Medical Journal of the
Islamic Republic of Iran

Volume 7
Number 1
Spring 1372
May 1993

Review Article

ALUMINUM TOXICITY: A REVIEW IN RELATION TO CHRONIC RENAL FAILURE PATIENTS MAINTAINED ON REGULAR HEMODIALYSIS

A.A. MOSHTAGHIE, B.Sc, M.Sc, Ph.D.

Form the Department of Biochemistry, School of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Islamic Republic of Iran.

ABSTRACT

Aluminum is present in very small amounts in living organisms but abundant in the environment. A growing literature links with the biochemistry of aluminum and also with a series of diseases in chronic renal failure patients on treatment with hemodialysis. The initial description of potential aluminum toxicity in renal failure patients relates to description of dialysis encephalopathy syndrome in 1972. The major emphasise of this review will be on the recent literature involving aluminum metabolism and epidemiology of aluminum related disease. Finally the possibility that aluminum contributes to hypochromic microcytic anemia, dialysis osteomalacia (Newcastle bone disease), encephalopathy and Alzheimer disease in hemodialyzed patients has been also discussed.

MJIRI, Vol. 7, No.1, 63-72, 1993.

INTRODUCTION

In 1897, Von Dolleken described a patient with neurological symptoms and ascribed these to the high aluminum content of the dust in the mine in which the man had worked.[1] 24 years later, a patient presenting with amnesia, tremor, jerking movements and incoordination had these symptoms attributed to aluminum he had received from dust particles in the metal workshop in which he was employed.[2] Subsequently, pulmonary fibrosis was found to be prevalent in factories where the dust had high aluminum content.[3-6] Encephalopathy and pulmonary fibrosis developed in a 49-year-old man who had worked for thirteen and a half years in an aluminum factory and both conditions were attributed to his working environment.[6] The man died of progressive encephalopathy and bronchopneumonia and at autopsy his lungs and brain contained respectively 20 to 100 times more aluminum than that present in tissues of a healthy person of similar age.

The recognition of aluminum as a toxic agent in patients with chronic renal failure followed the work of Alfrey, et al. in 1976 who showed that aluminum could readily cross dialysis membranes and lead to hyperalbuminemia in patients on regular hemodialysis.[7] They had previously described a syndrome of dyspraxia and multifocal seizures in such patients and suggested these symptoms were enhanced by a toxin present in the water used to prepare the dialysate fluids. Indeed they stated that the toxin might be a trace metal.[8] There is now a considerable body of literature detailing the role of aluminum in the development of complications in patients with chronic renal failure, especially those on regular hemodialysis.

Aluminum has also been implicated as an etiological factor in the development of Alzheimer's disease[9] and

amyotrophic lateral sclerosis and parkinsonism dementia.[10]

Physicochemical properties of aluminum

Aluminum has an atomic number of 13 with a mass number of 26.77 and is the most abundant metallic element in the earth's crust, occurring in a variety of aluminosilicates such as clay, micas, and feldspars. Aluminosilicate structures are dominated by oxygen but require additional cations generally potassium, sodium, or calcium.[12,13] Ferric ions may substitute for aluminum in some mineral structures due to similarity in ionic radius and charge. The ionic radius of aluminum in solution has been reported to be 0.59Å and that for iron 0.65Å.[14,15]

In solution, oxygen donor ligands such as carboxylate and phosphate form complexes with aluminum as do salicylic, oxalic, and malonic acids.[15] Phenolic groups do not favour attachment of aluminum because the phenolic hydrogen is not dissociated significantly at pH levels where aluminum cations can exist in important proportions.[16] Complexes of aluminum with citric acid are thought to be important in the passage of aluminum through the gastrointestinal tract.[17,18] Aluminum also forms strong complexes with hydroxide, fluoride, and sulphate ions,[19] but weak complexes with amines and sulphydryl ligands.[15]

Table I. Concentration and pH dependence of mononuclear aluminum species[20]

Concentration (10-5M) species	pH_3	pH_5	pH_6	pH_7	pH_8	pH_9	pH_{10}
$Al(H_2O)_6^{3+}$	98	50	-	-	-	-	-
$Al(H_2O)_5(OH)^{2+}$	2	20	5	-	-	-	-
$Al(H_2O)_4(OH)_2^{1+}$	-	30	30	5	-	-	-
$Al(H_2O)_3(OH)_3$	-	-	50	70	20	5	-
$Al(H_2O)_2(OH)_4^{1-}$	-	-	5	20	75	95	100

In solution at pH less than 5, aluminum exists as the octahedral hexahydrate ion $Al(H_2O)_6^{3+}$. With increasing pH $Al(H_2O)_6^{3+}$ undergoes successive deprotonation to yield $Al(OH)^{+2}$, $Al(OH)_2^{+}$, $Al(OH)_3$ and $(OH)_4^{-}$.[15] The appropriate equations and dissociation constants are shown below:

$$Al(H_2O)_6^{3+} + H_2O \rightarrow Al(H_2O)_5(OH)^{2+} + 2H_2O$$
$$Al^{+3} + H_2O \rightarrow Al\,OH^{2+} + H^+ \quad K_{a1} = 10^{-5.5}$$
$$AlOH^{2+} + H_2O \rightarrow Al(OH)_2^{+} + H^+ \quad K_{a2} = 10^{-5.6}$$
$$Al(OH)_2^{+} + 2H_2O \rightarrow Al(OH)_4^{-} + 2H^+ \quad K_{a3} = 10^{-12.1}$$

Aluminum metabolism in health

Aluminum can enter the body by three routes, i.e. orally, via the lung, or by absorption through the skin, but of these only the first two are believed to be significant.[21]

Aluminum excretion can either be fecal or urinary. In relation to oral intake there are varying amounts of aluminum in food itself and some patients take aluminum containing medicines either as antacids or as phosphate binders.[25,26] Absorption of aluminum from the gastrointestinal tract occurs largely in the duodenum. The absorption process is inefficient with low rates.[27] Absorption can be enhanced in the presence of citrate and reduced in the presence of iron overload.[17,28,29]

During aluminum balance studies of healthy volunteers with an average intake of 2.5 mg/day, individuals showed a slight negative balance (1 mg/day) whereas when the same individuals were given oral aluminum supplements increasing their intake to 1-3 g/day there was a positive aluminum balance raging from 23-313 mg/day.[26]

Urinary aluminum excretion in the healthy has been found to he less than 25 µg/day.[23] However, when oral aluminum intakes were increased to 1-4 g/day urinary aluminum was as high as 495 µg/day.[30] Although the ability of the kidney to excrete aluminum has not been studied in detail, aluminum clearance can approach 50% of the glomerular filtration rate.[31] Fecal aluminum excretion is usually in excess of 90% of the oral intake.[26]

Aluminum in disease

The importance of aluminum as an etiological factor in disease did not become apparent until reliable methods for measurement of plasma and tissue aluminum became available in the 1970s. Prior to that there had been occasional reports describing aluminum toxicity in individuals who had been exposed during their work to very high concentrations of the element.

Patients with chronic renal failure usually take oral aluminum hydroxide to reduce the abosrption of phosphate and thus reduce hyperphosphatemia. Berlyne, et al.[32] determined hyperalbuminemia in such patients and this has been the stimulus for many investigators. Although a high incidence of encephalopathy and dementia was noted in chronic renal failure patients in 1972,[8] it was not until some years later when aluminum overload was implicated in this.[7] The major source of the aluminum was however not only the oral medicaments but also aluminum in dialysis fluids which also readily transfers across the appropriate membranes to the blood.[33]

Using dogs, Kovalichick, et al.[31] were able to demonstrate that after hemodialysis the plasma aluminum of healthy animlas returned to pre-dialysis levels within 48 hours, whereas in dogs with renal failure, the plasma aluminum remained elevated. In 71 patients with chronic renal failure being trated by regular hemodialysis, clinical assessment showed a good correlation between the incidence of dialysis dementia and osteodystrophy and the

aluminum concentration of the dialysate. The transfer of aluminum across dialysis membranes is dependent on the nature of the aluminum in the dialysate and this varies according to pH. Close to pH 7.0, most of the dialysis fluid aluminum is in the colloidal $Al(OH)_3$ from[34] and the amounts transferred across such membranes increase if the dialysate is more alkaline.[35]

Gill, et al.[36] have demonstrated that as the dialysis fluid for peritoneal dialysis is prepared at lower pH levels this tends to lead to a greater transfer of aluminum during peritoneal dialysis than during hemodialysis. Aluminum transfer across dialysis membranes can occur against a concentration gradient, one explanation for this being that the plasma aluminum exists partly in a protein bound form.[33,37] Overall, therefore, transfer of aluminum from the dialysate whether during hemodialysis or peritoneal dialysis is dependent on the concentration and speciation of the aluminum in the dialysis fluid and the concentration of the non-protein bound form of aluminum in the plasma.[36]

Aluminum and neurological disease

The potential of aluminum as a neurotoxin was first suggested by Dollken in 1897 who observed neuronal degeneration in rebbits given largeoral doses of aluminum salts.[1] More than 60 years later McLaughlin described a patient with dementia and attributed the symptoms to aluminum toxicity.[6] Extremely high levels of aluminum were found in tissues and it was claimed that these produced behavioral deterioration without neurofibrillary degeneration.[6] Following administration of aluminum salts to experimental animals a slow progressive encephalopthy characterized histologically by neurofibrillar degeneration was reported.[40,41]

Alzheimer's disease, a devastating neurologic disease of later life, is the most common dementia associated with loss of memory and personality changes. It is an irreversible disorder of the central nervous system and aluminum has been implicated as a factor in the etiology of this disease.[7,42] There has been an increasing burden of literature on the association between Alzheimer's disease and aluminum and the early literature has been well reviewed by Wills and Savory.[43]

Dialysis dementia, also called dialysis encephalopathy, is a progressive and frequently fatal neurologic disease described in dialysis patients by Berlyne, et al.[32] They also noted that the patinets were taking aluminum hydroxide to reduce hyperphosphatemia.

Alfrey and coworkers[9] were prompted to investigate the cause of this neurological disorder and suggested that a toxin was present in the tap water used for the preparation of the dialysis fluids. They subsequently found high concentrations of aluminum in the post-mortem muscle, bone, and brain of patients with dialysis dementia, and aluminum toxicity was then implicated as a contributing factor in the syndrome.[7] McDermott, et al. has described seven cases of dialysis dementia in a group of 19 dialyzed patients and were able to correlate the levels of aluminum in brain gray metter with the overall duration of hemodialysis treatment. The dementia occurred more frequently when softened or untreated tap water was used to make up the dialysis fluid.[44]

Behavioral abnormalities and other neuropathological disorders have been described in experimental animals injected with aluminum salts.[45] Measurement of the aluminum content of the brains of animals showed that pathology became evident when the concentration of aluminum in the brain reached 4 to 8 μg/g dry wight.[46] Analysis of post-mortem brain tissue from patients with Alzhemier's disease has shown that aluminum levels reach 4 μg/g dry weight and this is associated with severe neuropathological disturbances.[47] Although the early literature concentrated on the distinctive neurological findings of the diseaes,[8] more recent data from both Europe and USA has proposed that some forms of dialysis dementia might be part of a multisystemic disorder including encephalopathy, osteomalacia, proximal myopathy and anemia.[48-51] Neurological disorders of the Alzheimer's type are more common in geographical areas where there are high soil concentrations of aluminum which can be leached out by acid rain.[11]

The exact mechanisms by which aluminum causes Alzheimer's disease or dialysis dementia is not yet fully clear, but aluminum accumulates in the nuclei of neuronal filaments.[42] In this connection, choline acetyltransferase activity is greatly reduced in the cortex and hippocampus of the brain of Alzheimer's disease patinets[52] and aluminum has been found to inhibit choline uptake by rat brain synaptosomes.[53] In patients with dialysis dementia aluminum is located in the cytoplasm of brain cells whereas in Alzheimer's disease, aluminum is found to be associated with the nucleolus.[54] Although the concentration of aluminum in the brain of dialysis dementia patients is several folds greater than that found in Alzheimer's disease, the characteristic neurofibrillary tangles or neurofibrillary degeneration has not been found.[55]

Dialysis dementia has recently been classified into three groups.[55] These are an epidemic form which is related to the elevation of aluminum in the dialysate, a sporadic form in which aluminum intoxication is less likely,[8] and a third form associated with the early childhood renal disease.[56-58]

Aluminum and bone disease

There are several types of osteodystrophy associated with chronic renal failure, including osteitis fibrosacystica, osteosclerosis, osteoporosis, and osteomalacia. Bone pain is a common symptom in patients with chronic renal failure and is a consequence of metabolic bone disease. In

patients with chronic renal failure, Ellis and Peart found that osteitis due to secondary hyperparathyroidism occurred in 93%, osteomalacia in 40%, and osteosclerosis in 30%.[59] Their histological findings indicated that hyperparathyroidism and osteitis fibrosa occurred early in chronic renal failure, with osteomalacia developing later.

Accumulation of aluminum in bone occurs in uremic patients undergoing hemodialysis. Parsons, et al. were the first to report an increase in bone aluminum in patients with end stage chronic renal failure. The aluminum content of bone as determined by neutron activation analysis was highest in patients who have been longest on hemodialysis and the high aluminumcontent of the bone was attributed to the hemodialysis procedure itself.[60] Five years later, Alfrey and his colleagues reported a high incidence of osteomalacia and encephalopathy in chronic renal failure patients being maintained on hemodialysis and also related this to the high aluminum content of the dialysis fluid. Platts, et al. showed a high prevalence of dialysis encephalopathy and spontaneous features in 202 patients with chronic renal failure on hemodialysis and demonstrated that the water supply used for the preparation of dialysis fluid contained high concentrations of aluminum and manganese.[61] They recommended that deionized water be used to prepare dialysis fluids. In patients maintained on regular hemodialysis in Newcastle-Upon-Tyne, the incidence of osteomalacia showed a marked reduction when deionized water replaced untreated water in making up the dialysis fluids. After 1-4 years of dialysis, osteomalacia was observed in only 15% of dialysis patinets when the dialysis fluids were made with deionized water, but in 70% of patients when softened water from the same source was used.[49]

Both dialysis encephalopathy and osteomalacia occurred more frequently in centers with a high tap-water aluminum content.[49] An epidemiological survey of 1293 patients in 18 British dialysis centers showed a highly significant relationship between the aluminum content of water to prepare the dialysis fluid and the incidence of osteomalacic dialysis osteodystrophy and dialysis encephalopathy.[62] In Europe, this disease was known as Newcastle bone disease, although it occurred in other parts of the UK such as Sheffield,[61] Plymouth,[63] and Leeds.[64] Using neutron activation analysis of the bone from 34 patients with chronic renal failure and eight control subjects, Ellis, et al. in 1979 demonstrated increased bone alumium contents in 17 patients treated by hemodialysis.[65] With patients who had undergone transplantation after a long period of hemodialysis, the bone aluminum was still high but less so than in hemodialysis patients.

Following intraperitoneal administration of aluminum chloride to 20 rats for three months, aluminum accumulated in the bone and the levels were comparable to those found in the bone of dialysis patients.[65] Osteomalacia was evident in the animals after eight weeks of aluminum administration and it was suggested that the aluminum in the bone of dialysis patinets and experimental animals interferes with the mineralization process. Following administration of aluminum to uremic rats and in the liver of non-uremic animals.[66]

The mechanism whereby aluminum causes osteomalacia in patients with chronic renal failure maintained on regular hemodialysis is not fully understood. An alteration in vitamin D metabolism has been found in aluminum related osteomalacia.[67] This aluminum related disease is different from classical osteomalacia in being resistant to very large doses of vitamin D. The patients have bone fracture and bone pain.[67,68] The possibility that aluminum might interfere with parathyroid hormonefunctions was suggested by Morrissey, et al.[69] who investigated the effect of adding aluminum to *in vitro* cultures of the parathyroid cellsand found thataddition of 0.5-20 mmoles/L of aluminum to culture medium containing low concentrations of calcium ions progressively inhibited the secretion of PTH. Aluminum did not effect protein synthesis nor was the conversion of pro-PTH to PTH affected. Other workers have also demonstrated a good correlation between aluminum deposition and parathyroid hormone secretion.[70-77] Norris, et al.[78] have identified aluminum-induced bone disease as being of two types, an epidemic form in which the aluminum overload is derived from the dialysis fluid anda sporadic form due to theoral aluminum hydroxide.[78] Using cultured mouse osteoblast-like and osteoclast-like cells, Lieberherr, et al.[77] showed that the low rates of bone formation observed during aluminum intoxication might be due to the inhibtion of collagen synthesis and to depressed cell proliferation. They also suggested that aluminum might indirectly influence bone remodelling by interfering with the action of PTH and 1,25 $(OH)_2 D_3$ on bone cells.

With regard to the location of aluminum within the bone, Cournot-Witmer, et al.[68] and Boyce, et al.[79] reported that the aluminum was localized at the mineralization front between the osteoid and the calcified bone and this was confirmed. In patients with aluminum associated bone disease the accumulation of aluminum within the mineralization front interferes with bone mineralization.[74] Other evidence confirmed the reduction in the mineralization front contributes to the osteomalacia in patients on long-term hemodialysis.[80]

Aluminum and anemia

An association between anemia and chronic renal failure was first described by Richard Bright in 1837. It is now recongnized that the anemia is a complex and multifactorial disorder involving both destruction and production of red cells.[81] In 1978, Elliot and MacDougall[82] described anemia in six patients with osteomalacic dialysis

osteodystrophyand with dialysis encephalopathy and identified that a reduction in hemoglobin preceded the onset of neurological symptoms and evidence of bone disease. In the saune year, Elliot, et al.[83] suggested a possible causal relationship between the anemia and aluminum intoxication in patients on regular hemodialysis. Their findings were confirmed by a further study.[84] The anemia associated with aluminum overload is non-iron deficient, microcytic, and hypochromic. It is reversible in so far as the use of dialysis fluids with a low aluminum content leads to improved hematology.[85,86]

In experimental animal models, daily injection of 30 nmol aluminum salts to uremic rats significantly reduced the hematocrit, hemoglobin and MCV as compared with non-uremic control animals. However, the plasma iron, transferrin concentrations, and the iron-binding capacity remained within the reference range. It has been claimed that aluminum intoxication of the uremic animals leads to a microcytic anemia by interfering directly with hemoglobin synthesis.[87] The exact mechanism by which aluminum causes anemia in chronic renal failure patients has not been clearly reported. *In vitro* experiments showed that trivalent cations including aluminum inhibited the action of the copper-containing protein ferroxidase(ceruloplasmin) which promoted the incorporation of ferric ion into transferrin.[88]

When rat liver mitochondria were also incubated with 2 mol/L of aluminum, delta-amino-laevulinic acid dehydratase activity was increased, whereas with 4 mol/L of aluminum the enzyme was inhibited.[89] This *in vitro* inhibition of the delta-amino-laevulenic acid dehydratase by aluminum has been confirmed later.[90] mcGonigle and Parsons have proposed that the disturbance in hemoglobin synthesis and porphyrin metabolism might be due to secondary effects of PTH on the bone marrow.[91] Decreased erythropoietin production with diminished erythropoiesis and reduced red cell survivial time have also been considered as the primary causes of anemia in patients maintained on hemodialysis.[81] Animal studies have confirmed that aluminum overload can cause anemia. In addition, aluminum-induced anemia is generally preceded by development of significant degres of microcytosis and a reduction in the red blood cell production. In the latest study the binding of aluminum to serum human transferrin has been reported. In 1983, G.A. Trapp using spectrophotometric titration and gel filtration techniques postulated the binding of two molecules of aluminum per molecule of transferrin.[92] This finding was then confirmed by a number of laboratories throughout the world[93] using different biochemical techniques including spectrophotometric titration,[94] equilibrium dialysis,[95] and polyacrylamide gel electrophoresis.[96] Thebinding of aluminum to serum transferrin has been investigated in our laboratory. We have also found that each molecule of transferrin could bind two atoms of aluminum. On the other hand, each transferrin could be bound to 0.67 μg of aluminum.[97] The binding of aluminum and other ions including chromium to serum transferrin could interfere with iron motabolism including heme synthesis which might be the cause of anemia in chronic renal failure patients.[98-99]

Transferrin is a β-glycoprotein with a molecular weight of 80 KD and responsible for the transportation of iron from its site of absorption to the site of utilization in the cell.[99] Using everted gut sac it has been reported recently that aluminum might interfere with iron absorption[100,101] and to the reduction of iron transport in the blood.[102]

The next step in iron metabolism is uptake by the cell through transferrin receptors which are present at cell surface membrane.[103] Aluminum-transferrin as well as iron transferrin is able to bind to the saune receptor at the placental membrane with a binding constant of $Ka=10^{+15}M^{-1}$.[104] Subcellular fractionation studies of rat liver showed that the majority of the aluminum was tightly bound to nuclei and mitochondria. In the nucleus, the majority of the aluminum was in the non-DNA part of the nucleoprotein and electrophoresis techniques showed that histones could bind aluminum and iron.[105]

The aluminum uptake by rat isolated hepatocytes and its effect on oxygen uptake has been investigated. The hepatocytes' aluminum content has increased after incubation in media containing aluminum-transferrin or free aluminum. The free aluminum influx to the cell is two times more than aluminum bound transferrin. The aluminum uptake from transferrin depends on the degree of saturation of transferrin with aluminum.[106] Aluminum-transferrin complex and ultrafiltrable fractions of aluminum lead to the reduction of oxygen uptake and heme synthesis by rat isolated mitochondria.[98,106] The exact mechanism by which iron as well as aluminum is taken up by the mitochondria is still a matter of speculation. It has been reported that transferrin is a direct iron donor to isolated mitochondria for heme synthesis.[107] The existence of transferrin receptors on the mitochondrial membrane and transferrin molecule in the mitochondria has been reported recently by our laboratory using affinity chromatography technique.[108] In this regard, we have prepared rat liver mitochondria and the probable cytosolic contamination was checked by determination of lactate dehydrogenase. Aliquots (500 μL) of solubilized mitochondria were then applied to a column which was packed with anti-human transferrin coupled to Sepharose-LE CNBr. Transferrin and transferrin receptors were eluted and identified by immunoelectrophoresis and sodium dodecyl sulfate-polyacrylamide electrophoresis (SDS/PAGE) techniques as reported elsewhere.[108] Postulation of transferrin receptors on the mitochondrial membrane may therefore suggest the internalization of iron-transferrin as well as aluminum transferrin to the mitochondria. Aluminum as a com-

plex with transferrin significantly reduced iron uptake and subsequently heme synthesis by the mitochondcia.[98] Our datashowed thataluminum does notalter the ferrochelatase activity which is responsihle for the incorporation of Fe(II) into protoporphyrin. We may now come to the conclusion that the reduction in serum iron concentration, hemoglobin, andotherseum iron parameters[102] is initially due to the competition between aluminum with iron metaholism in these patients, particularly at the mitochondrial level. We believe more investigation should be done to elucidate the exact mechanism by which aluminum causes dialysis osteodystrophy, neurological disease and hypochromic microcytic anemia.

Prevention and treatment of aluminum overload

To prevent aluminum overload in hemodialysis patients, it is clear that all sources of aluminum must he avoided. Thus, the use of aluminum-containing oral phosphate binders should be replaced by other phosphate-hinding agents such as magnesium hydroxide and calcium carbonate.[109] During dialysis, aluminum traverses the dialysis membrane against a concentration gradient.[33] Reversal of this process can be effected, hut requires almost complete elimination of aluminum from dialysis fluid. It has been recommended that the aluminum contents of dialysis fluid should be less than 0.2 μmol/L,[110] or less than 0.5 μmol.[111] Overall, efforts have been directed towards reducing the aluminum content of the dialysis fluid.

Hemodialysis itself has not been effective in reducing the hody burden of aluminum since more than 80% is tightly hound to protein.[112] Desferrioxamine is an iron-chelating agent which after infusion into patients allows substantial quantities of aluminum to be removed by hemodialysis.[112-115]

Desferrioxamine is a colourless crystalline base and one of the metaholites of actinomycetes. It forms a brown-red colour complex with iron and has maximum absorption at 420-440 nm. The formation of iron and desferrioxamine complex is pH dependent and occurs very quickly in the pH of range of 2-4.5 and very slowly at pH 7.5. Structurally, it is composed of one molecule of acetic acid, two molecules of succinic acid and three molecules of 1-amino-5 hydroxylamine pentane. The association constant of Fe^{3+} and desferrioxamine is $10^{31}M^{-1}$.[116] Desferrioxamine is mainly used as an iron-chelating agent to treat iron overload. Mobilization of iron stores in both parenchymal and reticuloendothelial cells occurs following use of desferrioxamine.[117-119]

Chemically, trivalent aluminum is similar to iron in terms of ionic radius. In solution, aluminum has an ionic radius of 0.054 nm and iron 0.065 nm.[118] Due to chemical similarities between aluminum and iron, aluminum forms a strong 1:1 complex with desferrioxamine to produce the aluminum chelate aluminoxamine with a molecular weight of approximately 630 daltons.[119] The stability constant of the aluminum to desferrioxamine complex has been reported to be $10^{22}M^{-1}$.[119-120]

Administration of desferrioxamine leads to an increase of plasma aluminum levels in patients on chronic hemodialysis[115] and in aluminum overload patients there is a significant increase in both the ultrafiltrahle and protein-hound aluminum of plasma.[112,122,123] This is probably due to mohilization of aluminum from tissue. In patients with aluminum overload, 80% of the plasma aluminum is protein hound whereas after infusion of desferrioxamine, only 70% is protein bound.[115] Others have found that the proportion of plasma aluminum which can be ultrafiltered through selective membranes is increased more than four-fold after treatment with desferrioxamine.[113] It has been suggested that after desferrioxamine infusion, aluminum might be removed from hone marrow and bone trabeculae.[111] Histological investigation of bone of hemodialysis patinets with aluminum overload, after desferrioxamine administration, has shown a significant reduction in the stainahle aluminum on the surface and an increase in new hone formation.[124] Removal of aluminum from the bone traheculae causes the successful reversal of the calcification defect and restoration of mineralization. Removal of aluminum from bone marrow was thought to beam explanation for an improvement in the anemia.[125,126]

REFERENCES

1. Von-Dolleken: Ueber wirkung des Aluminium. Arch Exp Bath Pharm 39: 97-120, 1897.
2. Spofforth J: Case of aluminum poisoning. Lancet 1:1301, 1921.
3. Wyatt JP, Riddle A: The morphology of bauxitefume pneumoconiosis. Am J Pathol 25: 447-460, 1949.
4. Mitchell J: Pulmonary fibrosis in aluminum workers. Br J Indust Med 16: 123-125, 1959.
5. Mitchell J, Manning GB, Molyneux M, Lane RE: Plumonary fibrosis in workers exposed to finely powdered aluminum. Br J Indust Med 18: 10-20, 1961.
6. McLaughlin AIG, Kazantz G, King E, Tear D, Porter RJ, Owen R: Pulmonary fibrosis and encephalopathy associated with the inhalation of aluminum . Br J Indust Med 19: 253-263, 1962.
7. Alfrey AC, Legendre G, Kaehny WD: The dialysis encephalopathy syndrome, possible aluminum intoxication. New england J Med 294: 184-188, 1979.
8. Alfrey AC, Mishell MM, Burks J, Contigulia SR, Rudolph H, Lewin E, Holmes JH: Syndrome of dyspraxia and multifocal seizures associated with chronic hemodialysis. Trans Am Soc Artif Inter Organs: 18: 257-261, 1972.
9. Crapper DR, Krishan SS, Dalton A: Brain aluminm distribu-

tion in Alzheimer,'s disease and experimental neurofibrillary degeneration. Science 180: 511-519, 1973.
10. Perl DP, Brody AR: Alzheimer's disease, x-ray spectrometric evidence of aluminum accumulation in neurofibrillary tangle-bearing. Science 208: 297-298, 1980.
11. Perl DP, Gajdused DC, Garrut ORM: Interneuronal Al(III) accumulation in amyotrophic lateral sclerosis and parkinsonism of Gauma. Science 217: 1053-1055, 1982.
12. Liptrot GE: In: Modern Inorganic Chemistry. Fourth edition, Bell Hyman, pp 205-211, 1983.
13. Hem JD: Geochemistry and aqueous chemistry of aluminum. Kidney Int 29:18: S-3-S-7, 1986.
14. Trap GA: Aluminum binding to organic acids and plasma proteins. J Environ Path Toxicol Oncol 6: 15-20, 1985.
15. Martin RB: The chemistry of aluminum as related to biology and medicine. Clin Chem 32: 1797-1806, 1986.
16. Lind CJ, Hem JD: Effects of organic solutions on chemical reactions of aluminum. Geological survey watersupply paper, 1827-G. U.S.A. Preting Affair, Washington DC, 1975.
17. Slanina P, Fech W, Ekstrom L-G, Loff LG, Slorach S, Cederger A: Dietary citric acid enhances absorption of aluminum in antacids. Clin Chem: 32: 539-541, 1986.
18. Moshtaghie AA, Ani M, Taher M: Aluminum interferences with iron uptake by rat everted gut sacs. Abs Clin Chem 36: 970, 1990.
19. Driscoll CT, Baker JP, Bisogni JJ, Schofield J: Effect of aluminum speciation on fish in dilute acid waters. Nature 284: 161-164, 1980.
20. Siegel N: Aluminum interaction with biomolecules. The molecular basis for aluminum toxicity. Am J Kindey Dis 60: 353-357, 1985.
21. Campbell IR, Cass JS, Cholack J, Kohoe RA: Aluminum in the environment of man. Arch Ind Health 15: 359-448, 1957.
22. Sorenson JRJ, Campbell IR, Tepper LB, Lingg RD: Aluminum in the enviroment and human health. Environ Health Perspect 83: 3-95, 1974.
23. Alfrey AC: Aluminum. Advances in Clinical Chemistry 23: 69-71, 1983.
24. Davenfort A, Davison AM, Newton KF, Will EJ, Giles GR, Toothil C: Urinary aluminum excretion following renal transplantation and the effect of pulse steroid therapy. Ann Clin Biochem 27: 25-31, 1990.
25. Ondreick R, Kortus J, Ginter E: Aluminum: its absorption, distribution and effect on phosphorous metabolism. In: Intestinal Absorption of Metal Ions, Trace Elements and Radionuclides. Skoryna SS, Woldron D, (eds). Pergammon, Oxford, London, pp, 293-305, 1971.
26. Gorsky JE, Dietz AA, Spencer M, Osis D: Metabolic balance of aluminum studied in six men. Clin Chem 25: 1739-1793, 1979.
27. Feinroth M, Feinroth MW, Berlyne G: Aluminum absorption in the rat everted gut sac. Min Elect Metabol 8: 29-25, 1984.
28. Brown S, Savory J, Wills MR: Absorption of aluminum from either citrate or chloride in rat everted gut sac. (Abs) Clin Chem 33: 933, 1987.
29. Canata JB, Suarz Sc, Cuesta V, Rodriguez RR, Allende MT: Herrara J. Perezlianderal J: Gastrointestinal aluminum absorption, it is modulated by iron absorption. Proceeding European Dialysis Transplantation Association 21: 354-359, 1989.
30. Recker RR, Blotcky AA, Lefller JA, Rock EP: Evidence of aluminum absorption from the gastrointestinal tract and bone deposition by aluminum carbonate with normal renal function. J Lab Clin Med 90: 810-815, 1977.
31. Kovalchick MT, Kaehny WD, Heyy AD, Jackson JT, Alfrey AC: Aluminum transfer during hemodialysis. J Lab Clin Med: 92: 712, 1978.
32. Berlyne GM, Pest D, Ben Ari J, Weinberger J, Stern M, Gilmore GR, Levine R: Hyperalbuminemia from aluminum resins in renal failure. Lancet II: 494-496, 1970.
33. Kaehny WD, Hegg AP, Alfrey AC: Gastrointestinal absorption of aluminum from aluminum-containing antacids. N Engl J Med 296: 1389-1390, 1977.
34. Parkinson IS, Ward MK, Kerr DNS: Dialysis encephalopathy, bone disease and anemia, the aluminum intoxication syndrome during regular hemodialysis. J Clin Pathol 34: 1285-1294, 1981.
35. Sidemen S, Manor D: The dialysis dementia syndrome and aluminum intoxication. Nephron 31: 1-10, 1982.
36. Gill P, Debatiani P, Fayioli F: Positive aluminium balance in patients on regular peritoneal treatment and effect of low dialysate pH. Proceeding European Dialysis Transplantation Association 17: 219-224, 1980.
37. Berlyne GM: Plasmapheresis, aluminum and dialysis: 1153, 1978.
38. Ludin AP, Caruso C, Sars M, Berlyne GM: Ultrafiltrable aluminum in serum of normal man. Clin Res 26: 636A, 1978.
39. Wills MR, Savory J: Aluminum homeostasis. In: Aluminium and Other Trace Elements in Renal Disease. Taylor A. (ed.), Bailliere-Tindall, London, pp 24-35, 1986.
40. Klatzo I, Wisnieski H, Streicker E: Experimental production of neurofibrillary degeneration I. Light microscopic observation. J Neuropathol Exp neurol 24: 187-199, 1965.
41. Terry RD, Pena C: Experimental production of neurofibrillary degeneration. II. Electron microscopy, phosphate histochemistry and electron probe analysis. J Neuropathol Exp Neurol: 24: 200-210, 1965.
42. Shore D, Wayatt RJ: Aluminum and Alzhemimer's desease. J Nerv Mental Dis 171: 553-557, 1983.
43. Wills MR, Savory J: Aluminum poisoning, dialysis encephalopathy, osteomalacia and anaemia. Lancet ii: 29-30, 1983.
44. McDermott JR, Al, Ward MK, Parkinson IS, Kerr DNS: Brain aluminum concentration in dialysis encephalopathy. Lancet i: 901-904, 1976.
45. Tomoko GJ, Crapper DR: Neuronal variability. Non-stationary responses to identical visual stimuli. Brain Res 79: 405-418, 1974.

46. Crapper DR, Tomoko GJ: Neuronal correlates of an encephalopathy associated with aluminum neurofibrillary degeneration. Brain Research 97: 253-264, 1978.
47. Crapper DR, Krishnan SS, Quittkat S: Aluminum neurofibrillary degeneration and Alzheimer's disease. Brain 99: 67-80, 1976.
48. Flendring JA, Kruish H, Das HA: Aluminum intoxification, the cause of dialysis dementia. Proceedings European Dialysis Transplatation Association 13: 355-361.
49. Ward MK, Ellis HA, Feest TG, Parkinson IS, Kerr D, Herrington J, Goode GL: Osteomalacia, dialysis osteodystrophy: evidence for a water-borne aetiological agent, probably aluminium. Lancet I: 841-845, 1978.
50. Pierides AM, Edward WG Jr, Gullum VT Jr, McCallJR, Ellis HA: Hemodialysis encephalopathy with osteomalacia, fractures, and muscle weakness. Kidney Int: 18: 115-124, 1980.
51. Prior JC, Cameron EC, Knickerbrocker WJ, Sweeney VP, Suchoweskey O: Dialysis encephalopathy and osteomalacia bone disease. Am J Med 72: 33-42, 1982.
52. Davies P: Neurotransmitter related enzyme in dementia of Alzheimer's type. Brain Res 171: 319-327, 1979.
53. Lai JCK, Guest JF, Leung TK, Lim L, Davison AW: The effects of calcium, manganese and aluminum on sodium, potassium-activated, and magnesium-activated ATP activity and choline uptake in rat brain synaptosomes. Biochem Pharmacol: 29: 141-146, 1980.
54. Petit TL: Aluminium in human dementia. Am J Kidney Dis 6: 313-315, 1985.
55. Arieff AI: Aluminum and pathogenesis of dialysis encephalopathy. Am J Kidney Dis 6: 317-321, 1985.
56. Rotundo A, Nevins TE, lipton M: Progressive encephalopathy in children with chronic renal insufficiency, infancy. Kidney Int 21: 486-411, 1982.
57. Androli SP, Bergstein JM, Sherrad DJ: Aluminum intoxication from aluminum-containing phosphate binders in children with azotemia not undergoing dialysis. N Engl J Med 310: 1079-1084, 1984.
58. Millinear DS, Malekzadeh M, Liberman E, Coburn JW Plasma aluminum levels in pediatric dialysis patients. Comparison of hemodialysis and continuous ambulatory peritoneal dialysis. Mayo Clin Pro 62: 269-274, 1987.
59. Ellis HA, Peart RM: Azotemic renal osteodystrophy. A quantitative study on iliac bone. J Clin Pathol 26: 83-101, 1973.
60. Parsons SV, Davies C, Godde C, Ogg C, Siddigi J: Aluminum in bone from patients with renal failure. Br Med J 4: 273-278, 1971.
61. Platt MM, Good: GC, Hislop JS: Composition of the domestic water supply and the incidence of fractures and encephalopathy in patients on hemodialysis. Br Med J 2: 657-660, 1977.
62. Parkinson IS, Ward MK, Feest TG, Fawcet RWP, Kerr DNS: Fracturing dialysis osteodystrophy and dialysis encephalopathy. Lancet 406-409, 1979.
63. Leather HM, Lewing IG, Calder E, Braybroode J, Cox KR: Effect of water deionisers on Fracturing osteodystrophy and dialysis encephalopathy in plymouth. Nephron 29: 83-84, 1981.
64. Walder CG, Aaron JE, Peacock M, Robinson PJA, Davison AM: Dialysate aluminum concentration and renal bone disease. Kidney Int 21: 411-415, 1982.
65. Ellis HL, McCarty JH, Herrington J: Bone aluminium in hemodialysis patients and in rats injected with aluminium chloride, relationship to impaired bone mineralization. J Clin Pathol 32: 832-844, 1979.
66. Chan YL, Alfrey AC, Solomon P, Lessner D, Hills E, Dunstan CR, Evans RA: Effect of aluminum on normal and uremic rat's tissue distribution, vitamin D metabolites and quantitine bone histology. Calcif Tissue Int 35: 344-351, 1983.
67. Massrey SG, Ritz E, Verbeckmoes R: Role of phosphate in genesis of secondary hyperparathyroidism. Nephron 18: 77-81, 1977.
68. Courent-Witmer G, Zingraff J, Plachat JJ , Essaig F, Leferre R, Boumatic P, Bourdea A, Gorabdia M, Calle P, Boufdon R, Brueke T, Balson S: Aluminum localization in bone from hemodialysis patients, relation to matrix mineralization. Kidney Int 20: 375-385, 1981.
69. Morrisey J, Rothstein M, Mayor G, Slatopolsky E: Suppression of parathyroid hormone secretion by aluminum. Kidney Int 23: 699-704, 1983.
70. Cournot-Witmer G, Plachot JJ, Dourbeau A, Leiberherr M, Joryetti V, Mendes V, Harper S, Hemmerle J, Drueke J, Balsan S: Effect of aluminum on bone and cell localization. Kidney Int 29: Suppl: 18: S-37-S-40, 1986.
71. Ott SM: Aluminum accumulation in individuals with normal renal function Am J Kidney Dis 6: 297-301, 1985.
72. Malluche HH, Faugree MC: Aluminum. Toxin or innocent bystander in renal osteodystrophy? Am J Kidney Dis 6: 336-341, 1985.
73. Goodman WG: Bone disease and aluminum pathogenic considerations. Am J Kidney Dis 6: 303-335, 1985.
74. Goodman WG: Experimental aluminum-induced bone disease: studies *in vivo*. Kidney Int 29 suppl. 18: S-32-36, 1986.
75. Andress DL, Endress DB, Ott SM, Sherrard DJ: Parathyroid hormone in aluminum bone disease. A comparison of parathyroid hormone assay. Kidney Int. 29 supply 18: S-87-S-90, 1986.
76. Bourdau AM, Plachot J, Cournot-Witmer G, Pointillart A, Balson S, Sach SC: Parathyroid response to aluminum *in Vitro* ultrastructural changes and PTH release. Kidney Int 31: 15-24, 1987.
77. Lieberherr R, Migrorsse B, Cournot-Witmer G, Herman-Erle MPM, Balson S: Aluminum action on mouse bone cell mediated and response to PTH and $1,25(OH)_2D_3$. Kidney Int 31: 747, 1987.
78. Norris KC, Crooks PW, Verbeken HG, Herz G, Milliner D, Kornel G, Slutopsky E, Andress DL, Sherrand DL, Coburn

J: Clinical and laboratory features of aluminum-related bone disease: difference between sporadic and epidemic forms of syndrome. Am J Kidney Dis 6: 342-347, 1985.
79. Boyce BF, Elder HY, Fell GS, Junors BJ, Elliot HL, Beastall G, Fogelman I, Boyce II: Hypercalcemic osteomalacia due to aluminum toxicity. Lancet ii: 1009-1012, 1982.
80. Posner AS, Blumhthal NC, Bosky AL: Model of aluminum induced osteomalacia: inhibition of apatite formation and growth. Kidney Int. 29 Suppl 18: S-17-S-19, 1986.
81. Kaiser L, Schwartz KA: Aluminum-induced an-aemia. Am J Kidney Dis 6: 348-352.
82. Elliot HL, MacDougall AI, Haase G, Cumming RLC, Gardner PNE, Fell GS: Plasmapheresis in the treatment of dialysis encephalopathy. Lancet 11: 940, 1978.
84. Elliot HL, MacDougall AE, Fell GS: Dialysis encephalopathy: evidence implicating aluminum. Dial Transpl 9: 1027-1030, 1980.
85. Short AEK, Winney RI, Robson JS: Reversible microcytic hypochromic anemia in dialysis patients due to aluminum intoxication. Proceeding European Dialysis Transplantation 17: 233-236, 1980.
86. O'Hare AE, Murnagham DJ: Reversal of aluminum-induced hemodialysis anemia by low aluminium dialysate N Engl J Med 306: 354-656, 1982.
87. Touam M, Martinez F., Lacour B, Bourdon R, Zincyraff, J;, Giulio SD, Drueke T: Aluminium-induced reversible microcytic anaemia in chronic renal failure. Clinical and experimental studies. Clinical Nephrology 19: 295-298, 1983.
88. Huber CT, Friden E: The inhibition of ferroxidase by trivalent and other metal ions. J Biol Chem 245: 3979-3984, 1970.
89. Meredith PA, Moore MR, Goldbert A: The effect of aluminum, lead, zinc on delto-amino laevulenic dehydratase. Biochem Soc Trans 2: 1243, 1974.
90. Adbulla M, Svesson S, Haeger-Aronson B: An antagonistic effect of zinc and aluminum and lead inhibition of delta-amino laevulenic acid dehydratase. Arch Environ Health 36: 464-469, 1979.
91. McGonigle RJS, Parsons V: Aluminum-induced anemia in hemodialysis Patients. Nephron 39: 1-9, 1985.
92. Trapp GA: Plasma aluminum is bound to transferrin. Life Science 33: 311-316.
93. Ani M, Moshtaghie AA, Bazraphshani MR: The characteristics of aluminum bindings to human transferrin. (Abst) Clin Chem 36: 970, 1990.
94. Moshtaghie AA, Ani M, Bazrafshani MR: Comparative binding studies of aluminum and chromium to human transferrin. Effect of iron. Biol Trace Element Res 32: 39-46, 1992.
95. Skillen AW, Moshtaghie AA: The binding of aluminum by human transferrin and the effect of desferrioxamine. An equilibrium dialysis study. In: Taylor A(ed). Aluminum and Other Trace Elements in Renal Disease. Bailliere-Tindall, London, pp 81-85, 1986.
96. Moshtaghie AA, Skillen AW: Binding of aluminum to transferrin and lactoferrin. Biochemical Society Trans 14: 916-917, 1986.
97. Cochran M, Coates JH, Kureser T: Direct spectrophotometric determination of the two site binding of transferrin. FEBS lett 176: 129-132, 1987.
98. Moshtaghie AA, Skillen AW: Study of the relationship between aluminum toxicity and heme synthesis. Iranian Journal of Medical Sciences 15: 46-52, 1990.
99. Ani M, Moshtaghie AA: The effect of chromium on parameters related to iron metabolism. Biol Trace Element Res 32: 57-64, 1992.
100. Schade AL, Caroline L: An iron binding component in human blood plasma. Science 104: 340-346, 1946.
101. Brown S, Savory J, Wills MR: Absorption of aluminum from either citrate or chloride in rat everted gut sacs (Abst) Clin Chem 33: 933, 1987.
102. Moshtaghie AA, Ani M, Taher: The relationship between aluminum toxicity and iron metabolism in rats. J Sci IR Iran 1: 335-336, 1990.
103. Seligman, PA Schleider R.B, Allen RH: Isolation and characterization of the transferrin receptor from human placenta. J Biol Chem 254: 9943-9946, 1979.
104. Skillen AW, Moshtaghie AA: The effect of aluminum on the interaction between transferrin and it's receptor on human placental plasma receptor. In: Taylor A(ed). Aluminum and Other Trace Elements in Renal Disease. Bailliere-Tinal, London, pp 86-90, 1986.
105. Moshtaghie, A.A: Interrelationships between aluminum and iron metabolism in man. Ph.D. Thesis, The University of Newcastle-Upon-Tyne, UK, 1988.
106. Moshtaghie AA, Skillen AW: Aluminum uptake by rat isolated hepatocytes and its effect on mitochondria oxygen uptake. J Journal of Islamic Academy of Science 3: 11-14, 1990.
107. Nilsen T, Romslo I: Transferrin as a donor of iron to mitochondria. Biochem Biophys Acta 802: 448-453, 1984.
108. Moshtaghie AA, Ani M, Taher M: Identification of transferrin in mitochondria isolated from rat liver. Biochemical Society Transaction 19 (1): 675-109, 1991.
109. Ackrill P, Day JP: Therapy of aluminum overload. Contr Nephrol 38: 78-80, 1984.
110. Graf H, Stammvoll HK, Mesinger V: Dialysate aluminum concentration during hemodialysis. Lancet I: 46-47, 1982.
111. Leung FY, Hoodsman AB, Muirhead N, Henderson R: Ultrafiltrable studies *in vitro* of serum aluminum in dialysis patients after desferrioxamine chelation therapy. Clin Chem 31: 20-23, 1985.
112. Moshtaghie AA, Skillen AW: Desferrioxamine treatment in aluminum overload patients: an aluminum binding study. Indian J Pharmacol 23: 75-80, 1991.
113. Ackrill P: Aluminum removal by desferrioxamine. In: taylor A(ed) Aluminum and other Trace Elements in Renal Disease. Baillere-Tindall, London, pp 193-199, 1982.
114. Ackrill P, Day P, Garstang FM: Treatment of fracturing

renal osteodystrophy by desferrioxamine. Proceeding European Dialysis Transplantation Association 19: 203-207, 1982.
115. Stummvoll HK, Craft H, Mesinger V: Effect of DFO on aluminum kinetic during hemodialysis. Mineral Electro Metabol 10: 263-266, 1984.
116. Keberle H: The biochemistry of DFO and its relation to iron metabolism. Ann NY Acad Sci 119: 758-768, 1964.
117. Harker L, Funck DD, Finch CA: Evaluation of storage iron by chelates. Am J Medicine 45: 105-115, 1968.
118. Martin RB, Savory J, Brown S, Bertholf RL, Wills MR: Transferrin binding to Al and Fe. Clin Chem 33: 405-407, 1987.
119. Day P: Chemical aspects of aluminum chelation by desfrrioxamine. In: Taylor A(ed). Aluminum and Other Trace Elements in Renal Disease. Baillere-Tindall, London. pp 184-192, 1986.
120. Hueher SH, Csiba E, Josephson B, Huehers E, Finch C: Interaction of human differric transferrin with reticulocytes. Proc Natl Acad Sci 78: 621-625, 1981.
121. Rahman H, Channon SM, Skillen AW, Word MK, Kerr DNS: Protein binding of aluminum in normal subjects and in patients with chronic renal failure. Proceeding European Dialysis Transplatation Association 21: 360-365, 1984.
122. Rahman H, Skillen AW, Ward MK, Channon SM. Kerr DNS: Affinity of aluminum binding protein. Int J Artif Organs 9: 93-96, 1986.
123. Rahman H, Skillen AW, Ward MK, Kerr DNS: Methods for studying the binding of aluminum by serum protein. Clin Chem 31: 1969-1973, 1985.
124. Ott SM, Andreos DL, Neheker HG, Millinear DS, Maloney NA, Coburn YW, Sherrard DJ: Changes in hone histology after treatment with desferrioxamine. Kidney Int 29 suppl 18: S-108-S-113, 1986.