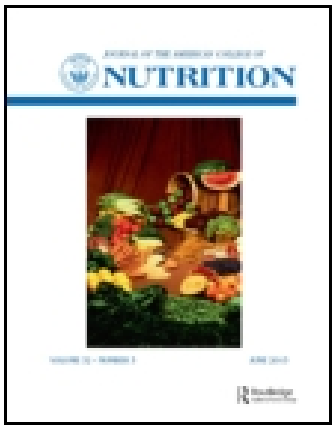

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The role of vitamin D in toxic metal absorption: a review.

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The Role of Vitamin D in Toxic Metal Absorption: A Review

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Key words: vitamin D, metal toxicity, lead, cadmium, aluminum, radioactive isotopes

Vitamin D increases intestinal calcium and phosphate absorption. Not so well known, however, is that vitamin D stimulates the co-absorption of other essential minerals like magnesium, iron, and zinc; toxic metals including lead, cadmium, aluminum, and cobalt; and radioactive isotopes such as ^{89,90}strontium and ^{137}cesium. Vitamin D may contribute to the pathologies induced by toxic metals by increasing their absorption and retention. Reciprocally, lead, cadmium, aluminum, and strontium interfere with normal vitamin D metabolism by blocking renal synthesis of 1,25-dihydroxyvitamin D. This is the first review of the role of the vitamin D endocrine system in metal toxicology.

Key teaching points:

- Vitamin D increases absorption of several toxic metals including lead, cadmium, aluminum, and cobalt.
- Vitamin D increases absorption of radioactive isotopes of strontium and cesium.
- Lead, cadmium, aluminum, and strontium interfere with normal vitamin D metabolism.
- These effects should be taken into consideration when establishing regulations regarding use of vitamin D.

INTRODUCTION

A role for vitamin D in calcium (Ca^{2+}) and phosphate (HPO_4^{2-}) metabolism has been known since the discovery of the anti-rickets vitamin in the early 1920s. Since 1930, a much broader role for the vitamin D endocrine system in mineral balance and metal toxicology has been developing. In 1932 Shelling [1] demonstrated that irradiated ergosterol (vitamin D_2 or ergocalciferol) increased lead (Pb^{2+}) absorption in rats. Sobel [2] confirmed this and extensively studied the relationship between vitamin D intake, and Pb^{2+} and HPO_4^{2-} absorption. Greenberg [3] demonstrated that vitamin D increases stable strontium (Sr^{2+}) absorption in chicks and rats. This was extended to radioactive isotopes of strontium ($^{89,90}Sr^{2+}$) by Mraz and Bacon [4]. Worker and Migicovsky [5] reported the uptake of all Group IIA elements (Ca^{2+}, Be^{2+}, Mg^{2+}, Sr^{2+}, Ba^{2+}) from an oral dose was significantly increased in chicks by vitamin D_3; no effect was observed from a subcutaneous dose of the minerals, leading to the conclusion that the effect of vitamin D on these elements is due to increased intestinal absorption rather than to a direct effect of vitamin D on bone. Worker and Migicovsky [6] studied the effect of vitamin D_3 on the absorption of Group IIB elements in chicks, finding zinc (Zn^{2+}) and cadmium (Cd^{2+}) increased in bone from an oral dose but not from subcutaneous injection, while mercury (Hg^{2+}) absorption was not affected by vitamin D treatment. Masuhara and Migicovsky [7] demonstrated that vitamin D-induced absorption of Fe^{2+} and Co^{2+} is increased when dietary Ca^{2+} is low, suggesting a common absorptive mechanism for these elements.

Following discovery of the vitamin D-induced Ca^{2+}-binding protein [8], Wasserman and Corradino [9] demonstrated binding properties of the protein for the various cations of Group IIA in the order: $Ca^{2+} > Sr^{2+} > Ba^{2+} > Mg^{2+}$. The role of Ca^{2+}-binding protein in absorption of cations is still not clear. Nevertheless, these studies established the foundation for current understanding of the emerging role for the vitamin D endocrine system in mineral homeostasis and metal toxicology. In addition to the effect of the vitamin D endocrine system on the absorption of cations, a number of cations (Pb^{2+}, Cd^{2+}, Sr^{2+}, Al^{3+}) adversely influence renal production of 1,25-dihydroxyvitamin D (1,25$(OH)_2$D), resulting in metabolic bone disease. In the present article current knowledge of the interactions of the vitamin D endocrine system with Pb^{2+}, Cd^{2+}, Al^{3+}, Sr^{2+}, Fe^{2+}, $^{137}Cs^{+}$, and plutonium ($^{239}Pu^{4+}$) is reviewed. Effects of the vitamin D endocrine system on Ca^{2+}, Mg^{2+}, and HPO_4^{2-} have been reviewed by others

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[10–13], and will not be included in the present discussion. No studies have been conducted on the possible role of vitamin D on vanadium or arsenic absorption, although as vanadate and arsenate these may be absorbed in a fashion similar to phosphate absorption.

THE ROLE OF VITAMIN D IN TOXIC METAL ACCUMULATIONS

Vitamin D Administration Increases Pb^{2+} Absorption

Early investigators demonstrated summer outbreaks of pediatric Pb^{2+} poisoning long before vitamin D was discovered. After the discovery of vitamin D, this observation lead to the suggestion that solar synthesis of vitamin D is a contributing factor to the increased Pb^{2+} poisoning that occurs in summer months [14]. Sobel et al [2] concluded that normal rations of vitamin D_2 cause a rise in Pb^{2+} content of bone ash and blood of rachitic Pb^{2+}-poisoned rats, and that the biochemical behavior of Pb^{2+} is influenced by vitamin D, Ca^{2+}, and HPO_4^{2-}. This was confirmed and extended by Sobel and his various co-workers [15–18]. Prior to 1980 interrelationships among Pb^{2+}, Ca^{2+}, HPO_4^{2-}, and Fe^{2+} were recognized [19–23], but the role of the vitamin D endocrine system in Pb^{2+} absorption and retention remained largely unexplored.

One effect of vitamin D is the induction of Ca^{2+}-binding protein by intestinal cells. Although the relationship between the vitamin D-induced Ca^{2+}-binding protein and Pb^{2+} absorption has not been fully established, Edelstein et al [24] showed that an increase in Ca^{2+}-binding protein might be involved. An increase in Pb^{2+} absorption in chicks that were maintained on vitamin D_3 and fed a low Ca^{2+} diet was associated with increased intestinal Ca^{2+}-binding protein. However, when chicks were maintained on $1,25(OH)_2D_3$ as the sole source of vitamin D and fed a low Ca^{2+} diet, no increase in intestinal Ca^{2+}-binding protein or in Pb^{2+} absorption was observed. Although these apparently contradictory results have not been fully explained, Edelstein et al [24] concluded that an increase in the calcium-binding protein is necessary for increased Pb^{2+} absorption.

Fullmer et al [25] studied the Pb^{2+}-binding properties of the intestinal Ca^{2+}-binding protein. The chick Ca^{2+}-binding protein binds 4 Ca^{2+} atoms with high affinity ($k_aCa^{2+} = 2 \times 10^6\ M^4$). Ca^{2+} displacement studies indicate higher affinity for Pb^{2+} than for Ca^{2+}, with a binding constant of ($k_aPb^{2+} = 1.6 \times 10^7\ M^{-1}$). Since Ca^{2+}-binding protein also binds Sr^{2+}, Ba^{2+}, Pb^{2+}, and Cd^{2+} in a fashion apparently related to their ionic radii [9]. Fullmer et al [25] suggest that the Ca^{2+}-binding protein may be basic to the absorption of all of these cations. Calmodulin, troponin C, and oncomodulin also bind Pb^{2+} with high affinities and in preference to Ca^{2+}, suggesting that Pb^{2+}-binding is a general property of proteins belonging to the troponin C superfamily of Ca^{2+}-binding proteins [25].

In the late 1970s, increasing environmental contamination by Pb^{2+} stimulated interest in the relationship between Pb^{2+} and vitamin D. Smith et al [26] and Mahaffey et al [27] demonstrated that in rats (using both in vivo and in vitro systems) vitamin D markedly enhanced Pb^{2+} absorption. Mahaffey et al [27] reported that in vivo absorption of Pb^{2+} acetate (0.01 mM) was around 16% in rats in the absence of vitamin D. This increased to 31% with 6.25 μg/day vitamin D_3, and 49% with 25 μg/day. The greatest enhancement observed was in the distal small intestine, which is a site of minimal vitamin D stimulation of Ca^{2+} absorption. Thus, although a high Ca^{2+} diet decreases Pb^{2+} absorption, the absorption of the two cations may not be controlled by the same absorptive mechanism. Smith et al [26] pointed out that vitamin D also stimulates HPO_4^{2-} transport especially in the distal small intestine, suggesting that Pb^{2+} transport may be related in some way to HPO_4^{2-} absorption.

Physiologic doses of vitamin D may enhance Pb^{2+} absorption as much as high doses [26]. Hart and Smith [28,29] demonstrated that in young growing rats vitamin D_3 treatment increases intestinal Pb^{2+} absorption and deposition in kidney and bone, concluding that tissue deposition of Pb^{2+} is a primary effect of vitamin D and is not secondary to increased Pb^{2+} absorption. Mykkänen and Wasserman [30,31] demonstrated that in rachitic chicks, the rate of absorption of Pb^{2+} is greater in the distal than in the proximal segments of the intestine, whereas after vitamin D repletion, the degree of absorption in all segments is similar. On acute dosage with $1,25(OH)_2D_3$, both Pb^{2+} and Ca^{2+} absorption increased, but the time course and patterns of absorption differed, again suggesting separate absorptive mechanisms. Barton et al [32] reported that dietary vitamin D deficiency and repletion resulted in increased absorption of Pb^{2+} in intact rats presumably due to prolonged gastrointestinal transit time, since manipulation of dietary vitamin D content did not affect the absorption of Pb^{2+} from isolated gut loops.

Andrushaite et al [33,34] demonstrated a doubling in ^{210}Pb absorption 72 hours after administration of 500 IU vitamin D_3 to rachitic chicks. Among rats, ingestion of 0.82% Pb^{2+} suppressed plasma levels of $1,25(OH)_2D$ on a low phosphorus or a low Ca^{2+} diet and blocked the intestinal Ca^{2+} transport response to vitamin D_3, 25-hydroxyvitamin D_3 ($25\text{-}OHD_3$), and $1,25(OH)_2D_3$ [35]. It thus appears that vitamin D ingestion increases Pb^{2+} absorption, and Pb^{2+} absorption interferes with vitamin D functions.

Children with high blood Pb^{2+} (> 60 μg/dL) have low levels of circulating 25-OHD which may be due to reduced

intake of vitamin D, since appetite impairment is a subtle clinical manifestation of Pb^{2+} intoxication [36,37]. There is a decrease in $1,25(OH)_2D_3$ in children with increased Pb^{2+} absorption due to an effect of the Pb^{2+} ion which impairs renal hydroxylation of 25-OHD [38]. A significant negative correlation ($r = -0.88$) was observed between $1,25(OH)_2D_3$ and blood Pb^{2+} concentrations for 177 subjects from 1 to 16 years old over the entire range of blood Pb^{2+} levels (12–120 μg) [39]. Thus, low serum $1,25(OH)_2D_3$ appears to be a sensitive index of Pb^{2+} toxicity.

Vitamin D Administration Increases Cd^{2+} Absorption

Wasserman [9] demonstrated that Ca^{2+}-binding protein binds Cd^{2+} as well as most other divalent cations. Worker and Migicovsky [6] reported a vitamin D_3-induced increase in Cd^{2+} absorption among chicks. This was confirmed and extended by Koo et al [40], who found a lack of correlation between Cd^{2+} absorption and Ca^{2+}-binding protein and concluded that the vitamin D-dependent Ca^{2+}-binding protein was not directly involved in Cd^{2+} absorption. On the other hand Washko and Cousins [41], using male rats, demonstrated an increase in Ca^{2+}-binding protein and Cd^{2+} absorption on low Ca^{2+} diets, and concluded that Ca^{2+}-binding protein is responsible for Cd^{2+} absorption. Cd^{2+} concentrates in kidney and bone, two organs of primary importance in vitamin D metabolism and function. An effect of Cd^{2+} on renal biosynthesis of $1,25(OH)_2D$ might therefore be expected. This is supported by the observation that osteomalacia is induced by Cd^{2+} [42,43]. Feldman and Cousins [44] reported that Cd^{2+} blocks renal 1-α hydroxylation of 25-OHD_3 which may explain the induction of osteomalacia by this cation. Ando et al [45] demonstrated inhibition by Cd^{2+} of vitamin D stimulated Ca^{2+} transport in rats, also attributed to a decreased renal production of $1,25(OH)_2D_3$. On the other hand, Kawashima et al [46] found no evidence of suppression of production of $1,25(OH)_2D_3$ in monkeys treated with Cd^{2+} for 9 years. Further studies regarding Cd^{2+} and vitamin D are needed.

Vitamin D Administration Increases Al^{3+} Absorption

Al^{3+}-induced osteomalacia resulting from dialysis osteodystrophy has been known for a number of years [47,48]. The presence of Al^{3+} in bone prevents bone response to vitamin D [49]. In addition to the harmful effects of Al^{3+} on bone mineral metabolism, recent interest has focused on Al^{3+} as a neurotoxin possibly involved in Alzheimer's senile dementia [50–52]. For these reasons there has been increased interest in the role of the vitamin D endocrine system in Al^{3+} toxicology within the last few years.

Colussi et al [53] identified $1,25(OH)_2D_3$ as a risk factor in Al^{3+} bone toxicity, since a patient being treated with $1,25(OH)_2D_3$ for hyperparathyroidism unexpectedly developed superimposition of Al^{3+}-related osteomalacia on previous osteitis fibrosa. In chronically uremic rats receiving oral Al^{3+} supplementation, Drüeke et al [54] reported a decrease in liver Al^{3+} content accompanied by elevated serum Al^{3+} following treatment with $1,25(OH)_2D_3$. Al^{3+}-induced osteomalacia in rats has been attributed to chronic renal failure [55]. In Al^{3+}-induced osteomalacia in dogs, reduced levels of $1,25(OH)_2D_3$ have been found [56], but not confirmed [57]. Adler and Berlyne [58] studied duodenal Al^{3+} absorption in rats using an in vivo isolated gut segment technique, finding that Al^{3+} is absorbed by both a nonsaturable mechanism and a vitamin D-dependent saturable mechanism for which it may compete with Ca^{2+}. In a review of gastrointestinal absorption of Al^{3+}. Ihle and Becker [59] include parathyroid hormone (PTH) and vitamin D metabolites as factors that increase Al^{3+} absorption. Elevated PTH may explain why some patients reach high serum Al^{3+} levels on low doses of Al^{3+}. Mayor et al [60,61] demonstrated in rats that vitamin D and its metabolites increase tissue Al^{3+} burdens independently of PTH. The parathyroid glands tend to concentrate Al^{3+}, and thus contained significantly more Al^{3+} per unit mass than did thyroid glands or cervical muscle [62]. Anthony et al [64] found an increase in levels of Al^{3+} in muscle and heart of rats following administration of vitamin D_3.

Vitamin D Administration Increases the Body Burden of Radioactive Nuclides

Mraz and Bacon [4] showed an increase in tissue levels of $^{89}Sr^{2+}$ in rats fed $^{89}Sr^{2+}$ and excess vitamin D, confirming an earlier report by Greenberg [3]. Worker and Migicovsky [6] and Wasserman and Corradino [9] also found increased Sr^{2+} absorption under the influence of vitamin D. As well, Sr^{2+} interferes with Ca^{2+} absorption and utilization, resulting in Sr^{2+}-induced rickets in laboratory animals [65]. Sr^{2+}-induced does not respond to vitamin D treatment, but increased dietary Ca^{2+} reverses the lesions. It is believed that this action of Sr^{2+} is mediated via blockage of renal synthesis of $1,25(OH)_2D_3$ [65]. Giza et al [66] reported that rickets induced by radioactive isotopes of Sr^{2+} in rats is not reversible by treatment with vitamin D_2, suggesting that there may an association between $^{89,90}Sr^{2+}$ levels in bone and vitamin D-resistant rickets. Spencer et al [67] have summarized $^{90}Sr^{2+}$-Ca^{2+} interrelationships. In addition to increasing the body burden of $^{89,90}Sr^{2+}$, vitamin D increases intestinal absorption and bone deposition of $^{137}Cs^{+}$ [9].

In a unique study of the effects of vitamin D on skeletal $^{239}Pu^{4+}$ levels in mice, Battacharyya and Peterson [69]

attempted to remove skeletally deposited $^{239}Pu^{4+}$ with large doses of vitamin D_3, but were unable to demonstrate an increase in release of $^{239}Pu^{4+}$ from its sites of deposition in the skeleton.

CONCLUSIONS

In addition to its traditional role in Ca^{2+} and HPO_4^{2-} metabolism, the vitamin D endocrine system is important in the absorption and balance of other essential minerals (Mg^{2+}, Fe^{2+}, Zn^{2+}). As well, absorption of several toxic metals (Pb^{2+}, Cd^{2+}, Al^{3+}, Co^{2+}, $^{89,90}Sr^{2+}$, $^{137}Cs^{+}$) is increased under the influence of vitamin D. Reciprocally, these metals exert an adverse effect on vitamin D metabolism which results in impaired renal production of $1,25(OH)_2D_3$ and metabolic bone disease. Although the significance of this information remains to be clarified, these effects should be taken into consideration when establishing regulations regarding use of vitamin D.

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