Biochemical and Physiologic Consequences of Boron Deprivation in Humans

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Boron deprivation experiments with humans have yielded some persuasive findings for the hypothesis that boron is an essential nutrient. In the first nutritional study with humans involving boron, 12 postmenopausal women first were fed a diet that provided 0.25 mg boron/2000 kcal for 119 days, and then were fed the same diet with a boron supplement of 3 mg boron/day for 48 days. The boron supplementation reduced the total plasma concentration of calcium and the urinary excretions of calcium and magnesium, and elevated the serum concentrations of 17β-estradiol and testosterone. This study was followed by one in which five men over the age of 45, four postmenopausal women, and five postmenopausal women on estrogen therapy were fed a boron-low diet (0.23 mg/2000 kcal) for 63 days, then fed the same diet supplemented with 3 mg boron/day for 49 days. The diet was low in magnesium (115 mg/2000 kcal) and marginally adequate in copper (1.6 mg/2000 kcal) throughout the study. This experiment found higher erythrocyte superoxide dismutase, serum enzymatic ceruloplasmin, and plasma copper during boron repletion than boron deprivation. The design of the most recent experiment was the same as the second study, except this time the diet was adequate in magnesium and copper. Estrogen therapy increased plasma copper and serum 17β-estradiol concentrations; the increases were depressed by boron deprivation. Estrogen ingestion also increased serum immunoreactive ceruloplasmin and erythrocyte superoxide dismutase; these variables also were higher during boron repletion than depletion for all subjects, not just those ingesting estrogen. Dietary boron had no effect on those variables in the men and women not ingesting estrogen. These findings suggest that boron can both enhance and mimic some effects of estrogen ingestion. The findings from all three studies are consistent with the hypothesis that boron has an essential function that affects macromineral and cellular metabolism at the membrane level. — Environ Health Perspect 102(Suppl 7):59-63 (1994)

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Results—Human Experiments 1 and 2

Boron deprivation experiments with animals and humans have yielded some persuasive findings for the hypothesis that boron is nutritionally essential. In experimental animals, boron deprivation apparently affects the function or composition of several body systems, including the skeleton, kidney, and brain (1,2). The variables affected by boron deprivation are associated with the metabolism of several other nutrients including calcium, copper, and nitrogen (1,2). Responses to low dietary boron have been most marked when an experimental animal has had to respond to a stressful situation that adversely altered hormonal or cellular membrane status such as the deprivation of calcium, cholecalciferol, magnesium, or potassium (1,2). Therefore, the first nutritional study of boron (B) with humans used postmenopausal women (3,4); they undergo hormonal changes during perimenopause associated with an increased loss of calcium from bone or the body.

Twelve postmenopausal women first were fed a diet that provided 0.25 mg B/2000 kcal for 119 days and then were fed the same diet with a boron supplement of 3 mg/day for 48 days. During the experiment, seven of the women were fed a diet low in magnesium (116 mg/2000 kcal); the other five had their diet supplemented with 200 mg Mg/day. The boron supplementation of the boron-deprived women decreased the urinary excretion and plasma concentration of calcium and magnesium, decreased the urinary excretion and plasma concentration of phosphorus in the women fed the magnesium-low diets, and increased plasma testosterone and 17β-estradiol concentrations. Generally, the effects of boron deprivation, or supplementation, seemed more marked in the women fed the magnesium-low diet.

Another study was performed with five men over the age of 45, nine postmenopausal women (five postmenopausal women on estrogen therapy) and one premenopausal woman (originally thought to be postmenopausal). They were fed a boron-low diet, or 0.23 mg/2000 kcal for 63 days (5,6). Then they were fed the same diet supplemented with 3 mg B/day for 49 days. The diet was low in magnesium, 115 mg/2000 kcal, and marginally adequate in copper, 1.6 mg/2000 kcal, throughout the study. When all 15 subjects were in the comparison, serum calcium, 25-hydroxycholecalciferol and ceruloplasmin concentrations, plasma copper concentration and erythrocyte superoxide dismutase activity were lower whereas serum creatinine, glucose, and blood urea nitrogen concentrations were all higher during the boron depletion period than the boron repletion period. Boron supplementation of the boron-deprived women on estrogen therapy, but not the other two groups, also tended to increase serum 17β-estradiol concentrations. Table 1 shows the nature of the changes induced by dietary boron in erythrocyte superoxide dismutase, serum 17β-estradiol, plasma copper, and serum glucose.

Discussion—Human Experiments 1 and 2

The two human experiments described above yielded a bewildering and surprising array of significant findings, considering that boron has a biochemical role apparently so subtle it was considered nutritionally unimportant until the 1980s. However, a close analysis of the findings from these two experiments indicates that boron affects many of the same variables as calcium. Analysis suggests this similarity occurs because both elements affect a similar sys-

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Table 1. Effect of boron on erythrocyte superoxide dismutase (SOD) activity, and plasma copper, serum glucose, and serum 17β-estradiol concentrations in subjects fed a diet low in magnesium and copper. 

| Dietary boron a | SOD, U/g Hb | 17β-estradiol, pg/ml | Copper, µg/dl | Glucose, mg/dl |
|----------------|-------------|----------------------|---------------|---------------|
| Men over age 45 (n = 5)          |             |                      |               |               |
| 0                           | 2287        | 33                   | 91            | 94            |
| 3                           | 2552        | 35                   | 93            | 90            |
| p value                      | 0.41        | 0.50                 | 0.52          | 0.21          |
| Postmenopausal women (n = 4)    |             |                      |               |               |
| 0                           | 2213        | 23                   | 127           | 94            |
| 3                           | 2386        | 18                   | 128           | 88            |
| p value                      | 0.57        | 0.26                 | 0.75          | 0.007         |
| Postmenopausal women on estrogen therapy (n = 5) | | | | |
| 0                           | 2160        | 107                  | 141           | 91            |
| 3                           | 2736        | 145                  | 152           | 86            |
| p value                      | 0.04        | 0.09                 | 0.03          | 0.009         |
| Above combined plus one premenopausal woman (n = 15) | | | | |
| 0                           | 2257        | 52 c                 | 117           | 93            |
| 3                           | 2578        | 64 c                 | 122           | 88            |
| p value                      | 0.03        | 0.13                 | 0.03          | 0.0004        |

a There was a depletion period of 63 days when no boron supplement was given. This was followed by a repletion period of 49 days when the boron supplement was given. Values obtained during the last 42 days of depletion and last 35 days of repletion were compared (5,6). 

b Amount of boron (B) as sodium borate supplemented per day to a diet containing 0.25 mg B, 115 mg Mg and 1.6 mg Cu/2000 kcal. 

Values do not include the premenopausal woman.

Table 2. Effect of boron on mean corpuscular hemoglobin content (MCH), hemoglobin concentration, hematocrit, and platelet counts in subjects fed a diet apparently adequate in all nutrients. a

| Dietary boron a | MCH, pg | Hemoglobin, g/dl | Hematocrit, % | Platelets, 10^4/1 |
|----------------|---------|------------------|---------------|------------------|
| Men over age 45 (n = 4)          |         |                  |               |                  |
| 0                           | 30.4    | 14.7             | 43.4          | 290              |
| 3                           | 31.9    | 14.8             | 42.5          | 256              |
| p value                      | 0.003   | 0.45             | 0.03          | 0.008            |
| Postmenopausal women (n = 4)    |         |                  |               |                  |
| 0                           | 29.6    | 12.9             | 38.2          | 312              |
| 3                           | 30.6    | 13.1             | 37.8          | 278              |
| p value                      | 0.008   | 0.26             | 0.42          | 0.007            |
| Postmenopausal women on estrogen therapy (n = 5) | | | | |
| 0                           | 30.3    | 13.0             | 38.7          | 297              |
| 3                           | 31.8    | 13.3             | 37.5          | 268              |
| p value                      | 0.01    | 0.02             | 0.003         | 0.007            |
| Above combined plus one premenopausal woman (n = 14) | | | | |
| 0                           | 30.1    | 13.4             | 39.8          | 297              |
| 3                           | 31.3    | 13.6             | 38.9          | 269              |
| p value                      | 0.0001  | 0.007            | 0.0001        | 0.0001           |

a There was a depletion period of 63 days when no boron supplement was given. This was followed by a repletion period of 49 days when the boron supplement was given. Values obtained during the last 35 days of depletion and last 35 days of repletion were compared (8). 

b Amount of boron (B) as sodium borate supplemented per day to a diet containing 0.25 mg B/2000 kcal.

Results and Discussion—Human Experiment 3

Dietary boron affected indices associated with erythropoietic or hematopoietic activity (8). That is, boron supplementation after boron depletion decreased hematocrit, red blood cell count, and platelet count, but increased total hemoglobin and mean

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*There was a depletion period of 63 days when no boron supplement was given. This was followed by a repletion period of 49 days when the boron supplement was given. Values obtained during the last 35 days of depletion and last 35 days of repletion were compared (8). 

b Amount of boron (B) as sodium borate supplemented per day to a diet containing 0.25 mg B/2000 kcal.

The presence of one or both of the elements, cellular signal transduction would alter hormone action, or transmembrane signaling. These alterations would affect a large array of variables including those associated with hematopoiesis, erythropoiesis, macromolecular and electrolyte metabolism, and even the response to estrogen therapy. Unfortunately, in the first two human studies, examination of the specific effect of boron on these processes was prevented because the studies were complicated by diets low in magnesium and marginal in copper, both dietary substances that also affect these processes. To rectify this oversight, a third experiment recently was completed with the subjects consuming a diet apparently adequate in all nutrients (including copper and magnesium).
Table 3. Effect of boron on erythrocyte superoxide dismutase (SOD) activity, and serum 17β-estradiol, plasma copper, and serum immunoreactive ceruloplasmin concentrations in subjects fed a diet apparently adequate in all nutrients.  

| Dietary boron ¹ | SOD, U/g Hb | 17β-estradiol, pg/ml | Copper, µg/dl | Ceruloplasmin, mg/day |
|-----------------|-------------|---------------------|---------------|----------------------|
| Men over age 45 (n = 4) | 0 | 3091 | 20 | 83 | 25 |
| 3 | 3231 | 17 | 86 | 28 |
| p value | 0.79 | 0.12 | 0.14 | 0.06 |
| Postmenopausal women (n = 4) | 0 | 2666 | 11 | 107 | 30 |
| 3 | 3189 | 11 | 106 | 33 |
| p value | 0.04 | 0.86 | 0.71 | 0.06 |
| Postmenopausal women on estrogen therapy (n = 5) | 0 | 2520 | 99 | 146 | 42 |
| 3 | 3327 | 157 | 159 | 50 |
| p value | 0.03 | 0.02 | 0.04 | 0.05 |
| Above combined plus one premenopausal woman (n = 14) | 0 | 2735 ² | 48 ² | 115 ² | 33 |
| 3 | 3243 ² | 69 ² | 121 ² | 38 |
| p value | 0.04 | 0.06 | 0.02 | 0.002 |

¹There was a depletion period of 63 days when no boron supplement was given followed by a repletion period of 49 days when the boron supplement was given. Values obtained during the last 35 days of depletion and the last 35 days of repletion were compared (9). ²Amount of boron (B) as sodium borate supplemented per day to a diet containing 0.25 mg B/2000 kcal. ³Values do not include the premenopausal woman.

decreased after boron supplementation began. The difference between the last 35 days of each period was 39.8 vs 38.9, and was significant at the 0.0001 level. Also, during boron depletion, platelet counts were elevated. Two subjects actually had platelet counts of over 400 x 10⁷ per liter. After boron supplementation began, all platelet counts dropped below 300 x 10⁷ per liter.

The changes in blood variables that have been presented are all within normal ranges for adults and are not of clinical significance. But the changes are statistically significant and, because of their magnitude, they are most likely indirectly the result of boron altering some cellular function or structure which can influence blood cell or hemoglobin formation.

In the third and latest experiment, boron supplementation after boron deprivation increased erythrocyte superoxide dismutase activity in postmenopausal women on estrogen therapy, and (as shown in Table 3) in postmenopausal women not ingesting estrogen. Table 3 also shows that estrogen therapy increased serum 17β-estradiol and plasma copper concentrations in the postmenopausal women. For both variables, the elevation was significantly enhanced by boron supplementation. These changes were similar to those found with these two variables in the second human boron experiment when the diet was low in magnesium and marginal in copper. In both experiments, serum 17β-estradiol and plasma copper concentrations were not significantly affected by the dietary boron changes in men and those postmenopausal women not on estrogen therapy.

The finding that physiologic amounts of boron supplementation after boron deprivation causes higher peak serum 17β-estradiol concentrations in women ingesting estrogen suggests that boron can enhance estrogen absorption or decrease 17β-estradiol breakdown or excretion. This effect of boron on serum 17β-estradiol was the most likely reason for the significant increase in plasma copper concentration. In other words, because estrogen increases plasma copper, and boron increases estrogen retention or concentration in blood, boron—through estrogen—affects plasma copper concentrations.

Because of the effects on copper and 17β-estradiol, other variables that seemed responsive to estrogen therapy were examined to see if dietary boron affected the response in the same way. It was found that boron affected some other variables responsive to estrogen therapy. However, for most

| Dietary boron ² | 25-OH-D₃, ng/ml | HP, mmol/day | HP/creatinine, ratio | Calcium, g/day |
|-----------------|-----------------|---------------|---------------------|---------------|
| Men over age 45 (n = 4) | 0 | 18 | 0.0418 | 0.0038 | 0.263 |
| 3 | 26 | 0.0470 | 0.0044 | 0.256 |
| p value | 0.34 | 0.36 | 0.19 | 0.74 |
| Postmenopausal women (n = 4) | 0 | 18 | 0.0546 | 0.0082 | 0.182 |
| 3 | 20 | 0.0706 | 0.0101 | 0.204 |
| p value | 0.75 | 0.05 | 0.09 | 0.10 |
| Postmenopausal women on estrogen therapy (n = 5) | 0 | 18 | 0.0520 | 0.0077 | 0.162 |
| 3 | 30 | 0.0609 | 0.0092 | 0.163 |
| p value | 0.06 | 0.05 | 0.16 | 0.94 |
| Above combined plus one premenopausal woman (n = 14) | 0 | 18 | 0.0405 | 0.0069 | 0.198 |
| 3 | 25 | 0.0601 | 0.0082 | 0.205 |
| p value | 0.04 | 0.01 | 0.006 | 0.36 |

²There was a depletion period of 63 days when no boron supplement was given followed by a repletion period of 49 days when the boron supplement was given. Values obtained during the last 35 days of depletion and the last 35 days of repletion were compared (8,9). ³Amount of boron (B) as sodium borate supplemented per day to a diet containing 0.25 mg B/2000 kcal.

corpuscular hemoglobin concentration and content. Table 2 shows the nature of some of these changes. Mean corpuscular hemoglobin content (MCH) slightly decreased between the start of the study and the end of boron depletion, and then steadily increased during boron repletion. Whether the statistical analysis was by each group, i.e., men, women, and women on estrogen therapy, or as a group of 14, the difference in MCH between the last 35 days of each dietary period was significant. For instance, when all 14 subjects were used in the comparison, the difference was 30.1 vs 31.3 and was significant at the 0.0001 level. In contrast to the MCH and hemoglobin concentration, hematocrits stayed fairly constant throughout boron depletion, but
of these, the boron supplementation seemed to mimic, rather than enhance, the effects of estrogen therapy. For example, as shown in Table 3, serum immunoreactive ceruloplasmin apparently was increased by estrogen. Boron supplementation after boron deprivation increased this variable in all groups in a similar fashion. Unlike with plasma copper, the change did not occur only in the postmenopausal women ingesting estrogen. A similar effect was observed with plasma triglycerides (9). Thus, some variable, such as a similar calcium like estrogen, evidence from this experiment, that boron supplementation after boron deprivation increased serum 25-hydroxycholecalciferol concentrations (Table 4).

Urinary hydroxyproline is used as an indicator of changes in bone metabolism. As shown in Table 4, the urinary excretion of hydroxyproline significantly increased during the boron repletion period. This change suggests that boron increased collagen turnover. Because increased urinary hydroxyproline usually is associated with bone loss, this finding is difficult to explain in light of the fact that most of the other changes related to calcium metabolism induced by boron supplementation after boron deprivation suggest boron has a positive effect on calcium and bone metabolism. However, urinary hydroxyproline is also derived from collagen synthesis during the breakdown of the procollagen N-terminal extension peptides and of neosynthesized collagen molecules (10,11). Therefore, it may be possible that boron supplementation increases active bone formation and causes a greater need for collagen (on which calcification is initiated). As a result, urinary hydroxyproline is slightly increased. The urinary excretion of calcium (Table 4) certainly does not suggest bone breakdown; dietary boron did not significantly affect this variable.

Because boron apparently influences calcium and bone metabolism, and because some of the effects of boron supplementation after a period of boron deprivation are similar to estrogen therapy, boron may be acting in a manner similar to estrogen in affecting calcium and bone metabolism. Unfortunately, the mechanism through which estrogen affects calcium metabolism has not been clearly established (12,13), but estrogen apparently can modify the actions of hormones that affect calcium metabolism. Some of this modification probably occurs at the cell membrane level. The possibility that boron has a similar effect is supported by findings with plants. They indicate boron has a regulatory role involving hormones such as auxin, gibberellic acid, and cytokinin, and the control of a second messenger such as calcium at the cell membrane level (14,15).

Some recent work with rats in my laboratory also supports the possibility that boron can alter membrane function. In this experiment, weaning rats were fed marginally deficient, adequate, and luxuriant amounts of potassium (0.18%, 0.36% and 0.72% of the diet) and two amounts of boron—0 and 3 mg/kg of diet. After 12 weeks on these diets, blood platelets were obtained. And, through the use of the fluorescent marker FURA-2, cellular ionized calcium concentrations were measured in the resting stage and after activation with 0.25 units per ml thrombin with and without the presence of 1.0 mM external calcium. Preliminary results suggest that the amount of calcium released from stores after activation with thrombin may be decreased by dietary boron. However, when the platelets were activated by thrombin in the presence of 1.0 mM external calcium, the response suggested that boron caused changes in the cell membrane that altered calcium transport in and out of the cell. Increasing potassium increased the transport of calcium into platelets from boron-deprived rats (454 to 548 to 586 nM). In boron-supplemented rats, the dietary potassium changes did not have much of an effect (501 to 510 to 536 nM). These cellular ionized calcium concentration findings need to be confirmed and extended before any conclusive statement can be made about their meaning. Nonetheless, the hypothesis that boron and calcium interact to influence hormone action, transmembrane signaling and/or membrane function or stability is made more attractive by these preliminary findings. Moreover, if this hypothesis is true, it provides a simple explanation for the large variety of effects of varying characteristics when boron and calcium are altered in the diet, including those found in the human experiments described above.

Summary and Conclusions

In summary, boron most likely is an essential element in the human diet. However, the exact biochemical function of boron has not been elucidated. Many findings to date suggest that boron and calcium action are interrelated, or that these two elements affect similar systems that influence many variables, including the modification of hormone action, the alteration of cell membrane characteristics, and/or transmembrane signaling. Because of its apparent nutritional importance in calcium metabolism and utilization, humans should consume foods luxuriant in boron (fruits, vegetables, legumes, and nuts).

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