

META ANALYSIS AND SYSTEMATIC REVIEW

Nutritional management of chronic pancreatitis: A systematic review and meta-analysis of randomized controlled trials

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Introduction

Chronic pancreatitis (CP) is a progressive inflammatory disease of the pancreas, in which repeated episodes of inflammation induce fibrosis¹ that eventually results in gradual loss of pancreatic exocrine and endocrine function.² The worldwide incidence has been reported to range from 1.6 to 23 per 100 000.³ Various modifiable and non-modifiable⁴ risk factors for CP have been identified. Among them, immoderate consumption of alcohol and tobacco smoke is the best established one.^{5–7} The burden related to CP is considerable, both for the patient and the health-care system.⁸

Abstract

Background and Aim: Malnutrition is a frequent complication of chronic pancreatitis. Adequate nutritional support is imperative, but there is still uncertainty about the optimal nutritional treatment. This work systematically compiles evidence from randomized controlled trials investigating dietary interventions in chronic pancreatitis and, in a further step, contrasts those findings with existing dietary recommendations.

Methods: The literature search (PubMed and Cochrane Central Register of Controlled Trials) included English and German full-text articles, which had been published in peer-reviewed journals. Two independent reviewers identified and selected studies. For meta-analysis, forest plots with 95% confidence intervals were generated using a random-effects model.

Results: Eleven randomized controlled trials fulfilled all selection criteria. In these trials, the following dietary interventions were tested: antioxidant treatment ($n = 6$), vitamin D supplementation ($n = 3$), supplementation with oral nutritional supplements ($n = 1$), and symbiotics supplementation ($n = 1$). Studies were of good methodological quality (mean Jadad score of 3.6) but heterogeneous in terms of interventions and study populations. Only for vitamin D, there was convincing evidence for efficacy of supplementation. We found no effect for antioxidant treatment on pain relief (standardized mean difference = -0.12 ; 95% confidence interval -0.73 to 0.48) and limited generalizability for interventions with oral nutritional supplements and symbiotics.

Conclusions: Nutritional management in chronic pancreatitis remains challenging. As well-designed randomized controlled trials are scarce, in large part, recommendations can only be based on low-level evidence studies or expert opinion. For now, consumption of a balanced diet remains the cornerstone recommendation for prevention, whereas more goal-directed interventions are indicated for specific nutrient deficiencies.

Individual implications of CP include overall reduced quality of life (QoL),^{9,10} unemployment or early retirement,^{11,12} and ultimately an increased mortality risk.^{12,13} Beyond that, annual costs for the treatment of CP consume significant amounts of public resources despite occurring in a relatively small number of individuals.^{14,15}

Malnutrition is a frequent complication of CP caused by pancreatic exocrine insufficiency,¹⁶ small intestinal bacterial overgrowth,¹⁷ pain-induced anorexia, or ongoing alcohol and nicotine consumption. In ~30–50% of patients, elevated resting energy expenditure may further impair nutritional status.¹⁸ Although there are inconsistent definitions for malnutrition, which

make an accurate estimation of malnutrition in CP patients difficult, current data suggest that energy and/or nutrient deficiency is rather the norm than the exception in patients with CP. For instance, prevalence of malnutrition based on body mass index (BMI) ranges from 8% to 39%,^{9,19} and fat-soluble vitamin deficiency varies from 1% to 35% and from 33% to 87% for vitamin A^{20–23} and vitamin D^{21–23} deficiency, respectively.

Because concomitant malnutrition is associated with increased morbidity and mortality in CP patients,^{13,23} nutrition therapy can be regarded as imperative. Consequently, the question arises, which dietary treatment CP patients should receive. To answer this question, the concept of evidence-based medicine requires that treatment must be based not only on clinical expertise but also on the best available evidence from research. It is widely recognized that randomized controlled trials (RCTs) provide the highest

quality of evidence regarding the effectiveness of a given intervention. Therefore, this work systematically compiles available evidence from RCTs investigating the effect of dietary interventions in CP patients compared with placebo or routine care on nutritional status, QoL, and pain. In a further step, those findings are contrasted with existing dietary recommendations.

Methods

This systematic review with meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.²⁴

Identification of potentially eligible studies. A systematic literature search was performed to identify studies

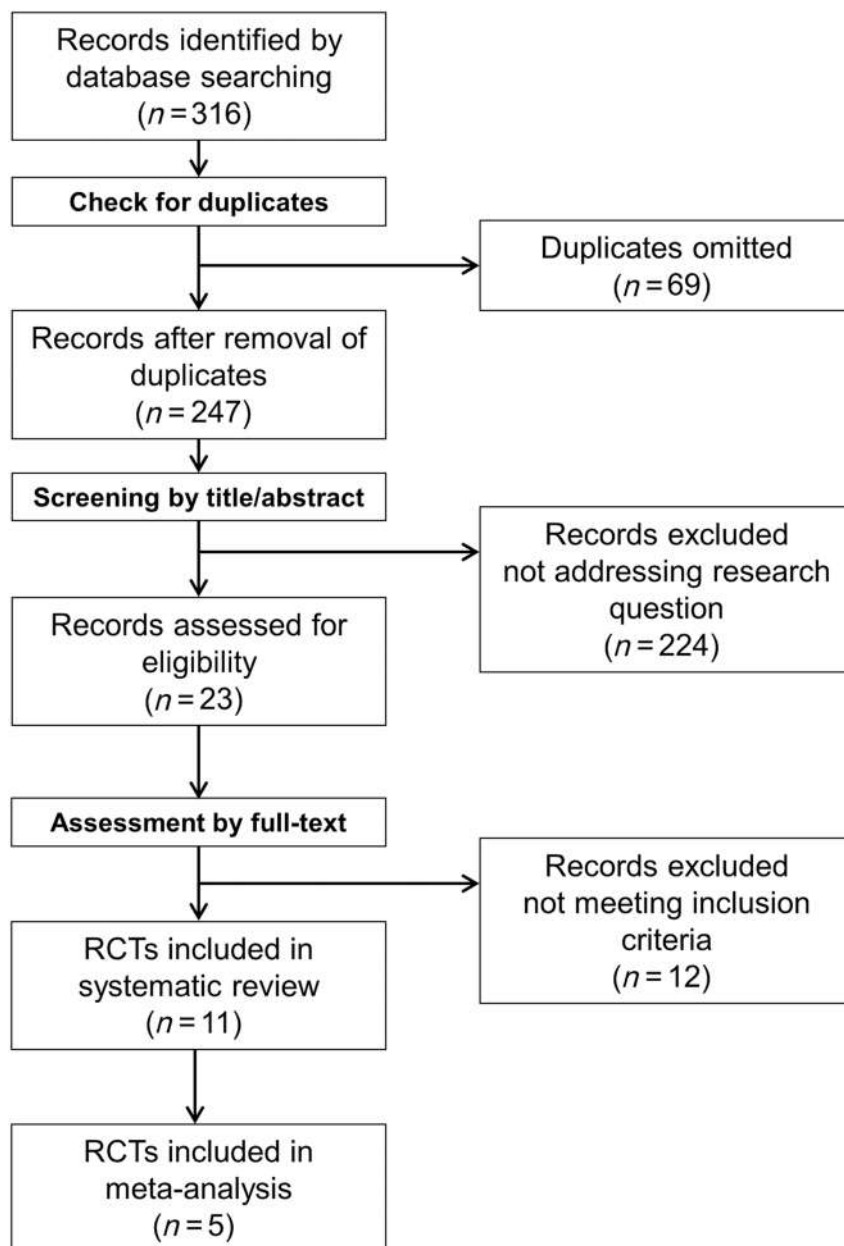


Figure 1 Flowchart illustrating the study selection process. RCTs, randomized controlled trials.

Table 1 Characteristics of the randomized controlled trials testing dietary interventions in patients with chronic pancreatitis

Study	Country	Design	Total number of participants (etiology)	Duration	Intervention	Control treatment	Principal findings
AO treatment Durgaprasad <i>et al.</i> ³⁹	India	Parallel	20 (tropical)	6 weeks	Daily supplementation of 1500 mg curcumin + 15 mg piperine	Placebo	Significant reduction of malonyldialdehyde in red blood cells No significant increase of glutathione in red blood cells No significant difference in perceived pain Improved QoL and reduction of pain
Kirk <i>et al.</i> ⁴¹	Ireland	Cross-over	36 (not specified)	10 weeks	Daily AO supplementation (300 µg selenium, 12 mg β-carotene, 188 mg d-α-tocopherol acetate, 600 mg ascorbic acid, and 1.6 g methionine)	Placebo	Significant increase in serum levels of selenium, vitamin C, vitamin E, and β-carotene but not in total serum AO capacity Significantly higher reduction in the number of painful days and number of analgesic tablets
Bhardwaj <i>et al.</i> ³⁷	India	Parallel	147 (miscellaneous)	6 months	Daily AO supplementation (600 µg organic selenium, 540 mg ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol, and 2 g methionine)	Placebo	Significantly increased levels of AOs and lowered markers of oxidative stress in blood
Siriwardena <i>et al.</i> ³⁸	United Kingdom	Parallel	92 (miscellaneous)	6 months	Daily AO supplementation (300 µg selenomethionine, 757.8 mg ascorbic acid, 25.2 mg β-carotene, 680.4 mg α-tocopherol, and 2.88 g methionine)	Placebo	No significant difference in change of reported pain between the two groups Significantly increased AO blood levels only in the treatment group
Dhingra <i>et al.</i> ⁴²	India	Parallel	61 (alcoholic and idiopathic)	3 months	Daily AO supplementation (600 µg organic selenium, 540 mg ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol, and 2 g methionine)	Placebo	Significant reduction in serum levels of platelet-derived growth factor but not transforming growth factor β1 Reduction in platelet-derived growth factor levels was associated with reduction in pain and analgesic requirements

(Continues)

Table 1 (Continued)

Study	Country	Design	Total number of participants (etiology)	Duration	Intervention	Control treatment	Principal findings
Singh <i>et al.</i> ⁴⁰	India	Parallel	107 (miscellaneous)	6 months	Daily AO supplementation (600 µg organic selenium, 540 mg ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol, and 2 g methionine)	Placebo	No significant difference in endocrine and exocrine function, markers of fibrosis, oxidative stress and inflammation, nutritional status, pain, and QoL
Vitamin D supplementation Bang <i>et al.</i> ⁴³	Denmark	Parallel	30 (miscellaneous)	10 weeks	Daily oral vitamin D supplementation (1520 IU cholecalciferol) + 800 mg calcium + 6-min tanning bed w/o UVB radiation weekly	(1) 6-min tanning bed with UVB radiation weekly + 800 mg calcium (2) Placebo + 800 mg calcium + 6-min tanning bed w/o UVB radiation weekly	Significantly greater change in 25-hydroxyvitamin D, but not calcitriol, concentrations
Bang <i>et al.</i> ⁴⁴	Denmark	Parallel	30 (miscellaneous)	10 weeks	Daily oral vitamin D supplementation (1520 IU cholecalciferol) + 800 mg calcium + 6-min tanning bed w/o UVB radiation weekly	(1) 6 min tanning bed with UVB radiation weekly + 800 mg calcium (2) Placebo + 800 mg calcium + 6-min tanning bed w/o UVB radiation weekly	Significantly higher increase in ionized calcium but no other marker of bone metabolism Significant correlation of changes in 25-hydroxyvitamin D and calcitriol with maturation of CD4 ⁺ and CD8 ⁺ regulatory T lymphocytes Significant difference in proportion of vitamin D sufficiency between groups
Reddy <i>et al.</i> ⁴⁵	India	Parallel	40 (tropical)	9 months	(1) Single intramuscular injection of 600 000 IU vitamin D ₃ + 1 g calcium and 500 IU vitamin D ₃ orally per day (2) Single intramuscular injection of 300 000 IU vitamin D ₃ + 1 g calcium and 500 IU vitamin D ₃ orally per day	Placebo + 1 g calcium and 500 IU vitamin D ₃ orally per day	Significant difference between groups 1 and 2 after 6 months but no longer after 9 months
Supplementation with ONS Singh <i>et al.</i> ⁴⁶	India	Parallel	60 (alcoholic and idiopathic)	3 months	Adjuvant supplementation of MCT-enriched ONS	Dietary counseling for an isoenergetic homemade diet	Improvements in dietary intake, anthropometric measures, nitrogen balance, and pain in both groups without significant differences between treatments

(Continues)

Table 1 (Continued)

Study	Country	Design	Total number of participants (etiology)	Duration	Intervention	Control treatment	Principal findings
Symbiotics supplementation Dos Santos et al. ⁴⁷	Brazil	Parallel	60 (miscellaneous)	3 months	12 g of symbiotics (composed of fructooligosaccharides, <i>Lactobacillus casei</i> , <i>Lactobacillus rhamnosus</i> , <i>Lactobacillus acidophilus</i> , and <i>Bifidobacterium bifidum</i>)	Placebo	Significant reduction in bowel frequency No significant changes in anthropometric characteristics Significant increase in levels of hemoglobin, hematocrit, red blood cells, total lymphocyte count, serum magnesium, and albumin Significant reduction of total cholesterol levels

AO, antioxidant; MCT, medium chain triglyceride; ONS, oral nutritional supplements; QoL, quality of life; UVB, ultraviolet B.

potentially eligible for this review. The PubMed and Cochrane Central Register of Controlled Trials databases were searched for all English and German language full-text articles published in peer-reviewed journals up to this date (last inquiry May 12, 2020). As a search strategy, the following three groups of search terms, of which at least one had to be present in title or abstract of the article for each group, were compiled: (i) “randomized,” “randomised,” “clinical trial,” and “clinical study”; (ii) “diet,” “nutrition,” “nutrition therapy,” “carbohydrate,” “dietary fiber,” “fat,” “medium chain triglycerides,” “protein,” “alcohol,” “vitamins,” “minerals,” “trace elements,” “antioxidants,” “supplementation,” “supplements,” “oral nutritional supplements,” “enteral nutrition,” and “parenteral nutrition”; and (iii) “chronic pancreatitis” or “exocrine pancreatic insufficiency.”

Study selection. For this systematic review, all studies met the following inclusion criteria: (i) study design: RCTs investigating effects of dietary interventions in CP patients; (ii) treatments: interventions consisting of supplementation of single nutrients or nutrient combinations, provision of oral nutritional supplements (ONS), and enteral or parenteral nutrition; (iii) comparison: control patients receiving either placebo or standard medical care; and (iv) outcomes: changes in anthropometric measures, body composition, biomarkers reflecting nutritional status, QoL, or pain.

Further, diagnosis of CP had to be confirmed by imaging modalities and/or function tests. No restrictions in terms of etiology were made; that is, results on patients with any form of CP, including tropical and idiopathic CP, were included. Clinical studies not restricted to CP patients and covering other entities were excluded, unless separate subgroup data for CP could be extracted from the article.

Two reviewers (M. W. and A. A. A.) independently screened the title and abstract of records identified during the search for fulfillment of the above eligibility criteria. In case of disagreement between the reviewers regarding the eligibility of a particular article, a consensus decision was reached on the basis of the full text of the article.

Data extraction. One reviewer (M. W.) entered data on study design, publication year, country, patient characteristics, interventions, control treatments, and outcome data into a standardized data extraction form. A second reviewer (A. A. A.) checked data extraction process for quality.

Quality and risk of bias assessment. Scientific quality of the studies included was assessed by employment of the Jadad score. Briefly, the Jadad score is an easy-to-use tool to assess the quality of reporting of RCTs by answering five questions on randomization, blinding, and dropouts.²⁵ High scientific quality is indicated by scores > 2, meaning that reliable conclusions can be drawn from this trial.²⁶

Studies included were also assessed for risk of bias using domain-based risk of bias tables, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (<https://training.cochrane.org/handbook>). Therefore, each study was examined with regard to random sequence generation, allocation concealment, blinding, reporting of incomplete outcome data, and selective reporting.

Data synthesis and statistical analysis. If two or more RCTs addressed the same research question, feasibility of a

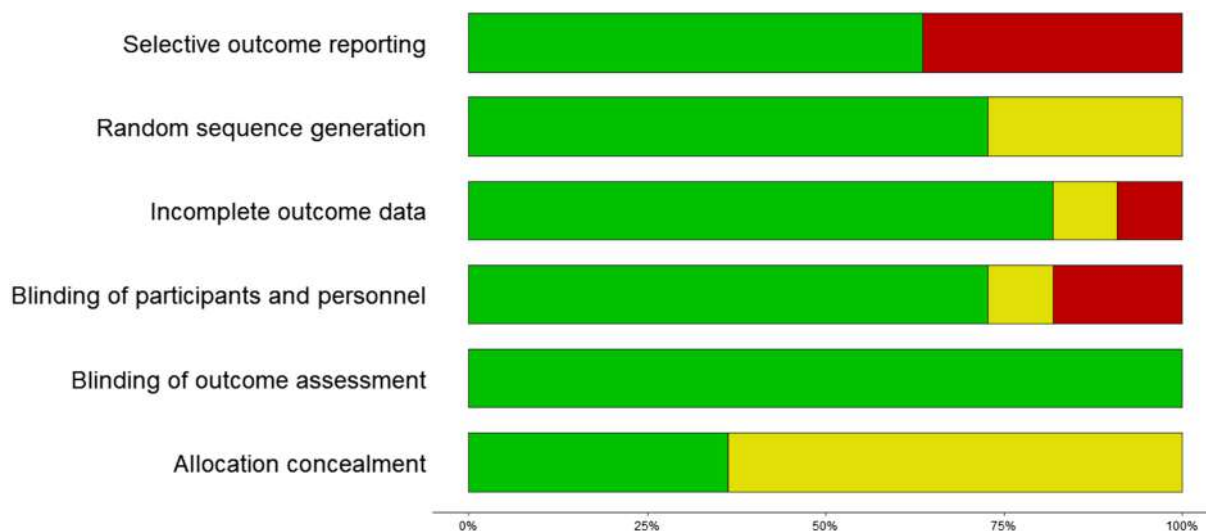


Figure 2 Risk of bias summary for randomized controlled trials testing dietary interventions in patients with chronic pancreatitis (■, low risk of bias; ■, unclear risk of bias; ■, high risk of bias).

meta-analysis to estimate the overall effect of an intervention was checked based on the extracted data. In case of feasibility of a meta-analysis, data were pooled using a random-effects model applying the Hartung–Knapp–Sidik–Jonkman method to obtain a more conservative estimate of the treatment effect.^{27–31} We also conducted sensitivity analyses applying the DerSimonian–Laird method for the random-effects model as well as a fixed effects model.³² The estimates of treatment effects were expressed as standardized mean difference (SMD) with 95% confidence interval (CI) for continuous data and risk ratio (RR) with 95% CI for binary data. SMD was calculated as a summary statistic for all continuous variables to take employment of various scales and scoring systems into account. In case an effect was reported in form of multiple outcome measures, we included the data specified as the primary outcome measure by the authors. If such specification was missing, we chose the outcome measure that provided best comparability between the studies. Sensitivity analyses were performed to test for an effect of outcome selection on the estimate of treatment effect. For binary data, we used continuity correction by adding the value 0.5 in all cells where a zero value was reported.³³ Heterogeneity between studies was assessed using the I^2 statistic and the χ^2 test. Significant heterogeneity was defined as $I^2 \geq 25\%$ and/or $P < 0.10$ for χ^2 test. Degree of heterogeneity was classified as low, moderate, and high for I^2 values $\geq 25\%$, $\geq 50\%$ and $\geq 75\%$, respectively.³⁴ To address heterogeneity between studies, we performed subgroup analyses. Forest plots were generated to illustrate results for all meta-analyses. We also created funnel plots to examine the risk of publication bias.

All statistical analyses were performed with R software (R Core Team, Vienna, Austria) for statistical computing (version 3.6.1)³⁵ employing the “meta” package.³⁶

Results

Study identification and selection. The process of study identification and selection is outlined in Figure 1. Briefly,

316 initially identified records (247 after removal of duplicates) were screened by title and abstract. Following exclusion of irrelevant records, 23 records were checked for eligibility on the basis of the full-text articles. Of these, 12 records were excluded for non-fulfillment of the predefined criteria, leaving 11 RCTs to be included in this review, of which 5 were also comprised in the meta-analysis.

Study characteristics. The characteristics of the included RCTs are summarized in Table 1. With regard to dietary interventions, the RCTs tested the following treatments: antioxidant (AO) treatment ($n = 6$),^{37–42} vitamin D supplementation ($n = 3$),^{43–45} supplementation with ONS ($n = 1$),⁴⁶ and symbiotics supplementation ($n = 1$).⁴⁷ Considerable differences in duration were found between the identified RCTs. The shortest duration was 6 weeks,³⁹ whereas the longest intervention lasted 9 months.⁴⁵ In addition, there was a wide variation in the number of participants included in the studies. While the largest RCT³⁷ included 147 participants, the smallest sample size was 20.³⁹ Most RCTs^{37–40,42–47} used a parallel design, with the exception of one trial⁴¹ that was designed as a cross-over study. In the majority of studies,^{37,38,40–44,46,47} patients with miscellaneous etiologies of CP were included, with alcoholic or idiopathic CP being the most common forms. Two RCTs from India,^{39,45} however, only tested the intervention in patients with what was then termed tropical pancreatitis. Six of the eligible studies^{37,39,40,42,45,46} were conducted in India, whereas four originated from European countries^{38,41,43,44} and one from Brazil.⁴⁷ Overall, the included trials were of good methodological quality as indicated by a mean Jadad score of 3.6 (single scores not shown). In total, we also found only low to moderate risk of bias in the included studies. Only selective reporting of outcome data was identified to present substantial risk of bias in about one-third of all trials (Fig. 2).

Antioxidant treatment. In five single-center studies,^{37,38,40–42} the effect of AO treatment in CP was

investigated, and a combination of selenium, β -carotene, α -tocopherol, ascorbic acid, and methionine was administered. Although the primary outcome measures differed between studies, all RCTs examined an effect on pain. Overall, daily doses of AO supplementation were similar among studies. While three studies^{37,40,42} used identical doses of the individual compounds (600 μ g organic selenium, 540 mg ascorbic acid, 9000 IU β -carotene, 270 IU α -tocopherol, and 2 g methionine), the formulations administered in the RCTs by Kirk *et al.*⁴¹ (300 μ g selenium, 12 mg β -carotene, 188 mg α -tocopherol, 600 mg ascorbic acid, and 1.6 g methionine) and Siriwardena *et al.*³⁸ (300 μ g selenomethionine, 757.8 mg ascorbic acid, 25.2 mg β -carotene, 680.4 mg α -tocopherol, and 2.88 g methionine) were slightly different. With respect to the effectiveness of AO treatment, three studies^{37,41,42} found an attenuation of pain indicated by ease of reported pain^{41,42} and/or a reduction of analgesics requirements.³⁷ In contrast, the interventions by Siriwardena *et al.*³⁸ and Singh *et al.*,⁴⁰ despite showing elevated plasma AO levels, did not result in a significant reduction of pain. Further, the Singh study,⁴⁰ which also investigated potential effects on various other parameters, including exocrine and endocrine pancreatic function as well as nutritional status, found no significant differences between groups for any of the outcomes. No significant effect of AO

supplementation was also observed in a pilot study³⁹ testing the pain-attenuating potential of curcumin, the active constituent of turmeric. A 6-week supplementation of 500 mg curcumin combined with 5 mg piperine three times daily failed to improve pain in a population of patients suffering from tropical pancreatitis.

Vitamin D supplementation. The effectiveness of vitamin D supplementation in patients with CP and vitamin D deficiency (serum 25-hydroxyvitamin D < 75 nmol/L) was examined in three RCTs.^{43–45} Two of them^{43,44} reported different outcomes despite the same intervention and the same study population. In those studies, participants were randomized to receive one of the following treatments: (i) daily oral vitamin D supplementation of 1520 IU cholecalciferol plus 800 mg calcium and weekly 6 min of tanning bed sessions without ultraviolet B (UVB) radiation; (ii) weekly 6 min of tanning bed sessions with UVB radiation plus 800 mg calcium; or (iii) weekly 6 min of tanning bed sessions without UVB radiation plus 800 mg calcium daily. Serum 25-hydroxyvitamin D concentrations were assessed at screening, randomization, and 2, 6, and 10 weeks. After 10 weeks, levels of 25-hydroxyvitamin D, but not 1,25-dihydroxyvitamin D,⁴³ as well as ionized calcium⁴⁴ were significantly higher in the

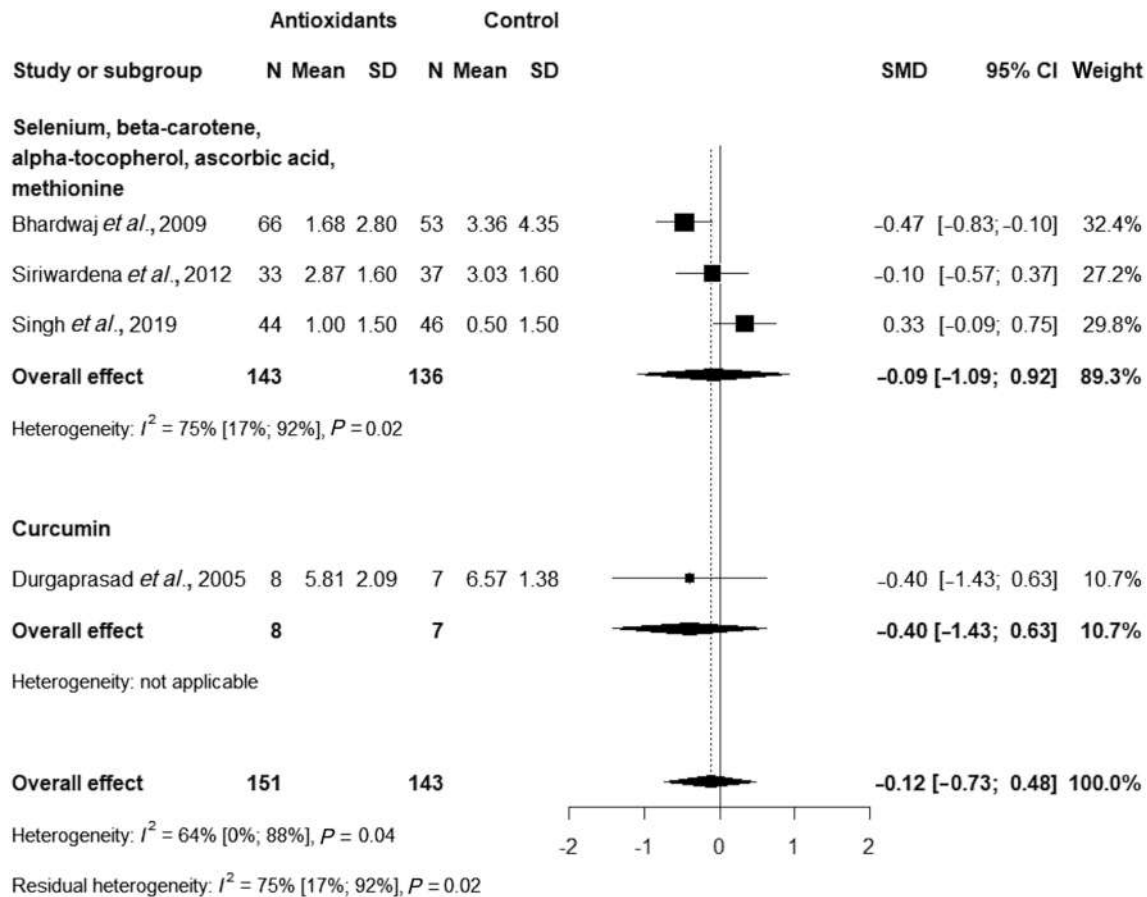


Figure 3 Forest plot of randomized controlled trials testing the efficacy of antioxidant treatment on pain in patients with chronic pancreatitis. Standardized mean differences (SMDs) (95% confidence intervals [CIs]) for adverse effects with the use of a random-effects model.

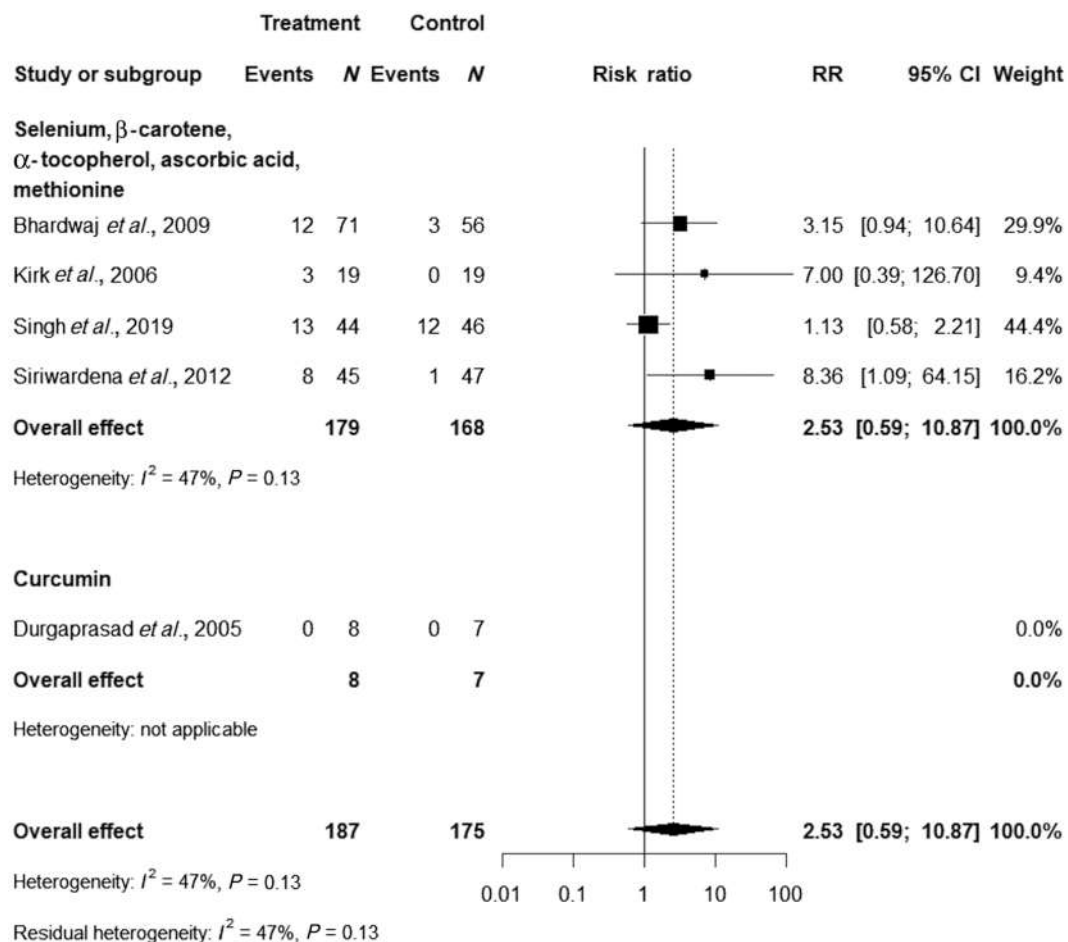


Figure 4 Forest plot of randomized controlled trials testing the efficacy of antioxidant treatment on pain in patients with chronic pancreatitis. Risk ratios (RR) (95% confidence intervals [CIs]) for adverse effects with the use of a random-effects model.

oral supplementation group but not in the other two groups. No other markers of bone metabolism were altered. Furthermore, in a subsample of study participants, changes of both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D serum levels were correlated with changes of CD4⁺ and CD8⁺ regulatory T lymphocytes.⁴⁴

In the third study, which was conducted by Reddy *et al.*,⁴⁵ the relative efficacy of single intramuscular vitamin D₃ injections in patients with tropical calcific pancreatitis was tested. Initially, patients received either a single injection of 600 000 or 300 000 IU of vitamin D₃ or saline as placebo. The injections were followed by 9 months of daily oral supplementation of 500 IU vitamin D₃ and 1 g calcium across all groups. Fasting blood samples were collected at baseline and at 1, 3, 6, and 9 months of intervention. After 6 months, the proportion of patients with sufficient vitamin D levels (serum 25-hydroxyvitamin D > 75 nmol/L) significantly differed between the 600 000 IU, the 300 000 IU, and the placebo group (85%, 29%, and 0%, respectively). However, after 9 months, there was no longer a significant difference between the 600 000 IU and the 300 000 IU arm (46% vs 27%).

Oral nutritional supplements. With regard to ONS, only a single study⁴⁶ was identified, which tested the efficacy of ONS

for the treatment of malnutrition in CP. In this study, 60 malnourished patients (BMI < 18.5 kg/m² or loss of > 10% of usual bodyweight within the last 6 months) were randomized to receive either supplementation with ONS or dietary counseling. The supplement used was a commercially available polymeric formula enriched with 8.25 g of medium chain triglycerides (MCTs) per 100 mL. Patients in the control group received dietary counseling, which was conducted by an expert dietitian who encouraged patients to eat small and multiple meals of a balanced homemade diet to increase dietary intake. Both interventions were designed to compensate the patients' dietary energy deficit, which is defined as the recommended subtracted by the calculated energy intake. After 3 months of intervention, dietary intake, nitrogen balance, anthropometric measures as well as pain improved in the supplementation group. However, similar changes were observed in the dietary counseling group. There was ultimately no significant difference between the two groups with regard to any of the outcome parameters.

Symbiotics supplementation. One RCT⁴⁷ tested the effect of symbiotics supplementation, that is the combined administration of prebiotics and probiotics, on nutritional status,

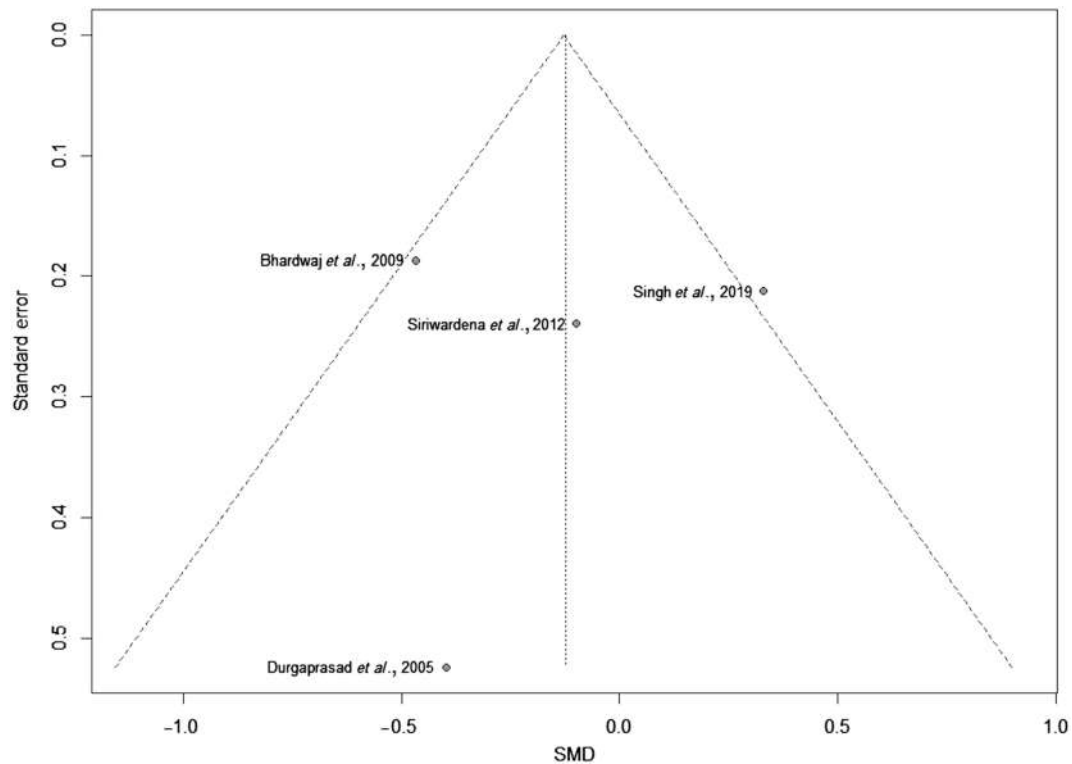


Figure 5 Funnel plot of randomized controlled trials testing the efficacy of antioxidant treatment on pain in patients with chronic pancreatitis. SMD, standardized mean difference.

laboratory parameters, and intestinal habits. In this study, 60 CP outpatients were randomized to receive either a supplementation of 2×6 g symbiotics daily or placebo. Each symbiotic supplement sachet was composed of 6 g of fructooligosaccharides and *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, and *Bifidobacterium bifidum* (10^9 colony-forming unit of each). After 3 months of intervention, average daily bowel frequency was significantly reduced in the symbiotics group, while it was unchanged in the placebo arm. Furthermore, only in the symbiotics group, there was an improvement of different blood parameter levels, that is hemoglobin, hematocrit, red blood cells, total lymphocyte count, serum magnesium, and albumin. A reduction in total cholesterol was observed. Regarding the nutritional status of the patients, no changes in BMI and body composition were seen in the symbiotics and the placebo arm.

Meta-analysis. Because of the limited number of studies, it was only possible to conduct a meta-analysis for AO treatment. Besides their effect on pain, we also analyzed potential adverse effects. Four^{37–40} and five studies^{37–41} provided sufficient data to be included in meta-analysis on pain (Fig. 3) and adverse effects (Fig. 4), respectively. Overall, with regard to pain, we found no significant effect of AO treatment (SMD = -0.12 ; 95% CI -0.73 to 0.48). A subgroup analysis stratified by substance did not show a significant effect either for the combination of selenium, β -carotene, α -tocopherol, ascorbic acid, and methionine or for curcumin. We found significant heterogeneity between studies

both with (I^2 : 75%, $P = 0.02$) and without stratification by substance (I^2 : 64%, $P = 0.04$). None of the conducted sensitivity analyses did alter the results in a meaningful way. Although employment of the DerSimonian–Laird method and a fixed-model approach resulted in narrowed CIs for the overall effect, none of these models resulted in significant effects (SMD = -0.12 ; 95% CI -0.54 to 0.29 and SMD = -0.13 ; 95% CI -0.36 to 0.10 , respectively). Regarding potential adverse effects, we found no significantly increased risk in patients receiving AO treatment (Fig. 4; RR = 2.53; 95% CI 0.59–10.87). Applying the fixed effects model, the increase of RR was significant, though (RR = 2.15; 95% CI 1.25–3.67). Risk assessment stratified by substance was not feasible, as the curcumin study did not report adverse effects in any of the groups. Visual inspection of the funnel plot did not reveal any risk of publication bias (Fig. 5).

Discussion

Summary of evidence. Only few RCTs investigated dietary interventions in patients with CP. The majority of them evaluated the efficacy of AO treatment with a special focus on pain relief. However, results are inconsistent, which might be caused by a heterogeneity in the study design in terms of interventions and study populations. Our meta-analysis does not support efficacy of such treatment, although prior meta-analyses found contradicting results.^{48–50} Yet these latter meta-analyses included studies that did not meet our meticulous eligibility criteria. In particular,

all of these meta-analyses also included non-randomized trials and did not apply any restrictions in terms of language, publication status, or type. In agreement with our findings, most international guidelines do not recommend the use of AOs for attenuation of pain. While some guidelines explicitly recommend against them,^{51,52} other guidelines do not either include any recommendation at all^{53–57} or provide such recommendation but point towards the low level of evidence.^{58–60} Rightly, the guideline for CP by the German Society for Digestive and Metabolic Diseases⁵¹ further argues that smoking is common among CP patients and that certain AO combinations, that is the combination of β -carotene with retinol or α -tocopherol, could even increase the risk of lung cancer in smokers.^{61,62} Considering the unclear benefit and the potential adverse effects of AOs at present, it appears legitimate to refrain from a recommendation for AO supplementation for attenuation of pain in CP patients.

Vitamin D supplementation in CP is another treatment option, which has been tested in RCTs.^{43–45} Both oral and intramuscular administrations are suited to treat vitamin D deficiency in CP patients, whereas weekly UVB tanning bed sessions are ineffective. Almost unanimously, international guidelines acknowledge the general risk of micronutrient deficiency in CP and recommend specific supplementation if indicated, however not routinely.^{51–54,56–60} For vitamin D supplementation, the guidelines by the German Society for Digestive and Metabolic Diseases⁵¹ and the Spanish Pancreatic Club⁵⁹ provide specific recommendations. Supplementation with calcidiol (= 25-hydroxyvitamin D) is preferred over other compounds, for example cholecalciferol (= vitamin D₃).⁵⁹ However, this recommendation is solely based on the theoretical benefit of higher polarity calcidiol and is not supported by RCTs, in which vitamin D sufficiency was achieved by supplementation of cholecalciferol. A statement regarding the preferred route of administration is not included in the Spanish recommendations. More evidence-based recommendations are provided in the Pan-European guidelines from the United European Gastroenterology.⁵² On the basis of the same trials, which were identified in this review, the authors likewise conclude that both oral supplementation and a single intramuscular injection are suitable to treat vitamin D deficiency and are considered to be of equal efficacy. Furthermore, a replacement of fat-soluble vitamins seems practical in patients with low serum levels, malabsorption, and poor dietary intake. To the best of our knowledge, other fat-soluble vitamins have not been investigated in RCTs. Therefore, data regarding efficacy and safety of such treatment are missing. In addition, relevant outcome parameters, other than blood vitamin levels, such as bone fractures or osteodensitometry were not included in the trials.

Regarding the efficacy of ONS, we found that only a single RCT⁴⁶ has tested the effect of such supplementation on nutritional status in CP patients: Singh *et al.* showed that 3-month supplementation with ONS improved nutritional status of malnourished patients with CP. Interestingly, it was also shown that an equal improvement could be achieved by dietary counseling. On the basis of these findings and the limited available evidence in this area, recommendations regarding the use of ONS are rare. Thus, ONS is reserved for those patients, in whom a combination of pancreatic enzyme replacement therapy and dietary modification failed to improve nutritional status.^{51,52,57,59} Nevertheless, the generalizability of this single study is limited, especially when treating CP patients in Western countries.

Secondly, the study by Singh *et al.*⁴⁶ is often taken as a basis to evaluate the efficacy of MCT supplementation in CP patients, as they used an MCT-enriched polymeric formula. As there are no RCTs that only tested for MCT supplementation, most international guidelines base their recommendations on the findings from this single study. Consequently, supplementation of MCTs is not recommended in general^{52,58} or should only be considered when adequate fat absorption cannot be achieved by pancreatic enzyme replacement therapy.^{51,57,59,60} These recommendations are further supported by the inferiority of MCTs over long-chain triglycerides shown in older, non-randomized studies^{63,64} and also by the poor taste and high costs of MCT supplements.^{57,59} Yet one must keep in mind that no studies exist that were designed to test exclusively the efficacy of MCTs for the treatment of CP. Consequently, evidence of MCT supplementation is limited, and recommendations should be regarded with caution.

Symbiotics supplementation in CP patients has only been tested in one RCT so far.⁴⁷ It failed to provide clear evidence for the benefit of symbiotics supplementation. Although biochemical parameters improved and bowel frequency was reduced after 3 months of supplementation, there was no clear benefit in nutritional status. Nevertheless, symbiotic treatment represents a rather novel approach for therapy of CP. Recent studies indicate that gastrointestinal dysbiosis is quite common in CP^{65,66} and that pancreatic exocrine function is an important host factor shaping the human intestinal microbiome.⁶⁷ Currently, the clinical benefit of such intervention remains elusive. In addition, this study did not analyze the composition of the intestinal microbiome and therefore failed to provide insights into the mechanistic effects of symbiotics supplementations.⁴⁷ Because of these limitations and the just recently widening understanding of interactions between microbiome and the pathogenesis of CP, current guidelines do not address dietary interventions that aim to modulate intestinal microbiota composition. Although probiotic prophylaxis aggravates severe acute pancreatitis,⁶⁸ dietary interventions with symbiotics seem to have favorable effects in many other chronic disorders^{69,70} and might be a feasible alternative to antibiotics, which are problematic in many ways and rather exacerbate than improve dysbiosis.⁷¹ In view of the deleterious effect of probiotics in acute pancreatitis,⁶⁸ no recommendation of their use in CP can presently be made before evidence from high-quality RCTs is available.

Finally, also the absence of RCTs on dietary interventions commonly recommended by guidelines for the treatment of CP needs to be discussed. For instance, there are conflicting recommendations regarding intake of dietary fiber. While some guidelines^{54,57,59} recommend a low fiber intake to avoid inhibition of digestive enzymes, both endogenously produced and supplemented ones,^{51,52,58,60} discourage from a general restriction. As a matter of fact, the effect of dietary fibers on nutritional status in CP patients has not been tested in RCTs, and current recommendations are solely based on evidence from low-level evidence studies.^{72,73} The difficult interpretation of these data underlines the need for well-designed RCTs, which could finally lead to less heterogeneous recommendations.

Limitations. Considering only findings from RCTs can be regarded as a limitation of this systematic review. However, it should be seen as a limitation by design. Instead of gathering all

available evidence for nutritional management of CP to derive evidence-based guidelines,^{51–60} this systematic review was specifically conducted to identify findings from RCTs. However, systematic identification of existing RCTs and subsequent contrasting of results with current guideline recommendations contributes to existing knowledge by revealing the lack of support for many of these recommendations. As it is widely accepted that RCTs provide the best scientific evidence for the efficacy of an intervention, this work highlights the relative weakness of these guideline recommendations.

Secondly, we cannot entirely rule out publication bias that might contribute to a paucity of RCTs on one specific topic. However, as many of the RCTs even published nonsignificant effects, this risk might be comparatively small. In addition, the funnel plot of RCTs testing the efficacy of AO treatment on pain did not reveal any risk of publication bias. Finally, as there is no recommendation for which we found strong evidence from RCTs, there is little risk that, at present, certain dietary interventions are supported by biased reporting of results.

The strength of published guidelines varies as well, because not all guidelines were generated in an evidence and consent-based way after a systematic search and assessment, which is done in S3 guidelines.⁷⁴

Lastly, we were only able to conduct a meta-analysis for AO treatment. Meta-analyses have great value in interpretation of clinical data, as they aggregate data from multiple studies on one specific research question leading to greater statistical power. Unfortunately, it was impossible to perform meta-analyses on other dietary interventions. However, one must keep in mind that also, results of meta-analyses should be considered with caution, especially when the number of included studies is limited and meaningful heterogeneity is present.

Conclusion. Nutritional management in CP remains challenging. As there is a lack of well-designed RCTs, recommendations can only be based on low-level evidence studies or expert opinion. Consequently, there is a wide room for interpretation, which can ultimately lead to conflicting guideline recommendations, which we have pointed out. Consumption of a balanced diet, meeting individual nutritional requirements, and respecting personal tolerance remain the cornerstone recommendations for prevention of malnutrition in CP. In case of an overt deficiency, a more goal-directed dietary intervention is indicated, and choice of treatment should be based on the form and severity of malnutrition. Unfortunately, highest level evidence is often missing and thus cannot endorse the best treatment option. Therefore, conduction of additional RCTs testing efficacy of dietary interventions is highly warranted.

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