Calcium Support Nutrients

For enhancing the absorption, utilization and function of calcium

By Z.X. Liu, Ph.D. Gerontology, Biochemistry and Nutrition

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The literature was reviewed for the function and clinical data of 21 nutrients that have been found to enhance the absorption, utilization and various functions of calcium, including normal bone growth and remodeling. The data suggests that supplementation of these nutrients with calcium may be beneficial in individuals with potential deficiencies.

Vitamin D3

The process of intestinal calcium absorption represents the mechanism for dietary calcium to enter into the physiological processes that contribute both to the skeletal growth of the organism and to the maintenance of calcium homeostasis (both intracellular and extracellular). Because there is a large variation worldwide in the availability of dietary calcium and because there is a changing physiological need throughout life (growth, puberty, pregnancy, lactation, and menopause) for absorption of dietary calcium, it is essential that the process of intestinal calcium absorption be adaptable and responsive to both the dietary and physiological circumstances. This adaptation process is largely orchestrated by the vitamin D endocrine system, and the steroid hormone 1,25-dihydroxycholecalciferol has been shown to stimulate intestinal calcium absorption by both genomic (receptor mediated) and nongenomic (transcaltachia mediated) mechanisms (Norman 1990). Vitamin D, with parathyroid hormone and calcitonin, is an essential factor in the homeostatic regulation of systemic calcium in most vertebrate species. Targets for this aspect of vitamin D action, through its biologically active metabolites, are primarily the intestine, kidney and bone. Each of these tissues or organs are stimulated by 1,25(OH)2D3 to increase the transport calcium into the extracellular fluid compartment when plasma calcium levels are below normal and/or when there is a greater need for calcium to meet the requirements of physiological processes, such as growth, gestation and lactation. During such periods, the efficiency of the absorption of calcium from the intestine increases, the resorption of calcium salts from bone is stimulated, and the efficiency of the reabsorption of filtered calcium by the renal tubule is increased (Wasserman, Brindak et al. 1990). 1 alpha,25-Dihydroxyvitamin D3 [1 alpha, 25(OH)2D3], the active form of vitamin D3, stimulates intestinal calcium absorption and osteoclastic bone resorption, resulting in the elevation of plasma calcium(Miyaura and Suda 1993). The intestinal absorption of Ca2+ occurs by both a saturable, transcellular process and a nonsaturable, paracellular path. The transcellular path is a multistep process, comprised of the transfer of luminal Ca2+ into the enterocyte, the translocation of Ca2+ from point of entry (the microvillus border or membrane) to the basolateral membrane, and the active extrusion from the cell into the circulatory system. Each step in the transcellular movement of Ca2+ has a vitamin D-dependent component. (Miyaura and Suda 1993; Wasserman and Fullmer 1995). Vitamin D3 undergoes sequential hydroxylations in the liver and kidney to form 1,25-dihydroxyvitamin D3, the biologically active form of the vitamin. 1,25-dihydroxyvitamin D3 is metabolized by several processes in various target tissues that decrease the biological activity of the sterol. In addition, 1,25-dihydroxyvitamin D3 is excreted in the bile as polar metabolites, such as glucuronides and, possibly sulfates and neutral polar steroids. These compounds undergo an enterohepatic recirculation in both man and experimental animals. 1,25-dihydroxyvitamin D3 increases the absorption of calcium in the intestine and the reabsorption of calcium in the kidney. It induces the synthesis of several proteins, the most notable of which is calcium binding protein that is thought to play a role in the absorption of calcium. The vitamin D-dependent calcium binding proteins and the calcium-magnesium ATPase calcium pump are co-localized in several tissues that play a role in the absorption of calcium (Kumar 1990).

Magnesium

Magnesium is an element that occurs ubiquitously in nature, and magnesium and calcium metabolism are closely related (Hardwick, Jones et al. 1991; Saris, Mervaala et al. 2000). The intestinal absorption and the renal excretion of the two ions are interdependent (Chou, Wasserman et al. 1978; Schaafsma 1997). Magnesium participates in a number of biochemical pathways involved in bone (Okuma 2001). There is an important functional link between magnesium and

calciotropic hormones. PTH stimulates magnesium reabsorption in the renal tubule, absorption in the gut and release of the ion from bone. Magnesium on the other hand is essential for the normal function of the parathyroid glands, metabolism of vitamin D and adequate sensitivity of target tissues to PTH and active vitamin D metabolites. Magnesium deficit is usually associated with hypoparathyroidism, low production of active vitamin D metabolites, in particular 1,25(OH)2 vitamin D3 and resistance to PTH and vitamin D (Zofkova and Kancheva 1995). Animal study indicates that Mg has the ability to increase the Ca absorption in the gastrointestinal tract in sheep when the dietary Mg level is raised (Kozakai, Uozumi et al. 2002). Mg deficiency is known to impair parathyroid hormone (PTH) secretion and action in humans and will result in osteopenia and increased skeletal fragility in animal models (Rude and Olerich 1996). In vitro studies have demonstrated that magnesium can modulate parathyroid hormone (PTH) secretion in a similar way to calcium. An acute decrease in magnesium concentration stimulates PTH secretion, and an acute increase in concentration decreases secretion. Magnesium is likely to play an important role in vitamin D metabolism. Magnesium is involved in many of the biochemical reactions that take place in the cell, and particularly in processes involving the formation and utilization of ATP. Thus, at the cellular level, magnesium plays a key role in ionic transport processes (Paunier 1992). Calcium transport studies in D-replete animals indicate that intestinal calcium transport is influenced by the progressive depletion in magnesium (Lemay and Gascon-Barre 1992). Alkaline phosphatase, an enzyme for bone forming new calcium crystals, is activated by magnesium (Iseri and French 1984).

L-Lysine

Studies in animals and humans have shown that L-lysine can significantly increased the intestinal Ca absorption of the mineral, in that L-lysine can both enhance intestinal Ca absorption and improve the renal conservation of the absorbed Ca, and the combined effects may contribute to a positive Ca balance (Murillo, Campos et al. 1972; Tardivel, Toure et al. 1980; Wolinsky and Fosmire 1982; el Maraghi-Ater, Hourdry et al. 1987; Sheikh, Santa Ana et al. 1988; Civitelli, Villareal et al. 1992).

Boron

Study with postmenopausal women indicated boron supplementation markedly reduced the urinary excretion of calcium and magnesium, and the depression seemed more marked when dietary magnesium was low (Nielsen, Hunt et al. 1987).

Vitamin E

Study on young rats show that in intact animals vitamin E deficiency induced moderate hypocalcemia, a tendency to decreased Ca active transport in the small intestine and mineral saturation of the bone tissue. Combined vitamin D and E deficiency intensified disorders, reflects a synergy of such a negative effect. A delay in the recovery of Ca metabolism parameters, bone tissue condition and 25-OVD circulating concentration persisted, indicates a possible role of vitamin E deficiency in the rickets development, that is, probably, mediated, to a certain extent, by its influence on metabolism and (or) biochemical function of vitamin D (Sergeev, Kha et al. 1987).

Vitamin A

In vitro study shows that retinol and carotenoids stimulate bone cells by evaluating cell growth, alkaline phosphatase activity and the mRNA expression of a differentiation marker protein of osteoblastic cells. Retinol induced differentiation of the osteogenic cells in vitro, by increasing alkaline phosphatase activity. Beta-carotene also increases alkaline phosphatase activity in a dose-related manner. Osteopontin is one of the matrix proteins which osteoblasts produce. Retinol increased the expression of osteopontin mRNA, and beta-carotene also increased osteopontin mRNA expression. These results indicate retinol and beta-carotene have a direct stimulatory effect on the differentiation of osteoblasts at the physiological concentration (Park, Ishimi et al. 1997). During the process of endochondral bone formation, chondrocytes undergo a series of complex maturational changes. Studies indicate that this maturational process is influenced by the vitamin A derivative retinoic acid (RA). Treatment with RA, expression of type X collagen and alkaline phosphatase, osteonectin, and osteopontin genes were detected, there was also abundant calcium accumulation in the RA-treated cultures. Electron microscopy confirmed the formation of large matrix-associated mineral crystals and the presence of numerous matrix vesicles (Iwamoto, Yagami et al. 1994). Using a standardized guinea pig model, bone formed entirely during a retinol-deficient (A --) period contained less calcium than did control (A+) samples (Harris and Navia 1977; Navia and Harris 1980).

Vitamin K, B6, B12, and Folic Acid

Osteoporosis is a condition of bone fragility resulting from micro-architectural deterioration and decreased bone mass; adult bone mass depends upon the peak attained and the rate of subsequent loss; each depends on the interaction of genetic, hormonal, environmental and nutritional factors. An adequate supply of calcium is essential to attain maximum bone mass, and adult intakes below about 500 mg/day may predispose to low bone mass. Supplementation with calcium may conserve bone at some skeletal sites, but whether this translates into reduced fracture rates is not clear. Chronically low intakes of vitamin D--and possibly magnesium, boron, fluoride and vitamins K, B12, B6 and folic acid (particularly if co-existing)--may pre-dispose to osteoporosis (Bunker 1994).

The K vitamins, a group of napthoquinones, are required for the carboxylation of a limited number of proteins including the bone matrix protein osteocalcin. Epidemiological studies provide evidence for an association between a low vitamin K intake and an enhanced osteoporotic fracture risk (Zittermann 2001). The peak bone mass of humans can be raised by consuming sufficient amounts of vitamins K2 and D and calcium continuously from childhood, and that this diet will suppress the rate of decrease in bone mass, thus ultimately preventing bone fractures caused by osteoporosis (Hirano and Ishii 2002).

Vitamin B6 deficient diets produced osteoporosis rats (Sguazzini-Viscontini 1966; Benke, Fleshood et al. 1972; Miller, Groziak et al. 1996; Weber 1999). Vitamin B6 is a cofactor in the enzymatic crosslinking of collagen strands, which increases the strength of connective tissue (1986; Masse, Vuilleumier et al. 1988; Masse, Pritzker et al. 1994). Vitamin B6 also involves in the breakdown of homocysteine, which is believed to promote osteoporosis (Seashore, Durant et al. 1972).

High prevalence of osteoporosis occurs in homocystinuria, abnormal homocysteine metabolism would contribute to the pathogenesis of osteoporosis (Miyao, Morita et al. 2000). Classical homocystinuria is an autosomal recessive disorder caused by cystathionine beta-synthase deficiency and characterized by distinctive alterations of bone growth and skeletal development. Skeletal changes include a reduction in bone density (Masse, Boskey et al. 2003). Osteoporosis occurs commonly in homocystinuria, and the underlying pathobiochemical mechanism remains unclear, disturbed cross-linking of collagen has been suggested (Lubec, Fang-Kircher et al. 1996). Hyperhomocysteinaemia is an independent risk factor for arteriosclerosis, recurrent thromboembolic complications and osteoporosis. Folate and vitamin B12 deficiencies are considered to be major risks for hyperhomocysteinaemia (el-Swefy, Ali et al. 2002). Osteoporosis occurred more often among women whose vitamin B-12 status was considered marginal or deficient than in women with a normal status (Dhonukshe-Rutten, Lips et al. 2003). A suppressed activity of osteoblasts may contribute to osteoporosis and fractures in patients with vitamin B12 deficiency (Kim, Kim et al. 1996). Case study demonstrates that osteoporosis associated with pernicious anemia may be markedly improved by vitamin B12 replacement and cyclic etidronate therapy (Melton and Kochman 1994). Vitamin B12 and folic acid are directly involved in the breakdown of homocysteine, which has long been believed to promote to osteoporosis (Seashore, Durant et al. 1972).

Vitamin B1

In vitamin B1-deficient animals, a specific decrease (30-32%) was observed in Ca and Zn uptake with a 59% increase in the intestinal uptake of Cd. These altered metal ion uptake rates were probably not a result of hormonal disturbances due to the vitamin-deficient states (Prasad, Lyall et al. 1982).

Vitamin B2

In cross-sectional study, the nutritional status to bone density was evaluated by ultrasonic measurements, ultrasonic bone density (UBD). In In premenopausal women daily intakes of fat, animal fat, animal protein, calcium (Ca) and vitamin B2 (Vit B2) were positively associated with UBD. The intake of Vit B2 had a significant positive correlation with ultrasonic bone density index, i.e., daily intakes of animal fat and Vit B2 might be effective to maintain higher bone density for ultrasonic premenopausal women (Shono, Kugino et al. 1997).

Vitamin B3

The association between nutrient intake and bone mineral density (BMD) at the calcaneus (quadrangular bone at the back of the tarsus, also called heel bone) was cross-sectionally examined in 243 pre- (aged 29-60 years) and 137 postmenopausal (aged 39-60 years) Japanese women who participated in a BMD checkup and have kept a stable diet for at least 3 previous

years and had no dietary therapy. Nutrient intakes were assessed with a self-administered diet history questionnaire. BMD at calcaneus was measured with dual-energy X-ray absorptiometry. In a multiple regression analysis with adjustments for nondietary factors such as age, body height, fat body weight, nonfat body weight, and number of deliveries, calcium ($p<0.01$) and niacin ($p<0.05$) significantly and positively correlated in premenopausal women with BMD (Sasaki and Yanagibori 2001).

Vitamin C

Ascorbate (reduced vitamin C) is required for bone formation (Dixon, Kulaga et al. 1991), and is essential to the biosynthesis of collagen (Ogawara, Aoki et al. 1997). Ascorbic acid is essential for the formation of bone by osteoblasts, the mechanism by which osteoblasts transport ascorbate may be that osteoblasts possess a stereoselective, high-affinity, Na+-dependent transport system for ascorbate, and this system may play a role in the regulation of bone formation (Wilson and Dixon 1989). It is also suggested that vitamin C may play an important role in endochondral bone formation by modulating gene expression in hypertrophic chondrocytes (Leboy, Vaias et al. 1989). Ascorbate has a general anabolic effect on chondrocytes in culture and enhances matrix assembly through mechanisms other than its redox function (Wright, Wei et al. 1988). Ascorbate is essential for collagen synthesis, especially the hydroxylation of prolyl residues (the hydroxylation of proline) (Roach, Hillier et al. 1985). It has been shown that ascorbate regulates collagen production through its direct role in proline hydroxylation, and there was a linear correlation between the extent of body weight lost during the 3rd and 4th wk of scurvy and the rate of collagen synthesis in scorbutic bone, which indicates that ascorbate deficiency in guinea pigs leads to a specific decrease in collagen polypeptide synthesis (Chojkier, Spanheimer et al. 1983). Ascorbic acid is a required cofactor in the hydroxylations of lysine and proline necessary for collagen formation, and study of the cross-sectional relation between dietary vitamin C intake and bone mineral density (BMD) in women from the Postmenopausal Estrogen/Progestin Interventions Trial indicates a positive association of vitamin C with BMD in postmenopausal women with dietary calcium intakes of at least 500 mg (Hall and Greendale 1998). During the process of endochondral bone formation, proliferating chondrocytes give rise to hypertrophic chondrocytes, which then deposit a mineralized matrix to form calcified cartilage. Chondrocyte hypertrophy and matrix mineralization are associated with expression of type X collagen and the induction of high levels of the bone/liver/kidney isozyme of alkaline phosphatase, and it has been suggested that vitamin C may play an important role in endochondral bone formation by modulating gene expression in hypertrophic chondrocytes (Leboy, Vaias et al. 1989).

Silicon

Silicon performs an important role in connective tissue, especially in bone and cartilage. Silicon's primary effect in bone and cartilage appears to be on formation of the organic matrix. Bone and cartilage abnormalities are associated with a reduction in matrix components, resulting in the establishment of a requirement for silicon in collagen and glycosaminoglycan formation. Additional support for silicon's metabolic role in connective tissue is provided by the finding that silicon is a major ion of osteogenic cells, especially high in the metabolically active state of the cell. Further studies also indicate that silicon participates in the biochemistry of subcellular enzyme-containing structures. Silicon also forms important relationships with other elements. Although it is clear from the body of recent work that silicon performs a specific metabolic function, a structural role has been proposed for silicon in connective tissue (Carlisle 1988). Silicon's primary effect in bone and cartilage is on the matrix, with formation of the organic matrix appearing to be more severely affected by silicon deficiency than the mineralization process. Furthermore, silicon reaches relatively high levels in the mitochondria of these cells. A relationship established between silicon and ageing probably relates to glycosaminoglycan changes (Carlisle 1981; Carlisle 1982; Carlisle 1986). Studies were undertaken to investigate the effect of feeding a silicon (Si) -deficient diet containing a natural protein. Feeding this Si-deficient basal diet with or without supplemental Si to day-old cockerels under trace element-controlled conditions resulted in the production of skull abnormalities in the deficient chicks under conditions of near optimal growth. On macropathological examination, gross changes were found in the architecture of the skulls of the deficient chicks; the frontal area was narrower and the dorsal median line at the frontal parietal junction was depressed with a narrowing both posterior and laterally, forming a stunted parietal, occipital and temporal bone area. X-ray and histological examination of this area showed less trabeculae and calcification. Biochemical

analyses of the skull frontal bones for bone mineral, non-collagenous protein, hexosamine and collagen demonstrated that the frontal bones from the Si-deficient chicks had a significantly reduced collagen content. In this study, the major effect of Si appears to be on the collagen content of the connective tissue matrix, a deficiency resulting in abnormal skull matrix formation. Support is given to the earlier postulate that Si is involved in an early stage of bone formation (Carlisle 1980). In another study investigating long bone changes in silicon deficiency, long bone abnormalities have been produced in silicon-deficient chicks fed a casein-based rather than amino acid-based diet. The long bones of cockerels fed a silicon-supplemented basal diet and sacrificed at 4 weeks had a significantly greater amount of articular cartilage and water content as compared with the silicon-deficient group. Biochemical analyses of tibia for bone mineral, non-collagenous protein, hexosamine and collagen demonstrated that tibia from supplemented chicks had a significantly greater percentage and total amount of hexosamine and greater percentage of collagen than deficient chicks, the difference being greater for hexosamines than collagen. Tibia from silicon-deficient chicks also showed marked lesions, profound changes being demonstrated in epiphyseal cartilage, especially striking in the proliferative zone. The disturbed epiphyseal cartilage sequences resulted in defective endochondral bone growth indicating that silicon is involved in the metabolic chain of events required for the normal growth of bone (Carlisle 1980).

Manganese

Manganese is required for bone mineralization, and for synthesis of connective tissue in cartilage and bone. Animal studies have shown that manganese plays a role in the synthesis of chondroitin sulfate, an important component of articular cartilage (Leach, Muenster et al. 1969). Subcutaneous implantation of devitalized demineralized bone powers (DBP) and mineral-containing bone particles (BP) into rats raised on either a control (C), low manganese and low copper (L), or manganese-deplete (D) diet, allowed the separate evaluation of bone formation and of bone resorption, respectively. DBP failed to induce chondrogenesis or osteogenesis in D rats. Cartilage formation was delayed in the L rats compared to C rats. There was significantly less resorption of BP by L and D rats than C rats. These results show multiple cellular effects of long-term manganese (Mn) and copper (Cu) deficiencies on bone metabolism including decreased osteogenesis and a decrease in osteoclast activity ((Strause, Saltman et al. 1987). Manganese deficiency inhibits the biosynthesis of mucopolysaccharides that are used for bone matrix formation (Saltman and Strause 1993).

Zinc

Zn deficiency causes a reduction in osteoblastic activity, collagenand chondroitin sulafte synthesis and alkaline phosphatase activity (Saltman and Strause 1993). It has been shown that zinc is highly concentrated in the hypertrophic zone of epiphyseal cartilage. It has also been shown that zinc deficiency can result in abnormal bone development, suggesting a direct or indirect role for zinc in calcification. Because matrix vesicles have been implicated in the initiation of calcification, the effect of zinc and its chelators on ATP-dependent Ca uptake by rat matrix vesicles was studied. Zinc exerted a striking enhancing effect on ATP-dependent Ca uptake in matrix vesicles in a dose-dependent manner. The observed partial inhibition of ATPase and the activation of ATP-dependent Ca uptake of Zn2+ suggest that, in addition to ATPase, some other Ca and/or Pi uptake activators responsive to Zn2+ treatment are present in mammalian matrix vesicles (Hsu and Anderson 1995). The effect of dietary zinc deficiency was studies in ectopic bone formation subsequent to Achilles tenotomy and also following the implantation of demineralized bone matrix in the muscle of rats. The results indicated that, with the commercial ration, zinc increased concomitantly with calcium during ectopic bone formation in rats. Dietary zinc deficiency caused a retardation of ectopic bone formation and a significant reduction of in situ zinc and calcium concentration. Dietary zinc repletion to zinc-deficient animals restored the zinc concentration in ectopic bone to a level comparable to that of zinc-sufficient animals. Thus, these experiments present strong evidence that zinc plays an active role in bone metabolism (Calhoun, Smith et al. 1974; Calhoun, Smith et al. 1975). The effect of calcium-regulating hormones on bone metabolism was investigated in weanling rats orally administered zinc sulfate. Results indicate that zinc synergistically enhances 1,25(OH)2D3-stimulated bone metabolism. This suggests a physiologic significance of zinc in the regulation of bone metabolism (Yamaguchi and Inamoto 1986). The interaction of vitamin D3 and zinc on bone metabolism was investigated in the femur of weanling rats. The data suggest that the combination of vitamin D3 and zinc has a multiple effect on the stimulation of bone growth and

mineralization in weanling rats, and that this effect is based on a stimulation of the DNA synthesis in bone cells (Yamaguchi and Sakashita 1986). It was demonstrated that the development of experimental avitaminosis A in chicks led to secondary zinc deficiency. The balance of Zn in the chick became negative, while the Zn content of various tissues decreased. Thus in vitamin-A-deficient chicks the serum Zn content was considerably lower than that in controls. Zn absorption was considerably reduced throughout the entire small intestine of vitamin-A-deficient chicks and most markedly in the ileal region. After retinyl acetate administration Zn absorption was fully restored in this region of the intestine. A vitamin-A-dependent Zn-binding protein (ZnBP), absent in vitamin-A-deficient chicks is involved in the binding of Zn in the ileal mucosa of chicks (Berzin and Bauman 1987).

Copper

The role of trace minerals in bone metabolism, particularly for Cu, Mn and Zn have been extensively studies in animals (Rucker, Riggins et al. 1975; Opsahl, Zeronian et al. 1982; Strause, Hegenauer et al. 1986; Strause, Saltman et al. 1987; Saltman and Strause 1993). Cu, a cofactor for lysyloxidase, is required in the cross-linking of collagen and elastin (Saltman and Strause 1993). Experiments show biochemical changes in both serum and bone in rats by long-term dietary deficiencies of manganese (Mn) and copper (Cu). In the two deficient groups, increased serum Ca was negatively correlated with bone Ca. This biochemical association may represent alterations in regulatory control of Ca at the level of the bone (decreased mineralization) combined with an increase in bone resorption. The effect of long-term dietary deficiencies in Mn and Cu should be considered in human bone metabolism (Strause, Hegenauer et al. 1986). The most significant mineral interaction with copper is zinc (Davis 1980). Zinc has a strong negative effect on copper bioavailability, zinc intakes slightly above RDA levels induces copper deficiency (Greger, Zaikis et al. 1978; Festa 1985). Therefore, it has been suggested to adjust zinc and copper intake in an RDA amount ratio of 1:1 (Black, Medeiros et al. 1988; Hoffman, Phyliky et al. 1988; Samman and Roberts 1988).

Strontium

The processes of bone resorption and formation are tightly governed by a variety of systemic and local regulatory agents. In addition, minerals and trace elements affect bone formation and resorption through direct or indirect effects on bone cells or bone mineral. Some trace elements closely chemically related to calcium, such as strontium (Sr), have pharmacological effects on bone when present at levels higher than those required for normal cell physiology. Indeed, strontium was found to exert several effects on bone cells. In addition to its antiresorptive activity, strontium was found to have anabolic activity in bone, and this may have significant beneficial effects on bone balance in normal and osteopenic animals. Accordingly, strontium has been thought to have potential interest in the treatment of osteoporosis. Recently, Marie et al. presented an excellent summary for the mechanisms of action of strontium on bone cells, the evidence for its beneficial effects on bone mass in vivo, and its potential therapeutic effects in osteopenic disorders (Marie, Ammann et al. 2001).

Selenium and Iodine

Normal thyroid gland is responsible for the proper function of calcitonin, a calcium-regulating hormone. Several minerals and trace elements are essential for normal thyroid hormone metabolism, e.g., iodine, iron, selenium, and zinc. Coexisting deficiencies of these elements can impair thyroid function. The normal thyroid gland retains high selenium concentrations even under conditions of inadequate selenium supply and expresses many of the known selenocysteine-containing proteins. Among these selenoproteins are the glutathione peroxidase, deiodinase, and thioredoxine reductase families of enzymes. Adequate selenium nutrition supports efficient thyroid hormone synthesis and metabolism and protects the thyroid gland from damage by excessive iodide exposure (Zimmermann and Kohrle 2002). Apart from the essential trace element iodine, which is the central constituent of thyroid hormones, a second essential trace element, selenium, is required for appropriate thyroid hormone synthesis, activation and metabolism. The human thyroid gland has the highest selenium content per gram of tissue among all organs. Several selenocysteine-containing proteins respectively enzymes are functionally expressed in the thyroid, mainly in thyrocytes themselves: the glutathione peroxidases, the type I 5-deiodinase, thioredoxin reductase and selenoprotein P. As thyrocytes produce H_2O_2 continuously throughout life an effective cell defense system against H_2O_2 and reactive oxygen intermediates derived thereof is essential for maintenance of normal thyroid function and protection of the gland (Kohrle 1999). Normal thyroid status is dependent on the presence of many trace elements for both the

synthesis and metabolism of thyroid hormones. Iodine is most important as a component of the hormones, thyroxine and 3,3',5-tri-iodothyronine (T3) and selenium is essential for normal thyroid hormone metabolism being involved with selenium-containing iodothyronine de-iodinases that control the synthesis and degradation of the biologically active thyroid hormone, T3. Additionally, selenoperoxidases and thioredoxin reductase protect the thyroid gland from peroxides produced during the synthesis of hormones. The roles of iron, zinc and copper in the thyroid are less well defined but sub- or supraoptimal dietary intakes of all these elements can adversely affect thyroid hormone metabolism (Miniero, D'Archivio et al. 1998; Arthur and Beckett 1999).

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