4% *vs* 16.2%, $P < 0.05$) or dual sphincter hypertension (29%, $P < 0.05$). These results support the theory that an untreated pancreatic SOD may cause recurrent pain in patients who have undergone biliary sphincterotomy alone. A previously cited study by the same authors[16] showed that manometry of both pancreatic and biliary portions of the SO is necessary for complete evaluation for SOD. Other studies have drawn the same conclusions[22,85].

Guelrud *et al*[86] reported the response to four different therapeutic options in patients with normal pancreatography and elevated sphincter pressures (pancreatic type Ⅱ SOD). Symptomatic improvement occurred in 28% of patients treated by biliary sphincterotomy alone, in 54% who had biliary sphincterotomy combined with pancreatic orifice dilatation, in 77% who underwent dual sphincterotomies at two separate sessions and in 86% of patients who had dual sphincterotomies performed during a single session. Compared to biliary sphincterotomy alone, dual sphincterotomy had significantly better outcomes ($P < 0.0005$), irrespective of whether they were performed at a single or at separate sessions. The authors suggested that pancreatic sphincter ablation should be considered for patients with type Ⅱ SOD and an abnormal pancreatic basal sphincter pressure. Other studies have shown similar results. Soffer and Johlin[87] found symptomatic improvement following pancreatic sphincterotomy in 16 out of 25 (64%) patients unresponsive to biliary sphincterotomy. In a further trial, 43 patients who had not responded to biliary sphincterotomy were followed up for a median of 14 mo after pancreatic sphincterotomy. 39/43 patients (91%) showed clinical improvement with 31/43 having a complete response[88].

Another group of investigators followed-up 313 patients who had undergone endoscopic dual sphincterotomy for manometry documented SOD of at least one sphincter for a mean of 43.1 mo[77]. Hypertension was demonstrated in both sphincters in 57%, in the pancreatic sphincter alone in 35% and in the biliary sphincter alone in 26%. Immediate complications occurred in 15% of patients and re-intervention was required in 24.6% of patients at a median follow-up of 8 mo. Re-intervention rates were similar irrespective of ducts with abnormal basal sphincter pressure or previous cholecystectomy. Compared to biliary sphincterotomy alone in historical controls, dual sphincterotomy had a lower re-intervention rate in patients with pancreatic SOD alone (21.3% *vs* 39.4%, $P = 0.034$) and a comparable outcome in those with SOD of both ducts (26.6% *vs* 29%, $P = 0.412$) or isolated biliary SOD (25% *vs* 16.2%, $P = 0.285$). Immediate complication rates occurred in 47/313 patients (15%) with pancreatitis in 45/313 (14.4%). Severe pancreatitis occurred in 0.9% of patients. These complication rates are lower than those reported for biliary sphincterotomy in the prospective study by Freeman *et al*[36] when 21.7% of patients developed pancreatitis, of which 3.7% were severe. This may relate to differences in the quality of pancreatic drainage between the two trials. Fogel *et al*[26] also noted that biliary, as opposed to dual, sphincterotomy was more likely to induce pancreatitis in patients with suspected SOD. Therefore, dual sphincterotomy seems to be beneficial for patients with pancreatic SOD, but not in those with biliary SOD alone. It remains unclear

whether dual sphincterotomy should be performed at the initial procedure. Further randomized trials comparing single versus dual sphincterotomy in patients with SOD are necessary to determine the most appropriate sphincter therapy based on SOM findings. However, other factors should also be taken into account. In a recent trial which included patients with biliary types Ⅰ, Ⅱ and Ⅲ SOD, all 121 patients underwent biliary sphincterotomy[89] and 49 patients had pancreatic sphincterotomy at initial or subsequent ERCP if there was a history of abnormal pancreatic manometry in the setting of continuous pain, persistent pain after biliary sphincterotomy or a history of amylase elevation. There was no significant difference in patient response according to Milwaukee classification. (However, this may reflect the numbers of patients involved, with only 18 meeting the criteria for type Ⅰ SOD). Significant predictors of poor response were normal pancreatic manometry, delayed gastric emptying, daily opioid use and age < 40. Abnormal liver function tests and a dilated bile duct were not significant predictors of outcome. These findings support the argument that we cannot rely on the Milwaukee classification alone to predict response to treatment. The authors suggested that patient factors and pancreatic manometry may be more important predictors of outcome of dual sphincterotomy for SOD. These issues should be taken into account before embarking on therapy.

POST-ERCP PANCREATITIS IN SOD

Overall pancreatitis rates post- ERCP are usually quoted to be between 5%-15%[36,90]. Prospective studies have consistently shown that SOD confers increased risk of post-ERCP pancreatitis (PEP). Cheng *et al*[38] evaluated risk factors for ERCP-induced pancreatitis in 1115 patients who had undergone ERCP. Suspected SOD was a significant risk factor with an OR of 2.6. In a prospective study of 1223 ERCP procedures, Vandervoort *et al*[91] found that patients with manometrically proven SOD had a threefold risk of PEP (21.7% *vs* 7.2%). Freeman *et al*[92] found an overall pancreatitis rate of 6.7% in 1963 ERCP procedures with an odds ratio of 2.6 for suspected SOD. A meta-analysis of 15 prospective clinical trials found that patients with suspected SOD had a relative risk of developing pancreatitis of 4.09 (95% CI 3.37-4.96, $P < 0.001$)[93]. SOD is therefore an independent risk factor for post-ERCP acute pancreatitis and the decision to proceed to ERCP, with or without SOM and/or sphincterotomy, should be made with care.

Sphincterotomy for SOD increases the risk of PEP. One randomized control trial, albeit small ($n = 36$), found a post-sphincterotomy pancreatitis rate of 33% in patients with SOD in whom a PD stent was not placed[94]. Five prospective randomized trials have compared PEP rates between high risk patients with or without PD stent placement. Four of these included patients with SOD (Table 3)[25,35,94,95]. Of these four studies all showed a trend to reduction of PEP with PD stent placement, and two reached statistical significance. A meta-analysis of five prospective studies showed a 3-fold increased risk of post-ERCP pancreatitis if a pancreatic stent was not used (15.5% *vs* 5.8%, OR 3.2, 95% CI 1.6-6.4)[96].

Table 3 Role of pancreatic stent insertion in prevention of post- ERCP pancreatitis; results of randomized controlled trials that included patients with SOD

Author	Year	No. of patients	Pancreatitis rate (%)		
			Stent	No stent	
Smithline *et al*[95]	1993	93	14	18	$P = 0.299$
Tarnasky *et al*[25]	1998	80	7	26	$P = 0.03$
Patel *et al*[94]	1999	36	11	33	$P > 0.05$
Fazel *et al*[35]	2003	76	5	28	$P < 0.05$

At least three case control studies have also included patients with SOD. In two of these there was a significant reduction in PEP with a pancreatic stent[26,88] and in the other the reduction of pancreatitis rate from 66.7% to 14.4% did not quite reach significance ($P = 0.06$)[97]. Therefore, there is substantial evidence that pancreatic stent placement reduces the incidence of post-ERCP pancreatitis in high-risk groups such as SOD. However, failure to deploy the stent successfully may occur in up to 10% of patients[98], and failed pancreatic stent placement can increase the rate of PEP sixteen fold[97]. Therefore, pancreatic stent placement should not be attempted unless the likelihood of success is very high.

CONCLUSION

The relationship between SOD and pancreatitis is a complex one. An association between SOD and acute pancreatitis appears to be beyond doubt, not least because of the high frequency of abnormal SOM in IARP. SOD also carries a significantly increased risk of post-ERCP pancreatitis with rates of over 30%, although correct placement of a pancreatic stent at the time of the procedure appears to reduce this risk. However, although various mechanisms have been postulated, the exact role of SOD in the pathophysiology of pancreatitis is not known and it is unclear if SO dysfunction as a primary event or secondary to other factors is the principal mechanism. There is also evidence linking SOD with chronic pancreatitis but whether this is a cause or effect relationship is still unknown.

Sphincterotomy remains the management of choice for SOD. All patients with type Ⅰ SOD should have their sphincter ablated and, by general consensus, this group does not require manometry prior to the procedure. The question whether dual sphincterotomies should be carried out remains unanswered and further randomized trials are required to clarify this. For patients with type Ⅱ SOD grade A studies have found that SOM is a useful guide in predicting response to sphincterotomy, although some smaller studies showed that manometric findings do not correlate with clinical outcome. However, most experts agree that patients with suspected type Ⅱ SOD should have SOM before considering sphincterotomy.

The management of patients with type Ⅲ SOD is more difficult still with response rates to sphincterotomy ranging from 8% to 65%. In general, sphincter ablation is probably warranted if SOM is abnormal but medical

therapy should be tried before proceeding to manometry. Detailed history taking is paramount for these patients. The more the pain pattern differs from that set out in the Rome Ⅱ criteria, the less likely is the patient to benefit from treatment. Until there is a more adequate method of characterizing patients with type Ⅲ SOD it will not be possible to carry out a randomized trial of sphincterotomy against placebo. Ultimately, this will be the only way of proving the benefit or otherwise of sphincterotomy for patients with presumptive type Ⅲ SOD.

Recent evidence supports the need to measure both portions of the SO to maximize the detection rate of SOD. This dual classification has prompted a call for a single overall classification system from some quarters. A recently published trial[89] has also shown that other patient factors such as age, opioid use, delayed gastric emptying and pancreatic manometry are more important predictors of response to dual sphincterotomy than abnormal liver function tests and a dilated ductal system, on which the traditional classification system is heavily based. Further large prospective trials are required to identify other potential patient factors that may help predict response to therapy; such factors should be taken into account in any future overhaul of the current classification system.

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