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*RAPID COMMUNICATION*

# Sphincter of Oddi hypomotility and its relationship with duodenal-biliary reflux, plasma motilin and serum gastrin

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## Abstract

**AIM:** To detect whether patients with a T tube after cholecystectomy and choledochotomy have duodenal-biliary reflux by measuring the radioactivity of Tc99m-labeled diethylene triamine penta-acetic acid (DTPA) in the bile and whether the patients with duodenal-biliary reflux have sphincter of Oddi hypomotility, by measuring the level of plasma and serum gastrin of the patients. Finally to if there is close relationship among sphincter of Oddi hypomotility, duodenal-biliary reflux and gastrointestinal peptides.

**METHODS:** Forty-five patients with a T tube after cholecystectomy and choledochotomy were divided into reflux group and control group. The level of plasma and serum gastrin of the patients and of 12 healthy volunteers were measured by radioimmunoassay. Thirty-four were selected randomly to undergo choledochoscope manometry. Sphincter of Oddi basal pressure (SOBP), amplitude (SOCA), frequency of contractions (SOF), duration of contractions (SOD), duodenal pressure (DP) and common bile duct pressure (CBDP) were scored and analyzed.

**RESULTS:** Sixteen (35.6%) patients were detected to have duodenal-biliary reflux. SOBP, SOCA and CBDP in the reflux group were much lower than the control group ($t$ = 5.254, 3.438 and 3.527, $P$ < 0.001). SOD of the reflux group was shorter than the control group ($t$ = 2.049, $P$ < 0.05). The level of serum gastrin and plasma motilin of the reflux group was much lower than the control group ($t$ = -2.230 and -2.235, $P$ < 0.05). There was positive correlation between the level of plasma motilin and SOBP and between the level of serum gastrin and SOBP and CBDP.

**CONCLUSION:** About 35.9% of the patients with a T tube after cholecystectomy and choledochotomy have duodenal-biliary reflux. Most of them have sphincter of Oddi hypomotility and the decreased level of plasma motilin and serum gastrin. The disorder of gastrointestinal hormone secretion may result in sphincter of Oddi dysfunction. There is a close relationship between sphincter of Oddi hypomotility and duodenal-biliary reflux.



**Key words:** Sphincter of Oddi; Tc99m-labeled diethylene triamine penta-acetic acid; Pressure; Motilin; Gastrin

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## INTRODUCTION

Endoscopic sphincterotomy (EST) is an important surgery to treat choledocholithiasis. About 50% of the patients after EST had biliary gas indicating reflux of duodenal contents[1]. The duodenal-biliary reflux rate was as high as 100% in the patients after EST[2]. The stone recurrence rate was 9.8% in the patients with EST[3], but in the patients after cholecystectomy for gallbladder stones, the choledocholithiasis recurrence rate was only about 2.5%[4]. Thus, EST destroyed the sphincter of Oddi, resulting in duodenal-biliary reflux which may have close relationship with the recurrence of choledocholithiasis.

The stone recurrence rate was about 10.3% in the patients with T tubes after cholecystectomy and choledochotomy without apparent difference from that of patients after EST[3]. To understand whether sphincter of Oddi hypomotility and duodenal-biliary reflux existed in these patients and if these patients had abnormal secretion of gastrointestinal hormones it needs further studies. To detected if the duodenal-biliary reflux existed the radioactivity of Tc99m-labeled diethylene triamine pentaacetic acid (DTPA) in the bile from the T tubes. Besides, we investigated whether the patients with duodenal-biliary flux had sphincter of Oddi hypomotility and we measured the level of plasma motilin and serum gastrin of the patients. Finally, we discuss the relationship of duodenal-biliary flux with sphincter of Oddi hypomotility, serum gastrin and plasma motilin.

## MATERIALS AND METHODS

### Patients

Forty-five patients (16 men, 29 women, and mean age 58.9 years), who underwent cholecystectomy and choledochotomy at least 1.5 mo (mean 2.5 mo) after T tube drainage, were selected at the Second Affiliated Hospital of China Medical University between April 2004 and August 2005. They were divided into reflux group and control group. The amount of radioactivity of DTPA in the bile was measured and their blood was taken at fasting state in the morning for detecting serum gastrin and plasma motilin. The blood of 12 healthy volunteers (9 men, 3 women and mean age 51.6 years) was taken as control. Thirty-four patients (12 men, 22 women, and mean age 58.3 years) were selected for sphincter of Oddi manometry randomly and double-blindedly.

### Observation of duodenal-biliary reflux

The patients were fasted overnight and took 1 mL water orally containing 185 MBq (5mCi) $^{99m}$Tc-DTPA, then drunk 240 mL water and took a prostrate position. The bile of 2 h was collected and 20 mL of the bile were taken for detection. The intensity of radioactivity was counted in the RM905 radioactivity-detecting meter. Patient was thought to have duodenal-biliary reflux when radioactivity was detected in the bile. $^{99m}$Tc-DTPA was prepared just before administration and radiochemical purity was detected by radiochromatography. The radiochemical purity of $^{99m}$Tc-DTPA was more than 99% while the free $^{99m}$Tc was less than 1%.

### Detection of plasma motilin and serum gastrin

Four mL vein blood was obtained from the patients and healthy volunteers in the early morning and was put into two test tubes undividedly. One of them was filled with 30 μL 10% ethylene diamine tetraacetic acid disodium and 30 μL aprotinin. Then they were centrifuged at 1500 r/min for 15 min, serum and plasma isolated were put into Eppendorf tubes and stored in freezing refrigerator at -70℃.

Plasma motilin and serum gastrin were measured by radioimmunoassay. The sample of serum, plasma misce bene was collected before measurement, then centrifuged at 1500 r/min for 15 min, The supernatant was taken and tested. The motilin radioimmunoassay kit was supplied by Peking Huaying Biotechnology Research Institute. The gastrin radioimmunoassay kit was provided by Isotope Research Center of the China Atomic Energy Academy.

### Method and apparatus of sphincter of Oddi manometry

A triple lumen polyethylene manometry catheter 200 cm in length with an outer diameter of 1.7 mm was used for manometry. The three side holes in the distal end were located 2 mm apart. Sterile water was infused through the catheter at a flow rate of 0.5 mL/min by a hydraulic capillary infusion system. PC polygraph HR (Swedish CTD-Synectics Medical Company) and relevant program were used to record and analyze the tracings. Manometry was performed after all the stones were removed from the common bile duct. The catheter was introduced via the side-pore of choledochoscope into duodenum directly, when the pressure was stable, duodenal pressure-curve was recorded. It was then withdrawn in a stepwise fashion; the position of catheter in the sphincter could be confirmed by direct observation under choledochoscope or by the characteristic pressure changes on the screen. The Oddi's sphincter and common bile duct motility tracings were recorded respectively.

Sphincter of Oddi basal pressure (SOBP), amplitude of phasic contractions (SOCA), frequency of phasic contractions (SOF), duration of phasic contractions (SOD), duodenal pressure (DP) and common bile duct pressure (CBDP) were recorded and analyzed with a special computer program.

Statistical analysis was carried out using Student's *t* test. Data were analyzed with software SPSS11.5. The results were expressed as mean ± SD. Levene's test was used to test the homoscedasticity of the data; *t* test would be used when data had no homoscedasticity. A two-tailed *P* value of $< 0.05$ was considered significant statistically. Pearson correlation test was used to test correlation of the data.

## RESULTS

### Duodenobiliary reflux

There were 16 (35.6%) patients with duodenal-biliary reflux among 45 patients who underwent cholecystectomy, choledochotomy and T tube drainage. The mean technetium count of the bile was 132.73 ± 246.07 KBq (counting performed at the second hour after the isotope ingested). The rest 29 bile samples detected had no radioactivity.

### Plasma motilin and serum gastrin

Plasma motilin (377.54 ± 130.44) and serum gastrin (68.33 ± 28.56) of the reflux group is apparently lower than that of the control group and the non-reflux group (Table 1).

### Manometry of SO

Thirty-four patients were selected (12 men, 22 women,

**Table 1 Plasma motilin and serum gastrin of patients with a T tube after cholecystectomy and choledochotomy (pg/mL)**

| | Cases | Level of plasma motilin | Level of serum gastrin |
|---|---|---|---|
| Reflux group | 16 | 377.54 ± 130.44[a,d] | 68.33 ± 28.56[a,d] |
| Non-reflux group | 29 | 525.37 ± 184.47 | 97.64 ± 26.93 |
| Control group | 12 | 499.02 ± 157.77 | 92.95 ± 25.67 |

[a]$P < 0.05$ *vs* the control group; [d]$P < 0.01$ *vs* the nonreflux group.

and mean age 58.3 years) for sphincter of Oddi manometry randomly and double-blindedly. Among them 13 were classified into the reflux group and 21 into the control group (Table 2).

The sphincter of Oddi's basal pressure, amplitude, common bile duct' pressure in the reflux group were significantly lower than that of the control group ($P < 0.001$), the duration of contractions of the reflux group was shorter than that of control group while there was no significant difference in the frequency of contractions and duodenal pressure between the two groups. The change of SOCA was most remarkable; and the mean value of the reflux group was lower than that half of the control group. In the reflux group, there were 10 (76.9%) patients with DP higher than SOBP and 8 (61.5%) patients with DP higher than CBDP while no patient with DP higher than SOBP and only 2 (9.5%) patients with DP higher than CBDP in the control group (Table 2).

### *Pearson correlation test*

There was no evident correlation between plasma gastrin and serum motilin (the Coefficient of Correlation was 0.146) while plasma motilin showed obviously positive correlation with sphincter of Oddi basal pressure (the Coefficient of Correlation was 0.366) ($P < 0.05$). Moreover serum gastrin showed apparent positive correlation with sphincter of Oddi basal pressure (the Coefficient of Correlation is 0.429) ($P < 0.05$) and common bile duct pressure (the Coefficient of Correlation is 0.359) ($P < 0.05$).

## DISCUSSION

Sphincter of Oddi was at the lower end of the bile duct and pancreatic duct. It plays a major role in controlling bile and pancreatic juice flowing into the duodenum and equally importantly to prevent reflux of duodenal contents into the biliary and pancreatic duct. One-hundred years ago, a variety of names were given to malfunction of sphincter of Oddi, including odditis, biliary dyskinesia, postcholecystectomy and sphincter of Oddi stenosis. Now based on manometry, sphincter of Oddi dysfunction was subdivided into two groups; one of a stenotic pattern and the other a dyskinetic pattern[5]. Reports about sphincter of Oddi hypomotility and sphincter of Oddi dilation were rare. Does sphincter of Oddi hypomotility exist? Does it have close relationship with duodenal-biliary reflux? Does it have close relationship with recurrent cholangitis and recurrent gallstone? Our study would discuss these questions profoundly.

Digestive juice reflux is an abnormal phenomenon of the digestive tract. Duodenal-gastric reflux and gastric-esophagus reflux were most common among them which would result in reflux gastritis and esophagitis[6,7]. Under some conditions, such as after intestinal anastomosis and EST, duodenobiliary reflux may occur, resulting in ascending cholangitis. But whether duodenobiliary reflux existed in patients with gallstones and without EST and in healthy people, has been rarely studied. Feng *et al*[8] found only two of 30 patients with gallbladder stones had duodenobiliary reflux. Wang *et al*[9] studied 53 patients who suffered from the recurrent inflammation of biliary duct after operation and found that the incidence rate of duodenobiliary reflux was as high as 66.67%. The change of biliary tract anatomy could result in pneumatosis of the duct of Wirsung, suggesting duodenopancreas reflux[10]. Li *et al*[11] found that there was apparent duodenobiliary reflux during the process of T tube drainage and the main bacterium infecting bile was $G^-$ bacterium (especially the *E. coli*). We employ $^{99m}$Tc-DTPA for the first time to determine duodenobiliary reflux in patients undergoing choledocholithotomy plus T-tube drainage. The only machine used was RM905 radioactivity meter. For its high molecular weight, $^{99m}$Tc-DTPA had no other pathway to enter into the bile and it was hard for it to penetrate the intestinal mucosa[12]. If there was radioactivity detected in patients' bile, we could infer they had duodenobiliary reflux. The method was simple, less expensive and safe. It was easy to repeat within a short period for the short half-life of the technetium. The results could be easily understood. It had a high specificity (100%), and the sensibility was still unknown since the occurrence of duodenobiliary reflux also could be influenced by many factors, such as the state of the sphincter of Oddi. This means the real duodenobiliary reflux incidence among patients undergoing choledocholithotomy may be higher than our results. We found that the morbidity of duodenobiliary reflux among these people was 35.9% (28/78). It was so high, resulting in bacterial infection and recurrence of stone.

As a valve to prevent duodenal juice reflux, does state of Oddi sphincter have intimate relationship with duodenobiliary reflux? There were numerous and thorough researches on sphincter of Oddi disorder[13-17], but reports about sphincter of Oddi hypomotility and sphincter of Oddi dilation were relatively rare. Early in the 1890, Courvoisier found that 14% of the patients with common bile duct stones had dilation of the duodenal ampulla. Deng *et al*[18] found that the mean contraction period was shortened ($P < 0.02$), and that the frequency ($P < 0.005$) and amplitude ($P < 0.001$) of sphincter phasic waves during phase Ⅲ were decreased in the patients with proximal duodenal transection performed during gastrectomy; this suggested that duodenal transection produced significant changes in interdigestive sphincter of Oddi motility, possibly contributing to augmented duodenobiliary reflux and then lithogenesis. There were many case reports about

**Table 2 Results of sphincter of Oddi manometry of patients with a T tube after cholecystectomy and choledochotomy (mmHg)**

| Groups | *n* | M/F | Age (yr) | SOBP | SOCA | SOD | SOF | CBDP |
|---|---|---|---|---|---|---|---|---|
| Reflux group | 13 | 7/6 | 62.4 ± 8.4 | -3.48 ± 4.77 | 33.81 ± 29.51 | 4.34 ± 1.26 | 7.46 ± 2.80 | -1.64 ± 4.91 |
| Control group | 21 | 6/15 | 55.7 ± 14.2 | 12.26 ± 10.08[b] | 91.40 ± 66.97[b] | 5.27 ± 1.31[b] | 7.08 ± 2.78 | 6.70 ± 7.58[b] |

[b]$P < 0.01$ *vs* control group.

patients who had sphincter of Oddi hypomotility which expressed pneumobilia, lower SOBP and SOCA (patients with chronic intestinal pseudo-obstruction[19], common bile duct stones[20] and progressive systemic sclerosis[21]). Factors correlated to sphincter of Oddi hypomotility including dragging of SO by postoperative adhesion, intra-abdominal abscess, pancreatitis, incompetence of SO resulting from tumors, retrograde peristalsis of duodenum, functional disorder of nerves of the sphincter, passing of stones and actions of drugs.

We found that 16 patients had duodenal-biliary reflux among 45 patients who underwent cholecystectomy and T tube drainage (35.6%), a large number of whom had sphincter of Oddi hypomotility. There were ten (76.9%) patients with DP higher than SOBP and 8 (61.5%) patients with DP higher than CBDP (61.5%) while no patient with DP higher than SOBP and only two (9.5%) patients with DP higher than CBDP (9.5%) in the control group. Sphincter of Oddi structure of human is resembled to that of cats. The bile flow stopped at the contraction state while expelling to the duodenum in the intervals of contraction, but the sphincter of opossum can expel bile during the contraction stage. Sphincter of cats and opossums could expel bile into the duodenum when the duodenum pressure was as high as 45 $cmH_2O$ and no duodenobiliary reflux occurred[22]. Sphincter of Oddi function played an important role in preventing the occurrence of duodenobiliary reflux. It would lose its function of non-return valve in the hypomotility state and could not prevent the duodenal fluid refluxing into the biliary duct and pancreatic duct.

It has been verified that when duodenal juice was added to lithogenic bile, gallstones formed[23]. Bacterial pathogens gained access into the biliary system by descending *via* the portal venous circulation or through the sphincter of Oddi. Bacteria thrived as glycocalyxenclosed microcolonies, coalescing to form an adherent biofilm. The establishment of biofilm was a key event in the formation of biliary sludge and pigment gallstones[24]. There were about 35.9% of the patients with a T tube after cholecystectomy and choledochotomy who had duodenal-biliary reflux. Most of them had sphincter of Oddi hypomotility. We thought that sphincter of Oddi hypomotility may be one of the most important factors which would result in duodenal-biliary reflux, and reflux of duodenum juice into biliary duct is a main cause of stone recurrence.

Motilin is a kind of multiple peptide hormones which contains 22 amini acids and is secreted by the endocrine cells of gut (mainly produced by cells of sinus ventriculi, duodenum and upper part of small intestine). It had the effect of strongly stimulating the contraction of the upper digestive tract and physiological myoelectric activity of its smooth muscle cells. Motilin can invoke contractions of smooth muscle of gallbladder and stimulate secretions of bile. Motilin had prokinetic effect on the sphincter of Oddi and its function had intimate relationship with the dosage used[25-27]. When large dose of motilin used, the sphincter of Oddi of animals contracted, even spasmed. Gastrin is a kind of gastrintestinal hormone, which has been studied earlier and intensively. It is mainly secreted by the G cells of the sinus ventriculi mucosa and small intestines. The researches about effect of gastrin on sphincter od Oddi are rare[28-30]. A few reports showed gastrin could increase SOBP and SOCA. Chen suggested that the patients with post-cholecystectomy pain had sphincter of Oddi dysfunction with characteristics of high tension and it was related to elevation of serum gastrin[31]. Our study found that many patients with a T tube after cholecystectomy and choledochotomy had duodenal-biliary reflux. Most of them had sphincter of Oddi hypomotility, and decreased plasma motilin and serum gastrin. Plasma motilin showed obviously positive correlation with sphincter of Oddi basal pressure while serum gastrin showed apparent positive correlation with sphincter of Oddi basal pressure and common bile duct pressure. Disorder of gastrointestinal hormone secretion might result in sphincter of Oddi dysfunction and the sphincter of Oddi hypomotility caused by it had intimate relationship with duodenal-biliary reflux and recurrence of gallstones.

## COMMENTS

### Background

Sphincter of Oddi is at the lower end of the bile duct and pancreatic duct. It plays a major role in controlling the flowing of bile and pancreatic juice into the duodenum and equally importantly to prevent the reflux of duodenal contents into the biliary and pancreatic duct. Based on manometry, sphincter of Oddi dysfunction was subdivided into two groups; one characterized by a stenotic pattern and the other a dyskinetic pattern. The reports about sphincter of Oddi hypomotility and sphincter of Oddi dilation are fairly rare.

### Research frontiers

Whether sphincter of Oddi hypomotility and duodenal-biliary reflux existed in patients with a T tube after cholecystectomy and choledochotomy and if they had abnormal secretion of gastrointestinal hormones needed further researches. Does sphincter of Oddi hypomotility exist? Does it have close relationship with duodenal-biliary reflux? Does it have close relationship with recurrent cholangitis and recurrent gallstone? This study discussed these questions profoundly.

### Innovations and breakthroughs

This study found many patients with a T tube after cholecystectomy and choledochotomy had duodenal-biliary reflux. Most of them had sphincter of Oddi hypomotility, plasma motilin and serum gastrin of them decreased. The disorder

of gastrointestinal hormone secretion might result in sphincter of Oddi dysfunction and sphincter of Oddi hypomotility caused by it had intimate relationship with duodenal-biliary reflux and recurrence of gallstones.

### Applications

The reports about sphincter of Oddi hypomotility and sphincter of Oddi dilation are relatively rare. Authors found the disorder of gastrointestinal hormone secretion might result in sphincter of Oddi dysfunction and sphincter of Oddi hypomotility caused by it had intimate relationship with duodenal-biliary reflux and recurrence of gallstones. So regulating the level of hormones might be helpful in the treatment of sphincter of Oddi dysfunction.

### Peer review

It is a very interesting study, and the presentation of manuscript is good. Title accurately reflects the major topic and contents of the study. Although it is not a multi-center study the results are very interesting because they demonstrated more about the function of the Sphincter of Oddi. Discussion is well organized, and references are appropriate and relevant.

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