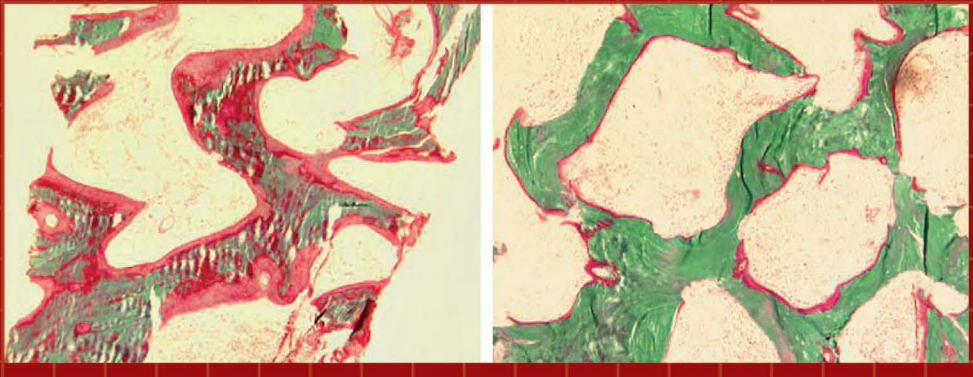
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CLINICAL FOCUS SERIES

# Bone and Mineral Disorders




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CHAPTER 3

# Nutritional Aspects of Calcium and Vitamin D: Global Prospective

*Mohammad S Kuchay, Ambrish Mithal*

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## INTRODUCTION

Nutrition is an important factor in the development and maintenance of bone mass and in the prevention of osteoporosis. The skeleton needs balanced nutrition, containing both macronutrients (protein, fat, and carbohydrate) and micronutrients (vitamins and minerals) for its normal growth and development, and subsequent maintenance. Since calcium and vitamin D has traditionally been considered essential for bone health, epidemiological evidence for the role of calcium and vitamin D in maintenance of bone health and prevention of osteoporosis will be discussed in this chapter.

## CALCIUM FOR BONE HEALTH

Calcium is a principle structural component of bone tissue. About 99% of the body's calcium resides in the skeleton. It is an essential element in diet, but there is continuing debate regarding its optimal level of intake for preserving bone health. The principle role of dietary calcium is ensuring adequate availability of calcium for bone mineral deposition. Bone calcium accrues at a rate of 80–150 mg/day between birth and 10 years of life; this rate reaches to a maximum of 200 mg/day in girls and 270 mg/day in boys during the adolescent growth spurt. At the cessation of growth, the rate of calcium accrual falls gradually to zero. Approximately 90% of the total bone mass is formed by the age of 20. The remaining 10%, which determines the maximum attainable bone mass, is accumulated during the second and third decade. Subsequently, bone mass decreases continually. Thus, the strategies aimed at attainment of maximum peak bone mass and slowing down of subsequent bone loss would help in prevention of osteoporosis.

## CALCIUM FOR CHILDREN AND ADOLESCENT BONE HEALTH

A body of evidence suggests that calcium intake may be more beneficial in growing phase than in adult life. A number of studies carried out in children and adolescents have shown that supplementation with dietary calcium (dairy products, fortified foods) increases the rate of bone mineral accrual compared with unsupplemented groups.[1,2] At the population level, a predicted 10% increase in peak bone mass could mitigate the risk of osteoporotic fractures during adult life by 50%.[3] A review of literature suggests that dietary calcium (especially obtained via dairy products) is beneficial mainly for

younger subjects. In one review, there are four times more positive studies (showing benefit) than neutral or negative ones in subjects <30 years of age, while the ratio is 1:1 in later adulthood.[4] A meta-analysis that included 21 randomized controlled trials (RCTs) showed that an increased intake of dietary calcium, with or without vitamin D, considerably increased bone mineral content (BMC) in children with low baseline intakes.[5] Several cross-sectional studies have confirmed that regular dietary calcium intake during growing phase goes along with higher bone mineral density (BMD) in adulthood and at postmenopausal age.[6,7] Furthermore, low dietary calcium intake in childhood goes along with lower BMD and smaller bones.[8] In National Health and Nutrition Examination Survey study, women with low milk intake during childhood and adolescence had less bone mass in adulthood. They also had an enhanced risk of fracture.[9] In China, where the nutritional calcium intake is usually low (<500 mg/day), supplementing the diet of children with milk powder (providing 1,300 mg elemental calcium) augmented bone mineral accrual.[10] However, the positive effect of 2 years of school milk supplementation[11] was not evident anymore 3 years after withdrawal. This is because the calcium intake had dropped again to presupplementation (low) values.[12] The daily administration of calcium (850 mg) to prepubertal females in Switzerland revealed that the greatest benefits were observed in girls with dietary calcium intakes below a median of 880 mg/day.[13] In a study from India, mean dietary calcium intake was 264 mg/day in rural and 354 mg/day in urban population.[14] A case-control study including young Indian children found that rickets developed when low dietary calcium intake (204 ± 129 mg/day) coexisted with a low or borderline vitamin D nutrition status.[15]

The above evidences are in favor of positive effect of increasing dietary calcium intake on skeletal health in children and adolescents, and particularly in populations who have low calcium intakes. The evidence also suggests that the adequate calcium intake has to be ongoing, as the benefit mitigates once people switch to low calcium diet. This is critical in countries like India, where a recent IOF publication had pegged the average intake at approximately 400 mg/day.[16]

## CALCIUM FOR ADULT BONE HEALTH

In later adulthood, calcium intake seems to bring lesser benefits than in childhood and adolescence. There are a large number of studies looking at the effect of dietary calcium or calcium supplementation on the BMD, especially in postmenopausal women. To see the effect of calcium on BMD in adults, two important meta-analyses are worth discussing. A meta-analysis of 15 trials (1,806 patients) that randomized postmenopausal women to calcium supplementation or usual calcium intake in the diet. The study found calcium to be more effective than placebo in reducing rates of bone loss after two or more years of treatment. The pooled difference in percentage change from baseline was 2.05% for total body BMD, 1.66% for the lumbar spine, 1.64% for the hip, and 1.91% for the distal radius. The analysis also showed a trend towards reduction in vertebral fractures, but not in nonvertebral fractures.[17] Another meta-analysis that included 59 RCTs, showed that increasing calcium intake from dietary sources increased BMD by 0.6–1.8% over 1–2 years at all sites, except the forearm where there was no effect. Calcium supplements on the other hand increased BMD by 0.7–1.8% at all sites and all-time points. In the RCTs of calcium supplements, the increases in BMD were present by 1 year, but there were no further subsequent increases. Thus, the increases from baseline at both two and over two and half years at each site were similar to the increases at 1 year.[18]

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In the recent years, more and more studies have revealed that the benefit of increasing calcium intake (dietary or supplementation) is mainly in people with low dietary calcium intake. The average dietary calcium intake varies greatly around the globe.[19-20] Calcium supplementation has variable effects on BMD depending on the population studied. Daily supplementation with as little as 500 mg of elemental calcium retarded bone loss in perimenopausal Japanese females with low calcium intake.[21] Similar effects of calcium supplementation have been observed in postmenopausal women from Hong Kong,[22,23] Chile,[24] China,[25] Nigeria,[26] and Argentina.[27] On the other hand, calcium supplementation had no consistent effects on BMD in studies of calcium-sufficient populations.[28-30] A study clearly demonstrated these differential effects of calcium supplementation on skeleton. Daily calcium supplementation (500 mg) positively influenced bone mineral in subjects with low calcium intake but not in subjects with higher calcium intake.[31] Evidences from cross-sectional studies also show that the association between BMD and dietary calcium intake varies based on the study population. In countries where the average dietary calcium intake is less than 500 mg/day, there are positive associations between BMD and calcium intake.[32-36] However, this positive association is not found in studies using calcium-replete populations. Calcium intake exceeding the recommended dietary allowance (RDA) did not provide any benefits for hip or lumbar BMD in subjects more than or equal to 50 years of age whose daily calcium intake ranged between 890 and 1,000 mg.[37] These findings indicate that the benefits of calcium supplementation on skeleton vary across the globe and are dependent on the dietary calcium intake of the subjects. Simply speaking, calcium supplementation has greater benefits for people in regions with low dietary calcium intake whereas the benefits may be marginal or absent for people with adequate dietary calcium intake. In India, the average daily dietary calcium intake is approximately 265 and 315 mg/day in rural and urban populations, respectively.[38] It is, therefore, safe to assume that increasing calcium intake (preferably dietary) will benefit the skeleton in Indian population. The influence of calcium on fracture risk is still a matter of debate. Low calcium intake correlates with increased risk of hip fracture but increasing intake above 750 mg/day does not correlate with progressively lower risks of hip fracture.[39,40] According to a meta-analysis, there is no evidence currently that increasing dietary calcium intake prevents fractures.[41] In South Korean adults aged more than or equal to 50 years, a study examined associations of quintiles of calcium intake with BMD within three categories of serum 25(OH)D levels: less than 20, 20–30, and more than 30 ng/mL.[42] Within each category of serum 25(OH)D, higher calcium intake improved BMD of the femoral neck. Within the lower two 25(OH)D categories, calcium intake also improved BMD of the spine. The mean calcium intake of the older adults was 485 mg/day, and the top quintile consumed at least 666 mg/day. The Korean RDA for calcium for adults age more than or equal to 50 years is 700 mg.[43] Over 80% of the older segment of the South Korean population has calcium intake below their RDA. The positive associations of bone mass with calcium intake strongly suggest that a higher calcium intake would improve bone mass in older South Korean adults.

## VITAMIN D FOR BONE HEALTH

An adequate level of vitamin D is essential for an effective intestinal absorption of calcium and for maintenance of normal blood levels of calcium and phosphate, which in turn are essential for bone mineralization. Severe deficiency of vitamin D in growing years of life leads to rickets, a mineralization defect at the growth plate. Severe deficiency of vitamin D leads to mineralization defect in adult bones called osteomalacia. The deficiency of vitamin D, which does not lead to rickets or osteomalacia, is proposed to



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lead to impairment of bone health like low BMD or BMC in both children as well as in adults.

A meta-analysis aimed to assess the efficacy of vitamin D supplementation in healthy children and adolescents. It included six clinical trials involving a total of 343 participants receiving placebo and 541 receiving vitamin D. It showed that supplementation with vitamin D had no significant effect on BMD measured at total hip and forearm, but was effective on bone density at the lumbar-spine, although no significant differences were found between subjects with low and high serum levels of vitamin D. However, there was a trend for a greater effect in patients with lower baseline values.[44] The authors concluded that dietary supplementation with vitamin D might be relevant in children who were deficient, especially with regard to bone density at the lumbar-spine and the total BMC.[45]

Several experts suggest that 20 ng/mL represents a threshold value that should be achieved throughout the year in all individuals. Supplementation with vitamin D in individuals with serum 25(OH)D levels below 20 ng/mL has been demonstrated to lead to improvements in many clinical aspects.[46,47] Thus, the presence of low levels of 25(OH)D is a serious public health problem since majority of the population falls into this category for a few months or for most of the year. The cut-off of 20 ng/mL still represents an important "line of demarcation" between supporters and opponents of vitamin D supplementation.[48] There is no evidence that the levels of serum 25(OH)D above 40 ng/mL provides any additional benefit in any clinical outcome. Therefore, serum 25(OH)D between 20 and 40 ng/dL seems to be a reasonable range for most of people.

An Institute of Medicine report defines vitamin D deficiency as serum 25(OH)D levels less than 20 ng/mL.[49] Australian guidelines recommend serum 25(OH)D levels more than 20 ng/mL at the end of winter, or 24 ng/mL in summer for optimal bone health.[50] To aim for a target level more than 20 ng/mL at the end of winter, most individuals will require between 800 and 2,000 IU vitamin D per day. A recent US Endocrine Society guidelines recommends that all adults aged 50–70 years and more than 70 years of age will require at least 600 and 800 IU of daily vitamin D, respectively.[51] However, to raise the serum level of 25(OH)D above 30 ng/mL, as both the Endocrine Society and the IOF[52] recommend, individuals may require at least 1,500–2,000 IU/day of supplemental vitamin D.[51]

A meta-analysis of 12 RCTs for nonvertebral fractures (n = 42,279) and eight RCTs for hip fractures (n = 40,886) assessed the antifracture efficacy of oral vitamin D supplementation in elderly population. The relative risk for the prevention of nonvertebral fractures was 0.86 [95% confidence interval (CI) 0.77–0.96] and 0.91 (95% CI, 0.78–1.05) for the prevention of hip fractures. However, there was significant heterogeneity for both endpoints. When examining the trials with a high (482–770 IU/day) received dose of vitamin D (that is, dose adjusted for adherence), nonvertebral fractures were reduced by 20% and hip fractures by 18%. It must be noted that daily doses of less than 400 IU did not show any effect.[53]

Data from 11 double blind RCTs of oral vitamin D supplementation (daily, weekly or every 4 months), with or without calcium, were compared with placebo or calcium alone in persons more than or equal to 65 years of age. A total of 31,022 persons (mean age, 76 years; 91% women) with 1,111 incident hip fractures and 3,770 nonvertebral fractures were included. The participants who were randomly assigned to receive vitamin D, as compared with those assigned to control groups, had a nonsignificant 10% reduction in the risk of hip fracture and a significant 7% reduction in the risk of nonvertebral fracture. Fracture risk reduction was shown only at the highest intake level (median, 800 IU daily), with a 30% reduction in the risk of hip fracture and a 14% reduction in the risk of any nonvertebral fracture.[54] Another meta-analysis of 23 studies evaluated effect of vitamin

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D supplementation on BMD. The average study was approximately 23.5 months and 92% of the patients were women. In fifteen of the studies, the mean baseline vitamin D level was over 20 ng/mL. The meta-analysis did not show an effect of vitamin D supplements on BMD.[55]

Most guidelines do not recommend very high dose of vitamin D supplementation. Two trials have shown that very high annual doses of either intramuscular ergocalciferol (300,000 IU) or oral cholecalciferol (500,000 IU) resulted in an increase in falls and/or fractures in elderly postmenopausal women compared with placebo.[56]

There is little evidence that vitamin D alone has beneficial effects on BMD. Treatment with the combination of calcium and vitamin D either prevents bone loss or results in small increases in BMD. For long-term maintenance of BMD up to 5 years, the combination of calcium and vitamin D appears to be better.

Like in the case of calcium, vitamin D supplementation seems to improve BMD and reduce fracture risk only in deficient populations—those with low baseline serum levels of 25(OH)D.

Overall, calcium and vitamin D play a critical role in bone health. Deficiency of these key components can lead to rickets in children and render the bone osteomalacic or osteoporotic in adults. Benefits of supplementation with calcium and vitamin D are seen in populations that are deficient in these key bone nutrients.

Interventional Studies for Osteoporosis are summarized in Appendix 1.

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