Chronic pancreatitis: dietary supplements

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ABSTRACT

INTRODUCTION: Chronic pancreatitis affects 3 to 9 people in 100,000; 70% of cases are alcohol-induced. METHODS AND OUTCOMES: We conducted a systematic overview aiming to answer the following clinical question: What are the effects of dietary supplements in people with chronic pancreatitis? We searched: Medline, Embase, The Cochrane Library, and other important databases up to October 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 73 studies. After deduplication and removal of conference abstracts, 41 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 20 studies and the further review of 21 full publications. Of the 21 full articles evaluated, two systematic reviews were added at this update. We performed a GRADE evaluation for four PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for three interventions based on information about the effectiveness and safety of calcium, pancreatic enzyme, and vitamin/antioxidant supplements.

QUESTIONS

INTERVENTIONS

Key points

- Chronic pancreatitis is characterised by long-standing inflammation of the pancreas due to a wide variety of causes, including recurrent acute attacks of pancreatitis.

  Chronic pancreatitis affects between 3 and 9 people in 100,000; 70% of cases are alcohol-induced.
- Pancreatic enzyme supplements reduce steatorrhoea in people with chronic pancreatitis, but they may have no effect on pain.
- We don't know whether calcium supplements or vitamin/antioxidant supplements are effective.

Clinical context

GENERAL BACKGROUND

Pancreatitis is inflammation of the pancreas. The inflammation may be sudden (acute) or on-going (chronic). Acute pancreatitis usually involves a single 'attack', after which the pancreas returns to normal. Chronic pancreatitis is characterised by long-standing inflammation of the pancreas owing to a wide variety of causes, including recurrent acute attacks of pancreatitis.

FOCUS OF THE REVIEW

Because alcohol is the most common cause of chronic pancreatitis, we sought to identify if dietary modifications could help such patients. The cited evidence varies on the role of dietary modification for chronic pancreatitis. We sought to review the evidence for such recommendations.

COMMENTS ON EVIDENCE

Most available sources of evidence are not randomised controlled trials. Rigorous review reveals minimal effect of dietary medication.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, August 2011, to October 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 73 studies. After deduplication and removal of conference abstracts, 41 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 20 studies and the further review of 21 full publications. Of the 21 full articles evaluated, two systematic reviews were added at this update.

DEFINITION

Pancreatitis is inflammation of the pancreas. The inflammation may be sudden (acute) or ongoing (chronic). Acute pancreatitis usually involves a single 'attack', after which the pancreas returns to normal. Chronic pancreatitis is characterised by long-standing inflammation of the pancreas owing to a wide variety of causes, including recurrent acute attacks of pancreatitis. Symptoms of chronic pancreatitis include recurring or persistent abdominal pain and impaired exocrine function. The most reliable test of exocrine function is the demonstration of increased faecal fat — although, this test is frequently not performed if imaging is consistent (particularly calcification of the pancreatic gland on computerised tomography scan). **Diagnosis** There is no consensus on the diagnostic criteria for chronic pancreatitis. [1] [2] [3] [4] Typical symptoms include pain radiating to the back and people may present with malabsorption, malnutrition, and pancreatic endocrine insufficiency. However, these symptoms may be seen in people with more common disorders such as reflux disease and peptic ulcers (also more common in heavy drinkers), and also in people with more serious diseases such as pancreatic or periampullary cancers. Diagnostic tests for chronic pancreatitis include faecal elastase measurement (to prove pancreatic insufficiency) and imaging. [1] [2] [3] [4] Biopsy may be required to resolve diagnostic uncertainty.

INCIDENCE/ PREVALENCE

The annual incidence of chronic pancreatitis has been estimated in one prospective study and several retrospective studies to be between 3 and 9 cases/100,000 population. Prevalence is estimated at between 0.04% and 5%. [5] [6] [7] Alcoholic chronic pancreatitis is usually diagnosed after a long history of alcohol abuse, and is the most common cause.

AETIOLOGY/ RISK FACTORS

The TIGAR-O system describes the main predisposing factors for chronic pancreatitis as: toxic-metabolic (which includes alcohol-induced [70% of all cases], smoking, hypercalcaemia, hyperlipidaemia, and chronic renal failure); idiopathic (which includes tropical pancreatitis and may form up to 20% of all cases); genetic (which includes cationic trypsinogen, CFTR, and SPINK1 mutation); autoimmune (which includes solitary and syndromic); recurrent and severe acute pancreatitis (which includes postnecrotic and radiation-induced); and obstructive (which includes pancreatic divisum and duct obstruction owing to various causes). [1] Although 70% of people with chronic pancreatitis report excessive consumption of alcohol (>150 g/day) over a long period (>20 years), [5] [8] only 1 in 10 heavy drinkers develop chronic pancreatitis, [9] suggesting underlying genetic predisposition or polymorphism, although a link has not been established conclusively. [1]

PROGNOSIS

Mortality in people with chronic pancreatitis is higher than in the general population, with mortality at 10 years after diagnosis estimated at 70% to 80%. Diagnosis is usually made between 40 and 48 years of age. Reported causes of mortality in people with chronic pancreatitis are: complications of disease as well as treatment; development of pancreatic cancer or diabetes; and continual exposure to risk factors for mortality, such as smoking and alcohol. [10] [11]

AIMS OF INTERVENTION

To minimise pain of chronic pancreatitis, alleviate symptoms and sequelae of pancreatic exocrine insufficiency, improve quality of life, and reduce complications, with minimal adverse effects of treatment.

OUTCOMES

Mortality; **pain relief**; reduction of **steatorrhoea** (includes alleviation of nutritional insufficiency); **global symptom improvement**; **weight gain/maintenance**; **quality of life**; **development of complications** (includes incidence of diabetes and incidence of pancreatic cancer); **adverse effects**.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date October 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to October 2014, Embase 1980 to October 2014, The Cochrane Database of Systematic Reviews 2014, issue 4 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, at least single-blinded, and containing 20 or more individuals, of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributor. In consultation with the expert contributor, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' sections (see below). **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included

in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributor may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previously reported questions: What are the effects of lifestyle interventions in people with chronic pancreatitis? What are the effects of drug interventions in people with chronic pancreatitis? What are the effects of nerve blocks for pain relief in people with chronic pancreatitis? What are the effects of different invasive treatments for specific complications of chronic pancreatitis? **Data and Quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 11). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of dietary supplements in people with chronic pancreatitis?

OPTION CALCIUM SUPPLEMENTS

- For GRADE evaluation of interventions for Chronic pancreatitis: dietary supplements, see table, p 11 .
- We don't know whether calcium is effective.
- Reduction in calcium intake is advised for people with hyperparathyroidism or renal failure associated with chronic pancreatitis (to manage the underlying disease).

Benefits and harms

Calcium supplements:

We found no systematic review or RCTs of sufficient quality.

Comment: **Clinical guide**

In current clinical practice, calcium supplements are no longer considered as useful treatment for most people with chronic pancreatitis. Reduction in calcium intake is advised for people with hyperparathyroidism or renal failure associated with chronic pancreatitis (to manage the underlying disease).

OPTION PANCREATIC ENZYME SUPPLEMENTS

- For GRADE evaluation of interventions for Chronic pancreatitis: dietary supplements, see table, p 11 .
- Pancreatic enzyme supplements may reduce steatorrhoea in people with chronic pancreatitis; however, the evidence is limited.

- We don't know how pancreatic enzyme supplements and placebo compare for any other outcomes, including pain relief, in people with chronic pancreatitis.
- Pancreatic enzymes may be associated with major changes in fasting glucose levels.

Benefits and harms

Pancreatic enzyme supplements versus placebo:

We found two systematic reviews (search date 2009; [12] and 2012 [13]). Both reviews identified the same two RCTs meeting *BMJ Clinical Evidence* reporting criteria; therefore, we only report the data from the first systematic review. [12] We also report results from the individual studies included in the systematic review for outcomes not covered by the review, or where analysis by the review included multiple studies not meeting *BMJ Clinical Evidence* reporting criteria. [14] [15] See Further information on studies for data on protein absorption.

Mortality

No data from the following reference on this outcome. [12] [14] [15]

Pain relief

Pancreatic enzyme supplements compared with placebo We don't know whether pancreatin is more effective than placebo at reducing pain in people with chronic pancreatitis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain relief					
[12] Systematic review	Number of people and characteristics not reported 4 RCTs in this analysis	**Analgesic use** with pancreatic enzyme with placebo Absolute results not reported The review did not perform a meta-analysis owing to heterogeneity (data description, presentation, and different pain scales) The review reported that most included RCTs had inadequate allocation concealment, and that none of the trials adequately reported withdrawals and loss to follow-up; in addition, it was unclear for most trials whether intention-to-treat (ITT) analyses had been used	Reported as not significant	⟷	Not significant
[12] Systematic review	Number of people and characteristics not reported 5 RCTs in this analysis	**Pain intensity** with pancreatic enzyme with placebo Absolute results not reported The review did not perform a meta-analysis because of heterogeneity (data description, presentation, and different pain scales). It reported that 3 of 4 RCTs that reported on pain intensity found that pancreatic enzymes significantly reduced pain compared with placebo The review reported that most included RCTs had inadequate allocation concealment, and that none of the trials adequately reported withdrawals and loss to follow-up; in addition, it was un-	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		clear for most trials whether ITT analyses had been used			

No data from the following reference on this outcome. [14] [15]

Steatorrhoea

Pancreatic enzyme supplements compared with placebo Pancreatin may be more effective than placebo at increasing faecal fat absorption at 2 weeks, reducing faecal fat at 2 weeks, and decreasing stool frequency at 2 weeks in people with chronic pancreatitis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Faecal fat					
[12] Systematic review	People with chronic pancreatitis 2 RCTs in this analysis	**Amount of faecal fat , 2 weeks** with pancreatic enzyme with placebo Absolute results not reported 55 people in this analysis The review reported that most included RCTs had inadequate allocation concealment, and that none of the trials adequately reported withdrawals and loss to follow-up; in addition, it was unclear for most trials whether intention-to-treat analyses had been used	SMD –1.03 95% CI –1.60 to –0.46	○○○	pancreatic enzyme
Fat absorption					
[15] RCT **Crossover design**	29 people with chronic pancreatitis, 27 (93%) alcohol-induced, 28 men, mean age 53 years, with faecal fat >10 g/day In review [12]	**Fat absorption , at 15 days** 81% with pancreatin for 2 weeks (4 capsules at meal times and 2 with snack) 54% with placebo Absolute numbers not reported There was a 1-week pre-treatment washout	P = 0.002	○○○	pancreatin
[14] RCT	27 people with chronic pancreatitis, 9 men, mean age 51 years, faecal fat values greater than or equal to 10 g/day and/or a fat absorption <80% In review [12]	**Fat absorption increase from baseline , 2 weeks** 37% with pancreatin (4 capsules at meal times and 2 with snacks) 12% with placebo Absolute numbers not reported There was a 2-week placebo run-in A high-fat diet was followed on 6 of the treatment days	P = 0.02	○○○	pancreatin
Stool frequency					
[14] RCT	27 people with chronic pancreatitis, 9 men, mean age 51 years, faecal fat values greater than or equal to 10 g/day	**Stool frequency reduction from baseline , 2 weeks** 5 stools/day with pancreatin (4 capsules at meal times and 2 with snacks) 11 stools/day with placebo	P = 0.0015	○○○	pancreatin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	and/or a fat absorption <80% In review [12]	There was a 2-week placebo run-in A high-fat diet was followed on 6 of the treatment days			

Global symptom improvement

Pancreatic enzyme supplements compared with placebo We don't know whether pancreatin is more effective than placebo at improving investigator-assessed global symptom scores (measured by the Clinical Global Impression Disease Symptoms Scale [CGIDS]) in people with chronic pancreatitis, or at improving patient-assessed global symptom scores (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptom improvement					
[14] RCT	27 people with chronic pancreatitis, 9 men, mean age 51 years, faecal fat values greater than or equal to 10 g/day and/or a fat absorption <80% In review [12]	**Mean difference in patient-scored Clinical Global Impression Disease Symptoms Scale (CGIDS) from baseline , 2 weeks** –0.3 with pancreatin (4 capsules at meal times and 2 with snacks) +0.4 with placebo There was a 2-week placebo run-in A high-fat diet was followed on 6 of the treatment days CGIDS scored from 1 (very much improved) to 7 (very much worse)	P = 0.06	⟷	Not significant
[14] RCT	27 people with chronic pancreatitis, 9 men, mean age 51 years, faecal fat values greater than or equal to 10 g/day and/or a fat absorption <80% In review [12]	**Improvement in investigator-scored CGIDS from baseline , 2 weeks** –0.3 with pancreatin (4 capsules at meal times and 2 with snacks) +0.4 with placebo There was a 2-week placebo run-in A high-fat diet was followed on 6 of the treatment days CGIDS scored from 1 (very much improved) to 7 (very much worse)	P = 0.04	○○○	pancreatin

No data from the following reference on this outcome. [15]

Weight gain/maintenance

No data from the following reference on this outcome. [12] [14] [15]

Quality of life

No data from the following reference on this outcome. [12] [14] [15]

Development of complications

No data from the following reference on this outcome. [12] [14] [15]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] RCT **Crossover design**	29 people with chronic pancreatitis, 27 (93%) alcohol-induced, 28 men, mean age 53 years, with faecal fat >10 g/day In review [12]	**Blood glucose control , 4 weeks** with pancreatin (4 capsules at meal times and 2 with snack) with placebo Absolute results not reported There was a 1-week pre-treatment washout 28/29 (97%) people had major changes in fasting glucose levels on crossover; 1 person developed diabetic ketoacidosis after commencing pancreatin	Significance not assessed		
[14] RCT	27 people with chronic pancreatitis, 9 men, mean age 51 years, faecal fat values greater than or equal to 10 g/day and/or a fat absorption <80% In review [12]	**Non-serious adverse effects (include nausea, mild tremor, mild weakness, and abdominal pain) , 2 weeks** 6/13 (46%) with pancreatin (4 capsules at meal times and 2 with snacks) 11/14 (79%) with placebo There was a 2-week placebo run-in A high-fat diet was followed on 6 of the treatment days	P = 0.5	⟷	Not significant
[14] RCT	27 people with chronic pancreatitis, 9 men, mean age 51 years, faecal fat values greater than or equal to 10 g/day and/or a fat absorption <80% In review [12]	**Serious adverse effects , 2 weeks** 0/13 (0%) with pancreatin (4 capsules at meal times and 2 with snacks) 0/14 (0%) with placebo There was a 2-week placebo run-in A high-fat diet was followed on 6 of the treatment days	Significance not assessed		

Further information on studies

[15] The RCT found a significant increase in protein absorption with pancreatin compared with placebo at 15 days (86% with pancreatin *v* 81% with placebo; P = 0.004).

Comment: **Clinical guide**

Pancreatic enzyme supplementation is the most commonly used treatment for steatorrhoea as there is consensus that pancreatic enzymes ameliorate exocrine insufficiency. However, change in pancreatic enzyme levels can exacerbate pancreatic endocrine dysfunction, and supplementation may need monitoring if introduced suddenly. Fat absorption seems best if pancreatic enzyme supplements are taken during or after meals. [16] Besides reiterating the beneficial effects of pancreatic enzyme supplements on fat absorption, the most recent systematic review does not add any further information. [12]

OPTION VITAMIN/ANTIOXIDANT SUPPLEMENTS

- For GRADE evaluation of interventions for Chronic pancreatitis: dietary supplements, see table, p 11 .
- We don't know whether vitamin/antioxidant supplements are effective in people with chronic pancreatitis.

Benefits and harms

Oral citrate versus placebo:

We found one systematic review (search date 2012, 12 RCTs, 585 people) evaluating the effects of antioxidants on pain in people with chronic pancreatitis. [17] The review included any design of RCT evaluating antioxidants in chronic pancreatitis, including studies of any size, with any length or size of follow-up, studies that were open-label in design, and that compared antioxidants with placebo and with each other. None of the RCTs identified by the review met *BMJ Clinical Evidence* reporting criteria, either being too small, of open-label design, population including a proportion of people with acute pancreatitis, or attrition rate of greater than 20%. For these reasons, the results of meta-analyses presented in the review are not reported here. We found one additional RCT comparing oral citrate (20–40 g/day) with placebo. [18] See Further information on studies for data on calcification.

Mortality

No data from the following reference on this outcome. [18]

Pain relief

Vitamin/antioxidant supplements compared with placebo We don't know whether oral citrates are more effective than placebo at reducing pain at 18 months in people with chronic pancreatitis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[18] RCT **Crossover design**	44 people aged 36 to 64 years with symptoms of chronic pancreatitis for a median 11 years, 37 of whom consumed >80 g alcohol/day, 17 with diabetes, steatorrhoea, or both	**Proportion of people pain free , 18 months** 14/19 (74%) with oral citrate 13/17 (76%) with placebo/no treatment Pre-crossover results 36 people in analysis; 20/36 (55%) were pain free before trial	Significance not assessed		

Steatorrhoea

No data from the following reference on this outcome. [18]

Global symptom improvement

No data from the following reference on this outcome. [18]

Weight gain/maintenance

No data from the following reference on this outcome. [18]

Quality of life

No data from the following reference on this outcome. [18]

Development of complications

No data from the following reference on this outcome. [18]

Adverse effects

No data from the following reference on this outcome. [18]

Further information on studies

[18] The RCT found that oral citrate significantly reduced calcification at 18 months compared with placebo (proportion of people with reductions in calcification: 7/19 [37%] with oral citrate 40 g/day *v* 1/17 [6%] with placebo; P <0.05).

Comment: **Clinical guide**
Vitamin supplements may benefit people with chronic pancreatitis independent of altering the clinical course of the disease, because of underlying nutritional deficiency, especially in people with pancreatitis associated with heavy alcohol consumption.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Pancreatic enzyme supplements One systematic review added. [13] Categorisation unchanged (likely to be beneficial).

Vitamin/antioxidant supplements One systematic review added. [17] Categorisation unchanged (unknown effectiveness).

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Disclaimer

GRADE **Evaluation of interventions for Chronic pancreatitis: dietary supplements.**

Important outcomes	Development of complications, Global symptom improvement, Mortality, Pain relief, Quality of life, Steatorrhoea, Weight gain/maintenance								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of dietary supplements in people with chronic pancreatitis?									
4 (not reported) [12]	Pain relief	Pancreatic enzyme supplements versus placebo	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, inclusion of poor-quality RCTs, and no significance assessment between groups
3 (55) [12] [14] [15]	Steatorrhoea	Pancreatic enzyme supplements versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (27) [12] [14]	Global symptom improvement	Pancreatic enzyme supplements versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and short follow-up; directness point deducted for use of subjective outcome
1 (36) [18]	Pain relief	Oral citrate versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted as only 16 people had pain before trial started

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.