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Up-regulatory impact of boron on vitamin D function — does it reflect inhibition of 24-hydroxylase?

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Summary Nutritional intakes of boron have been shown to lessen the adverse consequences of vitamin D deficiency in rodents. Pilot clinical studies suggest that this effect may be mediated, in whole or in part, by an increase in serum 25-hydroxyvitamin D. We propose that, in concentrations achievable with good diets, boron suppresses the activity of the microsomal enzyme 24-hydroxylase, chiefly responsible for catabolism of this steroid. This inhibition may reflect a direct interaction with the enzyme, or perhaps boron's ability to form a covalent complex with the product of its activity, 24,25-dihydroxyvitamin D. An up-regulatory impact of boron on 25-hydroxyvitamin D is potentially beneficial in light of the fact that the vitamin D status of many individuals is poor during winter months, and traditional supplemental doses of this vitamin are often too low to correct this problem. There is growing evidence that good vitamin D status — as reflected by 25-hydroxyvitamin D levels — may reduce risk for a host of prominent disorders; thus, boron may have the ability to potentiate this protection. Clinical studies also suggest that nutritional boron can up-regulate 17β-estradiol levels in women, including postmenopausal women receiving hormone replacement therapy. The catabolism of this hormone is achieved by microsomal enzymes catalyzing vicinal hydroxylations — a description that also applies to 24-hydroxylase. This suggests the more general hypothesis that nutritional boron can inhibit a range of microsomal enzymes which insert hydroxyl groups vicinal to existing hydroxyls in steroids — including the enzymes which catabolize estradiol and 25-hydroxyvitamin D.

Dietary boron modulates vitamin D metabolism

Daily intakes of boron comparable to those supplied by boron-rich natural diets have been shown to ameliorate the effects of vitamin D deficiency in rats and chickens [1—8]. A clinical study conducted by Nielsen and colleagues [9] may shed some light on this intriguing phenomemon. 15 volunteers — primarily middle-aged men and women — were placed on a low-boron diet (0.23 mg B/2000 kcal) that was also marginal in magnesium and copper status for 63 days. They then continued to consume this diet for an additional 49 days while being supplemented with boron (3 mg daily as sodium borate). Serum levels of 25-hydroxyvitamin D (25-OH-D), the best marker for vitamin D status, were found to average 44.9 nM after the 63 days of boron

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deprivation, and 62.4 nM after the 49 days of boron repletion; thus, 25-OH-D rose significantly by about 39% when poor boron nutrition was corrected. The 3 mg daily boron dose chosen for repletion is within the range of boron intakes encountered in varied natural diets.

Is this phenomenon contingent on correction of overt boron deficiency? Possibly not. In a recent open pilot study, 25-OH-D levels were studied during boron supplementation in 13 middle-aged subjects pre-determined to be vitamin D deficient (serum 25-OH-D $<$12 ng/ml) [10]. During 60 days of supplementation with boron (6 mg daily in the form of calcium fructoborate, an organic complex that occurs naturally in fruit), 25-OH-D rose significantly by an average of 20%. This change was not likely to reflect a seasonal fluctuation, since the supplementation commenced in October and was concluded by January (in Serbia); if anything, one would expect vitamin D status to worsen during this time. On the other hand, since the subjects were pre-selected for poor vitamin D status, it is conceivable that regression to the mean contributed to the observed increase in 25-OH-D; evidently, a double-blind design will be required to achieve a conclusive confirmation of this effect. Nonetheless, these findings are consistent with the possibility that supplemental boron, administered in high-nutritional doses, can boost 25-OH-D status even in subjects who are not notably boron deficient.

Does boron suppress 24-hydroxylase activity?

Assuming that this is a genuine effect, how does boron increase 25-OH-D levels? Since it seems unlikely that boron status would influence endogenous synthesis of cholecalciferol — a non-enzymatic dermal reaction in which 7-dehydrocholesterol, an intermediate in cholesterol synthesis, is cleaved by ultraviolet light and then undergoes a spontaneous rearrangement — it seems likely that boron is either up-regulating the 25-hydroxylation step, or suppressing the major pathway of 25-OH-D catabolism, 24-hydroxylation. We would like to hypothesize that boron is acting to suppress the latter reaction.

Boron readily forms covalent complexes with *cis*-vicinal dihydroxy compounds. Thus, it is conceivable that it can form such a complex with 24,25-dihydroxyvitamin D, the end product of the reaction of 25-OH-D with 24-hydroxylase. This postulated complex might either act as a competitive inhibitor of the 24-hydroxylase reaction, or, alternatively, perhaps could act to down-regulate expression of this enzyme. Another possibility is that boron is a direct inhibitor of the enzyme at very modest concentrations; indeed, boron can inhibit numerous enzymes, albeit usually in supra-physiological concentrations [7]. It should be reasonably straightforward to test this hypothesis in vitro using hepatocytes or other cells expressing 24-hydroxylase activity. Clinically, the testable implication of this hypothesis is that boron supplementation should increase serum 25-OH-D, while serum levels of 24,25-dihydroxyvitamin D remain constant or decline. (On the other hand, the latter compound should concurrently increase if the influence of boron is exerted at the level of 25-hydroxylation.)

Practical significance of boron

Assuming that improved boron nutrition can indeed up-regulate 25-OH-D, why should this be of practical significance? Granting the growing evidence that good vitamin D status may reduce risk for a range of common pathologies [11,12], it would seem logical to improve this status simply by supplementing with increased amounts of vitamin D — particularly in winter months when ultraviolet exposure is minimal. The problem with this argument is that, for some time to come, most nutritionists will be hesitant to recommend doses of vitamin D sufficiently high to replicate the benefit of ample ultraviolet exposure. The physiological capacity for daily production of cholecalciferol via ultraviolet exposure is about 10,000 IU [13], whereas most authorities currently recommend supplemental intakes in the range of 400—800 IU (10—20 mcg). Although Vieth [13] has demonstrated that a daily supplemental intake of cholecalciferol of 4000 IU, administered to women during the Canadian winter, is safe and raises serum 25-OH-D about halfway to the levels typically observed in lifeguards [14], the current misimpression that 2000 IU is the upper safe limit for vitamin D supplementation is likely to discourage the use of optimally effective supplemental intakes of this vitamin for some time to come. Thus, given that vitamin D status is suboptimal for many people during substantial portions of the year — even if they use standard vitamin supplements [15,16] — the postulated ability of supplemental boron to up-regulate 25-OH-D levels (or otherwise act to boost the efficacy of suboptimal vitamin D stores) could be of real benefit to health.

Although healthful natural diets rich in fruits, vegetables, and legumes can provide up to about 10 mg boron daily, surveys show that many people obtain no more than 1 mg boron from their habitual diets [17] — high in refined grains, sugars, oils, and animal products. Daily intakes of boron up to 20 mg are considered completely safe. Thus, there is considerable scope for appropriate nutritional supplementation to improve the boron status of the public. The capacity of such supplementation to modulate vitamin D metabolism and activity evidently requires further clinical evaluation.

A more general impact on vicinal hydroxylations of steroids?

Vitamin D is not the only bioactive steroid whose metabolism appears to be influenced by nutritional intakes of boron — several reports indicate that 17β-estradiol concentrations increase when boron in supplemented [18—21]. Notably, this effect is seen in post-menopausal women receiving hormone replacement therapy — suggesting that a reduction in estradiol catabolism (rather than synthesis) is responsible. The major routes of estradiol catabolism each involve introduction of a vicinal hydroxyl group — hydroxylations at the 2,4, or 16 position of 17β-estradiol, which is hydroxylated at the 3 and 17 positions. This raises the interesting possibility that boron may be a potent inhibitor for a range of microsomal enzymes which catalyze the insertion of hydroxyl groups vicinal to existing hydroxyl groups in steroids — specific examples being 24-hydroxylase and the estradiol hydroxylases.

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