

Calcium and Vitamin D Supplementations: 2015 Position Statement of the Korean Society for Bone and Mineral Research

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Calcium and vitamin D are essential components for bone health, thus calcium and vitamin D supplementation is an important strategy in the management of osteoporosis. However, the benefit of calcium and vitamin D supplementation on bone health is still controversial. Moreover, potentially harmful effects of excessive calcium supplementation on cardiovascular health are recently suggested. Too high a level of vitamin D has been also reported to have several, possibly related, harmful events. Korea is well known for low dietary calcium intake and vitamin D deficiency in its population. This position statement developed the following recommendation for adequate levels of calcium and vitamin D intake in Korean, postmenopausal women and men older than 50 years: Adequate calcium intake and optimal vitamin D level are essential for preventing and treating osteoporosis in postmenopausal women and men older than 50 years. We recommend a daily calcium intake of 800 to 1,000 mg/day. Food remains the best source of calcium; however calcium supplements should be considered when dietary intake of calcium is inadequate. We recommend dietary vitamin D intake of more than 800 IU per day, a level which appears to reduce the risk of fractures. When vitamin D deficiency is suspected, serum 25-hydroxy-vitamin D (25-[OH]D) level should be tested. We suggest that a serum 25-(OH)D level greater than 20 ng/mL is generally appropriate for prevention of osteoporosis. However, a serum 25-(OH)D level greater than 30 ng/mL is probably helpful for management of osteoporosis and prevention of fractures.

Key Words: Bone, Calcium, Cardiovascular diseases, Fractures, Osteoporosis, Vitamin D

INTRODUCTION

Calcium is an essential component of bone mineral and thus, adequate calcium intake is considered important for skeletal health.[1] Based on the biologic roles of calcium, the positive relationships between calcium intake and bone density or bone quality have been validated in several epidemiologic studies.[2,3] Therefore, encouraging adequate calcium intake, or use of calcium supplements, has become a fundamental strategy in the treatment or prevention of osteoporosis.[4] However, there are still some controversies about the beneficial effects of calcium sup-

plementation on bone health.[5,6] Detrimental effects of calcium supplementation have been suggested recently by several large epidemiologic studies, especially in regard to increased risks of cardiovascular diseases (CVDs).[7-9] Conversely, low dietary calcium intake has also been proposed to be related to an increased risk of cardiovascular events or mortality.[10] Asian populations tend to have low dietary calcium intake with a mean dietary calcium intake in people older than 50 years of about 470 mg/day, which is much lower than that of comparable Western populations.[11] However, most of the epidemiologic studies have been conducted in Western countries and evidence about Asian populations is scarce.

Vitamin D is also well known for its critical role in bone and mineral metabolism. It facilitates the intestinal absorption of calcium and phosphate, thereby making these materials available for bone mineralization. Vitamin D has also been shown to have a direct effect on bone cells.[12] Accordingly, low vitamin D status is clinically associated with osteoporosis and fractures, and vitamin D deficiency can lead to bone mineralization defects such as rickets and osteomalacia. Therefore, maintaining adequate vitamin D status is an essential prerequisite for skeletal health. Meanwhile, there is growing interest in the potential preventive role of vitamin D in nonskeletal disorders, including CVDs, diabetes mellitus, cancers, infections, and autoimmune diseases.[13-19] However, clinical evidence for a nonskeletal role of vitamin D is still limited, and few clinical trials have demonstrated an effect of vitamin D on nonskeletal health conditions. Therefore, it seems reasonable that optimal serum 25-hydroxy-vitamin D (25-[OH]D) level or adequate vitamin D intake should be established based on the beneficial effects of vitamin D on skeletal health. Unfortunately, however, optimal 25-(OH)D level has not been clearly established. Moreover, an individual's 25-(OH)D level may vary due to genetic, environmental, and behavioral factors including skin pigmentation, air pollution, indoor lifestyle, sunscreen use, and dietary habits. These factors contribute to huge variations in mean 25-(OH)D levels in different geographic populations. Therefore, recommendations for adequate vitamin D intake required for skeletal health should be established for each geographic area. Although there is no universal consensus on the criteria for vitamin D deficiency, South Korea has the highest level of vitamin D deficiency in the world.[20,21] National surveys showed that

South Korea has a lower mean 25-(OH)D level (21.2 ng/mL in men and 18.2 ng/mL in women) and a higher prevalence of vitamin D deficiency (47.3% of men and 64.5% of women have serum 25-(OH)D levels less than 20 ng/mL, 86.8% of men and 93.3% of women have serum 25-(OH)D levels less than 30 ng/mL) than are found in the U.S. and Canada.[20,22] In addition, vitamin D deficiency is not only prevalent in the elderly, but also in the younger Korean population.[22]

Considering the importance of calcium and vitamin D supplementation in the management of osteoporosis in Korean men older than 50 years and in postmenopausal women, the Korean Society for Bone and Mineral Research has developed recommendations for calcium and vitamin D intake, and for adequate levels of those components in this segment of the Korean adult population.

1. Calcium

1) Efficacy of calcium supplements

Although the importance of adequate calcium intake or calcium supplements in management of osteoporosis has been emphasized for a long time, there is little information about the efficacy of calcium supplements in preventing bone fractures in the Korean population. A limited number of studies have strongly suggested a significant association between a decreased risk of osteoporosis and a higher calcium intake by Korean individuals.[23,24] The calcium intake level positively correlated with bone mineral density (BMD) values in all skeletal sites. Osteoporosis groups showed a significantly lower level of calcium intake (440 mg/day) compared to the normal group (596 mg/day).[25] Moreover, an increasing association between calcium intake and BMD was observed up to the level of 800 to 1,200 mg/day in dietary calcium intake.[26,27] There are also several data available from other Asian countries about the beneficial effects of calcium intake on bone health. Because biological and environmental characteristics among Asian populations are similar, these data could have meaningful implications for Korean populations. The preventive effects of calcium on bone loss have been demonstrated both in short-term and long-term studies in Chinese or Japanese women.[28,29]

Based on the above significant findings from clinical studies in Korea or other Asian countries, we cautiously conclude that the level of calcium intake has significant associations

with BMD values or risk of osteoporosis, therefore adequate calcium intake should be a fundamental strategy in management of osteoporosis. However, the beneficial effects of calcium at a level of 800 to 1,200 mg/day were only recently observed, and we could not confirm whether a higher level would be even more beneficial on bone health or not.

2) Safety issue about calcium

Beyond calcium's beneficial effects on the bone health, increasing attention is focused on the potentially harmful effects of excessive calcium supplementation on human health, especially those related to risk of CVD.[7-9] Several recent epidemiologic or meta-analysis studies have raised the issue about the increased risk of cardiovascular events with a higher calcium intake after the report from Auckland Calcium study.[8,9] In the Swedish Mammography Study of a population-based cohort including 61,433 women, dietary calcium intakes greater than 1,400 mg/day were associated with a higher all-cause and cardiovascular mortality compared with intakes of 600 to 1,000 mg/day. In the meta-analysis data including 11 prospective studies, cardiovascular mortality started to increase at a daily dietary calcium intake level above 1,200 mg.[30] In the data from National Institutes of Health-AARP Diet and Health Study, a prospective cohort study including 388,229 men and women older than 50 years, total CVD mortality had a U-shaped association with total calcium intake in men, with increased total CVD mortality observed at calcium intakes of 1,500 mg/day and higher.[31]

On the other hand, several observational studies have reported the lack of association or even an inverse association between calcium intake level and risk of CVDs or mortality, indicating that higher levels of calcium intake might be associated with the reduction of CVD or mortality: From the Women's Health Initiative randomized trial of calcium plus vitamin D supplementation, it was reported that calcium and vitamin D supplements neither increased nor decreased coronary or cerebrovascular risk in postmenopausal women over a 7-year use period.[32] In the Iowa Women's Health Study which included more than 30,000 postmenopausal women, high dietary or supplemental calcium intake was associated with lower ischemic heart disease mortality.[33] Moreover, the studies which have suggested increased risk of CVDs or mortality with higher level of calcium intake also showed the increasing tenden-

cy or significant increase of those events with lower calcium intake.[7] Regarding these beneficial effects of calcium on the occurrence of CVDs, several potential biological mechanisms have been proposed including improvements in the lipid profile or reduction in blood pressure.[34]

3) Adequate level of calcium intake

Regarding bone health status, we observed strong positive associations between calcium intake level and BMD in several clinical studies. The average dietary calcium intake in South Korea and other Asian countries is just around 300 to 500 mg/day.[11] In calcium balance study conducted in elderly Japanese people who had very similar anthropometric profiles with comparable Korean population, the recommended dietary allowance (RDA) for calcium was suggested as 842 mg/day for men and 946 mg/day for women.[35] Moreover, data from Caucasian populations, neutral calcium balance was observed between 507 to 1,035 mg/day.[36] In terms of health risks in calcium intake, the evidence for calcium supplementation being causally related to the risk of cardiovascular events appears to be inconclusive. However, several studies have proposed that higher level of calcium intake related with the increased risk of CVDs or mortality at the level of higher than 1,200 mg/day,[30] 1,400 mg/day [7] or 1,500 mg/day,[31] respectively. Unfortunately, there is no clear evidence about which calcium intake level might have harmful negative effects on the occurrence of CVDs in Korea. On the basis of clinical data from Korea and Asian countries and calcium balance studies conducted in Japanese and Caucasian, we carefully conclude that a daily calcium intake level up to 800 to 1,000 mg might be beneficial for bone health in Korean adults without risk to cardiovascular health. However, further longitudinal studies are needed to address both risk and benefit issues of calcium intake in Korean populations with low dietary calcium intake.

2. Vitamin D

1) Optimal level of 25-(OH)D

Although efforts have been made to define the optimal level of 25-(OH)D, there is still controversy over the adequate level of vitamin D required for skeletal health. In a study based on histomorphometric analysis of iliac crest bone biopsies in 675 autopsy cases, osteomalacia was found in approximately 24% of total cases. However, no cases of

osteomalacia were found in those with serum 25-(OH)D levels above 30 ng/mL and only 3.5% of those with serum 25-(OH)D levels between 20 and 30 ng/mL had histomorphometrically defined osteomalacia.[37] The optimal 25-(OH)D level was also estimated based on large population-based surveys or cohort studies that investigated the association between serum 25-(OH)D levels and skeletal health outcomes. In a cross-sectional study based on the Korean adult population, the association between 25-(OH)D levels and BMD and proximal femur bone geometry was examined.[38] In this study, there was a positive relationship between serum 25-(OH)D levels and BMD and proximal femur geometric properties until serum 25-(OH)D level reached 20 to 30 ng/mL. However, there were no significant differences in these parameters between the groups with 20 to 30 ng/mL and more than 30 ng/mL of serum 25-(OH)D level, suggesting that a serum 25-(OH)D level greater than 20 ng/mL is generally appropriate for skeletal health in Korean adults. Likewise, a number of studies suggest a serum 25-(OH)D level of 16 to 20 ng/mL or greater as the optimal level in the general adult population.[39-41] The Longitudinal Aging Study of Amsterdam, a cohort study in the Netherlands, showed that a threshold level of serum 25-(OH)D for peak BMD appeared to exist at serum 25-(OH)D levels of approximately 20 ng/mL.[39] This study also showed that bone turnover markers such as serum osteocalcin and urinary deoxypyridinoline decreased steeply until serum 25-(OH)D levels reached approximately 16 ng/mL, followed by a plateau, suggesting an increased bone turnover at serum 25-(OH)D levels below 16 ng/mL. The Uppsala Longitudinal Study of Adult Men, a population-based cohort study in Sweden, investigated the association between baseline 25-(OH)D levels and fracture risk for a median of 11 years.[40] This study showed that men with serum 25-(OH)D levels below 16 ng/mL had a greater risk of fracture compared to those with levels above 16 ng/mL. On the other hand, some other studies showed results inconsistent with the aforementioned studies and suggested that the optimal serum 25-(OH)D concentration was above 30 ng/mL. A meta-analysis based on 12 randomized controlled trials (RCTs) on non-vertebral fracture risk and eight RCTs on fall risk showed that optimal fracture and fall prevention occurred with achieved mean serum 25-(OH)D levels of approximately 30 to 44 ng/mL.[42] Therefore, a serum 25-(OH)D level of 30 ng/mL or greater may be needed

for those who are vulnerable to fractures and falls. More information in various populations with different skeletal health conditions is necessary before we reach a definite conclusion.

2) Adequate intake of vitamin D

Determining adequate intake of vitamin D is somewhat more complicated because vitamin D in the body comes not only from dietary sources but also from cutaneous synthesis in response to sunlight. Due to the heavily indoor lifestyle of modern society, it is difficult to get adequate sunlight exposure for sufficient vitamin D production. Therefore, dietary sources of vitamin D such as dairy products and fish may play more important roles in maintaining people's vitamin D status in modern society. Studies assessing the effect of vitamin D on fracture and fall risk reduction indicate that vitamin D, combined with calcium, can reduce the risk of fractures and falls, but vitamin D alone may be ineffective.[41,42] Regarding the effective doses for preventing fractures, a meta-analysis of RCTs that used calcium, or calcium in combination with vitamin D in the preventive treatment of osteoporosis in people aged 50 years or older recommended minimum doses of 1,200 mg of calcium, and 800 IU of vitamin D for the best therapeutic effect.[43] A pooled analysis that included RCTs of oral vitamin D supplements with or without calcium, as compared with a placebo or calcium alone in persons 65 years of age or older showed that a daily vitamin D supplement of more than 800 IU was somewhat favorable in the prevention of hip fracture and any nonvertebral fracture.[44] Unfortunately, we could not find a well-designed clinical trial that assessed the effective dose of vitamin D on fractures in Koreans.

3) Safety of vitamin D

High intakes of vitamin D can cause toxicity through hypercalcemia, although it is rarely seen unless the vitamin D dose is very high.[45] Less severe symptoms may include hypercalciuria and renal stones. The Women's Health Initiative study showed an increased incidence of urinary tract stones in those who were taking vitamin D with calcium supplements.[46] However, there is no strong evidence that treating vitamin D deficiency with vitamin D alone will increase the risk of urinary tract stones. Recently, some observational cohort studies have shown a reverse-J-shaped

curve for the relationship between mortality and serum 25-(OH)D level with the lowest mortality risk at a serum level of 20 to 24 ng/mL.[47,48] All-cause or CVD mortality increased in both lower and higher serum levels of 25-(OH)D in those studies. However, recent meta-analyses showed that overall mortality is not increased by vitamin D, but is even decreased by vitamin D₃. [49,50]

CONCLUSION

This is the 2015 Position Statement of the Korean Society for Bone and Mineral Research for calcium and vitamin D supplementations in Korean adults, especially for postmenopausal women and men older than 50 years.

1. Adequate calcium intake and maintenance of an optimal vitamin D level are essential for preventing and treating osteoporosis in postmenopausal women and men older than 50 years.

2. We recommend daily calcium intake of 800 to 1,000 mg per day which shows positive associations with BMD. Food remains the best source of calcium, however use of supplements should be considered when adequate dietary intake of calcium cannot be achieved.

3. We recommend dietary vitamin D intake of more than 800 IU per day, which appears to reduce the risk of fractures.

4. When vitamin D deficiency is suspected, serum 25-(OH)D level should be tested.

5. We suggest a serum 25-(OH)D level greater than 20 ng/mL is generally appropriate for prevention of osteoporosis. However, a serum 25-(OH)D level greater than 30 ng/mL is probably helpful for management of osteoporosis and prevention of fractures and falls.

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