International Journal of Gerontology 8 (2014) 183–188

Contents lists available at ScienceDirect

International Journal of Gerontology

journal homepage: www.ijge-online.com

Review Article

Calcium and Vitamin D Supplementation on Bone Health: Current Evidence and Recommendations☆

Li-Ru Chen [1, 2], Yu-Tang Wen [2], Chih-Lin Kuo [1], Kuo-Hu Chen [3, 4 *]

[1] Department of Physical Medicine and Rehabilitation, Mackay Memorial Hospital, Taipei, [2] Department of Mechanical Engineering, National Chiao-Tung University, [3] Department of Obstetrics and Gynecology, Taipei Tzu-Chi Hospital, The Buddhist Tzu-Chi Medical Foundation, Taipei, [4] School of Medicine, Tzu-Chi University, Hualien, Taiwan

ARTICLE INFO

Article history:
Received 11 February 2014
Received in revised form
14 March 2014
Accepted 25 June 2014
Available online 14 November 2014

Keywords:
calcium,
cancer,
fracture,
myocardial infarction,
vitamin D

SUMMARY

Population aging and osteoporosis are global public health challenges. Osteoporosis markedly increases the risk of fractures, and further morbidity and mortality. Calcium is a major constituent of the bone and vitamin D helps maintain calcium homeostasis. Calcium and vitamin D supplements have long been recognized as the cornerstones for prevention and management of osteoporosis and fractures. Although the associations between calcium and vitamin D supplementation and bone mineral density, fracture prevention, and potential adverse outcomes from available evidence are inconsistent, the Institute of Medicine Committee and the American Geriatrics Society support a key role of calcium and vitamin D in skeletal health. There is insufficient evidence to conclude that calcium with or without vitamin D supplementation increases the risk of cardiovascular events and cancer. Older adults should obtain at least 1000 IU/day of vitamin D with 1000–1200 mg/day of calcium to reduce the risk of fractures. The actual supplementation levels of calcium and vitamin D should be advised individually to specific patient or situation.

1. Introduction

Population aging is a phenomenon that occurs worldwide. With aging, a gradual loss of bone mass results in osteopenia and osteoporosis. Osteoporosis, falling, and related fragile fracture have been identified as being a serious public health issue. The cumulative lifetime fracture risk for a 50-year woman with osteoporosis is as high as 60%[1]. For elderly people in residential care facilities or nursing homes, the annual risk of fall is > 50%[2]. The most common sites of osteoporotic fracture are the hip, humerus, wrist, and spine[3]. Among these fractures, hip fracture is life-threatening[4]. Approximately 5–20% of these patients die within 1 year, and 50% of survivors have difficulties performing daily activities and, thus, need extra care[5]. The direct medical expenditure for nonfatal fall-related fractures is approximately $12 billion in 2013[6]. Many elders who fall have high incidence of recurrent falls[7]. They will develop a fear of fall and tend to limit their activities, resulting in reduced mobility and loss of physical fitness and bone mass.

Effective prevention of osteoporotic fracture needs comprehensive management, including healthy lifestyle, regular exercise, adequate nutrition, safe living environment, and reducing medication dosage. Calcium and vitamin D supplements have long been recognized as the cornerstones for prevention and management of osteoporosis and fractures. Calcium is a major constituent of bone. It would make sense that calcium supplementation or the consumption of calcium-rich foods was helpful in maximizing peak bone mass, retaining acquired bone mass, and thus reducing the risk of osteoporosis. A recent study has shown that women took calcium supplements for about half of their daily calcium requirement to meet the National Academy of Sciences guidelines, some even exceeding daily recommended intakes[8].

Vitamin D, a group of hormones rather than vitamins, is majorly synthesized in the skin during exposure to UV B and less absorbed from the diet. 25-hydroxyvitamin D [25(OH)D], the major circulating and storage metabolite, is viewed as the most useful maker to

☆ Conflicts of interest: The authors certify that all affiliations with or financial involvement in, within the past 5 years and foreseeable future, any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript are completely disclosed (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, royalties). The authors also certify that we have no financial interests related to the material in the manuscript.

* Correspondence to: Professor Kuo-Hu Chen, Department of Obstetrics and Gynecology, Taipei Tzu-Chi Hospital, The Buddhist Tzu-Chi Medical Foundation, No. 289, Jianguo Road, Xindian Section, New Taipei City, Taiwan.
E-mail address: alexgfctw@yahoo.com.tw (K.-H. Chen).

http://dx.doi.org/10.1016/j.ijge.2014.06.001

determine overall vitamin D status. 1,25-dihydroxyvitamin D [1,25(OH)$_2$D], the biologically active metabolite, enhances intestinal calcium absorption and interacts with the parathyroid hormone to help maintain calcium homeostasis between the blood and bones (Fig. 1). 1,25(OH)$_2$D also affects neuromuscular and immune function. The Institute of Medicine Committee, an American non-governmental organization established in 1970, examined the totality of the available evidence and concluded that calcium absorption reaches near maximum at serum 25OHD levels of 8–20 ng/mL[9].

Beyond the role of calcium and vitamin D supplements in maintaining bone health, emerging evidence suggests that calcium with or without vitamin D supplementation might have potential adverse effects in the general population, such as cardiovascular events[10–15], sudden death, cancer, or urinary tract stone[16–18]. Although several studies showed a reduction in cancer incidence for those taking vitamin D or vitamin D plus calcium[12,18–22], the evidence is insufficient to make a conclusion about the benefits or harms of vitamin D or vitamin D plus calcium supplementation for cancer prevention[18,23]. The inconsistent results of studies and meta-analysis of calcium and vitamin D supplements and risk of cardiovascular events raised the question as to whether the cardiovascular adverse effect is large enough to abrogate the beneficial effects on fractures. In this article, we review current evidence of calcium and vitamin D supplements on bone health and possible adverse outcomes to encourage clinicians to think of the benefits and possible adverse effects prior to advising calcium and vitamin D supplementation for the prevention of osteoporotic fracture.

2. Recent evidence of effect of calcium and vitamin D supplements on bone health

Because the primary goal of the calcium and vitamin D supplementation is the prevention of osteoporotic fracture, the

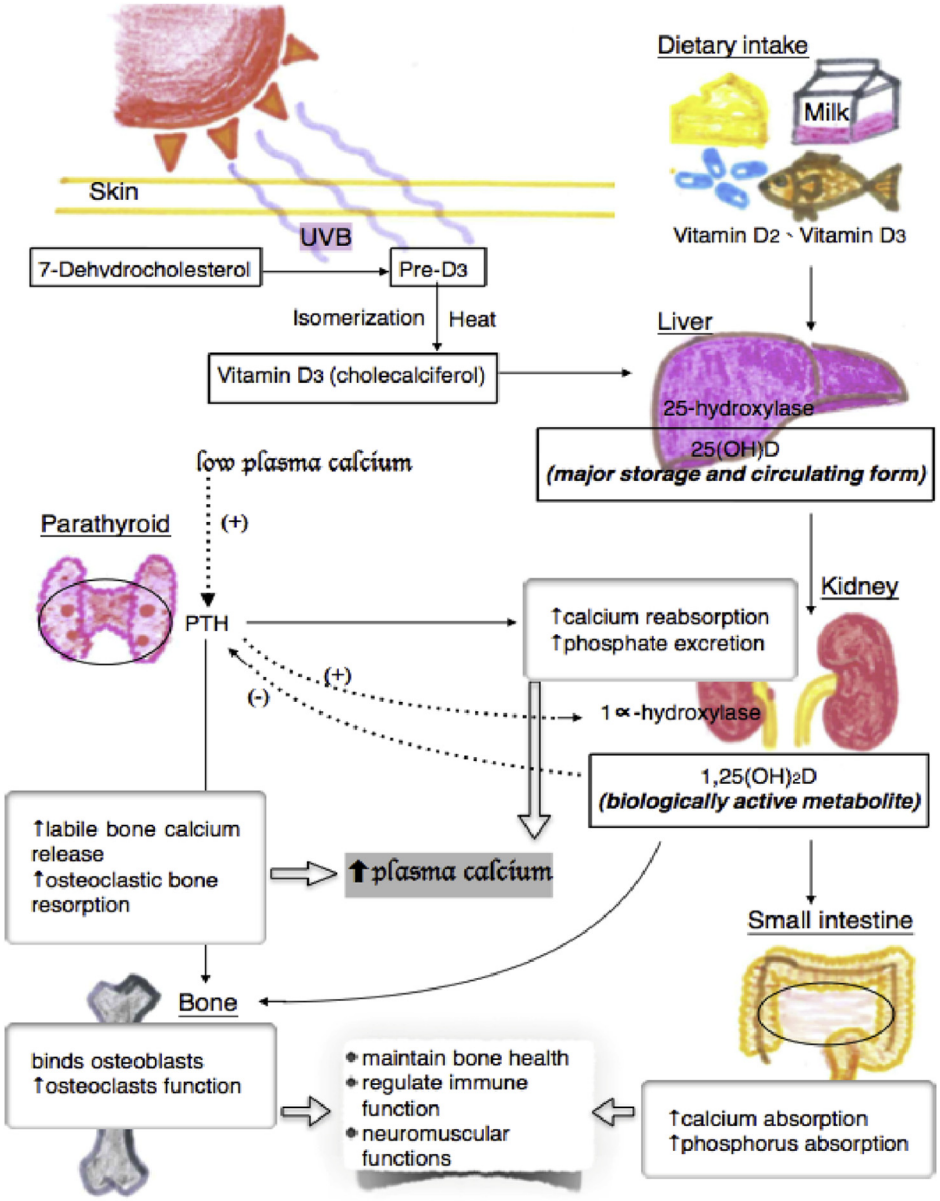

Fig. 1. Schematic diagram of synthesis of vitamin D and regulation of calcium homeostasis. Vitamin D is majorly synthesized in the skin during exposure to UV radiation and less absorbed from the diet. 25-hydroxyvitamin D [25(OH)D], the major circulating and storage form of vitamin D, is converted in the liver. The biologically active form of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)$_2$D], is generated in the kidney. 1,25(OH)$_2$D increases the efficiency of intestinal calcium absorption and has been shown to have antiproliferative effects on parathyroid cells to help maintain calcium homeostasis between the blood and bones. PTH = parathyroid hormone.

effectiveness of interventions should best be measured using fracture outcomes. Although few review articles have reported that taking vitamin D alone is unlikely to prevent fracture and vitamin D plus calcium did appear to reduce risk of hip fractures among institutionalized adults[24,25], most trials and meta-analysis of vitamin D with or without calcium supplement showed statistically significant reduction in fractures. Vitamin D doses of 400 IU and lower did not show antifracture efficacy. There was a dose–response relationship between supplemental vitamin D and fracture reduction[26]. Oral vitamin D dose of 700–800 IU/day, alone or in combination with calcium supplementation, reduced the risk of hip fracture [$n = 5572$; pooled relative risk (RR) 0.74; 95% confidence interval (CI) 0.61–0.88) and any nonvertebral fracture ($n = 6098$; pooled RR 0.77; 95% CI 0.68–0.87) in ambulatory or institutionalized elderly persons (age $\geq$ 60 years)[27]. For higher doses of vitamin D (median, 800 IU daily; range, 792–2000; $n = 3966$ individuals), the reduction rate was 30% [hazard ratio (HR) 0.70; 95% CI 0.58–0.86; $p < 0.001$) for hip fractures and 14% (HR 0.86; 95% CI 0.76–0.96; $p = 0.007$) for nonvertebral fractures. The effect was independent of age, sex, additional calcium intake, and type of dwelling[28]. However, extremely high doses of vitamin D were not consistently associated with greater benefits and might led to potential adverse effects. An annual intramuscular injection of 300,000 IU vitamin D_2 was ineffective in reducing nonvertebral fractures[29]. Furthermore, an annual oral administration of 500,000 IU D_3 resulted in an increased risk of falls (RR 1.15; 95% CI 1.02–1.30; $p = 0.03$) and fractures (RR 1.26; 95% CI 1.00–1.59; $p = 0.047$)[30].

Data on the effects of calcium supplementation on bone mineral density and fracture rates in the general population are conflicting. Calcium and calcium plus vitamin D (CaD) were associated with a reduction in bone loss[17,31,32] and fracture risk[31,33]. On the contrary, Grant et al[34] reported that the incidence of new, low-trauma fractures did not differ significantly: between with the use of oral calcium (1000 mg) and placebo; between oral vitamin D3 (800 IU) and placebo; or between combined Vitamin D (800 IU) and calcium (1000 mg) supplements and placebo. Another two meta-analyses[17,35] and the US Preventive Services Task Force's recommendations[24] confirmed these findings. However, some researchers performed several meta-analyses with subgroup stratification and found that the fracture risk reduction was significantly greater in trial with a high adherence rate of calcium and vitamin D supplementation[17,31,36]. The fracture risk reductions were significantly greater among women who took at least 80% of their study supplements (HR 0.71; 95% CI 0.52–0.97)[17] or followed $\geq$ 5 years of treatment (HR 0.65; 95% CI 0.44–0.98)[36], and among participants with compliance rate of $\geq$ 80% (RR 0.76; 95% CI 0.67–0.86; $p = 0.002$)[31]. The antifracture efficacy was better in individuals who were older than 70 years, lived in institutions[18,25,31,37], and had low bodyweight[31].

In summary, calcium and CaD were associated with a reduction in bone loss. Vitamin D doses of 400 IU and lower did not show antifracture efficacy. A daily oral administration of 800–2000 IU vitamin D, with or without calcium supplementation, may reduce the risk of hip fracture. The fracture risk reductions were significantly greater among participants with high compliance rate and longer administration.

3. Potential adverse outcomes of calcium and vitamin D

Bolland et al[10–12], Reid and Bolland[13], and Reid et al[14,15] reported the possible increased risk of adverse cardiovascular events associated with calcium with or without vitamin D supplementation. A 5-year randomized controlled trial found possible increases in rates of myocardial infarction (MI) in healthy postmenopausal women allocated to calcium supplementation (RR 2.12; 95% CI 1.01–4.47; $p = 0.047$)[11]. The following studies reported similar findings that calcium supplements with or without vitamin D increased the risk of MI[10,12,38] and the composite end point of MI or stroke (RR 1.15; 95% CI 1.03–1.27; $p = 0.009$)[12]. The associations between calcium supplementation and CVD mortality were null[10–12,38]. An increased risk of MI was more pronounced for calcium supplement only users (HR 2.39; 95% CI 1.12–5.12)[38]. In comparison with calcium supplementation, a moderately higher dairy calcium intake (mean = 466 mg/day) significantly reduced MI risk (HR 0.68; 95% CI 0.50–0.93)[38]. The possible mechanism of the adverse effect of calcium supplements on MI risk might be related to the acute increase in serum calcium levels after ingestion of calcium supplements. High–normal serum calcium levels have been known to be associated with an increased risk of vascular calcification and cardiovascular events.

Randomized controlled trials on vitamin D effects on cardiovascular risk factors showed inconsistent results. Although few meta-analysis of randomized controlled trials indicated a significant decrease in mortality with using vitamin D supplements[39–42], the majority of the researches did not report statistically significant associations between vitamin D and cardiovascular events, stroke, and death[23,36,43–45]. Moreover, higher serum 25(OH)D levels were not necessarily better and U-shaped associations of some outcomes related to vitamin D were observed[23,46–49].

Findings on calcium and vitamin D intake and cancer are inconsistent. In the Women's Health Initiate (WHI) trial of CaD (1000 mg calcium and 400 IU vitamin D daily), Bolland et al[50] found women who were not taking personal calcium or vitamin D supplement at the time of WHI enrollment, CaD significantly decreased the risk of total cancer (HR 0.86; 95% CI 0.78–0.96; $p = 0.007$), breast cancer (HR 0.82; 95% CI 0.70–0.97; $p = 0.021$), and invasive breast cancers (HR 0.80; 95% CI 0.66–0.96; $p = 0.015$) and nonsignificantly decreased the risk of *in situ* breast cancer and colorectal cancer. In women who were taking personal calcium or vitamin D supplements, CaD did not change cancer risk. However, Prentice et al[36] reanalyzed the WHI data further and stated that the statistical reduction in breast cancer risk and total invasive cancer risk among CaD users was nominal. Several meta-analyses and clinical trials revealed allocation to calcium, vitamin D, or the combination did not alter the risk of total cancer[19,51], colorectal cancer[51,52], breast cancer[51–54], and cancer-related mortality[19,51]. Significant treatment interactions on incident cancer were found for a family history of cancer[20], highest dose of vitamin D[20,52,55], and smoking[20].

Calcium is the major component of 85% of kidney stones. Urinary tract stone occurrence was more common in women who took supplemental CaD than placebo (HR 1.17; 95% CI 1.02–1.34) in the WHI trial[17,56], consistent with previous research[16]. In contrast with adverse effects of calcium supplements on renal calculi, dietary calcium may lower new kidney stone formation[16] through binding of dietary oxalate and calcium in the intestinal lumen that decreases urine calcium oxalate supersaturation.

In summary, consumption of calcium from supplements might increase the risk of adverse cardiovascular events and urinary tract stones, but not from diet. No statistically significant associations between vitamin D and cardiovascular events, stroke, and death were reported. The available evidence is still insufficiently robust to draw conclusions the influence of calcium/vitamin D intake on cancer risk.

4. Current recommendations and daily intakes of calcium and vitamin D

After reviewing > 1000 higher-quality studies, the Institute of Medicine updated the estimated average requirement (intake that

Table 1
Dietary reference intakes for calcium and vitamin D for adults aged ≥ 51 years.

Institute of Medicine recommendations for bone health in general population[a]								
Life stage group	Calcium			Vitamin D				
	EAR (mg/d)	RDA (mg/d)	UL (mg/d)	EAR (IU/d)	Serum 25(OH)D[b] for the EAR (ng/mL)	RDA (IU/d)	Serum 25(OH)D[c] for the RDA (ng/mL)	UL (IU/d)
51–70 y (M)	800	1000	2000	400	16	600	20	4000
51–70 y (F)	1000	1200	2000	400	16	600	20	4000
71+ y (M+F)	1000	1200	2000	400	16	800	20	4000

Endocrine Practice Guidelines Committee recommendations for patients at risk for vitamin D deficiency			
Life stage group	Vitamin D		
	Daily requirement (IU/d)	Target serum 25(OH)D (ng/mL)	UL (IU/d)
51–70 y (M)	1500–2000	30	10,000
51–70 y (F)	1500–2000	30	10,000
71+ y (M+F)	1500–2000	30	10,000

EAR = estimated average requirement for intake that meets the needs of 50% of the North American population (median); F = female; M = male; RDA = recommended dietary allowance for intake that meets the needs of 97.5% of the North American population; UL = tolerable upper intake level, above which there is risk of adverse events. The UL is not intended as a target intake (no consistent evidence of greater benefit at intake levels more than the RDA).
[a] The recommendation was established by the Institute of Medicine for the needs of the North American population, released on November 30, 2010.
[b] Measure of serum 25-hydroxyvitamin D (25OHD) level corresponding to the EAR and covering the needs of 50% of the North American population.
[c] Measure of serum 25OHD level corresponding to the RDA and covering the needs of at least 97.5% of the population.

meets the needs of 50% of the population) and recommended dietary allowance (RDA; intake that covers needs of ≥ 97.5% of the population) intakes for calcium and vitamin D of North American population on November 30, 2010[9,48] (Table 1). The Committee concluded that available scientific evidence supports a key role of calcium and vitamin D in skeletal health, consistent with a cause-and-effect relationship. However, for their roles in cancer, including cardiovascular disease, diabetes, and autoimmune disorders, the evidence was inconsistent. The RDA for calcium is 1000 mg/day for men aged 51–70 years, and 1200 mg/day for women aged 51–70 years and for women and men aged ≥ 71 years. The RDA for vitamin D was 600 IU/day for adults aged 51–70 years, and 800 IU/day for adults aged 71 years and over to maintain serum 25(OH)D at or above 20 ng/mL.

On the promise that vitamin D deficiencies are common among all age groups and that few foods contain vitamin D, the Endocrine Society prefers 30 ng/mL (75μM) of 25(OH)D as the target level for maximal benefits and recommends daily supplements of 1500–2000 IU are required for US, Canadian, and European adults[57] (Table 1), although the Institute of Medicine committee disagree with these viewpoints[58].

In 2014, the American Geriatrics Society stated that clinicians are strongly advised to recommend vitamin D supplementation of at least 1000 IU/day with calcium to older adults (age > 65 years) residing in the community or institutional settings to reduce the risk of fractures and falls. A serum 25(OH)D concentration of 30 ng/mL (75μM) should be a minimal goal for older adults, particularly for frail adults, who are at higher risk of falls, injuries, and fractures. An average daily vitamin D input of 4000 IU from all sources is required to result in 92% of older adults in the United States achieving target 25(OH)D levels. Routine laboratory testing for 25(OH)D serum concentrations before supplementation begins or for safety or efficacy when supplementation is within the recommended limits are not necessary. Clinicians may monitor 25(OH)D after 4 months of vitamin D_3 supplementation to confirm that appropriate levels have been achieved[46].

Increasing dietary calcium should be considered first. When adequate dietary calcium intake cannot be achieved or patients are unwilling to do so, calcium supplement tablets could be used. Calcium carbonate is bioavailable when taken with a meal. Calcium citrate is recommended for individuals with a history of renal stones[59]. Very few foods are naturally rich in vitamin D. Additional vitamin D supplements are usually needed to meet the recommendations for daily intake. Natural sources of vitamin D and calcium are listed in Table 2.

Table 2
Natural sources of vitamin D and calcium.

Sources	Vitamin D content
Sunlight/UVB radiation	About 3000 IU = Exposure of the arms and legs in bathing suit or shorts and short sleeved shirt without the use of sunscreen products to 0.5 minimal erythemal dose
Salmon	
fresh, wild (100 g)	600–1000 IU
fresh, farmed (100 g)	100–250 IU
Cod liver oil (5 mL)	400–1000 IU
Sardines, canned (100 g)	~300 IU
Mackerel, canned (100 g)	~250 IU
Tuna, canned (102 g)	About 230 IU
Shiitake mushrooms	
Sun-dried (100 g)	About 1600 IU
Fresh (85 g)	About 100 IU
Egg yolk	About 20 IU
Sources	**Calcium content (mg)**
Yogurt (236 mL)	450 mg
Tofu prepared with calcium (118 mL)	435 mg
Sardines (85 g)	370 mg
Milk (240 mL)	300 mg
Cheese (28 g)	195–335 mg (higher calcium in hard cheese)
Soy milk (240 mL)	300 mg
Figs, dried, uncooked (236 mL)	300 mg
Mackerel, canned (85 g)	250 mg
Spinach, cooked (236 mL)	240 mg
Soybeans, boiled (236 mL)	200 mg
Broccoli, cooked (236 mL)	180 mg
Arugula, raw (236 mL)	125 mg
Almonds, toasted unblanched (28 g)	80 mg
Orange (1 medium)	60 mg
Kiwi, raw (236 mL)	50 mg

5. Summary

Calcium and vitamin D play a key role in skeletal health. However, the evidence of potential adverse outcomes of calcium and vitamin D supplementation is inconsistent. Although emerging evidence suggests that calcium with or without vitamin D supplementation might increase the risk of myocardial infarction, most experts conclude that individuals who do not obtain sufficient intake of calcium and vitamin D from their diet should not be advised to avoid using calcium and vitamin D supplementation[60]. While the primary purpose of supplementation is to reduce the risk of fractures, vitamin D supplementation of at least 1000 IU/day with calcium of 1000–1200 mg/day to older adults is recommended, particularly to frail adults[46,48]. It seems that vitamin D has a biphasic effect for bone mass and U-shaped associations of some outcomes[23,47–49]. The supplementation levels of vitamin D need adjustments for sun exposure, skin pigmentation, and high body mass. Clinicians should review patient's calcium and vitamin D intake from all sources and individualize decision making to the specific patient or situation.

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