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Postmenopausal Osteoporosis Treatment and Risk of Urinary Calculus Development

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Osteoporosis is a chronic progressive bone disease in which bone resorption exceeds bone formation, leading to a reduction in bone mineral density and disruption of bone micro-architecture. It becomes a serious health threat for postmenopausal women by predisposing them to an increased risk of fracture. Osteoporotic fractures are associated with substantial morbidity and mortality, especially in elderly women. The incidence of osteoporosis increases with age and occurs most frequently in this group, because the decrease in ovarian estrogen associated with the menopause accelerates bone loss and increases bone remodeling.[1] The evaluation of postmenopausal women for osteoporosis risk requires a medical history, physical examination, and diagnostic tests. Major risk factors for postmenopausal osteoporosis include advanced age, genetics, lifestyle factors (such as low calcium and vitamin D intake and smoking), and thinness. The most common risk factors for osteoporotic fracture are advanced age, low bone mineral density, and previous fracture as an adult. Management of osteoporosis focuses first on nonpharmacologic measures, such as a a balanced diet, adequate calcium and vitamin D intake, adequate exercise, smoking cessation, avoidance of excessive alcohol intake, fall prevention, and pharmacologic interventions.[2]

In this issue of the *Iranian Journal Of Kidney Diseases*, Haghighi and colleagues[3] show that calcium and vitamin D replacement has no risk for kidney stone formation through evaluating 53 postmenopausal women followed up for 1 year. There is a threshold between low circulating levels of 25-hydroxyvitamin D and increased secretion of parathyroid hormone (PTH), which induces bone loss in the elderly through increased bone resorption.[2,4] Published studies estimate the level of circulating 25-hydroxyvitamin D required to maintain normal levels of PTH ranges between 30 nmol/L and 100 nmol/L.[5] In a study of 8532 postmenopausal osteoporotic European women, 79.6% were found to have vitamin D insufficiency where the serum 25-hydroxyvitamin D threshold was considered to be 80 nmol/L, and 32.1% if the threshold was set at 50 nmol/L.[6] After discussion of current evidence, it was agreed that 80 nmol/L may be an overestimate and that 50 nmol/L to 80 nmol/L (20 ng/mL to 32 ng/mL) was a more conservative and acceptable threshold. The majority of studies that have investigated the effects of combined calcium and vitamin D in postmenopausal women have shown a reduction in fracture risk, providing that sufficient patient adherence to treatment (75% to 80%) was reached.[7]

Dietary intake of calcium and vitamin D generally

falls in the elderly. In addition, endogenous production of vitamin D decreases due to a combination of decreasing exposure to sunlight and age-related changes in the dermis, which diminish the capacity for cutaneous synthesis of vitamin D. Intestinal absorption and renal tubular re-absorption of calcium both decrease with age, as does the ability to adapt to a low calcium diet.[8,9] Meta-analysis of data from 9 randomized controlled trials, including a total of 53 260 patients, found that when the effects of supplementation with vitamin D alone were explored (in a total of 9038 patients), this was not sufficient to significantly reduce the risk of hip fracture in postmenopausal women. However, the same study found that combined supplementation with vitamin D and calcium reduced the risk of hip fracture by 25%. The recommended dose was in the range of 800 IU of vitamin D and 1000 mg to 1200 mg of calcium daily.[2]

National osteoporosis foundation recommends that postmenopausal women obtain 800 IU to 1000 IU of vitamin D daily.[10] Vitamin D is produced from the interaction of ultraviolet rays from sunlight with 7-dehydrocholesterol in the skin. Unprotected exposure of the skin to sunlight is not recommended as a means of addressing vitamin D deficiency.[11] In addition, age, geographic location, time of the day, and season all affect the skin production of vitamin D. Dietary sources of vitamin D are limited to fortified dairy products and fatty fish. Therefore, the use of a supplement containing vitamin D is the most practical means of addressing vitamin D insufficiency. A high prevalence of vitamin D insufficiency has been found in young adults with seemingly adequate sun exposure as well as in postmenopausal women receiving treatment for osteoporosis. The national Academy of Science has established the upper limit of a safe intake for vitamin D as 2000 IU/d.[12,13] However, many authorities consider this amount to be overly conservative. Doses greater than 10 000 IU/d may be associated with risks of hypercalciuria and hypercalcemia. A meta-analysis of 12 randomized clinical trials in postmenopausal women (mean age, 71 to 85 years) found that the higher vitamin D dose of 700 IU/d to 800 IU/d was associated with significant reductions in the risk of both hip and nonvertebral fractures, whereas no risk reduction was seen in trials or cohorts using a dose of 400 IU vitamin D. In the Women Health Initiative,[14] although no reduction in hip fracture risk from vitamin D and calcium supplementation was seen in the entire cohort, when the analysis was restricted to adherent women, there was a significant reduction in hip fracture risk with 400 IU of vitamin D and 1000 mg of elemental calcium per day. Vitamin D supplementation also has been found to improve muscle strength and balance and risk of falling.[15]

Twenty-two vitamin D trials reported data on adverse events; 19 included adult populations only. Daily doses ranged from 400 IU/d to 4000 IU/d of vitamin D3 (19 trials) and from 5000 IU to 10 000 IU of vitamin D2 (2 trials). Biochemical abnormalities, such as hypercalcemia and hypercalciuria, were the most frequently reported adverse events. Although more of these events occurred in vitamin D groups, the difference in the rates of these events between vitamin D and placebo groups was not significant, and the events were not associated with clinical symptoms. Seven trials reported kidney calculus incidence; 5 of these trials reported no cases, and in the Women Health Initiative, they reported an absolute increase of 17% in kidney calculi in women taking 400 IU vitamin D3 in combination with 1000 mg of calcium daily compared with women taking calcium only. Overall, there is fair evidence from the trials that adults tolerated vitamin D at doses above current dietary reference intake levels, although we had no data on the association between long-term harms and higher doses of vitamin D. In the trial published in this issue,[3] vitamin D3 dose was 400 IU which is the lowest dose in all trials, and there is no expectation for increasing the risk of urinary calculi.

The situation regarding an acceptable threshold for dietary calcium intake is far less clear, and recommendations range from 400 mg/d to 1500 mg/d. The calcium dose based on elemental calcium as in 500 mg of calcium carbonate there is 200 mg elemental calcium. Evidence has established the role of adequate calcium intake in bone health, primarily in the development of peak bone mass and in preventing bone loss. The evidence for calcium ability to reduce fracture risk is not as strong. However, in a 5-year double-blinded placebo-controlled trial of postmenopausal women with a mean age of 75 years, the 830 women who were compliant with their calcium supplements had a

significant reduction in the hazard ratio for fracture of 0.66.[16] Data suggest that daily calcium intake tends to decline with advancing age. Additionally, intestinal transport studies suggest that intestinal absorption of calcium is less in older women than the young. Vitamin D deficiency, now recognized as exceedingly widespread, will contribute as well to declining calcium absorption.[17] Renal insufficiency may result in 1,25-dihydroxyvitamin D deficiency quite independently of inadequate sun exposure or vitamin D intake. Estrogen deficiency also appears to result in an increase in urinary calcium excretion.[18] This combination of circumstances necessitates an increase in the daily calcium intake in women over age 50 years and in the setting of estrogen deficiency.

Most postmenopausal women consume a diet that is approximately 500 mg less than the recommended 1200 mg/d. No single laboratory test can accurately detect calcium deficiency. However, a 24-hour urine calcium level of less than 50 mg suggests either insufficient intake or poor absorption. Calcium supplements and calcium fortified foods are additional sources of calcium for women unable to consume sufficient dietary calcium; most women will need an additional 600 mg/d to 900 mg/d over their usual daily intake to reach the recommended levels. Calcium supplements are available in a variety of different calcium salts, such as calcium carbonate or calcium citrate. Calcium citrate supplements are well absorbed when taken with meals or on an empty stomach; calcium carbonate is better absorbed when taken with food. In addition, oxalate excretion decreases when calcium supplement binds with food rich in oxalate. It will be the best to take calcium in divided doses for better absorption.

Total calcium intakes of up to 1500 mg/d do not appear to increase the risk of developing urinary calculi and may actually reduce it.[19,20] Calcium supplements are contraindicated in a woman with calcium containing kidney calculus until her urinary biochemical profile has been assessed. The upper limit of tolerable intake for calcium for adults is 2500 mg/d. A new study presented at the Endocrine Society's 94th Annual Meeting reveals that calcium and vitamin D supplements are linked to high levels of calcium in the blood and urine, which could raise the risk of developing kidney calculi.[21] In this study, they included163 healthy, postmenopausal women aged between 57 and 85 years and at some point during the study period about 33% of the participants (n = 48) developed high levels of calcium in their urine. Overall, the researchers noted 88 episodes of high urinary calcium. Earlier studies provided evidence that high calcium levels in the urine are linked to an elevated risk of kidney calculi. However, there were no incidents of kidney calculi during the 1-year study period. It is true that the follow-up is too short; however, it is possible that long-term use of supplements causes hypercalciuria and hypercalcemia, and this can contribute to kidney calculi. For these reasons, it is important to monitor blood and urine calcium levels in people who take these supplements on a long-term basis. This point is usually will not be taken by physician and rarely done in clinical practice.[21]

Overall, urinary calculi have been linked to a high calcium intake, but this appears to depend on the source and dose of calcium. Several prospective studies reported that a diet high in calcium is associated with a reduced risk of kidney calculi, possibly by reducing intestinal absorption of oxalate, which is one of the main components of kidney calculi.[22,23] In the current trial,[3] a total of 400 mg elemental calcium was used, which was far from recommended dose and we do not expect kidney calculi in short time. If we consider following the required tests for adverse effect of calcium and vitamin D supplementation, we can prevent kidney calculi and monitor the dose for reducing risk of further deteriorating osteoporosis and fractures.

CONFLICT OF INTEREST

None declared.

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Immunoglobulin M Nephropathy
Not Uncommon But Still a Controversial Entity

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Analogous to the prominent or co-dominant deposits of Immunoglobulin (Ig) A in the mesangial region encountered in IgA nephropathy (IgAN),[1,2] investigators have also described a morphologic lesion, characterized by sole or dominant diffuse and generalized distribution of granular IgM deposits within the mesangium, and termed it *IgM nephropathy* (IgMN).[3-7] However, despite the