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PERSPECTIVES

The Relation Between Serum Calcidiol and Calcitriol

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Calcitriol (1,25$[OH]_2$D), which is regarded as the physiologically active form of vitamin D, is formed in the kidneys (and elsewhere) from its substrate calcidiol (25OHD), which is the storage form of the vitamin. Despite this well-documented sequence, a recent paper by Hewison *et al*. (1) repeated the common assertion that the plasma concentrations of these two vitamin D metabolites are unrelated, quoting in support earlier publications by Tjellesen and Christiansen (2) and Vieth *et al*. (3). This is such a widespread belief that evidence to the contrary tends to be attributed to poor technology (4). Behind it lies the assumption that the thousandfold excess of calcidiol over calcitriol in the plasma excludes the possibility that deficiency of the former could ever lower the concentration of the latter. However, the excess of calcidiol over calcitriol in the plasma is more apparent than real; because of the difference in the binding of these metabolites to D-binding protein, the ratio of free calcidiol to free calcitriol is only about 10 to one (5). Even if this were not the case, there is at least one other situation in human biology in which product concentrations are unequivocally related to substrate concentrations, despite very high substrate/product ratios. Thus, there is in postmenopausal women a highly significant correlation between the picomolar concentrations of estrone and the nanomolar concentrations of androstenedione, which is its precursor/substrate (6) (Fig. 1). We know of no reason why there could not be a comparable correlation between the serum concentrations of calcidiol and calcitriol, despite the apparent great excess of substrate.

So much for the theoretical objections to a correlation between serum calcidiol and calcitriol. The empirical objection – the actual failure by so many investigators to observe a correlation between these metabolites – may be because the relationship is biphasic (*i.e.*, it is positive if calcidiol is in the normal range, but negative if it is subnormal). This was first noted in Australia, in a series of 496 untreated postmenopausal women in whom there was a break in the relation between the two metabolites at a serum calcidiol level of about 40 nmol/L (7) (Fig. 2). Above that level, the correlation was significantly positive, with a slope of 0.32 pmol/nmol, whereas below it, the slope was significantly negative, with a gradient of -0.82 pmol/nmol. The authors attributed the decrease in calcitriol with falling calcidiol (in the normal range of calcidiol) to substrate deficiency and the increase in calcitriol (at calcidiol levels < 40 nmol/L) to secondary hyperparathyroidism caused by a decrease in ionized calcium. The major increase in PTH (at calcidiol levels < 40 nmol/L) is shown in the same 496 women in Fig. 3. This series was later increased to 918 postmenopausal women and showed a sharp increase in PTH at calcidiol levels < 50 nmol/L (8) (Fig. 4). The biphasic relationship between the two metabolites probably explains why most investigators do not find a significant correlation between them; even in the Australian data, there was no correlation between calcitriol and calcidiol in the set as a whole.

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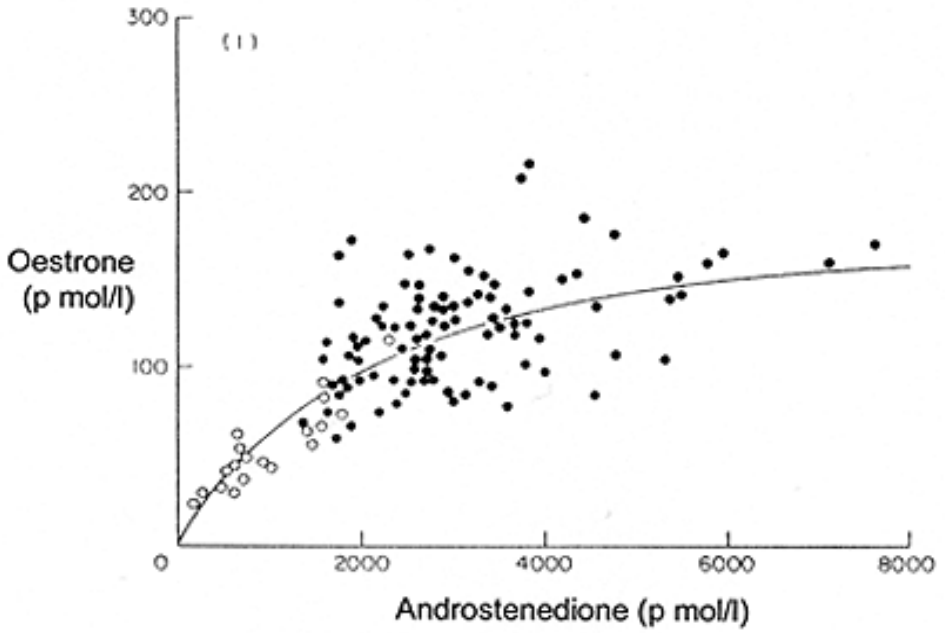

Figure 1: The relation between serum androstenedione and serum estrone in 96 untreated (•) and 18 corticosteroid-treated (o) postmenopausal women. The line is described by an equation based on Michaelis-Minten kinetics (6). Permission to reprint granted from *Clinical Endrocrinology*.

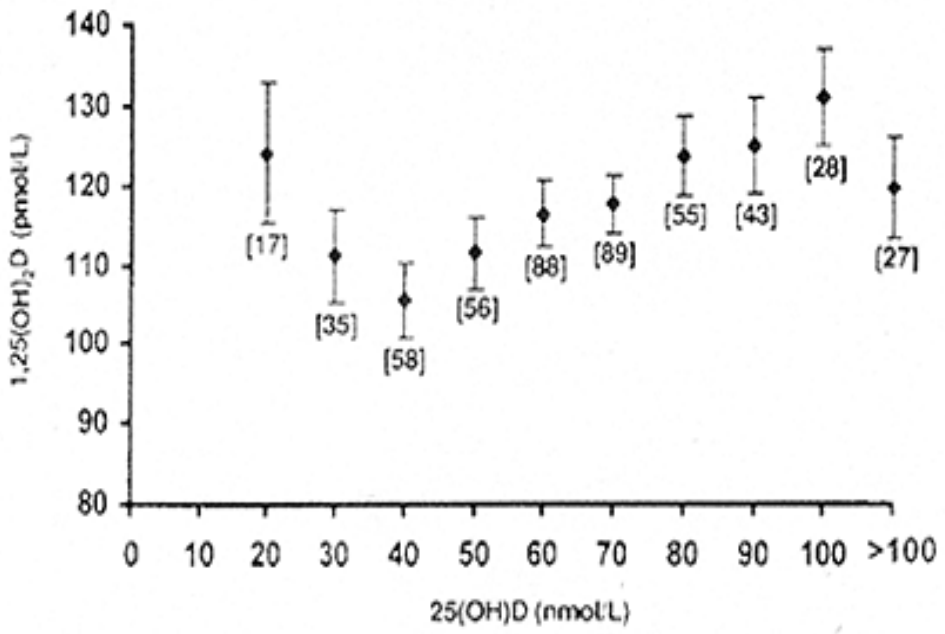

Figure 2: Mean (± standard error of the mean) serum calcitriol concentrations at 10-nmol/L intervals of serum calcidiol in 496 postmenopausal women; 25OHD concentrations </= 40 nmol/L. The relation is inverse at calcidiol concentrations </= 40 nmol/L and positive at concentrations > 40 nmol/L (7). Reproduced with permission by the *American Journal of Clinical Nutrition.*© Am J Clin Nutr. American Society for Clinical Nutrition.

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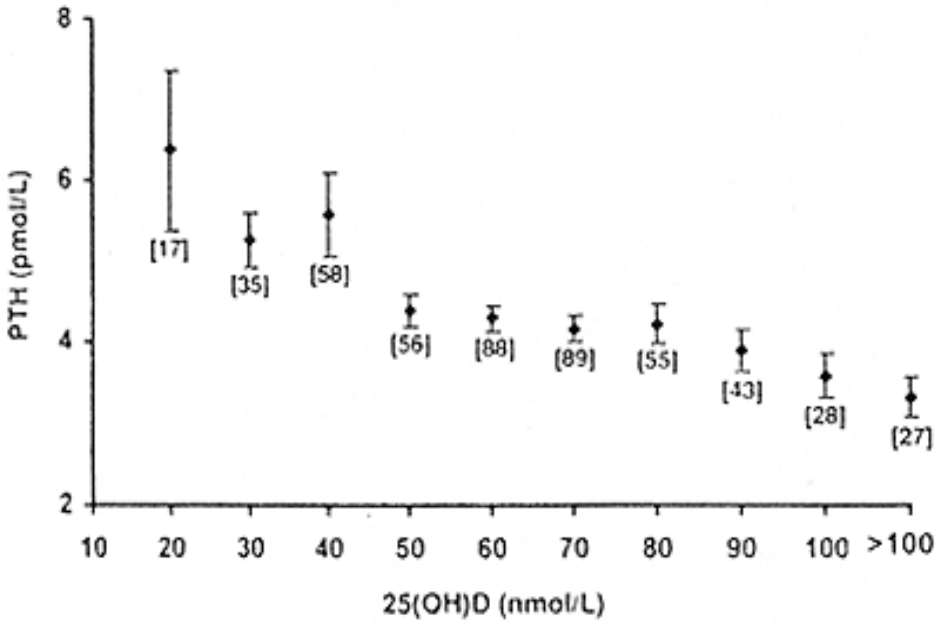

Figure 3: Mean (± standard error of the mean) serum PTH concentrations at 10-nmol/L intervals of serum calcidiol in 496 postmenopausal women. Serum PTH was significantly higher in women with 25(OH)D concentrations < 40 nmol/L (P < 0.001) (7). Reproduced with permission by the *American Journal of Clinical Nutrition.*© Am J Clin Nutr. American Society for Clinical Nutrition.

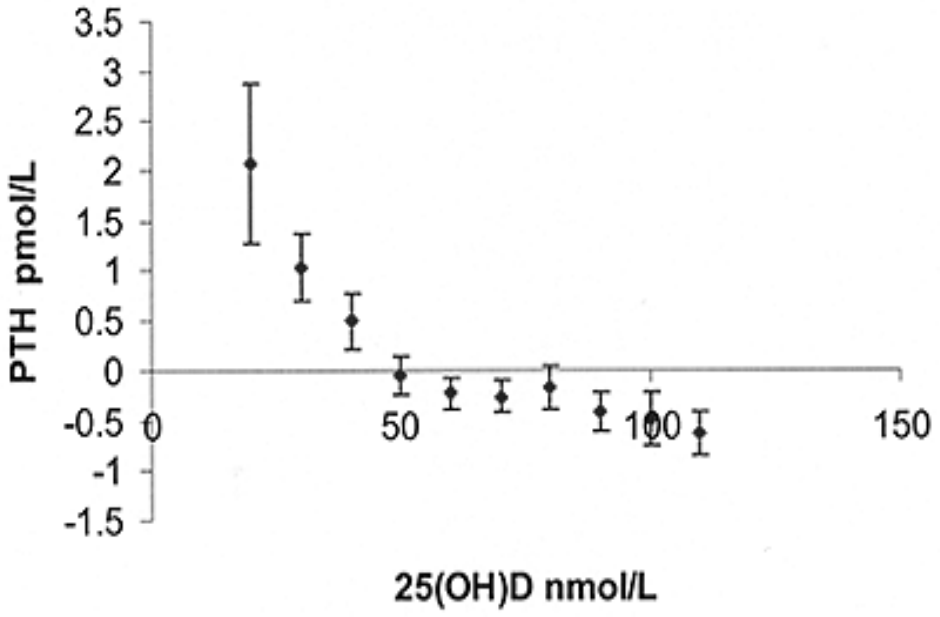

Figure 4: Residual serum PTH after adjustment for age, weight, and serum ionized calcium, plotted against calcidiol in 918 postmenopausal women (mean standard error) (8). *Copyright 2004, The Endocrine Society.*

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Vitamin D Sufficiency

In normal subjects, calcidiol and calcitriol both tend to decrease with age and vary with season, which suggests that the two are related. Thus, in 1987, Bouillon *et al.* (9) reported mean serum calcidiol concentrations of 29 ± 21 (SD) nmol/L in elderly subjects and 61 ± 21 nmol/L in young control subjects ($P < 0.001$). Mean serum calcitriol was 91 ± 45 pmol/L in the elderly and 130 ± 38 pmol/L in young control subjects ($P < 0.001$). The ratio of the calcitriol difference to the calcidiol difference was 1.22 pmol/nmol. The difference between elderly subjects at home and in care was also significant, in terms of both calcidiol and calcitriol (Table 1). Short-term treatment with 25OHD in 15 elderly subjects with vitamin D deficiency increased the serum levels of both calcidiol ($P < 0.01$) and calcitriol ($P < 0.05$). There were comparable increases in both metabolites in subjects with sufficient vitamin D as well, but the change in serum calcitriol was not significant. In the whole set of elderly subjects, there were significant seasonal changes in both serum calcidiol ($P < 0.05$) and calcitriol ($P < 0.01$), but in the young control subjects, there was no significant seasonal change in calcitriol. This important paper does not seem to have been noted by later investigators, not even by those who have unwittingly confirmed the Belgian findings. Thus, in 2004, Meier *et al.* (10) reported amplitudes of seasonal change of 22.2% in serum calcidiol and 19.3% in calcitriol in a group of 16 young adults. The authors also reported amplitudes of 32.6% and 35.3%, respectively, in another group of 27 young adults. In another seasonal study, Zitterman *et al.* (11) measured the vitamin D metabolites in 38 young women in winter and the same number in summer. Mean calcidiol levels were 30.3 +/- 19.1 nmol/L in winter and 69.8 +/- 27.0 nmol/L in summer; the corresponding calcitriol levels were 65.5 +/- 31.8 and 87.3 +/- 29.0 pmol/L, respectively.

Table 1: Published Series of Concordant Differences in Serum Calcidiol (nmol/L) and Calcitriol (pmol/L) and the Ratio of the Latter to the Former (pmol/nmol)

Ref. #	Independent variable	N	Calcidiol			Calcitriol			Ratio
			1	2	*P* value	1	2	*P* value	
9	Age	662	61 (21)**	29 (21)	<0.001	130 (38)	91 (45)	<0.001	1.22
9	Sunlight	231 (elderly)	31 (22)	18 (11)	<0.001	95 (42)	86 (42)	<0.05	0.68
11	Season	76	69.8 (27)	30.3 (19)	<0.001	87.3 (29)	65.5 (32)	<0.001	0.55
12	Season (medians)	281	95.8	72.9	<0.005	71.4	58.1	<0.005	0.58
13	Serum calcidiol***	421	57.8 (20.3)	22.4 (6.4) *	<0.001	81.3 (19.7)	36.8 (20.4) *	<0.001	1.58
14	Sunlight	244	31.4 (16.5)	51.9 (21.5)	<0.001	68.4 (17.7)	53.0 (24.7)	<0.001	0.74
16	Hip fracture	199	32.9 (13.6)	18.5 (10.6)	<0.001	105 (31)	79 (46)	<0.001	0.55

*Calculated from authors' data
**Numbers in parenthesis indicate standard deviation
***Up to and over 30 nmol/L

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The ratio of the calcitriol difference to the calcidiol difference was 0.55 pmol/nmol (Table 1). Sherman *et al.* (12) reported no effect of age on either vitamin D metabolite in a healthy population of 167 men and 114 women aged 20-94 years. However, the authors found significant seasonal variations in both metabolites in both sexes (P < 0.005). The differences between the seasonal nadir and zenith values were 13.3 pmol/L for calcitriol and 22.9 nmol/L for calcidiol, a ratio of 0.58 pmol/nmol (Table 1).

Sahota *et al*. (13) measured both vitamin D metabolites in 421 postmenopausal women with osteoporosis. The women were divided into two groups: serum calcidiol > 30 nmol/L (N = 257) and serum calcidiol </= 30 nmol/L (N = 164). Mean serum calcitriol was 81.3 +/- 19.7 pmol/L in women with calcidiol levels > 30 nmol/L, compared with 36.8 +/- 20.4 pmol/L in those with serum calcidiol levels below that threshold. Similarly, Gloth *et al.* (14) reported a mean serum calcitriol of 53.0 +/- 24.7 pmol/L and a mean calcidiol of 31.4 +/- 16.5 nmol/L in 116 sun-deprived elderly subjects, compared with a mean calcitriol of 68.4 +/- 17.7 pnol/L and a mean calcidiol of 51.9 +/- 21.5 nmol/L in 128 control subjects (P < 0.001 for both). The ratio of the calcitriol difference to the calcidiol difference was 0.74 pmol/nmol (Table 1).

In an earlier study, Dubbelman *et al.* (15) reported that serum calcidiol and calcitriol levels were significantly higher in white women in Curacao than in those in the Netherlands (P < 0.002). In another early paper, Lips *et al.* (16) reported significantly lower mean serum calcidiol and calcitriol levels in 125 patients with hip fracture than in 74 age-matched control subjects (P < 0.001). The same group (17) later showed an increase in serum calcidiol and calcitriol in response to vitamin D administration, if the initial calcidiol level was < 30 nmol/L. Another study by the same group (18) showed that 400 I.U. of vitamin D given daily for two years to 177 women raised the median serum calcidiol level from 27.0 to 62.0 nmol/L (P < 0.001) and the median calcitriol level from 111 to 115 pmol/L (P = 0.03), a ratio of 0.11 pmol/nmol. In a paper by Arya *et al.* (19), serum calcitriol correlated significantly with serum calcidiol (r = 0.51; P < 0.001) and sun exposure (r = 0.40; P = 0.002) in 92 healthy young volunteers.

In his latest paper, Lips (20) observed that "in vitamin D deficiency, the synthesis of $1,25(OH)_2D$ becomes dependent on the availability of the substrate 25(OH)D. In that case a positive correlation has been observed between serum 25(OH)D and serum $1,25(OH)_2D$" (p. 612). Bettica *et al.* (21) concluded from their studies of elderly women that "with normal renal function the major determinant of circulating levels of $1,25(OH)_2D$ is vitamin D status (as measured by 25[OH]D serum levels)" (p. 228).

So much for the evidence of positive correlations between the two vitamin D metabolites. Some reports, however, fail to show the correlations described above and exemplified in Table 1. One of these, a study by Rejnmark *et al.* (22) of Greenlanders and Danes, showed seasonal changes in serum calcidiol, but not calcitriol. Another is the previously mentioned work of Vieth *et al.* (3), whose data span the whole range of serum calcidiol (from 10-120 nmol/L); thus, it is impossible to know whether the authors would have found a negative correlation at low serum calcidiol and a positive one at higher values had they looked for it. Another discordant set of data is provided by Kinyamu *et al.* (23), who found no decrease with age in either metabolite and no difference between housebound and free-living women, possibly because of the fortification of foods with vitamin D in the United States. However, most publications seem to show concordance between the two metabolites with respect to seasonal and age-related changes.

Vitamin D Insufficiency

There is equally good evidence that the correlation between the two metabolites becomes negative at low calcidiol levels caused by the stimulation of renal production of calcitriol by secondary hyperparathyroidism. Thus, in the osteomalacia of extreme vitamin D deficiency, serum calcidiol is low, but serum

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PTH is high, and calcitriol is generally normal (24). The low serum calcidiol levels observed in African-Americans is associated with elevated PTH and calcitriol levels (25). Heaney (26) has assembled data from 13 published studies; in 12 of the studies, calcidiol was lower in blacks than whites, whereas calcitriol and PTH were higher in blacks than whites. The author attributes the secondary hyperparathyroidism in blacks to "resistance" to the bone-resorbing action of PTH rather than to calcidiol deficiency, although they may in fact be the same thing (see below).

The inverse relation between serum calcidiol and PTH, particularly in the elderly, is of course very well documented (27-32), but its mechanism is not well understood. Some investigators (33;34) believe that the increase in PTH with age is a response to malabsorption of calcium, which is of course a well-known feature of vitamin D deficiency, but this is unlikely to be correct; calcium absorption decreases at menopause, without change in PTH (35;36), and malabsorption of calcium is common in postmenopausal women with vertebral fractures (37) who seldom have increased serum PTH. Only when malabsorption of calcium is associated with a low calcidiol level (as in osteomalacia) or a low calcitriol level (as in renal disease) does PTH increase, which in both cases is probably the result of a decrease in ionized calcium. As previously noted by Aaron *et al.* (38) and Parfitt (39), malabsorption of calcium *per se* leads to osteoporosis, not osteomalacia; secondary hyperparathyroidism is not a feature of osteoporosis. So why does PTH rise when calcidiol falls?

The Calcemic Action of Vitamin D

The key to the secondary hyperparathyroidism of vitamin D insufficiency lies in the neglected (but all-important) calcemic action of vitamin D on bone itself. This action was first reported in 1955 by Carlsson and Lindquist (40) when they showed that a small dose of vitamin D was sufficient to correct the malabsorption of calcium in rachtic rats; increasing the dose did not enhance calcium absorption any further, but did increase serum calcium (Fig. 5).

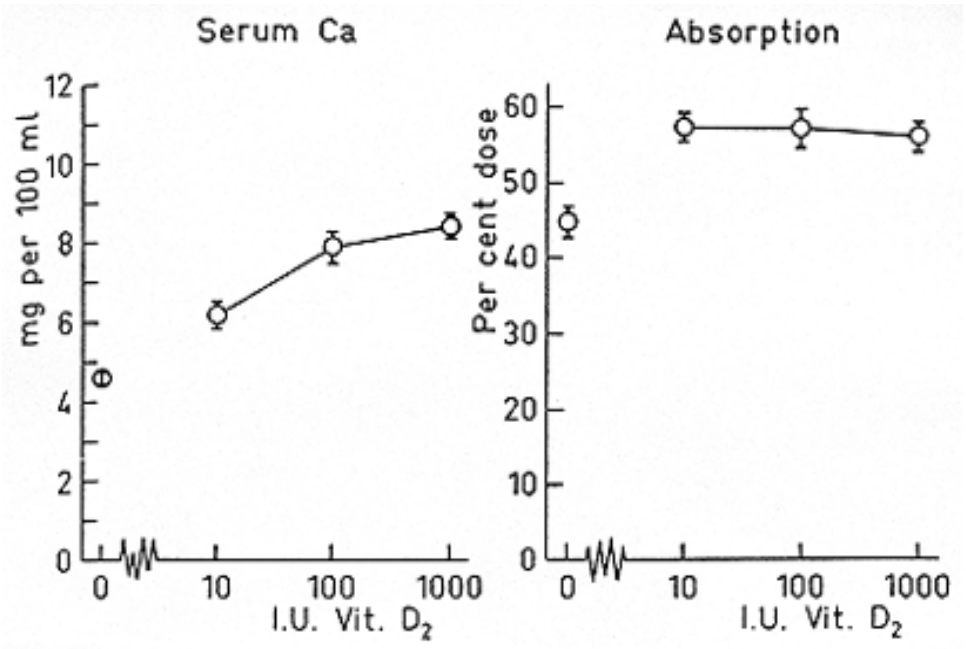

Figure 5: The serum calcium and absorption of Ca^{45} after varying doses of vitamin D_2 given to rats on a rachitogenic low-calcium diet (40). Permission to reprint granted from *Acta Physiol Scand*.

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The authors concluded that vitamin D had a calcemic action on bone that was independent of its promotion of calcium absorption. It was this action that was subsequently invoked by Nordin (41) to explain why and how calcium deficiency caused osteoporosis, whereas vitamin D deficiency caused rickets/osteomalacia.

The calcemic action of vitamin D on bone is widely quoted in reviews of vitamin D (42) without being fully explained. It is known, of course, that vitamin D has bone-resorbing properties (42) and that calcitriol stimulates osteoclasis in tissue culture (43), but as Parfitt (44) and Heaney (45) have recently noted, calcium homeostasis does not normally depend on bone resorption, except in states of calcium deficiency; the constancy of plasma water calcium is more suggestive of a physicochemical equilibrium between extracellular calcium and bone mineral. Heaney excludes this possibility on the ground that bone mineral is too insoluble to support the calcium level in tissue fluids, but there is evidence that bone mineral would support tissue fluid calcium and phosphate if the pH was about 6.8 (rather than 7.4) at the bone/tissue fluid interface (46). This is very close to intracellular pH (47) and may well be the prevailing pH at the mineral surface. Another explanation of the apparent calcemic action of vitamin D may be that as vitamin D deficiency progresses, the bone surface becomes increasingly covered with osteoid, until bone surface diminishes to a point where additional PTH is needed to maintain the tissue fluid calcium. In support of this concept, Jesudason *et al.* (48) have shown that the progressive decrease in serum calcidiol with age is accompanied by a progressive increase in serum alkaline phosphatase, which is compatible with (but does not prove) that osteoid surfaces are increasing as serum calcidiol decreases. However, whether deficiency of calcidiol is directly responsible for the decrease in ionized calcium and stimulation of PTH is unclear. It could be that a secondary reduction in serum calcitriol is the essential trigger, as it is in renal failure, but that this serum calcitriol is not seen because it is immediately corrected by PTH. But, this is a more fanciful explanation of the observed phenomena that needs first to give way to a simpler one that is in accordance with Occam's Principle: "the fewest possible assumptions are to be made in explaining anything" (49). The simplest way of explaining the observed data is to say that vitamin D facilitates the bone-resorbing action of PTH, period!

Conclusion

We conclude that there is a significant biphasic relationship between serum calcitriol and serum calcidiol, which is positive at "normal" calcidiol levels because of the effect of substrate deficiency on calcitriol production, but negative at low calcidiol levels because secondary hyperparathyroidism stimulates the synthesis of calcitriol. The activation of PTH at low calcidiol levels is caused by a decrease in ionized calcium resulting from the loss of calcemic action of calcidiol and/or calcitriol on bone, the nature of which is not entirely clear, but is independent of the positive effect of calcitriol on calcium absorption.

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