



Serum zinc and copper levels in maintenance haemodialysis patients and its relationship with depression and anxiety

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ABSTRACT

Hemodialysis (HD) patients are at risk for both deficiency, and accumulation of trace elements, although the data remains controversial. Low serum zinc level is associated with major depression in the general population; and copper interferes with zinc levels since it shares the same absorption pathways as zinc. Previous data suggest a possible zinc deficiency and copper excess is associated with depression in haemodialysis patients. The aims of this study are to assess depression and anxiety in HD patients using the Beck Depression Inventory and Beck Anxiety Inventory scoring system, and, to determine the association of serum zinc and copper levels with depression and anxiety in HD patients. A cross sectional study was conducted on 65 Haemodialysis patients stratified across equal numbers of study subjects relevant to age and sex; and compared to an apparently healthy cohort of individuals over a period of 3 months. All study subjects were analyzed for serum zinc, copper, urea, creatinine, haemoglobin and albumin after collecting detailed demographic data. Anxiety and depression were assessed by using the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) scoring system. The results of this study demonstrated that 89% and 98 % of haemodialysis patients suffered from depression and anxiety respectively. The mean levels of serum zinc and albumin were $56.25 \pm 22.85 \mu\text{g/dl}$ vs $83.8 \pm 18.12 \mu\text{g/dl}$ and $3.14 \pm 0.49 \text{ gm/dl}$ vs $3.95 \pm 0.37 \text{ gm/dl}$ respectively; which were significantly decreased in HD patients when compared to controls. A negative correlation was found between serum zinc levels and severity of depression; but, not for anxiety in HD patients. Serum copper levels in haemodialysis patients were indifferent from the controls ($118.2 \pm 41.59 \mu\text{g/dl}$ vs $102.23 \pm 30 \mu\text{g/dl}$). This study concluded that the majority of patients undergoing chronic haemodialysis were severely depressed and anxious. Patients on regular haemodialysis had decreased zinc levels and had more severe psychiatric disturbances than others.

Keywords: Haemodialysis, Depression, Anxiety, Serum Zinc, Serum Copper

INTRODUCTION

Depression; and anxiety, are common psychological problems in patients undergoing long term hemodialysis.^{1,2} It affects the recovery and mortality in patients with end stage renal disease (ESRD); especially those on Hemodialysis.³

The incidence of depression in haemodialysis patients is very high ranging from 10 – 100% as compared to 1 – 3% in the general population.⁴ The incidence of anxiety in HD patients is quoted to be 27–46%.⁵ Depressed haemodialysis patients have

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greater levels of fatigue and anxiety, greater suicide risk, and a poorer quality of life than non-depressed patients. Depression and anxiety are considered robust indicators of suicidal tendencies.⁶

In uraemia, concentrations of trace elements are modified partly as a consequence of endogenous toxicities, and impaired renal function; and, also to a lesser extent, due to dietary restriction, and other therapeutic measures. In haemodialysis patients, trace element decreases occurs through losses to the dialysate, and through urinary losses.⁷

Zinc is an essential trace element and an antioxidant required for the action of many enzymes. It plays a key role in polymeric organization of macromolecules such as DNA and RNA, protein synthesis, and cell division.⁸ Decreased zinc levels are associated with growth retardation, delayed wound healing, anaemia; and may result in depression and other psychiatric disorders in the general population. A few studies have suggested that antidepressant therapy showed effective response when zinc was combined to current treatment.^{4,9}

Copper (Cu), an essential trace metal plays an important role in redox reactions because of its easy conversion from Cu⁺ to Cu⁺⁺. Copper is a catalytic component of numerous enzymes, and is a structural component of many important proteins. Copper is not a toxic element; but, it interferes with absorption pathways; and, the distribution of other elements like zinc and iron each sharing the same process of intestinal absorption. These two vital elements zinc and copper antagonize each other at high levels of copper.

End stage renal failure patients frequently require renal replacement therapy (RRT) in the form of haemodialysis altering the trace element status. Although there are many causes of malnutrition with chronic kidney disease; RRT is likely to affect nutrition via two mechanisms; 1) losses of nutrients through the filtration and dialysis processes; and, 2) the supply of substrates and other components are potentially diluted by the replacement fluids.¹⁰ Bhogade et al have showed significant

reduction in serum zinc and copper levels of haemodialysis patients.⁷

Based on this background, this study was aimed at assessing the levels of zinc and copper in haemodialysis patients, and analyzing the relationship with depression and anxiety.

MATERIALS AND METHODS

This study was a cross sectional observational study conducted in the Nephrology Unit of Vinayaka Missions Kirupananda Variyar Medical College & Hospitals (VMKVMC & H), Salem. Clearance from the Institutional ethical committee was obtained, and the study was conducted over a period of 3 months. Study subjects were stratified into two groups consisting of 65 haemodialysis patients, and 60 healthy controls; who were then age and sex matched.

Inclusion criteria

Patients on regular haemodialysis (3 times weekly) for more than one year were included for the study.

Exclusion criteria

Patients on antidepressants or zinc supplements were excluded from the study.

All study subject patients were subjected to proper history taking, with particular attention to age and sex; marital and socioeconomic status; symptoms and etiology of ESRD; duration of the disease and haemodialysis; and history of medications.

After securing informed consent from the study subjects, venous samples were collected and assessed. Laboratory investigations included serum urea, creatinine, albumin, and Haemoglobin all were analysed by standard methods. Serum Zinc and Copper were analysed by colorimetric methods. Zinc was analysed based on the principle zinc reacting with Nitro PAPS to form a purple coloured complex in alkaline medium.

Beck Depression Inventory and Beck Anxiety Inventory were used for assessing depression and anxiety in HD patients.



BDI is a multiple choice questionnaire with a self-report inventory which is widely used for measuring the severity of depression.¹¹ The elements of this questionnaire include 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.

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 are as follows: 0 to 9 – no depression, 10 to 15 – mild depression, 16 – 23 moderate depression, 24 to 36 severe depression; and 37 or more very severe depression.¹² It is a reliable and well validated measure of depressive symptoms in both clinical and nonclinical samples.¹³ The BDI has been extensively used in ESRD populations.^{14,15}

BAI is a 21-question multiple-choice self-report inventory that is used for measuring the severity of an individual's anxiety. The BAI consists of twenty-one questions about how the subject has been feeling in the last week, expressed as common symptoms of anxiety (such as numbness and tingling, sweating not due to heat, and fear of the worst happening). BAI

mainly includes two components both cognitive and somatic. The cognitive subscale provides a measure of fearful thoughts, and impaired cognitive functioning; and the somatic subscale measures the symptoms of physiological arousal.¹⁶ A value of 0 to 3 is assigned for each answer with a maximum score of 63. The BAI has a maximum score of 63. The cut offs for anxiety inventory include 0 to 7- minimal level of anxiety, 8 to 15 - mild anxiety, 16 to 25- moderate anxiety, 26 to 63- severe anxiety.

STATISTICAL ANALYSIS

Statistical analysis was carried out using SPSS software. Values were expressed as Mean \pm Standard deviation. The Student't' test was used to find the difference in means of the two groups. Pearson correlation was used to analyse the correlation between the variables. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

This cross sectional study on 125 subjects included 65 haemodialysis patients and 60 healthy individuals. Table I shows the demographic information of the study subjects. The mean age was 53.17 ± 11.76 yrs. According to the data collected, 66% of them were males, 95 % were married.

Table 1 Demographic Information of the Study Subjects

	HD patients (n=65)	Controls (n=60)
Age (Yrs)	53.17 \pm 11.76	51.93 \pm 12.34
Gender (M/F)	43/22	40/20
Marital status(Y/N)	62/3	60/0
Dialysis duration(Months)	21.02 \pm 10.57	-
BDI Score	23.99 \pm 11.17	-
BAI Score	6.68 \pm 3.57	-

The Beck's scores and laboratory findings of the study subjects are shown in Table II. Table III depicts

the psychological status of HD patients. 89% of patients had depression out of which 11%, 28%, 32%



and 19% of them had mild, moderate, severe and very severe depression. 2% suffered from moderate anxiety whereas the remaining 98% suffered from

minimal to mild anxiety based on the Beck's anxiety inventory. Table IV shows the correlation of serum zinc and copper levels with depression and anxiety.

Table 2 Laboratory Findings of the Study Subjects

Variable	HD patients	Controls	p-value
Serum Zinc ($\mu\text{g/dl}$)	56.25 ± 22.85	83.80 ± 18.12	< 0.05
Serum copper ($\mu\text{g/dl}$)	118.20 ± 41.59	106.23 ± 30.0	> 0.05
Haemoglobin (gm/dl)	7.99 ± 1.6	12.6 ± 2.4	< 0.05
Urea (mg/dl)	83.28 ± 40.81	23.53 ± 6.01	< 0.05
Creatinine (mg/dl)	6.55 ± 2.96	0.86 ± 0.19	< 0.05
Albumin (gm/dl)	3.14 ± 0.49	3.95 ± 0.37	< 0.05

Table 3 Psychological Status of HD Patients

Severity	Anxiety (n = 65)	Depression (n = 58)
Minimal	41 (63%)	-
Mild	23 (35%)	7 (11%)
Moderate	1 (2%)	18 (28%)
Severe	-	21 (32%)
Very severe	-	12 (19%)

Table 4 Correlation of Serum Zinc and Copper Levels with Depression and Anxiety

	BDI Score		BAI Score	
	R-value	p-value	R-value	p-value
Zinc	- 0.40	< 0.05	- 0.08	> 0.05
Copper	- 0.13	> 0.05	- 0.10	> 0.05

Serum zinc ($56.25 \pm 22.85 \mu\text{g/dl}$ vs $83.8 \pm 18.12 \mu\text{g/dl}$) and albumin levels ($3.14 \pm 0.49 \text{ gm/dl}$ vs 3.95 ± 0.37

gm/dl) were significantly decreased in HD patients when compared to the controls (p-value < 0.05); and



had a significant positive correlation between them (R-value = 0.65). Significant negative correlation was found between serum zinc levels and severity of depression in HD patients (R-value = - 0.40, p-value < 0.05), whereas no correlation was found with anxiety.

There was no significant difference in serum copper levels of haemodialysis patients as compared to the controls. Severity of depression and anxiety had no association with the copper levels of haemodialysis patients.

DISCUSSIONS

Psychonephrology¹⁷ which refers to the psychiatric problems in patients of kidney disease particularly those undergoing maintenance dialysis is gaining attention in the recent past. Although there are many estimates of psychiatric illnesses in the haemodialysis patients, the association of trace elements with them is not well studied.

Haemodialysis significantly and adversely affects the lives of patients, both physically and psychologically.^{1,18,19} Haemodialysis patients suffer not only from the disease and feelings of being tethered to a machine for survival; but, also from the accompanying modifications in the quality of life. Among them, the psychiatric problems are modifiable ones; and the treatment of which could improve the outcome of the patients. It has been clearly demonstrated that depression predicts mortality in a variety of medical conditions²⁰ and as well as in patients receiving long term dialysis.²¹

Depression, the most common psychiatric abnormality in haemodialysis patients, is often overlooked because both the patients, and dialysis physicians, often fail to recognize the psychiatric symptoms. This study sought to explore the extent of depression and anxiety in haemodialysis patients; and to find out the association of serum zinc and copper levels with depression and anxiety.

Copper and zinc are two essential trace elements that have been studied in a variety of disorders including psychiatric problems. As haemodialysis is said to alter the status of these elements; the monitoring of which is necessary to prevent the associated defects.

Serum zinc levels were significantly decreased in HD patients when compared to controls in this study. This finding aligns well with Maha A. Hassan et al., who have showed a significant decrease in zinc levels of HD patients.²² This decrease could result from the significant loss of zinc in haemodialysis due to blood loss. Other possible causes of low zinc level reported by Navarro et al.; are 1) low protein intake 2) a decrease in zinc absorption from the gastrointestinal tract; 3) decreased albumin levels as it is the main carrier 4) fecal losses.²³

This study's results demonstrate a direct relationship of severity of depression with the levels of serum zinc in Haemodialysis patients. This result is in accordance with a few other studies like Maha A. Hassan et al., ZHANG Chun-hua et al.²⁴ and Roozbeh et al.²⁵, who have shown low plasma level of zinc associated with a higher rate of depression in patients undergoing HD.

Although a majority of HD patients suffered from anxiety; serum zinc levels did not show any association with anxiety.

Serum copper levels of HD patients did not differ from the controls. This finding is similar to that of Yilmaz et al.²⁶, who did not find any difference in serum copper levels between long- and short-term dialyzed patients. Whereas, Maha A. Hassan et al., and Huang et al.²⁷, have reported a significant increase in copper levels of HD patients. Serum copper levels did not show any significant association with depression or anxiety.

In the present study, albumin and haemoglobin were significantly decreased in HD individuals as it is well known that these patients suffer from malnutrition and anemia. The nutritional status of these patients is generally poor because of a combination of hypermetabolism, accelerated protein catabolism, and an altered response to nutritional support.²⁸

CONCLUSION

Haemodialysis patients should be routinely screened for symptoms of anxiety and depression; and, the trace elements status especially zinc to diminish the suffering, morbidity and mortality of these patients. Replacement of zinc in these patients, and



improvement in the depressive score should be studied to find out the benefits.

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