Calcium and Vitamin D Supplementation: Efficacy and Safety

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Biographical information: Dr Naim Maalouf is an Assistant Professor of Medicine in the Division of Mineral Metabolism. His clinical interests include management of patients with osteoporosis, nephrolithiasis, and calcium and parathyroid disorders. His research interests include the pathogenesis of nephrolithiasis (in particular in relation to the metabolic syndrome), osteoporosis (in particular in HIV-infected individuals), and the non-calciotropic effects of vitamin D.

Calcium and Vitamin D Supplementation: Efficacy and Safety

Purpose: While concerns regarding insufficient intake of calcium and vitamin D persist in the United States, questions regarding the efficacy and safety of calcium and vitamin D supplements are surfacing.

Educational objectives:

1. Provide an overview of calcium and vitamin D physiology
2. Review the efficacy and safety of calcium and vitamin D supplementation
3. Summarize current recommendations on optimal intake of calcium and vitamin D

I- Introduction

While most commonly associated with bone metabolism, calcium and vitamin D are also involved in a number of extra-skeletal processes in the human body. In the past decade, calcium intake in the U.S. has increased considerably in segments of the population in response to concerns regarding insufficient intake and osteoporosis. At the same time, testing and pharmacological therapy for vitamin D insufficiency has grown exponentially in response to numerous studies suggesting enhanced roles for vitamin D in human health. While concerns regarding insufficient intake of calcium and vitamin D persist, questions regarding the efficacy and safety of calcium and vitamin D supplements are surfacing.

II- Overview of Calcium and Vitamin D

A- Physiology

Serum ionized calcium concentration is maintained within a very narrow range since it is essential for several bodily functions including bone metabolism, muscle contraction, nerve conduction, intracellular signaling, and hormonal secretion. Over 99% of total body calcium is found as calcium hydroxyapatite in bones and teeth, where it provides tissue strength and serves as a reservoir for and source of calcium for critical metabolic needs through bone remodeling. Calcium metabolism is regulated in large part by the parathyroid hormone–vitamin D endocrine system, which is characterized by a series of homeostatic feedback loops that maintain adequate levels of ionized calcium in serum.

In the gastrointestinal tract, calcium is absorbed by active transport (dependent on the action of calcitriol) and by passive diffusion across the small intestinal mucosa. Mean calcium absorption is approximately 25 percent of calcium intake and fecal loss 75 percent of total calcium intake based on controlled metabolic studies undertaken by the USDA[1]. Mean urinary loss averages 22 percent of intake, with minor losses from sweat, skin, hair, etc... Besides calcium intake, determinants of fractional intestinal calcium absorption include age[2], menopausal status/postmenopausal estrogen use[3], fiber intake, and vitamin D stores / serum 1,25-OH2-D[4].

Vitamin D from the skin and diet circulates bound to the vitamin D- binding protein. The initial step in vitamin D metabolism involves its hepatic hydroxylation at the 25 position, generating 25-hydroxyvitamin D (25-OH-D). 25-OH-D is the principal circulating form of vitamin D, has a half-life in circulation of approximately 2-4 weeks, and is the best biomarker of vitamin D status[5]. 25-OH-D is further hydroxylated in the kidney by the mitochondrial 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) enzyme to form 1,25 dihydroxyvitamin D (1,25-$(OH)_2$-D), the physiologically active form of vitamin D. The *classical actions* of 1,25-$(OH)_2$-D include enhancement of intestinal calcium and phosphorus absorption, suppression of parathyroid hormone secretion, and stimulation of

bone resorption. These *classical actions* occur via interaction of 1,25-$(OH)_2$-D with the vitamin D receptor (VDR), a nuclear receptor in small intestinal cells, parathyroid cells, and osteoblasts (which activate osteoclastic bone resorption via secretion of RANKL). The renal production of 1,25-$(OH)_2$-D is tightly regulated by circulating 1,25-$(OH)_2$-D, 24,25-$(OH)_2$-D calcium, phosphorus, parathyroid hormone (PTH), and fibroblast growth factor 23 levels.

B- Indicators of Calcium and Vitamin D Sufficiency

Urine calcium is determined by dietary intake, bone turnover, and renal excretion mechanisms, and at steady state, urinary calcium excretion corresponds to the net calcium absorption in the gut. Thus, 24-hr urine calcium excretion is a crude marker of intestinal calcium absorption. Values below 50 mg/day are suggestive of insufficient calcium intake or absorption. Conversely, hypercalciuria (urine calcium > 300 mg/day) may be indicative of excess calcium intake.

The "optimal range" for serum 25-OH-D is a debatable question[6, 7] and depends on the method used to estimate this range. While a serum 25-OH-D below 20 ng/ml is widely accepted to define *vitamin D deficiency*, some authors have argued that optimal serum 25-OH-D should exceed 30 ng/ml to indicate adequate vitamin D stores, and *vitamin D insufficiency* is proposed to indicate serum 25-OH-D between 20 and 30 ng/ml[8]. Reports suggesting a 25-OH-D level above 30 ng/ml to indicate vitamin D sufficiency are based on the association between serum 25-OH-D and total hip bone mineral density (BMD) that plateaus above 25-OH-D over 32 ng/ml[8], and the fact that serum PTH plateaus above 25-OH-D of 30 ng/ml[9]. On the other hand, the association of serum 25-OH-D with bone turnover markers shows a threshold at a lower level, with serum osteocalcin and urine N-telopeptides increasing only below a serum 25OHD of approximately 18 ng/ml[10]. The optimal serum 25-OH-D (which in turns determines prevalence of vitamin D deficiency and optimal intake of vitamin D) continues to be debated.

III- Efficacy and Safety of Calcium and Vitamin Supplementation

In postmenopausal women and elderly individuals in whom intestinal calcium absorption and cutaneous vitamin D production are reduced, bone is used as a source of calcium to maintain homeostasis in extracellular Ca concentration (Figure 1). With increased remodeling rate primarily from higher PTH secretion, bone mass

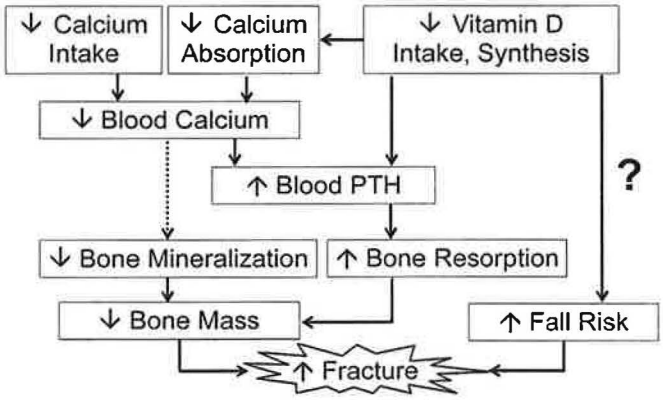


Figure 1. Fracture risk with low calcium and vit. D intake

decreases raising the risk of osteoporotic fracture. In cases of severe hypocalcemia, reduced bone mineralization may further contribute to fragility fractures. Finally, vitamin D deficiency may contribute to increased risk of falls. In the face of this pathophysiology, calcium and vitamin D supplementation have been studied as agents to reduce the risk of fracture.

A- Calcium Supplements

Skeletal effects: The first randomized, placebo-controlled study to show efficacy of calcium and vitamin D at reducing the risk of hip and non-vertebral fractures was published in 1992[11]. In that study, conducted in 3,270 older ambulatory women in France, intake of calcium (1,200 mg/d) with vitamin D (800 IU/d) significantly reduced the risk of hip fracture by 43% and non-vertebral fracture by 32%[11]. Since that initial report, several studies have been conducted. A meta-analysis of 29 randomized trials including 63,897 subjects over age 50[12] shows that calcium treatment is associated with a 12% risk reduction in fractures of all types (risk ratio: 0·88, 95% CI 0·83–0·95; p=0·0004). The fracture risk reduction was significantly greater (24%) in trials in which the compliance rate was high (p<0·0001) (Table 1). The treatment effect was better with calcium doses of 1200 mg or more than with doses less than 1200 mg, and with vitamin D doses of 800 IU/day or more than with doses less than 800

Table 1. Calcium Supplements and Fracture Risk Reduction

Subgroup analyses from a meta-analysis of 29 randomized trials in 63,897 subjects over age 50 (Trang, Lancet, 2007)

	RR (95% CI)	p-value
Clinical Setting		
Community	0.94 (0.90-0.99)	0.003
Institutionalized	0.76 (0.66-0.88)	
Compliance		
≥80%	0.76 (0.67-0.86)	0.002
60-69%	0.92 (0.71-1.19)	
50-59%	0.96 (0.91-1.01)	
Age (years)		
50-69	0.97 (0.92-1.02)	0.003
70-79	0.89 (0.82-0.96)	
≥80	0.76 (0.67-0.87)	
Gender		
Women-only studies	0.88 (0.80-0.97)	0.33
Men and women studies	0.88 (0.80-0.96)	
Dietary calcium intake		
Low	0.80 (0.71-0.89)	0.008
Normal	0.95 (0.91-1.00)	
Calcium dose		
<1200 mg	0.94 (0.89-0.99)	0.006
≥1200 mg	0.80 (0.72-0.89)	
Vitamin D dose		
<800 IU	0.87 (0.71-1.05)	0.03
≥800 IU	0.84 (0.75-0.94)	
Fracture sites		
Hip	0.87 (0.75-0.99)	0.72
Vertebral	0.87 (0.75-1.01)	

IU/d (Table 1). Older and institutionalized patients also experienced greater fracture reduction[12].

Extra-skeletal benefits: In epidemiologic studies, insufficient dietary calcium intake is associated with higher blood pressure[13], worse lipid profile[14], greater body weight[15], higher risk of colon and breast cancer[16], and enhanced risk of pre-eclampsia[17]. However, data on calcium supplementation preventing or reversing these disorders are scarce and inconclusive[18-20]. At this point, calcium supplementation is not recommended for prevention or treatment of non-skeletal disorders except for possibly reducing the risk of pre-eclampsia[17].

Side-effects: The most common side-effects experienced by patients ingesting calcium supplements are gastrointestinal discomfort and constipation. Serious side-effects include development of hypercalcemia, hypercalciuria and kidney stones. Excessive intake of calcium (over 3 grams per day) predisposes to the development of the "calcium-alkali syndrome", the newly suggested name for the "milk-alkali syndrome" renamed to reflect the shifting epidemiology of this condition[21]. This syndrome results from excessive calcium intake and often of thiazide diuretics and/or absorbable alkali, producing the classic triad of hypercalcemia, metabolic alkalosis, and varying degrees of renal insufficiency. The syndrome has seen a recent resurgence, in large part due to increased awareness of osteoporosis leading to greater use of over-the-counter calcium and vitamin D supplements. In recent years, the calcium-alkali has been described as the third most common cause of hospital admission for hypercalcemia after hyperparathyroidism and hypercalcemia of malignancy[22]. Intake of calcium is known to significantly increase urine calcium thus predisposing to kidney stone formation. Epidemiologic studies have found that high intake of *dietary* calcium is associated with lower risk of stone formation, while intake of *supplemental* calcium is associated with greater risk of stone formation[23]. The Women's Health Initiative (WHI) randomized clinical trial of calcium plus vitamin D supplements, daily supplementation with 1,000 mg calcium carbonate and 400 IU vitamin D daily for 7 y was associated with a significant 17% increase in the number of self-reported urinary tract stones[24]. Based on metabolic studies, calcium citrate may not increase the risk of kidney stone formation to a significant extent[25]. An association of calcium intake with prostate cancer incidence has recently been described. Two observational studies have found that calcium intake exceeding 2,000 mg/d was associated with slight but statistically significant higher risk for prostate cancer, particularly with advanced and metastatic prostate cancer[26, 27]. In one randomized controlled multicenter clinical trial, 672 men receiving either 3 g of calcium carbonate or placebo daily for 4 years, calcium supplementation did not significantly alter the risk of prostate cancer during follow up for up to 12 years (relative risk [RR] = 0.83; 95% CI: 0.52–1.32)[28]. Data regarding the association of calcium supplementation with prostate cancer is still emerging, and no definitive conclusion can be made at this time.

B- Vitamin D Supplements

Skeletal effects: One of the major biological functions of vitamin D is to regulate bone mineralization. While combined vitamin D and calcium supplementation significantly reduces fracture risk, the impact of vitamin D supplements *alone* on fracture prevention is not clear-cut. One large study showed that vitamin D supplementation alone prevented fractures[29], another showed increased fracture risk with vitamin D supplementation[30], and other studies showing a neutral effect[31]. In a recent meta-analysis[31], combined vitamin D and calcium supplementation, but not vitamin D supplementation alone, can reduce the fracture risk in older adults. It has also been suggested that a higher achieved serum 25-OH-D results in greater fracture prevention with vitamin D supplementation alone[32]. In addition to its effect on fractures, vitamin D supplements have been suggested to reduce fall risk by interacting with receptors in the muscle tissue and improving muscle strength[33]. Several randomized trials have examined the impact of vitamin D supplementation on fall risk, and a number of meta-analyses have examined pooled results with mixed conclusions[34-36]. The majority of the evidence is derived from trials enrolling elderly women, and vitamin D combined with calcium significantly reduces the risk of falls, but the reduction in studies without calcium co-administration did not reach statistical significance[34]. The underlying mechanisms are still a matter of debate.

Extra-skeletal benefits: In the past decade, a large literature has emerged on potential extra-skeletal benefits of vitamin D supplementation[37, 38] (Table 2). This

Table 2. Summary of evidence supporting the role of UVB and/or vit D in reducing the risk of disease

Diseases	*Geographical*	*Seasonal*	*Observational*	*Cross-Sectional*	*Strength*
Cardiovascular disease		Y	Y	Y	Strong
Cancer—bladder	Y		Y		Strong
Breast, colorectal	Y		Y	Y	Strong
Non-Hodgkin's lymphoma	Y		Y		Strong
Ovarian	Y		Y		Strong
Pancreatic	Y		X, Y		Moderate
Prostate	Y		N		Weak
12 other cancers	Y		N		Moderate
All cancer	Y		Y	Y	Strong
Respiratory infections		Y	Y	Y	Strong
Other respiratory diseases		Y	N	Y	Weak
Tuberculosis		Y	Y		Strong
Diabetes mellitus type 2			Y		Moderate
Alzheimer's disease			Y		Weak
Falls and fractures		Y	Y	Y	Strong
Meningitis		Y			Weak
Parkinson's disease	Y		Y		Weak
Sepsis		Y	Y	Y	Moderate
Maternal hypertension		Y	Y		Moderate
Multiple sclerosis	Y	Y	Y		Strong

N, null finding; X, contradictory finding; Y, supporting evidence.

literature is primarily based on findings from epidemiologic studies (Table 2,[39]) and animal experiments[38] that indicate that adequate vitamin D levels are important for cancer prevention, modulating cardiovascular risk factors, and controlling hormone levels and regulating the immune response. However, the published epidemiologic literature on extra-skeletal effects of vitamin D is fraught with problems including confounding and residual confounding (incomplete control for obesity, limited physical activity, low socioeconomic status as covariates), reverse causality (illness can limit sunlight exposure through inactivity, and disease *could lead to* vitamin D deficiency) and publication bias [40]. Studies on tissue-specific expression of the CYP27B1-encoded 25-hdroxyvitamin D-1α-hydroxylase and of the vitamin D receptor have led to an understanding how locally produced 1,25-dihydroxyvitamin D acts as a key regulator of cellular proliferation, differentiation and function. Since extra-skeletal effects of vitamin D are supported by biological plausibility[16, 38], vitamin D and its analogues are being evaluated for the prevention and treatment of a variety of conditions. Early findings have shown mixed results[37], leading the Institute of Medicine to use only bone health as a biomarker of sufficiency[36]. Future evidence from on-going large randomized clinical trials[41] will establish or reject the proposed extra-skeletal indicators of vitamin D supplementation.

Side-effects: Side-effects of excessive vitamin D intake include hypercalcemia and hypercalciuria. The former has not been described at chronic intakes of vitamin D below 10,000 IU/day or with a serum 25-OH-D below 80 ng/ml. Increasing vitamin D intake may theoretically raise the risk of hypercalciuria and subsequent nephrolithiasis[42]. While vitamin D supplementation *with calcium* significantly is associated with a greater likelihood of kidney stone formation[24], no study has reported greater nephrolithiasis with vitamin D supplementation alone. The IOM committee considered another potential adverse effect of vitamin D in setting its upper limit (UL): all cause—mortality. This was because several studies suggest a reverse J curve or a U-shaped curve for overall mortality, with risk from low vitamin D (<10 ng/ml) progressing to benefit with risk again increasing at higher concentrations (>30 ng/ml) in whites and above 28 ng/ml in African-Americans[43-45].

Cardiovascular Effects of Calcium and Vitamin D:

- **Calcium:** Observational research has suggested an inverse relationship between *dietary* calcium intake and cardiovascular diseases[46-48]. This potential beneficial effects of calcium has been ascribed to its effects or CV risk factors including hypertension, dyslipidemia and obesity[13, 15]. On the other hand, calcium *supplements* have been suggested to increase cardiovascular risk[49], with a relative risk of incident myocardial infarction in individuals allocated to calcium increased by 31% compared to placebo (HR 1.31, 95% CI 1.02 to 1.67)[49]. The postulated mechanism is that calcium supplements may acutely elevate serum calcium levels more than dietary calcium, and as a result, may enhance vascular calcification[50].

- **Vitamin D:** Vitamin D supplementation is thought to be potentially protective against cardiovascular (CV) disease, based on strong epidemiologic studies linking vitamin D deficiency to CV risk factors[51] and CV events[52]. At the same time, excess vitamin D intake may potentially worsen risk of CV disease by raising serum calciumXphosphate product[53] and/or by directly promoting vascular calcification[54]. Trials specifically assessing effects of vitamin D on CV diseases as a primary endpoint are lacking. Evidence from other intervention studies have been mixed with one meta-analysis suggesting that vitamin D supplements alone may reduce CVD risk[55], while another found no significant effect on myocardial infarction or stroke[56]. It is therefore premature to recommend supplemental vitamin D intake for the prevention of cardiovascular diseases or hypertension.

- **Combined calcium and Vitamin D:** With respect to combined calcium and vitamin D supplementation, conflicting reports have been published. In the WHI, the largest published placebo-controlled study, daily supplementation with 1,000 mg calcium carbonate and 400 IU vitamin D daily neither increased nor decreased coronary or cerebrovascular risk in healthy postmenopausal women[57]. A recent re-analysis of the same study suggested that calcium and vitamin D supplement significantly increased the risk of myocardial infarction in the subgroup of women who were not taking calcium supplements at study entry, whereas in the women taking personal calcium supplements cardiovascular risk was not affected by allocation to calcium and vitamin D. More prospective cohort studies and large-scale randomized trials needed to clarify the risks and benefits of calcium and vitamin D supplements on CVD endpoints as primary outcome.

IV- Current Recommendations and Intakes, Available Sources

A- Calcium

Recommended Intake: Recommendations regarding optimal intake of calcium were revised in 2010 by the Institute of Medicine [36] (Table 3). These are gender and age-dependent, and are primarily based on balance studies to estimate calcium intake needed to offset daily gastrointestinal, renal and cutaneous losses[1]. These recommendations are

Table 3. Institute of Medicine recommendations on calcium intake

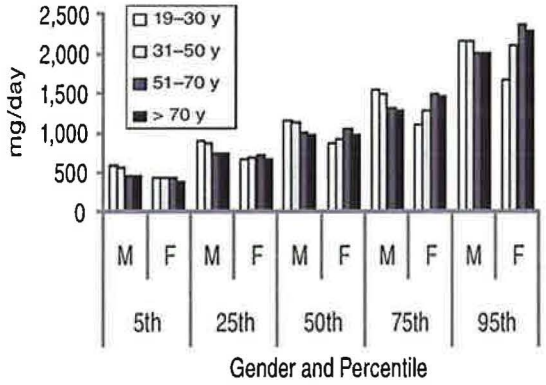
Life stage group	Recommended Daily Allowance	Upper Level Intake
9-18 years old	1,300 mg/day	3,000 mg/day
19-50 years old	1,000 mg/day	2,500 mg/day
51-70 year old men	1,000 mg/day	2,000 mg/day
51-70 year old women	1,200 mg/day	2,000 mg/day
> 70 years old	1,200 mg/day	2,000 mg/day

RDA: covers the requirement for 97.5% of the population.
UL: Highest average intake that is likely to pose no risk.

accepted by major groups including the National Osteoporosis Foundation and the Endocrine Society.

Actual Intake in the U.S.: Data from the National Health and Nutrition Examination Survey (NHANES) 2003-2006 survey provides an interesting snapshot of the actual intake in the U.S. Forty-three percent of the U.S. population reported using calcium supplements[58]. For users, dietary supplements provided the adequate intake recommendation for calcium intake for ~12% of those above age 71 years[58]. Still, 50-60% of women above age 50 years consumed less than the RDA of 1,200 mg/day, while at least 5% of adults above age 50 years consume more than the Upper Limit of 2,000 mg/day (Figure 2).

Figure 2. Usual calcium intake (mg/d) from dietary and supplemental sources in U.S. adults, from NHANES 2003-2006



Source: Bailey RL, et al. *J Nutr. 2010;140:817-822*

Calcium Sources: Calcium is classically associated with dairy products, and in the United States, an estimated 72% of calcium comes from milk, cheese, yogurt and foods to which dairy products have been added (e.g., pizza, lasagna). The remaining dietary calcium comes primarily from vegetables (7%); grains (5%); legumes (4%)[59]. Fortification with calcium for a number of foods that do not naturally contribute calcium (e.g. orange juice, ready-to-eat cereals) is becoming commonplace in the U.S. The calcium content of commonly consumed foods is shown in table 4. Since the majority of U.S. adults do not meet the recommended daily allowance, calcium supplements are frequently needed. U.S. Pharmacopeia (USP)–verified calcium supplements meet vigorous manufacturing and quality requirements. Calcium from carbonate and citrate are the most common forms of calcium supplements. Calcium carbonate, the most cost-effective form, should be taken with a meal to ensure optimal absorption. Calcium citrate is better tolerated with less GI side-effects, can be taken without food, and is the supplement of choice for individuals with achlorhydria or who are taking histamine-2 blockers or proton-pump

Table 4. Calcium content in various food sources*

Food, serving size	Calcium
Sardines, canned, with edible bones, 3 oz	300 mg
Cheddar cheese, 1½ oz. shredded	300 mg
Milk , 8 oz. cup (full fat, 2% fat, no fat)	300 mg
Yogurt, plain, low-fat, 1 cup	200-300 mg
Orange juice, fortified with calcium, 6 oz.	200-250 mg
Cottage cheese, 1% milk fat, 1 cup	150 mg
Cereal, fortified with calcium, 1 cup	100-1000 mg
Cheese pizza, 1 slice	100 mg
Broccoli, raw, 1 cup	100 mg
Ice cream, vanilla, ½ cup	100 mg

*Adapted from the 2004 U.S. Surgeon General's Report on Bone Health and Osteoporosis

inhibitors. Calcium lactate and calcium gluconate are less concentrated forms of calcium and less practical oral supplements. The maximum dose of elemental calcium that should be taken at a time is 500-600 mg. Important considerations should be kept in mind when prescribing calcium supplements to avoid drug-drug interactions (Table 5).

Table 5. Interactions between calcium supplements and other drugs, and recommendations

Drug / Class	*Interaction*	*Recommendation*
Bisphosphonates	*Bisphosphonate absorption significantly reduced in presence of calcium (or other meds)*	*Bisphosphonates should be taken > 30 min before Ca supplements*
Levothyroxine	*Calcium reduces levothyroxine absorption by forming insoluble complexes*	*Administration of levothyroxine and calcium should be separated by 4 h*
Tetracyclines, Quinolones	*Calcium reduces the absorption of tetracycline and quinolones by forming insoluble complexes*	*Tetracyclines and quinolones should be taken 2 h before or 4–6 h after calcium supplements*
Proton Pump Inhibitors, H2 blockers	*Reduced gastric acid production decreases solubility and absorption of calcium carbonate*	*Calcium citrate is the preferred calcium supplements in patients on H2 blockers and PPIs*
Thiazide Diuretics	*Thiazide diuretics decrease the renal excretion of calcium*	*Increased risk of milk-alkali syndrome in concomitant thiazide and Ca supplement use*
Digoxin	*Hypercalcemia increases the risk of fatal cardiac bradyarrhythmias. Digoxin potentiates the pro-arrythmic effects of hypercalcemia*	*In the presence of hypercalcemia, digoxin levels are less reliable for diagnosing digoxin toxicity*
Glucocorticoids	*Glucocorticoids at high doses reduce intestinal Ca absorption and increase renal Ca excretion*	*Ensure adequate calcium and vit. D intake (some patients may need supplements)*
Phenytoin, Carbamazepine, Phenobarbital	*These agents reduce calcium absorption by increasing vit. D catabolism. Hypocalcemia and osteomalacia described with chronic therapy*	*Ensure adequate calcium and vit. D intake (some patients may need supplements)*

Vitamin D

Recommended Intake: The recommended intake of vitamin D is age-dependent (Table 5). There is some disagreement between the 2010 Institute of Medicine and the 2011 Endocrine Society guidelines with respect to the recommended intake and upper tolerable limit, as well as regarding the optimal serum 25-OH-D level.

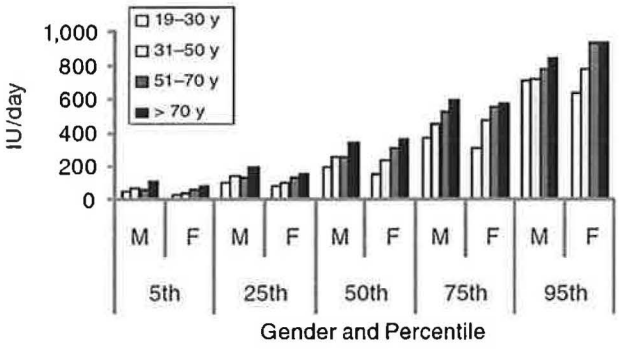
Table 6. Recommendations on vitamin D intake

	Institute of Medicine 2010 Recommendations		Endocrine Society 2011 Recommendations	
Life stage	**RDA**	**Upper Level Intake**	**Daily Requirement**	**Tolerable Upper Level Intake**
9-18 years old	600 IU/d	4,000 IU/d	600-1,000 IU/d	4,000 IU/d
19-70 years old	600 IU/d	4,000 IU/d	1,500-2,000 IU/d	10,000 IU/d
> 70 years old	800 IU/d	4,000 IU/d	1,500-2,000 IU/d	10,000 IU/d
Optimal Serum 25-OH-D	20-50 ng/ml (50-125 nM/L)		30-80 ng/ml (75-200 nM/L)*	

RDA: covers the requirement for 97.5% of the population.
UL: Highest average intake that is likely to pose no risk.
* Endocrine Society considers 25-OH-D levels of 20-30 ng/ml (50-75 nM/L) to represent "vitamin D insufficiency"

Actual Intake: Based on NHANES data, 37% of U.S. adults used some vitamin D supplement in 2005-2006[58]. While use of supplemental vitamin D was associated with a greater probability of meeting the recommended intake of vitamin D, median total intake of vitamin D (from diet+supplements) was well below the recommended intake (Figure 3).

Figure 3. Usual vitamin D intake (IU/d) from dietary and supplemental sources in U.S. adults, from NHANES 2003-2006



Bailey RL, et al. *J Nutr. 2010;140:817-822*

Vitamin D Sources: Cutaneous production of vitamin D is affected by factors such as skin pigmentation, sunscreen use, clothing, age, latitude and season. The typical U.S. diet provides very limited vitamin D as major dietary sources include fatty fish, fish liver oil, shiitake mushrooms, and fortified foods (cereals, milk, etc...). Vitamin D supplements are therefore important contributors to vitamin D intake in most adult Americans[58]. Available preparations in the United States include vitamin D_3 (cholecalciferol) found in 400-5,000 IU of vitamin D, but 1,000 IU is the most commonly available dose. Vitamin D_3 is also found in calcium and multivitamin supplements. Larger doses that may be needed for vitamin D repletion in deficient individuals are only found in the form of vitamin D_2

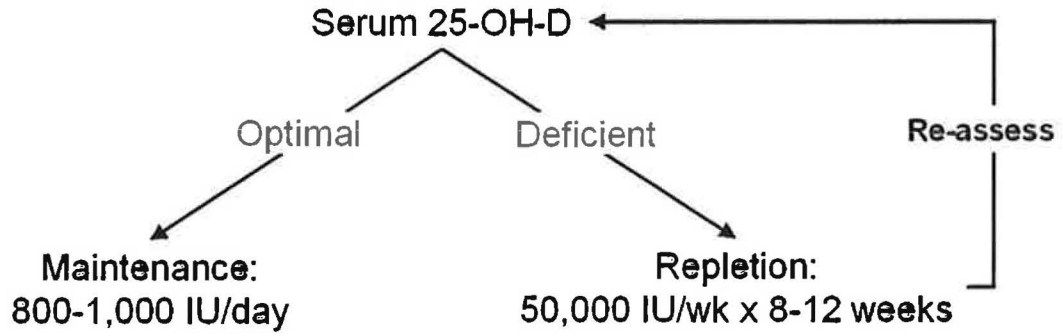
Table 7. Vitamin D preparations in the United States

Preparation	Commercial name	Forms	Remarks
Cholecalciferol (vit. D3)	--	400-1000 u supplement	Found in multivitamins or with calcium preparations
Ergocalciferol (vit. D2)	Drisdol	50,000 u capsule	Inexpensive, long half-life
Calcitriol (1,25$(OH)_2$-D)	Rocaltrol	0.25, 0.5 mcg caps	Expensive, short half-life Hypoparathyroidism, CKD

(ergocalciferol, Drisdol ®), which may be less potent that vitamin D_3. Calcitriol (Rocaltrol ®), the active form of vitamin D, is typically reserved to individuals who cannot synthesize 1,25-$(OH)_2$-D such patients with chronic kidney disease or hypoparathyroidism. Patients with adequate vitamin D stores are likely to require 1,000 IU per day to maintain vitamin D sufficiency. On the other hand, patients with vitamin D deficiency, repletion can be achieved with ergocalciferol 50,000 IU

given weekly for 8-12 weeks. Serum 25-OH-D should be re-checked at the end of the ergocalciferol course, with maintenance doses of vitamin D given to those whose stores are repleted, and a repeat ergocalciferol course given to those who are still insufficient (Figure 4). Patients with bowel disease, cystic fibrosis or post-bariatric surgery are likely to require long-term high doses of vitamin D.

Figure 4. Proposed algorithm for vitamin D supplementation



Vitamin D_2 vs. D_3: Whether vitamin D_2 is equivalent to vitamin D_3 in terms of potency has also been debated. A recent study randomized 64 community dwelling adults to receive daily (1,600 IU) or once-monthly (50,000 IU) vitamin D_2 or vitamin D_3 for 1 yr. Overall, vitamin D_3 was slightly, but significantly, more effective than vitamin D_2 to increase serum 25-OH-D[60]. Importantly, substantial between-individual response to administered vitamin D_2 or D_3 was observed[60].

V- Conclusions, Future Directions

In summary, adequate calcium and vitamin D intake is essential for optimal bone health, particularly in postmenopausal and elderly individuals. Calcium and vitamin D supplements significantly reduce fracture risk, with the greatest benefit seen in older, institutionalized, adherent individuals with low Ca intake at baseline. Calcium intake from supplements (but not diet) increases the risk of nephrolithiasis, and possibly of CV events, although more prospective studies are needed to clarify the risks and benefits of calcium supplements on CVD endpoints as primary outcome. Dietary sources of vitamin D are limited, and vitamin D deficiency is highly prevalent in the United States and around the world. Optimal vitamin D intake and target serum 25-OH-D for the general population continue to be debated. Large randomized trials assessing the role vitamin D supplementation are currently in progress, and should provide important answers on the skeletal and non-skeletal effect of vitamin D.

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