REVIEW

Gall stones and chronic pancreatitis: the black box in between

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The relation between gall stones and chronic pancreatitis is uncertain; there are differing opinions on this issue. Firstly, gall stones are the most common reason for acute pancreatitis, but it cannot cause chronic pancreatitis. Secondly, a connection between gall stones and chronic inflammation of the pancreas might exist. Numerous studies or investigations have shown that changes associated with chronic pancreatitis are common in gallstone patients. Although it seems that gall stones might be a cause of chronic pancreatitis according to these findings, clinical and experimental studies are still needed for confirmation, and further studies are required to determine the mechanisms involved.

gall stones or cholelithiasis is a possible cause of chronic pancreatitis according to clinical studies and epidemiological investigations in both Western and Eastern countries.^{7–10} This paper will provide a review of studies on gallstone diseases or chronic pancreatitis, and discuss whether gall stones or cholelithiasis could be a cause of chronic pancreatitis and its possible mechanism.

DIFFERENT OPINIONS ON THE RELATION BETWEEN GALL STONES AND CHRONIC PANCREATITIS

There are numerous possible causes and alcohol misuse is believed to be the most common cause of chronic pancreatitis (box 1). Gall stones are well known to cause acute pancreatitis.^{11, 12} However, the role of gallstone diseases in the causation of chronic pancreatitis is controversial. There are two kinds of differing opinions on the relation between gall stones and chronic pancreatitis. Firstly, gall stones are the most common reason for the development of acute pancreatitis, but gallstone pancreatitis virtually never becomes chronic, gall stones cannot cause chronic pancreatitis.^{3–6} The proposed mechanism involves gall stones and biliary stricture or obstruction, which are secondary to the compression of the intrapancreatic portion of the common bile duct (CBD) by a fibrotic pancreas,¹³ and are considered as complications but not causes of chronic pancreatitis.^{14–16} Additionally, Kahl *et al*¹⁷ studied the relation between stricture of CBD and pain in patients with alcoholic chronic pancreatitis and jaundice. After stent insertion for endoscopic drainage, the jaundice disappeared but pain did not change. They concluded that successful endoscopic drainage of biliary obstruction had no influence on the pain pattern and that CBD obstruction could not cause pain in patients with chronic pancreatitis. It seemed to show that alcohol was more important in the development of chronic pancreatitis, whereas the stricture of CBD was secondary to it.

Secondly, a connection between gall stones or cholelithiasis and chronic inflammation of the pancreas might exist, because pathological pancreatograms are more frequent in gallstone patients than in other persons, and chronic pancreatitis is frequently associated with cholangiographic evidence of biliary obstruction.^{7, 18–21}

Abbreviations: SO, sphincter of Oddi; CBD, common bile duct; CCK, cholecystokinin; GACP, gallstone associated chronic pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography

Chronic pancreatitis is a progressive disease with complications, such as diabetes and malabsorption, which usually lead to increased morbidity and social problems. Chronic pancreatitis is usually developed increasingly, and characterised by fibrogenesis and impairment of pancreatic function.

The main aetiological, clinical, and histological aspects of chronic pancreatitis were initially described by Sarles *et al*.¹ From then on, many scholars became interested in this disease and some studies or investigations on chronic pancreatitis were performed, which resulted in different conclusions and opinions on aetiology, category, clinical and pathological features, and treatment of chronic pancreatitis. Generally, four prominent theories on pathogenesis of chronic pancreatitis have emerged in past decades, including the toxic-metabolic theory, the stone and duct obstruction theory, the oxidative stress hypothesis, and the necrosis-fibrosis hypothesis.² Although these theories are all formulated based on scientific research, substantial contradictory data also exist for each. On one hand, because of the recent scientific progress in the underlying genetic, molecular, and cellular pathophysiology, there have been evident advances in the understanding of chronic pancreatitis pathogenesis; on the other hand, as far as whether gall stones could be a cause of chronic pancreatitis is concerned, there are different opinions at present. In Western countries, alcohol misuse is considered the most common cause for chronic pancreatitis, whereas gall stones are usually not supposed to be important in the pathogenesis of chronic pancreatitis.^{3–6} In contrast with this, there are different suggestions that claim that

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Box 1 Causes of chronic pancreatitis³

- (1) Alcohol misuse
- (2) Idiopathic pancreatitis,
 - Early onset
 - Late onset
- (3) Obstruction of pancreatic duct
 - Trauma to pancreatic duct
 - Duct stricture or stone
 - Pancreas divisum, with associated, accessory papillary stenosis
 - Longstanding pancreatic duct stent
- (4) Genetic causes
 - Cystic fibrosis
 - Familial pancreatitis
- (5) Tropical pancreatitis
- (6) Autoimmune chronic pancreatitis
- (7) Recurrent or severe acute pancreatitis
 - Hyperlipidaemia
 - Severe necrotising pancreatitis

Epidemiological investigations in Asia seem to confirm the possible association between gall stones and chronic pancreatitis (table 1). Clinical studies have shown that the main cause of chronic pancreatitis in China seems to be cholelithiasis, cholecystitis, or diseases of the choledochus.^{8,9}

It is undoubted that alcohol has a strong association with chronic pancreatitis, but not all of them are ascribed to alcohol even in Western societies; other causes should exist.³ Therefore, gall stones or cholelithiasis might be another occult cause. As there is a dispute on this issue, many clinical studies or reports have been presented in past decades. From these clinical findings, we may find some clues as to the possible relation between gall stones and chronic pancreatitis.

CLINICAL FINDINGS IN GALLSTONE PATIENTS**Symptoms and signs**

The clinical course and features were studied in 102 cases of chronic pancreatitis. As a result, cholelithiasis was present as an important manifestation, and most symptoms and signs in these patients were attributable to cholelithiasis.²² Ohta *et al*²³ conducted a statistical analysis of both clinical symptoms and signs of different aetiologies of chronic pancreatitis by using odds ratios, and found that jaundice and other items that were closely related to gall stones and acute cholecystitis were more significantly seen in biliary pancreatitis than in alcoholic and idiopathic pancreatitis. Hardt *et al*⁷ found symptoms such as upper abdominal pain, bloating, and fat intolerance were more common in gallstone patients. Gu *et al* reported the most common clinical presentations of chronic pancreatitis in China were abdominal pain, fever, jaundice,

emaciation, diarrhoea, abdominal mass, and melaena attributable to cholelithiasis.⁸ However, not all patients with chronic pancreatitis had typical symptoms and signs, some patients just showed retained stones in biliary tree.^{7,8,20} Sato *et al*²⁴ studied the relation between duration of symptoms and the histological changes of the pancreas, and found that 16.7% of gallstone patients without pain had mild changes in the pancreas. They concluded that there was no significant difference between the histological changes of pancreas and the duration of symptoms.

Pancreatic secretion function test

Impaired pancreatic exocrine function was found in 25% of patients with cholelithiasis.²⁴ Wakabayashi *et al*²⁵ performed comparative assessments of the endocrine and exocrine functions of the pancreas associated with chronic gallstone pancreatitis or cholelithiasis. The result was that patients with cholelithiasis showed exocrine hypersecretion of the pancreas, and all the assessed parameters of exocrine function were depressed in the patients with gallstone pancreatitis. Another study⁷ of 91 gallstone patients and 94 age matched controls were investigated and reported that abnormal levels of faecal elastase 1, which was regarded as a marker of severe exocrine dysfunction of pancreas,²⁶ were more common in gallstone patients.

Endoscopic and imaging findings

It was reported that chronic pancreatitis was frequently associated with cholangiographic evidence of biliary obstruction.²¹ Joergensen *et al*²⁷ reported a case of chronic pancreatitis in a girl associated with gall stones and an impacted gall stone in the ampulla of Vater was found. Okazaki *et al*²⁸ performed a clinical study, in which they endoscopically measured pressures of the pancreatic duct and the sphincter of Oddi (SO), in patients with GACP and in controls. In patients with GACP, the pressures of the pancreatic duct and the frequencies of the papillary sphincter waves were significantly higher than in controls, and there were correlations between the pressures of the pancreatic duct and the motility of SO. In another endoscopic retrograde cholangiopancreatography (ERCP) study,⁷ 77% of gallstone patients, while 47% of non-gallstone patients were found to have chronic pancreatitis according to the Cambridge classification.

Gu *et al* summarised several ERCP studies and concluded that chronic pancreatitis in China was mainly secondary to cholelithiasis and other diseases of the bile duct. Stones in the common bile duct were extremely frequent. Of a group of 114 patients who had chronic pancreatitis, 46.5% had cholelithiasis or cholangitis, or both. Among another 15 chronic pancreatitis patients, eight patients had stones in the bile duct, three had a dilated choledochus, and one had stenosis of the distal CBD. Studies in this country also found stenosis of the SO.⁸

Misra *et al*²⁰ carried out a study to assess pancreatic duct abnormalities by ERCP in 50 patients with gall stones but without a history of acute pancreatitis, and compared with 33 patients as controls who were found to have a normal biliary tree. Abnormal pancreatograms were obtained in 24 (48%) patients with gallstone disease and in only two (6%) of the

Table 1 Gallstone associated chronic pancreatitis (GACP) in China and Japan

Reference	Area	Ratio of GACP	Year
Qian <i>et al</i> ⁹	China	47.0%	1958–1989
Qian <i>et al</i> ⁹	China	36.8%	1990–2000
Otsuki <i>et al</i> ¹⁰	Japan	13.8%	1970–1977

control group; the differences were statistically significant. Pancreatic duct abnormalities were more severe and occurred more frequently in patients who had stones in the biliary tree than in patients with a normal biliary tree. The results showed that nearly half of all patients with gallstone disease had pancreatic duct abnormalities, and 16% of these patients were severe enough to be labelled as chronic pancreatitis.

Holcomb *et al*²⁹ reported on six children with extrahepatic biliary disorders with chronic relapsing pancreatitis secondary to stenosis of the ampulla of Vater.

Surgical findings

Kelly *et al*³⁰ found in their study that 83% of the patients with gallstone pancreatitis had stones in the common bile ducts, 23% of which were impacted at the ampulla of Vater. Gu *et al* in a necropsy study reported that 10 patients with septic shock secondary to cholelithiasis and severe cholangitis found that two had only intrahepatic bile duct stones, six had both intrahepatic and extrahepatic stones, and the other two had stones only in the choledochus. Five of these 10 patients had chronic pancreatitis, among whom four had distal bile duct obstruction and ampullary stenosis, and, in contrast with Western countries, stones in pancreatic duct were not frequent.⁸ Chitkara³¹ studied the pathological features of 53 gall bladders from patients with clinical and laboratory evidence of gallstone pancreatitis and found that the presence of intraepithelial neutrophilic cells aggregates was the most common pathological finding. Changes of acute cholecystitis and chronic cholecystitis were found in 15 (28.3%) and 6 (11.3%) gall bladders, respectively. The author concluded that the role of choledocholithiasis in the pathogenesis of cholelithiasis associated pancreatitis might be important.

Distal bile duct stenosis was found in a surgical study of eight patients with non-alcoholic chronic pancreatitis. Stricture shapes of the common bile ducts were smooth and tapering in five patients, funnel shaped in two, and rat tail in one.¹⁴

PROPOSED HYPOTHESES OF GALLSTONE CHRONIC PANCREATITIS

According to the results of clinical studies or investigations mentioned above, it seems that there is a possible connection between gall stones and chronic pancreatitis. Then, what might be the mechanism of pancreatic damage in gallstone patients? The following may be possible reasons.

Inflammation

Gall stones or sludge in gall bladder or bile duct system can induce relapsing inflammation, obvious or occult, in local area, such as bacterial cholecystitis, cholangitis, papillitis, and so on. Also, the prolongation of necrosis, abscess, or pseudocyst after acute gallstone pancreatitis (perhaps occult) can lead to chronic inflammation of the pancreas.^{8 31} Inflammatory cytokines release will be promoted in the course of inflammation. Inflammatory oedema can induce stenosis or obstruction of bile and pancreatic ducts.

Obstruction of duct system

Bile duct obstruction and ampullary stenosis induced by stones were common in some gallstone patients.⁸ Stones could impact mechanically at the ampulla of Vater during their migrations.^{27 30} Histological findings, associated with CBD obstruction, showed the role of choledocholithiasis in the pathogenesis of pancreatitis from another aspect.³¹ Bile or pancreatic duct obstruction can induce higher pancreatic duct pressure, leading to pancreatic juice regurgitation and autodigestion, and result in damage of the pancreas eventually.

Five key references

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A focus of chronic pancreatitis pathogenesis is whether acute gallstone pancreatitis could result in chronic pancreatitis. It is postulated that repeated episodes of gallstone pancreatitis might result in a mechanical block at the ampulla of Vater, induced by the inflammatory process, including regurgitation of bile, and this might evolve into chronic pancreatitis. An update study shows the relation between acute biliary pancreatitis and chronic pancreatitis. Forty patients with acute biliary pancreatitis were prospectively and consecutively studied by Pareja *et al*.³² The authors assessed the morphology of the pancreas and the main pancreatic duct with magnetic resonance cholangiopancreatography five years after the episode of pancreatitis, and found scarring lesions as a consequence of the acute episode in the long term, unrelated to its severity. The results seem to show an association between chronic pancreatitis and biliary disease.

Gall stones or cholelithiasis and secondary abnormal bile or pancreatic duct system may influence pancreatic secretion function.²⁵ This shows that exocrine hypersecretion might induce hypertension in pancreatic ducts and then result in pancreatic damage finally.

Even in patients with alcohol misuse, occult microlithiasis, which can induce stenosis or obstruction of pancreatic duct in the dark, might contribute to the development of chronic pancreatitis together with alcohol rather than alcohol itself.^{33 34}

Ampullary stenosis or sphincter of Oddi dysfunction

Repeated stones and sludge passage or biliary disorders could induce papillary stenosis or repeated episodes of acute pancreatitis, which could result in eventual chronic pancreatitis.^{4 8 29 35} Gu *et al*⁸ reported ampullary stenosis in chronic gallstone pancreatitis from a surgical point of view. Sphincter of Oddi dysfunction is considered to be associated with chronic pancreatitis.^{36–38} Okazaki *et al*²⁸ found increased pancreatic ductal pressure and motility of SO in patients with GACP, and considered that the increased pancreatic ductal pressure was attributable in part to papillary dysfunction.

Others

Cholecystokinin (CCK) is an important gastrointestinal hormone that plays an important part in regulation of pancreatic secretion and gallbladder contraction. Gall stones

and secondary chronic inflammation may influence CCK secretion. Plasma CCK concentrations are high in patients with acute gallstone pancreatitis, but not in patients with alcoholic and idiopathic pancreatitis. A transient disturbance of bile flow into the duodenum by stones or oedema of the pancreas together with impairment of pancreatic exocrine function might cause the increase of CCK release in plasma in gallstone pancreatitis. Another study reported that patients with chronic pancreatitis with mild to moderate impairment of exocrine function and abdominal pain, had significantly higher plasma CCK concentrations, whereas patients with pancreatic insufficiency had a significantly lower plasma CCK response to a test meal than the healthy subjects.³⁹ The changes of CCK concentrations in plasma showed that CCK might play an important part in the pathogenesis of gallstone pancreatitis.

Oxidative stress is an important molecular pathogenesis of chronic pancreatitis.² Dudnik⁴⁰ found increased serum concentrations of two products of lipid peroxidation (LPO) in patients with gallstone disease and concluded that serum LPO products could be diagnostic markers of associated pancreatitis. This shows that oxidative stress maybe effect on development of gallstone chronic pancreatitis.

Another disease that can induce chronic pancreatitis is ampullary duodenal diverticulosis.⁴¹ Kubota *et al*⁴² found incidence of duodenal diverticula near papillary was significant in patients with choledocholithiasis. Leinkram *et al* found higher frequencies of gallstones disease and relapsing or chronic pancreatitis in patients with duodenal diverticula.⁴³

Patients with idiopathic chronic pancreatitis are not all ascribed to gene mutation,⁴⁴ some "idiopathic" chronic pancreatitis may be associated with microlithiasis as some acute idiopathic pancreatitis are attributable to occult gall stones.^{35 45}

REMAINED PUZZLING PROBLEMS

Although ongoing basic and clinical research during past years have further characterised the genetic, molecular, and clinical aspects of chronic pancreatitis, studies on aetiology still have to be improved.

Among these studies mentioned above, most of them are retrospective studies or case reports, from which a close association between gall stones and chronic pancreatitis can be seen, but the conclusion that whether gall stones cause chronic pancreatitis or chronic pancreatitis causes gall stones cannot be made certainly. According to the studies of Hardt *et al*⁷ and Misra *et al*,²⁰ it seems that patients with gall stones tend to develop to chronic pancreatitis, but long term follow up studies on pancreatic functions, pancreaticobiliary changes, and the effect of removal of the gall stones are needed to clarify the issue further in these patients, especially those patients who have abnormal cholangiopancreatograms.

No matter whether the role of bile or pancreatic duct obstruction or ampullary stenosis in the pathogenesis of chronic pancreatitis of gallstone patients is true or not, the hypothesis is based on the truth that the common bile duct and the main pancreatic duct have a common pancreatobiliary channel in the ampullary of Vater. A good case of point is the study of Jones *et al*,⁴⁶ in which the authors found that 67% of patients with gallstone pancreatitis had a common channel present on intraoperative cholangiography. Then, for patients who have not the common pancreatobiliary channel, do gall stones still cause chronic pancreatitis? Is mechanical obstruction the only reason for gallstone pancreatitis? And, does pancreatic function or pancreatogram change in these patients?

Some results of studies seem to show the effects of CCK, oxidative stress, and duodenal diverticulum on chronic

pancreatitis in gallstone patients, but there is no direct evidence.

It is well known at present that inflammatory cytokines play an important part in activation of pancreatic stellate cells, which in turn cause fibrosis of pancreas.⁴⁷ The changes of inflammatory cytokines, activation of pancreatic stellate cells, changes of immune system, and their interactions in patients with gall stones have not been deeply studied.

Animal research on alcoholic pancreatitis and pancreatic stellate cells are highlights today. In contrast, we are lacking such animal studies on GACP. The differences of initiation factors, histopathological and molecular changes between gallstone associated and other types of chronic pancreatitis remain obscure.

SUMMARY

We are beginning to better understand the causes of chronic pancreatitis, but the relation between gall stones and chronic pancreatitis still remains unknown. Based on the results of many clinical studies on pancreatic secretion, ERCP, magnetic resonance cholangiopancreatography, or necropsy in patients with gall stones or GACP, it seems that gall stones, including sludge, and repeated episodes of acute gallstone pancreatitis could result in chronic pancreatitis, which might be attributable to biliary inflammation, bile and/or pancreatic duct obstruction, papillary stenosis or impaction, and sphincter of Oddi dysfunction. Sludge should be considered in some "idiopathic" patients. Thus, in contrast with common belief, it seems to be possible that gall stones, cholelithiasis or microlithiasis, and recurrence of acute gallstone pancreatitis might be causes of chronic pancreatitis, followed by pancreatic exocrine, even endocrine impairment. However, all the hypotheses should be further testified by well designed clinical or animal studies from anatomical, pathophysiological, and molecular aspects.

MULTIPLE CHOICE QUESTIONS (ANSWERS AT END OF REFERENCES)

- At present, gall stones are considered certainly as a cause of:
 - Chronic pancreatitis
 - Acute pancreatitis
 - Both chronic and acute pancreatitis
- Which is the common cause of chronic pancreatitis?
 - Gall stones
 - Autoimmune diseases
 - Alcohol
- According to ERCP, what are found to have associations with chronic pancreatitis?
 - Biliary obstruction
 - Pancreatic duct abnormalities
 - Both (A) and (B)
- It is supposed that gall stones can result in chronic pancreatitis because they may induce:
 - Inflammation and stenosis or obstruction of ampulla of Vater
 - Fever
 - Abdominal pain
- What patients with gall stones tend to induce pancreatitis?
 - Those patients who have common pancreatobiliary channels in the ampullary of Vater

- (B) Those patients who do not have common pancreatobiliary channels
 (C) Anyone who has gall stones

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ANSWERS

1. (B); 2. (C); 3. (C); 4. (A); 5. (A).