# **Copper, Zinc, Selenium, Cadmium and Lead Levels in plasma** of Hemodialysis Patients.

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#### Abstract

Introduction: Hemodialysis patients are at risk of developing trace elements imbalance and increase in heavy metals. **Objective**: The objective of this study was to asses plasma levels of copper, zinc, selenium, cadmium and lead of hemodialysis patients. Design: The study comprised 40 patients aged 27-65 years under regular hemodialysis for 1.8-13 years and 28 healthy age and sex matched the control. Copper, zinc, selenium, cadmium and lead plasma levels were determined by atomic absorption spectrophotometry. Results: Levels of copper, zinc and selenium were significantly decreased in dialysis patients compared with the control group; the percentage decrease was 25.5%, 20.4% and 19.0% for copper zinc and selenium, respectively. Moreover, cadmium and lead plasma levels showed significant increases among hemodialysis patients versus their matched controls with percentage of 144.6% and 28.1% for cadmium and lead, respectively. Conclusions: Levels of trace elements are altered and heavy metals showed increased plasma levels by hemodialysis. Regular monitoring of trace elements and heavy metals in hemodialytic patients is advisable.

Keywords: Hemodialysis, Copper, Zinc, Selenium, Cadmium, Lead.

#### **Introduction:**

Altered blood and tissue concentrations of trace elements have been described in patients with chronic renal failure treated by hemodialysis (HD) (Berlyne, 1995). The most important factors for this alteration are the degree of renal failure and the modality of renal replacement therapy (Vanholder et al., 1996).

Copper (Cu) is an important element for hemoglobin synthesis, connective tissue metabolism and bone development (Brody, 1994). Copper may play a role in the antioxidant defene system such as copper/zinc superoxide dismutase (Cu/ZnSOD), ceruloplasmin and intracellular thioneins. (Linder, 1996). Serum copper tends to be generally low in patients treated with HD (Lee et al., 2000). Suspected copper deficiency was also supposed to play a role in the pathogenesis of anemia and growth retardation of dialyzed patients. (D'Haese and De Broe, 1996).

Zinc (Zn) is an essential trace element; it is used by a great number of enzymes, such as alkaline phosphates, superoxide dismutase, protein kinase C and carboxypeptidase A, B (Brody, 1994). Serum and plasma zinc in HD patients were found either to be normal (Agenet et al., 1989) or more often decreased (Cabral et al., 2005). Zinc depletion was suggested to play a role in the pathogenesis of some uremic symptoms, e.g. impotence (testicular atrophy), immunological impairment,

growth retardation, abnormalities of taste (dysgeusia, anorexia) and olfaction (Zima *et al.*, 1999).

Selenium (Se) is an essential trace element with several important roles in the human body: synthesis of thyroid hormones; role in antioxidant mechanisms, as an essential component of the antioxidant enzyme glutathione peroxidase; production of prostaglandins and promotion of growth and fertility (Brody, 1994). Selenium is probably decreased in plasma, erythrocytes and white cells of dialyzed patients (Mestek et al., 2002). Selenium deficiency has been implicated as contributing to the development of cardiovascular (congestive disease cardio-myopathy), accelerated atherosclerosis, skeletal muscle myopathy, anemia, infertility and deranged immune function (Zima et al., 1999). Almost all these problems are common in patients with renal failure.

Cadmium (Cd) is toxic and lead to growth retardation, impairment reproduction, hypertension, cancer and also decreased zinc, copper and calcium absorption in the gastrointestinal tract (Linder, 1991). Serum levels of cadmium in patients with chronic renal failure were reported to be normal (Malecka *et al.*, 1994)), high (Turan *et al.*, 1992)) or even decreased (Thomson *et al.*, 1983). The whole blood cadmium levels were increased in HD patients (Hsu *et al.*, 1997).

Accumulation of lead (Pb) has been reported in patients with renal failure. In a study conducted by Staessen et al. (1992), on a random population of 965 men and 1016 women, the creatinine clearance was found to be inversely correlated with blood lead values. Furthermore, a 10-fold increase in blood lead was associated with a 10-13 ml/min reduction in creatinine clearance. Thus, the hypothesis that renal impairment resulted in blood lead accumulation could not be ruled out. In Egypt, as nutritional awarness is iasufficient and environmental pollution is high, hemodialysis patients are at risk of developing imblavced trace element levels. The present study was carried out to determine the concentration of copper, zinc, selenium, cadmium and lead in plasma of hemodialysis Egyptian patients

### Subjects and methods:

Forty patients with end stage renal failure undergoing regular hemodialysis were recruited from the outpatient's dialysis unit of Ahmed Maher teaching hospital, Cairo, Egypt, during the period from November 2004 to March 2005. All patients were on bicarbonate-dialysis with cellulose for duration of 1.8-13 years  $(4.5\pm2.4)$ . Their characteristics is illustrated in table (1). The control group comprised 28 age and sex matched healthy persons. Informed consent was obtained from all the participants. Patients were not taken any constituent drug including copper, zinc or selenium.

Fasting (12 hours) venous blood samples were collected from patients (before dialysis) and controls in heparinzed tubes. The plasma was separated by centrifugation. Plasma levels of copper, zinc, selenium. Cadmium and lead were determined according to AOAC (1990), using AAS Vario 6 atomic absorption spectrometer.

#### Statistical analysis:

The data were subjected to statistical analysis using computer programme SPSS (1996). Independent *t*-test and one-way analysis of variance (ANOVA) were used, the difference was considered significant at p-value< 0.05 (Zar, 1984).

# **Results:**

The HD patients had significantly lower plasma levels of copper (25.5%), zinc (20.5%) and selenium (19.0%) than the healthy control group (table 2).

The mean plasma levels of copper, zinc and selenium of HD patients were within the normal values. However, 5 (12.5%), 8 (20%) and 11 (27.5%) patients were classified as copper, zinc and selenium deficient, respectively.

With regard to the measured heavy metals, both cadmium and lead (table 3) were significantly elevated in HD patients as compared with the control group; the percentage increase was 144.6% and 28% for cadmium and lead, respectively.

Variable	
Age (mean±SE)	49.5±11.3 years
Sex: Males	24 (60%)
Females	16 (40%)
Dialysis time (hours/session)	6 hours
Kt/v (mean±SE)	1.12±0.23
Causes of renal disease:	
Hypertensive nephropathy	16 (40%)
Diabetic nephropathy	8 (20%)
Pyelonephritis	4 (10%)
Renal stones	4 10%)
Polycystic kidney	2 (5%)
Hyperthyroidism	1 (2.5%)
Unknown causes.	5 (12.5%)

#### Table (1): Characteristics of Hemodialysis Patients.

# Table (2): Plasma levels of copper, zinc and selenium of the HD patients and control. (Mean±S.D)

parameters	HD patients (n=40)	Control (n=28)	% change
Plasma copper (NV=80- 140 ug/dl)	99.195±28.30*	133.066±27.94	- 25.5%
Plasma zinc (NV=70-140 ug/dl)	98.123±13.20*	123.233±23.15	- 20.4%
Plasma selenium (NV= 6- 17 ug/dl)	7.427±1.87*	9.171±1.87	- 19.0%

\* Significant at P < 0.05

NV= Normal value. (Versiek and Cornetis, 1980)

#### Table (3): Plasma levels of cadmium and lead of the HD patients and control. (Mean±S.D)

parameters	HD patients	Control	% change
	(n=40)	(n=28)	
Plasma cadmium (NV= 0- 2 ug/l)	$0.592{\pm}0.179^*$	0.242±0.092	+ 144.6
Plasma Lead (NV=0.8-2.5	1.237±0.399*	0.965±0.281	+ 28.2
ug/l)			

\* Significant at P < 0.05

NV= Normal value (Versiek and Cornetis, 1980).

#### **Discussion:**

Plasma levels of copper were found significantly lower in dialysis patients compared with normal controls. These results are in keeping with a number of studies reporting lower copper plasma concentrations in hemodialysis-treated patients (Lee *et al.*, 2000 and Weissgarten *et al.*, 2001). On the other hand, high (Hsieh *et al.*, 2006) or normal plasma levels of copper (Berger *et al.*, 2004) have been reported. Decreased plasma copper may in some dialyzed patients correlate with erythrocyte superoxide dismutase activity (Vandecateele *et al.*, 1993). However,

Weissgarten *et al.* (2001) found that plasma ceruloplasmin levels as well as ceruloplasmin-bound copper fraction were significantly lower in HD patient compared with normal subjects, and that the free copper fraction was significantly higher in this patient group. This would tend to suggest that ceruloplasmin capacity to bind copper was decreased in uremic plasma.

Previuos reports have indicated a significant decrease in plasma zinc concentration in hemodialysis patients as compared with healthy controls (Cabral *et al.*, 2005; Hsieh *et al.*, 2006). The result of the present study agreed with these findings. However, in another study, zinc levels were found to be normal in HD patients (Agenet *et al.*, 1989).

The observed decreased plasma zinc levels in HD patients may be connected with low zinc intake, dietary restriction in association with augmented zinc excretion which may be caused by either decreased zinc absorption or increased its excretion or both by gut (Kimmel et al., 1988; Mahajan et al., 1989). Moerover, affinity of zinc to albumin in uremic patients was found to be decreased (Foote and Hinks, 1988). However, the decreased serum zinc concentration found in HD patients may be related to a redestribution of zinc in the tissues and not to its true deficiency because in most studies reporting a reduction in serum zinc levels, the concentration in red blood cells is elevated (Peuchant et al., 1994).

In this study, selenium level was significantly lower in HD patients than control group. Similar results have been reported in previous studies (Yavuz et al., 2004 : Hsieh et al., 2006 ). These findings seemed to be justifiable because in human among other organs, the kidney contains the highest level of selenium (Zachara et al., 2001a) and plays an important regulatory role in homeostasis of the element (Robinson et al., 1985). Glutathione peroxidase is a selenium dependent glycosylated enzyme synthesized primarilty in the proximal tubular cells of the kidney (Avissar et al., 1994). Decreased activity of this enzyme has been detected in red blood cells and plasma of chronic renal failure patients

(Zachara *et al.*, 2000& 2001b). Renal failure itself may have some influence on selenium concentration probably through decreased absorption in the small intestine (Bonomini *et al.*, 1996). Moreover, a low dialysate concentration of selenium may result in its removale during HD with resulting in deficiency (D'Haese *et al.*, 1996).

The trace elements status in chronic renal failure patients may also be influenced by residual renal function, the dialyzer membrane and size, the nature of the water used for preparation of dialysate, the method of purification and the composition of dialysis concentrate (Gault et al., 1991). Efficient water purification processes and ultra-low dialysate levels of a number of trace elements may lead to a deficiency in some essential elements (D'Haese et al., 1996). However, Padovese et al. (1992) found that the concentration of copper, zinc and selenium in HD dialysate were low and suggested that these elements should be considered more carefully in studies determining the profiles in body fluids and tissues of uremic patients undergoing regular dialysis treatment.

With regard to heavy metals, Plasma cadmium levels of HD patients were significantly higher than healthy control. This results agreed with other reports (Turan *et al.*, 1992 & Lee *et al.*, 2000). Furthermore, increased tissue concentration of cadmium in the liver and spleen and decreased concentrations in the kidneys were detected in HD patients (Smythe *et al.*, 1982).

The source of cadmium in HD patient are currently unknown, but environmental factors such as cosmetics containing heavy metals, polluted water and air may be involved (Klein *et al.*, 1972 & Sondheimer *et al.*, 1988). In healthy individual, normal functioning kidneys eliminate toxic elements from the body. However, in renal failure, declining kidney functions leads to an accumulation of potentially nephrotoxic elements which may contribute to the deterioration of renal function (Vanholder *et al.*, 1996).

Many investigators have described increased levels of lead in renal failure

patients (D'Haese et al., 1999 ; Kim et al., 2006). The results of the present study are consistent with these reports. The kidney is the main organ excreting lead from pool. Thus, lead burdens have a tendency to be accumulated in the patients with renal failure (Silbergeld et al., 1988). In patients with end stage renal disease, hyperparathyroidism, abnormal vitamin D metabolism, and consequent osteoporosis have frequently been observed (Llach and Bover, 2000). Taken together with the lack of renal excretion and stimulated bone resorption, may confirm the increased blood levels of lead in patients with end stage renal disease. Major forms of lead poisoning are colic, hypertension, and neuropathy. It is not easy to define these symptoms in patients with end stage renal disease because uremia itself may cause of and/or aggravate these symptoms. Furthermore, chronic lead poisoning may be a cause of end stage renal disease (Thun et al., 1982).

However, increased heavy metals concentrations in renal failure patients can result from excessive homeopathic intake, industrial or environmental exposure, and inhalation of cigarette smoke, administration of parental fluids or blood contact with contaminated dialysate (Vanholder *et al.*, 1996).

In conclusion; levels of trace elements are altered and heavy metals showed increased plasma levels by hemodialysis. Regular monitoring of trace elements and heavy metals in hemodialytic patients is advisable.

#### Recommendation

Further investigation on large scale on Egyptian hemodialysis patients should be carried out to assess the real situation of these elements

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مقدمة: يتعرض مرضى الغسيل الكلوي لخطر عدم توازن العناصر الدقيقة و كذلك ارتفاع مستوى بعض المعادن الثقيلة. الغرض من هذه الدراسة: هو تعيين مستوى كل من النحاس و الزنك و السيلينيوم و الكادميوم و الرصاص فى بلاز ما مرضى الغسيل الكلوي. التجربة: اشترك في هذة الدراسة 40 مريضا يقومون بعمل غسيل كلوي بشكل منتظم و كذلك 28 من الأصحاء (كمجموعة ضابطة) يماثلونهم فى السن و الجنس. و قد تم قياس العناصر السابقة باستخدام جهاز الامتصاص الذرى. النتائج: قد وجد انخفاض معنوي فى مستوى كل من النحاس و الزنك و السيلينيوم فى بلاز ما المرضى بالمقارنة بنظائر هم الأصحاء بنسبة 5.52%, 1920% لكل من النحاس و الزنك و السيلينيوم على من النحاس و الزنك و السيلينيوم فى بلاز ما المرضى بالمقارنة بنظائر هم الأصحاء بنسبة 5.52%, 2015% لكل من النحاس و الزنك و السيلينيوم على التوالي. كما زاد تركيز كل من الكادميوم و الرصاص فى بلاز ما مرضى الغسيل الكلوي زيادة معنوية عن المجموعة الضابطة بنسبة 144.4%, 2.81% لكل من الكادميوم و الرصاص على التوالي. الاستنتاج: نستنتج من هذة الدراسة أن تركيز العناصر الدقيقة و المعادن الثقيلة يتأثر بعملية الغسيل الكلوي و أنه يجب أن يتم تقدير هذه العناصر لهؤلاء المرضى بشكل منتظم.