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ORIGINAL ARTICLE

Retrospective Cohort Study

Zinc deficiency in patients with chronic pancreatitis

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Abstract

BACKGROUND

Zinc is a key element in numerous proteins and plays an important role in essential cell functions such as defense against free radicals and DNA damage repair. Chronic pancreatitis (CP) is a chronic inflammation with progressive fibrosis of pancreas ultimately resulting in pancreatic exocrine insufficiency (PEI), which is associated with malnutrition. Studies analyzing zinc levels in patients with CP are sparse and lead to conflicting results.

AIM

To investigate serum zinc levels in patients with CP of various etiologies.

METHODS

Between October 2015 and March 2018, patients with a diagnosis of CP were identified and recruited from the Pancreatic Outpatient Clinic at the Karolinska University Hospital in Stockholm, Sweden. Demographic, clinical and laboratory data were analyzed. Etiology of CP was determined according to the M-ANNHEIM classification system into the following etiological subcategories: alcohol consumption, nicotine consumption, hereditary factors, efferent pancreatic duct factors and immunological factors. Pancreatic exocrine function

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was defined as normal (fecal elastase 1 > 200 μg/g), mildly reduced (100-200 μg/g) and severely reduced (fecal elastase 1 < 100 μg/g).

RESULTS

A total of 150 patients were included in the analysis. Zinc deficiency (< 11 μmol/L) was present in 39 (26.0%) of patients: 22 females and 17 males. In the group of patients with zinc deficiency, 76.7% of patients had an exocrine pancreatic insufficiency (FE-1 < 200 μg/g). Older age was significantly associated with low zinc levels. Following a univariate analysis, patients aged 60-69 and patients ≥ 70 years of age had a significantly higher prevalence of zinc deficiencies compared to patients < 40 years of age [OR: 3.8, 95%CI (1.08-13.4); P = 0.04]; [OR 6.26, 95%CI (1.94-20.2), P > 0.002]. Smoking and number of pack-years were additionally associated with low zinc levels. The risk of zinc deficiency in current smokers and smokers with ≥ 20 pack-years was approximately three times higher compared to those who had never smoked. Gender, body mass index, etiology of CP, presence of diabetes mellitus, levels of glycated hemoglobin (HbA1c), bone mineral density, alcohol intake and presence of PEI were not associated with low zinc levels.

CONCLUSION

Zinc deficiency is common in patients with CP and is significantly associated with age ≥ 60, smoking and the number of pack-years, but not with PEI.

Key words: Zinc; Pancreas; Pancreatic exocrine insufficiency; Chronic pancreatitis; Malnutrition

Core tip: Normal levels of zinc are pivotal to maintain a homeostasis in a wide variety of important cellular systems and immune response. Chronic pancreatitis (CP) is a chronic inflammation of the pancreas resulting in pancreatic exocrine insufficiency, which is associated with malnutrition. There are conflicting published results of zinc levels in patients with CP. Most of the studies were restricted to patients with alcoholic etiology of CP and had limitations due to the small number of studied patients. We are presenting the results of the largest study so far comparing serum zinc levels in relation to different etiological groups of CP.

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INTRODUCTION

Zinc is a key element in numerous proteins and plays an important role in essential cell functions such as defense against free radicals and DNA damage repair[1]. Approximately 10% to 40% of dietary zinc is absorbed in the small bowel and 0.5 to 1.0 mg/day is secreted into the biliary tract followed by passing the small and large bowel[2]. Pathophysiology of zinc deficiency in patients with chronic pancreatitis (CP) is not fully elucidated. It has been proposed that decreased secretion of binding proteins in the pancreatic juice explain compromised absorption of zinc in pancreatic exocrine insufficiency (PEI)[3]. Zinc deficiency may be the effect of reduced absorption and can be a contributory factor in disease progression, *via* the reduction of free radicals[4]. It is known that zinc affects many aspects of the immune system, from the barrier of the skin to gene regulation in lymphocytes, and is crucial for development and function of neutrophils and natural killer cells[5].

There are conflicting published results of zinc levels in patients with CP[6]. Most of the studies included only patients with alcoholic etiology of CP and small number of patients. We are presenting the results of the largest study so far comparing serum zinc levels in patients with CP of various etiologies.

MATERIALS AND METHODS

Patients and methods

Between October 2015 and March 2018, patients with a diagnosis of CP were identified from a database maintained by the Pancreatic Outpatient Clinic at Karolinska University Hospital in Stockholm, Sweden. Demographic, clinical and laboratory data were analyzed. Alcohol intake was recorded, including the number and type of drinks per week and the frequency of consumption.

Smoking status was recorded as current/former/never. For former or current smokers, the number of cigarettes per day over a given number of years was recorded, and pack-years were calculated accordingly. Etiology of CP was determined according to the M-ANNHEIM classification system as: alcohol, nicotine, hereditary, efferent pancreatic duct and immunological factors[7]. Levels of fecal elastase-1 (FE-1) > 200 μg/g, 100-200 μg/g and < 100 μg/g were considered as normal pancreatic exocrine function, mild PEI and severe pancreatic insufficiency, respectively[8]. Zinc was analyzed in serum or plasma on a Cobas C system, Roche Diagnostics, Mannheim, Germany using a colorimetric assay from Sentinel Diagnostics, Milan, Italy. Zinc levels of 11-17 μmol/L were considered as normal.

Statistical analysis

The frequency of zinc deficiency was tabulated according to patients' characteristics. Logistic regression was used to assess the association between patients' characteristics and the presence of zinc deficiency. Factors showing statistical significance at univariable analysis were subsequently included in a multivariable model. Analyses were performed using the SAS software (version 9.4, Cary, NC, United States). All tests were two-sided and *P*-values < 0.05 were considered statistically significant.

Ethics

The study was approved by the Stockholm Ethic Committee (SLL), numbers 2014/1094-31, 2016/491-3172 and 2016/1571-31.

RESULTS

In the observed period, 226 patients with CP were diagnosed. In 76 patients zinc results were not available and these patients were excluded from analysis. A total of 150 patients were included in the analysis. Zinc deficiency (< 11 μmol/L) was present in 39 (26.0%) of patients: 22 females and 17 males. In the group of patients with zinc deficiency, only 23.3% of patients had normal FE-1. Demographic data are presented in Table 1.

Age ≥ 60 years was significantly associated with low zinc levels. Following a univariate analysis, patients aged 60-69 and patients ≥ 70 years of age had a significantly higher prevalence of zinc deficiency compared to patients < 40 years of age [OR: 3.8, 95%CI (1.08-13.4); $P = 0.04$]; [OR 6.26, 95%CI (1.94-20.2), $P > 0.002$]. Smoking and number of pack-years were additionally associated with low zinc levels. The risk of zinc deficiency in current smokers and smokers with ≥ 20 pack-years was approximately three times higher compared to those who had never smoked. Gender, body mass index (BMI), etiology of CP, presence of diabetes mellitus (DM), levels of glycated hemoglobin (HbA1c), bone mineral density, alcohol intake and presence of PEI were not associated with low zinc levels (Table 1). The associations with age and smoking were confirmed to be statistically significant in a multivariable analysis (Table 2).

DISCUSSION

Normal levels of zinc, an essential mineral and trace element, are pivotal to maintain a homeostasis in a wide variety of important cellular systems and immune response[1,5]. In this large study of 150 patients with CP, one in four patients was shown to have a zinc deficiency. CP is a chronic inflammation of the pancreas triggered by various factors including alcohol misuse, smoking, autoimmunity, anatomical variants and genetic factors. Due to progressive fibrosis and destruction of the pancreas, both enzyme and insulin production ultimately become severely impaired, resulting in pancreatic exocrine and endocrine insufficiency. Deficiency of enzymes (exocrine insufficiency) leads to maldigestion and malnutrition which are associated with reduced absorption of fat-soluble vitamins. The essential role of zinc and its deficiency was described in 1963[9]. There is accumulating evidence that different patient groups

Table 1 Factors associated with low zinc levels in patients with chronic pancreatitis (*n* = 150)

	Total, *n*	Zinc		Univariable analysis	
		≥ 11 μmol/L, *n*	< 11 μmol/L, *n* (%)	OR (95%CI)	*P* value
All patients	150	111	39 (26.0)		
Age					
0-39	43	38	5 (11.6)	1.00	
40-49	18	13	5 (27.8)	2.92 (0.73-11.7)	0.13
50-59	34	27	7 (20.6)	1.97 (0.57-6.87)	0.29
60-69	24	16	8 (33.3)	3.80 (1.08-13.4)	0.04
70+	31	17	14 (45.2)	6.26 (1.94-20.2)	0.002
Gender					
Female	86	64	22 (25.6)	1.00	
Male	64	47	17 (26.6)	0.95 (0.46-1.99)	0.89
Body mass index					
Underweight	12	9	3 (25.0)	0.74 (0.18-2.96)	0.67
Normal weight	77	53	24 (31.2)	1.00	
Overweight	38	30	8 (21.1)	0.59 (0.24-1.47)	0.26
Obese	20	16	4 (20.0)	0.55 (0.17-1.83)	0.33
Etiology					
Alcohol	40	27	13 (32.5)	1.00	
Autoimmune	45	32	13 (28.9)	0.84 (0.34-2.13)	0.72
Efferent duct factors	11	8	3 (27.3)	0.78 (0.18-3.43)	0.74
Smoking	15	11	7 (38.9)	1.32 (0.42-4.20)	0.64
Hereditary	18	14	1 (6.7)	0.15 (0.02-1.25)	0.08
Idiopathic	21	19	2 (9.5)	0.22 (0.04-1.08)	0.06
Diabetes					
No	108	82	26 (24.1)	1.00	
Yes	42	29	13 (31.0)	1.41 (0.64-3.11)	0.39
Diabetes treatment					
No diabetes	108	82	26 (24.1)	1.00	
Diet	3	3	0 (0.0)	-	0.99
Per oral	7	5	2 (28.6)	1.26 (0.23-6.89)	0.79
Insulin	32	21	11 (34.4)	1.65 (0.70-3.88)	0.25
HbA1c					
Normal	9	7	2 (22.2)	1.00	
Elevated	30	21	9 (30.0)	1.50 (0.23-6.02)	0.65
Bone mineral density					
Normal	41	30	11 (26.8)	1.00	
Osteopenia	14	10	4 (28.6)	1.09 (0.28-4.21)	0.90
Osteoporosis	5	2	3 (60.0)	4.09 (0.60-27.8)	0.15
Smoking					
Never	76	62	14 (18.4)	1.00	
Former	25	19	6 (24.0)	1.40 (0.47-4.14)	0.54
Current	48	29	19 (39.6)	2.90 (1.28-6.58)	0.01
Smoking pack-years					
Never	76	62	14 (18.4)	1.00	
1-19 pack-years	21	16	5 (23.8)	1.38 (0.43-4.41)	0.58
≥ 20 pack-years	51	31	20 (39.2)	2.86 (1.27-6.41)	0.01
Alcohol					
No	105	81	24 (22.9)	1.00	
< 30g	13	8	5 (38.5)	2.11 (0.63-7.05)	0.23
≥ 30g	31	21	10 (32.3)	1.61 (0.67-3.88)	0.29
Pancreatic exocrine insufficiency					
No	60	46	14 (23.3)	1.00	

Mild/moderate	14	11	3 (21.4)	0.90 (0.22-3.67)	0.88
Severe	66	45	21 (31.8)	1.53 (0.70-3.38)	0.29

OR and 95%CI obtained from univariable logistic regression model; OR: Odds ratios; CI: Confidence intervals; HbA1c: Levels of glycated hemoglobin.

are at risk of developing zinc deficiency[10]. Zinc is not stored in the body, and the level of zinc is determined by the balance of dietary intake, absorption, and losses[11].

Results of studies on zinc levels in patients with CP have been controversial. Van Gossum *et al*[12] reported no difference in serum zinc levels when comparing 35 alcoholic CP patients with healthy controls. Similar results were noted in 32 pediatric patients with cystic fibrosis and PEI determined either at the time of diagnosis or one year later[13]. However, both studies were performed either in a small group of patients or in children with a short duration of PEI. In contrast, Lindkvist *et al*[14] found 7.1% of zinc deficiency among 56 patients, mostly with alcoholic etiology. In a group of 101 patients from India with alcoholic and tropical etiology of CP, erythrocyte zinc levels were significantly reduced in CP compared to controls, and zinc levels were significantly lower in patients with tropical CP compared to alcoholic etiology[4].

Our study is the first to determine zinc levels in patients with CP based on all known key etiologies of CP (alcohol, autoimmune, efferent duct factors, idiopathic and hereditary). Zinc was shown to be deficient in 26% of patients regardless of CP etiology. Interestingly, zinc deficiency was present in patients with and without PEI as reported by others, suggesting that impaired secretion of pancreatic enzymes is not the main factor resulting in a reduced absorption or increased excretion of zinc[14]. Due to the lower sensitivity of the fecal elastase-1 test for diagnosing mild and moderate forms of CP, the true prevalence of PEI may be underestimated suggesting that a number of CP patients are misclassified as not having PEI[15]. However, zinc deficiency was even noted in CP patients in which PEI was excluded by a ^{13}C-mixed triglyceride breath test which has a higher sensitivity for detecting PEI compared to a standard fecal elastase-1 test[14].

Pancreatic endocrine insufficiency with DM has been identified as an independent risk factor for zinc deficiency in a previous study of CP patients[4]. However, in our study this correlation was not confirmed. This difference can be explained by different patient numbers and different etiologies (*e.g.*, tropical CP has a faster progression with an earlier onset of DM)[4].

Smoking and number of pack-years were correlated with low zinc levels in our patient cohort, and the risk of zinc deficiency in current smokers and smokers with ≥ 20 pack-years was approximately three times higher compared to those who had never smoked. In a large study from France with the inclusion of 1821 women and 1307 men aged 45-60 years, zinc serum levels were significantly reduced in women who were current smokers but not men[16]. Others found reduced seminal zinc levels in smokers, which was associated with oxidative stress reduced DNA integrity and diminished sperm vitality[17].

We were also able to demonstrate a correlation between BMI and zinc values. The lack of other anthropometric parameters such as grip strength, triceps skin-fold thickness and mid upper arm circumference is a limitation of the study, as these parameters are established methods for identifying patients with malnutrition. Apart from serum markers of malnutrition, BMI was recorded which represents a further parameter indicating malnutrition (< 18.5 kg/m^2)[6]. Numerous studies indicate that zinc deficiency has a strong effect on key immunological functions, and zinc deficiency has been shown to increase the risk of infectious diseases[5]. Zinc deficiency results not only in decreased lymphocyte concentrations but also in depressed T and B lymphocyte function[5]. It has been shown that zinc deficiency *in vivo* increase oxidative stress increase DNA damage in rat peripheral blood cells[1]. However, the exact mechanisms by which zinc deficiency affects DNA damage is not elucidated. Several studies have demonstrated the benefits of zinc supplementation in patients with infectious diseases[5]. A Cochrane review included six studies with a total of 5193 children (2-59 mo of age) and evaluated the role of zinc in the prevention of pneumonia. Zinc supplementation was associated with a reduced incidence rate of pneumonia[18]. Another meta-analysis including 22 studies demonstrated that zinc supplementation reduces the duration and severity of acute and chronic diarrhea in children in developing countries[11].

Furthermore, epidemiological studies reveal an association between low circulating zinc concentrations and increased risk of cancer[19,20]. The relationship between serum zinc and cancer mortality appeared to be nonlinear with a significantly reduced risk for people with higher zinc values, according to a US national survey including 3000

Table 2 Multivariable analysis of risk factors for low zinc levels in chronic pancreatitis (*n* = 150)

	Multivariable analysis	
	OR (95%CI)	*P* value
Age		
0-39	1.00	
40-49	2.82 (0.68-11.7)	0.15
50-59	1.30 (0.34-4.91)	0.70
60-69	2.64 (0.69-10.1)	0.16
70+	6.30 (1.87-21.3)	0.003
Smoking		
Never	1.00	
Former	0.99 (031-3.17)	0.98
Current	3.14 (1.23-8.02)	0.02

OR and 95%CI obtained from multivariable logistic regression model; OR: Odds ratios; CI: Confidence intervals.

men and 3244 women[19]. It is largely unknown how zinc may modulate the chronic inflammatory process in the pancreas in CP patients. A positive correlation between erythrocyte zinc and erythrocyte superoxide dismutase activity suggests connection between zinc deficiency and oxidative stress in CP and is another possible mechanism by which zinc deficiency may impact on the pathogenesis of CP and its complications[4]. Of note, it is well established that CP harbors the risk of pancreatic cancer. Future studies are needed to establish whether the risk of malignant transformation in CP patients is increased by zinc deficiency by triggering DNA damage and oxidative stress. Both mechanisms are implicated in carcinogenesis.

Assessing zinc levels in the plasma represents a limitation of the present study. Measuring zinc in erythrocytes has the advantage of reflecting the zinc status over a longer period compared to the rapid turnover of the plasma pool of zinc[19,20]. However, the high number of analyzed patients, a well-balanced ratio of male and female patients together with the inclusion of patients with a large array of different CP etiologies represents a strength of this study.

In conclusion, this is the first study to analyze the prevalence and risk factors of zinc deficiency in a large number of patients with different etiologies of CP. According to our data, zinc deficiency is relatively common in patients with CP and is significantly associated with higher age, smoking and the number of pack-years. Further studies are warranted to better define how zinc modulates chronic pancreatic inflammation in patients with CP.

ARTICLE HIGHLIGHTS

Research background

Malnutrition with deficiencies of fat-soluble vitamins, minerals and trace elements are well-known consequences of maldigestion and poor absorption of nutrients. Malnutrition has been frequently identified in patients with chronic pancreatitis (CP) and pancreatic exocrine insufficiency (PEI). Zinc is important for normal functioning of immune system and its deficiency was recognized more than 50 years ago. Studies analyzing zinc levels in patients with CP are sparse and lead to conflicting results. However, studies analyzing zinc levels in patients with CP are sparse and most of them included only patients with alcoholic etiology. In this study, prevalence and risk factors of zinc deficiency in a large number of patients with different etiologies of CP were determined.

Research motivation

The main topic was zinc insufficiency and its relation to patients' demographic and clinical parameters: Gender, age, smoking, alcohol intake, body mass index (BMI), diabetes mellitus (DM), bone mineral density, PEI and etiology of CP.

Research objectives

In this large study of 150 patients with CP, one in four patients was shown to have a zinc deficiency, which was the main objective. Zinc deficiency was not related to gender, BMI, etiology of CP, presence of DM, bone mineral density and alcohol intake. It is of significance that zinc deficiency was present in patients with and without PEI, suggesting that impaired secretion of pancreatic enzymes is not the main factor resulting in a reduced absorption or increased

excretion of zinc. These objectives should be better analyzed in future research in this field.

Research methods

We performed retrospective analysis of demographic, clinical and laboratory data, with detailed information on alcohol intake and smoking status. For former or current smokers, the number of cigarettes per day over a given number of years was recorded, and pack-years were calculated accordingly. Results showed that smoking status was very important in this study: Number of pack-years was correlated with low zinc levels and the risk of zinc deficiency in current smokers and smokers with ≥ 20 pack-years was approximately three times higher compared to those who had never smoked.

Research results

We showed that zinc deficiency is significantly associated with higher age, smoking and the number of pack-years. On the other hand, zinc deficiency was not related to gender, BMI, etiology of CP, presence of DM, bone mineral density, alcohol intake and presence of PEI. The fact that zinc deficiency was present in patients with and without PEI is very important. Future studies on this topic are necessary for better understanding of mechanisms included in zinc insufficiency.

Research conclusions

This is the first study to analyze the prevalence and risk factors of zinc deficiency in a large number of patients with different etiologies of CP. One in four patients was shown to have a zinc deficiency. There is significant association of zinc deficiency with higher age, smoking and the number of pack-years. We showed no correlation of zinc deficiency with gender, BMI, etiology of CP, presence of DM, bone mineral density, alcohol intake and presence of PEI. Due to the lower sensitivity of the fecal elastase-1 test for diagnosing mild and moderate forms of CP, the true prevalence of PEI may be underestimated. Future studies with ^{13}C-mixed triglyceride breath test, which has a higher sensitivity for detecting PEI compared to a standard fecal elastase-1 test, can help us to solve this problem.

Research perspectives

Assessing zinc levels in the plasma represents a limitation of the present study. Future studies with measuring of zinc in erythrocytes can be of interest due to the advantage of reflecting the zinc status over a longer period compared to the rapid turnover of the plasma pool of zinc. Impaired secretion of pancreatic enzymes is probably not the main factor resulting in a reduced absorption or increased excretion of zinc. Future studies on this topic are necessary. The results from the present study suggest that zinc deficiency is relatively common in patients with CP. Clinicians dealing with CP, regardless of etiology, should be aware of the clinical importance of zinc malnutrition, especially in older patients and smokers.

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