

ADVANCES IN ENDOSCOPY

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Recent Research on Extracorporeal Shock Wave Lithotripsy with ERCP for Treatment of Chronic Calcific Pancreatitis



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G&H What is chronic calcific pancreatitis?

RK Chronic calcific pancreatitis (CCP) is a condition in which the pancreas is scarred and chronically inflamed. Stones form, usually within the pancreatic duct, and can cause pain or relapsing attacks of pancreatitis.

CCP can have several causes. The condition can be caused by mutations in the *SPINK1*, *SPINK2*, or hereditary trypsin inhibitor gene. The condition can also be caused by chronic renal failure in patients on dialysis or by high levels of calcium. Traditionally, it has been thought that CCP was caused by excessive alcohol intake, but only 1 in 6 or 7 individuals who drink excessive alcohol develop CCP. Over the last 4 or 5 years, it has become clear that chronic smokers have a marked increased incidence of CCP and that chronic smoking induces scar formation by stimulating stellate cells in the pancreas. Although CCP is caused by a variety of etiologies, the common denominator is that stones formed in the pancreas block the pancreatic duct, causing pain and pancreatitis.

G&H How is CCP usually treated?

RK Historically, this condition has been treated with chronic pain medications because many of these patients experience severe pain. If patients develop endocrine or exocrine insufficiency from sufficient damage to the pancreas, they may require oral hypoglycemic agents or insulin for treatment of diabetes. Classically, many of these patients were treated with pancreatic enzymes if they had maldigestion of food. In addition, some doctors

believe that taking pancreatic enzymes decreases pain in a subset of these patients. In some parts of the world, antioxidant therapy—such as selenium, vitamin E, or vitamin C—is used in an attempt to reduce the number of free radicals in the pancreas, which may be associated with pain.

The pain of CCP can also be treated with nonmedical therapies. One treatment option is a nerve block, such as a celiac axis block. Historically, most CCP patients have been treated surgically when pain becomes severe. A number of operations have been available. One is a longitudinal pancreaticojejunostomy (a so-called Puestow procedure), in which a Roux-en-Y loop of jejunum is sewn to the body and tail of the pancreas. Another surgical option is a Whipple procedure, in which the head of the pancreas is resected. A third option is a combination of these procedures, either a Beger procedure (a duodenal-preserving pancreatic head resection) or a Frei procedure (in which the head of the pancreas is removed in conjunction with a longitudinal pancreaticojejunostomy). Over the last 15 years or so, doctors have also tried to treat CCP endoscopically via extracorporeal shock wave lithotripsy (ESWL) and endoscopic retrograde cholangiopancreatography (ERCP).

G&H Could you discuss the use of ESWL in these patients?

RK Stones in CCP frequently form upstream to a stricture, and, as the saying goes, it is impossible to get an elephant through a keyhole without enlarging the keyhole or dismantling the elephant. Many of these

stones are impacted very close to the duodenum, making an approach with direct pancreatoscopy and either electrohydraulic or laser lithotripsy quite difficult. Therefore, in my experience, over 50% of patients with CCP need ESWL, which is simply a variation of kidney lithotripsy, a procedure that has been used for almost 4 decades. In ESWL, 2 devices that look like large spark plugs are used to deliver shock waves in a very fine focal point at an area of calcification or a stone. In my medical center, my colleagues and I use up to 3,000 shock waves for areas of calcification or stones, assuming that they can be seen via fluoroscopy, which the vast majority can. Figure 1 shows the use of ESWL and ERCP in a patient with CCP.

G&H Could you discuss the design of your recent study in this area?

RK My colleagues and I recently conducted a 20-year retrospective study on the use of ESWL in conjunction with ERCP for removal of stone fragments immediately afterward. Since 1990, we have been using these procedures at our medical center to treat CCP patients with amenable lesions; patients with small pancreatic ducts and diffuse punctate calcifications are not amenable to the use of shock wave therapy, in the latter case because these stones are too diffuse. Patients with 100 stones in the head of their pancreas (known as a pseudotumor of the pancreas if there is a large inflammatory mass) are better handled surgically than via ESWL.

My colleagues and I have historically used ESWL in patients in whom abdominal imaging (either computed tomography or magnetic resonance imaging) shows the presence of a large stone with a dilated upstream pancreatic duct in symptomatic patients with CCP (ie, patients who have refractory pain, relapsing bouts of pancreatitis, or both). If the stone is over 6 mm—most stones are over 1 cm—we perform ESWL first followed by immediate ERCP, which includes sphincterotomy, lavage of stone fragments, and mechanical removal of stone fragments with stone baskets and balloons followed by placement of 1 or more pancreatic stents. If the stone is less than 6 mm, ERCP is performed first via pancreatic sphincterotomy with or without balloon dilation of a downstream stricture for removal of the stone and placement of 1 or more pancreatic stents.

In our study, we looked at our total patient volume (215 patients) and determined through a prospective database that 177 of these patients were still alive. Two of these patients were excluded for having undergone surgery, so we sent out questionnaires to the other 175 patients. Completed surveys were received from 120 patients, for a survey completion rate of 68%.

The questionnaire asked patients about their lives both before and after their combined therapy of ESWL and ERCP, particularly in terms of quality of life, pain, narcotic usage, and factors that have been associated with pancreatitis (eg, smoking and alcohol).

G&H What were the main findings of this study, and what are their implications for the treatment of this condition?

RK The main finding was that, in fact, there was a very significant decrease in pain scores after endoscopic therapy. The main pretreatment pain score was 7.9 on an analog pain scale; this score dropped to 2.9 after ESWL and ERCP (a highly statistically significant finding, with a *P*-value of .001). In addition, following this combined therapy, 85% of patients reported improved pain, and half of the patients had complete pain relief and were no longer using narcotics. An improvement in the quality-of-life score was also found after combined therapy (from 3.7 to 7.3 on the scale, another highly statistically significant finding).

The study also found that patients who used enzymes before combined therapy continued to need them. In addition, patients who were diabetic before combined therapy were still diabetic afterward, and a subset of patients developed diabetes over a mean follow-up period of 4 years. Also, we found that smokers who quit smoking after undergoing pancreatic ESWL and ERCP had significantly fewer narcotic requirements than individuals who continued to smoke.

These study results support the views of our medical center, including our pancreatic surgeons, that ESWL and ERCP should be performed before CCP patients with amenable anatomy are considered for surgery; these patients should undergo surgery only if these procedures fail.

G&H What have other studies reported on the use of ESWL with ERCP for treatment of CCP?

RK Our studies confirm those of Cremer, Deviere, and the Brussels group by showing that ESWL in conjunction with ERCP is safe and effective for the treatment of CCP patients. Reported complications are usually limited to cutaneous and mucosal ecchymoses, although minor flares of pancreatitis can also be seen.

G&H Should ERCP always be used after ESWL?

RK Dumonceau and colleagues reported that patients with CCP experienced the same amount of pain whether or not they underwent ERCP after ESWL. However,

a significant subset of patients who experienced initial pain relief in this study went on to subsequently require ERCP for removal of stone fragments. Most of the studies that have suggested that ERCP is not needed actually use multiple (usually 7 or 8) sessions of ESWL in an attempt to obtain progressively finer stone fragments, almost to the consistency of sand, to be expressed through the papillae. In one study, up to 13 sessions of ESWL were used. However, the use of multiple sessions is not very cost-effective. In our medical center, combined therapy of ESWL followed by ERCP is always used, except for rare exceptions.

G&H What are the causes of pain in patients with CCP? Are pancreatic calculi the most significant cause?

RK This issue is unclear. Pain is multifactorial in CCP. Some of these patients are narcotic-habituated, some of these patients have pain related to perineural fibrosis and inflammatory change, and some of these patients have pain related to strictures with or without stones. Therefore, it may not be clear whether the stones per se are causing enough obstruction to account for the level of discomfort that the patients are claiming to experience. However, if patients are well selected for ESWL and ERCP, the majority of them will experience decreased pain. Patients should be excluded from this combined therapy if their pancreas is two thirds calcified or if they have small duct disease, as these patients may experience pain even without a duct obstruction. In our study, following ESWL and ERCP, 50% of patients experienced no pain and were not taking narcotics. Therefore, stones are obstructive only in a subset of patients; their mere presence does not indicate that they are the cause of pain.

G&H How often is surgery needed to treat pain in these patients?

RK In almost every study on ESWL, with or without subsequent ERCP, approximately 20% of patients require subsequent surgery. Many of those patients come from early in our experience, when it was thought that all patients could experience pain relief after undergoing ESWL. However, we now know that this is not possible. For example, we have learned that patients with popcorn kernel calcifications throughout the head of the pancreas (ie, a very large mass in the head) do not respond very well to combined therapy. These patients respond much better to a Whipple procedure, and they almost never respond well to a Puestow procedure. Thus, there is a subset of patients (perhaps 1 in 5) that will ultimately require surgical intervention.

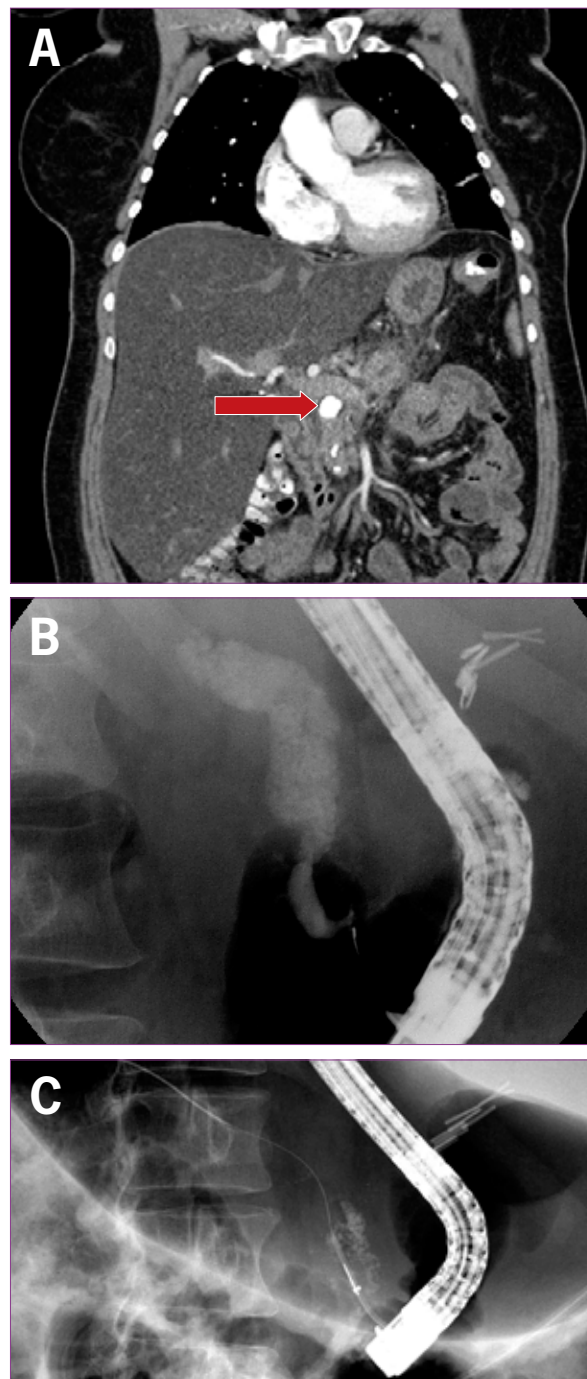


Figure 1. A computed tomography scan shows a large stone (arrow) within the pancreatic duct (A). A pancreatogram outlines the large stone within the pancreatic duct (B). Six weeks after extracorporeal shock wave lithotripsy and initial endoscopic retrograde cholangiopancreatography, a significant decrease in stone burden is seen on a pancreatogram (C). (Images courtesy of Andrew S. Ross, MD, Virginia Mason Medical Center, Seattle, Washington.)

In this subset of patients, it might be assumed that surgery will be the final solution for them, but this is

not often the case. In a study from 2002, my colleagues and I showed that these surgical patients actually experienced more pain than patients who were treated endoscopically, perhaps due to selection bias. Surgical patients had more yearly hospitalizations than those treated with combined ESWL and ERCP, albeit statistically fewer than preoperatively, and they still required several endoscopic procedures to drain the undrained portion of the pancreas or to treat anastomotic strictures or other problems. The previously mentioned group of 20% who require surgery do not necessarily do well in the long run.

G&H What is the association between smoking and CCP?

RK Recent studies examining this issue have had a clear take-home message: CCP patients who smoke should stop. Animal models have shown that smoking can stimulate stellate cells and cause chronic pancreatitis. It is unclear why this association was not acknowledged sooner; in the past, it was often assumed that these patients were closet drinkers. Looking back at some of the epidemiologic data, it is clear that many of the patients who drank also smoked. When alcohol is factored out, smoking becomes a very significant risk factor, particularly in older women who have a single stone in the head of their pancreas. Many of these patients are ex-smokers and have no alcohol intake at all. Our data suggest that patients have less pain and are less likely to need surgery or any repeat intervention if they stop smoking.

G&H What studies would you like to see in this area?

RK I would love to see the development of an oral or direct instillation agent for dissolving stone fragments or stones in the pancreatic duct that truly works and

is not toxic to the pancreas or the rest of the body. Even though these stones are broken into fragments, they can still be very difficult to retrieve. This process is particularly difficult if there is a downstream stricture or if the initial stone burden is high, in which case the stones break but fill the entire pancreatic duct, making it difficult to insert a basket for their removal; even if it is possible to insert a catheter in this area and wash out the fragments, there may be no room for them to come out. Therefore, it would be helpful to develop a stone dissolution agent, ideally one that could be administered orally. However, more realistically, the agent could be administered via an endoscope while the fragments are being removed.

In addition, better methods are needed to treat downstream strictures to prevent stone recurrence because so many stones form at these sites. Currently, these strictures are treated via balloon dilatation and simultaneous placement of 1 large or 2–4 smaller stents in an attempt to remodel the pancreatic duct. However, this process can be very difficult. Perhaps some of the self-expandable metal stents that are being developed in Korea for treatment of CCP patients will lead to further advances.

Dr. Kozarek would like to acknowledge his coauthors from his recent study in Gastrointestinal Endoscopy.

Suggested Reading

Seven G, Schreiner MA, Ross AS, et al. Long-term outcomes associated with pancreatic extracorporeal shock wave lithotripsy for chronic calcific pancreatitis. *Gastrointest Endosc.* 2012;75:997-1004.e1.

Kozarek RA, Brandabur JJ, Ball TJ, et al. Clinical outcomes in patients who undergo extracorporeal shock wave lithotripsy for chronic calcific pancreatitis. *Gastrointest Endosc.* 2002;56:496-500.

Mergener K, Kozarek RA. Therapeutic pancreatic endoscopy. *Endoscopy.* 2003;35:48-54.

White DM, Correa RJ, Gibbons RP, Ball TJ, Kozarek RJ, Thirlby RC. Extracorporeal shock-wave lithotripsy for bile duct calculi. *Am J Surg.* 1998;175:10-13.

Lawrence C, Siddiqi ME, Hamilton JN, et al. Chronic calcific pancreatitis: combination ERCP and extracorporeal shock wave lithotripsy for pancreatic duct stones. *South Med J.* 2010;103:505-508.

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Suggested Reading

Odze RD. Pathology of eosinophilic esophagitis: what the clinician needs to know. *Am J Gastroenterol.* 2009;104:485-490.

Genevay M, Rubbia-Brandt L, Rougemont AL. Do eosinophil numbers differentiate eosinophilic esophagitis from gastroesophageal reflux disease? *Arch Pathol Lab Med.* 2010;134:815-825.

Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol.* 2011;128:3-20.e6; quiz 21-22.

Doyle LA, Odze RD. Eosinophilic esophagitis without abundant eosinophils? The expanding spectrum of a disease that is difficult to define. *Dig Dis Sci.* 2011;56:1923-1925.

Yantiss RK, Odze RD. Optimal approach to obtaining mucosal biopsies for assessment of inflammatory disorders of the gastrointestinal tract. *Am J Gastroenterol.* 2009;104:774-783.