

## Effect of pancreatic endotherapy on quality of life in chronic pancreatitis patients: A systematic review

Samuel Y Han, Georgios I Papachristou, Raj J Shah, Darwin L Conwell

**ORCID number:** Samuel Y Han 0000-0001-7373-7984; Georgios I Papachristou 0000-0001-9915-703X; Raj J Shah 0000-0002-9736-4139; Darwin L Conwell 0000-0003-0449-3730.

**Author contributions:** Han SY and Conwell DL wrote the paper; Papachristou GI and Shah RJ reviewed and revised the paper.

**Conflict-of-interest statement:** Papachristou GI is a Consultant for Olympus, and has received research funding from AbbVie; Author Shah RJ is an Advisory Board Member and Consultant for Boston Scientific and Consultant for Olympus and Cook Endoscopy; Conwell DC received support from the National Cancer Institute and National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award number U01 DK108327.

**PRISMA 2009 Checklist statement:** This manuscript was presented in accordance with the PRISMA guidelines for a systematic review.

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**Samuel Y Han, Georgios I Papachristou, Darwin L Conwell,** Division of Gastroenterology, Hepatology and Nutrition, The Ohio State University Wexner Medical Center, Columbus, OH 43210, United States

**Raj J Shah,** Division of Gastroenterology and Hepatology, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, United States

**Corresponding author:** Samuel Y Han, MD, MS, Assistant Professor, Division of Gastroenterology, Hepatology and Nutrition, The Ohio State University Wexner Medical Center, 395 W 12th Ave. 2nd Floor Doan Office Tower, Columbus, OH 43210, United States.

[samuel.han@osumc.edu](mailto:samuel.han@osumc.edu)

### Abstract

#### BACKGROUND

Pancreatic endotherapy provides treatment options for the management of chronic pancreatitis-related structural complications such as pancreatic duct stones, strictures, and pancreatic fluid collections. Most studies detailing endotherapy, however, have focused on technical success outcomes such as stone clearance or stricture resolution.

#### AIM

To review the effect of pancreatic endotherapy on patient-centered outcomes.

#### METHODS

Systematic review of studies examining pancreatic endotherapy.

#### RESULTS

A total of 13 studies including 3 randomized clinical trials were included. The majority of studies found an improvement in quality of life with pancreatic endotherapy.

#### CONCLUSION

While pancreatic endotherapy does appear to improve quality of life, there are clear gaps in knowledge regarding many pancreatic endotherapy modalities. Furthermore, qualitative analysis is lacking in these studies and further work is needed to elucidate the patient experience with pancreatic endotherapy.

**Key Words:** Chronic pancreatitis; Pancreatic endotherapy; Endoscopic retrograde cholangiopancreatography; Quality of life

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**Manuscript source:** Invited manuscript

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** United States

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B  
Grade C (Good): 0  
Grade D (Fair): 0  
Grade E (Poor): 0

**Received:** February 12, 2021

**Peer-review started:** February 12, 2021

**First decision:** May 5, 2021

**Revised:** June 11, 2021

**Accepted:** July 13, 2021

**Article in press:** July 13, 2021

**Published online:** August 16, 2021

**P-Reviewer:** Dedemadi G

**S-Editor:** Zhang H

**L-Editor:** A

**P-Editor:** Xing YX



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**Core Tip:** Chronic pancreatitis remains difficult to treat and pancreatic endotherapy offers one option for the management of chronic pancreatitis-related complications. Pancreatic duct decompression *via* pancreatic duct stone lithotripsy and stenting appears to improve the quality of life of these patients in the short-term. More studies, however, are needed to examine the effect of endotherapy modalities such as endoscopic transmural drainage of pancreatic fluid collections, celiac plexus blocks and more recent innovations on quality of life in these patients.

**Citation:** Han SY, Papachristou GI, Shah RJ, Conwell DL. Effect of pancreatic endotherapy on quality of life in chronic pancreatitis patients: A systematic review. *World J Gastrointest Endosc* 2021; 13(8): 336-355

**URL:** <https://www.wjgnet.com/1948-5190/full/v13/i8/336.htm>

**DOI:** <https://dx.doi.org/10.4253/wjge.v13.i8.336>

## INTRODUCTION

Pain, the hallmark feature of chronic pancreatitis (CP), remains difficult to manage effectively and can significantly worsen patients' quality of life[1-3]. A variety of factors likely play a role in the mechanism of pain, which can include ductal hypertension, inflammation, or neuropathic pain from varying degrees of sensitization of the nervous system[1,4]. Targeted treatment based on the etiology of the pain therefore is challenging and initial treatment will typically consist of medical management.

Pancreatic endotherapy (PET) offers a treatment option for patients with CP-related structural complications such as pancreatic duct (PD) stones, strictures, stones, or pancreatic fluid collections such as pseudocysts. Patients must typically fail medical management before PET is considered with persistent pain being the most common indication. The last decade has ushered in a wave of new PET modalities that have advanced the field beyond standard endoscopic retrograde pancreatography. For PD stones, per-oral pancreatoscopy (POP)-guided lithotripsy using electrohydraulic lithotripsy or laser lithotripsy have dramatically increased the rates of successful PD stone clearance[5,6]. For pancreatic duct strictures, the use of fully covered metal stents, wire-guided cystotomes, and POP-guided laser dissection have greatly expanded the armament of the endoscopist for these refractory stenoses[7-11]. Lastly, the development of lumen-apposing metal stents has revolutionized the drainage of pancreatic fluid collections by facilitating endoscopic transmural drainage in a single step[12,13].

Despite these advances in PET, published studies have largely focused on technical success outcomes such as stricture resolution or stone clearance[5,6,14-16]. Furthermore, the few randomized studies have centered on pain improvement as the primary outcome, which while important, does not capture the holistic impact of PET on patients. As patients and physicians will have different priorities, expectations, and preferences regarding treatment choices, it is critically important to incorporate patient-centered outcomes such as quality of life in the evaluation of these modalities [17]. Therefore, the aim of this review is to detail the effect of PET on quality of life in patients with CP.

## MATERIALS AND METHODS

### Literature search strategy

We searched PubMed for relevant English-language articles published by January 5, 2021 with no restriction on earliest publication date. The search terms included quality of life and each of the following: endoscopic therapy, endoscopic retrograde cholangiopancreatography (ERCP), celiac plexus block, pancreatic duct stone, pancreatic duct stricture, pancreatic duct stent, pancreatic fluid collection, pseudocyst, pancreatoscopy, lithotripsy, and endoscopic ultrasound.

### **Inclusion and exclusion criteria**

The relevance of the studies was determined using the hierarchical approach as recommended by the PRISMA statement. We assessed the studies by examining the title, abstract, and/or full text of the studies. We also examined the references of included studies to identify any additional studies. Inclusion criteria included the following: (1) Studies involving PET that included quality of life as an outcome; (2) Publication in the English language; (3) Availability of the full text; and (4) Publication date by January 5<sup>th</sup>, 2021. Exclusion criteria included the following: (1) Non-original studies including reviews, editorials, commentaries, and study protocols; (2) Insufficient data; and (3) Duplicate studies (*i.e.*, conference abstract and full-text manuscript).

## **RESULTS**

The literature search flow diagram is presented in [Figure 1](#). The initial PubMed database search yielded a total of 10, 242 articles. Upon title and abstract review, the full text of 123 articles were reviewed. Upon excluding 110 of these studies, which were found to be irrelevant, a total of 13 studies, including 3 randomized clinical trials and 10 observational studies were included ([Table 1](#)).

### **Comparison of surgery with endoscopy for pancreatic duct drainage**

The major randomized trials comparing endoscopy with surgery focus on pancreatic duct drainage to relieve ductal hypertension. In the landmark trial comparing endoscopic treatment [ERCP with stricture dilation for PD strictures ± extracorporeal shock-wave lithotripsy (ESWL) for concomitant PD stones] with a side-to-side pancreaticojejunostomy, at 2 year follow-up patients who received endotherapy ( $n = 19$ ) had an improvement in both physical health ( $31 \pm 8$  to  $38 \pm 9$ ) and mental health ( $33 \pm 8$  to  $40 \pm 9$ ) on the 36-Item Short Form Health Survey (SF-36) questionnaire[18]. While this was less than the improvement in quality of life seen in the surgery arm, in the follow-up study examining long-term (mean follow-up of 79 mo) outcomes of both arms, the improvement in both physical and mental quality of life persisted, but there was no longer any difference between the two arms[19]. More recently, the ESCAPE trial from the Dutch pancreatitis study group randomized patients with painful CP and a dilated PD to either early pancreatic drainage surgery ( $n = 44$ ) or endotherapy (ERCP ± ESWL) first ( $n = 44$ )[20]. At 18 mo follow-up, patients in the endotherapy arm did experience an improvement in both physical ( $31 \pm 8$  to  $36 \pm 9$ ) and mental ( $36 \pm 11$  to  $41 \pm 11$ ) health on the SF-36 with no difference seen in quality of life between the two treatment groups. Lastly, in a retrospective study comparing surgery with endotherapy, the European Organization for Research and Treatment of Cancer (EORTC) quality of life instrument and the pancreatic cancer module (PAN26) instrument were utilized with the primary finding that patients treated with surgery had less nausea and vomiting [21].

### **Pancreatic duct stone therapy**

Internationally, the combination of ESWL with ERCP represents the most common form of treatment for symptomatic PD stones. Starting with a prospective study by Brand *et al*[22] in 2000, ESWL followed by ERCP was associated with an improvement in pain, weight loss, fevers/chills, jaundice, and global quality of life on the EORTC instrument. Within an Indian patient population, Tandan *et al*[23] presented a large study ( $n = 636$ ) of this treatment modality, finding that using a scale of 1-10 (10 representing the best quality of life), quality of life improvement was seen in 92.8% of patients at 2-5 year follow-up and in 92.6% of patients at > 5 year follow-up. In a large Chinese patient cohort using the SF-36, a significant improvement was seen in overall quality of life and physical health, but not in mental health[24,25]. Seven *et al*[26] presented data on this PET combination in a United States cohort, utilizing a 1-10 quality of life score (10 being the best quality of life), finding a significant improvement in quality of life ( $3.7 \pm 2.4$  to  $7.3 \pm 2.7$ ) after completion of therapy. Similarly, in a study from Germany, Milovic *et al*[27] reported a significant improvement in quality of life after ESWL and ERCP on a 5-point quality of life scale (2.5 to 4).

In the only study examining pancreatoscopy-guided lithotripsy that included quality of life as a study outcome, Gerges *et al*[28] utilized both electrohydraulic and laser lithotripsy in 20 patients. They found that post-therapy, 89% of patients had no or only mild disability in daily activities and 47% of patients described their health as

Table 1 Key characteristics of included articles

Ref.	Study design	Endoscopic modality	n	Quality of life measurement	Quality of life findings
Cahen <i>et al</i> [18,19]	Randomized clinical trial	ERCP ± ESWL	19	SF-36	Physical health: 31 ± 8 to 38 ± 9 (2 yr) and 43 ± 11 (7 yr); Mental health: 33 ± 8 to 40 ± 9 (2 yr) and 46 ± 9 (7 yr)
Issa <i>et al</i> [20]	Randomized clinical trial	ERCP ± ESWL	44	SF-36	Physical health: 31 ± 8 to 36 ± 9; Mental health: 36 ± 11 to 41 ± 11
Stevens <i>et al</i> [31]	Randomized study	Celiac plexus block	40	SF-12	Change in physical score: -0.2 ± 7.5 (triamcinolone + bupivacaine), 1.7 ± 8.8 (bupivacaine); Change in mental score: 1.3 ± 10.0 (triamcinolone + bupivacaine), -2.1 ± 12.9 (bupivacaine)
Brand <i>et al</i> [22]	Prospective study	ERCP + ESWL	48	EORTC	Pain: 37.8 (range 0-81.5) to 18.8 (range 0-83.3); Weight loss: 66.7 (range 0-100) to 0 (range 0-100); Global quality of life: 41.7 (range 16.7-100) to 58.3 (range 8.3-100)
Hu <i>et al</i> [24]	Prospective study	ERCP + ESWL	214	SF-36	Physical health: 56.9 ± 18.7 to 59.2 ± 14.8 (no significant difference); Patients with pseudocysts: 95 (range 35-100) to 100 (range 75-100); Mental health: 52.2 ± 21.5 to 58.5 ± 16.4; Patients with pseudocysts: 68 (range 36-100) to 76 (range 28-100)
Milovic <i>et al</i> [27]	Prospective study	ERCP + ESWL	32	1-5 scale	4 (range 2-5) to 2.5 (range 1-4)
Basiński <i>et al</i> [32]	Prospective study	Celiac plexus block	92	EORTC	Quality of life significantly improved with greatest improvement seen in those with high religiosity
Rutter <i>et al</i> [21]	Retrospective study	ERCP	150	EORTC	Patients treated with surgery had less nausea/vomiting compared to those treated with endoscopy
Tandan <i>et al</i> [23]	Retrospective study	ERCP + ESWL	636	1-10 scale	252 (92.6%) patients had improved quality of life
Seven <i>et al</i> [26]	Retrospective study	ERCP + ESWL	120	1-10 scale	3.7 ± 2.4 to 7.3 ± 2.7
Gerges <i>et al</i> [28]	Retrospective study	Pancreatocopy-guided lithotripsy	20	Generic quality of life instrument	89% had no or only mild disability in daily activities, 47% had "excellent" or "very good" general health
Vitale <i>et al</i> [29]	Retrospective study	Minor papilla stenting	32	Generic quality of life survey	100% stated improved quality of life, 100% stated satisfaction with treatment

ERCP: Endoscopic retrograde cholangiopancreatography; ESWL: Extracorporeal shock-wave lithotripsy; SF: Short Form Health Survey; EORTC: European Organisation for Research and Treatment of Cancer.

"excellent" or "very good."

### Minor papilla endotherapy

Minor papilla endotherapy typically involves performing a minor papilla sphincterotomy and/or stenting. Depending on the presence of strictures or stones, endotherapy can also include dilation or stone lithotripsy. A single-center study examining 32 patients with CP and pancreas divisum-related strictures assessed quality of life through telephone surveys asking about their overall quality of life and their level of satisfaction post-treatment[29]. All subjects treated *via* endotherapy reported improved quality of life and satisfaction in their treatment.

### Pancreatic fluid collection drainage

There were no studies examining transmural drainage of CP-associated pancreatic fluid collections that included quality of life as an outcome. In regards to patients with acute necrotizing pancreatitis, however, Smith *et al*[30] performed a single-center cross-sectional study examining patients treated with endoscopic ultrasound-guided transmural drainage of walled-off necrosis. Using the SF-36, the authors found that at 2 year follow-up, patients treated with transmural drainage had equivalent scores to a healthy control population in nearly all domains with the exception of the physical role and general health domains, where they had significantly lower scores (physical role: 58.5 ± 40.9 *vs* 81.0 ± 34.0, general health: 56.9 ± 25.8 *vs* 72.0 ± 20.3) Notably, these subjects had significantly higher quality of life scores in domains such as pain and vitality compared to patients with irritable bowel syndrome.

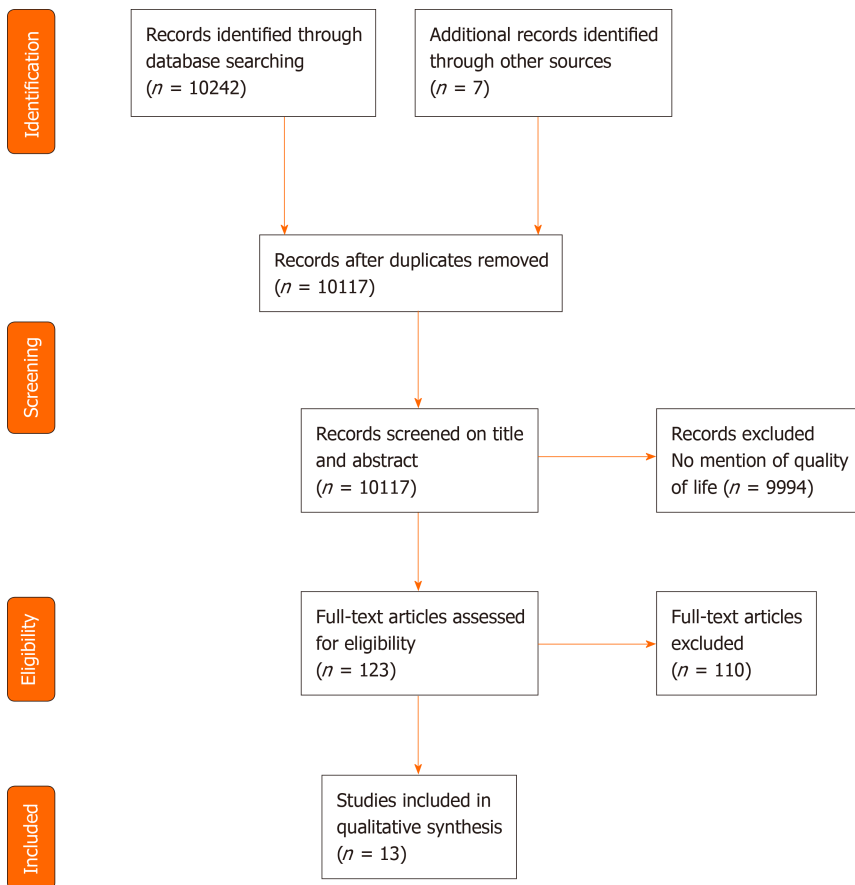


Figure 1 PRISMA flow diagram of article selection.

### Celiac plexus block

In a single-center randomized study comparing celiac plexus block (using bupivacaine) with and without triamcinolone for patients with painful CP, pre and post-therapy quality of life was assessed using the SF-12[31]. The study was stopped prematurely at interim analysis due to no difference between the two treatment arms in improving pain and no significant differences in physical and mental quality of life were seen between the 2 arms. The triamcinolone arm saw a change of  $-0.2 \pm 7.5$  for physical health and a change of  $1.3 \pm 10.0$  in mental health while the control arm saw a change of  $1.7 \pm 8.8$  in physical health and a change of  $-2.1 \pm 12.9$  in mental health. In a study from Poland, Basiński *et al*[32] utilized the EORTC quality of life questionnaire, finding improvement in quality of life at 1- and 4-wk follow-up. Stratifying patients on their level of religiosity, the greatest improvement in quality of life was seen in those with high religiosity at both time points.

## DISCUSSION

In this systematic review, while we demonstrate that PET does appear to improve quality of life in patients with CP, the most striking finding is the overall lack of evidence in many of these PET modalities. The majority of evidence comes from endoscopic treatment of pancreatic ductal obstruction secondary to PD stones and strictures with the 2 Landmark trials by Cahen *et al*[18] and Issa *et al*[20] comparing surgical with endoscopic drainage. There remain clear gaps in knowledge regarding how endoscopic therapies such as celiac plexus block, pancreatoscopy-guided therapies, endoscopic transmural drainage of pancreatic fluid collections and minor papilla endotherapy affect quality of life in the CP population. This highlights the continued emphasis of endoscopic studies on technical success outcomes rather than patient-centered outcomes and while PET modalities will continue to expand, without understanding the impact of these therapies on patients, choosing the best treatment for each individual patient becomes even more challenging.

As shown in [Table 1](#), studies most often measured quality of life using the SF-36 and the EORTC quality of life instrument, which while validated, are not disease-specific for chronic pancreatitis. The remaining studies assessed quality of life by simply asking about quality of life, speaking to need for more rigorous research in quality of life within this field of endotherapy. The PANcreatitis Quality of Life Instrument is a validated chronic pancreatitis-specific quality of life instrument consisting of 18 items that includes sub-scores for physical function, role function, emotional function, and self-worth domains[33]. Additionally, the National Institute of Health has developed the Patient-Reported Outcomes Measurement Information System instruments to standardize measurement of patient-reported outcomes such as quality of life and pain. Incorporating instruments such as these can facilitate future research in this arena by capturing critical quality of life aspects pertinent to this patient population.

Pain remains the center point of quality of life in patients with CP as constant pain and severe pain, in particular, are associated with worse quality of life[2,34]. Similar to quality of life, pain has been poorly measured in prior PET studies with most reporting a visual analog scale score or the Izbicki pain score, which are simplified assessments of pain[35]. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials has recently called for improved phenotyping of pain in an effort to deliver the most appropriate therapy based on an individual patient's pain characteristics[36]. In line with this, pancreatic quantitative sensory testing (QST) represents a novel method of characterizing sensory processing in the peripheral and central pain pathways[37]. While data has demonstrated how QST can be used to predict the efficacy of pregabalin in CP patients, much work is needed to determine if QST can help predict a priori which patients will respond to PET[38]. Nevertheless, there remains much promise in using tools such as QST to better characterize pain profiles in patients with CP to ultimately develop an algorithm-based approach to the management of this challenging disease.

In addition to the quantitative analysis done in these studies, qualitative studies are needed to truly encapsulate subjects' experiences with PET and better understand how PET affects their disease. Quantitative assessment of quality of life captures only a portion of the patient's overall well-being and given the lack of qualitative studies centered around endotherapy, future endeavors are certainly needed to incorporate the patient's perspective. Understanding factors such as patient expectations, regret, suffering, and coping may help design future randomized sham-controlled trials with patient-centered outcomes to help determine which PET modalities are most effective in which patients.

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## CONCLUSION

In summary, given the dearth of treatment options for CP, PET offers a viable therapy for patients with CP-related complications such as PD stones and strictures. Much work is needed, however, to elucidate the patient experience with PET and identify who will respond to PET with the ultimate goal of providing individualized treatment plans for these patients.

## ARTICLE HIGHLIGHTS

### **Research background**

While pancreatic endotherapy is frequently performed for the treatment of chronic pancreatitis-related complications, most studies examining endotherapy have focused on technical success outcomes, such as stricture resolution or stone clearance. Studies reporting patient-centered outcomes such as quality of life are lacking, however, making it difficult to determine how endotherapy affects these patients.

### **Research motivation**

The motivation for this systematic review stems from the primary criticism of pancreatic endotherapy on whether endotherapy improves the lives of patients with chronic pancreatitis. While it is well-known that endotherapy can treat the structural complications of chronic pancreatitis, the effect of endotherapy on patient-centered outcomes is poorly studied.

### Research objectives

The primary objective of this systematic review was to detail the literature regarding how pancreatic endotherapy affects quality of life in chronic pancreatitis patients.

### Research methods

A systematic review was performed to identify studies reporting on various pancreatic endotherapy modalities and quality of life.

### Research results

The search yielded 13 studies for review out of 10242 articles. All of the modalities examined found an improvement in quality of life.

### Research conclusions

Pancreatic endotherapy does appear to improve quality of life, but the assessment of quality of life is very heterogeneous and not disease-specific. Furthermore, there is a lack of evidence regarding many modalities such as transmural fluid drainage, pancreatoscopy-guided therapy and celiac plexus block.

### Research perspectives

Further studies are clearly needed to elucidate the patient experience with receiving pancreatic endotherapy and future trials will benefit from having patient-centered outcomes as the primary outcome.

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