Physiology of Vitamin D and Calcium Homeostasis

David R. Fraser

Department of Animal Science, The University of Sydney, New South Wales 2006, Australia

In the past 20 years a voluminous literature has been written on the role of vitamin D in calcium homeostasis. This outpouring of experimental findings stemmed from the discovery that vitamin D was the precursor of a steroid hormone, 1,25-dihydroxyvitamin D \([1,25(\text{OH})_2\text{D}]\), which affects calcium transport across cell membranes (1–4). Knowledge of the function of this steroid hormone now explains the observation of Nicolaysen, 50 years ago, that calcium absorption by the small intestine was impaired in rachitic rats and was subsequently increased on administration of vitamin D (5). A deficiency of 1,25(OH)_2D leads to a defect in active transport of Ca across the mucosal cell of the small intestine.

The conversion of vitamin D to 25-hydroxyvitamin D \([25(\text{OH})\text{D}]\) in the liver and the further hydroxylation of 25(OH)D to 1,25(OH)_2D in the kidney are now well known (see chapter by M. Holick for a review). Only aspects of vitamin D metabolism relevant to understanding rickets will be considered in this chapter.

Apart from helping to define the function of vitamin D, the metabolic pathway to 1,25(OH)_2D revealed two previously unknown features of vitamin D physiology. The first of these is that vitamin D is not a natural nutrient. In most populations, vitamin D status is determined mainly by exposure to solar ultraviolet light which by photochemical action converts 7-dehydrocholesterol in skin to previtamin D. The second significant finding was that a specific vitamin D-binding protein (DBP) transports vitamin D and its metabolites in the circulation (6). These two features, are of considerable importance in understanding the etiology of vitamin D deficiency.

INTERPRETATION OF VITAMIN D METABOLITE CONCENTRATIONS

Studies of vitamin D metabolism \textit{in vivo} indicate that the more vitamin D that is given to an animal, the higher the concentration of 25(OH)D in plasma (7). Although the production of 25(OH)D is not directly proportional to vitamin D input, nevertheless 25(OH)D concentration in plasma, within the range 0.025–0.125 \(\mu\text{M}\) (10–50 ng/ml), is a good indicator of vitamin D supply. Thus, in temperate geographical
regions the plasma concentration of 25(OH)D is highest in late summer and lowest in late winter. This reflects the seasonal change in the intensity of solar ultraviolet-B radiation (290–320 nm) (6). However, even with extensive solar irradiation, in tropical regions or with whole-body exposure beside the sea in summer, the plasma concentration of 25(OH)D rises to no higher than 0.2 \mu M (80 ng/ml). Evidently, the greatest rate of formation of vitamin D in skin cannot maintain 25(OH)D concentrations above this level. Nevertheless, the capacity to synthesize 25(OH)D is considerably greater than the plasma levels produced by ultraviolet irradiation would suggest. Large oral doses of vitamin D, which give rise to signs of vitamin D toxicity, can raise the plasma concentration of 25(OH)D to more than 1 \mu M (400 ng/ml).

These observations lead to the conclusion that a key factor determining plasma 25(OH)D concentration is the input of vitamin D to the site of hydroxylation in the liver. Hence, these plasma levels are a good index of vitamin D status and help to discriminate between vitamin D deficiency and other causes of bone disease.

The concentration of 1,25(OH)\textsubscript{2}D in plasma (0.072–0.123 nM) (30–50 pg/ml) is 1000-fold lower than that of 25(OH)D. Furthermore, the 1,25(OH)\textsubscript{2}D concentration is mainly independent of the supply of the 25(OH)D precursor. A multiplicity of physiological controls have been proclaimed to influence the formation of 1,25(OH)\textsubscript{2}D in the cells of the proximal convoluted tubules in the kidney (7). The postulated controlling factors include parathyroid hormone (PTH), calcitonin, prolactin, growth hormone, insulin, glucocorticoids, gonadal steroids, calcium, phosphate, hydrogen ions, potassium, and even 1,25(OH)\textsubscript{2}D itself. Because of this multitude of factors claimed to regulate the renal 1-hydroxylase there is considerable uncertainty as to how to interpret the controlled production of 1,25(OH)\textsubscript{2}D.

Because 1,25(OH)\textsubscript{2}D is a hormone, its formation is presumed to be regulated according to the requirements for its endocrine function. The concentration in plasma in general bears no relationship to vitamin D status except in severe deficiency when there is insufficient 25(OH)D precursor to maintain the synthesis of 1,25(OH)\textsubscript{2}D.

The standard view of the regulated secretion of 1,25(OH)\textsubscript{2}D is that this active metabolite is produced to maintain calcium homeostasis by stimulating target cells in the intestinal mucosa, in the renal tubules, and in bone to increase their transport of calcium. Thus PTH, secreted in response to a fall in extracellular Ca\textsuperscript{2+} concentration, enhances the activity of the renal 1-hydroxylase. The action of the extra 1,25(OH)\textsubscript{2}D in “stimulating” the target cells, increases the extracellular Ca\textsuperscript{2+} concentration leading to a fall in PTH secretion. Such a negative feedback control is typical of the endocrine loops which link the secretion and function of peptide hormones. In general, however, steroid hormones have effects which appear to be permissive rather than stimulatory and such negative feedback loops do not occur. It may well be that the function of 1,25(OH)\textsubscript{2}D is permissive and not stimulatory, enabling cells to have variable capacity for transporting calcium. This interpretation is compatible with observations on the function of 1,25(OH)\textsubscript{2}D and removes the need to find a specific biological role for each factor reported to influence the secretion of 1,25(OH)\textsubscript{2}D by the kidney.

Although the production of 1,25(OH)\textsubscript{2}D appears to be independent of variation in
the supply of 25(OH)D, concentrations of the two metabolites are related during growth (8) and during the recovery from vitamin D deficiency (9). In both these circumstances, the 1-hydroxylase activity is elevated and the amount of 1,25(OH)_2D produced is partly determined by the supply of 25(OH)D. These findings support the concept that the 1-hydroxylase is regulated by varying the accessibility of the 25(OH)D substrate to the enzyme (7). They also reinforce the view that the concentration of 1,25(OH)_2D in plasma cannot be related quantitatively to a required degree of response in target cells.

THE ROLE OF DBP

The affinity of binding of 25(OH)D to DBP (K_d = 6.4 \times 10^{-8} \text{ M}) is higher than for 1,25(OH)_2D (K_d = 3.4 \times 10^{-7} \text{ M}) or for vitamin D (cholecalciferol) itself (K_d = 4.3 \times 10^{-7} \text{ M}) (10). This variation in binding affinity probably contributes to marked differences in the half-life or clearance of the metabolites from plasma. The half-life for 25(OH)D is estimated to be between 15 and 45 days (11). In contrast, 1,25(OH)_2D, with its lower affinity for DBP is cleared from plasma with a half-life of about 5 to 8 hours (12).

The prolonged time of clearance of 25(OH)D has no apparent parallel with any other plasma constituent. Other endocrine factors are cleared from the circulation in minutes or a few hours. The long time of residence of 25(OH)D in plasma is even more surprising, considering that the transporting DBP is cleared rapidly (half-life in rabbits = 1.7 days) (13). This suggests that DBP, along with its associated 25(OH)D, is taken up by cells, the protein is degraded, and 25(OH)D is then released back into the circulation where it binds again to more DBP. The prolonged half-life of 25(OH)D would thus represent a composite clearance curve derived from the repeated removal and re-entry of 25(OH)D as DBP itself is turned over.

This very long residence of 25(OH)D in extra-hepatic tissues could explain the ability of vitamin D reserves to be maintained for long periods of time. Studies in children have shown that only a few hours exposure to summer sunlight is able to produce sufficient vitamin D to avoid deficiency for several months (14,15). In contrast, in chickens, where affinity of DBP for 25(OH)D is 10-fold lower than in mammals (16), the rate of removal of 25(OH)D is 5–10 times faster so that without a continuous supply of vitamin D, deficiency rapidly develops (L. Berven, personal communication).

Therefore, in humans, the association of 25(OH)D with DBP in the circulation provides a reserve of the precursor for 1,25(OH)_2D formation, it provides an accurate index of vitamin D status, and it provides a means for investigating the cause of vitamin D deficiency by studying the kinetics of 25(OH)D turnover in plasma.

CALCIUM HOMEOSTASIS

Calcium homeostasis is the process of effectively maintaining a constant extracellular Ca^{2+} concentration. In all vertebrate species this desired concentration is
close to 1.25 mM (5 mg/dl) (17). In mammals, the means of achieving this constancy are to increase the absorption capacity of the small intestine and to mobilize calcium from bone when the Ca\(^{2+}\) concentration tends to fall. The main mechanism for preventing the Ca\(^{2+}\) concentration from rising above the desired level is to increase excretion of calcium by the kidney.

The vitamin D metabolite 1,25(OH)\(_2\)D is the primary regulating factor determining changes in intestinal absorption capacity and bone resorption to maintain the extracellular Ca\(^{2+}\) concentration. In comparison to its action in intestine and bone, vitamin D appears to have a quantitatively minor influence on calcium transport in the kidney (18).

Although the action of 1,25(OH)\(_2\)D is frequently described as “stimulating” intestinal calcium absorption and bone calcium resorption, this interpretation is possibly too simplistic. Most studies to identify the function of vitamin D in intestine and bone have made use of vitamin D-deficient animals. When such animals are repleted with vitamin D there is, after several hours delay, an increase in the absorption capacity for calcium across the mucosa of the small intestine. Likewise, as the abnormal rachitic bone is repaired, there is mobilization of mineral from bone.

Both these responses to vitamin D are inevitable consequences when the abnormal state of vitamin D deficiency is corrected. Because the ability to maintain calcium homeostasis is impaired in vitamin D deficiency, then correction of this deficiency will activate mechanisms which control extracellular Ca\(^{2+}\) concentration. In animals with an adequate vitamin D status the action of 1,25(OH)\(_2\)D on extracellular Ca\(^{2+}\) concentration appears to be that of a permissive factor, enabling cells in intestine and bone to have the capacity to transport Ca\(^{2+}\). This transporting mechanism could then be modified by other short-term regulators according to the immediate needs for calcium homeostasis. Evidence has been found which suggests that PTH (19), growth hormone (20), and even calcitonin (21) could be short-term modifiers of vitamin D-dependent active transport of calcium in the intestine.

A similar interpretation can be made for the role of 1,25(OH)\(_2\)D in bone. Experiments with bone in organ culture demonstrate that 1,25(OH)\(_2\)D is a potent stimulator of osteoclastic bone resorption in vitro (22). This reinforces the long held view that the function of 1,25(OH)\(_2\)D in bone is to “stimulate” resorption. If the concentration of 1,25(OH)\(_2\)D in blood is experimentally raised in human subjects, then an enhanced rate of bone resorption is indeed found, providing that the subjects are eating a low calcium diet (23). Yet, if the supply of dietary calcium is adequate, an increase in serum level of 1,25(OH)\(_2\)D has no stimulatory effect on the resorption of bone (24). These observations again suggest that 1,25(OH)\(_2\)D has a permissive role, enabling bone cells to transport calcium. A homeostatic increase in bone resorption could be mediated by PTH which activates the vitamin D-dependent calcium transport process when extracellular Ca\(^{2+}\) concentration falls. Perhaps the function of 1,25(OH)\(_2\)D in bone may be a general one of giving cells the capability to handle Ca\(^{2+}\) so that normal growth and turnover of bone takes place. Such a role could apply also to the action of 1,25(OH)\(_2\)D in cells not directly concerned with whole-body calcium homeostasis.

Any function of bone as a calcium reservoir must, of necessity, be a limited one
in mammals. Some calcium is released from bone to compensate for the loss in milk during lactation in women (25) and dairy cows (26). However, extensive mineral mobilization would affect the mechanical properties of bone and diminish its structural strength. Hence, the main long-term control of calcium homeostasis is at the level of absorption of calcium by the small intestine.

The regulated, vitamin D-dependent transport pathway accounts for about 75% of calcium absorbed by the small intestine from a diet adequate in calcium (27). The mechanism by which 1,25(OH)₂D promotes this absorption capacity is still uncertain despite the well-known action of 1,25(OH)₂D to induce the synthesis of a specific calcium-binding protein (CaBP, molecular weight = 8800 daltons) in the intestinal mucosa (28).

An elegant analysis by Bronner (29) of the kinetics of calcium transport now suggests that CaBP facilitates the inward flux of Ca²⁺ by amplifying the intracellular calcium gradient between the brush border and basolateral poles of the mucosal cells. This interpretation of experimental and theoretical values for transcellular calcium movement is the most convincing analysis to date for the mechanism of action of 1,25(OH)₂D on the absorption of calcium.

Apart from endocrine control of absorption, another factor determining the supply of calcium to meet homeostatic requirements is variation in the availability of calcium from the diet. The actual proportion of dietary calcium which is utilized is seldom more than 50% and usually, in adults, is no more than 30% (30). The formation of complexes with phytate (31), oxalate (32), and unavailable carbohydrate (dietary fiber) (33–35) decreases the accessibility of calcium to the absorptive surface of the small intestine. Therefore, when the intake of dietary calcium is low and it is in an unavailable form, any increase in the absorptive capacity of the small intestine will be ineffective in raising the supply of calcium.

It is difficult to explain how calcium homeostasis can be maintained in populations consuming diets which are both low in calcium (Table 1) and where the calcium is apparently unavailable for absorption by the small intestine (Table 3). Experiments

| TABLE 1. Dietary calcium in countries where vitamin D deficiency rickets has been reported |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| Total dietary calcium (mg/head/day)         | 1961–65         | 1970            | 1977            |
| Egypt                                       | 412             | 423             | 427             |
| Greece                                      | 652             | 804             | 889             |
| India                                       | 379             | 363             | 354             |
| Iran                                        | 310             | 324             | 398             |
| Libya                                       | 279             | 419             | 655             |
| Nigeria                                     | 403             | 443             | 445             |
| Saudi Arabia                                | 314             | 399             | 560             |

Data kindly provided by Dr. J. B. Mason, United Nations Administrative Committee on Coordination—Subcommittee on Nutrition.
with rats (36) and humans (37) have demonstrated that calcium can be absorbed from the colon and that the capacity for absorption is increased by 1,25(OH)D. Because bacteria in the colon are able to break down any fiber and phytate that has resisted digestion in the small intestine, the calcium complexes carried into the colon could become available for absorption from the large intestine. A persistently low calcium intake with low theoretical availability from cereal, vegetable, and fruit diets, may in fact induce an adaptive increase in calcium absorption from the colon. The efficiency of utilizing calcium in these circumstances may be greater than has previously been considered likely.

THE INFLUENCE OF CALCIUM SUPPLY ON VITAMIN D STATUS

From the evidence of variation in plasma 25(OH)D levels and the minimal effect of dietary vitamin D at less than 5 µg per day, it is apparent that vitamin D status is determined mainly by exposure to sunlight (6). It is therefore surprising that in those regions of the world where vitamin D-deficiency rickets is most common such as in the Indian subcontinent (38), Egypt (39), Ethiopia (40), Libya, Morocco, and Tunisia (41), solar ultraviolet light is plentiful.

The appearance of rickets in the 1960s in children of Asian immigrants in the United Kingdom was also difficult to explain (42). It appeared that dietary factors as well as limited sunlight exposure contributed to the particular susceptibility of the Asian children to rickets (43). The nutritional factors correlated with rickets were a vegetarian diet and one with a high content of whole-meal flour (43–45). Hence, some mechanism other than just the supply of vitamin D was inducing clinical vitamin D deficiency.

Studies with rats have shown that vitamin D deficiency can be induced by feeding a diet where the calcium content or availability is low (46). Calcium deprivation promotes mild hyperparathyroidism which stimulates the production of 1,25(OH)D.

<table>
<thead>
<tr>
<th>Country</th>
<th>Calcium from milk (mg/head/day)</th>
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<tbody>
<tr>
<td>Egypt</td>
<td>102</td>
</tr>
<tr>
<td>Greece</td>
<td>346</td>
</tr>
<tr>
<td>India</td>
<td>123</td>
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<tr>
<td>Iran</td>
<td>137</td>
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<tr>
<td>Libya</td>
<td>127</td>
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<tr>
<td>Nigeria</td>
<td>11</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>87</td>
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Data kindly provided by Dr. J. B. Mason, United Nations Administrative Committee on Coordination—Subcommittee on Nutrition.
TABLE 3. Estimates of the proportion of dietary calcium which may be poorly available in countries where vitamin D deficiency rickets has been reported

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<tr>
<td>Egypt</td>
<td>73</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Greece</td>
<td>41</td>
<td>38</td>
<td>34</td>
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<tr>
<td>India</td>
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<td>89</td>
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<tr>
<td>Saudi Arabia</td>
<td>70</td>
<td>62</td>
<td>40</td>
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However, the increased utilization of 25(OH)D for 1,25(OH)_{2}D synthesis is not the direct cause of depletion of vitamin D reserves. The extra 1,25(OH)_{2}D has now been shown to enhance the metabolic inactivation of 25(OH)D in the liver (46). A similar enhanced destruction of 25(OH)D, related to elevated concentrations of 1,25(OH)_{2}D in plasma, has also been found in humans (11). There are now several reports which support this conclusion (47–51). It is also evident that mild hyperparathyroidism, which would lead to an increased rate of inactivation of 25(OH)D, occurs frequently in the susceptible Asian population in the United Kingdom (52).

Therefore, a deficiency in the availability or supply of calcium such as is found in countries (Table 1) where rickets is still reported, where the intake of calcium from milk is low (Table 2), and where calcium is obtained from high fiber vegetable products (Table 3; 53), could be suspected to lead to induced vitamin D deficiency. The enhanced metabolic destruction of 25(OH)D in the liver is not thought to be a physiological mechanism for regulating hepatic vitamin D metabolism. Rather, this destruction would appear to be secondary to some other primary effect of 1,25(OH)_{2}D on liver function. Thus, an adequate supply of calcium may be as important for maintaining vitamin D status as it is for meeting the needs of calcium homeostasis. An inadequate supply of calcium could be a key factor in understanding the etiology of vitamin D deficiency in those parts of the world where it is still a public health problem.

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CALCIUM HOMEOSTASIS


DISCUSSION

*Dr. Holick:* Is it possible that 1,25(OH)2D is inducing enzymes to enhance its own destruction, and that, 25(OH)D being recognized by those enzymes as a substrate, its half-life is subsequently decreased.

*Dr. Fraser:* This possibility is supported by *in vitro* data. However there is not a great deal of evidence to suggest that this is the mechanism for the increased destruction of 25(OH)D. I would favor increased catabolism in the liver. The response to 1,25(OH)2D is very rapid. A single intracardial injection of 20 ng of 1,25(OH)2D, in the normal rat, induces an increase in the excretion rate of 25(OH)D metabolites into the bile within 6–8 hours.
Dr. Pettifor: Do the different alleles of the vitamin-D-binding protein (DBP) have any effect on vitamin D metabolism in man, and are the roles of vitamin D$_2$ and vitamin D$_3$ different?

Dr. Fraser: The different genetic variants of plasma DBP each have the same binding affinities for cholecalciferol and its metabolites (1). Nobody has looked at the DBP genotypes of humans or other animals and compared them with the half-life of 25(OH)D in the circulation. As far as vitamin D$_2$ and vitamin D$_3$ comparisons are concerned, I do not think that vitamin D$_2$ has had much evolutionary influence. To me it is a substance mainly created by man in this century and has little to do with the evolutionary origins of vitamin D biochemistry and physiology. Vitamin D$_2$ can be found in irradiated pasture and this is probably the source of 25(OH)D$_2$ found in the plasma of animals that are consuming plants. Nevertheless, I hold the view that in nature, vitamin D physiology has evolved based upon the form of vitamin D produced in the skin, i.e., vitamin D$_3$ or cholecalciferol.

Dr. Pettifor: Since we use vitamin D$_2$ as treatment supplements, it is important to know if there is a difference between the two analogs.

Dr. Fraser: The function of vitamin D$_2$ is exactly the same as that of vitamin D$_3$ but there may be a quantitative difference in the efficiency of utilization of D$_2$ compared with D$_3$. There is evidence in rats and pigs (2) and perhaps in humans (3) that molecule for molecule, vitamin D$_2$ is less biologically active than vitamin D$_3$. This does not matter very much if an excessive amount of vitamin D$_2$ is given as a pharmacological preparation.

Dr. Paunier: Since vitamin D is necessary not only for calcium homeostasis but also for cellular differentiation and function, what in the physiopathology of rickets are the respective roles of the mineral and of the cellular defects?

Dr. Fraser: There has been argument for many years as to whether or not vitamin D metabolites are actually needed at the site of bone formation or whether vitamin D function is entirely concerned with calcium homeostasis: ensuring that enough calcium is absorbed across the intestinal mucosa to meet the needs of bone formation. Certainly, in experiments where calcium was infused into vitamin D-deficient rats to maintain plasma concentration at the normal level, calcium is taken up by bone (4). However, the bone of a vitamin D-deficient animal has a large amount of osteoid which is able to be calcified so it is not surprising that extra calcium would be incorporated into rachitic bone.

Dr. David: You indicated that 1,25(OH)$_2$D synthesis appears not to be substrate dependent. However, there is clinical evidence that there might be substrate dependency in border line vitamin deficiency. Could you comment on that?

Dr. Fraser: Clearly, there has to be some relationship between the supply of 25(OH)D substrate and the amount of 1,25(OH)$_2$D produced. In vitamin D deficiency, a point will be reached where there is not enough 25(OH)D to meet the requirements for the synthesis of 1,25(OH)$_2$D. Nevertheless, within the normal range of 25(OH)D there is no increase in the formation of 1,25(OH)$_2$D with a rise in the supply of 25(OH)D. However, in growing children (5) and in lactating dairy cows, an increase in the plasma concentration of 25(OH)D is reflected by an increase in the concentration of 1,25(OH)$_2$D. I interpret this as evidence for regulation of the 1α-hydroxylase by a change in the accessibility of the substrate to the mitochondrial enzyme.

Dr. Delvin: Do you have evidence that phosphate deprivation, on its own or through an alteration of the phosphate handling by the tissues, can affect vitamin D$_3$ metabolism?

Dr. Fraser: In humans there is good evidence that a decrease in dietary phosphorus can provoke an increase in serum concentration of 1,25(OH)$_2$D (6).

Dr. Holick: I would like to follow up on the previous question regarding the infusion of calcium and phosphorus into a vitamin D-deficient rat. What was the outcome?
Dr. Fraser: If plasma calcium and phosphorus concentrations are maintained by infusion in vitamin D-deficient rats (4) or by feeding a high-calcium, high-phosphorus diet with lactose (7), bone mineralization and bone morphology are similar to normal. This suggests that at least for rat bone mineralization, vitamin D is not essential in bone itself. Nevertheless, there are receptors for 1,25(OH)_2D in bone cells and in vitro experiments show that 1,25(OH)_2D modifies specific functions, such as the synthesis of osteocalcin by osteoblasts. Thus, bone cells, like many other cells in the body, are directly affected by 1,25(OH)_2D.

Dr. Bonjour: You mentioned that the action of 1,25(OH)_2D_3 on intestinal Ca absorption can be modulated by several factors. Could you further elaborate on the factors that could be important in this modulation, and whether it concerns the passive flux of calcium, or its active transport component.

Dr. Fraser: Before vitamin D metabolism was discovered, there were several investigations to see whether PTH, as well as vitamin D, might enhance calcium absorption. This effect is now considered to be indirect—as a stimulator for the synthesis of 1,25(OH)_2D in the kidney. However, PTH could modify the action of 1,25(OH)_2D in the intestinal mucosa. One striking example which indicates short-term variability in the regulation of calcium absorption occurs with the egg-laying hen. There is a marked increase in calcium absorption capacity across the small intestine during the 8 hours when the egg shell is being formed. Yet renal production of 1,25(OH)_2D does not increase during that time (8). Clearly some factor(s) other than 1,25(OH)_2D is stimulating calcium absorption by modulating the action of 1,25(OH)_2D.

Dr. Guesry: Could you clarify your provocative statement that vitamin D supplementation is not playing an important role in the coverage of the vitamin D needs.

Dr. Fraser: It is only in this century that humans have developed a concerted campaign to provide vitamin D as a dietary supplement. Previously, before the discovery of vitamin D, there was evidence that cod-liver oil could be beneficial in preventing or treating rickets. When you look at all the vertebrate animals, none of them seem to be getting vitamin D from their diet under the conditions of nature. From available evidence, I consider that it is only sunlight, on the skin, which under natural conditions is the physiological source of vitamin D for all vertebrate species. In this century, because of the artificial environment of towns and cities, humans are providing themselves with oral vitamin D supplements to compensate for the lack of exposure to sunlight.

Dr. Elidrissy: Along those lines, we find the incidence of nutritional rickets to be high in Saudi Arabia but very low in Sudan. The diet is almost the same in the two countries, but the main difference is in the way of life. Sudan is a poorer country, where most people spend a long time under the sun. Whereas, in Saudi Arabia, people have moved away from rural areas, to live in urban flats, where they have little exposure to sun.

Dr. Moya: Do plasma levels of 1,25(OH)_2D accurately reflect calcium needs? Could you comment on this in the light of low and high vitamin D intakes?

Dr. Fraser: Although 1,25(OH)_2D levels rise when there is increased requirement for calcium, such as during growth or lactation, it is very difficult to relate the plasma concentration of 1,25(OH)_2D to any particular need for calcium. It is much easier to use the concentration of 25(OH)D as an indicator of vitamin D status. Here, there is a clear relationship between the supply of vitamin D and the plasma levels of 25(OH)D.

Dr. Glorieux: Dr. Holick and yourself mentioned no vitamin D metabolites other than the 25 and 1,25 derivatives. Does this imply that the other described metabolites of vitamin D have no physiologic significance?

Dr. Fraser: I did not mention other vitamin D metabolites, simply because they did not come within the terms of reference that I was asked to discuss.
Dr. Holick: There are probably 22 to 24 metabolites of vitamin D identified today. All of them are either less active, or inactive compared to 1,25(OH)\(_2\)D. The only one that has been of interest and of curiosity is 24,25(OH)\(_2\)D. In some systems, including the one described by Dr. Garabedian (9) in chondrocytes, it seems that 24,25(OH)\(_2\)D may play a role. But it is still a very debatable issue.

Dr. Glorieux: A lactone derivative has recently been showed by Seino et al. (10) to possibly play an important role in promoting bone mineralization. So the issue remains open.

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