ALUMINUM TOXICITY SYNDROMES

IN

CHRONIC HEMODIALYSIS

MEDICAL GRAND ROUNDS

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Introduction

Chronic hemodialysis developed in the 1960'ties as the standard of care for maintaining life in patients with end stage kidney disease. It reverses most of the gastrointestinal, neurological, and cardiovascular abnormalities associated with uremia. However, it fails to adequately reverse other abnormalities. It has little effect on the anemia of chronic renal failure. Also, phosphorus retention is a problem for all dialysis patients and leads to metabolic bone disease in many despite vigorous attempts to control it with dietary adjustments and medications. Finally, chronic hemodialysis itself appears to bring on toxicity problems that are not part of uremia per se. The aluminum intoxication syndromes are examples of these and are the subject of this grand rounds. Clinical experience from the 1970'ties and 1980'ties with chronic hemodialysis uncovered several clinical syndromes which could be linked to exposure to high aluminum levels (Table 1). Historically, the first disorder

TABLE 1

DISORDERS IN DIALYSIS PATIENTS IN WHICH ALUMINUM MAY BE INVOLVED

1. DIALYSIS ENCEPHALOPATHY
2. MICROCYTIC ANEMIA
3. VITAMIN D-RESISTANT OSTEOMALACIA

linked to aluminum was dialysis encephalopathy. Shortly thereafter, a microcytic anemia was recognized in the same patients with encephalopathy. Later studies suggested this too was the result of aluminum intoxication. The most recent development has been the description of a dialysis-related bone disease which appears only in dialysis patients with a large body burden of aluminum. This grand rounds will describe these syndromes and survey the evidence that links aluminum to their pathogenesis.

Aluminum Metabolism

The hemodialysis patient is particularly at risk to develop increased tissue levels of aluminum. Aluminum is normally absorbed by the gastrointestinal tract and is excreted by the kidneys (Table 2). In patients with renal failure, decreased renal excretion leads to elevated blood aluminum. The aluminum in the water used to prepare the dialysate mixture can also be a major cause of an elevated blood aluminum. Aluminum in the dialysate gains access to the patient's blood by moving from the

TABLE 2

ALUMINUM METABOLISM

ABSORPTION: GASTROINTESTINAL
EXCRETION: RENAL
CAUSES OF EXCESSIVE EXPOSURE TO ALUMINUM:
DIALYSATE WATER
ALUMINUM CONTAINING ANTACIDS

dialysate to the blood across the dialysis membrane. This certainly occurs at high dialysate aluminum levels, but also may occur at lower "acceptable" water aluminum levels, since aluminum binds to blood proteins which maintain a favorable dialysate to blood gradient for aluminum. Aluminum is naturally present in water, but the amount in treated water supplies is usually greatly increased, since aluminum sulfate is added as a flocculent which precipitates organic material. Water used to prepare the dialysate is now treated to remove trace metals such as aluminum.

Dialysis Encephalopathy

Dialysis encephalopathy was recognized as a distinct clinical entity by Alfrey and co-workers in 1972 (1). It is a disorder seen primarily in chronic hemodialysis patients, but has been reported in non-dialyzed uremics treated with aluminum-containing antacids (2). It is characterized by a complex speech disturbance, myclonic seizures, and a characteristic change in the electroencephalographic pattern. It is also known by the names dialysis dementia and progressive myoclonic dialysis encephalopathy. Alfrey and his coworkers (3) were also the first investigators to implicate aluminum in the etiology of dialysis encephalopathy. They noted that brain aluminum in patients with the syndrome was elevated to values 11 times that of the control brains, whereas the aluminum content in brains of patients without the syndrome was elevated only 3 times that of controls.

The clinical features of dialysis encephalopathy are dominated by the speech disturbances which are seen virtually in every patient (Table 3). Myoclonic jerking, particularly of the upper

TABLE 3

CLINICAL FEATURES OF DIALYSIS ENCEPHALOPATHY

COMPLEX SPEECH DISTURBANCE
MYOCLONUS
SEIZURES
APRAXIA
MENTAL DETERIORATION
CHARACTERISTIC EEG CHANGES

extremities, and chronic seizures are present in a high percentage of patients. In more advanced cases, mental deterioration with global cerebral and cerebellar dysfunction may occur. These clinical abnormalities combined with the characteristic EEG findings establish the diagnosis. O'Hare et al (4) described the speech disorder found in 14 of these patients (Table 4). Early in the disorder, speech is

TABLE 4. Presenting and ultimate clinical features of 14 patients with dialysis encephalopathy

Abnormality	Presenting feature	Ultimately affected	
	No.	No.	%
Speech abnormality	5	14	100
Seizures: myoclonic	2	14	100
generalized	4	12	86
partial/complex	—	8	57
Mental deterioration	3	12	86
Cerebellar ataxia	—	2	14
Abnormal electroencephalogram	1	14	100

Ref. 4

characterized by hesitancy and slowness with a loss of normal fluency (Table 5). Patients frequently stutter and show a

TABLE 5

DIALYSIS ENCEPHALOPATHY: SPEECH DISORDER

HESITANCY AND SLOWNESS
LOSS OF NORMAL FLUENCY
STUTTERING AND SLOWING
FREQUENT ATTEMPTS TO CORRECT MISPRONOUNCED WORDS
FREQUENTLY DEVELOPS DURING OR AFTER DIALYSIS
SPEECH ARREST WITH DISSOCIATED STATE
EXPRESSIVE DYSPHASIA
DYSGRAPHIA
MUTISM

general slowing of the normal speech tempo. Speech disturbances may be episodic and characteristically develops following the hemodialysis treatment or shortly afterwards. In more advanced cases, there may be actual speech arrest with the patient being unable to form any words. Also, the patient may display a dissociated state. In the very late stages, the patient may become totally mute. Paralleling the changes in speech are changes in the skeletal and neuromuscular systems (Table 6). In addition to the myoclonic jerking of the extremities, asterixis also may be present. Like the speech disturbances, tonic-clonic seizures commonly occur during or after the hemodialysis treatment. A proximal muscle weakness also occurs, but this may be difficult to distinguish from the myopathy frequently seen in

long-term hemodialysis patients without encephalopathy. The mental changes may be overt or subtle. There may be personality

TABLE 6

DIALYSIS ENCEPHALOPATHY

SEIZURE DISORDER
- MYOCLONIC JERKING OF HANDS
- ASTERIXIS
- TONIC-CLONIC SEIZURES DURING OR AFTER HEMODIALYSIS
- PARTIAL SIMPLE SEIZURES (ABSENCES, LIP SMACKING)

PROXIMAL MYOPATHY

MENTAL DISTURBANCES
- SUBTLE PERSONALITY CHANGES
- WITHDRAWAL
- UNCOMMUNICATIVENESS
- FORGETFULNESS
- UNCOOPERATIVENESS
- DEPRESSION
- VISUAL HALLUCINATIONS DURING OR AFTER DIALYSIS
- GLOBAL DEMENTIA

changes such as withdrawal, uncommunicativeness, forgetfulness, depression, visual hallucinations, and in its very late stage, global dementia. The electroencephalogram characteristically shows high voltage frontal delta waves, 1-3 Hz (Figure 1). In

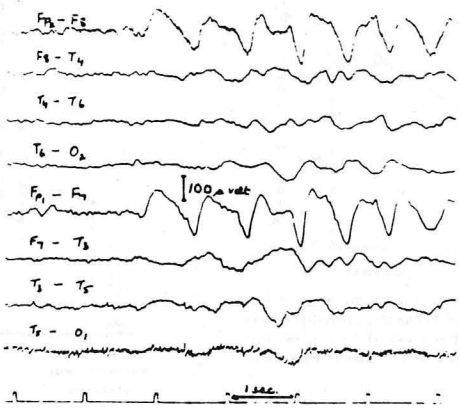

FIG. 1. Showing typical high-voltage paroxysmal delta (1-3 Hz) waves in frontal region, and normal background activity—early case.

Ref. 4

more advanced cases, spike and slow wave complexes appear. The EEG pattern frequently worsens in the post dialysis period.
The most convincing evidence that dialysis encephalopathy is related to aluminum intoxication comes from reports showing that dialysis units with a high aluminum concentration in the water had a high incidence of the disease and that removal of aluminum from the water led to improvement (4-6). Figure 2 shows the effect of a high and a low aluminum dialysate on serum aluminum in 14 hemodialysis patients (4). The low aluminum dialysate was prepared using water treated by a mixed bed deionizer. Figure 3 shows the progressive drop in serum aluminum occurring when patients were transferred to a dialysis unit using treated water. Three patients with encephalopathy survived and two improved markedly upon transfer to the new unit. The role of aluminum in the pathogenesis of sporadic cases of dialysis encephalopathy

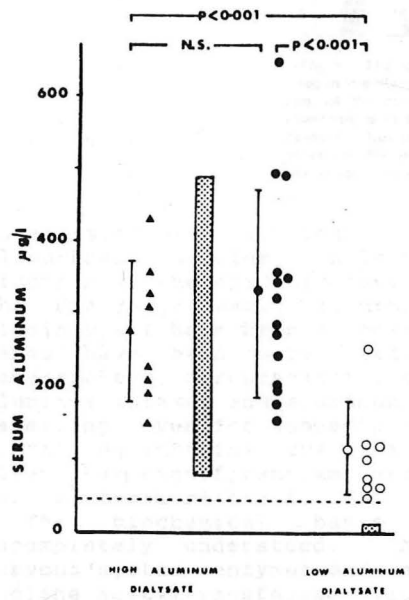

FIG. 2 Serum aluminum in dialysis patients exposed to high dialysate aluminum concentration, with (▲) and without (●) dialysis encephalopathy, compared to patients exposed to low dialysate—aluminum concentration (○). Speckled columns represent the range of dialysate aluminum concentration, dashed line represents the upper limit of normal for serum aluminum: mean ± S.D.

Ref. 4

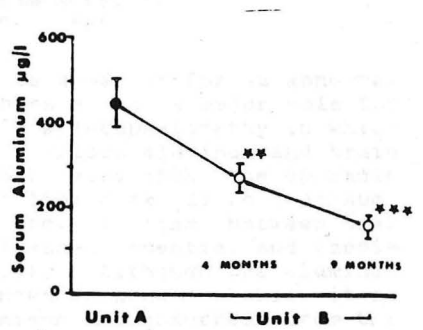

FIG. 3 Serum aluminum concentrations (mean ± S.E.M.) in unit A (patients exposed to high aluminum dialysate) and after transfer to unit B (deionized water unit-low aluminum dialysate). Significance: **P < 0.01; ***P < 0.001 compared to unit A.

Ref. 4

has not been proven to the satisfaction of all the experts. Arieff (7) points out that oral aluminum intake seems an unlikely candidate as the cause of this disorder since the use of this compound is almost universal in dialysis patients, yet the majority of cases have occurred in epidemics and are geographically clustered. Brain aluminum is unquestionably high in patients with dialysis encephalopathy. However, Arieff emphasizes that aluminum is elevated in so many diverse disorders (Figure 4) and yet the syndrome occurs only in dialysis patients, just one of the patient groups with high aluminum levels. Thus,

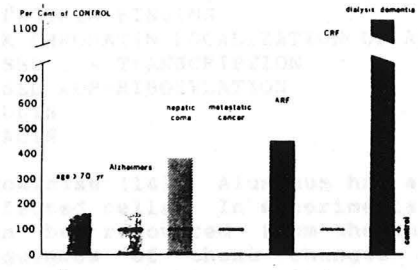

Fig 4. The brain aluminum content in patients cited in the literature. Values are expressed as a percent of the control value (normal = 100%). Brain aluminum is 11 times normal in patients with dialysis dementia, but is also elevated in patients with six other conditions that can affect the blood brain barrier. (Reprinted with permission.[7]) Ref. 7

an elevated brain aluminum may simply be a marker for an abnormal blood brain barrier. While most authors accept a major role for aluminum in the epidemic form of dialysis encephalopathy in which the dialysate water aluminum level, blood aluminum and brain aluminum all have been demonstrated to be very high, the sporadic cases have been more difficult to link directly to aluminum. Nevertheless, circumstantial evidence for a link between oral aluminum intake and aluminum bone disease, dementia, and anemia is strong, even for sporadic cases (8,9). Although the aluminum containing antacids are as a class known as nonabsorbable, it is clear that significant amounts of aluminum are absorbed from the gastrointestinal tract.

The biochemical basis of aluminum encephalopathy is incompletely understood. Aluminum affects several central nervous system enzymes and metabolic pathways systems, including choline acetyltransferase, acetylcholinesterase (10), monoamine oxidase (11), and glycolysis (12). Aluminum also increases blood- brain barrier permeability (13). Aluminum appears to interfere with enzyme activity in the body in two ways: substrate level inhibition and direct protein binding (Table 7). Aluminum

TABLE 7

ALUMINUM TOXICITY: BIOCHEMICAL BASIS

1. SUBSTRATE LEVEL INHIBITION
   - AL-ATP
   - HEXOKINASE INHIBITION
   - GLYCEROKINASE

2. DIRECT PROTEIN BINDING
   - NUCLEAR CHROMATIN LOCALIZATION OF AL
   - DECREASED DNA TRANSCRIPTION
   - DECREASED ADP-RIBOSYLATION
   - CALMODULIN
   - ENKEPHALIN

inhibits brain hexokinase (14). Aluminum has a high avidity for the nucleolus of affected cells. In experimental animals, 80% of brain aluminum can be recovered from the chromatin fractions (15). The consequences of these changes appears to be a reduction in protein synthesis, since a decrease in DNA transcription and decreased ADP-ribosylation have been demonstrated (16). In addition to these abnormalities in nuclear protein functions, aluminum binding to calmodulin, a multifunctional intracellular calcium-binding protein, may interfere with cellular regulatory mechanisms that are calcium dependent (17). Lastly, aluminum binds to (Leu^5)-enkephalin, an endogenous central nervous system peptide, which appears to interfere with intramolecular hydrogen bonding (18). This is likely to denature this protein.

The pathological findings in the brains of patients dying with dialysis encelphalopathy is characterized by the presence of neurofibrillary material in cortical neurons (19). This finding suggests that aluminum has a specific effect on neuronal protein synthesis and results in the accumulation of these neurofilaments. This change is superficially similar to that found in Alzheimer's disease, but the pathological findings in these disorders are clearly different. Aluminum does accumulate in the brains of patients with Alzheimer's disease and a causative role for aluminum in the development of the neurofibrillary tangles of this disorder has been proposed (20).

Treatment of dialysis encephalopathy is aimed at removing aluminum from the patient's environment (Table 8). The most

TABLE 8

DIALYSIS ENCEPHALOPATHY:TREATMENT

1. TRANSFER TO AL-FREE DIALYSATE (<10 µg/L)
2. AL CHELATION WITH DFO
3. RENAL TRANSPLANTATION

dramatic results of treatment have occurred in those patients with the epidemic form who have shown reversal or considerable improvement in the clinical signs following removal of aluminum from the dialysate (3,4,9). Also, limited success has been reported with the use of aluminum chelators such as deferoxamine (21). Lastly, renal transplantation has been performed in 5 patients, but three of these patients died with accelerated encephalopathy following the procedure (4). Two others seemed to improve following the transplantation, although seizures continued in one patient.

Microcytic Anemia

Almost all patients with chronic renal disease experience anemia. Table 9 lists the major causes of anemia in these patients. In hemodialysis patients, the anemia is generally

TABLE 9

ANEMIA OF CHRONIC RENAL FAILURE

1. DECREASED ERYTHROPOIETIN
2. UREMIC TOXINS
3. SHORTENED RED CELL SURVIVAL
4. BLOOD LOSS DURING HEMODIALYSIS
5. IRON DEFICIENCY
6. FOLIC ACID DEFICIENCY
7. ALUMINUM INTOXICATION

normochromic and normocytic and is usually considered to represent the anemia of chronic disease. Additional factors in its pathogenesis include reduced erythropoietin production by diseased kidneys, a shortened red blood cell survival, and a consistent and measurable blood loss during the hemodialysis procedure. Until relatively recently, the development of a microcytic anemia in a hemodialysis patient was usually thought to be due to iron deficiency. In 1978, Elliott and MacDougal (22) reported that a microcytic anemia was associated with the presence of osteomalacic dialysis osteodystrophy and with dialysis encephalopathy. The fall in hematocrit preceeded the osteodystrophy and the neurological symptoms. Elimination of aluminum in the dialysate water (Figure 5) led to an improvement in the anemia (23). Also, prolonged therapy with the chelating agent DFO (Figure 6) has led to a reversal of the aluminum associated anemia (24-26). Aluminum-induced microcytic anemia may also develop in patients undergoing chronic peritoneal dialysis (26).

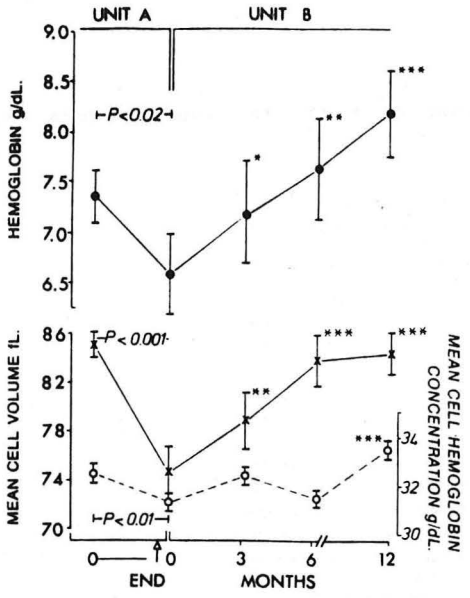

Figure 5 Changes in Hemoglobin Concentration, Mean Cell Volume, and Mean Cellular Hemoglobin Concentration from the Beginning of Dialysis in Unit A to the End of Dialysis in Unit A and through 12 Months in Unit B.

Results are expressed as means; bars denote S.E.M. The significance of the changes from the end of dialysis in Unit A to the period spent in Unit B is shown by asterisks; one asterisk indicates P<0.05, two P<0.01, and three P<0.001. Open circles denote the mean cellular hemoglobin concentration.

Ref. 23

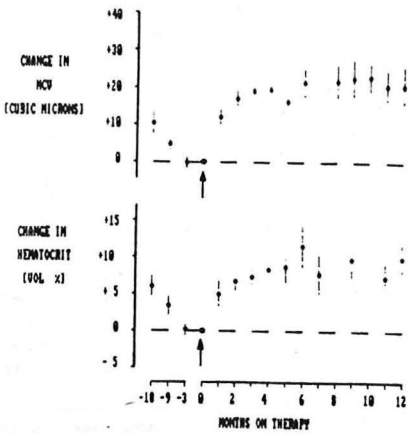

Fig 6 Time course of the change in MCV (upper panel) and hematocrit (lower panel) at several times before and during deferoxamine therapy. The arrow denotes initiation of deferoxamine; the zero, baseline for the MCV and hematocrit. Values on the graph are mean ± SEM.

Ref. 24

Table 10 lists the characteristics of the aluminum-induced anemia. The anemia is not associated with an iron deficient

TABLE 10

ALUMINUM-INDUCED ANEMIA

1. NON-IRON DEFICIENT
2. USUALLY MICROCYTIC, HYPOCHROMIC
3. MAY PRECEDE OSTEOMALACIA
4. REVERSIBLE FOLLOWING CHELATION WITH DFO

state as measured by serum iron, serum ferritin, or Prussian blue stainable iron in the bone marrow. Typically, the anemia is microcytic and hypochromic. Interestingly, a recent report demonstrates that DFO treatment in hemodialysis patients with aluminum-induced bone disease led to a significant improvement in hematocrit and mean corpuscular volume (Table 11) in 10 patients who were initially normochromic and normocytic (27). Since these patients had been dialyzed against a dialysate aluminum concentration of no more than 0.9 μmol/L, the aluminum containing antacids used by them was the most likely factor responsible for

the anemia. However, this pathway to aluminum-induced anemia is

Table 11 Evolution of several parameters before (period 1) and during (period 2) DFO therapy

Parameters	Period 1	Period 2	1 vs 2
$\bar{T}$ m (units patient month)	0.8 (0–1.5)	0.2 (0–0.5)	$p < 0.025$
RBC (10^6 µl)	3.17 ± 0.1	3.26 ± 0.1	NS
Hct (%)	28.1 ± 0.7	30.6 ± 1.1	$p < 0.02$
Hb (g dl)	9.1 ± 0.2	10.0 ± 0.4	$p < 0.02$
MCV (fl)	89.1 ± 2.9	93.8 ± 1.8	$p < 0.02$
MCH (pg)	28.9 ± 1.1	30.5 ± 0.8	$p < 0.05$
MCHC (%)	32.1 ± 0.4	32.6 ± 0.4	NS
WBC (µl)	8074 ± 378	8198 ± 323	NS
Plts (10^3 µl)	229.2 ± 20.7	227.4 ± 19.5	NS
iPTH (pg ml)	1065 ± 142	1359 ± 175	NS
serum Alp (µmol l)	18.8 ± 2.8	10.7 ± 2.0	$p < 0.05$

$\bar{T}$ m: mean number of packed red cells units transfused monthly per patient to maintain hematocrit at 25%; RBC: number of red blood cells/µL; Hct: hematocrit; Hb: hemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; WBC: white blood cells; Plts: platelets; iPTH: immunoreactive parathyroid hormone; serum Alp: serum Al 48 hrs after a deferoxamine infusion. $\bar{T}$ m is expressed as mean and range, other results as means ± s.e.m. NS: not significant. ref. 27

not accepted by all authors (23). This finding suggests that the spectrum of aluminum-induced anemia must be expanded to that group of patients traditionally thought to have simply the anemia of chronic disease secondary to kidney failure. The microcytic anemia of aluminum intoxication may precede the effects of aluminum to cause osteomalacia or encephalopathy (22).

The mechanism of aluminum-induced anemia is currently a matter of debate, but a number of potential mechanisms have been offered (Table 12). Aluminum interferes with δ-aminolevulinic acid

TABLE 12

ALUMINUM-INDUCED ANEMIA: POTENTIAL MECHANISMS

1. ENZYME INHIBITION
   - A. δ-AMINOLEVULINIC ACID DEHYDRATASE
   - B. FERROXIDASE
   - C. DIHYDROPTERIDINE REDUCTASE
2. ALUMINUM BINDS TO TRANSFERRIN
3. DIRECT ALUMINUM TOXICITY TO MARROW

dehydrogenase action (28), reduces ferroxidase activity (29), and a reduction in erythrocyte dihydropteridine reductase, an enzyme also essential for the maintenance of normal brain concentrations of tetrahydrobiopterin, a substance required in the formation of specific neurotransmitters (e.g. tyrosine, dopa, norepinephrine, and 5-hydroxytryptophan) (30). A second potential mechanism of aluminum-induced anemia may involve the interference by aluminum of the binding of iron to transferrin (31). This aluminum binding to transferrin could prevent both the binding and the release of iron (31). Thirdly, aluminum toxicity may operate by a direct effect on marrow macrophages, possibly by interfering with macrophage digestion of senescent erythrocytes, or by impairing macrophage storage of iron as ferritin, or finally by impairing macrophages from providing iron to proerythroblasts for heme biosynthesis (32).

Clinical studies showing that aluminum removal from dialysate water led to an improvement in the microcytic anemia may be open to alternative explanations since more things were changed than just the removal of aluminum from the dialysate. Thus, key animal studies suggests that aluminum indeed is the toxin leading to the microcytic anemia. Kaiser et al (33) demonstrated that aluminum loaded normal and uremic rats developed microcytic anemia. Moreover, the anemia was preceded by the development of significant microcytosis and the absence of reticulocytosis, suggesting that aluminum intoxication decreases red cell production.

The treatment of aluminum-induced anemia will usually be a by-product of the treatment of the more serious encephalopathy or osteomalacia induced by the aluminum. The removal of aluminum from dialysate water and a reduction in the amount of aluminum containing antacids that patients are exposed to should lead to a resolution of the microcytic anemia. In more serious cases of osteomalacia or encephalopathy, DFO chelation therapy would be expected to also treat the microcytic anemia. Whether aluminum intoxication may be involved at least partly in the normochromic normocytic anemia commonly seen in hemodialysis patients in the absence of overt bone or neurological disease is at present unclear. This question may be answered by ongoing studies currently evaluating calcium containing antacids which are being used as phosphorus binders in place of aluminum containing antacids (see below). An improvement in hematocrit after changing to non-aluminum containing phosphate binders in those patients who have a normochromic normocytic anemia would suggest that aluminum was playing at least a partial role in the anemia.

Aluminum-Associated Osteomalacia

In the daily management of dialysis patients, control of serum phosphorus remains a constant challenge. Hyperphosphatemia is a central factor in the pathogenesis of renal osteodystrophy, a disorder that will develop to some degree in all dialysis

patients, and in a small percentage of patients will be a serious cause of misery and morbidity. Patient compliance with attempts to control the serum phosphorus is not always satisfactory, since the antacids used for this purpose may be unpalatable and may cause unpleasant side effects. Also, unlike the problem of excessive fluid ingestion between dialyses where the consequences of non-compliance may be immediate and dramatic (e.g. pulmonary edema), failure of the patient to comply with measures aimed at phosphorus control rarely lead to immediate adverse effects. Nevertheless, the rationale behind phosphorus control in patients on regular dialysis therapy to prevent uremic bone disease and its sometimes devastating consequences is sound and worth the effort required to achieve it. Until recently, modest dietary phosphorus restriction coupled with the administration of phosphorus binding antacids had been the unchallenged treatment of choice to control serum phosphorus in dialysis patients. However, the recognition that aluminum, the substance in aluminum-containing antacids that physically binds dietary phosphorus and prevents its absorption, may be toxic to neural, hematopoietic, and bone tissue, has led to a reevaluation of its use and to a search for alternative therapies.

Phosphate Handling in Chronic Renal Failure. Serum phosphorus is a central factor in the pathogenesis of renal osteodystrophy. Coburn (34) measured serum phosphorus in 103 chronic renal failure patients and found it to be low or normal when the GFR was greater than 35 ml/min. However, when GFR fell below 35 ml/min, serum phosphorus rose progressively. A rising serum phosphorus is known to depress serum calcium (35), cause skeletal resistance to parathyroid hormone (36), and decrease the level of 1,25 $(OH)_2D$ by inhibiting the activity of the renal 1-hydroxylase enzyme which is responsible for the conversion of 25(0H)D3 to 1,25$(0H)_2$D3 (37). Thus, there are several pathways by which phosphorus retention can be linked to the major forms of renal osteodystrophy (Table 13).

TABLE 13

HYPERPHOSPHATEMIA

1. DEPRESSES SERUM CALCIUM, ELEVATES PTH
2. CAUSES SKELETAL RESISTANCE TO PTH
3. INHIBITS RENAL 1-α-HYDROXYLASE ENZYME AND DECREASES CONVERSION OF 25(0H)D3 TO 1,25$(OH)_2$D3

Controversy remains regarding the exact pathway or combination of pathways by which phosphorus retention produces secondary hyperparathyroidism, but clearly if hyperphosphatemia can be avoided, secondary hyperparathyroidism can be prevented. In dogs with chronic renal insufficiency ingesting a normal phosphate diet, each decrement in GFR led to a progressive rise in PTH

(38). This rise in PTH could be prevented if dietary phosphorus was proportionately reduced as GFR fell. In man, dietary phosphorus restriction in proportion to the decrement in GFR also reduces high PTH levels toward normal (39). Lastly, the marked elevation of PTH and severe osteitis fibrosa and osteomalacia that developed in uremic dogs on a normal phosphate diet could be completely prevented if dietary phosphate was restricted and 25(OH)D3 was given three times weekly (40).

The "trade-off" hypothesis of uremic bone disease as described by Slatopolsky and Bricker (41) places hyperphosphatemia as the principal uremic abnormality leading to secondary hyperparathyroidism. With the fall in GFR, phosphorus rises and complexes serum calcium, transiently depressing ionized serum calcium. This depression of ionized calcium stimulates PTH secretion which returns serum phosphorus to normal through enhanced renal excretion and also returns ionized calcium to the normal range. Thus, calcium and phosphorus homeostasis is restored at the expense of an elevated PTH level, i.e. the "trade-off". While hyperphosphatemia appears to be the primary stimulus to secondary hyperparathyroidism, other important factors include an altered set point for calcium in hyperplastic parathyroid glands (i.e. a higher ionized serum calcium is required to shut off PTH secretion) and reduced circulating levels of $1,25(OH)_2D3$ (42). In vitro, $1,25(OH)_2D3$ has an inhibitory effect on PTH release (43), and, when administered intravenously to dialysis patients, can markedly suppress PTH levels (44).

Aluminum Containing Antacids as Phosphate Binders. If phosphate clearance by the artificial kidney were more efficient, there would be considerably less need for dietary phosphate restriction and phosphate binding antacids. Phosphate is cleared by most hollow fiber dialyzers at only 57% of the rate of urea, and urea is the marker used to determine the adequacy of and time required for the dialysis treatment (45). As dialysis times become even shorter, we can expect phosphate clearance to be further reduced making the need for more effective phosphorus control even more urgent. The mainstay therapy for hyperphosphatemia in uremia is the aluminum containing antacid (aluminum hydroxide or aluminum carbonate). These agents are well suited to this purpose since ingested phosphate is adsorbed to the surface of the aluminum hydroxide particles and, in addition, soluble aluminum formed through acid neutralization of the aluminum hydroxide in the stomach readily reacts with phosphate to form insoluble aluminum phosphate (Table 14). In

TABLE 14

MECHANISM OF ALUMINUM PHOSPHATE BINDING

1. ADSORPTION OF PHOSPHORUS TO ALUMINUM HYDROXIDE PARTICLES
2. REACTION OF PHOSPHORUS WITH SOLUBLE ALUMINUM FORMED THROUGH ACID NEUTRALIZATION OF ALUMINUM HYDROXIDE IN THE STOMACH

either case, soluble phosphate is converted to an insoluble form which is excreted in the feces. Since intestinal fluid phosphate is in equilibrium with serum phosphate, the net result of this therapy will be a fall in serum phosphate. Thus, the aluminum containing phosphate binding gels are effective in lowering serum phosphorus. However, the appearance of aluminum-related clinical disorders in chronic hemodialysis patients has led to a reevaluation of the use of these drugs.

Aluminum related osteodystrophy, also known as vitamin D resistant osteomalacia and low-turnover osteomalacia, has been intensively studied in the past 4-5 years. Affected patients have bone pain, proximal muscle weakness, and occasionally pathological fractures (Table 15). The biochemical features of

TABLE 15

CLINICAL FEATURES OF VITAMIN D-RESISTANT OSTEOMALACIA

1. BONE PAIN
2. PROXIMAL MUSCLE WEAKNESS
3. PATHOLOGICAL FRACTURES
4. NORMAL OR SLIGHTLY INCREASED SERUM CALCIUM
5. NORMAL OR SLIGHTLY INCREASED ALKALINE PHOSPHATASE
6. NORMAL OR SLIGHTLY INCREASED PTH, i.e. "RELATIVE DEFICIENCY OF PTH"
7. TENDENCY TO DEVELOP HYPERCALCEMIA AFTER VITAMIN D OR CALCIUM
8. HIGH MORTALITY RATE
9. CONGESTIVE HEART FAILURE

this disorder include a normal or slightly elevated serum calcium, a normal or slightly elevated serum alkaline phosphatase activity, and a normal to moderately elevated serum PTH concentration (46). Llach et al (47) performed bone biopsies on 142 hemodialysis patients and found low turnover osteomalacia in 25%; of these, 40% experienced muscle weakness, 35% bone pain, and 27% fractures (Table 16). The diagnosis of low-turnover osteomalacia is suspected when the baseline plasma aluminum level is high or the DFO test is positive. The plasma aluminum is a

useful starting point in evaluating a patient with suspected

TABLE 16

BONE BIOPSIES IN 142 UNSELECTED HEMODIALYSIS PATIENTS

25% HAD LOW TURNOVER OSTEOMALACIA, OF WHICH
40% HAD MUSCLE WEAKNESS
35% HAD BONE PAIN
27% HAD FRACTURES

aluminum-induced osteomalacia (Table 17). Normal individuals regularly have aluminum values <10 µg/L, while dialysis patients have higher levels the magnitude of which corresponds generally with whether or not they have a aluminum intoxication syndrome. A plasma aluminum >100 µg/L suggests the presence of low-turnover osteomalacia, while a value of >200 µg/L has a 93% specificity

TABLE 17

PLASMA ALUMINUM

1. NORMALS <10 µg/L
2. DIALYSIS PATIENTS, TREATED H_2O, <100 µg/L
3. DIALYSIS PATIENTS, CONTAMINATED H_2O, 200-500 µg/L
4. DIALYSIS ENCEPHALOPATHY AND OSTEOMALACIA, MOST >100 µg/L

for the disease (48). The deferoxamine infusion test (Figure 7) appears to be useful in diagnosing aluminum-related osteodystrophy (48). An increment in serum aluminum of 200 micrograms/liter over baseline values 24 hours after a 40 mg/kg dose of deferoxamine infused over a 2 hour period was strongly associated with aluminum-related osteodystrophy. While these clinical and biochemical features support a diagnosis of aluminum

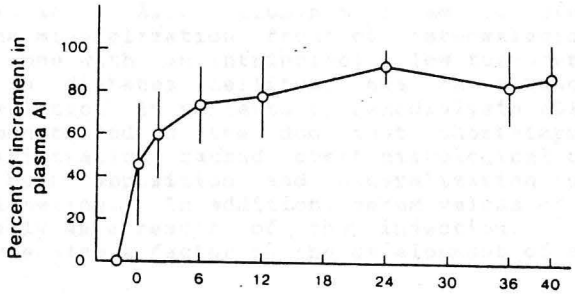

Fig 7 Ref. 48

related osteodystrophy, the definitive diagnosis appears to depend on a bone biopsy specimen that shows significant aluminum accumulation and a low bone formation rate using double tetracycline labeling (Table 18)(48).

TABLE 18

HISTOLOGICAL FEATURES OF ALUMINUM INDUCED OSTEOMALACIA

1. DEFECTIVE BONE MINERALIZATION
2. DECREASE IN MINERALIZATION FRONT
3. INCREASED AMOUNT OF OSTEOID
4. ALUMINUM DEPOSITS AT OSTEOID-MINERALIZATION FRONT
5. ALMOST COMPLETE ABSENCE OF ACTIVE BONE WITH MARROW FIBROSIS

The evidence supporting a role for aluminum in the causation of osteomalacia came initially from its association with the characteristic bone disease (Table 19). Hodsman et al (49)

TABLE 19

EVIDENCE THAT ALUMINUM CAUSES OSTEOMALACIA

1. HIGHEST ALUMINUM CONTENT IN BONE OF PATIENTS WITH OSTEOMALACIA
2. ALUMINUM PREFERENTIALLY DEPOSITS AT THE MINERALIZATION FRONT
3. IN DOGS, SHORT TERM ALUMINUM ADMINISTRATION CAUSES OSTEOMALACIA, DECREASES BONE FORMATION RATE, AND DECREASES $1,25(OH)_2D3$ LEVELS
4. IN VIVO AND IN VITRO STUDIES SHOW THAT ALUMINUM DIRECTLY IMPAIRS BONE FORMATION

performed iliac crest bone biopsies in 59 hemodialysis patients and found the highest aluminum content in the bone of patients with osteomalacia. Also, aluminum seems to preferentially deposit at the mineralization front of osteomalacic bone (50). As expected, bone with an intrinsically low turnover rate, such as is found in diabetes mellitus, has an enhanced rate of aluminum accumulation in patients on hemodialysis (51). Goodman et al (52) demonstrated in the dog that short-term parenteral aluminum administration caused overt histological osteomalacia and decreased bone apposition and mineralization using double tetracycline labeling. In addition, serum values of $1,25(OH)_2D3$ fell dramatically as a result of the injection. Whether the later effect was also a factor in the development of osteomalacia

was unclear. However, by itself aluminum can be a potent inhibitor of calcification. Talwar et al (53) demonstrated that aluminum has an in vivo primary direct negative physical chemical effect on mineralization of bone matrix. This observation confirmed in vitro data showing that aluminum had a direct physical chemical effect on the precipitation of calcium phosphate.

Not all investigators agree that aluminum is an etiologic agent in renal osteodystrophy, at least not as a direct inhibitor off bone mineralization. Quarles et al (54), using vitamin D-deficient dogs with normal kidneys, showed that while aluminum accumulates preferentially in preexistent osteomalacic bone and localizes at the osteoid-bone interface, it does not prevent mineralization. However, this study does not deal with the question of the effect of uremia on bone aluminum accumulation.

Aluminum may also impair bone mineralization by directly affecting the parathyroid glands (Table 20). Andress et al (55)

TABLE 20

RELATIONSHIP OF ALUMINUM AND PARATHYROID GLAND FUNCTION

1. PATIENTS WITH OSTEOMALACIC BONE HAVE DIMINISHED PTH SECRETION AFTER DIALYSIS-INDUCED HYPOCALCEMIA
2. BONE ALUMINUM CORRELATES INVERSELY WITH SERUM PTH
3. IN VITRO, ALUMINUM INHIBITS PTH SECRETION FROM BOVINE PARATHYROID CELLS.
4. PARATHYROIDECTOMY MAY UNMASK ALUMINUM ASSOCIATED OSTEOMALACIA

demonstrated that hemodialysis patients with osteomalacia had diminished secretion of PTH in response to dialysis-induced hypocalcemia. In general, bone aluminum concentration correlates inversely with serum PTH levels. Whether this means that high PTH protects against aluminum deposition or that high aluminum levels depress parathyroid gland function is uncertain. Morrissey and Slatopolsky (56) showed using an in vitro system that aluminum in concentrations frequently found in the serum of hemodialysis patients inhibits the secretion of PTH from bovine parathyroid cells. There is evidence that PTH, i.e. its absence, may play a role in the development of the bone disease in these patients. Hodsman et al (57) noted that a number of their patients with vitamin D-resistant osteomalacia had had parathyroidectomies in the past. The advisability of performing parathyroidectomy in patients with osteitis fibrosa has been questioned by a report showing that 5 uremic patients subjected to subtotal parathyroidectomy later developed a syndrome similar to aluminum associated osteomalacia (58).

The management of patients with aluminum-associated osteomalacia has been disappointing. The importance of finding a good treatment is underscored by the unexpectedly high mortality rate (35%) of patients who develop symptomatic osteomalacia (47).

A high incidence of congestive heart failure and fractures were noted in the patients who died. The early encouraging use of combination $1,25(OH)_2D$ and $24,25(OH)_2D$ therapy for this disorder (57) has not been confirmed by other investigators (47). However, a study by Malluche et al (59) suggests at least a permissive role for vitamin D in the development of osteomalacia. They found that at low levels of vitamin D, a frequent finding in chronic hemodialysis patients, in the experimental animal led to enhanced bone uptake of aluminum independently of the level of PTH (Figure 8).

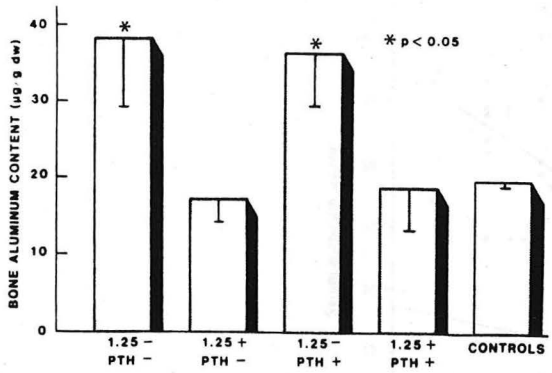

Figure 8 Bone aluminum content in 5/6 nephrectomized or sham-operated beagle dogs with various combinations in status of calcitriol (1.25) and PTH and in controls. ref. 59

Discontinuing the exposure to aluminum and/or removal of aluminum with deferoxamine improves aluminum-induced osteomalacia in rats with experimentally reduced renal function Finch, (60). Preliminary studies in hemodialysis patients suggest that in selected patients deferoxamine may decrease bone aluminum, and improve bone histology (61-63). Removal of the parathyroid glands in this disorder particularly should be avoided, as these patients seem to be at increased risk of developing aluminum-induced osteodystrophy (64,65). Other high risk groups (Table 21) include kidney transplant recipients (66), children with

TABLE 21

HIGH RISK FACTORS FOR ALUMINUM OSTEODYSTROPHY

1. **PARATHYROIDECTOMY**
2. **KIDNEY TRANSPLANTATION**
3. **CHILDREN WITH RENAL FAILURE**
4. **DIABETES**
5. **BILATERAL NEPHRECTOMY**

renal failure (67), the diabetic patient (51), and patients who have had bilateral nephrectomy (67). Part of the reason for the

high risk from bilateral nephrectomy may be explained by a report from Altmann et al (68) which showed that dialysis patients with residual renal function had lower serum aluminum levels (Figure 9) than those patients who were anuric (<10 ml/day), and further showed that the patients with residual function excreted significant quantities of aluminum in the urine.

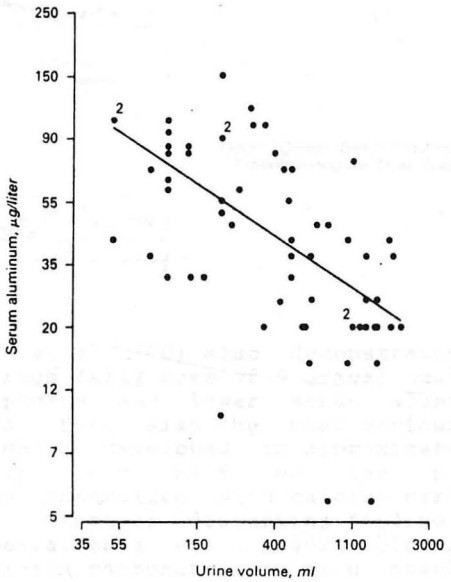

Fig. 9 *Relationship between urine flow (ml/day; log, scale) and serum aluminum (Al) concentration (μg/liter; log, scale) in 62 hemodialysis patients in whom urine flow was greater than 10 ml/day. (r = −0.58, P < 0.001).*

ref 68

Alternatives to the Use of Aluminum Containing Antacids as Phosphorus Binders. Because of the mounting evidence that the accumulation of aluminum secondary to ingestion of phosphate-binding gels is the most important source of aluminum in patients now undergoing long-term hemodialysis, alternative therapies are being investigated. Slatopolsky et al (69) have recently reported on their experience using calcium carbonate as a phosphate binder. They found that calcium carbonate (Os Cal) in an average dose of 8.5 grams per day (range 2.5-17 grams) successfully lowered serum phosphorus and raised serum calcium levels in most (60-70%) of the 20 patients studied (Figure 10), although serum phosphorus could not be controlled in six patients without the addition of aluminum hydroxide. They documented

seven episodes of hypercalcemia in patients who ingested large amounts of phosphorus and cautioned that calcium carbonate therapy should not be initiated until serum phosphorus levels have been reduced to the 5-7 mg/dl range by dietary restriction and/or the usual aluminum containing phosphorus binders. Hypercalcemia seemed to be a problem only for patients receiving the very large doses of calcium carbonate (greater than 12 grams

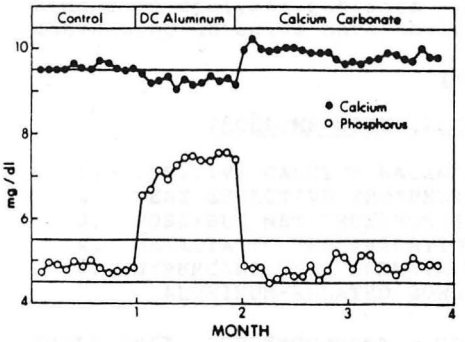

Figure 10 Mean Serum Calcium and Phosphorus Levels in 20 Patients during the Three Phases of the Four-Month Study. ref. 64

per day). Fournier et al (70) also demonstrated that calcium carbonate alone (average daily dose of 9 grams) could effectively control serum phosphorus and lower serum aluminum levels in hemodialysis patients. Here also the most serious side effect was hypercalcemia which developed in approximately 50% of the patients. Thus, in only half of the patients could hyperphosphatemia be controlled with calcium carbonate without causing hypercalcemia. Another disturbing finding was that the development of hypercalcemia was unpredictable and could occur after the dose of calcium carbonate had been stable for a long time. Other side effects were mild diarrhea and a dislike for the taste of the preparation after long-term treatment. Gonella et al (71) reported the development of hypercalcemia in a large percentage of dialysis patients receiving calcium carbonate as a phosphorus binder, especially in the immediate post dialytic period. They suggested that a lower dialysate calcium might decrease the incidence of this problem. They noted that hypercalcemia seemed more likely to occur in the patients with a normal predialytic serum phosphorus. Hercz et al (72) gave calcium carbonate to 29 dialysis patients and 12 of these developed hypercalcemia. Bone biopsies in 10 of these hypercalcemic patients revealed aluminum related bone disease in 9. Pediatric hemodialysis patients are especially at risk to develop aluminum-induced bone disease and dialysis encephalopathy, and calcium carbonate, despite its propensity to produce hypercalcemia in this population, has been recommended as the preferred phosphate binder (73). The problem of hypercalcemia poses a dilemma to the physician. The therapy

given to prevent and/or reverse the adverse effects of aluminum accumulation, i.e. calcium carbonate, may be contraindicated since those patients with the disorder are the very patients most likely to develop serious hypercalcemia.

Whether calcium carbonate can safely and effectively be substituted for aluminum containing antacids as a phosphorus binder in dialysis patients is as yet unknown. The calcium containing antacids have their own problems (Table 22). The

TABLE 22

PROBLEMS WITH CALCIUM CONTAINING ANTACIDS

1. POSITIVE CALCIUM BALANCE
2. LESS EFFECTIVE PHOSPHORUS BINDERS COMPARED WITH ALUMINUM
3. POSSIBLE NET PHOSPHORUS BALANCE
4. METASTATIC CALCIFICATION
5. HYPERCALCEMIA, ESPECIALLY IN PATIENTS WITH HISTOLOGIC ALUMINUM-RELATED BONE DISEASE

short-term consequences of the calcium containing agents (hypercalcemia, metastatic calcification) must be weighed against the long term and relatively infrequently occurring adverse consequences associated with aluminum containing antacids. Because of its ability to dissociate in the acidic environment of the stomach, relatively large amounts of calcium are absorbed from orally administered calcium carbonate (Figure 11)(74). Early studies by Clarkson, McDonald, and DeWardener (75) in uremic patients showed that daily doses of calcium carbonate as high as 20 grams did indeed increase fecal phosphate excretion but also reduced urinary phosphate excretion leading to a net positive phosphorus balance (Figure 12). Thus, serum phosphate control with calcium carbonate may be occurring but at the expense of metastatic calcification.

Magnesium containing antacids may be effectively substituted for aluminum containing antacids as phosphorus binders in dialysis patients if a magnesium free dialysate is used (76). When used in this manner, hypermagnesemia is rare, although diarrhea may limit their use in some patients.

Polyuronic acid polymers are the newest non-aluminum containing phosphate-binding agents (77). These agents are complex polymers of uronic acid charged with calcium, iron, or a combination of the two. High doses (10 grams) may cause hypercalcemia. Clinical trials are currently underway in Germany (72).

At present, the argument is not compelling that aluminum containing antacids should be abandoned in favor of calcium carbonate (Table 22). A combination of these drugs with a maximum daily dose of calcium carbonate of no more than 6-8 grams may provide adequate phosphorus control and lower the long-term risk of aluminum related bone disease. Given the potential for unpleasant short-term and long-term consequences of each agent,

more attention also should be given to limiting dietary phosphorus as a method of controlling serum phosphorus. Every attempt should be made to reduce dietary phosphorus to less than 900 mg/day by limiting those foods high in phosphorus.

In conclusion, phosphorus control in dialysis patients continues to be an important but difficult aspect of care. Regular chronic hemodialysis treatments with the standard hollow fiber artificial kidney will remove approximately 50% of absorbed phosphorus (45). Thus, reducing time on dialysis, as is the current trend, will demand even more effort aimed at reducing phosphorus absorption. Aluminum containing antacids are the most effective phosphorus binders, but carry the risk of aluminum related bone disease. Calcium carbonate is not as effective as a phosphorus binder and may cause serious hypercalcemia. The role of deferoxamine as a tool to diagnose aluminum-related bone disease is currently better documented than the use of deferoxamine as a treatment modality. Large multicenter studies will be required before recommendations can be made about this later use of deferoxamine.

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