

Zinc Status in Exocrine Pancreatic Insufficiency: A Systematic Review

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ABSTRACT

AIM: The present systematic review looks to available research to determine the effect of exocrine pancreatic insufficiency on zinc status.

MATERIALS AND METHODS: An exhaustive search was conducted amongst six databases up to September 2017 for studies reporting zinc status in patients with diagnosed exocrine pancreatic insufficiency. Thirteen studies of observational design met inclusion criteria.

RESULTS: Eleven of the 13 studies included in this review found an

association between zinc status and exocrine pancreatic insufficiency. Most of these studies found a correlation between zinc status and the degree of exocrine pancreatic insufficiency. However, considering the nature of the observational study design of the included studies, the strength of the evidence is low.

CONCLUSION: Those with exocrine pancreatic insufficiency may be at high risk for impaired zinc status. Larger, high-quality studies are necessary to estimate the prevalence of zinc deficiency and before clinicians routinely recommend supplementation. Based on this review, zinc supplementation cannot be routinely recommended.

Key words: Exocrine Pancreatic Insufficiency; Zinc Deficiency; Zinc

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INTRODUCTION

Exocrine pancreatic insufficiency (EPI) can be defined as a reduction in exocrine pancreatic enzymes to a level that can result in malabsorption^[1]. This inability to maintain adequate digestion can cause steatorrhea, weight loss, abdominal pain, and malnutrition^[1,2]. The most common cause of EPI is chronic pancreatitis^[2]. Additional populations at risk for EPI due to pancreatic causes include: severe necrotizing pancreatitis, gastrointestinal and pancreatic surgery, cancer of the pancreas head, and cystic fibrosis^[2,3]. Non-pancreatic causes of EPI are celiac disease, diabetes mellitus, Crohn's disease, short bowel syndrome, and Zollinger-Ellison syndrome^[4].

Patients with EPI are at increased risk for developing a zinc (Zn) deficiency^[5]. Endogenous Zn is released through the pancreatic duct into the small intestine to maintain homeostatic control. Therefore, there may be a connection between the regulation of pancreatic Zn metabolism and exocrine pancreatic function^[6]. Zn plays a vital role as an essential trace element required for over 300 different cellular processes^[7]. When Zn deficiency occurs, clinical manifestations include growth failure, skin changes, poor appetite, mental fatigue,

delayed wound healing, neurosensory disorders, and cell-mediated immune disorders^[8].

The current paper looks to systematically review available research to determine the effect of EPI on Zn status.

METHODS

The methodology for this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^[9]. A computer search of PubMed and the Cochrane database did not detect any prior systematic review of Zn status in EPI. PubMed, Cochrane, CINAHL, Web of Science, ProQuest were searched for original studies until September 2017. Specific search terms included: (exocrine pancreatic insufficiency OR zinc OR zinc status OR zinc deficiency) AND (exocrine pancreatic insufficiency OR pancreatic insufficiency OR pancreas OR pancreatoduodenectomy OR cystic fibrosis OR Shwachman-Diamond syndrome OR chronic pancreatitis OR pancreatic cancer OR gastric bypass). Medical Subject Headings (MeSH) in PubMed were used for appropriate search terms. The “similar articles” hyperlink in PubMed was utilized to broaden search results. Also, further articles that might have been missed during the web search were found by hand-searching reference lists of articles that met inclusion criteria. Lastly, a grey literature search was done using Open Grey and ProQuest.

Studies were deemed eligible if they met the following inclusion criteria: (1) Patients who had a diagnosis of EPI; (2) EPI diagnosis met defined diagnostic methods; (3) Published in the English language. Outcome data in the studies that qualified for inclusion had to characterize zinc status. All study designs were included; however, considering the subject matter, almost all studies were observational in design. Studies were excluded if full text was not available, as the abstract did not allow for complete data extraction.

All search results were imported into Thomas Reuters EndNote citation manager. Duplicates were removed with the assistance of the citation manager. Titles were examined for relevancy. The abstracts of those studies found potentially relevant were reviewed for appropriateness according to the inclusion criteria. The full text was obtained for most of abstracts to evaluate the studies in detail. Studies that did not match inclusion criteria were removed. After this process, 13 studies were included in this review. Figure 1 shows a summary of the research process that was performed by one reviewer. A second author assisted throughout the process.

For each of the studies that met inclusion criteria, the following data were extracted: study design, sample size, outcomes of interest, results, and characteristics of EPI (how EPI was diagnosed, the severity of EPI, and use of pancreatic enzyme replacement therapy). Risk of bias and the quality of the studies were evaluated using the Newcastle-Ottawa Scale^[10]. Different scales were used for case-control, cross-sectional, and case series studies, since quality criteria were different for each type of study design. An overall quality rating was determined for each study included in this review. The quality rating and the results of each study are included in Table 1. A systematic narrative synthesis analyzed the findings of the included studies and assessed the relationship between EPI and Zn status based on the studies’ outcomes.

RESULTS

Background Information

The condition of EPI is underdiagnosed and commonly undertreated^[11]. EPI symptoms are different for each patient and

depend on the severity of EPI and its etiology^[1]. In addition to abdominal pain and steatorrhea, another clinical sign of EPI is malnutrition^[3,11]. The gold standard for diagnosis of EPI is achieved after quantifying fecal fat after a 3-day collection then determining the coefficient of fat absorption^[1,3]. Severe steatorrhea is diagnosed at ≥ 15 g/day of fat per 100 g of stool. Greater than 7 g/day of fat excretion is considered abnormal^[2].

Due to the cumbersome process of a 3-day stool collection, the fecal fat test is rarely used in daily clinical practice^[1]. Instead, alternative methods for diagnosis of EPI have been developed such as a mixed ¹³C-triglyceride breath test and fecal elastase test. The mixed ¹³C-triglyceride breath test is also considered a method of choice for diagnosing EPI. However, it is also not generally available in clinical practice.^[3] The fecal elastase test has a high sensitivity in cases of severe EPI.^[2] Measuring fecal elastase in a stool sample serves as an indicator of pancreatic exocrine function. Fecal elastase levels less than 200 $\mu\text{g/g}$ of feces suggests EPI. However, this test has a lower sensitivity for detecting mild to moderate cases of EPI^[2].

Study Characteristics

Of the 13 studies, there were 4 cross-sectional studies, 1 case series, 1 before and after study, and 7 case-control studies published from 1982 to 2015. Findings of the included articles are summarized in Table 1 with each study’s quality rating. The most frequent etiology of EPI was cystic fibrosis, while the second most common was chronic pancreatitis and pancreatic surgery. One study did not state the cause of EPI^[12]. The percentage of participants taking pancreatic enzyme replacement therapy (PERT) varied from 20% to 100%. Three studies did not report whether PERT was in use^[13-15]. Overall, 11 studies showed an association between Zn status and EPI, while 2 did not show an association.

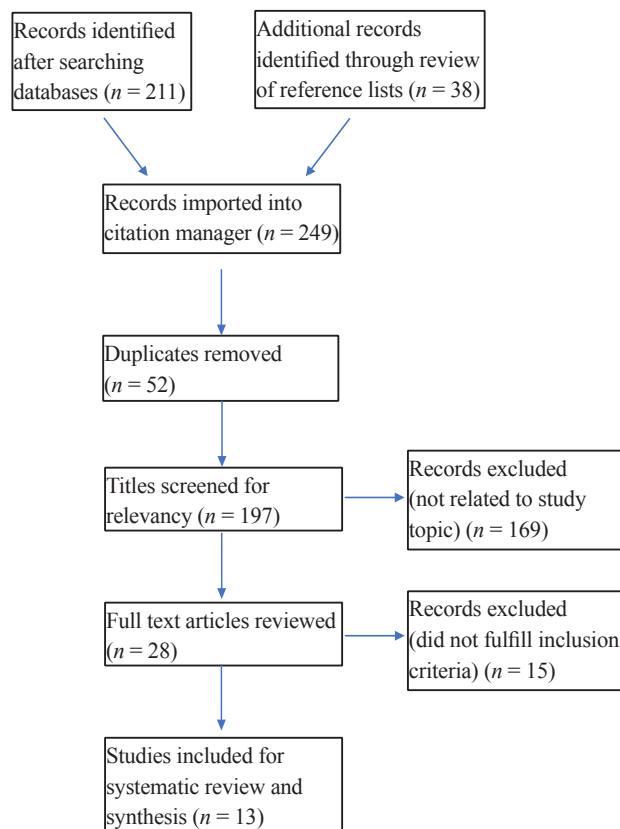


Figure 1 Flowchart of the article selection.

Table 1 Summary of studies-study demographics and characteristics.

	Study Design	Sample Size	Outcomes of Interest	EPI Diagnostic Assay	Degree of EPI	PERT Use	Results	Quality Rating based on Newcastle-Ottawa §
Studies showing an association between Zn status and EPI								
Adamama-Moraitou <i>et al</i> ^[13] (2001)	Case Control	<i>n</i> = 8	Zn status in EPI	Trypsin-Like Immunoreactivity test and autopsy	NR	NR	Dogs experimentally induced with EPI showed a significant decrease in serum Zn concentration ($p \leq 0.05$); the control dogs did not show any significant differences.	6; fair
Armstrong <i>et al</i> ^[16] (2002)	Before and after	<i>n</i> = 10	The effects of a Zn deficient diet and any digestive disturbance on Zn deficiency after PD	N-benzoyl-L-tyrosyl-p-aminobenzoic acid test and fecal elastase-1 **Patients were off PERT for these tests	Per fecal elastase-1 test, all 10 patients had severe EPI	Yes (70%)	Although adequate Zn intake was achieved, half of the patients displayed serum Zn deficiencies.	5; fair
Pichler <i>et al</i> ^[17] (2015)	Retrospective, Case Series	<i>n</i> = 21; 20 had EPI	Prevalence of Zn deficiency	Fecal elastase-1	Severe	Yes (95%)	33% of subjects found to have Zn deficiency. No statistical differences in serum values were found between first and last visit despite supplementation.	7; good
Yadav <i>et al</i> ^[18] (2014)	Case Control	<i>n</i> = 27	Prevalence of Zn deficiency	Fecal fat test	NR	Yes (22.2%)	Prevalence of Zn deficiency was significantly higher in cases than in controls. Twenty-six cases and 3 controls were Zn deficient ($p = 0.0001$).	8; good
Krebs <i>et al</i> ^[19] (2000)	Cross-sectional	<i>n</i> = 15; <i>n</i> = 11 had fecal fat test performed 6 had EPI	Fractional absorption and fecal excretion of endogenous Zn according to degree of fat malabsorption	72-hour fecal fat collection	NR	Yes (20%)	There was a positive correlation between endogenous fecal Zn losses and fecal fat excretion ($r = 0.89$, $n = 9$, $p = 0.001$).	3; poor
Girish <i>et al</i> ^[14] (2009)	Case control	<i>n</i> = 101; 67 had EPI	Zn status in relation EPI	Fecal elastase-1	Moderate ($n = 13$); Severe ($n = 54$)	NR	Erythrocyte Zn positively correlated with pancreatic stool elastase-1 ($p < 0.001$). Chronic pancreatitis patients had a significantly lower erythrocyte Zn level than controls ($p < 0.001$).	2; poor
Yu <i>et al</i> ^[20] (2011)	Retrospective, Cross-sectional	<i>n</i> = 48	Prevalence of Zn deficiency and its correlation with EPI	Fecal elastase-1, Stool fat analysis, DPR	NR	Yes (100%)	Zn deficiency was statistically significant in the PD population ($p = 0.006$). Lower fecal elastase-1 had lower Zn ($p = 0.030$); Patients with a positive stool fat analysis had a lower serum Zn level ($p = 0.016$); DPR was negatively correlated with Zn level ($p = 0.001$).	8; good
Dutta <i>et al</i> ^[21] (1998)	Case Control	<i>n</i> = 8	Metabolism of Zn in EPI	Fecal fat test, secretin test or histological evidence of chronic pancreatitis on surgically resected portion of pancreatic gland, and a d-xylose absorption test	NR	Yes (100%)	Decreased Zn absorption and increased urinary Zn excretion were countered by lower endogenous Zn excretion ($p < 0.05$) as seen in the second 4-day period with reduced excretion of Zn65 in feces.	3; poor
Ijuin, Hiroyasu ^[15] (1998)	Case Control	<i>n</i> = 382	Serum Zn levels and Zn absorption in patients with alcohol-induced disorders of the liver and pancreas	Fecal chymotrypsin test	NR	NR	Serum Zn concentration was significantly lower in the chronic pancreatitis and liver cirrhosis groups than in the control ($p < 0.01$). After administration of ZnSO ₄ , the serum Zn concentration in the abnormal fecal chymotrypsin group was lower than in the control group at 2 and 3 hours after administration in the liver cirrhosis patients ($p < 0.001$).	3; poor
Boosalis <i>et al</i> ^[12] (1983)	Case-Control	<i>n</i> = 5	Zn metabolism in EPI	Depressed pancreatic isoamylase levels and pancreatic calcifications	NR	Yes (100%)	Those with EPI had depressed Zn levels 2 hours after ingestion of Zn sulfate compared to Zn dicalcolinate ($p < 0.05$). When compared to healthy controls, those with EPI had a significant depressed peak of serum Zn values when given Zn sulfate ($p < 0.05$).	3; poor
Easley <i>et al</i> ^[22] (1998)	Cross-sectional	<i>n</i> = 8	The effect of pancreatic enzymes on Zn absorption in those with EPI	Fecal fat test	NR	Yes (100%)	Fractional absorption of Zn was lower when enzymes were withheld ($p = 0.05$).	5; fair
Studies not showing an association between Zn status and EPI								
Kelleher <i>et al</i> ^[24] (1986)	Case-Control	<i>n</i> = 117	Zn status in EPI	Fecal fat test	Yes	Yes (100%)	No evidence to support that varying levels of fat malabsorption affected Zn status as assessed by serum levels.	2; poor
Van Caillie-Bertrand <i>et al</i> ^[23] (1982)	Cross-sectional	<i>n</i> = 13	Zn status in EPI	Fecal fat test	Yes	Yes (100%)	Serum Zn levels did not differ from that of the control group.	4; poor

EPI: exocrine pancreatic insufficiency, Zn: zinc, DPR: pancreatic duct-parenchymal ratio, NR: not reported, PD: pancreaticoduodenectomy, PERT: pancreatic enzyme replacement therapy.

§ The Newcastle-Ottawa Scale evaluated various components of quality including selection, comparability, and exposure. The Newcastle-Ottawa Scale did not take into account the type of study design. Different scales are used based on study design and for this reason direct comparisons between study designs are not feasible.

Studies showing an association between Zn status and EPI

Serum Zn levels have been shown to be decreased in those with EPI. Adamama-Moraitou *et al* experimentally induced EPI in 8 dogs^[13]. Those dogs suffering from EPI, without use of PERT, were found to have a significant decrease in serum Zn concentrations compared to their control group. Armstrong *et al*^[16], Pichler *et al*^[17], and Yadav *et al*^[18] described similar results in humans with a diagnosis of severe EPI. Armstrong *et al* followed patients after a pancreaticoduodenectomy (PD), and 70% of the patients were receiving PERT. Despite adequate oral intake of Zn, half of the patients displayed serum Zn deficiencies. However, this study did not report findings that were statistically significant^[16]. Pichler *et al* studied EPI in children with Shwachman-Diamond Syndrome, and 95% of the study population were taking PERT. In this study, 33% of the children were found to have serum Zn deficiency^[17]. In a case-control study design, Yadav *et al* studied children in India who experienced cystic fibrosis with EPI, and found Zn levels to be significantly lower in cases when compared to controls. Only 22.2% of the cases were taking PERT at the time of the study^[18].

Some researchers evaluated Zn status and its relationship to diagnostic factors of EPI. Krebs *et al* performed a cross-sectional study of 15 young infants with cystic fibrosis. The study examined fractional absorption and fecal excretion of endogenous Zn according to type of feeding (formula vs. breastmilk) and degree of fat malabsorption^[19]. Six of the infants had confirmed EPI. A significant positive correlation was found between endogenous fecal Zn and fecal fat excretion. The authors suggested that the malabsorbed fat may interfere with endogenous Zn reabsorption^[19]. Girish *et al* had similar findings of Zn status in EPI, but amongst 101 patients with chronic pancreatitis instead of cystic fibrosis^[14]. In this case-control study, the authors found significantly lower erythrocyte Zn levels in those patients with a low fecal elastase-1 levels. Therefore, erythrocyte Zn levels positively correlated with pancreatic stool elastase-1^[14]. The authors concluded that Zn status has a direct correlation to EPI. An additional cross-sectional study examined Zn status in patients who previously underwent a PD^[20]. Yu *et al* found Zn deficiency was present after PD due to EPI. In the study, the 3 tests used to assess for EPI were all found to impact zinc status. Serum Zn levels were negatively correlated with the pancreatic duct-parenchymal ratio, an image-based method for assessing pancreatic exocrine function after pancreatic surgery. Lower fecal elastase-1 and a positive stool fat test were found to be positively correlated with Zn status despite the use of PERT^[20].

Four studies included in this review acknowledged the role of EPI on Zn status while trying to find answers to the etiology of Zn deficiency and methods to combat the deficiency. Dutta *et al* studied the metabolism of Zn in 8 male subjects with EPI while on PERT^[21]. The study found an increased Zn excretion in those with EPI. In addition, they found that the intestinal absorption of Zn was reduced by half in those with EPI compared to the alcoholic and non-alcoholic control participants. Despite the reduced intestinal Zn absorption and increased urinary excretion of Zn, Dutta *et al* found this was balanced by lower endogenous excretion of Zn. Dutta *et al* concluded that the EPI population is at high risk for Zn deficiency^[21]. Furthermore Ijuin^[15] and Boosalis *et al*^[12] used a Zn tolerance test to study Zn absorption in those subjects with EPI and control groups. Both case-control studies suggested that EPI plays a role in Zn metabolism. In each of these studies, Zn sulfate and Zn dipicolinate, were given to patients with EPI and their control subjects. Zn metabolism of both forms of supplementation was assessed using a Zn tolerance test. Ijuin^[15] and Boosalis^[12] *et al* had similar findings in that Zn sulfate

had impaired uptake in the diseased subjects compared to the control groups. However, levels of Zn were elevated in both EPI patients and controls when Zn dipicolinate was administered. Both studies proposed that picolinic acid, found in Zn dipicolinate, improves intestinal absorption of Zn due to its chelating capabilities. Finally, Easley *et al*, in cross-sectional study, observed reduced Zn fractional absorption in 8 subjects with EPI, but found that PERT improved this impaired Zn absorption. This suggests that the unabsorbed macronutrients may interfere with the intestinal absorption of Zn^[22]. However, the type of PERT utilized in the study was not reported.

Studies not showing an association between Zn status and EPI

Two studies included in this systematic review found no association between EPI and Zn status. One of the earliest studies included in this review was a cross-sectional study^[23]. This study included 13 children with cystic fibrosis with EPI who were all on PERT. The researchers found no significant difference in mean serum Zn concentrations in subjects with EPI vs. controls. Also, urinary Zn excretion was normal in 12 out of the 13 patients.

A similar case-control study included 117 patients with cystic fibrosis on PERT^[24]. However, not all participants underwent a fecal fat test to assess for EPI. Only 98 participants of the total 117 were tested. Of the 98 tested, 93% were found to have steatorrhea. The study defined steatorrhea as fecal fat > 6 grams per day and feces were only collected for 2 days. To be noted, current guidelines regarding fecal fat testing define abnormal results as fecal fat > 7 grams per day using a 3 day collection^[2]. With a lower threshold for fecal fat determination and the use of PERT, Kelleher *et al* found no correlation between the severity of fat malabsorption and serum Zn levels^[24].

DISCUSSION

The current systematic review evaluated 13 studies that looked to assess Zn status in EPI. The quality of studies was assessed using the specific Newcastle-Ottawa scale based on the type of study design. Since none of the studies were randomized, controlled trials, no studies were given a high quality score. Most of the included observational studies were given a lower quality score (Table 1). Also keeping in mind, quality summary scores may mask variations in quality by study design. Direct comparisons between study designs may not be analogous.

Strengths

A strength of the current study is the extensive literature search that was performed. Most of the included studies used qualitative measures which was a strength. Seven studies used a control group, giving strength to their findings^[12-15,18,21,24].

Limitations

There were several limitations in this systematic review. Considering the heterogeneity of the studies included in this review, the findings should be considered with caution. The observational design of all included studies is a weakness. In addition, retrospective and case-control studies are vulnerable to selection bias. In addition, some studies did not have a control group^[16,17,19,20,22,23]. The fact that there is not a universally accepted measure of zinc status currently available for humans points out an obvious weakness for included studies^[25]. Another source of potential weakness is that not all of the studies included in this review used the same parameters to diagnosis EPI (Table 1). In addition, some studies did not report if the participants

were taking PERT, while some studies utilized PERT and others did not. The use of PERT in this situation is an important confounding variable. Many studies included in this review did not identify explicit ways to reduce bias, leading to another potential weakness.

The fecal elastase-1 test used in some studies to diagnose EPI and its severity is not very sensitive in mild and moderate cases. Therefore this test may have led to potential spectrum bias, since these mild and moderate cases may have not been included^[26]. Studies that used fecal elastase-1 to diagnose EPI may have underestimated the true prevalence of EPI and thus the understanding of Zn status in this disease state^[14,16,17,20]. In addition, the sample size for most of the included studies was less than 100, which contributes to the studies' limitations.

Clinical Implications

Considering the heterogeneity of the current included studies in this review, larger and more homogenous studies are likely necessary to confirm Zn status in EPI. Additional studies have further confirmed Zn deficiency in disease states at high risk for EPI; however, these studies were not included in this review, because the EPI diagnostic assay was not defined. These studies highlight an additional factor to explain zinc status besides intestinal malabsorption and increased Zn loss associated with steatorrhea. Watson *et al.*^[27] and Damphousse *et al.*^[28] mentioned an association between a lower percentage of lean body mass and decreased Zn status, as the majority of Zn is found in muscle tissue. Nonetheless, the body of evidence surrounding Zn status in this population should be bolstered. Clinicians need a better understanding of whether Zn supplementation in this population is warranted or is adequately dosed PERT sufficient enough to maintain sufficient Zn status. Future studies should be carried out in a case-control design, ensuring the diagnosis and severity of EPI while controlling for confounders such as PERT use. Also in these studies, a measurement tool of Zn should not be varied and be classified in an objective manner. Furthermore, since picolinic acid is thought to enhance Zn absorption due to its chelating capabilities, it would be interesting to assess the effects of Zn dipicolinate supplementation in the EPI population, as well as to assess baseline and 3-month follow-up levels of serum Zn upon supplementation. Overall, based on this review, the supplementation of Zn cannot be routinely recommended at this time.

CONCLUSION

In conclusion, this review suggests that EPI is associated with impaired Zn metabolism and abnormal Zn status. Clinicians dealing with EPI should be aware of clinical manifestations of Zn deficiency while ensuring adequacy of PERT use and dietary Zn intake. Further research is needed to better investigate Zn metabolism in EPI. The true effectiveness of Zn supplementation in this setting and the type of Zn supplementation should be explored. Based on this review, Zn supplementation cannot be routinely recommended.

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