Aluminium toxicity: its relationship with bone and iron metabolism

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Introduction

Chronic renal failure leads to secondary hyperparathyroidism; the spontaneous evolution of this entity results in high bone remodelling. However, throughout the last decades we have learnt that several medical interventions, particularly those which involve a high degree of aluminium exposure, may change the evolution of secondary hyperparathyroidism, leading to other diseases such as aluminium-induced osteomalacia and aluminium-induced adynamic bone disease, both characterized by low-bone remodelling [1-6]. In addition to these two well-known effects of aluminium in bone, aluminium may also induce alterations in iron metabolism [7-10]. This review will focus on the mechanisms of aluminium toxicity in bone metabolism and also the interference of aluminium in erythropoiesis.

Aluminium effects on bone metabolism

One of the simplest explanations for the implication of aluminium as a toxic substance for bone remodelling lies in its capacity to be deposited in the mineralization front. Several reports have suggested this particular localization of aluminium as the main obstacle for adequate calcium deposition [11-14]. This physicochemical effect of aluminium may be important in the process of mineralization, but most authors agree that the toxic effect of aluminium in bone is multifactorial, altering not only the mineralization, but also the cellular activity of parathyroid and bone cells [13-19]. Aluminium can induce changes in bone remodelling via two main pathways: by acting directly on the matrix formation and mineralization, and, indirectly, by depressing parathyroid function, which in turn will influence the bone remodelling.

Direct effect of aluminium on bone

Aluminium-induced low bone remodelling disease is characterized by a reduction in the rate of new bone formation [14,18-20]. Even though it is very difficult to interpret this effect without considering the influence of parathyroid hormone (PTH), the experimental results indicate there is an independent direct effect of aluminium on bone cells, and it seems that PTH supplementation does not correct this alteration. In addition, this direct effect of aluminium seems to affect separately osteoblast metabolism and bone mineralization [18]. The decrease in osteoblasts—both number and activity—observed in aluminium-induced osteomalacia and also in aluminium-induced adynamic bone disease, may be due to the direct toxic effect of aluminium on the osteoblasts, but also to the decrease in PTH or, more likely, due to the combination of both mechanisms. PTH seems to mainly affect bone cell activity, and supplements of PTH may partly reverse the toxic effect of aluminium on bone cells, increasing their number and activity, but it seems that PTH supplements do not affect the mineral apposition rate, and consequently it does not improve the rate of bone formation [18].

Therefore, the most relevant toxic effect of aluminium on bone is its capacity to reduce mineralization, probably acting through different mechanisms such as altering the influx and efflux of calcium from bone cells [19], and also reducing the calcium uptake from osteoblasts [22,23]. Thus, chronic aluminium load results in a reduction in bone cell proliferation [24] and activity [23], but also has a major effect on calcium apposition and crystallization, resulting in inhibition of bone mineralization.

Indirect effect of aluminium on bone: role of PTH suppression

Aluminium may reduce PTH concentrations through different mechanisms. There is much evidence that aluminium accumulation in the parathyroid glands can reduce the parathyroid response to hypocalcaemia [25,26]. Even though in most studies the assumption of high concentrations of aluminium in the parathyroid tissue, responsible for the lower response to PTH, is...
Based not on the measurement of aluminium in the parathyroids but on the high concentrations of aluminium found in bone, other clinical and experimental studies have demonstrated a significant increase in the aluminium content of the gland [27], and consequently a significant reduction in the serum PTH [28-30].

Although there is little information regarding the levels of interference of aluminium, the experimental results seem to give more support to the hypothesis that aluminium interferes mainly with the secretion [30] and release of PTH [31,32], rather than with its synthesis, and inhibitory effect in experimental studies is achieved with high concentrations of aluminium [31,32]. Recent results suggest that the calcium sensing receptor, in addition to sensitivity to calcium changes, may also be sensitive to changes in other ions, including trivalent ions [33]. If that is the case, the calcium sensing receptor may also be sensitive to aluminium, which may act on the parathyroid gland at ionic levels, as was suggested some years ago [34].

In addition to the direct effect of aluminium on the parathyroid gland, acting through the different mechanisms discussed above, aluminium may exert a suppressor effect on PTH by inducing serum calcium elevation. It is well known that aluminium-overloaded patients have increased likelihood of developing hypercalcaemia, either spontaneously or when using vitamin D metabolites or calcium salts as a phosphorous binder. In fact, hypercalcaemia has been classically recognized among the signs and symptoms related with aluminium-induced bone disease [35].

The mechanism by which aluminium may indirectly decrease PTH through serum calcium elevation can be summarized as follows. Exposure to aluminium leads to its deposition in tissues, particularly in bone. This deposition interferes with the incorporation of calcium into osteoid, and this prevention of calcium deposition in bone leads to the return of the calcium to the circulation, with a rise in the serum level of calcium. This in turn inhibits PTH synthesis and release. Through this mechanism, aluminium can act as a mediator of PTH suppression rather than there being a direct agent acting on the parathyroid glands. Clinical findings of parallel increments of serum calcium after increments in serum aluminium give support to this hypothesis [12,36].

Independent of the mechanisms implicated in PTH suppression [37], follow-up studies have demonstrated that aluminium exposure is followed by a decrease in PTH, and the removal of aluminium is followed by increments in PTH [12,38].

All these effects of aluminium on PTH secretion and release are extremely important because the bulk of evidence indicates that the toxic aluminium effect on bone can be modulated by PTH. When the levels of PTH are adequately high—enough PTH is present—the bone seems to be, at least partly, protected from aluminium toxicity [34]. The best example of this is the lack of apparent deleterious effect of aluminium deposition in patients with hyperparathyroidism [27]. On the contrary, when PTH concentrations are 'inadequately' low, the bone seems to be less protected against aluminium toxicity [1,2,4,27]. The most clear and practical evidence of the protective role of PTH is given, clinically, by the high risk of having aluminium-induced bone disease after parathyroidectomy [40,41], and experimentally, in studies demonstrating the benefits of having high PTH in the prevention of low bone remodelling disease induced by aluminium [20,21].

In summary, aluminium and PTH have a dual-way relationship. On one side PTH can influence aluminium absorption, distribution and deposition in different tissues [42,43]; on the other side, aluminium can suppress PTH by direct and indirect mechanisms, inducing inadequately low PTH, insufficient to maintain satisfactory bone remodelling [12,34].

### Aluminium–iron interaction in chronic renal failure

During the second half of this century the development of new technology has allowed a better understanding of iron and aluminium metabolism. Both elements have some similar properties: they are carried by the same serum proteins [44,45]; they are chelated by the same drugs [46,47]; both are stained in bone with the same compounds—aluminon and solochrome of azure [48-50]; and also both have been blamed for inducing low bone remodelling [10,51,52]. Therefore, it is reasonable to think that both elements may share important biological pathways [7,8]. In addition, the interaction between iron and aluminium has become particularly relevant in clinical practice due to the increase in the use of desferrioxamine and erythropoietin, as these two drugs could independently modify the equilibrium between these elements opening a new field for research in biology and medicine [53].

On the basis of these comments, we believe that one useful way to approach the study of the interaction between iron and aluminium is to look independently to the two phases of this issue: first to study the effect of changes in iron status—iron depletion and iron overload—on aluminium absorption, distribution and uptake; and second to study the opposite situation, i.e. the effect of changes in aluminium load on iron absorption, distribution and uptake.

#### Influence of iron status on aluminium metabolism

In the first part of the study of iron–aluminium interaction, we shall concentrate on the influence of two clearly different situations—iron depletion and iron overload—to try and answer if different iron status modulates or influences aluminium absorption, distribution and cellular uptake.

Patients exposed to oral aluminium show wide individual variations in the percentage of the dose that is absorbed. Several factors have been suggested for modifying this absorption, including age, chronic renal failure, PTH, vitamin D metabolites, citrate and some dietary constituents [42,54-58]. For the first time, some years ago, we suggested a likely role for iron metabol-
ism in aluminium absorption [59], after observing that patients with normal and low serum ferritin showed, after 2 weeks of oral aluminium load, a significant increase in their serum aluminium, while on the contrary, patients with high serum ferritin did not show any increase in the serum aluminium [59]. These findings persuaded us to carry out further studies to confirm our first observations. The results obtained in animals with normal renal function and chronic renal failure demonstrated that chronic oral aluminium hydroxide and acute oral AlCl3 administration was followed by a significant increase in gastrointestinal aluminium absorption and also in brain aluminium content, only in iron-depleted rats. The iron-overloaded rats seemed to be protected against accumulation of aluminium in tissues [8,60–62]. Complementary studies done with epithelial intestinal and bone cells support the in vivo findings, as iron-depleted cells showed a greater cellular aluminium uptake [8].

Even though other recent studies using different experimental models have not found a role for iron [63,64], most of the clinical and experimental evidence [8–10,59–62] strongly suggests the status of iron may be an important factor in the modulation of aluminium metabolism, and transferrin receptors may play an important role [9,65]. In summary, it seems that in iron deficiency, not only the iron absorption can be augmented, but also, if enough aluminium is available, the intestinal absorption of aluminium will increase, and with it the risk of aluminium toxicity because in iron deficiency also the cellular uptake of aluminium will be augmented [8,60–62].

Iron and aluminium not only compete for the same mechanisms of absorption and cellular uptake, they may also share other biological pathways. The main serum aluminium carrier is transferrin, a protein which is partially saturated with iron but is able to increase its iron saturation when there is an increase in iron needs. This protein is also capable of carrying between 85% and 95% of total aluminium [44,45]. The degree of iron transferrin saturation may influence the binding of aluminium by transferrin. Clinical studies favor the hypothesis of this competitive transport, showing that ‘the higher the iron transferrin saturation, the lower the serum aluminium’ [67–69]. This inverse relationship is particularly evident when the percentage of iron transferrin saturation is greater than 45%, indicating that as the binding of iron by transferrin increases, the binding of aluminium decreases, presumably due to the decrease of free binding sites in transferrin [69].

In addition to the negative relationship between aluminium and iron in serum, the response to a single oral challenge of aluminium hydroxide demonstrated that patients with low serum iron and low serum aluminium have greater increments in serum aluminium after the oral load—likely due to a greater absorption of aluminium—suggesting there might be a feedback between serum iron and/or aluminium, and the iron/aluminium uptake [69,70].

Influence of aluminium load on iron metabolism

In the second part of this review of iron–aluminium interaction we shall concentrate on the opposite view, namely, the effect of aluminium overload on absorption and cellular uptake of iron. The study of this side of the relationship has a great clinical interest. One of the most known toxic effects of aluminium is on erythropoiesis, which in many cases results in clinically relevant microcytic anaemia. Although aluminium may act directly on erythropoiesis affecting enzymatic pathways [66,67], it may also interfere with iron metabolism in the same way that iron may alter aluminium metabolism [7].

To test this hypothesis, over recent years we carried out a series of experimental studies with chronic aluminium load in rats with and without renal failure. We achieved very high concentrations of aluminium in tissues, and obtained typical lesions of aluminium-induced osteomalacia, but also microcytic anaemia, resembling iron-deficiency anaemia (significant decrease in mean corpuscular volume, microhaematocrit and iron transferrin saturation and a significant increase in total iron binding capacity (TIBC), even in rats with normal renal function) [71]. Despite this pattern resembling iron deficiency, which would normally predict a higher iron uptake, the aluminium-intoxicated animals showed a significant reduction in gastrointestinal iron absorption.

In support of the interference of aluminium in iron absorption, recent in vitro studies have shown that preincubation of cells with aluminium was able to suppress the cellular iron uptake in cells previously depleted of iron [71]. This observation supports the hypothesis that aluminium interferes with iron uptake, demonstrating competition between iron and aluminium also at the cellular level.

The interference of aluminium in iron uptake at the cellular level has been recently supported with results obtained in red cells from patients accidentally overloaded with aluminium [74]. After a maximum period of 6 months of aluminium exposure, patients showed parallel and significant increases in serum and intra-erythrocytic aluminium concentration. By contrast, after the aluminium exposure, serum ferritin did not show any change but intra-erythrocytic ferritin, as a marker of iron content of red cells, showed a significant decrease, demonstrating that aluminium can interfere also with the iron uptake from red cells. This shows that in such circumstances, body iron stores assessed by serum ferritin are not valid to evaluate the mechanism of the aluminium-induced microcytosis, because intra-erythrocytic ferropenia can exist in spite of apparently normal iron stores [74].

Clinical implications of aluminium–iron interaction: the use of desferrioxamine and erythropoietin

Desferrioxamine (DFO) is currently used as a non-invasive test to assess aluminium body burden. Due to the DFO stability constant this drug will mobilize more actively iron than aluminium. Thus, the increase
in serum aluminium obtained after the DFO test may be influenced not only by the aluminium burden but also by the iron stores. Patients with similar degrees of aluminium body burden but with significant differences in their iron stores are difficult to compare [75]. Those patients with iron depletion are more able to increase their serum aluminium after the DFO test, while those with iron overload will have lesser chances to mobilize aluminium and therefore a lesser response to the DFO test [75]. Thus, iron status should be also considered when interpreting the DFO test, because differences in serum aluminium increments after the infusion of DFO could be a function not only of aluminium body burden but also of iron status.

The aluminium–iron interaction must also be taken into account when chronically administering DFO and erythropoietin, as both drugs will affect iron and aluminium metabolism. DFO will remove iron, and erythropoietin will increase the iron utilization making it necessary to replace iron. Thus, it is important to monitor carefully serum iron, iron transferrin saturation, serum ferritin, haematocrit and mean corpuscular volume. Iron deficiency must be avoided because it would involve aluminium, iron, erythropoietin and thyroid hormone and iron received support from FIS 91/032 and could be influenced not only by the aluminium burden but also by the iron stores. Patients with similar degrees of aluminium body burden but with significant differences in their iron stores are difficult to compare [75]. Those patients with iron depletion are more able to increase their serum aluminium after the DFO test, while those with iron overload will have lesser chances to mobilize aluminium and therefore a lesser response to the DFO test [75]. Thus, iron status should be also considered when interpreting the DFO test, because differences in serum aluminium increments after the infusion of DFO could be a function not only of aluminium body burden but also of iron status.

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