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Research Article

Serum trace element levels of liver cirrhosis and pancreatic cancer patients

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Abstract

The incidence of liver cirrhosis and pancreatic cancer varies between countries and stands out as an important health problem worldwide. Liver cirrhosis is the most advanced stage of chronic liver disease and is a widespread result of chronic liver damage. The etiology of liver cirrhosis and pancreatic cancer, which are major causes of cancer fatalities in developed countries, is poorly understood. Many metabolic and physiological processes in the human body utilize trace elements. The creation and development of many diseases like cancer, cardiovascular, and diabetes mellitus occur with the disruption of trace element metabolism in the body as a result of improper nutrition, environmental, and occupational exposure, and impaired digestion and absorption.

Methods and materials: In this study, copper (Cu), cadmium (Cd), iron (Fe), cobalt (Co), manganese (Mn), magnesium (Mg), nickel (Ni), zinc (Zn), and lead (Pb) concentrations were researched in the serum of liver cirrhosis and Pancreatic Cancer (PC) patients and healthy controls. Analysis of the elements was carried out by flame atomic absorption spectrophotometer.

Results: Fe and Zn serum levels were considerably lower in individuals with liver cirrhosis and pancreatic cancer than in controls ($p < 0.001$). Furthermore, mean serum levels of Cd and Mn in patients with liver cirrhosis and pancreatic Ca were considerably lower than in controls ($p < 0.01$). In addition, when compared to pancreatic cancer, mean serum Cu and Ni levels in liver cirrhosis patients and controls were considerably lower ($p < 0.05$). Mean serum levels of Pb in pancreatic Ca patients were significantly lower compared to liver cirrhosis patients and controls ($p < 0.05$). When comparing all cancer patients to controls, mean serum Co and Mg levels were not substantially different.

Conclusion: Deficiency in four trace elements (Cd, Mn, Fe, and Zn) was determined in patients with liver cirrhosis and pancreatic cancer. In addition, we have determined the deficiency of Cu and Ni trace elements (TEs) in pancreatic cancer patients. TE insufficiencies in cancer patients may be due to excessive consumption of foods and undernourishment. Epidemiological and physiological causes of trace element changes should be investigated further.

Introduction

Liver Cancer (LC) is the world's sixth most frequent malignancy, with over 906,000 new cases and 830,000 deaths expected in 2020. It is also the third leading reason for Ca deaths [1,2]. Cirrhosis and its complications, Hepatic Encephalopathy (HE), ascites, varicose bleeding, at least Hepatocellular Carcinoma (HCC), and infections represent the end of the spectrum of chronic liver diseases regardless of etiology [3-5]. The liver arranges the transport and metabolic pathways of Trace Elements (TEs) and thus their tissue distribution, bioavailability, and ultimate toxicity [5-7]. The liver also aids a role in removing TEs through the creation of bile [8,9]. Risk factors for LC and cirrhosis include hepatitis B, hepatitis C, long-term exposure to aflatoxin, chronic alcoholism, obesity, diabetes, oral contraceptive use, nutritional deficiency, etc. [10,11].

Pancreatic Cancer (PC) is one of the deadliest human cancers and an important reason for cancer-related deaths

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worldwide [12,13]. Most patients are faced with an advanced form of the disease at the time of diagnosis, as no specific symptoms are observed until pancreatic cancer reaches its advanced and incurable stage [13,14]. Risk factors for PC include environmental exposure (such as smoking, excessive alcohol intake, heavy metals, chlorinated hydrocarbon solvents, exposure to mutagenic nitrosamines, etc.), Type 2 Diabetes (T2D), and genetic factors [15,16]. It has been suggested that 80% of cancer cases are caused by environmental factors, nutritional and ecological reasons, physiological, and many specific interactions between certain elements, and element imbalances in biochemical events. Heavy metals and trace elements from environmental components are thought to play an important role [6]. The principal pollutants in the environment (drinking water, groundwater, soil, air, etc.) that pose a global health concern to humans and animals are trace elements. TEs play a very important role in continuing vital functions, and deficiency or excess leads to metabolic irregularities [4,17]. Metabolism of various nutrients can provide information about the presence and severity of the disease in liver diseases and pancreatic cancers. A significant relationship may be found between trace element metabolism and the presence and progression of liver and pancreatic diseases [18]. The role and consequences of trace metals in the etiology of liver cirrhosis are still not fully understood. It has not yet been determined whether varying concentrations of trace elements in the body are the cause or effect of malignancy [15,19]. Some of the trace elements are necessary for the organism (like cobalt, zinc), but can also aggravate liver damage (like lead, cadmium). Many trace elements are thought to play key roles in a variety of biological processes by activating or inhibiting enzymatic reactions, competing with other elements and metalloproteins for binding sites, which affects cell membrane permeability, and other mechanisms [9,17]. Some trace elements, such as Se and Zn, have essential protective or augmenting impacts on disease progression. Zn insufficiency has been linked to the etiology of liver illnesses and has been linked to decreased serum Zn levels in both acute and chronic liver disease states [20]. Low serum Zn levels are prevalent in patients with liver cirrhosis, owing to reduced intake, absorption, and bioavailability, which is primarily related to malabsorption. Oral Zn supplementation improves liver function and improves most biochemical indicators of nutritional status in Zn-depleted patients with cirrhosis by bringing their levels up to normal values [21]. There is also a correlation between metalloprotein and serum TEs (Cu, Fe, Zn, etc.) concentration in the body, and imbalances aid an important role in liver illness [4]. Occupational or non-occupational exposures to cadmium, lead, chromium (Cr), selenium (Se), and nickel have been correlated with a raised risk of PC [16,22-24]. Therefore, the utility of evaluating serum trace elements in the pathogenesis of cirrhotic complications and for cancer detection- prevention requires further investigation.

Since trace elements have a possible role in human health, this study aimed to investigate the serum levels of some trace elements (Co, Cu, Cd, Fe, Mn, Ni, Pb, Zn, and Mg) in patients with liver cirrhosis and pancreatic cancer, and compare them with the levels in controls.

Materials and methods

Sample collection

Our research included 31 patients with liver cirrhosis and pancreatic cancer who were admitted to a medical faculty hospital in Van, Turkey. Histopathological studies verified the diagnosis of cancer patients (11PC). Patients with liver cirrhosis were evaluated with laboratory tests and ultrasonography after a complete physical examination (22 liver cirrhosis). The control group comprised 21 healthy volunteers who underwent laboratory testing as part of routine medical examinations. The criteria for collecting serum samples from all groups were that all groups lived in the same region, had similar socioeconomic backgrounds, and had not received any mineral supplements for the past 3 months. All participants were informed about the study. The study followed the Declaration of Helsinki, and all subjects gave their informed consent.

Trace element analysis

Two milliliters (ml) of blood samples were taken from each participant. It was pipetted into isolated serum storage vials after centrifugation at 5500rpm for 20 minutes. Samples were kept at -40°C in a deep freezer until they were analyzed. 1ml of blood serum was transferred to a 25ml beaker. It was mixed with 10ml $HClO_4/HNO_3$ (1/7, v/v). In the adjustable heater, it was heated to 180°C. The samples were heated until white thick vapors developed at a soft boiling point. After adding 5 ml of distilled water, it was filtered through a blue band filter paper and the final volume was adjusted to 10ml. Under optimum conditions, the amounts of chosen TEs were measured using a Flame Atomic Absorption Spectrophotometer (FAAS) (Table 1). All reagents used are of high purity (Merck, >99.99%). 1000mg/l standard solutions were diluted in 0.5% HNO_3 to make working solutions (Merck).

Statistical analysis

The data were analyzed using descriptive statistics (means, medians, dual comparison, Standard Deviations (SDs), and ranges) using SPSS software, version 20 (IBM SPSS Statistics)]. Variables were checked for normality using the Shapiro-Wilk test. The data were analyzed using analysis of variance (ANOVA), and multiple comparisons were corrected using Tukey's test. The Kruskal-Wallis H test was performed to look at the differences between groups in qualitative characteristics. $p<0.05$ was considered a significant level.

Table 1: In FAAS, analytical conditions for trace metal analysis.

	Cd	Co	Cu	Fe	Mg	Mn	Ni	Pb	Zn
Wavelength (nm)	228.8	240.7	324.8	248.3	285.2	279.5	232	217	213.9
Slit width (nm)	0.7	0.2	0.7	0.2	0.7	0.2	0.2	0.7	0.7
Lamp current (mA)	4	7	20	30	10	30	30	15	20
Fuel-gas flow rate (l/min)	2	2	2	2	2	2	2	2	2
Detection limit (µg/l)	0.02	0.01	0.4	0.8	0.6	0.02	0.01	0.11	0.4

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Results

Table 2, compares the serum concentrations of TEs in patients with liver cirrhosis and PC patients to controls. Between all patients and controls, there is no significant variation in the levels of Co and Mg ($p>0.05$). However, significant differences were determined in the amounts of Cu, Cd, Pb, Fe, Ni, Zn, and Mn elements among liver cirrhosis, cancer patients, and controls ($p<0.05$). Fe, Cd, Zn, and Mn blood levels were considerably lower in liver cirrhosis and PC patients compared to controls ($p<0.005$, <0.001, <0.01, and <0.001). Furthermore, PC patients had considerably lower mean serum Pb levels than controls and liver cirrhotic patients ($p<0.04$). The liver cirrhosis and pancreatic cancer groups had lower mean serum Co and Mg levels than controls, although this difference was not significant (p: 0.096 and 0.216). In addition, when compared to PC patients, the mean serum levels of Cu and Ni in liver cirrhosis patients and controls were significantly lower ($p<0.041$ and <0.032), (Table 2). Figures 1,2 show the mean serum TE levels of liver cirrhosis and pancreatic cancer, respectively.

Discussion

Lifestyle, environmental toxins, nutritional intake, pollution, and exposure to trace elements play significant etiological roles in carcinogenesis [25-27]. Micronutrients are important for liver diseases. Liver cirrhosis is the common result of chronic liver damage [4,28]. Zn and Cu are two necessary trace elements with numerous physiological functions. Also, Cu and Zn are subject to stiff competition for binding sites on metallothionein (MT). Serum concentrations of both elements are affected by stress, trauma, infections, and malignant processes. Cu and Zn levels can be inversely proportional. High serum copper concentrations are, as a rule, associated with low zinc concentrations [5,29-31]. During cell injury and inflammation, liver cells require extra zinc to manufacture protein, nucleic acid, and zinc-related enzymes. Zn uptake and absorption are reduced due to the progression of liver damage, dysfunction of the intestine and stomach, loss of appetite, and high pressure in the portal vein [32,33]. By promoting the synthesis of Cu-MT in intestinal epithelial cells, zinc reduces copper absorption [5,34]. In prior research and literature, serum and tissue Zn levels were also found to be decreased in patients with various cancers [35,36]. Zn levels in liver metastasis are assumed to be lower than in healthy tissue due to increased Zn consumption by malignant tissues [5,10,37]. Accumulation of Ni composites in the body through chronic exposure can conclusion in diverse illnesses like cardiovascular diseases, lung and kidney cancers, etc. [38-40]. Most studies and this study found that zinc and copper content in liver cirrhosis and PC is lower than in normal controls and surrounding tissues [4,15,29,41-43].

Cadmium is a toxic element that has no beneficial role in the metabolism of living organisms [44]. Cd has teratogenic, carcinogenic effects, and sterilizing. Cd has a long biological half-life and over time becomes a toxin that accumulates in the body [45-47]. Cd binds to MT by high-affinity sequestration and accumulates in the kidney and liver [45]. Pb is a toxic metal

Table 2: Serum TE levels of liver cirrhosis, PC patients and controls (µg/l).

Trace Elements	Type	n	Median	Min	Max	*P*-value	Dual comparison
Cd	Liver cirrhosis (I)	22	0.079	0.030	0.135	0.005**	III > I, II
	Pancreatic Ca (II)	11	0.043	0.028	0.064		
	Controls (III)	21	0.149	0.072	0.196		
Co	Liver cirrhosis	19	0.133	0.021	0.272	0.096	-
	Pancreatic Ca	11	0.071	0.017	0.115		
	Controls	20	0.251	0.112	0.369		
Cu	Liver cirrhosis	22	2.074	1.240	2.917	0.041*	II> III, I
	Pancreatic Ca	11	3.271	3.244	3.398		
	Controls	21	2.313	1.130	3.746		
Fe	Liver cirrhosis	22	4.292	1.771	8.947	0.001***	III > I, II
	Pancreatic Ca	11	3.992	3.355	4.241		
	Controls[1]	21	10.62	9.238	22.22		
Mg	Liver cirrhosis	22	27.33	13.80	80.22	0.216	-
	Pancreatic Ca	11	15.59	12.51	20.29		
	Controls	21	28.28	22.96	36.49		
Mn	Liver cirrhosis[1]	18	0.075	0.039	0.328	0.01**	III > I, II
	Pancreatic Ca	11	0.052	0.017	0.089		
	Controls	21	0.278	0.067	0.470		
Ni	Liver cirrhosis[1]	18	0.264	0.011	1.623	0.032*	II > III, I
	Pancreatic Ca	11	0.993	0.022	1.445		
	Controls	21	0.955	0.552	1.998		
Pb	Liver cirrhosis	20	0.659	0.11	1.814	0.04*	III, I > II
	Pancreatic Ca	10	0.261	0.0	0.341		
	Controls[1]	18	0.985	0.673	1.122		
Zn	Liver cirrhosis	22	1.667	0.942	2.644	0.001***	III > II, I
	Pancreatic Ca	11	2.860	2.742	2.953		
	Controls[1]	21	3.843	2.395	21.49		

*p <0.05, significant; **p <0.01, very significant; ***p <0.001, indicates that groups are responsible for variance in the measured variable and are highly significant and the rest are not significant (p >0.05), [1] the Kruskal-Wallis H test.

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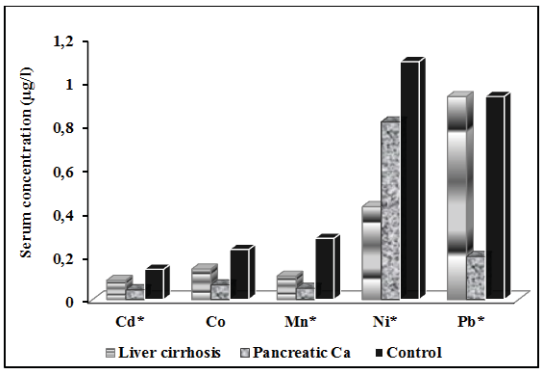
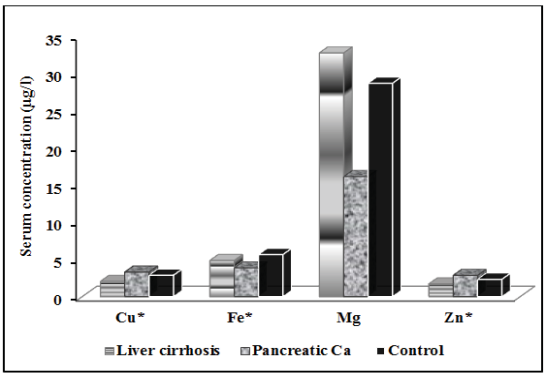


*p<0.05

Figure 1: Co, Cd, Ni, Pb, and Mn mean levels in the serum of liver cirrhosis, PC, and controls.



*p <0.05

Figure 2: Fe, Cu, Zn, and Mg mean levels in the serum of liver cirrhosis, PC, and controls.

and excessive exposure to lead increases the risk of carcinogenic in humans [48]. Increased Pb content in dietary intake was associated with cancers of the gastric, ovary, small intestine, lung, large intestine, all lymphomas, all leukemia, kidney, and myeloma [49,50]. Prostate, renal, ovarian, HCC, and bladder cancers can all be caused by long-term exposure to Cd [49,51]. Cadmium can activate or regulate various oncogenic and tumor suppressor proteins, such as the ras and p53 proteins, which are known to be overexpressed in human pancreatic tumors [13,52,53]. A farnesyl group must be added to ras proteins in order for them to become carcinogenic. Farnesyl: protein transferase is a zinc metalloenzyme that generally catalyzes this process. Cadmium can act as a zinc substitute in this process, farnesylating some H-ras motifs that are ordinarily unaffected by zinc [54]. Cadmium also increases the expression of the c-fos oncogene, which is upregulated in many pancreatic tumors and inhibits the p53 tumor suppressor protein's function [55]. Finally, cadmium can accelerate carcinogenesis caused by other carcinogens including dimethylnitrosamine and hepatitis B, as well as hinder DNA repair [56].

Because Fe is required for basic physiological processes, it is found in a variety of enzymes and proteins. Increased Fe content has been recognized as an important risk factor in carcinogenesis due to its role in the oxidative damage of cells [10]. The generation of oxygen radicals, suppression of apoptosis, and binding competition between chromatin and metal ions in other molecules all point to Mn and Fe's role in carcinogenesis [57,58]. Over-expression of manganese-superoxide dismutase (Mn-SOD) in carcinogenesis could be one cause [59,60]. In this study, in line with the findings in similar studies, Fe, Cd, and Mn levels in serums with cancer were significantly decreased compared to control serums [35,61,62]. All cancer patients' serum Co and Mg levels, however, were not significantly different from healthy controls.

Various researchers are investigating the link between TEs in cirrhosis and pancreatic Ca. Kazi et al. found that Se and Zn levels in the blood and serum samples of liver cirrhosis/Ca patients were lower than in healthy individuals [9]. In a Pakistan study, significantly low levels of zinc, selenium, and high cadmium were detected in biological samples (blood, serum, and scalp hair) of liver cirrhosis/Ca patients [6]. In another study on the development of hepatocellular carcinoma and trace element levels, it was reported that the iron and zinc content in HCC was lower than in the surrounding tissues and controls, and the Cu content in HCC was lower than in the surrounding tissues and cirrhotic controls. As a result, it was determined that Fe is a factor in carcinogenesis, copper and zinc may aid a role in the development of HCC [10]. Luckett, et al. demonstrated an etiological link between Cd exposure and PC in South Louisiana (ABD) population, an endemic region in pancreatic cancer [63]. In a case-control study conducted among 50PC patients of Greek descent, a statistically significant increase in serum Cu level was reported so far among patients suffering from PC [64]. A Polish case-control study shows that low serum selenium (Se) levels and high serum Cu levels can affect PC development, and higher Se levels are associated with longer survival in PC patients [15]. Low serum Zn and higher Cd levels were found in PC patients in an Iranian investigation compared to controls. Furthermore, no significant differences in serum Pb, Se, or Cu levels were identified between the groups [65].

In our previous study, which examined heavy metals in vegetables and fruits in the same region, Pb, Co, Cd, and Cu levels were found to be high and Zn levels in the soil were determined to be very low. Also, Cd, Co, Pb, Ni, Cu, and Mn were significantly higher in fruits and vegetables; the mean Zn level was determined as normal [25]. In addition, in our previous study, significantly low serum levels of trace elements were determined in cancer patients compared to high environmental levels of trace elements in the endemic upper gastrointestinal cancer region. This was thought to be the role of malignant excessive food consumption and malnutrition in the advanced tumor stage of anorexic patients [36]. In addition, several studies have shown the association between malnutrition such as Fe, Pb, Mn, and Zn, and gastrointestinal diseases and cancers [66-68].

Conclusion

We determined lower serum levels of Fe, Cd, Mn, and Zn in patients with liver cirrhosis and pancreatic cancer compared to controls and higher serum levels of Cu and Ni in pancreatic Ca patients compared to cirrhosis, cancer patients, and controls. The lifestyle, environmental toxins,

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nutritional intake, pollution, and exposure to trace elements play significant etiological roles in carcinogenesis. Patients with liver cirrhosis and pancreatic cancer should be tested for toxic and trace elements to minimize disease progression and consequences, and more studies should be done on this topic. Various limitations of the studied study; the nutritional processes and environmental conditions of the patients should be followed in terms of trace elements during and after the treatment, and the trace element levels should be monitored with more cases. Even though this is a very small group study, it has indicated that a healthy diet rich in TEs can be used as a cancer prevention strategy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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