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Nutritional Status and Blood Trace Elements in Cirrhotic Patients

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Background and Aims: **To determine the levels of zinc, copper, iron, albumin and zinc to copper ratio in sera of patients in different stages of cirrhosis and to find possible correlation between trace elements and anthropometrics measurements with liver cirrhosis presence and progression.**

Methods: **This cross-sectional analytic study was carried out on sixty continuous patients with liver cirrhosis referred to hepatology clinic, Tabriz University of Medical Sciences. The mean of daily calorie and protein intake was determined by Nutrition III software and compared to recommended dietary allowances (RDA), body composition was determined by bioelectrical impedance analysis (BIA) and serum Zn, Cu and Fe levels were determined by atomic absorption spectrophotometery and albumin level of serum was measured by calorimetric method.**

Results: **Among sixty studied patients, 39 were male and 21 were female. 53.8% of male patients were in Child-Pugh class B while 23.8% of female patients were in Child-Pugh class B. The mean energy and protein intake of all patients was lower than RDA values and there was no significant correlation between the mean of protein and energy intake with severity of liver cirrhosis. The serum levels of Zn, Albumin and Zn/Cu ratio in patients with Child-Pugh class B were significantly lower than those with Child-Pugh class A.**

Conclusions: **In general, these results suggested that changes in liver cell pathology compounded by functional impairment may alter the metabolism of trace metals, in particular, zinc.**

Keywords: **Liver Cirrhosis, Trace Elements, Malnutrition**

Introduction

Liver cirrhosis is the terminal phase of liver diseases. It may have a range of explanations such as viral hepatitis, alcohol consumption, metabolic disorders, cholestasis, autoimmune events, toxic substances, drugs, infections, congenital diseases; it does not heal in general and chronically progresses [(1)]. Among these etiologies, alcoholism in the west and HBV infection in the orient are the most common causes of cirrhosis [(2)].

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Owing to the pathomorphological characteristic of liver cirrhosis which may be followed by hepatocellular inflammation and necrosis, a broad spectrum of clinical conditions are caused by decreased liver function [3].

Protein-energy malnutrition (PEM) is a common complication in cirrhosis. It has been reported that the incidence of PEM is 20% or more in patients with compensated liver cirrhosis and 50% or more in patients with uncompensated liver cirrhosis [1, 4]. Predisposing factors of protein-energy malnutrition include increased energy expenditure, increased protein catabolism, decreased protein synthesis (hypoalbuminemia) in the damaged liver, increased catabolism of endogenous fat as an energy source and lack of essential amino acids, fat-soluble vitamins (vitamin A, D and K) and trace elements [1, 3-5]. Albumin and protein synthesis are stimulated physiologically by meal ingestion and/or by aminoacidemia, both of which appear to be inactive in cirrhotic patients.

In terms of biochemical function of the liver, trace elements such as iron, copper, manganese and zinc are constituents of many metalloproteins and metalloenzymes and act as co-factors of hepatic processes [1, 9]. Assessment of the disorders of trace element metabolism should be based not only on the dietary intake, but also on various factors such as absorption, transportation, storage, excretion, and metalloproteinase and metalloenzymes synthesis which are impaired when liver cell is damaged [10, 11]. So the levels of trace elements such as zinc, copper, and iron in serum and liver tissue and their metabolism may indicate the presence and severity of liver cirrhosis and can also reveal suitable nutritional treatment strategies.

In brief, nutritional assessment can be viewed as a triad of assessment techniques incorporating anthropometric measurements, predicting energy expenditure and screening of biochemical indices. Information on this subject is seriously lacking in Iran. In the present study we determined the levels of zinc, copper, iron, albumin and zinc to copper ratio in sera of patients in different stages of cirrhosis and tried to find a correlation between trace elements and anthropometrics measurements with liver cirrhosis presence and progression.

Materials and Methods

Subjects

This cross-sectional analytic study was carried out on sixty continuous patients with liver cirrhosis referred to hepatology clinic, Tabriz University of Medical Sciences. All of the patients were visited by the same hepatogastroenterologist. Patients were evaluated by laboratory tests and ultrasonography after full physical examination. Cirrhosis was confirmed by biopsy.

Patients with the following conditions or disorders were excluded: hepatocellular carcinoma, age under 18, Child-Pugh class C, use of anabolic hormones, diuretics or albumin (during the previous month), severe renal or respiratory disorders, pregnancy, lactation, ascitis or peripheral edema. The severity of liver failure was assessed by Child-Pugh score.

Dietary and biochemical assessment

Dietary intake was assessed by 3-day food recall questionnaire and to minimize the error of recalling memory, food album was used and the mean of daily calorie and protein intake was determined by Nutrition III software and compared to recommended dietary allowances (RDA).

Body composition was determined by bioelectrical impedance analysis (BIA) which measured anthropometric parameters such as total body water (TBW), fat free mass (FFM), fat mass (FM) and body mass index (BMI), based on age and sex. Serum Zn, Cu and Fe levels were determined by atomic absorption spectrophotometery and albumin levels of serum was measured by calorimetric method quickly after taking serum samples.

Statistical analysis

Data are given as mean ± standard error of mean. The differences between groups were calculated using by nonparametric Mann-Whitney U test. Linear regression analysis (Pearson) or Spearman and Kendall's tau-b coefficient (for nonparametric variables) of correlation were used to assess statistical significance. The results were considered significant at the level of $p<0.05$. SPSS version 13 was used for statistical analysis.

Results

Among sixty studied patients, 39 were male and 21 were female. The mean age of patients was 46±2.76 (51.61±2.76 in male and 40.38±2.93in female). Based on Child-Pugh score, 46.2% of male patients were in Child-Pugh class A and 53.8% were in Child-Pugh class B. 76.2% and 23.8% of female patients were Child-Pugh class A and class B, respectively. Hepatitis B surface antigen (HBsAg) was positive in 39.7% of patients, 7.9% were seropositive for anti-hepatitis C virus (HCV),

39.7% had autoimmune hepatitis and hepatitis in 12.7% was cryptogenic. The most common cause of cirrhosis in males was HBV while it was autoimmune hepatitis in females.

The mean energy and protein intake of patients compared to RDA based on Child-Pugh stage are shown in table 1. The mean energy and protein intake of all patients were lower than RDA values. There was no significant correlation between the mean of protein and energy intake with severity of liver cirrhosis.

The serum levels of Fe, Albumin, Cu, and Zn and the anthropometrics data of subjects are summarized in Table 2.

Table 1. Mean±SE mean of energy and protein intake in different stages of liver cirrhosis compared to recommended dietary allowances (RDA)

	Protein intake			Energy intake		
	g/kgwt/day	%RDA	g/day	Kcal/kgwt/day	RDA%	Kcal/day
All patients (n=60)	0.69±0.03	85.58±3.90	45.32±2.12	21.68±0.88	54.68±1.92	1404.40±49.89
Child-Pugh A (n=34)	0.69±0.04	86.47±5.14	44.87±2.67	21.81±1.15	55.38±2.63	1386.55±65.75
Child-Pugh B (n=26)	0.69±0.05	74.42±6.09	45.90±3.50	21.50±1.39	53.76±2.84	1428.69±77.81

Table 2. Distribution of anthropometrics and laboratory findings by sex and stage of liver disease

	All patients		Male		Female	
	Child-Pugh A	Child-Pugh B	Child-Pugh A	Child-Pugh B	Child-Pugh A	Child-Pugh B
BMI (kg/m^2)	25.82±0.76	25.65±0.74	26.02±0.98	25.80±0.86	25.58±1.34	25.04±1.56
Height (cm)	160.41±1.57	163.26±1.73	165.61±2.05	166.47±1.26	154.56±1.34	149.80±2.78
TBW (kg)	37.03±1.06	40.15±1.29	40.65±1.41	42.24±1.16	32.96±0.80	31.36±1.42
FFM (kg)	50.60±1.45	54.50±1.94	55.52±1.93	57.76±1.58	45.06±1.11	40.84±3.59
Fat mass (kg)	15.29±1.40	13.71±1.26	14.63±1.70	13.72±1.42	16.03±2.34	13.68±3.00
%Fat body (kg)	21.82±1.74	19.43±1.36	19.45±1.95	18.59±1.40	24.48±2.90	22.98±3.92
Zn (micg/dl)	70.49±3.15	58.18±3.35	71.57±5.14	60.76±3.61	69.26±3.53	44.64±5.54
Cu (micg/dl)	134.63±6.19	136.75±7.60	136.10±9.54	145.66±7.14	132.95±7.94	89.96±15.24
Fe (micg/dl)	150.92±15.94	179.58±2489	152.40±26.52	159.87±21.05	149.33±18.01	273.20±99.79
Zn/Cu	0.55±0.03	0.45±0.03	0.56±0.05	0.43±0.03	0.54±0.04	0.53±0.10
Albumin(g/dl)	4.25±0.08	3.55±0.09	4.18±0.12	3.50±0.10	4.33±0.11	3.74±0.16

Also the study results showed that levels of Zn, albumin in the serum and Zn/Cu ratio in patients with Child-Pugh class B were significantly lower than those with Child-Pugh class A. In contrast, we did not observe statistically significant difference in the levels of Cu and Fe in two groups. The correlation coefficient between serum levels of trace elements and stage of liver cirrhosis is shown in table 3. The correlations between Albumin (P=0.02, r=0.20) and Child-Pugh stage (P=0.05, r= 0.21) with FFM were significant as well.

Table 3. Correlation between serum levels of trace elements with stage of cirrhosis

	Child-pugh stage	
	P	r
Zn	0.005	-0.31
CU	0.39	0.09
Fe	0.57	0.06
Albumin	0.0001	-0.48
Zn/Cu	0.04	-0.22

The mean albumin level in the serum of patients with hepatic cirrhosis was correlated with serum zinc level (figure 1) and Zn/Cu ratio (p=0.001, r=0.442 and p=0.001, r=0.421 respectively).

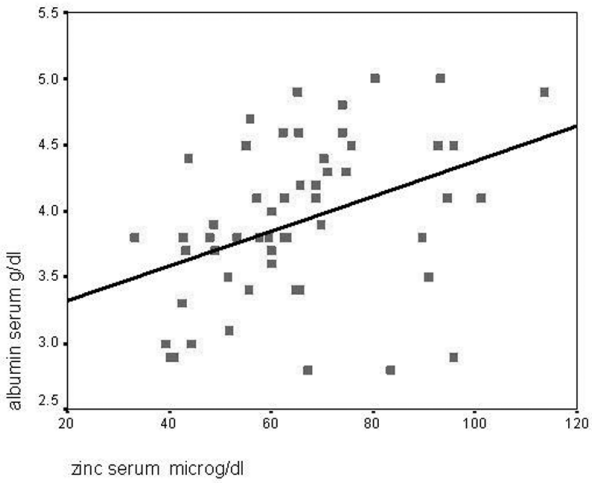

Figure 1. Linear regression between serum albumin and zinc levels in cirrhotic patients

Discussion

Malnutrition is a common complication in advanced stages of liver disease and aggravated with increasing severity of cirrhosis from Child class B to C due to: 1) inadequate protein and energy intake 2) malabsorption and 3) change in trace elements metabolism [12, 13].

Roongpisuthipong *et al.* reported that the mean of the protein and energy intake in patients with non-alcoholic cirrhosis was 0.91± 0.4 g/kg/day and 21.8± 4.7 kcal/kg/day, respectively [14]. Campillo *et al.* [15] and Gottschal *et al.* [12] noted that the mean protein and energy intake is low in cirrhotic patients, in agreement with the present study in which, the mean energy and protein intake in all of the cirrhotic patients was less than RDA values (30kcal/kg/day for energy and 1g/kg/day for protein intake).

There is a large body of evidence about obscure malnutrition status in cirrhotic patients according to BMI, because nutritional parameters which are derived from body weight could not be reliable in patients with ascites and fluid retention [12]. Hence, it has been widely accepted that the determination of body composition is useful for evaluating nutritional status. However, traditional methods such as skin fold measurements are easy to perform; it has lower accuracy and reproducibility. In recent years, BIA has emerged as a simple and reproducible method which can be used for evaluation of FFM [15-16].

Nutritional parameters such as FFM might provide prognostic information in these patients [7]. Kotoh *et al.* revealed the correlation between FFM and albumin [8], and in Roongpisuthiopong *et al.* survey, malnutrition was most common in Child C stage which level of albumin was lower than in Child-Pugh B and A [15]. In the present study, there was a significant correlation between FFM, Child-Pugh stage of liver disease and serum albumin level. These studies indicate that the increased protein requirement is due to both a defect in meal-induced protein synthesis in the liver and increased protein degradation during feeding as well as fasting.

The importance of trace elements in the process of maintaining life is well known. At present, it is recognized that 14 trace elements including copper, zinc and iron are essential for the human body. Much research has been done on the zinc concentration in the sera of cirrhotic patients and the results indicate that zinc concentration is associated with viral hepatitis, decreasing with the development of cirrhosis and low function of liver [17]. Oral zinc supplementation, increasing zinc levels to physiologic concentration in zinc depleted patients with cirrhosis, improves liver function and produces a slight but significant amelioration of most biochemical indices of nutritional status [11].

Loguercio *et al.* reported that cirrhotic patients had a significant decrease of serum Zn, Fe level, independent of the degree of liver function impairment and only partially affected by the nutritional status [17]. Lin *et al.* implied that the mean Zn level in the serum of patients with hepatic cirrhosis was significantly lower than that of control group and found markedly elevated Cu:Zn ratio in these patients [18]. Pramoolsinsap *et al.* showed that serum zinc levels were significantly decreased in patients with chronic active hepatitis, cirrhosis, and hepatocellular carcinoma ($P \leq 0.0001$) and copper contents were significantly increased only in patients with hepatocellular carcinoma ($P<0.0001$) [19]. Nagasue *et al.* implied that serum copper level was significantly higher in cirrhotic patients than in normal subjects [20]. Ko *et al.* revealed that the healthy content of Zn in plasma was significantly lower in hepatitis C patients than in controls and the content of Cu level in plasma was significantly higher in hepatitis C patients compared to healthy controls [21]. In Akihiro survey, zinc levels of the patients with liver cirrhosis, chronic hepatitis and hepatocellular carcinoma were lower than those of controls and copper levels of the patients with liver cirrhosis and hepatocellular carcinoma were

significantly higher than in patients with chronic hepatitis and controls [22]. Yasuhiro *et al.* showed that the mean serum zinc levels in patients with decompensated liver cirrhosis were found to be significantly lower than in controls and patients with compensated cirrhosis [23]. Jurczyk *et al.* concluded that the median value of serum iron concentration, though a higher level in patients with post-inflammatory cirrhosis, did not differ significantly [24].

In our study, we showed that the serum level of zinc and Zn/Cu ratio decreased by the progression of liver damage but serum Cu and Fe levels did not differ significantly.

There are some explanations for the decrease of zinc content in the serum of cirrhotic patients. During the cell damage and inflammation, liver cells take up more zinc to synthesize nucleic acid, protein and enzymes related with zinc. With progression of the liver damage, due to poor appetite, impaired function of intestines and stomach and high pressure of the portal vein, the zinc intake and absorption decreases and also the low content of serum albumin results in less combination with zinc and because of the diffusion characteristic of blood zinc, it is easily lost through urine and sweat [1, 11].

There have been various controversial reports on copper level in serum. In our study, serum copper level was higher in advanced stage of cirrhosis but didn't reach the significance. This increase may be explained by release of copper from damaged necrotic hepatocytes [19].

Patients with chronic liver disease have a tendency to accumulate an excessive amount of iron in their liver parenchyma. The reason for the iron excess is not known, but postulated mechanisms imply that acute-phase reactions associated with chronic inflammatory states increase uptake of iron through the gastrointestinal tract and cause to remove excess iron by the Kupffer cells. Moreover, there is ineffective erythropoiesis with redistribution of iron from sites of utilization to sites of storage. Consequently with the damage of hepatocytes, the release of iron from injured cells to serums develops [25].

Conclusion

The present study demonstrated a higher malnutrition status in patients with liver cirrhosis in our region. Due to the impairment of absorption, transportation, storage and excretion of trace elements in damaged liver cells, progression of the cirrhosis induces a decrease in the Zn level of the serum and furthermore Albumin synthesis.

In general, these results suggest that changes in liver cell pathology and functional failure may alter the metabolism of trace metals, in particular, zinc.

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