Micronutrients in Parenteral Nutrition: Boron, Silicon, and Fluoride

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Boron may be beneficial for bone growth and maintenance, central nervous system function, and the inflammatory response, and silicon may be beneficial for bone maintenance and wound healing. Fluoride is not an essential element but amounts provided by contamination may be beneficial for bone strength. Fluoride toxicity may be a concern in parenteral nutrition. Further studies are warranted to determine whether there are optimal amounts of boron and silicon that should be delivered to typical and special population patients receiving parenteral nutrition. In addition, further studies are needed to determine whether providing the dietary guideline of adequate intake amounts of fluoride parenterally would prevent or treat parenteral nutrition osteopenia.

Boron (B) is essential for some organisms in all phylogenetic kingdoms. Among the higher animals that require B are zebra fish and frogs. Boron-deprived male frogs show atrophied testes, decreased sperm counts, and sperm dysmorphology; female frogs show atrophied ovaries and impaired oocyte maturation.\(^1\,\text{,}^2\) During rapid cell division in embryogenesis, B-deprived zebra fish zygotes show blebbing of cell membranes, followed by cytoplasmic and yolk extrusion.\(^3\) These changes prevent the completion of the life cycle (ie, deficiency causes impaired growth, development, or maturation such that procreation does not occur), which is a criterion for essentiality.

Although there are data suggesting that B deprivation impairs early embryonic development in mice,\(^4\) the critical experiment showing that B is essential for a mammal to complete the life cycle, or defining a biochemical role for B necessary for life, is lacking. However, B-deprived experimental animals and human beings, when compared with controls fed nutritional amounts of B, show detrimental effects in bone growth and bone maintenance, brain function, and inflammatory response regulation. Boron deprivation impaired alveolar bone formation in mice, and alveolar bone repair after tooth extraction in rats; alveolus osteoblast surface was decreased and quiescent bone-forming surface was increased.\(^5\,\text{,}^6\) Boron deprivation decreased vertebral bone volume fraction and trabecular thickness, and increased trabecular separation and structural model index in rats.\(^7\) Boron deprivation exacerbated arthritis induced by an antigen in rats.\(^8\) Boron deprivation impaired cognitive processes of attention and memory, and psychomotor skills in human beings.\(^9\)

In addition, low dietary boron has been associated with prostate,\(^10\) cervical,\(^11\) breast,\(^12\) and lung\(^13\) cancer in human beings.

The diverse responses (many that may be secondary to a primary action) reported for low intakes of B have made it difficult to pinpoint a primary mechanism responsible for its bioactivity. However, the chemical characteristics of B may provide some clues as to a mechanism. At the pH of most biological fluids, about 96% of B exists as boric acid, \(\text{B(OH)}_3\), a Lewis acid that accepts a hydroxyl group during the production of a proton. This property allows boric acid to react with biomolecules with hydroxyl groups to form B esters. Boron deprivation may impair the actions of some hormones. Boron deprivation reportedly decreases insulin sensitivity\(^15\) and increases the requirement for vitamin D to prevent gross bone abnormalities\(^16\) and the need for exogenous thyroxine for tail resorption in frog development.\(^2\)

Boron as boric acid also readily forms complexes with several biologically important sugars, including ribose, a component of adenosine.\(^17\) S-adenosylmethionine (SAM) and diadenosine phosphates have higher affinities for B than any other currently recognized B ligands present in animal tissues.\(^18\) Diadenosine phosphates are present in all cells and function as signal nucleotides associated with neuronal response. SAM is one of the most frequently used enzyme substrates.\(^19\) About 95% of SAM is converted into S-adenosylhomocysteine, which is important for methylation of DNA, RNA, proteins, phospholipids, hormones, and neurotransmitters.\(^19\)

Abbreviations used in this paper: AI, adequate intake; B, boron; F, fluoride; PN, parenteral nutrition; SAM, S-adenosylmethionine; SI, silicon.

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tion of S-adenosylhomocysteine yields homocysteine. High circulating homocysteine and depleted SAM have been implicated in many human diseases including atherosclerosis, osteoporosis, arthritis, cancer, diabetes, and impaired brain function. The finding that B deprivation increased plasma homocysteine and decreased liver SAM levels in rats suggests that B may be bioactive through affecting the formation or use of SAM.20

Assessment of Deficiency and Toxicity

Boron is similar to most essential trace elements in that there is no single good indicator of status. About 90% of ingested B is absorbed and then efficiently excreted via the urine.21 Thus, urinary B assesses only the recent intake. However, urinary B combined with a B intake assessment may give an indication of whether an individual has a low B status. Human beings consuming less than 0.5 mg/day for 2–3 months respond to a nutritional B supplement (3 mg/day).9,22 Thus, a person on parenteral nutrition (PN) providing less than 0.5 mg B/day and excreting less than 0.5 mg B/day may have a low B status.

Plasma or serum B also may have some value as an indicator of B status. In one human study, a 9.0-fold increase in dietary B (mean from 0.36 to 3.23 mg/day) increased plasma B concentrations 1.5-fold (mean from 64 to 95 ng/mL).21 In another study, supplementing 43 perimenopausal women with 2.5 mg B/day for 60 days increased the median plasma B concentration from 33 ng/mL (range, 20–67 ng/mL) to 52 ng/mL (range, 28–75 ng/mL).22 These findings suggest that persons with serum or plasma B concentrations in the lower part of these ranges might be suspected of having a low B status. Plasma or serum B also may be used as an indicator of excessive B intake. Mean blood B concentrations were 68, 347, 585, 450, and 659 ng/mL in people from areas where drinking water provided 0.02, 0.08, 0.3, 0.4, and 0.5 mg B/kg body wt/day, respectively, in the drinking water.24 Thus, blood B concentrations greater than 300 ng/mL would indicate a B intake in excess of that needed to prevent signs of B deprivation. Plasma or serum B concentrations greater than 1 μg/mL may indicate B toxicity.25

Boron is not very toxic when administered orally. Its relatively low toxicity allowed boric acid and borates to be used as food preservatives and in oral medicinal products in the late 19th and early 20th centuries. Toxicity in animals generally occurs only after dietary B exceeds 100 mg/kg. The signs of chronic B toxicity, based mainly on animal findings, include poor appetite, weight loss, and decreased sexual activity, seminal volume, sperm count, and sperm motility.25

Dose Range Recommendation for Typical PN-Fed Patients

The Food and Nutrition Board of the National Academy of Sciences set no Recommended Dietary Al-
tilage calcification. Another hypothesized role for Si in higher animals is that it interacts (as silicic acid) with an aluminum species (eg, Al(OH)₃) to form an aluminosilicate that prevents aluminum from competing for iron-binding sites (eg, prolyl hydroxylase), and thus prevents adverse effects of iron replacement by aluminum on collagen synthesis and structure. In addition to alleviating aluminum toxicity, high intakes of Si apparently can be beneficial through facilitating the absorption or use of some minerals, including copper and magnesium, which are essential for bone growth and maintenance, cardiovascular health, and wound healing.

Assessment of Deficiency and Toxicity

An indicator of Si status has not been established. A recent report indicated that an average of 41% of dietary Si is excreted in the urine, and that the Si content of foods consumed is correlated with urinary Si excretion. Carlisle suggested that a daily minimum requirement for Si might be near 10–25 mg/day based on the amount excreted in urine in 24 hours. Silicon entering the bloodstream is transferred rapidly to tissues, which results in the Si concentration in blood remaining relatively constant over a range of dietary intakes. Reported mean or median fasting human serum levels range from 11 to 31 μg/Si/dL. Thus, serum Si concentrations in the lower part of this range and urinary excretion of less than 10 μg/day may be an indication of a low Si status.

In experimental animals, urinary excretion of Si increases with an increasing intake of siliceous substances, but reaches a maximum that is not exceeded by increasing intake. This maximum apparently is set by the rate and extent of Si absorption and not by the excretory ability of the kidney because peritoneal injection of Si can increase urinary excretion above the upper limit achieved by dietary intake. The limitation in absorption and efficient urinary excretion results in Si having a very low order of toxicity through oral intake. Moreover, these homeostatic control mechanisms would make effects of oral Si toxicity poor indicators of the effects of intravenously injected soluble Si, which apparently has been virtually ignored. One report stated that daily intravenous injection of 5 or more mg of “silica sol” in rabbits induced liver fibrosis, enlargement of the spleen, and interstitial nephritis. Two dialysis patients with high Si concentrations (385 and 235 μg/dL) showed skin eruptions, folliculitis, and disturbed hair growth. However, there was no mention of these effects in hemodialysis patients with high Si concentrations in plasma (420 μg/dL) in another study.

Dose Range Recommendation for Typical PN-Fed Patients

The Food and Nutrition Board judged that animal and human data were too limited for setting any Dietary Reference Intakes for Si. Based on the amount excreted in urine in 24 hours, a daily minimum requirement for Si might be near 10–25 mg/day. Thus, an intake near these amounts through typical PN may be beneficial for bone health and wound healing. High dietary molybdenum and aging may increase the amount of Si needed for beneficial effects. A very limited number of reports have indicated that most PN solutions do not supply this amount of Si, which comes only from contamination of ingredients. Bohrer et al determined the Si content in numerous commercial formulations used for parenteral administration and found that most supplied less than 1 mg Si/L. Urinary analysis of trauma patients receiving PN indicated that they received only 1–3 mg Si/day.

Fluoride

Metabolic Function

Fluoride (F) has a well-established beneficial action in human beings. Through a pharmacologic action, F imparts caries resistance to the enamel of teeth. In addition, high or pharmacologic amounts of F prevented anemia and infertility caused by iron deficiency in mice, improved growth of suboptimally growing rats, and alleviated nephrocalcinosis induced by phosphorus feeding and soft-tissue calcification caused by magnesium deprivation (see article by Nielsen et al for original citations for these effects). Fluoride cannot be considered an essential nutrient because the critical experiment showing F is essential to complete the life cycle, or defining a biochemical role for F necessary for life, is lacking. Moreover, unequivocal or specific signs of F deprivation have not been described for higher animals or human beings. Fluoride deprivation in goats has been reported to decrease life expectancy and induce pathologic histology in the kidney and endocrine organs. However, these findings need confirmation before being accepted as signs of F deprivation in higher animals. The mechanisms through which F has beneficial effects are making hydroxyapatite of tooth enamel and dentin less soluble and thus more resistant to acid attack, and altering calcium, magnesium and/or phosphorus metabolism, and tissue deposition and/or use. Manifestations of toxic amounts of F also may involve the alteration of calcium and magnesium metabolism and tissue deposition.

Assessment of Deficiency and Toxicity

Because F deficiency has not been defined, there is no basis for assessing a low F status. One sign of F toxicity is dental fluorosis, which is characterized by a more porous enamel. In some studies, high amounts of F in drinking water have been associated with an increased risk for bone fractures. However, in other studies, high F in drinking water was found to decrease risk, or had no relationship, to bone fractures. The reason for this inconsistency may be that there is biphasic response...
to high F intake. Animal studies suggest that F increases bone strength, reaching peak strength when it contains 1200 μg F/g, followed by a decline at higher concentrations, which eventually leads to impaired bone quality.\textsuperscript{50} Bone ash concentrations of 3500–5500 μg F/g result in osteosclerosis, stiffness and pain in joints, and slight calcification of ligaments, and concentrations of 9000 μg F/g in ash result in crippling skeletal fluorosis with bone exostoses and marked calcification of ligaments that limits joint mobility.\textsuperscript{47} Essentially 100% of F as fluoridated water ingested in the fasted state, and 50%–80% of F ingested with food is absorbed. Approximately 50% of F absorbed each day is deposited in calcified tissue (bone and developing teeth), and 50% is cleared by the kidney.\textsuperscript{51}

Thus, urinary F excretion may be used to assess the exposure to F. A urinary F concentration of 15 mg/L would suggest a daily exposure to 20–30 mg of F. It may take 10 years or more of daily exposure to about 20 mg F to reach skeletal F concentrations associated with crippling fluorosis.\textsuperscript{47}

A high serum F level also may be an indicator of risk for F toxicity. The use of F as a therapy for osteoporosis indicated that the threshold at which F affects bone cells is 95 ng/mL and the toxic threshold (fluorosis of bone characterized by enlarged lacunae, abnormal bone formation, impaired mineralization, and reduced bone strength) was 190 ng/mL of serum.\textsuperscript{52}

### Dose Range Recommendation for Typical PN-Fed Patients

The Food and Nutrition Board set Adequate Intake (AI) levels for F based on the amounts that protect against dental caries and generally do not result in any mottling of teeth.\textsuperscript{51} These AI in mg/day are as follows: infants (0–6 mo), 0.01; infants (7–12 mo), 0.5; children (1–3 y), 0.7; children (4–8 y), 1; children (9–13 y), 2; adolescents (14–18 y), 3; adult women (≥19 y), 3; and adult men (≥19 y), 4. The tolerable upper limits were set on the basis of the possibility of dental fluorosis in children and skeletal fluorosis in adults. The tolerable upper limits set in mg/day are as follows: infants (0–6 mo), 0.7; infants (7–12 mo), 0.9; children (1–3 y), 1.3; children (4–8 y), 2.2; and children and adults (≥8 y), 10.

A recommended intake of F for typical PN-fed patients could be amounts that are near the AI. When F intake is determined, the amount in drinking water must be considered. In one study, patients with chronic intestinal failure received home PN that provided a mean of 0.74 mg F/day, but intake from water and tea increased the F intake to a mean of 8.03 mg/day.\textsuperscript{53} This study and another study that determined the amount of F delivered in one feeding (1 mg) in a home PN program of a hospital in England\textsuperscript{54} indicated that PN solutions do provide significant amounts of F, but below the AI.\textsuperscript{54}

### Summary Recommendations

Because B may be beneficial for bone growth and maintenance, central nervous system function, and the inflammatory response, and Si may be beneficial for bone maintenance and wound healing, further studies are warranted to determine whether there are optimal amounts of B and Si that should be delivered to typical and special populations of patients receiving PN. In addition, further studies are needed to determine whether providing AI amounts of F parenterally would prevent or treat PN osteopenia.

### Question and Answer Session

**DR BERGER:** Are you advocating adding boron and silicon to standard solutions?

**DR NIELSEN:** That probably has to be approved by the FDA, but my personal opinion is yes. I recommend a milligram of boron per day and about 10 mg of silicon per day, which I think will have some health benefits.

**DR DELUCA:** When we make purified diets we don’t add boron. How much boron is inherent in something like highly purified casein? We’ve run experiments of 3 generations of rats without any detrimental effects from not adding boron to the diet. I’m wondering whether that’s because there is boron contamination in our diets.

**DR NIELSEN:** Do you use sucrose or do you use starch?

**DR DELUCA:** We use glucose monohydrate.

**DR NIELSEN:** If there is no starch, then boron is most likely a contaminant of your mineral mix, especially the calcium and magnesium sources. Some starch sources may be high in boron; ground corn must be acid-washed to make it low in boron. I have made diets that used sucrose and fructose with small amounts of ground corn and found that the diets are quite low in boron. Boron must be around 0.1 to 0.2 mg/kg to see deprivation effects. If the boron is 0.3, 0.4, or 0.5, you see only minor effects.

**DR SHIKE:** As you may remember, a number of years ago we did a study together.

**DR NIELSEN:** Yes.

**DR SHIKE:** We provided you with home PN solutions, which were complete solutions, and also the separate components to determine their trace element composition. As I remember, the conclusion of that study was that there were a number of unexpected trace elements, including silicon, provided in amounts through contamination that were more or less comparable to what people absorbed from a normal diet. However, boron was only about 10% of what we calculated people absorbed. So my question is, do you feel at this point there are adequate data that you would propose adding 1 mg boron/day?

**DR NIELSEN:** I believe the data warrant adding 1 mg of boron/day to PN solutions. I have performed 3 human studies in which I fed 0.25 mg of boron a day, provided
by natural diets low in fruits and vegetables, and the pulses. We observed altered responses to estrogen therapy, changes in lipid metabolism, and some effects on bone status indicators. When we supplemented these people with 3 mg/day of boron, we reversed these changes. We used 3 mg/day because that is what I thought was normally provided by diet, but I now know it is only 1.5 mg. I believe 1 mg/day in PN solutions would prevent the changes that occurred when dietary boron was low in my studies.

DR PIRONI: A study published in the American Journal of Clinical Nutrition demonstrated that patients on long-term home parenteral nutrition with a short bowel may absorb fluoride from their drinking water. Is it possible to supplement these patients with boron and silicon through their drinking water?

DR NIELSEN: Yes, it is possible. I don’t think there is any worry about fluoride deficiency. Of more concern is that PN patients are getting too much fluoride. Most parenteral nutrition solutions are going to supply about 1 mg of fluoride per day, which is probably adequate. The fluoride might be useful in reducing the osteopenia that is associated with long-term parenteral nutrition. In regard to silicon, there are indications that, in contrast to the study we did with Moshe, higher purification of PN solutions, and the wider use of plastic bags rather than glass, now results in silicon concentrations in parenteral nutrition solutions below 10 mg/day, and in fact, are closer to 1–3 mg/day; so adding more silicon would probably be of benefit.

DR BUCHMAN: Forrest, do you have any idea as to whether the water source for IV solutions, even though it is distilled and deionized, could in some locations be fluoridated?

DR NIELSEN: I am not sure. In some areas there is a trace of fluoride in water used for IVs. It should be noted that there are parts of the country, for example, California, where the water supply can have high boron content.

DR BERGER: You have provided evidence that boron and silicon are essential trace elements, what about vanadium and tin? Are we reaching the point where we should consider adding them also? Is vanadium involved in myocardial metabolism?

DR NIELSEN: I think the evidence for tin being essential is pretty slim. The initial work was done by Schwarz back in the 1970s. I and several others have tried to repeat his findings, but have been unsuccessful. At present, there is no strong evidence that supports a tin requirement. There might be some need for vanadium, but if there is an essential requirement it is very small, and those minute amounts probably would be supplied through contamination. At present, various vanadium compounds are being studied pharmacologically because vanadium has a positive effect in diabetes.

References


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