Aluminum Overload: An Easily-Ignored Problem in Dialysis Patients with Hyperparathyroidism

Wei-Chih Kan1,2, Chih-Chiang Chien1,2, Yi-Hua Lu1, Jyh-Chang Hwang1, Shih-Bin Su3,4 and Hsien-Yi Wang1,5

1Department of Nephrology, Chi-Mei Medical Center, Tainan
2Chung Hwa University of Medical Technology, Tainan
3Department of Family Medicine, Chi-Mei Medical Center, Tainan
4Department of Biotechnology, Southern Taiwan University, Tainan
5Chia Nan University of Pharmacy and Science, Tainan, Taiwan, R.O.C.

1. Introduction

Dialysis patients are at high risk for aluminum overload, especially patients with hyperparathyroidism, who may occasionally take aluminum-containing phosphate binders. Dialysis patients with aluminum overload may have various symptoms, such as general bone or muscle pain, iron-resistant anemia, hypercalcemia, and neurologic abnormalities, which are sometimes difficult to differentiate from clinical manifestations of hyperparathyroidism. Because of the different therapeutic strategies between aluminum overload and hyperparathyroidism, an overview of aluminum overload in dialysis patients with hyperparathyroidism is presented in the following sections.

2. Aluminum overload in dialysis patients

Dialysis patients are at high risk for aluminum overload (Jaffe, J.A. et al., 2005) because of long-term use of aluminum-containing phosphate binders (Humpfner, A. et al., 1993; Salusky, I.B., 2006), poor renal excretion of aluminum, and contact with aluminum-containing dialysate. Aluminum can be eliminated from dialysate by using reverse osmosis and deionization techniques. The dialysate concentration of aluminum is suggested to be maintained at <10 µg/L (Fernández-Martin, J.L. et al., 1998; National Kidney Foundation [NKF], 2003). Therefore, aluminum-containing phosphate binders had been documented as the predominant source of aluminum exposure in dialysis patients (Savory, J. et al., 1989; Slatopolsky, E., 1987). Because of multiple systemic aluminum-related complications, reducing the exposure of dialysis patients to aluminum by substituting calcium- and other non-aluminum-based phosphate binders is a well-known concept. However, some patients with refractory hyperphosphatemia or calcium-induced hypercalcemia still require aluminum therapy (NKF, 2003). While aluminum-based phosphate binders used as short-term therapy are suggested by the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, these medications are prohibited in some countries (Koiwa, F., & Sato, Y., 2009). Non-calcium and non-aluminum phosphate binders (such as sevelamer hydrochloride and
lanthanum carbonate) are suggested as substitutes. However, these newly developed medications have not become popular in many countries because of their high cost (Koiwa, F. & Sato, Y., 2009). In addition, the source of aluminum may contribute to extra aluminum intake from other medications (Bohrer, D. et al., 2009). Therefore, aluminum overload is still a potential problem in the dialysis population.

2.1 Frequency of aluminum overload

The declining exposure of aluminum-containing dialysate and medications with commonly use of high flux dialyzers has resulted in a low incidence of abnormal aluminum levels in current dialysis patients (Cannata-Andía, J.B. & Fernández-Martin, J.L., 2002). In one retrospective study on more than 43,000 dialysis patients, 2.5% of the patients had elevated serum aluminum levels (>50 µg/L) that significantly declined year by year (Jaffe, J.A. et al., 2005). However, the prevalence of aluminum overload might be higher in countries that still commonly used aluminum-containing phosphate binders (Kan, W.C. et al., 2010).

2.2 Clinical manifestations of aluminum overload

Aluminum can accumulate in many human organs; this accumulation has been implicated in various diseases, including dialysis encephalopathy, aluminum-induced bone disease (such as osteomalacia), hypercalcemia, and iron-resistant microcytic anemia (NKF, 2003; Berlyne, G.M. et al., 1970, 1972; Sherrard, D.J., 1974; Alfrey, A.C. et al., 1976, 1987; Ward, M.K. et al., 1978; Parkinson, I.S. et al., 1979; Drüeke T., 1980; Hewitt, C.D. et al., 1990). (Summary of Aluminum-related disorders: Features, Causes, and Considerations for therapy, http://www.kidney.org/professionals/kdoqi/guidelines_bone/images/table31l.jpg)

2.2.1 Dialysis encephalopathy

Dialysis encephalopathy is usually a slowly progressive disorder with symptoms appearing after a patient has undergone dialysis for 1 year or even longer. Increased aluminum is found in the brain tissue of affected patients (Alfrey, A.C. et al., 1976). It is characterized by myoclonic jerks, mental changes, speech disturbances, visual or auditory hallucinations, paranoid behaviors, and even seizures. These neurologic abnormalities maybe fluctuate and often worsen temporarily after hemodialysis. The typical electroencephalographic (EEG) findings differ from the generalized slow wave with other causes of metabolic encephalopathy (Hughes, J.R. & Schreeder, M.T., 1980). However, due to its insidious progression, diagnosing these neurological disorders depends on clinical observation and suspicion, the finding of elevated plasma aluminum levels, and associated EEG features. New cases of dialysis encephalopathy disappeared after the initiation of water purification in 1979, and no more new cases have been reported in the developed countries since then (NKF, 2003).

2.2.2 Aluminum-induced bone disease

Aluminum can affect normal bone formation via several mechanisms. First, it interferes with mineralization of the matrix by forming crystals to compete for the site of calcium deposition, and it inhibits the activity of osteoblasts, both of which impair bone-building (Jeffery, E.H. et al., 1996). Second, it binds in the parathyroid gland, which inhibits the normal secretion of parathyroid hormone (PTH) (Cannata, J.B. et al., 1988), and it impairs PTH synthesis at the transcriptional level (Díaz-Corte, C. et al., 2001). Because of abnormal
bone formation, osteomalacia is the most frequently seen aluminum-induced bone disease, but its prevalence is reported to have markedly decreased after reduced exposure to aluminum (NKF, 2003). Osteomalacia is characterized by a low rate of bone turnover, a decreased number of bone-forming and bone-resorbing cells, and an increased volume of unmineralized bone (Delmez, J.A. & Slatopolsky, E., 1992; Slatopolsky, E., 1987). In addition, because of its potential to excessively suppress PTH, aluminum overload may cause adynamic bone disease in a minority of cases.

2.2.3 Anemia

Aluminum can also affect normal hemopoietic processes via several mechanisms. First, it impairs intestinal absorption, serum transport, and cellular uptake of iron, because aluminum and iron share a common absorption pathway and, in the serum, they are transported on the same carriers in humans (Kausz, A.T. et al., 1999). These carriers include large proteins (such as transferrin and albumin) and small molecules (such as citrate and phosphate). In several animal and human studies, a significant negative correlation was found between aluminum load and iron transferrin saturation (Cannata, J.B. et al., 1991), and additional reductions in the use of aluminum-containing medications led to significant increases in hemoglobin and reductions in the need for intravenous iron supplementation in hemodialysis patients (Cannata, J.B. et al., 1983a). Second, aluminum may induce resistance to the hematopoietic effects of recombinant human erythropoietin (rHuEPO) in both rats and dialysis patients (Drüeke, T.B., 1990; Losekann, A. et al., 1990). Therefore, dialysis patients with an obvious aluminum overload may need larger doses of rHuEPO to overcome this resistance, which significantly increases the cost of patient care.

2.2.4 Hypercalcemia

Aluminum-related bone disease may cause hypercalcemia (Norris, K.C. et al., 1985). In a rat study, aluminum changed the relationships between serum PTH, calcium, and phosphorus (Felsenfeld, A.J. et al., 1993). In a study of 25 patients on continuous ambulatory peritoneal dialysis (Cannata, J.B. et al., 1983b) who had accidentally been exposed to high levels of aluminum in the dialysate for a month, serum calcium levels significantly increased from 2.27 to 2.44 mmol/L, while serum PTH levels declined from 744 to 580 ng/L. In another study of hemodialysis patients (Cannata, J.B. et al., 1983c), a high serum aluminum level was strongly associated with hypercalcemia and low serum PTH level. Therefore, the suspicion of aluminum overload should be kept in mind in the patient who does not have obvious elevations in serum intact PTH (e.g., less than 500 pg/mL) or who is not taking vitamin D therapy (NKF, 2003).

2.3 Screening and diagnosis for aluminum overload

A histological examination of bone biopsy specimens is still considered the gold standard for diagnosing dialysis patients with an aluminum overload. Biopsies, however, are invasive and expensive. Therefore, several studies have reported their efforts to develop less invasive diagnostic methods of diagnosing aluminum overload (Milliner, D.S. et al., 1984). Serum aluminum measurements are of limited value due to its high tissue accumulation. However, aluminum overload is unlikely in dialysis patients with baseline serum aluminum concentrations (without desferrioxamine (DFO) “stimulation”) less than 20 µg/L (NKF, 2003). In one study, 50 dialysis patients undergoing bone biopsy seemed distinguishable, after a DFO
infusion test, from those with a positive bone aluminum stain by an increase in serum aluminum and a relatively high serum iPTH level (McCarthy, J.T. et al., 1990). In another prospective study of 445 dialysis patients to evaluate noninvasive tests that combined the results of intact parathyroid hormone (iPTH) and DFO tests (Pei, Y. et al., 1992), the test were useful for predicting aluminum-related bone disease in dialysis patients using aluminum-based binders. However, they yielded a high incidence of false-negatives and low-sensitivity results after these patients had discontinued aluminum-based binders for more than 6 months. According to the present consensus, the DFO test affords a non-invasive method to identify patients with an increased body burden of aluminum (NKF, 2003) (Evaluation of aluminum-related disorders: considerations for DFO test and subsequent DFO treatment, http://www.kidney.org/professionals/kdoqi/guidelines_bone/Images/Algorithm7L.jpg).

2.4 Treatment

In addition to dialysis modalities, the K/DOQI guideline (NKF, 2003) also recommends DFO to treat dialysis patients with an aluminum overload. However, DFO has side effects of its own (Cronin, R.E. & Henrich, W.L., 2006), such as itchy skin, nausea, myalgia, and neurotoxicity (McCauley, J. & Sorkin, M.I., 1989). Although most of these side effects are mild and reversible, some rare and severe or even life-threatening side effects are possible, especially anaphylactic shock and mucormycosis (Boelaert, J.R. et al., 1991, 1993). Because of the common side effects of DFO, doses of 20-40 mg/kg of body weight (Bene, C. et al., 1989; Cases, A. et al., 1988; Pengloan, J. et al., 1987) have been abandoned. The toxicity of DFO is dose-dependent; thus, many studies (Barata, J.D. et al., 1996; D’Haese, P.C. et al., 1995; Janssen, M.J. & van Boven, W.P., 1996) were designed to find the optimal dose for aluminum overload treatment. According to the K/DOQI clinical practice guideline (NKF, 2003), the DFO standard dose is 5 mg/kg of body weight (DFO treatment, http://www.kidney.org/professionals/kdoqi/guidelines_bone/Images/Algorithm9L.jpg). Furthermore, several pharmacokinetic and small-scale, short-term studies (Canteros, A. et al., 1998; Jorge, C. et al., 1999) found that even doses lower than 5 mg/kg were as efficacious as the standard 5 mg/kg dose, but clinical trials verifying its efficacy at lower doses are lacking. Therefore, we compared the response to 2 months of treatment with the standard dose (5 mg/kg) versus a lower dose (2.5 mg/kg) of DFO in dialysis patients with aluminum overload. Both treatment groups showed similar therapeutic effects, there were relatively fewer side effects in the 2.5-mg/kg group (Kan, W.C. et al., 2010).

3. Managing aluminum overload in dialysis patients with hyperparathyroidism

In patients with hyperparathyroidism, calcium-based phosphate binders are always unsuitable because of the frequently associated symptoms of hypercalcemia. Therefore, aluminum-based binders were used, which created a high risk of aluminum overload. Because PTH can protect against aluminum deposition at the mineralization front, perhaps by increasing bone turnover (Slatopolsky, E., 1987), the symptoms of aluminum-related bone diseases may be “masked” in dialysis patients with hyperparathyroidism. However, this “protection” will disappear in patients who have undergone a parathyroidectomy (PTX), because lowered PTH levels will accelerate bone aluminum deposition (Slatopolsky, E., 1987). Therefore, it is generally suggested that aluminum bone disease be excluded before PTX. Similarly, medical treatment of hyperparathyroidism with active Vitamin D3 (calcitriol) also may accelerate aluminum bone disease. In addition, the risk of aluminum bone disease is greater in diabetics (Andress, D.L. et
Aluminum Overload: An Easily-Ignored Problem in Dialysis Patients with Hyperparathyroidism

63

al., 1987; Pei, Y. et al., 1993), which may be related to a lower bone turnover rate, which has been reported in type 1 diabetics before the onset of clinical renal disease (Andress, D.L. et al., 1987; Vincenti, F. et al., 1984). Therefore, because of the sometimes similar clinical manifestations of hyperparathyroidism and aluminum overload, physicians treating dialysis patients with hyperparathyroidism should consider the possibility of concurrent aluminum problems, especially in high-risk diabetic patients.

The side effects of DFO are dose-dependent and potentially life-threatening. Although the standard dose for aluminum overload is 5 mg/kg/week for a total of 8 weeks, there are still reports of fatal mucormycosis on such a regimen (Petrikkos, G. & Drogari-Apiranthitou, M., 2011). A lower dose of DFO, if it offers good efficacy with fewer side effects, may be promising for managing such complicated patients (Kan, W.C. et al., 2010).

4. Conclusion

Although the prevalence of aluminum overload in dialysis patients is decreasing, it is still an insidious problem worldwide, especially in these dialysis patients still often exposed to aluminum-containing medications. In these patients with hyperparathyroidism, calcium- and aluminum-based binders are not suitable for long-term use (particularly for patients on concurrent vitamin D therapy). Therefore, in these particular patients, especially those with a history of aluminum-containing medications or water exposure, possible concurrent aluminum overload should be kept in mind before medical or surgical intervention. Otherwise, aluminum-related bone disease will be aggravated after treatments. Therefore, several non-calcium, non-aluminum phosphate binders (such as sevelamer hydrochloride and lanthanum carbonate) are suggested despite the high cost and consequent unpopularity of these newly developed medications.

5. Acknowledgment

Sincerely thankful to Miss Hui-Li Hsiao, the Matron of the Dialysis Center in Chi-Mei Medical Center, and all the staff nurses, whose full support and encouragement enabled us to complete the related studies.

6. References

Alfrey, A.C., LeGendre, G.R., Kaehny, W.D. (1976). The dialysis encephalopathy syndrome. Possible aluminum intoxication. *N Engl J Med.*, Vol. 294, pp. 184–188, ISSN 1533-4406

Alfrey A.C. (1987). Aluminum metabolism and toxicity in uremia. *J UOEH.*, Vol. 9, Suppl, pp. 123–132, ISSN 0387-821X

Andress, D.L., Kopp, J.B., Maloney, N.A., Coburn, J.W., Sherrard, D.J. (1987). Early deposition of aluminum in bone in diabetic patients on hemodialysis. *N Engl J Med.*, Vol. 316, No. 6, pp. 292-296, ISSN 1533-4406

Barata, J.D., D’Haese, P.C., Pires, C., Lamberts, L.V., Simões, J., De Broe, M.E. (1996). Low-dose (5 mg/kg) desferrioxamine treatment in acutely aluminium-intoxicated haemodialysis patients using two drug administration schedules. *Nephrol Dial Transplant.*, Vol. 11, No. 1, pp. 125-132, ISSN 1460-2385

Bene, C., Manzler, A., Bene, D., Kranias, G. (1989). Irreversible ocular toxicity from single "challenge" dose of deferoxamine. *Clin Nephrol.*, Vol. 31, No. 1, pp. 45-48, ISSN 0301-0430
Berlyne, G.M., Pest, D., Ben-Ari, J., Weinberger, J., Stern, M., Gilmore, G.R., Levine, R. (1970). Hyperaluminaemia from aluminium resins in renal failure. *Lancet*, Vol. 296, No. 7671, pp. 494–496, ISSN 1474-547X

Berlyne, G.M., Ben-Ari, J., Knopf, E., Yagil, R., Weinberger, G., Danovitch, G.M. (1972). Aluminium toxicity in rats. *Lancet*, Vol. 299, No. 7750, pp. 564–568, ISSN 1474-547X

Boelaert, J.R., De Locht, M., Van Cutsem, J., Kerrels, V., Cantinieaux, B., Verdonck, A., Van Landuyt, H.W., Schneider, Y.J. (1993). Mucormycosis during deferoxamine therapy is a siderophore-mediated infection. In vitro and in vivo animal studies. *J Clin Invest.*, Vol. 91, No. 5, pp. 1979-1986

Bohrer, D., Bertagnolli, D.C., de Oliveira, S.M., do Nascimento, P.C., de Carvalho, L.M., Garcia, S.C., Arantes, L.C., Barros, E.J. (2009). Role of medication in the level of aluminium in the blood of chronic renal patients. *Nephrol Dial Transplant.*, Vol. 24, pp. 1277-1281, ISSN 1460-2385

Cannata, J.B., Ruiz Alegria, P., Cuesta, M.V., Herrera, J., Peral, V. (1983). Influence of aluminium hydroxide intake on haemoglobin concentrations and blood transfusion requirements in haemodialysis patients. *Proc Eur Dial Transplant Assoc.*, Vol. 20, pp. 719–724, ISSN 0308-9401

Cannata, J.B., Junor, B.J., Briggs, J.D., Fell, G.S., Beastall, G. Effect of acute aluminium overload on calcium and parathyroid-hormone metabolism. (1983). *Lancet*, Vol. 321, No. 8322, pp. 501–503, ISSN 1474-547X

Cannata, J.B., Briggs, J.D., Junor, B.J., Beastall, G., Fell, G.S. (1983). The influence of aluminium on parathyroid hormone levels in haemodialysis patients. *Proc Eur Dial Transplant Assoc.*, Vol. 19, pp. 244–247, ISSN 0308-9401

Cannata, J.B., Diaz Lopez, J.B., Fernandez Menendez, M.J., Virgos, M.J. (1988). The parathyroid gland and aluminum overload: an overview. *Contrib Nephrol.*, Vol. 64, pp. 113–119, ISSN 0302-5144

Cannata, J.B., Fernández-Soto, I., Fernández-Menendez, M.J., Fernández-Martín, J.L., McGregor, S.J., Brock, J.H., Halls, D. (1991). Role of iron metabolism in absorption and cellular uptake of aluminum. *Kidney Int.*, Vol. 39, No. 4, pp. 799–803, ISSN 1523-1755

Cannata, J.B., and Fernández-Martín, J.L. (2002). The clinical impact of aluminium overload in renal failure. *Nephrol Dial Transplant.*, Vol. 17, Suppl 2, pp. 9-12.

Canteros, A., Díaz-Corte, C, Fernández-Martín, J.L., Gago, E., Fernández-Merayo, C., Cannata, J. (1998). Ultrafiltrable aluminium after very low doses of desferrioxamine. *Nephrol Dial Transplant.*, Vol. 13, No. 6, pp. 1538-1542, ISSN 1460-2385

Cases, A., Kelly, J., Sabater, J., Campistol, J.M., Torras, A., Montoliu, J., López, I., Revert, L. (1988). Acute visual and auditory neurotoxicity in patients with end-stage renal disease receiving desferrioxamine. *Clin Nephrol.*, Vol. 29, No. 4, pp. 176-178, ISSN 0301-0430

Cronin, R.E., and Henrich, W.L. (2006). Aluminum toxicity in end-stage renal disease. In: *UpToDate*, Rose, BD (Ed), *UpToDate*, Waltham, MA, ISSN 0301-5718

Delmez, J.A., and Slatopolsky, E. (1992). Hyperphosphatemia: its consequences and treatment in patients with chronic renal disease. *Am J Kidney Dis.*, Vol. 19, No. 4, pp. 303-317, ISSN 1523-6838

D’Haese, P.C., Couttenye, M.M., Goodman, W.G., Lemoniatou, E., Digenis, P., Sotornik, I., Fagalde, A., Barsoum, R.S., Lamberts, L.V., De Broe, M.E. (1995). Use of the low-dose desferrioxamine test to diagnose and differentiate between patients with aluminium-
related bone disease, increased risk for aluminium toxicity, or aluminium overload. *Nephrol Dial Transplant.*, Vol. 10, No. 10, pp. 1874-1884, ISSN 1460-2385

Díaz-Corte, C., Fernández-Martín, J.L., Barreto, S., Gómez, C., Fernández-Coto, T., Braga, S., Cannata, J.B. (2001). Effect of aluminium load on parathyroid hormone synthesis. *Nephrol Dial Transplant.*, Vol. 16, pp. 742–745, ISSN 1460-2385

Drüeke T. (1980). Dialysis osteomalacia and aluminum intoxication. *Nephron* Vol. 26, pp. 78–81, ISSN 1460-2385

Drüeke, T.B. (1990). Resistance to recombinant human erythropoietin in hemodialysis patients. *Am J Nephrol.*, Vol. 10, Suppl. 2, pp. 34–39, ISSN 1421-9670

Felsenfeld, A.J., Machado, L., Bover, J., Trinidad, P., Rodriguez, M. (1993). Effect of aluminium on the development of hyperparathyroidism and bone disease in the azotaemic rat. *Nephrol Dial Transplant.*, Vol. 8, No. 4, pp. 325–334, ISSN 1460-2385

Fernández-Martín, J.L., Canteros, A., Serrano, M., Gonzalez-Carcedo, A., Diaz-Corte, C., Cannata, J.B. (1998). Prevention of aluminium exposure through dialysis fluids. Analysis of changes in the last 8 years. *Nephrol Dial Transplant.*, Vol. 13, Suppl 3, pp. 78–81, ISSN 1460-2385

Hewitt, C.D., Savory, J., Wills, M.R. (1990). Aspects of aluminum toxicity. *Clin Lab Med.*, Vol. 10, pp. 403–422, ISSN 1437-4331

Hughes, J.R., and Schreeder, M.T. (1980). EEG in dialysis encephalopathy. *Neurology.*, Vol. 30, No. 11, pp. 1148-1154, ISSN 1526-632X

Humpfner, A., Hummel, S., Schultz, W. (1993). Diagnosis and therapeutic approaches to aluminum overload in dialysed patients--representative study questionnaire in West German dialysis units in 1989-1990. *Nephrol Dial Transplant.*, Vol. 8, Suppl. 1, pp. S51-S54, ISSN 1460-2385

Jaffe, J.A., Lifman, C., Glickman, J.D. (2005). Frequency of elevated serum aluminum levels in adult dialysis patients. *Am J Kidney Dis.*, Vol. 46, No. 2, pp. 316-319, ISSN 1523-6838

Jeffery, E.H., Abreo, K., Burgess, E., Cannata, J., Greger, J.L. (1996). Systemic aluminum toxicity: effects on bone, hematopoietic tissue, and kidney. *J Toxicol Environ Health.*, Vol. 48, pp. 649–665, ISSN 0098-4108

Janssen, M.J., and van Boven, W.P. (1996). Efficacy of low-dose desferrioxamine for the estimation of aluminium overload in haemodialysis patients. *Pharm World Sci.*, Vol. 18, pp. 187-191, ISSN 1573-739X

Jorge, C., Gil, C., Possante, M., Catarino, M.C., Cruz, A., Andrade, R., Teixeira, R., Santos, N., Ferreira, A. (1999). Use of a desferrioxamine "microdose" to chelate aluminum in hemodialysis patients. *Clin Nephrol.*, Vol. 52, No. 5, pp. 335-336, ISSN 0301-0430

Kan, W.C., Chien, C.C., Wu, C.C., Su, S.B., Hwang, J.C., Wang, H.Y. (2010). Comparison of low-dose deferoxamine versus standard-dose deferoxamine for treatment of aluminium overload among haemodialysis patients. *Nephrol Dial Transplant.*, Vol. 25, No. 5, pp. 1604-1608, ISSN 1460-2385

Kausz, A.T., Antonsen, J.E., Hercz, G., Pei, Y., Weiss, N.S., Emerson, S., Sherrard, D.J. (1999). Screening plasma aluminum levels in relation to aluminum bone disease among asymptomatic dialysis patients. *Am J Kidney Dis.*, Vol. 34, No. 4, pp. 688-693, ISSN 1523-6838

Koiwa, F., and Sato, Y. (2009). Chemistry and history of phosphate binder. *Clin Calcium.*, Vol. 19, pp. 198-204, ISSN 0917-5857

Losekann, A., Urêna, P., Khiraoui, F., Casadevall, N., Zins, B., Bererhi, L., Zingraff, J., Bourdon, R., Drüeke, T. (1990). Aluminium intoxication in the rat induces partial resistance to the effect of recombinant human erythropoietin. *Nephrol Dial Transplant.*, Vol. 5, No. 4, pp. 258–263, ISSN 1460-2385
McCarthy, J.T., Milliner, D.S., Johnson, W.J. (1990). Clinical experience with desferrioxamine in dialysis patients with aluminium toxicity. *Q J Med.*, Vol. 74, pp. 257-276, ISSN 1460-2393

McCauley, J., and Sorkin, M.I. (1989). Exacerbation of aluminum encephalopathy after treatment with desferrioxamine. *Nephrol Dial Transplant.*, Vol. 4, No. 2, pp. 110-114, ISSN 1460-2385

Milliner, D.S., Nebeker, H.G., Ott, S.M., Andress, D.L., Sherrard, D.J., Alfrey, A.C., Slatopolsky, E.A., Coburn, J.W. (1984). Use of the defereroxamine infusion test in the diagnosis of aluminum-related osteodystrophy. *Ann Intern Med.*, Vol. 101, No. 6, pp. 775-779, ISSN 1539-3704

National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. (2003). *Am J Kidney Dis.*, Vol. 42, pp. S108-S122, ISSN 1523-6838

Norris, K.C., Crooks, P.W., Nebeker, H.G., Hercz, G., Milliner, D.S., Gerszi, K., Slatopolsky, E., Andress, D.L., Sherrard, D.J., Coburn, J.W. (1985). Clinical and laboratory features of aluminum-related bone disease: Differences between sporadic and "epidemic" forms of the syndrome. *Am J Kidney Dis.*, Vol. 6, pp. 342-347, ISSN 1523-6838

Parkinson, I.S., Ward, M.K., Feest, T.G., Fawcett, R.W., Kerr, D.N. (1979). Fracturing dialysis osteodystrophy and dialysis encephalopathy. An epidemiological survey. *Lancet*, Vol. 313, No. 8113, pp. 406-409, ISSN 1474-547X

Pei, Y., Hercz, G., Greenwood, C., Sherrard, D., Segre, G., Manuel, A., Saiphoo, C., Fenton, S. (1992). Non-invasive prediction of aluminum bone disease in hemo- and peritoneal dialysis patients. *Kidney Int.*, Vol. 41, No. 5, pp. 1374-1382, ISSN 1523-1755

Petrikkos, G., and Drogari-Apiranthitou, M. (2011). Zygomycosis in immunocompromised non-haematological patients. *Mediterr J Hematol Infect Dis.*, Vol. 3, No. 1, e2011012, ISSN 2035-3006

Pengloan, J., Dantal, J., Rossazza, C., Abazza, M., Nivet, H. (1987). Ocular toxicity after a single intravenous dose of desferrioxamine in 2 hemodialyzed patients. *Nephron*, Vol. 46, No. 2, pp. 211-212, ISSN 1660-2110

Salusky, I.B. (2006). A new era in phosphate binder therapy: What are the options? *Kidney Int.*, Vol. 105, pp. S10-S15, ISSN 1523-1755

Savery, J., Berlin, A., Courtoux, C., Yeoman, B., Wills, M. (1989). Summary report of an international workshop on “The role of biological monitoring in the prevention of aluminum toxicity in man: Aluminum analysis in biological fluids.” *Ann Clin Lab Sci.*, Vol. 13, pp. 444-451, ISSN 1550-8080

Sherrard, D.J. (1974). Letter: the myth of aluminum toxicity. *N Engl J Med.*, Vol. 290, pp. 750, ISSN 1533-4406

Slatopolsky, E. (1987). The interaction of parathyroid hormone and aluminum in renal osteodystrophy. *Kidney Int.*, Vol. 31, No. 3, pp. 842-854, ISSN 1523-1755

Vincenti, F., Arnaud, S.B., Recker, R., Genant, H., Amend, W.J., Jr., Feduska, N.J., Salvatierra, O., Jr. (1984). Parathyroid and bone response of the diabetic patient to uremia. *Kidney Int.*, Vol. 25, No. 4, pp. 677-682, ISSN 1523-1755

Ward, M.K., Ellis, H.A., Feest, T.G., Parkinson, I.S., Kerr, D.N. (1978). Osteomalacic dialysis osteodystrophy: evidence for a water-borne aetiological agent, probably aluminium. *Lancet*, Vol. 311, No. 8069, pp. 841-845, ISSN 1474-547X
This book is the result of the collaboration between worldwide authorities of different specialities in hyperparathyroidism. It aims to provide a general but deep view of primary/secondary and tertiary hyperparathyroidism, from a physiological basis to hyperparathyroidism in hemodialyzed patients, as well as new treatment approaches, techniques and surgical scenarios. We hope that the medical and paramedical researchers will find this book helpful and stimulating. We look forward to sharing knowledge of hyperparathyroidism with a wider audience.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Wei-Chih Kan, Chih-Chiang Chien, Yi-Hua Lu, Jyh-Chang Hwang, Shih-Bin Su and Hsien-Yi Wang (2012). Aluminum Overload: An Easily-Ignored Problem in Dialysis Patients with Hyperparathyroidism, Hyperparathyroidism, Dr. Gonzalo Diaz Soto (Ed.), ISBN: 978-953-51-0478-0, InTech, Available from: http://www.intechopen.com/books/hyperparathyroidism/aluminum-overload-an-easily-ignored-problem-in-dialysis-patients-with-hyperparathyroidism