Status of Trace Elements in Patients Undergoing Dialysis

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ABSTRACT

Introduction: Dialysis removes uremic toxins by allowing the equilibration of plasma water and dialysate across a semi-permeable membrane Present study was designed to look for status trace elements both in patients with conservative of treatment and undergoing dialysis.

Material and Methods: Total number of thirty patients were included present study and divided into three groups: Control group of ten patients Group I: chronic renal failure patients, Group II: conservative management of ten patients and Group III: chronic renal failure patients on haemo- dialysis for at least a month duration. Ten patients were included in this group. We analyzed blood samples of patients and control for trace elements. Tap water, water treated by reverse osmosis, prepared dialysate and waste was also analyzed for trace elements. Analysis for trace elements (chromium, copper, manganese, zinc, magnesium and lead) was done at Industrial Toxicology and Research Centre, Lucknow by Perkin Elmer-5000 Atomic absorption spectrophotometer.

Results: Level of chromium copper lead were elevated in waste water and in group III patients. Level of magnesium was increased in group III and group almost same in prepared II patients while it was dialysate and waste. Zn as trace metal was reduced in haemodialyzed patients. Values were higher in waste as compared to prepared dialysate (126% increase). Level of Mn in waste water was 10.34% less than that in prepared dialysate. Manganese level in group III patients were lowest as compared to group I and group II. Statistically significant (P < .01) difference was noted between group I and group III. No such significant difference was noted between group II and III patients (p > .10).

Conclusion: Despite immense published work we do not know in trace elements exact etiopathological role of causing morbidity and mortality in patients of chronic renal failure with conservative treatment and undergoing dialysis. Hemodialysis exposes patients to large volumes of water (>120 l/week) in the form of dialysate. Uremia itself also seems to be responsible for altered levels of trace elements in patients of chronic renal failure.

Keywords: Chronic Kidney Disease; Trace Elements; Minerals

INTRODUCTION

Dialysis removes uremic toxins by allowing the equilibration of plasma water and dialysate across a semi-permeable membrane. Dialysate is created by adding regulated quantitates of essential ions such as sodium, potassium, bicarbonate, calcium, and magnesium to water that has been treated to reduce solutes to very low levels. The concentration of the biologically essential ions can be matched to those of the patient to equilibrate to a desired plasma concentration.[1]

Given that essential trace elements play key roles in multiple biological systems including immunological defense against oxidation and infection, it has been hypothesized that the increased morbidity and mortality seen in HD patients may in part be due to the imbalance of trace elements that has not been recognized.[2] Studies have revealed that HD patients have significantly lower blood levels of zinc, manganese, and selenium, while blood levels of lead are likely to accumulate.[3]

It has been reported that metals such as cobalt (Co), copper (Cu), chromium (Cr), iron (Fe), magnesium (Mg), manganese (Mn), molybdenum (Mo), nickel (Ni), selenium (Se) and zinc (Zn) are essential nutrients that are required for various biochemical and physiological functions. Inadequate supply of these micro-nutrients results in a variety of deficiency diseases or syndromes.[4] Chemical contaminants can cause chemical toxicity and adverse effects if present at high enough concentrations. Chemical toxicity leads to a range of clinical outcomes, including but not limited to, speech and motor difficulties, seizures, nausea, hypotension, and diarrhea. Each chemical produces a specific reaction; for example, sulfate (>200 mg/l) is associated with nausea, vomiting, and metabolic acidosis, while lead (52–65 μg/l) has caused abdominal pain and muscle weakness. While there are defined ranges where toxicity is likely to occur, each person has a specific threshold before clinical symptoms will appear due to various physiological reasons and the individuals' health status.[5]

The kidney is the first organ affected by long-term exposure to cadmium. Severe renal cadmium poisoning may affect the glomerular filtration rate and cause tubular damage. It is unlikely that humans would ever encounter dietary exposures sufficiently high to produce these effects, except for an unusual contamination of foods.[6] Chronic lead exposure can affect a variety of organ systems, including the kidney, where it can produce lead nephropathy, a chronic interstitial nephritis. The high level of lead exposure required to cause lead nephropathy is now increasingly rare, particularly in developed countries, due to occupational controls and removal of lead from paint, gasoline, and other

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environmental sources. However, prolonged lead exposure at the lower levels encountered in developed countries may still contribute to kidney toxicity, an association that has been referred to as lead-related nephrotoxicity. [7]

Irreversible loss of nephron mass leads to development of chronic renal failure, a chemicopathological state where kidneys do not perform their usual excretor y and secretory function. It leads to disturbed chemical environment of body and impairment of various known and unknown functions of renal parenchyma. Trace metal alterations take place in Renal failure and this is understandable as some of the trace elements are excreted in abnormal amounts e.g. (zinc) and some are retained e.g.(magnesium) abnormal levels which in turn have far reaching resulting into consequences. [8]

Inspite of immense published work, lot of controversy still exists regarding the status of trace elements in patients of chronic renal failure as such and patients of CRF undergoing maintenance dialysis and the clinical implications of such alterations, are known but controversial. The present study, therefore, is designed to relate specific clinical syndromes encountered in patients of CRF specially those undergoing dialysis to specific alterations in levels of trace elements in our set up. This study also aimed to critically evaluate the trace element levels of our tap water, the role of reverse osmosis in reducing the load of for preparing dialysate and also trace metal water to trace metal levels in the dialysate concentrates being see marketed.

MATERIAL AND METHOD

Patients of end stage renal disease on maintenance dialysis for a minimum of one month duration were enrolled for the present study. Such patients are admitted in Gandhi Memorial Associated and Hospital or are being dialyzed on out patient Basis. Total number of thirty cases are included in present study. Cases were divided into three groups. Group I consisted of 10 control subjects admitted in medical wards for nonorganic illness and with intact renal functions. Group II consisted of 10 patients of end stage failure who were on conservative therapy including dietary control. All patients were treated on following lines i.e., meticulous control of fluid intake and output so that intake was equal to output + insensible loss. (Usually 500 mL), meticulous control of blood pressure by salt restriction and a combination of antihypertensive drugs, control of diabetic status where ever required by Inj. insulin or oral hypoglycemic drugs, control of infection by appropriate antibiotics or chemotherapeutic agents, dietary control by a diet chart of 30.0 gm protein, 80 mEg sodium and 60 MEg potassium daily. Control of Gastrointestinal symptoms by antiemetics and antacids, for renal bone disease calcium and vitamin D supplementation, anaemia associated with renal disease was treated by haematinics and blood transfusions whenever required and diuertics were used whenever oliguria or oligoanuría was encountered or to treat vascular over load. Group III consisted of 10 patients of end stage renal disease who were maintained on at least 10 hours of dialysis per weak for a minimum of one month period.

Haemodialysis was performed from arteriovenous fistula, A-V shunt. Usual dialysis schedule was or twice thrice a week with a single shift of 4-6 hour or duration. Haemodialysis was performed on centry 2 machine and hollow fibre Dialyzer of 1.3 mt^2 surface area. Dialysate contained acetate buffer. Concentrated dialysate of known composition was mixed with water treated by reverse osmosis in a ratio of 1:35. Blood flow rate was between 100-250 mL/minute depending upon clinical status of patient. Dialysate flow rate was 500 ml/minute. Conductivity of prepared dialysate was kept at 14. Heparin was used as anticoagulant by intermittent one hourly regimen. Injection protamine sulfate was used as antidote for heparin whenever required.

Cases were subjected to thorough clinical evaluation and investigations on following lines.

- Routine Haemogram
- Urine examination/including 24 hour urinary protein excretion, microscopic examination for casts, red blood cells, pus cells. etc.
- Serum urea, creatinine
- Serum Na^+, K^+, Ca^{++}
- Creatinine clearance as calculated by UV/P mL/minute
  U=urinary creatine
  P=Plasma creatinine
  V=Urine output/minute
- Serum protein and albumin
- To look for status of renal bone disease: serum calcium, serum phosphorus and alkaline phosphatase.
- Ultra sound study to look for renal size.

Sample collection and analysis for estimation of trace elements: Blood samples of group I and group II patients were drawn. For group III patients, a series of samples were drawn as

- Sample of Tap water
- Sample of RO water
- Sample of prepared dialysate
- Sample of waste water

Blood samples of control group, nondialysed group and dialysed group of patients.

All the samples were digested with nitric acid and perchloric acid and subjected to trace metal estimation at neurotoxicology laboratory, Industrial toxicology and Research Centre Lucknow by flame less atomic absorption spectrophotometry using a model Perkin Elmer- 5000 atomic absorption spectrophotometer.

All the data obtained by analysis of samples were analysis to obtain final subjected to statistical results.

RESULTS

In prsent study patients were divided into three groups. Group I consisted of 10 patients admitted in Medical ward for minor illnesses or functional disorders and all patients had normal renal functions. Group II comprised 10 patients of chronic renal of failure, who were maintained on conservative management. Group III comprised of 10 patients of end stage renal disease on maintenance haemodialysis. They all were on haemodialysis for at least a month period for 10 - 12 hours a week dialysis schedule.

Age and gender distribution of patients of all three groups have been shown in Table 1.

Patients of chronic renal failure whether on conservative management or on maintenance haemodialysis had symptoms and signs attributable to every organ system of body, mainly pertaining to cardiovascular system, nervous system, gastro-intestinal system as tabulated in table 2.

Symptoms mentioned 9,10,11,12 were related to haemodialysis and were observed in group III patients.

By analyzing the table 3 (graph 1) and 4 following points are evident:

1. Level of chromium copper lead were elevated in waste water and in group III patients.
2. Level of magnesium was increased in group III and group almost same in prepared II patients while it was dialysate and waste. So, for a state of hypermagnesemia tactors other than Haemodialysis appears to be important, in uremia like so many other substances are retained magnesium is also retained.

	Group I	Group II	Group III
Number of patients	10	10	10
Age in years	20-60	45-65	35-55
Male:Female	10:0	10:0	8:2

Table-1: Age and gender distributin of patients under present study.

Serial No.	Clinical features	Group II	Group III
1	Severe Anaemia Hb < 6 gm%.	2	2
2	Skin changes (darkening of complexion, itching)	2	3
3	Nausea, vomiting, anorexia	9	2
4	Taste disturbance	Nil	1
5	Hypertension	6	7
6	Irritability and sleep distubance	1	-
7	Abnormal behaviour and incoherent speech	1	nil
8	Lethargies and malaise	7	2
9	Episodes of hypotension and bradycardia and cardiac arrest	-	1
10	Chills and head ache during dialysis	-	2
11	Muscle cramps in lower limb during dialysis	-	1
12	Colicky abdominal pain during dialysis	-	1

Table-2: Clinical features of patients under present study.

Metal	Tap water	RO water	Prepared Dialysate	Waste	Group I	Group II	Group III
Cr µgm/dl	1±1.06	1±0.67	0.7±0.67	1.6±0.84	2.04±0.66	3.68±0.77	3.71±2.0
Cu µgm/dl	7.38±3.1	5.38±1.4	5.6±1.4	7.1±1.37	106.3±12.12	134.9±19.66	125.1±17.18
Mn µgm/dl	3.8±0.74	2±0.53	3.2±1.69	2.9±1.67	3.47±.50	2.69±0.39	2.38±0.42
Zn µgm/dl	88.8±31.4	21.25±11.6	49.8±20.13	112.6±109.8	606.8±26.29	522.1±24.53	569±110.4
Mg µgm/dl	255.8±17.5	115.12±51.49	249.9±18	253.5±7.12	1.41±0.44 (mg/dl)	2.46±0.43 (mg/dl)	2.77±.23 (mg/dl)
Pb µgm/dl	31.6±8.06	28.5±6.87	31.1±9.8	34.2±10.7	15.57±2.82	19.26±2.50	19.68±5.0

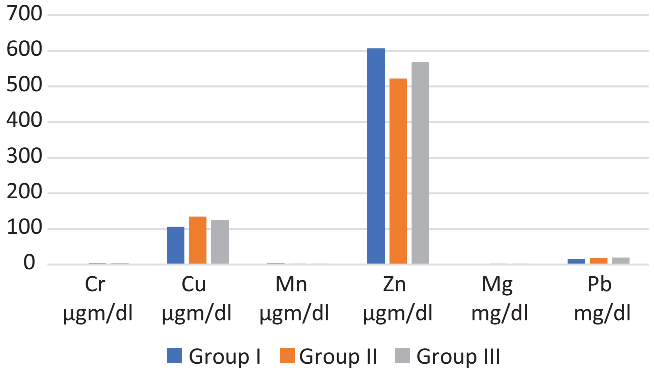
Table-3: Trace element concentration in tap water, RO water, prepared dialysate, waste, group I, II and III

Metal	Prepared Dialysate	Waste	% Change in mean value	Group III
Cr (µgm/dl)	0.7	1.6	128.5% increase	3.71
Cu (µgm/dl)	5.6	7.1	26.7% increase	125.1
Mn (µgm/dl)	3.2	2.9	10.34% decrease	2.38
Zn (µgm/dl)	49.8	112.6	126.1% increase	569.0
Mg (µgm/dl)	249.9	253.5	1.44% increase	2.77
Pb (µgm/dl)	31.1	34.2	9.96% increase	19.68

Table-4: Dialysed, waste and group iii and prepared dialysate metal waste % change in GR. III mean value

Metal	Mean values of ro water	Mean values of prepared dialysate
Cr (µgm/dl)	1.0	0.7
Cu (µgm/dl)	5.38	5.6
Mn (µgm/dl)	2.0	3.2
Mg (µgm/dl)	115.2	249.9
Pb (µgm/dl)	28.5	31.5

Table-5: Trace metal level in ro water and prepared dialysate



Graph-1: Comparison of trace elements in study groups

3. Zn as trace metal was reduced in haemodialyzed patients. Values were higher in waste as compared to prepared dialysate (126% increase).
4. Level of Mn in waste water was 10.34% less than that in prepared dialysate. So, for hypomagnesemia associated with dialysis, dialysis it self do not appear to be responsible. Manganese level in group III patients were lowest as compared to group I and group II. Statistically significant ($P < .01$) difference was noted between group I and group III. No such significant difference was noted between group II and III patients ($p > .10$). So, we can not comment as such whether process of dialysis itself is important for hypomagnesemia.

Analysis of trace elements in RO water and prepared dialysate shows that concentration of lead was more in prepared dialysate, similar was the case with Mg, Mn and Cu; that means increase in levels of Mn, Zn, Mg and Pb in dialysate (prepared from RO water and concentrated dialysate) as compared to level of trace elements in RO water is because of

impurities in dialysate concentrate, which is not mentioned by the firm in chemical composition of dialysate concentrate.

DISCUSSION

Many studies have been published concerning trace element concentrations in patients with CRF showing that the burden of a number of elements are abnormal in the dialyzed and non-dialyzed uremic patients. The type of element disturbances in uremic patients might be expected areas to vary in different geological areas, since trace element contaminants in tap water could be markedly different in different areas. Further, considerable variation in tissue concentration of trace elements is to be expected according to whether water for dialysate is simply filtered or treated by deionization or reverse osmosis.

We, in the present study, assessed the trace metal concentration in tap water, treated water with reverse osmosis and dialysate made out of dialysate concentrate and reverse osmosis treated water respectively. Waste water was also analysed (table 3).

From the present study, it is evident that reverse osmosis has role in reducing trace element load in tap water. It is clear that reverse osmosis effectively lowers the concentration of Zn (76% decrease), manganese (47.3% decrease) in RO water. Lead was decreased only by 9.8%. While no change was observed in concentration of chromium in tap water and RO water. It indicates that process of reverse osmosis is very effective for lowering the concentration of copper, manganese, zinc and magnesium. It is not at all effective in lowering the concentration chromium.

Prepared dialysate in table 5 showed increased levels of copper, manganese, magnesium, and lead as compared to RO. In table 3 we have compared trace element levels in study groups along with p value (significance value). In our study of 30 patients, we defined a number of important alterations in trace metal concentration with the blood and were able to compare these alterations in those seen in controls, non-dialyzed patients of CRF and patients on hemodialysis. Comparison of data collected in various groups of patients indicate that blood concentration of zinc and manganese were significantly decreased in both non dialyzed (group II) and dialyzed (group III) patients with CRF, while concentrations of lead and magnesium were increased in both groups of patients with CRF. Copper and chromium were also increased in both dialyzed and non dialyzed groups. The mechanism responsible for the trace element disturbances found in uremia are probably multiple and multifactorial. It is also difficult to ascertain what role these elements disturbances play in the symptoms of uremic patients.

Abnormalities of zinc metabolism have been studied in patients with chronic renal failure. Subnormal plasma zinc levels have been reported in uremic patients. In the present study we find a significantly reduced values of blood zinc concentrations in both groups of patients with CRF. Our findings are in accordance with Condon et al,[9] Tsukamoto et al,[10] Mahler et al,[11] who also reported a decreased plasma zinc concentration in both non-dialyzed and dialyzed patients with CFR.

Thomson et al,[12] in their study observed the normal plasma zinc concentration in both non-dialyzed and dialyzed group of patients with CRF. He reported that although plasma zinc concentrations were reduced 13% and 29% in non-dialyzed patients with CRF and in patients on hemodialysis respectively. This observation was at variance with that reported by Hosokawa et al,[13] who observed low zinc serum levels and high values of corpuscular zinc in chronic hemodialysis patients.

Condon et al,[9] also observed that despite low plasma zinc levels there was no tissue deficit of zinc in patients with CRF. He speculated that possibly it is something in renal failure itself rather than its chronic consequences which are depressing plasma zinc trace levels. Smythe et al,[14] in their study of trace metals in various tissues in uremic patients reported that the high tissue zinc levels may be a result of a translocation since muscle and plasma zinc concentration tend to be low in association with the increased zinc level in other tissues.

A number of investigators have reported an elevated copper concentration in dialyzed patients and in non dialyzed patient. In our study blood levels of copper were increased in both dialyzed and non dialyzed patients, but more elevation in non dialyzed patients was observed. Our findings are in accordance with in Tsukamoto et al,[10] who observed raised plasma copper in both dialyzed and non-dialyzed patients as compared to controls.

In present study we found that the levels of magnesium were elevated in non-dialysed patients 2.46±0.43 mg/dl as compared to control 1.41±0.44 mg/dl. The elevation in Mg values was more marked in dialysed group 2.77±0.23 mg/dl as compared control of patients to 1.41+0.44 mg/dl.

Our findings of hypermagnesemia are in accordance to that reported by Mahler et al,[11]and Mansouri et al.[15] They reported elevated levels of magnesium in both dialyzed and non-dialyzed group.

In the present study we observed that concentration of manganese was significantly low in both non dialyzed 2.69 ±0.39 µgm/dl ($p < .01$) and dialyzed 2.38±0.42 ($p < .01$) as compared to level in control group (3.47±0.50 µgm/dL). Findings are in contrary to Thomson et al,[12] who reported that plasma manganese concentrations were increased slightly in non dialyzed patients with CRF but were normal in patients hemodialysis. Hosokawa et al,[13] have reported that serum manganese levels were low in patients on hemodialysis and were correlated with RBC, Hb and hematocrit. He also observed a significant relationship between total proteins and serum manganese levels.

Sandstead[16] in his study also demonstrated that manganese deficiency occurs in uremia and causes skeletal abnormalities, abnormal otoliths, glucose intolerance, decreased serum cholesterol and bleeding.

The Blood levels of lead in present study elevated in both non dialyzed and dialyzed group as compared to control group. Thomson et al,[12] also reported a slight but significant rise in plasma and RBC lead in both groups of patients. In the present study, we observed significant rise in blood level of chromium in both dialyzed group and non dialysed group as compared to control group. By comparing chromium level in Tap water and RO water, we conclude that process of reverse osmosis is not effective in removing chromium. Chromium levels increased by 128.5% as prepared dialysate came in contact with blood and dialyzer membrane and became the out flow waste. Levels were also increased in haemodialyzed group, so the possible reason for this change could be increased levels as a result of uraemia itself as chromium levels were also increased in non dialyzed group of patients. Fevrier-Paul Aet al[17] investigated the potential for using trace element profiling in chronic kidney disease patients by analysing blood concentration levels of various elements and reported that three main correlation clusters were evident: firstly, vanadium, chromium, copper, silicon, and selenium, with mercury and barium more distantly related; secondly, lead, arsenic, nickel, and strontium; and thirdly, iron and zinc and study concluded that the decline in kidney function may result in the retention of non-essential trace elements.

Patients with chronic kidney disease undergoing hemodialysis (HD) are potentially at risk of deficiency and excess of trace elements. HD exposes patients to large volumes of water (>120 l/week) in the form of dialysate. Although levels of certain ions (such as potassium and calcium) are carefully regulated in dialysate, many others are measured infrequently, if ever. As a result, substances in lower concentrations in the dialysis may be leached from the body.[2]

CONCLUSION

There are number of elements present in tissues and environment in minute amount, animal trace metals. Despite immense published work we do not know in trace elements exact etiopathological role of causing morbidity and mortality in patients of chronic renal failure with conservative treatment and undergoing dialysis. Hemodialysis exposes patients to large volumes of water (>120 l/week) in the form of dialysate. Uremia itself also seems to be responsible for altered levels of trace elements in patients of chronic renal failure.

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