The Nutritional Essentiality of Silicon

Edith M. Carlisle, Ph.D.

During the last decade, silicon has been recognized as an essential trace element participating in the normal metabolism of higher animals. Among the trace elements, silicon occupies a unique position, because next to oxygen, silicon is the most prevalent element on earth, and crystalline silica in the form of quartz is the most abundant mineral in the earth's crust. Interest in the silica content of animal tissues and the effects of siliceous substances upon animals was expressed more than half a century ago. At that time, emphasis was being placed on the toxicity of silicon, its effect upon forage digestibility, urolithiasis and especially silicosis caused by dust inhalation. Several important reviews of this work are available.[1-3]

The element occurs in nature as the oxide, silica (SiO_2). Orthosilicic acid ($Si(OH)_4$) formed by hydration of the oxide is soluble in water in amounts up to about 120 ppm. Above 120 ppm, supersaturation causes dehydration and polymerization into complex, less soluble forms. Considering its slight solubility in water and its presence in most plants, it is not surprising that at least minute amounts of silicon may be found in most animal tissues and fluids. Nevertheless, many of the earlier results in animal tissues reported by some of the early French and German investigators before the development of suitable methods and the advent of plastic laboratory ware, are much higher than those found more recently.[1] Even with more recent methods using the ammonium molybdate colorimetric method, large differences in silicon levels in tissues are often observed.[4] It is most important therefore to compare the results of the colorimetric assays with an alternative analytical procedure (for example, emission spectrography). Microdetermination of silicon in biological tissues has been reported to be one of the most difficullt problems in analytical chemistry.

The highest levels of silicon are found in the epidermis and its appendages, and in connective tissues in general. The eggs of birds, milk and the fetuses of mammals have small quantities. The blood of man and other mammalian species averages about 0.5 mg per liter of blood plasma, a level that is not significantly increased by the inhalation of silica dust. Dietary silicon supplements have been reported[5] to have little effect on the silicon concentration of cow's milk. Moderate increases have been obtained in rat's blood, however, after feeding silicon as sodium metasilicate and much higher levels have been reached after feeding organic silicates. The consistently low concentrations of silica in most organs do not appear to vary appreciably during life. Parenchymal tissues such as liver, heart and muscle, for example, range from 2 to 10 mg per kilogram. The lungs are an exception. Varying amounts of silica entering the respiratory tract normally cross the barrier of the lung as silicic acid which is eventually eliminated. Nevertheless, the lungs ordinarily accumulate large amounts of silicon from long-continued inhalation of finely particulate silica.

Silicic acid in foods and beverages is readily absorbed across the intestinal wall and is rapidly excreted in the urine. Silicon absorption studies[6] using intestinal ligature techniques showed that the level of silicon in blood and intestinal tissues of male and female rats is affected by age, sex, castration, adrenalectomy and thyroidectomy.

Dr. Carlisle is Researcher and Adjunct Professor, Environmental and Nutritional Sciences, School of Public Health, University of California, Los Angeles, CA 90024.

Essential Element

A series of experiments has contributed to the establishment of silicon as an essential element. The first of these were in vitro studies on young bone which suggested a physiological role for silicon in bone calcification processes.[7,8] These were followed by in vivo studies showing an effect of silicon on the rate of bone mineralization.[9] Of paramount importance, however, was the establishment of a deficiency state in the chick and rat incompatible with normal growth, which could be corrected by a silicon supplement[10-12] thus establishing silicon as an essential element. Feeding a low silicon diet based on an optimal mixture of L-amino acids for the chick and using special trace element techniques, it was possible to show that silicon is required for normal growth and development. Increases of nearly 50 percent in growth rates in chicks were observed upon the feeding of silicon supplied as sodium metasilicate. The chicks on the deficient diet appear stunted. On subsequent examination all organs appeared relatively atrophied. Macropathologic examination showed that the skin and mucous membranes were somewhat anemic. The deficient chick had no wattles and the comb was severely attenuated. Significantly retarded skeletal development was also evident in the long bones. The skulls were also smaller and abnormally shaped. This effect of silicon on skeletal development supported earlier findings that silicon is involved in an early stage of bone formation.[7,13]

Silicon deficiency in rats also resulted in depressed growth and skull deformities.[12] Chemically defined diets based on amino acids in place of protein were also used. The addition of 50 mg of silicon per 100 g of diet produced a 25 to 34 percent increase in growth rates. The skulls were shorter and the bone structure surrounding the eye appeared distorted. Pigmentation of the incisors also was affected. Silicon was only partly effective in preventing the impairment of pigment deposition. Significant effects on the incisor pigmentation also were produced by physiological levels of tin, vanadium or fluorine.

In recent studies,[8,14] silicon essentiality has been demonstrated under entirely new conditions including: 1) a silicon-deficient basal diet using a natural protein (casein) in place of a crystalline amino acid mixture and an alternate mineral and vitamin mix; 2) a different environmental chamber; 3) chicks not deutectomized (removing yolk sac in hatching) as in previous studies and 4) chicks on a control diet growing at an optimal or near optimal rate. Under these new conditions, silicon deprivation caused skull abnormalities associated with a significant decrease in bone collagen content, long bone abnormalities as reported previously using amino acid diets and strong indications of other bone and connective tissue abnormalities. Deprivation of dietary silicon has resulted in consistent deficiency signs in all studies conducted so far, including effects on skull architecture, long bones and other connective tissues. These abnormalities are strong confirmatory evidence of silicon's essentiality for bone formation.

Later work emphasized silicon's importance in connective tissue as silicon has been shown to be involved in several aspects of connective tissue metabolism such as a structural component, in the formation of connective tissue, in aging of certain connective tissues, and at the cellular and subcellular level. Although a structural role has been proposed for silicon in connective tissue, more recent studies in this laboratory indicate that silicon assumes a far greater importance in a metabolic role.

Bone Formation

The earliest studies suggesting a physiological role for silicon were those reporting that silicon is involved in an early stage of bone calcification. In vitro[7,13] studies showed the unique localization of silicon in active growth areas in young bone where a relationship with calcium was established. This was followed by in vivo experiments[14,15] with weanling rats which showed a relationship between silicon and calcium in bone formation. These experiments demonstrated that dietary silicon increases the rate of mineralization. This effect was particularly apparent under conditions of low calcium intake. A

somewhat similar mechanism of action in bone formation has been demonstrated for vitamin D.[16] Most significant was the establishment of a silicon deficiency state in the chick[11] incompatible with normal skeletal development, evidenced by reduced circumference, thinner cortex and less flexible leg bones. In addition, the skulls were smaller and abnormally shaped with the cranial bones appearing flatter. Silicon deficiency in rats also resulted in skull deformations.[12] Subsequent in vivo studies with chicks demonstrated a relationship between silicon, magnesium and fluorine in growing bone.[17]

Recent studies also emphasize the importance of silicon in bone formation. Skull abnormalities associated with reduced collagen content have been produced in silicon-deficient chicks under conditions promoting optimal growth using a semi-synthetic diet containing a natural protein in place of the crystalline amino acid diet used in earlier studies.[8] A further finding was the striking difference in the appearance of the skull matrix between the silicon-deficient and silicon-supplemented chicks, the bone matrix of the deficient chicks totally lacking the normal striated trabecular pattern of the control chicks. The deficient chicks showed a nodular pattern of bone arrangement, indicative of a primitive type of bone. Trabecular bone formed later as the nodules coalesced. The findings demonstrated that silicon has a significant effect on the bone matrix and are strong confirmatory evidence of silicon's essentiality for bone formation and for a physiological role for silicon in chicks growing at an optimal rate.

Studies[18] using the same conditions as above, except for increasing the experimental variables by feeding three levels of vitamin D, have shown that silicon exerts an effect on bone formation independent of the action of vitamin D. All chicks on silicon-deficient diets, regardless of the level of dietary vitamin D had gross abnormalities of skull architecture, the silicon-deficient skulls showing considerably less collagen at each vitamin D level. These findings demonstrated that silicon has a significant effect on the collagen content of the connective tissue matrix independent of vitamin D. Similar to the previous study in the groups receiving vitamin D_3, the bone matrix of the deficient chicks totally lacked the normal striated trabecular pattern of the control chicks. In the rachitic groups of chicks, the appearance of the bone matrix was quite different from the groups receiving vitamin D_3, being considerably less calcified and more transparent, enabling the cells and underlying structure to be seen more easily. The deficient chicks appeared to have a marked reduction in number of osteoblasts compared to the controls. In both the above studies, the major effect of silicon appeared to be on the collagen content of the connective tissue matrix, a deficiency resulting in abnormal skull formation.

Cartilage Formation

Dietary deficiency studies[19] substantially identical with those which established the essentiality of silicon have provided clues to its metabolic role. Silicon deficiency proved to be associated with skeletal and other abnormalities involving glycosaminoglycans in formation of cartilage matrix and connective tissue. Tibial-metatarsal and tibial-femoral joints were smaller in the silicon-deficient chicks. The ends of the bones had less articular cartilage and were not as well formed. Both the amount of cartilage, comb connective tissue and glycosaminoglycan content were considerably less in the silicon-deficient chicks. These observations provided the first indication that silicon was involved with glycosaminoglycans in articular cartilage and connective tissue formation.

Additional support for a role of silicon in glycosaminoglycan metabolism is the finding that silicon is associated with animal glycosaminoglycans and their protein complexes as a result of extracting and purifying a large number of connective tissues under ultrapure conditions.[19] Silicon also has been reported to be a bound component of isolated glycosaminoglycans.[20] More recently, however, it has been reported[4] that many of the earlier observations on the occurrence of bound silicon in glycosaminoglycans were in error because they were based partially on results obtained with materials contaminated by silica or polysilicic acid, and that the hypo-

thesis that silicon acts generally as a cross-linking agent may have to be modified. The silicon content of the glycosaminoglycan-protein complexes is considerably less than the values that have been reported for isolated glycosaminoglycans.

In more recent studies[13] also, only using a semi-synthetic diet containing a natural protein in place of the crystalline amino acid diet used in the earlier study, long bone abnormalities similar to those reported previously have been produced in silicon-deficient chicks. A requirement for silicon in articular cartilage formation was again demonstrated. Tibia from silicon-deficient chicks had significantly less glycosaminoglycans and collagen, the difference being greater for glycosaminoglycans than collagen. A new finding was that tibia from silicon-deficient chicks showed rather marked pathology, profound changes being demonstrated in epiphyseal cartilage. The disturbed epiphyseal cartilage sequences resulted in defective endochondral bone growth indicating that silicon is involved in the metabolic chain of events required for normal growth of bone.

Connective Tissue Matrix, Collagen and Glycosaminoglycans

Although silicon may be involved in the mineralization process, silicon's primary effect in bone and cartilage appears to be on formation of the matrix. Recent in vivo studies show silicon to be involved in both intramembranous[8,18] and endochondral[13] bone formation. Formation of the organic matrix, whether of bone or cartilage, appeared to be more severely affected by silicon deficiency than the mineralization process.

These in vivo findings have been corroborated in studies of bone[21] and cartilage[22] in tissue culture, where it was demonstrated that silicon has a marked effect on bone growth, which appeared to be mainly due to an increase in collagen content. Silicon was also shown to be required for formation of glycosaminoglycans, the other major polymeric molecule of the bone matrix. In cartilage also, it was demonstrated that silicon is required for normal cartilage growth, especially marked in 14-day embryos as compared with ten- and 12-day embryos. Silicon's effect on collagen formation was also especially marked in 14-day embryos. Its effect on glycosaminoglycans formation was most marked in 12-day embryos. The requirement for silicon in collagen and glycosaminoglycan synthesis thus proves not to be specific for bone matrix. Cartilage and bone appear to be dependent on silicon for formation of collagen and glycosaminoglycans.

Cellular Component

Additional support for silicon's metabolic role in connective tissue is provided by evidence of its presence in connective tissue cells as demonstrated in the active bone-forming cell, the osteoblast, and its subcellular localization in the mitochondria.[23] X-ray microanalysis of active growth areas in young bone and isolated osteoblasts, and further studies including ultracentrifugation, demonstrate that silicon is concentrated in the cytoplasm of the osteoblast in the mitochondria. In subsequent studies[24] where the total silicon, calcium, phosphorous and magnesium stores of single osteogenic cells were successfully measured, silicon was shown to be a major anion of these cells which had been heretofore neglected. The amounts ot silicon were in the same range as that of calcium, phosphorus and magnesium. Moreover, silicon appeared to be especially high in the metabolically active state of the cell, the osteoblast.

Clear evidence that silicon occurs in the osteoblast and is localized in the mitochondria adds strong support to the proposition that silicon is required for bone matrix formation. It also supports the original proposal that silicon plays a fundamental role in the early stages of the bone calcification process.

Aging

Because connective tissue changes are prominent in aging, it is not surprising to find a relationship between silicon and aging in certain tissues. The silicon content of the aorta, other arterial vessels and skin was found to decline with age. The decline in silicon content was significant and was particularly dramatic in the aorta commencing at an early

17. E.M. Carlisle, *Fed. Proc.* 30: 462, 1971
18. E.M. Carlisle, *Calcif. Tiss. Intern.* 33: 27-34, 1981
19. E.M. Carlisle, *J. Nutr.* 106: 478-484, 1976
20. K. Schwarz, *Proc. Natl. Acad. Sci. USA* 70: 1608-1612, 1973
21. E.M. Carlisle and W.F. Alpenfels, *Fed. Proc.* 37: 404, 1978
22. E.M. Carlisle and W.F. Alpenfels, *Fed. Proc.* 39: 787, 1980
23. E.M. Carlisle, *Fed. Proc.* 34: 927, 1975
24. E.M. Carlisle, *Fed. Proc.* 35: 256, 1976
25. E.M. Carlisle, *Fed. Proc.* 33: 2758-2766, 1974
26. H. Brown, *J. Biol. Chem.* 75: 789-794, 1927
27. R.C. MacCardie, M.F. Engman, Jr., and M.F. Engman, Sr., *Arch. Dermat. Symph.* 48: 335-372, 1948
28. S.A. Kvorning, *J. Gerontol.* 5: 23-25, 1950
29. J. Loeper, J. Loeper and A. Lemaire, *Presse Med.* 74: 865-868, 1966
30. K. Schwarz, B.A. Ricci, S. Punsar and M.J. Karvonen, *Lancet* 1: 538-539, 1977
31. E.B. Dawson, M.J. Frey, T.D. Moore and W.J. McGanity, *Am. J. Clin. Nutr.* 31: 1188-1197, 1978
32. E.M. Carlisle, *Fed. Proc.* 38: 553, 1979