Interactions between Vitamin D Deficiency and Phosphorus Depletion in the Rat

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ABSTRACT To evaluate the role of vitamin D in the physiologic response to phosphorus depletion (P depletion) and the response to vitamin D administration in P depletion, we studied vitamin D-deficient (-D) rats, fed either a normal or low phosphorus diet and then injected intraperitoneally on alternate days with replacement vitamin D3, 1.25 µg qod (D3); 1,25-dihydroxy-vitamin D3 [1,25(OH)2D3] in physiologic, 54 ng qod (LD), and pharmacologic doses, 400 ng qod (HD); or vehicle alone (-D). The following results were obtained: (a) With P depletion, urinary excretion of inorganic phosphorus (Pi) fell to almost undetectable levels in -D rats, and two physiologic features of P depletion a calcemic effect and hypercalciuria, ensued. (b) With administration of vitamin D3 or 1,25(OH)2D3 in either doses to P-depleted rats, the renal retention of Pi was unaltered despite a significant elevation of serum Pi. (c) The calcemic response to P depletion was accentuated by vitamin D sterols, and the hypercalciuria of P depletion was reduced by 1,25(OH)2D3, HD > LD > D3. (d) In -D animals receiving normal Pi (+P), D3, and 1,25(OH)2D3, both LD and HD produced a significant calcemic and phosphatemic effect. (e) Urinary Pi excretion in +P animals was reduced slightly by vitamin D3 whereas 1,25(OH)2D3, both LD and HD, lowered urinary Pi markedly despite an increased serum Pi. (f) The serial values of serum Ca and Pi and urinary Ca in PD rats and the sequential values for urine and serum Pi in +P rats indicated more rapid effects of 1,25(OH)2D3, both HD and LD, compared with D3. We conclude that: (a) The renal adaptation and physiologic response to PD does not require the presence of vitamin D. (b) 1,25(OH)2D3 may directly enhance the renal tubular reabsorption of Pi even as serum Pi rises. (c) A hypocalciuric action of 1,25(OH)2D3 in rats on low phosphorus diet could be direct or occur as a consequence of an increase in serum Pi produced by 1,25(OH)2D3. The different sequential renal response to D3 compared with 1,25(OH)2D3 raises the possibility that other natural forms of vitamin D3 [i.e., 25(OH)D3, 24,25(OH)2D3, etc.] which may be present in vitamin D-fed rats but not those given only 1,25(OH)2D3, could modify the actions of 1,25(OH)2D3.

INTRODUCTION

With dietary phosphorus restriction and the appearance of phosphorus depletion, several physiologic events consistently occur: These include a marked reduction in urinary phosphorus excretion, the appearance of hypophosphatemia, hypercalciuria, and, in certain species, the development of hypercalcemia (1-5). There is indirect evidence in animals (3, 6) and direct measurements in humans (7) suggesting that physiologic hypoparathyroidism develops during phosphate depletion. However, it has been shown that administration of parathyroid hormone does not modify renal phosphate conservation during phosphorus depletion (8, 9) and only partially reduces the hypercalciuria (3). It is now well established that interactions exist between phosphorus metabolism and the bioconversion and actions of vitamin D. Thus, the administration of 1,25-dihydroxy-vitamin D3 [1,25(OH)2D3] enhances intestinal phosphorus transport in experimental ani-

1 Abbreviations used in this paper: +D, normal vitamin D; -D, vitamin D deficient; HD, high dose; LD, low dose; 1,25(OH)2D3, 1,25-dihydroxy-vitamin D3; +P, normal phosphorus; -P, low phosphorus; Pi, inorganic phosphorus; PTH, parathyroid hormone.
and inorganic phosphorus (Pi) were observed. Body weight remained unchanged in all groups for days 4 through 9, although weight gain occurred in each group from days 1 to 4 when they received no vitamin D sterol. The reason for the lack of weight gain is not certain, but frequent intraperitoneal injections and tail-vein bleedings may have contributed.

Calcium was analyzed in serum by EGTA titration utilizing the Automatic Calcium Analyzer (Calcette; Precision Scientific Group, Chicago, Ill.) and in urine utilizing atomic absorption spectrometry (Perkin Elmer model 303, Perkin-Elmer Corp., Norwalk, Conn.); phosphorus was measured in serum utilizing the malachite green micromethod (17) and in urine utilizing a standard method previously reported (3). Serum urea nitrogen levels were measured in blood samples obtained on day 9 using the method of Siest et al. (18). The statistical analysis involved one-way analysis of variance, the Dunnett's tests for multiple group comparison (19), and multiple correlations carried out in a manner previously described (20). All statistical comparisons of possible physiologic importance were made, but only the more pertinent P values are cited in the text.

RESULTS

Serial values of serum Pi in animals fed +P or −P diets are shown in Fig. 1. In the animals receiving the normal phosphorus (P) intake, there was a significant phosphatemic effect in the groups receiving either dose of 1,25(OH)₂D₃, with mean serum Pi reaching levels of 3.25 ± 0.05 mM and 3.82 ± 0.06 mM after 24 h (day 4) in the 1,25LD and 1,25HD groups compared with 2.40 ± 0.06 mM in the −D group (P < 0.01). Serum Pi increased in the vitamin D-fed group (+D) but to a lesser degree (P < 0.01 compared with 1,25LD and 1,25HD on day 4). After day 4, serum Pi remained stable in 1,25LD or even fell slightly in 1,25HD; the serum Pi rose to its maximal level, 4.10 ± 0.14 mM, on day 6 in the +D group.

In animals receiving the −P diet, serum Pi decreased substantially within 48 h after initiation of −P diet. By 24 h after administration of 1,25(OH)₂D₃, serum Pi increased predominantly to 1.09 ± 0.10 and 1.59 ± 0.06 mM in 1,25LD and HD groups, respectively, compared with 0.88 ± 0.012 mM in the −P animals (P < 0.01). Serum Pi remained low in vitamin D₃-treated animals until the end of day 6 when it reached a level similar to that of the −P group.

and phosphate depletion has not been thoroughly examined. In the present study, the physiologic response to phosphate depletion was evaluated in animals that were either depleted of vitamin D or replaced with known amounts of vitamin D₃ or specific quantities of 1,25(OH)₂D₃, the most active form of vitamin D.

METHODS

Weanling male Holtzman rats (Holtzman Co., Madison, Wis.) were fed an artificially prepared, vitamin D-deficient diet (15) containing 0.3% phosphorus and 0.5% calcium for 6 wk. At that time hypocalcemia was prominent (serum calcium, 1.70 ± 0.05 [SE] mM), and the animals weighed 140–160 g. The animals were then randomly separated into groups and housed in individual metabolic cages. 24-h urine samples were collected, and blood samples were obtained from the tail vein on alternate days. The animals were divided into two main groups: those receiving a low phosphorus (0.03%) diet (−P) and those receiving a normal phosphorus (0.3%) intake (+P).

After the animals had received the vitamin D-deficient −P or +P diet for 3 days, each major group was then subdivided into four subgroups of 8–10 animals, each of which received a vitamin D sterol or vehicle as indicated in Table I. The quantity of vitamin D₃ given was that considered to be a normal replacement dose (16), whereas the two levels of 1,25(OH)₂D₃ given were (a) near that needed for maintaining growth and serum calcium normal (low dose, LD), and (b) the quantity previously found to maximally stimulate intestinal calcium transport (high dose, HD). The vitamin D sterols or vehicle were injected intraperitoneally at the end of the 24-h urinary collections for days 3, 5, 7, and 8. The vitamin D₃ was obtained from n.V. Phillips-Duphar (Weesp, The Netherlands), and the 1,25(OH)₂D₃ was provided by Dr. M. Uskokovic of Hoffmann-La Roche (Nutley, N. J.).

Food intake was measured daily, and the animals were weighed on each morning of injection. Although the animals were not pair-fed, there was no difference in dietary intake in any of the groups, except for the −P vitamin D-deficient (−D) group, which consumed less food only on days 4 and 5 (P < 0.05). The average daily food intake ranged from 9.0 to 11.0 g/d in the −P −D group, compared with 8.8 to 13.5 g/d in the −P groups, and 11.0 to 15.0 g/d in the +P groups. In no group was there a significant change in food intake from days 4 through 8 when the changes in excretion of calcium

TABLE I

<table>
<thead>
<tr>
<th>Sterol treatment</th>
<th>Dose (every other day)</th>
<th>Dietary phosphorus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>Ethanol:propanediol, 1:1, 0.80 ml</td>
<td>0.03% (−P)</td>
</tr>
<tr>
<td>Vitamin D₃*</td>
<td>1.25 μg/l</td>
<td>−P − D</td>
</tr>
<tr>
<td>1,25(OH)₂D₃*</td>
<td>54 ng</td>
<td>−P + 1,25LD</td>
</tr>
<tr>
<td>1,25(OH)₃D₃*</td>
<td>400 ng</td>
<td>−P + 1,25HD</td>
</tr>
</tbody>
</table>

* Given in the ethanol:propanediol vehicle, 0.2 ml, by intraperitoneal injection. 1 Equivalent to 50 IU.
Ca plateaued after day 6 in the +D animals, and there was a small but statistically significant further increase in the 1,25LD rats from 2.40±0.059 to 2.60±0.019 mM (P < 0.01). Serum Ca continued to increase in 1,25HD rats, reaching 3.15±0.062 mM on day 9.

In −P−D rats, serum Ca increased from 1.70±0.050 to 2.62±0.055 mM by day 2 of P depletion (P < 0.01); thereafter, serum Ca was 2.49±0.068 mM on day 4 and 2.35±0.025 mM on day 9 (P = NS). In both 1,25LD and 1,25HD rats, serum Ca increased on day 4 within 24 h of treatment (P < 0.01); in the +D rats, serum Ca increased more slowly, and the difference between +D and −D did not become significant until day 6 (2.75±0.97 vs. 2.38±0.062, P < 0.01). For the 1,25HD and the 1,25LD groups, serum Ca did not show a significant change after day 4. In comparing levels of serum Ca between the −P and +P animals, the values were all significantly greater in the −P rats (P < 0.01) except for the values obtained in the 1,25HD group on day 9.

Rates of urinary Pi excretion are shown in Fig. 3 for both +P and −P animals. Within 24 h after administration of the −P diet, the urinary Pi fell markedly from 1.74±0.12 to 0.052±0.006 mmol Pi/mmol creatinine per 24 h (P < 0.01). During the remainder of the study, urinary Pi fell even further, and mean values were below 0.052 mmol/mmol creatinine per 24 h, regardless of the treatment given. Because of the very low quantities of Pi found in the urine, no statistical comparisons were made.

In the +P animals, urinary Pi remained relatively constant in −D rats with a small and insignificant decrease by the end of the study. In the +D rats, there

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FIGURE 1 Mean values of serum phosphorus (Pi) in −D rats receiving either a +P (0.3%) or a −P (0.03%). The doses of vitamin D₃ and 1,25(OH)₂D₃, LD and HD, are given in Table I. Each point represents mean±SEM in six to eight rats.

FIGURE 2 Mean±SEM values of serum Ca in −D rats continued on either a +P (0.3%) diet or given a −P (0.03%) diet and then given vitamin D₃ or different doses of 1,25(OH)₂D₃ as noted in Table I.

FIGURE 3 Urinary P excretion, expressed as the ratio of urinary P/urinary creatinine, in 24-h urine samples collected from −D rats fed either a +P (0.3%) or −P (0.03%) diet. The doses and regimen for treatment of vitamin sterols are given in Table I.

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were no differences in urinary Pi for the first 3 d of vitamin D$_3$ treatment, but the values fell significantly on days 7 and 9 (compared with day 3, $P < 0.01$); however, the values did not differ from the –D group. In the 1,25HD group, urinary Pi fell significantly on days 5 and 6 ($P < 0.01$), but later increased to a level not different from that observed in the –D rats. In the 1,25LD group, urinary Pi did not fall until day 6; however, the values were lower than those on day 3 throughout the remainder of the study ($P < 0.01$). Regardless of the vitamin D sterol given, urinary Pi was higher in the +P than in the –P rats ($P < 0.01$). When one compares the relationship between urinary and serum Pi, urinary Pi was lower on day 6 in both 1,25(OH)$_2$D$_3$ groups compared with the +D group, despite higher levels of serum Pi in the former.

The values for urinary Ca for both +P and –P rats are shown in Fig. 4. In the rats receiving the +P diet, urinary Ca was low during the control period, with a mean value of 0.89±0.003 mmol/mmol creatinine. There were no significant differences between urinary Ca in any +P group given any vitamin D sterol and the values in the –D+P group at any time of the study ($P > 0.05$).

In the –P rats, urinary Ca increased markedly within 24 h after initiation of the –P diet ($P < 0.01$), with a mean value of 1.41±0.028 mmol/mmol creatinine per 24 h. The maximal value on the 3rd day of the –P diet was 2.61±0.099 mmol/mmol creatinine per 24 h. The values fell somewhat thereafter, but urinary Ca continued to be high, and values ranged from 1.61±0.12 to 2.12±0.34 mmol/mmol creatinine per 24 h during the remainder of the study. In the +D group, urinary Ca did not differ from that in the –D rats except on day 8 when the mean value was marginally greater (2.65±0.33 vs. 2.09±0.11 mmol/mmol creatinine per 24 h, $P < 0.05$). In the 1,25LD group, mean urinary Ca fell below the values observed in the –D rats on days 4 and 6 ($P < 0.01$); for the other days, urinary Ca was not significantly lower, but serum Ca was clearly higher in the 1,25LD than in –D rats throughout the study (Fig. 2). In the +1,25HD, –P rats, urinary Ca fell markedly, with values not different from those in +P animals. When urinary Ca is compared with the corresponding serum Ca, the urinary excretion was lower on the 1st and 3rd d of treatment in the 1,25(OH)$_2$D$_3$-treated groups compared with +D rats, despite a higher serum Ca in 1,25(OH)$_2$D$_3$ groups on day 4.

Levels of serum urea nitrogen obtained on day 9 are shown in Table II. The values did not differ in any of the groups except for 1,25HD, both –P and +P groups, which showed an increase.

**DISCUSSION**

The present results indicate that several physiologic responses to phosphate depletion, including hypophosphaturia, hypercalcuria, and a rise in serum Ca, can occur without vitamin D and develop during the administration of known quantities of 1,25(OH)$_2$D$_3$ or vitamin D$_3$. Steele et al. (12) have provided evidence from a short-term study that there is increased renal tubular phosphate reabsorption in –D rats given a –P diet. The results of Steele et al. (12) and observations from the present study indicate that neither vitamin D nor alterations in vitamin D metabolism are required for enhanced renal tubular reabsorption of phosphate in the face of dietary phosphate restriction. This decrease in urinary Pi persisted during phosphate depletion even as serum Pi was raised by an acute phosphate infusion in the study of Steele et al., and as it increased more slowly as a consequence of the continued administration of 1,25(OH)$_2$D$_3$ in the present study. These results underscore the potency of dietary phosphate restriction in augmenting tubular Pi reabsorption, observations previously made by Tröhler et al. (21) and Steele et al. (12).
The present studies demonstrate that marked hypercalciuria occurs during P depletion in the \(-D\) as well as the vitamin \(D_3\)-treated animals. Hypocalciuria is very commonly found in vitamin \(D\) deficiency in man (22); however, the present data indicate that urinary \(Ca\) may be normal or even elevated when vitamin \(D\) deficiency and P depletion coexist in the rat. Metabolic acidosis occurs in \(-D\) rats (23); this factor could influence urinary \(Ca\); however, hypercalciuria was not reversed by vitamin \(D\) itself, nor was it seen in the \(+P\) group. Hence, any contribution of acidosis is speculative.

The initiation of phosphate restriction was associated with a calcemic effect in the \(-D\) animal, and treatment with various vitamin \(D\) sterols raised serum \(Ca\) even further. It has been shown that P depletion, per se, does not lead to increased intestinal absorption of \(Ca\) in the \(-D\) rat (24). Others found augmented release of radiocalcium from bone during P depletion produced in vivo (13) and from bone maintained in organ culture and exposed to a reduced phosphate concentration (25). Thus, bone is the most likely source of \(Ca\) that leads to both the rise in serum \(Ca\) and the hypercalciuria observed during P depletion. The present observations suggest that \(Ca\) can be mobilized from bone in response to P depletion in the absence of vitamin \(D\). The failure of either vitamin \(D\) deficiency or the administration of small amounts of vitamin \(D_3\) or moderate quantities of \(1,25(\text{OH})_2D_3\) to modify physiologic responses to P depletion casts doubt on the suggestion that altered bioconversion of vitamin \(D\) is responsible for these events (26).

The present data demonstrate a marked decrease in urinary \(Ca\) excretion in the P-depleted, hypercalciuric rat in response to treatment with \(1,25(\text{OH})_2D_3\). This effect was observed during the first 24-h period after administration of \(1,25(\text{OH})_2D_3\) and was greater in rats given the large dose of \(1,25(\text{OH})_2D_3\) compared with those receiving the smaller dose. Serum \(Ca\) increased at the same time; thus, there probably was an increase in tubular reabsorption of \(Ca\). Steele et al. (12) suggested that the fraction of filtered \(Ca\) excreted was reduced by \(1,25(\text{OH})_2D_3\), and Costanzo et al. (27) found lower clearance ratios of \(Ca\) in rats given a single dose of vitamin \(D_3\), 2.5 \(\mu g\). Taken together, these data suggest that \(1,25(\text{OH})_2D_3\) may enhance tubular \(Ca\) reabsorption when given to \(-D\) animals. However, there was no increase in serum \(Pi\) with the administration of the vitamin \(D\) sterol, and an inverse relationship existed between urinary \(Ca\) and serum \(Pi\) for all animals studied. An inverse relationship between serum \(Pi\) and urinary \(Ca\) has been previously noted in P-depleted dogs and rats (3, 12, 26), and it is possible that the alterations in serum \(Pi\) were responsible for the changes in urinary \(Ca\) observed during treatment with the vitamin \(D\) sterols. Steele et al. (12) found that the infusion of phosphate to \(-D\) rats previously fed either 0.03 or 0.1% \(P\) was associated with a substantial decrease in urinary \(Ca\). On the other hand, studies by Rizzoli et al. (28) demonstrated that urinary \(Ca\) increased in response to the administration of 11 ng/d of 1,25-(\(\text{OH})_2D_3\). Moreover, the administration of \(1,25(\text{OH})_2D_3\) to normal humans has generally produced an increase in urinary \(Ca\), although this may occur because of a small increase in filtered \(Ca\) (29, 30). Thus, the action of \(1,25(\text{OH})_2D_3\) may vary, depending on the \(Ca\) needs or stores of the organism.

The results of the present studies indicate that the administration \(1,25(\text{OH})_2D_3\) in only moderate doses can reduce urinary \(Pi\) excretion in \(-D\) rats receiving a \(+P\) diet. This was evident by the 2nd d of \(1,25(\text{OH})_2D_3\) administration (day 5) in the \(1,25\text{HD}\) group and on day 6 in the \(1,25\text{LD}\) group. These effects occurred earlier than observed in the vitamin \(D_3\)-treated rats. Also, urinary \(Pi\) excretion was lower in the \(1,25\text{LD}\) or \(1,25\text{HD}\) groups for any given level of serum \(Pi\). Popovtzer et al. (31) and Puschet et al. (32) both reported an antiphosphaturic action of \(25(\text{OH})_2D_3\) in rats that was dependent upon the presence of parathyroid hormone (PTH). The quantities of \(25(\text{OH})_D_3\) utilized in their studies were considerably greater than the amount of vitamin \(D_3\) given here and much greater than the amount of \(1,25(\text{OH})_2D_3\) employed. Costanzo et al. (27) found that a large dose of vitamin \(D_3\), 2.5 \(\mu g\), reduced urinary \(Pi\) excretion 48 h later in \(-D\) rats. The present results indicate that \(1,25(\text{OH})_2D_3\), in a quantity only 2.5 times greater than that described by Bonjour et al. (33) as a “replacement” dose in parathyroidectomized rats, was associated with a definite reduction in urinary \(Pi\) excretion in \(-D\) rat. Suppression of PTH secretion could contribute to this effect, and serum levels of PTH are not available in the present study. Serum levels of \(Ca\) were no different in the \(+P\) rats receiving \(D_3\) or the two doses of \(1,25(\text{OH})_2D_3\) on days 4 through 6 of the study. Hence, one would not anticipate greater inhibition of PTH secretion with \(1,25(\text{OH})_2D_3\) than with \(+D\); also, there was no increase in urinary \(Ca\), a finding that would be expected if there were marked suppression of PTH secretion. Bonjour et al. (33) have shown that \(1,25(\text{OH})_2D_3\) may permit greater phosphate excretion in parathyroidectomized rats given a high dietary \(Pi\) intake. Thus, it is possible that \(1,25(\text{OH})_2D_3\) can enhance \(Pi\) excretion in the phosphate-loaded or hyperphosphatemic state, whereas it can reduce urinary \(Pi\) excretion in a hypophosphatemic animal. Such effects could account, in part, for the effect of \(1,25(\text{OH})_2D_3\) to raise serum \(Pi\) in hypophosphatemic rats and cause a fall in serum \(Pi\) in hyperphosphatemic rats (34).

The possibility that altered dietary intake or a change in renal function may have accounted for the reduction in urinary \(Ca\) or the fall in urinary \(Pi\) should be considered. Only in the \(-P-D\) rats was food intake slightly lower than in the other groups; despite this, hypercal-
uric acid was most marked in this group. Also, there was no significant day-to-day differences in food intake for any group. Thus, altered dietary intake could not account for the changes in urinary excretion. The possibility that decreased renal function may have contributed to the fall in urinary Ca and decrease in urinary P in the 1,25HD groups exists, and the serum urea nitrogen levels were slightly increased. Parallel studies carried out in our laboratory indicate that decreased renal function and nephrocalcinosis do not occur in rats treated with 1,25(OH)2D3 until hypercalcemia supervenes (35). Moreover, the fall in urinary Ca in the −P+1,25HD rats occurred as soon as day 4, and the urinary Pi fell in the +P+1,25HD group by day 5; on the other hand, the hypercalcemia only appeared on day 9 in the 1,25HD groups. The serum urea nitrogen was not increased in the +1,25LD or +D groups, which also exhibited a fall in urinary Pi and Ca. Thus, we believe it unlikely that a decrease in renal function occurred early in the +1,25HD groups when the most pronounced effect on urinary Ca and Pi were seen.

Observations of serial changes in serum Ca and Pi and urinary Ca in the −P rats and of sequential alterations in urinary Pi and serum Pi in the +P rats indicate an earlier effect of 1,25(OH)2D3 with both the “low” and “high” dose than observed with vitamin D3. These findings were unexpected because the conversion of vitamin D3 to 25(OH)D3 and then to 1,25(OH)2D3 should proceed rapidly and effectively in rats with vitamin D deficiency, secondary hyperparathyroidism, and, in certain groups, P depletion as well (14). This “delayed” effect of vitamin D3 was observed with the administration of a quantity of vitamin D3 was observed with the administration of a quantity of vitamin D shown to be highly effective in healing rickets and promoting growth (16). The reasons for the more rapid appearance of action of 1,25(OH)2D3 are not known, but at least two explanations may be considered. It is possible that 54 ng of 1,25(OH)2D3, given on alternate days, exceeds the maximal capacity for renal production of this sterol. However, this amount is only 2.5 times the quantity of 1,25(OH)2D3 that can restore Ca absorption to normal in parathyroidectomized rats (27). The conversion of only 4% of the administered vitamin D3 to 1,25(OH)2D3 would have resulted in the generation of the quantity of 1,25(OH)2D3 given the +1,25LD group. Boyle et al. (36) and Norman and Wong (37) reported that as much as 25% of a single dose of vitamin D3 was recovered as 1,25(OH)2D3 from various tissues of −D rat given 0.125 ng of vitamin D3. Alternatively, it is possible that other naturally occurring vitamin D sterols, such as 25(OH)D3 or 24,25(OH)2D3, etc., present in the vitamin D3-treated rats but not in those given 1,25(OH)2D3, may have actions that oppose certain isolated effects of 1,25(OH)2D3. Although such a suggestion is speculative, it has been shown that 25(OH)D3 may exert effects on the skeleton different from the actions of 1,25(OH)2D3 (38, 39), and other data indicate that 24,25(OH)2D3 given in combination with 1,25(OH)2D3 has effects to suppress parathyroid gland weight much greater than 1,25(OH)2D3 alone (40). Such observations suggest that certain vitamin D sterols may have actions qualitatively different from those of other vitamin D compounds.

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