

## Serum Level of Zinc and Copper as Predictors of Severity of Depression in Chronic Hemodialysis Patients

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**Abstract:** Depression is a common psychological problem in patients undergoing chronic hemodialysis. And there is a significant association between it and mortality in the patients, so it is very important to identify its possible causes. In the general population, low serum zinc (Zn) level is associated with major depression and copper (Cu) interferes with the absorption pathways and distribution of zinc, which share the same process of intestinal absorption. So, the aim of this study was to assess changes in the zinc and copper levels in patients with chronic renal failure on regular hemodialysis as well as to evaluate their relationships with severity of depression and with other biochemical markers. This study was conducted on thirty patients on regular hemodialysis for more than one year from the hemodialysis (HD) unit of Al Zahraa University Hospital during the period from first of August 2013 to end of October 2013 compared to thirty healthy controls of the same age and sex. Serum zinc and copper; in addition to hemoglobin, serum iron, serum ferritin, albumin and blood urea were measured in both patients and healthy controls. Depression was assessed using the Beck Depression Inventory (BDI) scoring system. Correlation of Zn and Cu with depression was evaluated. All patients of the present study had depression and were classified according to its severity into four groups using the BDI score; patients with mild, moderate, severe and very severe depression. In all patients the mean serum Zn level was of high significant decrease and Cu was of high significant increase in comparison to the control. There was significant positive correlation between serum copper level and the severity of illness in depressed patients. On the other hand, significant negative correlation was found between serum zinc level and the severity of illness in the same cases. From these results it could be concluded that zinc deficiency and copper excess may have a role in pathogenesis of depression in HD patients. So, it is recommended to use zinc supplementation and copper chelating agents with these patients.

**Key words:** BDI score • Chronic hemodialysis • Depression • Serum zinc and copper levels

### INTRODUCTION

Chronic renal failure (CRF) patients have diminished quality of life (QOL) scores compared with healthy persons. CRF disease not only impacts patient survival, but also yields negative effects in their daily life [1]. Depression is the most common psychological problem

in dialysis patients. In particular, the prevalence of major depression in the general population is 1.1-15% in men and 1.8-23% in women, but is 24-50% in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). Furthermore, there is a significant association between depression and mortality in patients with CKD and ESRD. Clearly, it is very important to identify

the possible causes of depression in patients with CKD and ESRD [2]. Depression is characterized by both cognitive and somatic features. The somatic characteristics of depression have similarity to the symptoms of uremia, such as anorexia, sleep disturbances, fatigue, gastrointestinal disorders, aspects of volume overload and pain [3]. These similarities make the determination of the role of the association between depression and mortality potentially problematic [4]. Cognitive depression measures may be more useful in predicting outcome in HD patients than standard measures used in non-medically ill populations [5].

Currently, the importance of trace elements in the genesis and progression of certain diseases has increased considerably. Specifically, zinc (Zn) and copper (Cu) have been recognized as essential elements necessary for the correct function of our body and normal growth. Their presence has been confirmed in numerous enzymes where they play an important role as cofactors, such as superoxide dismutase [6]. Smith and Akinbamizo [7] reported that zinc is an essential trace element which is required for the action of many enzymes and has a key role in polymeric organization of macromolecules such as DNA and RNA, protein synthesis and cell division. Serum zinc deficiency is a common problem in the world especially in the Middle East and associated with major depression in the general population [8]. It is frequently reported in patients with ESRD undergoing HD [9]. The rate of zinc deficiency in patients undergoing HD has been reported to be between 40% and 78% [10]. Copper (Cu), is a trace metal essential for living cells. It plays an important role in redox reactions because of its easy conversion from  $\text{Cu}^+$  to  $\text{Cu}^{++}$ . Copper is transported mainly by ceruloplasmin, a copper-binding antioxidant protein that is synthesized in several tissues, including brain [11]. Copper is not toxic by itself; rather, it interferes with the absorption pathways and distribution of other elements like zinc and iron, which share the same process of intestinal absorption. Therefore, a mechanism of competitive inhibition could occur among these elements. Nevertheless, Milne *et al.* [12] clearly observed that, in humans, the two metals (zinc and copper) antagonize each other at high levels of copper and Navarro *et al.* [6], reported that zinc at adequate levels might be beneficial, if not required, for copper use by the body. End stage renal failure patients frequently require renal replacement therapy as hemodialysis (HD), which alters trace element metabolism [13].

So, the aim of this study was to assess changes in the zinc and copper levels in patients with chronic renal failure on regular hemodialysis; as well as to evaluate their

relationships with severity of depression and with other biochemical markers.

## PATIENTS AND METHODS

This study was a cross sectional case control study of three months duration from first of August 2013 to end of October 2013. It was conducted on sixty individuals, 30 patients from the hemodialysis unit of Al Zharaa University Hospital, Cairo, Egypt, who fulfilled the inclusion and the exclusion criteria; in addition to 30 healthy volunteers who were considered as control to represent the basic laboratory studied parameters. The controls were free from systemic or psychological diseases and were matched to the patients for age and sex.

**Inclusion Criteria:** Patients underwent regular HD, 3 times weekly for more than one year during the period of the study.

**Exclusion Criteria:** The patients who were being treated with antidepressants (because of their effects on the mood), oral iron, vitamin B12 or folate supplement (because of their effects on hemoglobin level which may be effective on the mood) were excluded from the study. All the subjects provided informed written consent to participate in the study. All the patients were submitted to the following:

- Full history taking (age, gender, marital status, level of education, employment and duration of HD).
- Complete Clinical examination: General examination, chest, heart, abdominal and neurological examination.
- Psychiatric interview and full psychiatric history to exclude other psychiatric symptoms other than depression.

The severity of depression was assessed using the Beck Depression Inventory (BDI) scoring system. It is a 21 multiple choice questionnaire with a self-report inventory which is widely used for measuring the severity of depression. The latest version of this questionnaire is designed for individuals aged = 13 years. The elements of this questionnaire related to symptoms of depression such as hopelessness and agitation, cognitions such as feelings of guilt or being punished as well as some physical symptoms such as fatigue, weight loss and lack of appetite [14]. When the test is scored, a value of 0 to 3 is assigned for each answer. At the end, the total score is compared with a key to determine the severity of

depression. The standard cut-offs were as follows: 0 to 9 no depression; 10 to 15 mild depression; 16 to 23 moderate depression; 24 to 36 severe depression and 37 or more very severe depression [15].

**Laboratory Investigation:** Serum zinc and copper were measured. Other biochemical tests as hemoglobin and serum iron level were measured to detect anemia which may cause dysphoria, serum ferritin level as an inflammatory phase protein, albumin was used as an index to detect the nutritional status and blood urea.

**Hemodialysis:** A conventional technique of hemodialysis was employed. The frequency of the therapy was three times per week, for four hours duration. The machine used was of the Fresenius and Gambro trademark. In the dialytic technique, the used dissolution with an osmolality of 295 mOsm/L had the following composition: sodium (103 mmol), potassium (2 mmol), magnesium (1.5 mmol), chlorine (109.5 mmol), bicarbonate (3mmol) and acetic acid (6.4ml). The flux from the dialysis bath was 800 ml/min.

**Blood Samples:** After the patient fasted overnight blood samples were taken directly from the vascular access in the first hemodialysis session of the week, just before the anticoagulation of the patient. The blood collection was conducted at the clinical laboratory of Al Zharaa hospital. The collected blood was left to coagulate spontaneously, after which it was centrifuged at 3000 revolutions per minute (rpm) for 10 min to obtain the serum, which was then frozen and maintained at -25°C. Biochemical markers were determined immediately, after collection at the Clinical Pathology department of Al Zahraa University Hospital using a Hitachi 911 automated analyzer using kits supplied by Roche-Diagnostic systems (Boehringer Mannheim, Germany). Frozen samples were brought to the Spectroscopy Department, Physics division, National Research Center (NRC) where further analytical determinations for zinc and copper were performed shortly afterward.

**Measurement of Zinc and Copper:** Trace element determination of Zn and Cu, were carried out using Varian Spectra 220 Flame Atomic Absorption Spectrometer (Varian, Australia). The spectral lines used for determination were 213.9 nm for Zn and 324.7 nm for Cu. The standard sources of the investigated elements are hollow cathode discharge lamps made by Cathodeon, England. The slit widths used for element determination are 1.0 and 0.5 nm for Zn and Cu respectively. The fuel used for the flame is acetylene for the two elements under investigation with oxidizing flame stoichiometry.

The oxidant (Air) flow rate was 3.5 l/min and the fuel rate ( $C_2H_2$ ) was 1.5 l/min.

To detect possible interference and matrix effects, the correlation of the absorption with the existing concentration was made by applying the normal calibration graph. No matrix interference for Zn and Cu was noted; as it can be deduced from the similarity of slopes corresponding to the two methods used (linear calibration and addition calibration method). No chemical interferences were measured while measuring the elements of interest in this work. An aliquot of 100  $\mu$ l sample was aspirated to measure the absorption signal using a homemade Teflon micro-funnel as explained by Shaban *et al.* [16]. Serum samples were diluted five times with double distilled water just before sample measurement. All solutions were prepared with ultrapure water with double distilled water commercially available. 1000-mg/l Zn and Cu standard solutions were used (Tritisol, Merck) in order to prepare the working standard solutions. The working standard solutions were freshly prepared and calibration graphs were constructed for each element with suitable standard samples according to the recommendations of the manufacturer of the instrument [17].

**Statistical Analysis:** The data was coded and entered using the statistical package SPSS version 15. The data was summarized using discipline statistics, mean and standard deviation, number and percentage for quantitative values. Statistical differences between groups or between quantitative variables were tested using one of these tests; chi square test, independent sample t test and ANOVA (analysis of variance) test. Pearson's correlation coefficient (r) test was used for correlating data.

#### Probability (P-value):

- P-value <0.05 was considered significant.
- P-value < 0.01 was considered as highly significant.
- P-value >0.05 was considered insignificant.

## RESULTS

This study was conducted on 60 Egyptian adults of both sexes (30 chronic hemodialysis patients and 30 healthy controls). Their ages ranged between 26 and 67 years with mean age of  $49.83 \pm 12.2$  years. In this study, 60% of the patients were males, 86.67% were married, 63.33% were illiterate, 36.67% were educated less than high school whereas 90% were unemployed and the mean duration of HD was  $5.40 \pm 3.529$  year as shown in Table 1.

Table 1: General data of the patients.

General data		
-----		All patients (n=30)
Age (year)	Mean±SD	49.83 ± 12.2
Gender	Male	18 (60%)
	Female	12 (40%)
Marital status	Yes	26 (86.67%)
	No	4 (13.33%)
Education	Yes	11 (36.67%)
	No	19 (63.33%)
Employment	Yes	3 (10%)
	No	27 (90%)
Duration of HD(year)	Mean±SD	5.400±3.529

n:number SD: standard deviation

Table 2 showed the comparison between the patients and the healthy controls according to their serum zinc (Zn) and copper (Cu) levels and the other biochemical tests. The mean serum Zn level ( $5.61 \pm 2.66 \mu\text{g/l}$ ) of the patients was of high significant decrease and Cu ( $1.91 \pm 3.78 \mu\text{g/l}$ ) of the patients was of high significant increase in comparison to the control. According to the other biochemical markers, albumin level ( $3.89 \pm 0.41 \text{ g/dl}$ ) and hemoglobin ( $10.52 \pm 1.52 \text{ g/dl}$ ) of the patients were of high significant decrease in comparison to the control, while ferretine ( $539.13 \pm 214.34 \mu\text{g/l}$ ) and blood urea ( $146.37 \pm 38.06 \text{ mg/dl}$ ) of the patients were of high significant increase in comparison to the control. Serum iron ( $97.63 \pm 42.80 \text{ mg/ml}$ ) of the patients insignificantly decreased.

Table 2: Laboratory Findings of the Patients in comparison to the control.

Measured parameters	Patients Mean±SD	Controls Mean±SD	t-test	p
Serum zinc $\mu\text{g/l}$	$5.61 \pm 2.66$	$9.84 \pm 0.59$	-8.48	<0.001
Serum copper $\mu\text{g/l}$	$1.91 \pm 3.78$	$1.00 \pm 0.12$	5.71	<0.001
HB concentration g/dl	$10.52 \pm 1.52$	$14.00 \pm 5.93$	-9.79	<0.001
Serum iron mg/mL	$97.63 \pm 42.80$	$100.23 \pm 5.93$	-0.29	0.775
Ferretine $\mu\text{g/l}$	$539.13 \pm 214.34$	$149.03 \pm 5.93$	9.64	<0.001
Albumin g/dl	$3.89 \pm 0.41$	$4.37 \pm 5.93$	-4.28	<0.001
Blood urea mg/dl	$146.37 \pm 38.06$	$22.13 \pm 5.93$	17.73	<0.001

SD: standard deviation t: Student's t test  $p > 0.05$ : Non-significant $P < 0.05$ : Significant difference  $p < 0.01$ : Highly significant difference

Table 3: General data of the patients according to their BDI Score.

		Group (I)	Group (II)	Group (III)	Group (IV)	P
General data		n=11 (36.67%)	n=5 (16.67%)	n=9 (30.00%)	n=5 (16.67%)	
Age (year)	Mean±SD	$44.00 \pm 13.64$	$47.60 \pm 15.08$	$57.44 \pm 5.70$	$51.20 \pm 9.60$	0.093
Gender	Male	6 (20%)	4 (13.33%)	5 (16.67%)	3 (10%)	0.791
	Female	5 (16.67%)	1 (3.33%)	4 (13.33%)	2 (6.67%)	
Marital status	Yes	9 (30%)	3 (10%)	9 (30%)	5 (16.67%)	0.141
	No	2 (6.67%)	2 (6.67%)	0 (0.0%)	0 (0.0%)	
Education	Yes	3 (10%)	2 (6.67%)	2 (6.67%)	4 (13.33%)	0.152
	No	8 (26.66%)	3 (10%)	7 (23.33%)	1 (3.33%)	
Employment	Yes	1 (3.33%)	0 (0.0%)	2 (6.67%)	0 (0.0%)	0.455
	No	10 (33.33%)	5 (16.67%)	7 (23.33%)	5 (16.67%)	
Duration of HD (year)	Mean±SD	$2.45 \pm 1.21$	$5.40 \pm 2.96$	$7.22 \pm 3.15$	$8.60 \pm 3.72$	<0.001

SD: standard deviation.

Group (I) mild depression BDI scores from 10 to 15.

Group (II) moderate depression BDI score from 16 to 23.

Group (III) severe depression BDI score from 24 to 36.

Group (IV) very severe depression BDI score 37 or more.

 $P > 0.05$ : Non-significant. $P < 0.05$ : Significant. $P < 0.01$ : Highly significant.

Table 4: Laboratory Findings of the Patients in Different Beck Depression (BDI) Score Groups.

BDI score groups	Serum zinc (µg/l)	Serum copper (µg/l)	Hb (g/dl)	Iron (mg/dl)	Ferritin (µg/l)	Albumin (g/dl)	Blood urea (mg/dl)
Group (I)	8.45±1.05	1.75±0.33	10.45±1.40	103.15±60.01	462.18±152.98	3.85±0.38	138.91±48.40
Group (II)	6.32±0.22	1.94±0.63	11.22±1.74	98.94±20.71	566.00±265.48	4.10±0.62	157.20±37.10
Group (III)	3.81±0.61	1.97±0.30	10.76±1.38	100.77±30.63	578.56±264.28	3.80±0.32	145.00±33.44
Group (IV)	1.88±0.67	2.82±0.28	9.54±1.72	78.52±37.52	610.60±193.21	3.90±0.41	154.40±25.50
F	10.193	7.250	1.147	0.385	1.946	0.594	0.329
P	0.000	0.022	0.349	0.765	0.147	0.625	0.804

SD (standard deviation).

f= ANOVA

P &gt; 0.05: Non-significant.

P &lt; 0.05: Significant.

P &lt; 0.01: Highly significant.

All patients of the present study had depression and were classified according to its severity into four groups using the Beck Depression Inventory (BDI) score:

**Group (I):** 11 patients (36.67%) with mild depression (BDI scores from 10 to 15), the mean age of them was (44 ± 13.64 years) 6 patients were males and 5 were females with mean duration of HD (2.45±1.21 years), 9 patients were married, 3 of the patients were educated of less than high school whereas only one of them were employed.

**Group (II):** 5 patients (16.67%) with moderate depression (BDI score from 16 to 23), the mean age of them was (47.6 ± 15.08 years), 4 patients were males and 1 was female, the mean duration of HD was (5.40±2.96 years), 3 of the patients were married, 2 of the patients were educated of less than high school whereas none of them were employed.

**Group (III):** 9 patients (30%) with severe depression (BDI score from 24 to 36), the mean age of them was (57.44 ± 5.7 years), 5 patients were males and 4 were females, mean duration of HD was (7.22±3.15 years), all of them were married, 2 of them were educated of less than high school and were employed.

**Group (IV):** 5 patients (16.67%) with very severe depression (BDI score 37 or more), the mean age of them was (51.2 ± 9.6 years), 3 were males and 2 were females, mean duration of HD was (8.60±3.72 years), all of them were married, 4 of them were educated of less than high school whereas none of them were employed

The BDI score was significantly higher in the patients undergoing HD for longer duration (p < 0.001) but showed insignificant differences according to the other characteristics as confirmed by Chi-square test (Table 3).

Table 5: Correlations of serum zinc level in chronic HD patients.

Parameters	Zinc	
	R	P
Age	-0.293	0.023
Duration of dialysis	-.0715	0.01
Hb	0.621	0.001
Iron	0.191	0.145
Ferretine	-0.681	0.001
Albumin	0.427	0.001
Blood urea	-0.717	0.001

r :Pearson's correlation coefficient.

P &gt; 0.05: Non-significant.

P &lt; 0.05: Significant.

P &lt; 0.01: Highly significant

Table 6: Correlations of serum copper level in chronic HD patients.

Parameters	Copper	
	r	P
Age	0.151	0.403
Duration of dialysis	0.582	0.009
Hb	0.357	0.031
Serum Iron	-0.112	0.535
S ferritin	-0.302	0.029
Albumin	0.474	0.038
Blood urea	-0.110	0.543

r :Pearson's correlation coefficient.

P &gt; 0.05: Non-significant.

P &lt; 0.05: Significant.

P &lt; 0.01: Highly significant.

Table 7: Correlation between serum zinc and copper levels and severity of depression assessed by Beck score.

Element	Beck score	
	r	p
Zinc	-0.937	<0.01
Copper	0.755	<0.01

r :Pearson's correlation coefficient.

P &gt; 0.05: Non-significant.

P &lt; 0.05: Significant.

P &lt; 0.01: Highly significant.

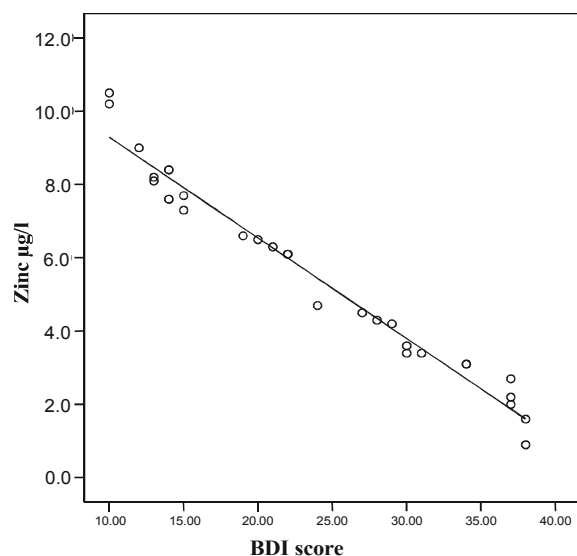


Fig. 1: The statistical negative correlation between serum zinc level and depression assessed by Beck score.

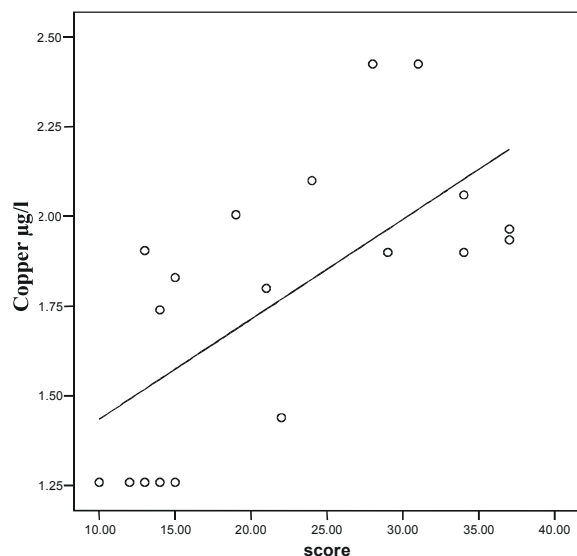


Fig. 2: The statistical positive correlation between serum copper level and depression assessed by Beck score.

Table 4 presented the mean values for zinc (Zn), copper (Cu) and the other biochemical markers of the patients according to their BDI score. Only for Zn ( $p < 0.001$ ) and Cu ( $p < 0.05$ ) were of statistical significant effect. The mean serum Zn level in group I ( $8.45 \pm 1.05 \mu\text{g/l}$ ) was the highest while group IV had the lowest mean serum Zn level ( $1.88 \pm 0.67 \mu\text{g/l}$ ). On the other hand, the mean serum Cu level in group I ( $1.75 \pm 0.33 \mu\text{g/l}$ ) was the lowest and group IV had the highest mean serum Cu level ( $2.82 \pm 0.28 \mu\text{g/l}$ ).

The serum zinc level was of significant positive correlation with the Hb, albumin and insignificant positive correlation with iron. Also, serum zinc level was of significant negative correlation with age, duration of dialysis, ferretine and blood urea as shown in Table 5.

The serum copper level was of significant positive correlation with the duration of dialysis, Hb and albumin and it was of significant negative correlation with ferretine. Also, serum copper level was of insignificant positive correlation with age and insignificant negative correlation with iron and blood urea as shown in Table 6.

The results of the current study showed significant negative correlation between serum zinc level and the severity of illness in HD depressed patients ;meaning that the severity of depression increased as the serum zinc level decreased. On the other hand, significant positive correlation was found between serum copper level and the severity of illness in the same cases; meaning that the severity of depression increased as the serum copper level increased (Table 7 and Figs 1, 2).

## DISCUSSION

Depression is the most common psychiatric illness in patients with end-stage renal disease (ESRD) and it has been associated with a poor outcome. Depression occurring in the context of another medical or psychiatric illness has been termed "compound" depression and it may be more resistant to treatment [18]. Higher levels of depression in ESRD patients treated with hemodialysis (HD) are associated with increased mortality and the effects of depression on patients' survival are of the same order of magnitude as medical risk factors [19]. Copper (Cu) and zinc (Zn) are two essential trace elements that have been studied in many diseases, including autoimmune, neurologic and psychiatric disorders [20]. Deficiency as well as excess in either zinc or copper can produce a variety of biochemical and pathological changes [21]. In addition, these two essential trace elements are neuroactive substances that can be synoptically released during neuronal activity. They have been implicated in diseases with neuropathological components [22]. Previous studies concluded an association between elevated serum Cu levels and decreased serum Zn levels and some psychiatric disorders [19]. A relation between low concentrations of zinc and mental health problems, especially in at-risk populations has been demonstrated. Zinc deficiency induced depression-like behavior in mice that was incompletely corrected by antidepressant therapy [23]. Whenever zinc

becomes deficient, copper tends to accumulate [24]. So, the aim of this study was to assess serum level of zinc and copper in patients with chronic renal failure on regular hemodialysis as well as their relationships with severity of depression and with other biochemical markers.

The mean serum zinc level was found statistically lower in the patients of the present study than in controls. This finding agreed with those found by Huang *et al.* [25] and Yilmaz *et al.* [26]. This decrease could be as a result of the significant loss of zinc in hemodialysis due to blood loss [27]. Another explanation of low zinc level in HD patients was reported by Navarro *et al.* [6], they said that this decrease may be due to one of the following mechanisms: 1) low protein intake as it is the main source of zinc, 2) a decrease of the total zinc absorption from the gastrointestinal tract, 3) a diminishing of serum albumin levels, as it is the main blood carrier (and this was in agreement with the results of the present study), 4) an increase of its excretion by fecal pathway. Therefore, an oral zinc supplementation [28] and addition of ZnCl<sub>2</sub> in the dialysis solution had been recommended to prevent the zinc deficit in these patients [29]. On the other hand mean serum copper level in patients of the current study was significantly higher than that found in healthy adult controls, this finding was in agreement with that of Huang *et al.* [25]. Also, Tonelli *et al.* [30] in their study found that levels of cadmium, lead, copper and vanadium were higher while levels of selenium, zinc and manganese were lower in hemodialysis patients, compared with controls. Navarro *et al.* [6] stated that this enhancement in the Cu level could be related either to a hemoconcentration or to a release from the dialyzer membrane. However, Emenaker *et al.* [31] did not find any influence of the type of membrane used in the hemodialysis on serum copper levels in kidney dialysis patients. Yilmaz *et al.* [26] did not find any significant difference in serum copper levels between long- and short-term dialyzed patients.

In the present study, albumin, hemoglobin and iron levels were found decreased in comparison to the control, while ferritin and blood urea increased in comparison to the control. These findings together indicated a tendency to anemia, malnutrition and liability of infection in HD patients and these results are in agreement with those obtained by Dogan *et al.* [1], Roozbeh *et al.* [8], Tang *et al.* [32] and were supported by Lee *et al.* [33] who stated that patients with end stage renal disease (ESRD) often suffer from anemia due to erythropoietin deficiency. All patients of the present study had depression and this

was coincided with Kimmel *et al.* [34], who stated that the incidence of depression in ESRD has been reported to range from 10% to 100% in different series, also Lee *et al.* [32] reported that depression is the most widely acknowledged psychosocial factor seen in patients with chronic kidney disease. In addition, Roozbeh *et al.* [8] reported in their study that the rate of depression was 76%. The exact pathogenesis of depression is still unknown, but genetic and environmental factors are believed to be important [35]. The presence of uremic products may also contribute to depression [2]. Chilcot *et al.* [36] explained that the causes of high rate of depression in HD patients may be due to loss of renal function, loss of work and also underlying anemia and uremia. These explanations were to somehow in agreement with the results of the present study as all the patients were anemic and of high level of blood urea and ferritin, but the general data of the patients in the current study including the age, gender, marital status, level of education, employment were of insignificant effect in severity of depression except for duration of HD where the BDI score was significantly higher in the patients undergoing HD for longer duration, these findings were coincided with Roozbeh *et al.* [8] and were supported by Cunha *et al.* [37], who reported that longer duration of dialysis had major effect in development of depression in patients undergoing HD.

In the current study, low serum level of zinc and high serum level of Cu was associated with a higher rate of depression in patients undergoing HD. This was explained by Rand and Murray [38], who stated that changes in plasma Cu and Zn contents can cause health problems because they can oxidize proteins and lipids, bind to nucleic acid and enhance the production of free radicals. Michel *et al.* [39] reported that copper/zinc superoxide dismutase coenzyme concentrations in postmortem pre-frontal cortical regions of the brain was significantly increased in patients with recurrent depressive disorder evidencing oxidative stress in the pathophysiology of depressive disorder. Narang *et al.* [40] suggested that ceruloplasmin, which accounts for 95% of copper in normal individuals, may affect the concentration of noradrenaline and 5-hydroxytryptamine in those areas of brain where these compounds act as neurotransmitter. Ceruloplasmin, by its effects on the life time of biogenic amines could function in the regulation of brain chemistry. Interference with this enzyme may lead to a chemical imbalance reflected in the appearance of abnormal mental status. High copper levels could also block the function of dopamine beta hydroxylase which is

highly concentrated in locus ceruleus resulting in impaired noradrenaline synthesis. Takeda *et al.* [41], stated that zinc has been found to be associated with gamma amino butyric acid (GABA) and glutamate regulation, particularly through anxiolytic activity, modulating GABAergic inhibition and seizure susceptibility. Zinc deficiency has also been found to be associated with GABAergic impairment.

On the other hand, Copper has been found to be a potent inhibitor of GABA-evoked responses, particularly in Purkinje cells. Copper toxicity, notably in Wilson's disease, could result, to some extent, from chronic GABA A receptor blockade. Data strongly suggested that Cu and Zn might interact with each other with GABA receptor complex and participate in modulation of synaptic transmission [42]. In the present study the high serum level of ferritin (as an inflammatory phase protein) and other factors such as presence of uremia, anemia and low level of albumin (as a nutritional status indicator) which may cause any sign of dysphoria and depression were of insignificant difference between the four groups. In contrast, Koo *et al.* [43] suggested that in patients on HD therapy, depression was related closely to nutritional status and could be an independent risk factor for malnutrition. Dogan *et al.* [1], found a relationship among high depression score and low albumin levels in their study. Furuland *et al.* [44], showed beneficial effects of hemoglobin normalization on depression in HD patients. Li *et al.* [45], found in their study that depressed patients had lower levels of serum albumin and higher levels of C-reactive protein (CRP). The results of the present study showed significant negative correlation between serum zinc level and the severity of illness in HD depressed patients. On the other hand, significant positive correlation was found between serum copper level and the severity of illness in the same cases. The results of the current study are in agreement with those reported by Ghanem *et al.* [19]. In addition, McLoughlin and Hodge [46] found clinical improvement of major depressed subjects by increments in serum zinc. Also, Maes *et al.* [47] found that Cu was significantly reduced by antidepressant treatment. The present study showed that the serum zinc level was positively correlated with Hb, albumin and iron, but it was negatively correlated with age, duration of dialysis, ferritin and blood urea. On the other hand serum copper level was positively correlated with age, duration of dialysis, Hb and albumin, but it was negatively correlated with iron, ferritin and blood urea. These results are in agreement with the findings of Navarro *et al.* [6].

## CONCLUSION

From the results of the present work, it was concluded that zinc deficiency and copper excess may have a role in pathogenesis of depression in HD patients; they are reversible causes so it is recommended to evaluate levels of both elements in depressed patients especially in HD patients as this may have a prognostic value of its severity.

**Recommendations:** It is recommended to use zinc supplementation and copper chelating agents as 2, 3-Dimercaptosuccinic acid (DMSA) during HD as it may improve response to therapy and/or decrease the dose that can minimize the side effects of antidepressants. Evaluation of psychiatric status should be part of the care provided to HD patients.

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