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Article

Estimation of some vital trace elements in patients with acute pancreatitis: A case-control study

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Trace elements have an important influence on the living system and play a major role in a variety of processes necessary for life. This case study was conducted as an attempt to expand our knowledge of the relationship between trace elements and their effect on acute pancreatitis. Sixty-five patients diagnosed with acute pancreatitis with mean age 43.6 years, along with sixty-five healthy volunteers with a mean age 45.7 years, were included in this study. The obtained results indicated a significant increase in the Cu, Ni and Cr levels, and a significant decrease in the Zn, Mg and Fe levels for acute pancreatitis patients compared with the control group ($p < 0.001$). In addition, a remarkable increase in the Cu/Zn ratio was observed in patients. The current work provides important evidence of correlation between changes in copper and zinc levels and the risk of acute pancreatitis. Also, an increased Cu/Zn ratio may be a useful indication for the diagnosis and monitoring of acute pancreatitis. Moreover, the current study concluded that there is a possible relationship of Mg, Fe, Ni and Cr with acute pancreatitis. Thus, it can be suggested that these elements are reliable to provide indications for warning of the risk of acute pancreatitis.

Keywords: Trace elements. Acute pancreatitis. Cu. Zn. Ni. Cr.

INTRODUCTION

Pancreatitis is a generic term used to refer to a common status marked by inflammation of the pancreas that can be either acute or chronic (Grendell, 1994). In acute pancreatitis, a sudden appearance of inflammation occurs causing varying degrees of damage to the pancreatic tissue and occasionally to nearby organs. The inflammatory attack quickly develops but gradually subsides after a few weeks (Rawla, Bandaru, Vellipuram, 2017). Two main causes of acute pancreatitis have been extensively investigated, those are: blocking of the common bile duct by gallstones and heavy alcohol consumption (Carter, 1993; Yadav *et al.*, 2009). Besides, various causes have also been pointed out such as some medications (Jones *et al.,* 2015), infections (Rawla, Bandaru, Vellipuram, 2017), and trauma (Debi *et al.,* 2013).

Acute pancreatitis is a common non-bacterial disease worldwide caused by stimulation, interstitial liberation, and auto-digestion of the pancreas by its own enzymes (Karne and Gorelick, 1999). The process may or may not be accompanied by permanent morphologic and functional changes in the gland. Much is known about the causes of pancreatitis, but despite the accumulation of a considerable amount of experimental data, the understanding of the pathogenesis of this disorder remains incomplete (Norman, 1998; Karne and Gorelick, 1999).

Trace elements are a set of elements that account for approximately 0.02% of the total body weight, yet, they make a substantial contribution to biological systems at various levels (different cell functions) (Al-Fartusie and Mohssan, 2017). It has been shown that some trace elements are involved in the activation of many proteins including pancreatic enzymes as they play a crucial role

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in their stabilization and normal functioning (Clayton, 1980). It has been suggested that the development of pancreatitis is related to iron stores (Herbert *et al.,* 1994); consequently, some experimental works have been carried out to examine the relationship between the incidence of the disease and different measurements of trace elements (Kashiwagi *et al.,* 1995; Ilbäck *et al.,* 2003).

Trace elements have been found to play an important role in a variety of cellular processes necessary for the human body, such as DNA synthesis, cellular immunity, antioxidant defense against the action of reactive oxygen species (ROS), and cell growth (Al-Fartusie and Mohssan, 2017). Moreover, metal ions are required as active ingredients of several proteins, including pancreatic enzymes. The most obvious is iron and its function as a part of the proteins involved in the transport of molecular oxygen (Clayton, 1980). Zinc is involved in zinc-dependent metal enzymes such as alcohol dehydrogenase, thymidine kinase and Cu/Zn superoxide dismutase (Prasad, 1995; Prasad, 2013). Likewise, copper is an integral part of copper-based metalloenzymes such as cytochrome oxidase, NADH dehydrogenase-2 and Cu/Zn superoxide dismutase. Cu is a part of the antioxidant barrier against the negative impact of oxidative stress and plays a role to stabilize cell membranes (Milne, 1994; Osredkar, Sustar, 2011).

The premature activation of digestive enzymes along with their retention in the pancreas irritates acinar cells and triggers the inflammation which raises a question about the potential role of trace elements in the pathogenesis of acute pancreatitis. Recently, many studies have focused on exploring and understanding the potential relationship between trace elements and some diseases such as toxoplasmosis, severe depression, and pancreatic cancer (Farzin *et al.,* 2013; Al-Fartusie *et al*., 2019a, Al-Fartusie *et al*., 2019b. In fact, the mechanism by how trace metals play roles in the etiology of acute pancreatitis is still unclear. On the other hand, the change in enzymatic activity and its correlations with element concentrations are well documented, even in the early phase of acute pancreatitis (Ferahman *et al.,* 2003). Hence, the aim here is to investigate the serum levels of copper (Cu), zinc (Zn), magnesium (Mg), iron (Fe), nickel (Ni) and chromium (Cr) of acute pancreatitis. With this aim in mind, in this paper, we present new useful information that help to further evaluate the role of trace elements in the pathogenesis of acute pancreatitis.

MATERIAL AND METHODS

Patients and Controls

This study was conducted between February, 2019 and December 2019 in the Chemistry department/ College of Science/ Mustansiriyah University in cooperation with the Poison Centre at Medical City/ Ministry of Health, Baghdad, Iraq. This research included sixty-five males of patients diagnosed with acute pancreatitis with ages of 35 to 58 (mean age 43.6 years) along with sixty-five males of healthy volunteers as the control group, with ages 35 to 60 years (mean age 45.7 years). Patient samples were collected from Baghdad Teaching Hospital, Baghdad, Iraq. Patients were diagnosed with acute pancreatitis by specialized hospital physicians. The collected samples' exclusion criteria included family history, smoking, drinking alcohol, hyper- and hypotension, diabetes mellitus, and taking nutritional supplements. Moreover, the healthy volunteer group was also subjected to the same procedures and exclusion criteria for acute pancreatitis patients.

Sample collection, preparation, and analytical methods

Blood samples were collected from all patients with acute pancreatitis and control volunteers. From each individual, 10 ml of blood were drawn through a vein puncture with disposable syringes. The blood samples were placed in gel tubes and allowed to clot at room temperature for 20-30 minutes. Sera were then separated from the coagulated blood by centrifuging at 2500 xg for 10 minutes, and the obtained sera were immediately transferred to another set of test tubes and kept frozen at -20 ° C until the assay for trace elements.

In this research, Cu, Zn, Mg, and Fe levels in sera for all patients and control samples were determined using the atomic absorption spectrophotometer (FAAS, AA646 Model, Shimadzu Corporation, Kyoto, Japan). In addition, Ni and Cr serum levels were determined using the atomic absorption spectrophotometer (GFAAS, model 210VGP,

Buck Scientific, USA) (Elmer, 1996). For Cu, Zn and Fe measurements, the samples were diluted 10-fold with deionized distilled water (nanopure water (18.3 ° C)) and then analyzed at wavelengths 324.7 nm, 213.9 nm, and 248.3 nm respectively. To measure magnesium, the samples were diluted 50-fold with lanthanum (III) chloride heptahydrate and the assay was conducted at wavelength 285.2 nm. Serum levels were determined for both Ni and Mn directly by injection into the graphite tube for the flameless atomic absorption spectrophotometer at wavelengths 232 nm and 379.5 nm, respectively. The calculated detection limits for Cu, Zn, Mg, Fe, Ni and Cr were 0.003, 0.007, 0.004, 0.003, 0.001 and 0.001 µg/dl, respectively. Furthermore, the accuracy of the measurements was confirmed using a certified reference material, NIST SRM 909 trace elements in serum (National Institute of Standards and Technology (NIST), USA).

Statistical Analysis

The collected data were analyzed by SPSS, version 22.0, using descriptive statistics and the Independent-Samples Student t test. The mean values, standard deviation (SD), standard error (SE), range and probability (*p*) values were calculated for each variable included in the study. In addition, to determine the correlations between all study trace elements, Pearson correlation analysis was also performed. Statistical analysis was considered significant at $p < 0.05$, while it was considered highly significant at $p < 0.01$ with 95% confidence interval.

RESULTS AND DISCUSSION

The statistical analysis of the collected data is presented in Table I as mean, standard deviation, standard error, range, and probability (*p*) values. The calculated mean values of Cu, Zn, Mg, Fe, Ni and Cr in sera of control group were (119.91, 94.14, 140.16, 106.34, 0.132 and 0.148 µg/ dl) respectively, while the values calculated for the patients' group were (158.46, 71.52, 113.73, 48.79, 0.169 and 0.213 µg/ dl) respectively, as shown in Table I and represented in Figures 1 and 2.

TABLE I - Serum concentrations of trace elements Cu, Zn, Mg, Fe, Ni and Cr in µg/ dl for acute pancreatitis patients and control groups

Variable (µg/ dl)	sample	Mean	Std. Deviation	Std. Error	Range	*p* value
Cu	patient	158.46	8.29	1.02	143-172	<0.001
	control	119.91	14.70	2.59	96-141	
Zn	patient	71.52	9.75	1.20	55-91	<0.001
	control	94.14	9.28	1.64	83-112	
Mg	patient	113.73	12.85	1.59	88-141	<0.001
	control	140.16	18.20	3.21	112-174	
Fe	patient	48.79	17.44	2.16	20-78	<0.001
	control	106.34	21.14	3.73	68-143	
Ni	patient	0.169	0.051	0.007	0.10-0.27	<0.001
	control	0.132	0.026	0.004	0.09-0.19	
Cr	patient	0.213	0.032	0.003	0.16-0.30	<0.001
	control	0.148	0.025	0.004	0.11-0.19	

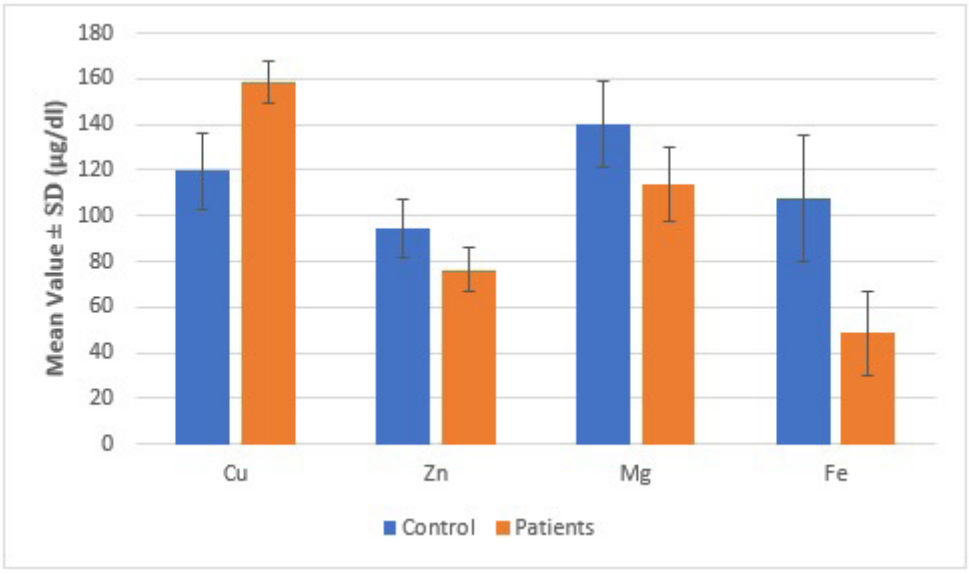

FIGURE 1 - Serum concentrations of Cu, Zn, Mg and Fe in acute pancreatitis patients in comparison with their concentrations in controls.

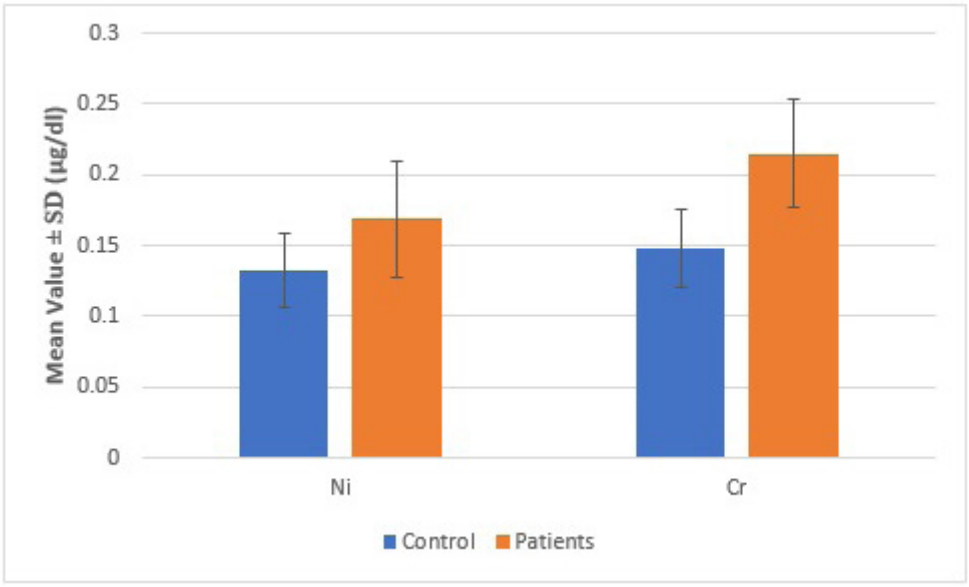

FIGURE 2 - Serum concentrations of Ni and Cr in acute pancreatitis patients in comparison with their concentrations in controls.

These results indicated that the differences in serum mean values of all variables between control and patients groups are highly significant (p<0.001). The results showed the presence of a highly significant increase in Cu, Ni and Cr levels, in contrast, a highly significant decrease in Zn, Mg and Fe concentrations was observed in the acute pancreatitis group in comparison with the control group, as shown in Table I.

The relationship between all parameters included in the present work was studied using Pearson's correlation analysis. The collective results are presented in Table II, where some statically important primary correlations were found between acute pancreatitis cases. The results showed that Cu was positively correlated with Ni and Cr, while negatively correlated with Zn and Mg. The statistical data analysis showed

that Zn was positively correlated with Mg, while negatively correlated with Ni and Cr. In addition, Mg was found to be negatively correlated with Ni and Cr, while Ni was found positively correlated with Cr. The analysis also revealed that there is no correlation between Fe levels and other elements.

TABLE II - Correlations coefficient between all variables in acute pancreatitis patients (r-value)

variable	Cu	Zn	Mg	Fe	Ni	Cr
Cu	1	-.853**	-.629**	-.140	.476**	.402**
Zn	-.853**	1	.702**	.096	-.584**	-.446**
Mg	-.629**	.702**	1	.229	-.459**	-.396**
Fe	-.140	.096	.229	1	.003	-.014
Ni	.476**	-.584**	-.459**	.003	1	.620**
Cr	.402**	-.446**	-.396**	-.014	.620**	1

** Correlation is significant at the 0.01 level (2-tailed).

In the present study, we used Cu and Zn as possible markers of pancreatic disorders. Where they can be easily assayed in the serum and their measurements are less expensive. The results demonstrated that there was a significant increase in serum Cu and a significant decrease in serum Zn (p <0.001) in acute pancreatitis patients compared with controls. This is consistent with what has been found in a previous study which documented higher Cu levels in chronic pancreatitis patients compared to controls (Girish *et al.,* 2009), but disagrees with the findings of other studies (Ferahman *et al.,* 2003) which documented lower Cu levels in patients with acute pancreatitis. Moreover, regarding Zn levels, the present findings agree with the results documented elsewhere (Ferahman *et al.,* 2003), which reported a significant decrease in Zn levels in patients with acute pancreatitis.

Alterations in Cu and Zn levels were the most important among all the trace elements analyzed here. Together, the present findings confirm and give important evidence for the association between alteration in Cu and Zn levels and the risk of acute pancreatitis. Therefore it could be suggested that high Cu levels associated with low levels of Zn may presumably interfere with the pathogenesis of acute pancreatitis. Bearing in mind to the protective role of copper and zinc against oxidative stress, where it was indicated that oxidative stress is one of the factors that affect pancreatic fibrogenesis, and therefore it is one of the main factors that influence the development of morphological changes in chronic pancreatitis (Shenkin, 2009; Marreiro *et al.,* 2017).

Zinc metalloenzymes are found almost everywhere in the body (McCall, Huang, Fierke, 2000). It is bound to carboxypeptidase in the pancreas. Zn is absorbed in the duodenum and proximal jejunum, and linked in the intestinal mucosa with metallothionine and carried by proteins in the blood to the liver and other tissues (Gjørup *et al.,* 1991). It has been found that 70-80% of the ingested Zn is excreted in saliva, sweat and urine. It has been shown that the pancreas cells have a high level of Zn, but the quantities secreted by the pancreas are unknown (Bosco *et al.,* 2015). Zinc deficiency and malabsorption have been described previously in patients with alcoholic pancreatitis and chronic pancreatitis (Girish *et al.,* 2009; Vujasinovic *et al.,* 2019). Moreover, it has been demonstrated that the secretion of copper is closely related to the secretion of zinc (Cunnane, 1982). A previous study has suggested that mineral metabolism, especially Cu and Zn, has contributed to the pathophysiology of the acute pancreas (Al-Khazraji, 2007). Furthermore, another

study has revealed a significant correlation between zinc metabolism and pancreatic cancer (Farzin *et al*., 2013).

A previous work has concluded that the Cu/Zn ratio might be a useful indicator for the diagnosis of chronic pancreatitis and pancreatic cancer compared to the levels of Cu or Zn separately (Vujasinovic *et al.,* 2019). In line with this, the current study records a remarked increase in the Cu/Zn ratio in patients with acute pancreatitis (2.07) compared to the control group (1.27). It is worth discussing these interesting facts revealed by current findings, and therefore we can suggest that the increased Cu/Zn ratio here may be a useful indication for the diagnosis of acute pancreatitis, and an indication of a weakening of the antioxidant defense system in patients, where a strong correlation has previously been reported between oxidative stress and the Cu/Zn ratio (Mezzetti *et al.,* 1998).

The current study shows that magnesium levels were higher in the healthy control group than in acute pancreatitis patients. These findings are consistent with those obtained by other authors who recorded low levels of magnesium among patients with acute pancreatitis (Ersil Soysal *et al.,* 2017). Indeed, it has been shown that a deficiency of magnesium affects many biological processes of the human body, and is accompanied by an increase in oxidative stress (Zheltova *et al.,* 2016). On this basis, it can be concluded that an increased risk of acute pancreatitis may be linked, in part, to a low concentration of magnesium.

Magnesium plays a crucial role in cellular processes, especially since the content of magnesium in enzymes involved in active metabolism, including the oxidation of glucose, lipids and proteins, is essential for the action of these enzymes (Guerrera, Volpe, Mao, 2009). In acute pancreatitis, hypomagnesemia is a common condition that occurs due to the deposition of this trace element in areas of fat necrosis (Al Alawi, Majoni, Falhammar, 2018). Hypomagnesemia is often associated with hypocalcemia. Hypocalcemia has been reported in 10-80% of acute pancreatitis patients which is considered a bad prognostic sign (Liamis, Gianoutsos, Elisaf, 2001). It has been reported that the mechanism of hypomagnesemia is similar to the mechanism partly responsible for hypocalcemia in acute pancreatitis (Regolisti *et al.,* 2010).

Iron is essential for normal cellular performance, especially for growth and development (Al-Fartusie, Mohssan, 2017). In fact, studies discussing the relationship between iron and acute pancreatitis are very rare. In this work, the results revealed a significant decrease in blood iron levels for patients with acute pancreatitis compared to controls. This outcome may reflect the valuable contribution of this element to the pathogenesis of this disease. However, more clinical trials should be conducted to verify the role of Fe in the pathophysiology of acute pancreatitis.

To date, the functional role of Ni and Cr in the human body remains unclear, and rare information on their effect on the pancreas is available. They are known as toxic agents to the human body. Nickel may increase DNA methylation, inhibit DNA repair, induce apoptosis and increase the generation of ROS (Hartwig *et al.,* 1994). Chromium may cause skin problems and lung cancer and can induce oxidative stress in the human body (Yao *et al.,* 2008).

In this study, Ni and Cr levels were statistically higher in patients with acute pancreatitis when compared to healthy controls. As toxic agents, both Cr and Ni have the potential to induce oxidative stress in the human body by causing ROS generation (Hartwig *et al.,* 1994; Yao *et al*., 2008). Therefore, it might be suggested that the high levels of nickel and chromium estimated in this study be associated with the pathogenesis of acute pancreatitis. Although the new findings may be an important and reliable source of information about the potential role of Ni and Cr in pancreatitis, further studies are still needed to clarify and improve understanding of the effects of Ni and Cr on the etiology of pancreatitis.

CONCLUSION

The current work provides important evidence of the correlation between changes in copper and zinc levels and the risk of acute pancreatitis. This allows the conclusion that low levels of zinc associated with high copper levels may interfere with the pathogenesis of acute pancreatitis. Moreover, it can be indicated that an increased Cu/Zn ratio may be a useful indication for the diagnosis of acute pancreatitis and for monitoring the progression of the

disease. Furthermore, this study reveals some significant changes in serum levels of Mg, Fe, Ni and Cr for acute pancreatitis patients, and perhaps has highlighted their partial embroilment in the disease disorder process. These disturbances in the content of the elements might be used to monitor the development of the disease. Collectively, the study concluded that there is a potential relationship of Mg, Fe, Ni and Cr with acute pancreatitis.

In conclusion, it can be stated that trace elements are reliable to provide indications for warning of the risk of acute pancreatitis. More comprehensive studies and additional evaluation are needed to illustrate the mechanism responsible for changes in levels of these elements in acute pancreatitis patients.

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