

Dear editor,

We would like to thank you and the reviewers for valuable comments.

We performed corrections in the text according to reviewers' comments.

Please find enclosed answers:

Reviewer #1: The manuscript is well-written, and the conclusions supported by results of the study.

Authors' answer: Thank you very much for your opinion.

Reviewer #2: Although a much-debated issue, this article is thorough, well-designed and written. Language-wise is fluent, precise and easy to read. Perhaps a couple of editing errors are there (e.g. page 10 - "zing deficiency's been shown to decrease the risk of infectious diseases" but this does not change the overall excellent presentation. My understanding is that the etiology and effect of zinc deficiency is far from being clear. An interesting finding is in table 1, where 20-39 pack-years are significantly associated, but >40 are not. Nevertheless, it is worth reading

Authors' answer:

Thank you very much for noticing editing error at page 10 – we made corrections in the text. We agree that etiology and effect of zinc deficiency is not fully elucidated, and we hope that our future studies on this topic (related to chronic pancreatitis) will help in better understanding.

The fact that the association for >40 pack-years is not significant is mainly due to the lower number of patients in that group. The association is still of “Borderline” significance with P=0.06 and with the 95% Lower confidence interval very close to 1.

Lack of significance does not imply lack of association: The OR is 2.66 and is very similar to that observed for 20-39 packs (3.05). This means that the risk for those who smoked >40 pack-year is about the same as that of those who smoked 20-39 PY (note that the median PY consumption in the group of 24 subjects (>40 pack-year) is just 45 pack-year).

This is why we merged the two categories that increased the statistical power, and gave the same message:

New table

	Total	Zinc		Univariable analysis	
		≥11 μmol/L	<11 μmol/L		
	N	N	N (%)	OR (95% CI)	P-value
All patients	150	111	39 (26.0)		
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

Original table

	Total	Zinc		Univariable analysis	
		≥11 μmol/L	<11 μmol/L		
	N	N	N (%)	OR (95% CI)	P-value
All patients	150	111	39 (26.0)		
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
20-39 pack-years	27	16	11 (40.7)	3.05 (1.16-7.97)	0.02
≥40 pack-years	24	15	9 (37.5)	2.66 (0.97-7.29)	0.06

Reviewer #3: 1. Please expand on the diagnostic criteria for chronic pancreatitis in this study. 2. What were the symptoms in the patient group 3. What were the other co-morbid states in the cohort ? 4. Any co-relation between the other co-morbid states and zinc levels ? 5. What were the medications in the cohort ? Any co-relation between drugs and zinc levels ? How many patients were on proton pump inhibitors ? 6. Any co-relation with dose of pancreatic enzymes and zinc levels ?

Authors' answer:

1. Etiology of chronic pancreatitis was determined according to the M-ANNHEIM classification system and we divided all patients in one of the following etiological subgroups: alcohol (according to patients' history from the medical charts), nicotine (according to patients' history from the medical charts), hereditary factors (genetic mutations in genes PRSS1, SPINK1, CFTR, CTSC), exocrine pancreatic duct factors (according to results of endoscopic ultrasound and/or magnetic resonance imaging and conclusions of multidisciplinary pancreas team that consists of radiologists, surgeons, pathologists and gastroenterologists from our center) and immunological (autoimmune pancreatitis type 1 and type 2 according to International Consensus Diagnostic Criteria; ICDC 2010).

2. Symptoms were as usual in patients in chronic pancreatitis: abdominal pain. In patients with genetic mutations recurrent acute pancreatitis and progress in chronic pancreatitis were common and in the patients with autoimmune pancreatitis obstructive icterus together with abdominal pain was dominant symptom. We did not emphasize the details in the manuscript because it was not the major scope.

3,4,5: Approximately one third of all patients with chronic pancreatitis the patients had diabetes mellitus. We do not have precise data on other comorbidities. This is the topic of our study that is currently ongoing: we are analyzing co-morbidities, possible connection with

surgical operations in the past, drugs used (not just PPI but also ASA, statins and different types of diabetes therapy) and effect of pancreatic enzymes.

6. we could not find any correlation because we include the very first level of zinc in serum and it is usual before the start of the enzyme therapy. Just like in the previous point, we are analyzing connection between enzyme therapy and doses in relation to zinc levels and its normalization after the treatment. The present study was important as a basis for further studies on this topic. We probably need 1-2 years for finishing the ongoing studies that will hopefully elucidate better the role of zinc deficiency. We are thankful for reviewer on the questions/tips and we agree on the topics, however, at present but now we are not able to answer these questions.

Reviewer #4: Zinc deficiency has not received enough attention in previous chronic pancreatitis. This study in this area is more systematic, revealing to the reader the reasons for possible zinc deficiency in patients with chronic pancreatitis, which is conducive to the next study. The sample size of this study is sufficient. But the research float on the surface and is just a general summary report. There is no deep mechanism for the cause of zinc deficiency in CP patients. The main causes of zinc deficiency are inadequate intake, increased dysfunction and loss. Whether the CP patients included in the study excluded all other factors that may cause zinc deficiency, the author needs to inform the reader of the above information. In short, it is recommended to publish this article after minor repairs.

Authors' answer: We absolutely agree with the comments. It was very important for us as a starting point for further studies and hopefully motivate other study groups to continue on the same topic. We performed a study in a large group of patients and what is more important on various etiologies. Now we know that this problem exists not just in the patients with alcoholic etiology but also in other etiologies. We did not find any other causes of zinc deficiencies. We are currently working on a study that maybe give us some more answers (larger group, connection with the surgery, connection to inflammation and morbidity/mortality in the longer follow up of patients with chronic pancreatitis.

With kind regards!

Miroslav Vujasinovic