

REVIEW ARTICLE

# Calcium and vitamin D supplementation: state of the art for daily practice

Robert Y. van der Velde<sup>1\*</sup>, Jacobus R. B. J. Brouwers<sup>2</sup>, Piet P. Geusens<sup>3,4</sup>,  
Willem F. Lems<sup>5</sup> and Joop P. W. van den Bergh<sup>1,3,4</sup>

<sup>1</sup>Department of Internal Medicine, VieCuri Medical Centre for North Limburg, Venlo, The Netherlands; <sup>2</sup>Department of Geriatric Medicine, Expertise Centre for Pharmacotherapy in the Elderly, Ephor-UMC Utrecht, The Netherlands; <sup>3</sup>Department of Rheumatology, CAPHRI, Maastricht UMC, Maastricht, The Netherlands; <sup>4</sup>Biomedical Research Centre, University of Hasselt, Diepenbeek, Belgium; <sup>5</sup>Department of Rheumatology, VU Medical Centre, Amsterdam, The Netherlands

## Abstract

**Background:** Calcium and vitamin D play an essential role in bone metabolism but deficiency and/or inadequate intake are common.

**Objectives:** To describe a practical approach based on the literature regarding clinically important aspects of calcium and vitamin D supplementation.

**Methods:** A systematic evaluation of relevant literature in Medline was conducted. We included physiological studies, publications on relevant guidelines, meta-analysis, randomized clinical trials, and cohort studies.

**Results:** An adequate calcium intake and vitamin D supplementation is recommended in most guidelines on fracture prevention. Daily supplementation with 800 IU is advocated in most guidelines, appears to be safe, and with this approach it is generally not necessary to determine vitamin D levels. There are no data on additional effects of loading doses of vitamin D on fracture or fall prevention. Calcium supplementation should be tailored to the patient's need: usually 500 mg per day is required. The intestinal absorption of calcium citrate is approximately 24% better than that of calcium carbonate independent of intake with meals. Data on difference between calcium absorption with calcium carbonate compared to calcium citrate with simultaneous use of proton pump inhibitors are lacking. Concern has arisen about a possible link between calcium supplementation and an increased risk of myocardial infarction. Probably only well-designed prospective randomized controlled trials will be able to allow definite conclusions on this subject.

**Conclusion:** Daily supplementation with 800 IU vitamin D is a practical and safe strategy without the need for prior determination of vitamin D levels. Calcium supplementation should be tailored to the patient's need based on total daily dietary calcium intake. In most patients 500 mg per day is required to achieve a total intake of 1,200 mg, or in some 1,000 mg per day. More calcium is absorbed from calcium citrate compared to calcium carbonate.

**Keywords:** *calcium absorption; vitamin D supplementation; fracture prevention; fall prevention; cardiovascular risk*

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The essential role of calcium for bone metabolism has been known since the animal studies (in 1928) and calcium balance studies (in 1946) performed by Albright (1). Rickets was first described more than 300 years ago (Glisson, 1599–1677), but the essential role of vitamin D with regards to bone metabolism only became clear following animal experiments with liver oil supplements by McCollum (2).

Vitamin D supplements reduce the risk of falls and fractures in vitamin D-deficient subjects. Vitamin D

deficiency is worldwide considered endemic and therefore vitamin D supplementation is recommended in most guidelines on fracture prevention.

Inadequate intake of calcium via the diet is also common, even more so in patients with a recent fracture, and adequate calcium intake is recommended in the guidelines. The absorption of calcium from the intestines occurs by means of an active, vitamin D-dependent process and to a lesser extent by passive diffusion and is determined – among other factors – by the solubility of

calcium and the pH in the different parts of the gastrointestinal system. Observational research indicates that excessive calcium intake could increase the risk of cardiovascular events.

In daily practice, the care of adequate calcium homeostasis will depend on the need of vitamin D and calcium. There are, however, few all-encompassing studies available about the relationship between the dosage of vitamin D supplementation and changes in serum 25(OH)D to answer questions about the need amongst the elderly, the target values for serum levels, and the quantity and frequency of vitamin D supplements. For calcium intake, the question that arises is what the minimum and maximum calcium dosages should be for recommendation.

This overview aims to provide an answer to these questions, based on a review of relevant literature.

### **Calcium and vitamin D recommendations in Guidelines on Osteoporosis and Fracture Prevention**

The 2011 Dutch Guideline on Osteoporosis and Fracture Prevention (CBO Guideline) advises in the case of patients taking medication to prevent fractures to aim for a total calcium intake (diet and supplements) of 1,000–1,200 mg calcium per day and an intake of vitamin D supplements of 800 IU per day (3).

The United Kingdom NICE 2012 guidelines on fractures and osteoporosis, that are mainly focused on fracture risk and other related NICE guidelines, have no special focus on calcium and vitamin D (<http://www.nice.org.uk/nicemedia/live/13857/60399/60399.pdf>) (last assessed on April 24, 2013). A new guideline on vitamin D will be available in 2014. Canadian guidelines (4) advise intake of 1,200 mg calcium daily in women 50 years and older and men 70 years and older. The vitamin D intake in elderly persons should be 1,000–1,200 IU daily. The Australian guideline (<http://www.osteoporosis.org.au/images/stories/updatedthinkgp.pdf>) (last assessed on April 24th 2013) advises for women over 50 years of age a calcium intake of 1,300 mg per day and a vitamin D intake of 800 IE. In the international literature, there is no consensus on the daily vitamin D supplementary intake (5).

In a recent statement, the US Preventive Services Task Force (USPSTF) recommends against daily supplementation with 400 IU or less of vitamin D and 1,000 mg or less of calcium for the primary prevention of fractures in non-institutionalized post-menopausal women (6). The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with greater than 400 IU of vitamin D and greater than 1,000 mg of calcium for the primary prevention of fractures in the same population (6).

Meta-analyses reveal that calcium supplementation reduces the risk of non-vertebral fractures, with the effect being amplified in combination with vitamin D (7, 8), particularly for hip fracture reduction (9). Supplementation of 400–1,200 IU of vitamin D per day for the elderly (>65 years), in combination with calcium, results in a relative reduction of the occurrence of non-vertebral fractures of 10–20% (10, 11).

An association between vitamin D deficiency, falls, and fracture rates in older women and men has been demonstrated in several studies (12–14).

In a 1-year randomized, population-based, controlled trial 1,000 IU of daily oral ergocalciferol treatment reduced the risk of falling over a year by about one-third in women with a serum 25 hydroxyvitamin D (25OHD) <60 nmol/L and a history of falls in the previous year (15).

In all randomized clinical trials on the effect of drugs with fracture prevention as primary endpoint, both the intervention group and the placebo group were supplemented with vitamin D and calcium (Table 1). However, there were large differences in the amount of calcium and vitamin D supplements in the various fracture studies.

Most of these studies were performed with standard dosages of 250–1,200 IU/day for vitamin D and 500–1,000 mg per day for calcium or dosages of calcium and vitamin D supplements adjusted for dietary intake and serum values of 25(OH)D. In some studies, vitamin D supplements were given before the start of the study, in daily doses during several weeks to months, or in bolus up to 125,000 IU.

### **Mechanism and functional aspects of intestinal absorption of the calcium salts**

The intestinal calcium absorption has been studied extensively in balance studies in patients with chronic renal insufficiency, revealing that a dietary intake of 1,000 mg calcium results in approximately 400 mg being absorbed in the digestive tract, whilst 200 mg of calcium is added to the intestinal lumen via excretion. The total amount of calcium that passes the digestive tract is therefore 1,200 mg, of which 800 mg is excreted via the feces. This means that the average fractional calcium absorption is  $400/1,200 = 0.33$  (16, 17). The serum calcium level and the 24-h calcium excretion can be measured accurately in clinical practice, but the actual quantity of calcium that is absorbed by the bones is much more difficult to measure. This requires the use of 'bio-markers', absorption of calcium isotopes, or – after extended treatment – bone densitometry. The absorption of calcium occurs primarily in the small intestine via an active trans-cellular process on the one hand, regulated by active vitamin D ( $1.25(\text{OH})_2\text{D}_3$ ), and via para-cellular diffusion on the other hand (18, 19), the latter being

**Table 1.** Calcium and vitamin D supplementation in medicinal fracture intervention studies

Study	Medicine	Calcium, mg/d	Vitamin D, IE/d
Black 1996	Alendronate	500 when required	250
Cummings 1996	Alendronate	500 when required	250
Harris 1999	Risedronate	1,000	500 when required <sup>a</sup>
Reginster 2000	Risedronate	1,000	500 when required <sup>a</sup>
McClung 2001	Risedronate	1,000	500 when required <sup>a</sup>
Chestnut 2004	Ibandronate	500	400
Black 2007	Zoledronate	1,000–1,500	400–1,200
Lyles 2007	Zoledronaat hip	1,000–1,500	25(OH)D < 37.5 nmol/L or not measured: Loading dose: 50–120,000 Thereafter 800–1,200
Ettinger	Raloxifen	500	400–600
Neer 2001	Teriparatide	1,000	400–1,200
Greenspan 2007	PTH	700	400
Meunier 2004	SR*SOTI	0–1,000 <sup>b</sup>	400–800
Reginster 2005	SR*TROPOS	0–1,000 <sup>b</sup>	400–800
Cummings	Denosumab	1,000	25(OH)D nmol/L: 30–50: 800 > 50: 400

<sup>a</sup>If the vitamin D level was lower than 40 nmol/L.

<sup>b</sup>To achieve a total intake of 1,000 mg per day.

SR\*: strontium ranelate.

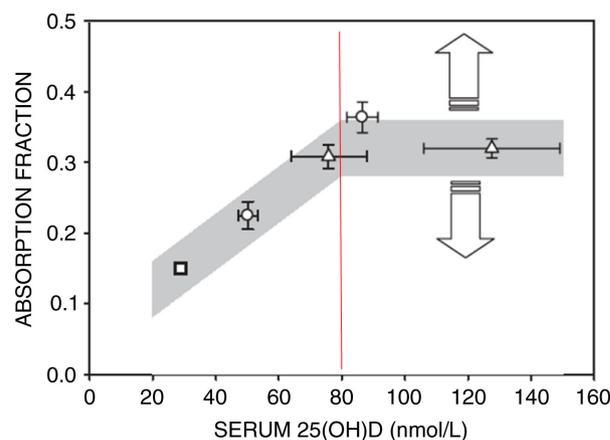
largely vitamin D independent. The active transport is a process that can become saturated and is particularly important in the event of limited calcium intake. This results in an upregulation of the production of active vitamin D. As the fractional calcium absorption is significantly determined by active vitamin D, vitamin D deficiency will also result in decreased calcium absorption. Heaney et al. demonstrated that the calcium absorption increases up to a serum 25(OH)D level of 80 nmol/L and reaches a plateau at >80 nmol/L (Fig. 1) (20). Assuming the fact that approximately 35% of the available calcium is absorbed in the gastrointestinal system, the question is how significant the contributions of the active and passive transport systems are and in which parts of the gastrointestinal system this absorption occurs.

The course of calcium absorption and, in particular, the contribution of active and passive absorption of calcium over the course of the jejunum, ileum, and colon is presented in Fig. 2 (19, 21).

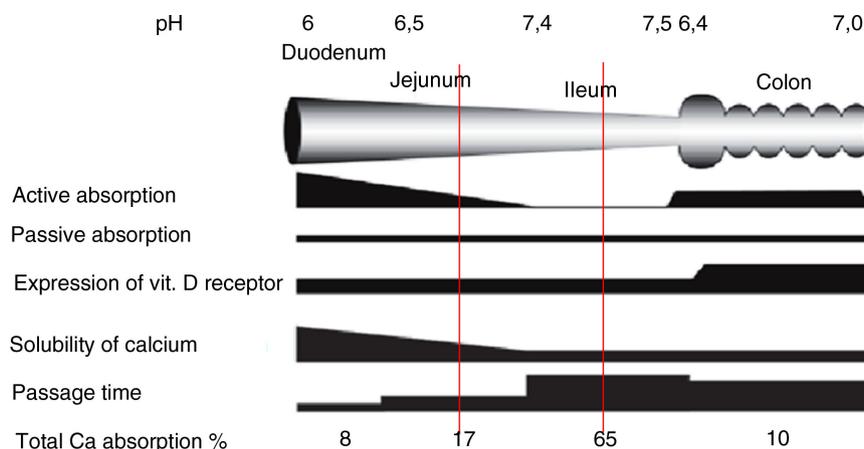
The solubility of the type of calcium salts is important for this absorption process, because calcium can only be absorbed in dissolved form (24, 25). However, the solubility of calcium is primarily dependent on pH, so that the pH of the digestive tract is an important factor in this absorption process. In addition, factors such as pCO<sub>2</sub> and the quantity of bicarbonate and phosphate play an additional role in the calcium absorption process. It is known that the pH changes over the course of the

digestive tract: very low in the stomach (pH 1–2), approximately pH 6 in the duodenum, gradually increasing in the small intestine from 6 or 6.5 in the proximal jejunum to 7.4 in the middle of the small intestine and to 7.5 in the ileum. The pH then decreases to 6.4 in the cecum and in the course of the colon gradually increases again to 6.7 and finally to 7 in the rectum (Fig. 2) (22, 26). The average pH is 7.3 in the small intestine and 6.6 in the colon (23).

In this context, it is important to realize that calcium is not absorbed in the stomach, but in the small and large intestine. The total amount of calcium that is absorbed



**Fig. 1.** Relationship between serum 25(OH)D level and fractional calcium absorption (20).



65% of the total calcium absorption takes place in the ileum (between the red lines).

**Fig. 2.** Calcium absorption, solubility of calcium, contribution of active and passive absorption of calcium and pH in the various segments of the small and large intestine (19, 22, 23).

therefore depends on the amount of calcium consumed, the passage time in the various segments of the small and large intestine, and the amount of soluble calcium available for absorption, which is primarily determined by the pH in each segment of the gastrointestinal tract. In the duodenum, and to a lesser extent the jejunum, there is active calcium transport in addition to passive transport; in the ileum there is primarily passive transport. The largest quantity, namely 65% of the absorbed calcium, is absorbed via passive transport in the ileum, because of the length of this segment compared to the other parts of the digestive tract (19, 21).

Calcium supplementation usually happens as a calcium salt in the form of calcium carbonate or calcium citrate. There are several calcium compounds available. When a compound containing calcium carbonate is taken, this is dissolved in the acidic environment of the stomach. When a compound which contains calcium carbonate and citric acid is taken then this will form calcium citrate when dissolved in a glass of water. These various calcium compounds are also available in various combination preparations with low – 400/440 IU – and higher – 800/880 IU – dosages of vitamin D.

The solubility of these salts has been tested in water, showing that calcium citrate dissolved more completely than calcium carbonate. However, dissolving calcium citrate results in a pH of 5.6 and calcium carbonate in a pH of 8.5, neither of which is an accurate reflection of solubility in the digestive system. After all, the pH varies per section of the digestive system and therefore the solubility of the calcium salt will also vary per section (27–29).

When the calcium salts are ingested and enter the acidic environment of the stomach, dissolved calcium ions become available (30).

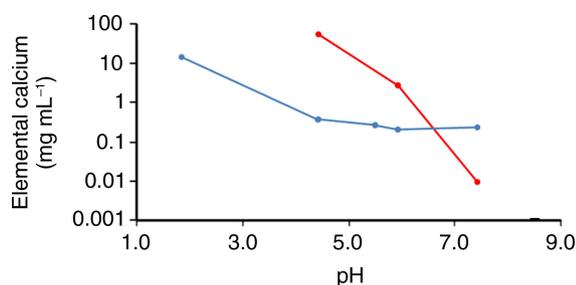
CaCO <sub>3</sub> (insoluble)	+ 2 HCl	→ Ca <sup>2+</sup> + 2Cl <sup>-</sup> + H <sub>2</sub> O + CO <sub>2</sub>
Calcium carbonate	Hydrochloric acid	→ Soluble calcium ion Carbon dioxide
Ca <sub>3</sub> (C <sub>6</sub> H <sub>5</sub> O <sub>7</sub> ) <sub>2</sub> · 4H <sub>2</sub> O	+ 6 HCl	→ 2C <sub>6</sub> H <sub>5</sub> O <sub>7</sub> <sup>3-</sup> + 6H <sup>+</sup> + 3Ca <sup>2+</sup> + 6Cl <sup>-</sup> + 4H <sub>2</sub> O
Calcium citrate	Hydrochloric acid	→ Citric acid Soluble calcium ion

An increasing pH in the duodenum and jejunum (due to bicarbonate production) will result in decreased solubility of calcium because calcium salts are formed once more:



*In vitro* study of the pH-dependent solubility of calcium carbonate compared to calcium citrate – taking into consideration the CO<sub>2</sub> tension that affects the solubility in the digestive tract – shows that the solubility of carbonate is higher at a pH < 6.5 and the solubility of the citrate form is higher at pH > 6.5 (Fig. 3). At a pH of 7.5, the solubility of citrate is around two times higher than that of carbonate. However, the solubility of both calcium salts decreases with increasing pH (27–29).

If we translate this to the practical setting, there are two clinical questions that need to be asked: Is the calcium absorption with use of a calcium-containing supplement the same for calcium carbonate and calcium citrate? and Does the absorption of calcium carbonate and calcium citrate differ in the event of a (relative) high stomach pH, as is the case with the use of antacids or hypochlorhydria or achlorhydria?



**Fig. 3.** Concentration of dissolved elemental calcium (Y-axis, log scale) depending on pH for calcium citrate (blue line) and calcium carbonate (red line), corrected for CO<sub>2</sub> tension in the digestive tract. Modified from Goss et al. (29).

Based on these *in vitro* models, the stomach pH does have an effect on the solubility of the various calcium salts, but because absorption occurs primarily in the small and large intestine – particularly the ileum – at a pH of around 7.5 (Fig. 2: ±65% of the total calcium absorption) it could well be that the pH of the stomach is far less relevant and that the solubility of the calcium salt in the pH range of 6.5 to 7.5 is of particular importance. Of course, the fact that the *in vitro* models

do not correct for other factors, such as buffering by amino acids, bile, and food components, should be taken into consideration (27–29).

The difference in calcium absorption with supplementation of calcium carbonate compared to calcium citrate has been studied extensively. A meta-analysis was published by Sakhaee et al. in 1999, which concluded that calcium absorption was (statistically significant) 24% higher in cases of supplementation with calcium citrate compared with calcium carbonate, both when taken on an empty stomach and when ingested during a meal (Table 2, upper portion) (31). A number of studies have been published since 1999 about this subject, using various techniques to determine calcium absorption, usually in healthy study subjects or post-menopausal women and applying various calcium dosages. The data of these studies are presented in Table 2, lower portion.

### The influence of achlorhydria and proton pump inhibitors on calcium absorption

Literature about the presence of achlorhydria in the elderly is limited. A systematic review by Hurwitz et al. (40)

**Table 2.** Clinical studies into the effect of intestinal calcium absorption with the use of calcium citrate versus calcium carbonate: the upper portion lists the studies in the meta-analysis by Sakhaee et al. (31) and the lower portion lists the studies published thereafter

Author	Year	N	Gender	Population	Method	Calcium dosage (mg)	Meal	Effect citrate vs. carbonate (%)
Bo-Linn	1984	6		Normal	Lavage	1,000	+	21.6
Nicar	1985	14	11 f, 3 m	Normal	Urine Ca excretion	1,000	–	70.5
Recker	1985	7		Normal	Dual isotope	250	–	8.0
Reid	1986	10		Normal	Urine Ca excretion	1,000	+	64.8
Smith	1987	10	f	Normal	Dual isotope	250	+	26.0
Harvey	1988	9		Normal	Faecal recovery	100 or 200	–	28.0
Miller	1988	12		Children	Dual isotope	250	+	36.9
Sheikh	1989	10		Normal	Lavage	1,000	+	4.8
Harvey	1990	20	f		Dual isotope	500	–	25.8
Harvey	1998	21	17 f, 4 m		Urine Ca excretion	1,000	–	55.7
Heaney	1999	17	f	Pre-men	Serum radioactivity	300	+	10.8
Sakhaee	1999				Meta-analysis			24% pooled effect
								Effect citrate vs. carbonate
Micheletti (32)	1996	14			Dual isotope	1 × 1,000 vs. 2 × 500	–	Ca > Ci
Heller (33)	1999	18	f	Post-men	Serum Ca, AUC Ca	500	+	Ci > Ca
Heller (34)	2000	25	f	Post-men 61	Serum Ca, AUC Ca, PTH, urine Ca	500	+	46–94
Heaney (35)	2001	24	f	Post-men 58	AUC serum Ca, PTH, urine Ca excretion	200	+	n.s.
Kenny (36)	2004	34	f		PTH, BSAP, urine Ca excretion, CTX, NTX	1,000 mg 12 week co	+	Ci > Ca (CTX, NTX)
Hanzlik (37)	2005	14	f	19–33	AUC Ca, PTH	1,200	–	Ci > Ca
Thomas (38)	2008	25	f	Post-men	PTH, CTX	500 Ci and 1,000 Ca	–	Ci > Ca
Karp (39)		12	f	22–30	BSAP, serum Ca, PTH	1,000	+	–

F = female, m = male, pre-men = pre-menopausal, post-men = post-menopausal, n.s. = not significant, AUC = area under the curve, BSAP = bone-specific alkaline phosphatase.

shows that only 11% of people older than 65 had a consistent stomach pH of  $>3.5$  at two consecutive measurements and 67% had a consistently low pH. A varying stomach pH (one time  $>3.5$  and one time  $<3.5$ ) was found in 22% (40). The effect of achlorhydria on the absorption of calcium with the use of various supplements has not been studied in any detail.

The effect of proton pump inhibitors on calcium absorption was studied in a review in 2008 (41). This reveals that varying and small groups of patients were studied, using different methods to evaluate calcium absorption and that a reliable answer cannot currently be provided on the question whether the use of antacids has a detrimental effect on calcium absorption (41). The most recent article on this issue was a randomized trial published in 2010 by the same author and revealed no difference in intestinal calcium absorption between 20 mg esomeprazole per day and placebo (42). There has been no research to determine whether there is a difference in calcium absorption between the various calcium salts with use of proton pump inhibitors. Furthermore, the conclusion in the CBO Guideline is that evidence based on observational research suggesting that protonpump inhibitor (PPIs) are fracture-inducing medicines is very weak, particularly as this association can also be linked to the diseases for which the PPIs are prescribed (3, 43).

In conclusion, the *in vitro* data and models are complex and do not entirely explain the calcium absorption process *in vivo*. Clinical studies point consistently to better absorption of calcium with use of citrate than with carbonate. This difference appears to be explained by a higher passive transport of calcium, because in the ileum – where 65% of calcium is absorbed by means of passive transport – calcium citrate dissolves better than calcium carbonate at a pH  $\geq 7.5$ . Studies on the effect of proton pump inhibitors on the absorption of calcium are not unanimous in conclusion and have poor methodology, any differences between calcium citrate and calcium carbonate in this regard were not studied.

### How much calcium and vitamin D should be prescribed?

The average calcium intake in Great Britain for post-menopausal women is 645–705 mg calcium per day (44). This figure is 720–820 mg calcium per day in Germany (45) and in France (46). The calcium intake was also studied in the Netherlands: one-third of the women in a study performed in Amsterdam consumed less than 950 mg calcium per day (47); 18% of the women of approximately the same age in a more rural area (Ede, the Netherlands) consumed less than 800 mg per day (48). In a population with an average age of 80 years, living independently or in care homes, 25% consumed less than 938 mg per day (49). This shows that there is a large variation in the average calcium intake between

the different countries. In addition, there is a large variation between individuals. It is particularly important to know what the calcium intake is of those individuals who are most in need of supplementation, for example, the patients with a recent fracture. This was demonstrated recently in a study in 502 patients over the age of 50 years with a recent fracture: only 11% had a calcium intake  $>1,000$  mg per day in combination with serum 25(OH)D levels  $>50$  nmol/L (Fig. 4) (50). An excessively low serum vitamin D level in combination with inadequate calcium intake occurred in 43% (50).

As demonstrated in Fig. 5, this shortage applies to both men and women, in all examined age categories  $>50$  years and with all types of fractures. It is noteworthy that the inadequate calcium intake occurred in equal measures with a normal BMD, osteopenia, and osteoporosis. Therefore, inadequate calcium intake is an endemic problem in patients presenting with a fracture (50). Based on these data, one can conclude that one should check the calcium intake and vitamin D level in all fracture patients, even in those with a normal BMD.

### Required calcium supplementation

Recently, the required calcium supplementation was studied in patients with a recent fracture (50, 51). In order to guarantee calcium intake of 1,000 per day, 12% of patients required supplementation of 1,000 mg per day and 57% required 500 mg. If one were to prescribe 500 mg calcium supplementation per day to all patients for pragmatic reasons, this would only be inadequate for achieving the required total intake of 1,000 mg per day in 12% of the patients, whilst only a very small group of patients achieves an unnecessary daily calcium intake  $>1,500$  mg. If one were to prescribe a standard 1,000 mg calcium supplementation per day, nearly 90% would exceed the limit of 1,500 mg per day. Except for a small group requiring 1,000 mg per day because they consume virtually no dairy products, 1,000 mg supplementation is too high a level of substitution, particularly in the light of indications about the potentially negative cardiovascular effects of high-dose calcium supplementation.

With the use of corticosteroids, there are many factors that play a role in increasing the risk of osteoporosis and fractures. One of these is the reduced intestinal absorption of calcium. A higher level of calcium intake is therefore required. All studies in patients treated with corticosteroids gave supplementation of 1,000–1,500 mg calcium per day, which is more than the recommended supplementation dose for post-menopausal women and age-related osteoporosis.

### Required vitamin D supplementation

Dawson-Hughes et al. reported an estimated average essential vitamin D intake of 800–1,000 IU per day (20–25  $\mu$ g per day) in order to achieve a 25(OH)D  $>75$  nmol/L

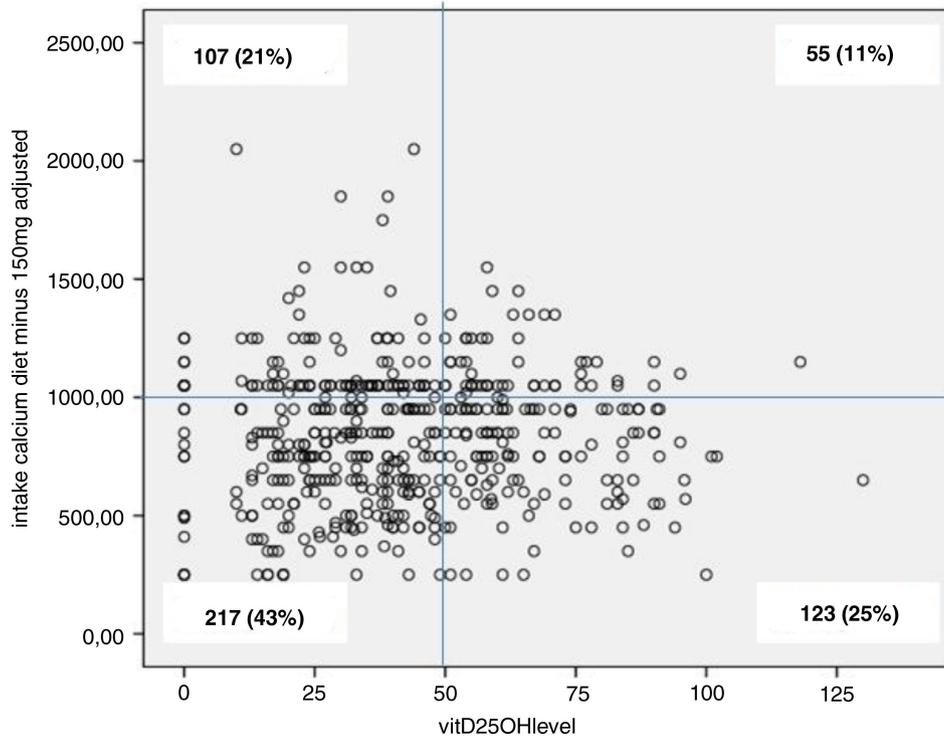


Fig. 4. Calcium intake and serum 25(OH)D in 50+ patients with a recent fracture.

in the elderly. Significantly higher dosages are required to ensure that virtually all elderly people achieve this level of vitamin D (52). However, there are no arguments for dosages higher than 800 IU per day (20 µg per day),

because there are not enough studies to support this. Cranney et al. performed a meta-analysis in 2007 on the relationship between serum 25(OH)D and the intake of vitamin D from the diet. The conclusion of this study was

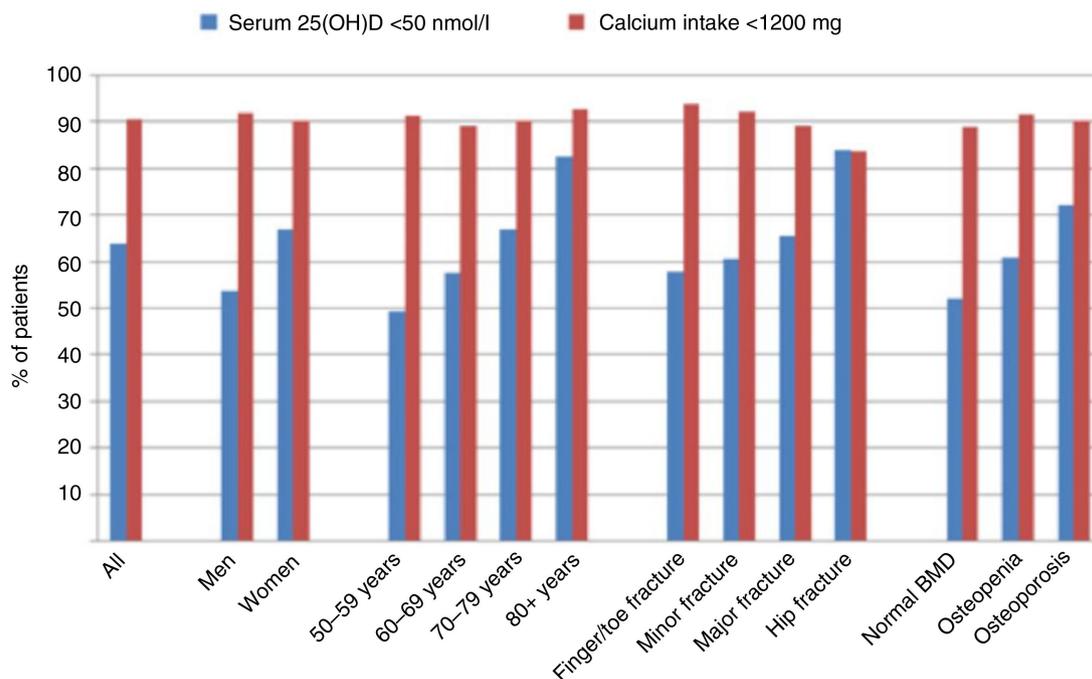


Fig. 5. Calcium intake and serum 25(OH)D in 50+ patients with a recent fracture, according to gender, age, fracture location and BMD.

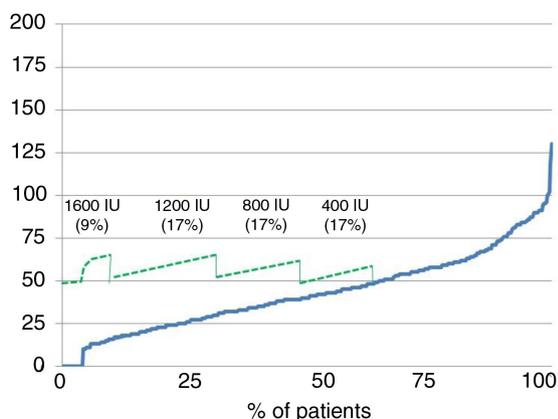
that vitamin D in the diet increased the serum 25(OH)D concentration, but it was not clear to which extent. The large discrepancies between the various studies (differences in initial vitamin D levels, different populations, different assays for vitamin D, etc.) made it impossible to indicate how much vitamin D is required for whom (53).

Studies by Heaney (54) show that every 100 IU added vitamin D causes the serum 25(OH)D level to increase by 2.5 nmol/L (range 1.75–2.75 nmol/L). Therefore, a dosage of 800 IU will cause an increase in serum 25(OH)D of approximately 20 nmol/L.

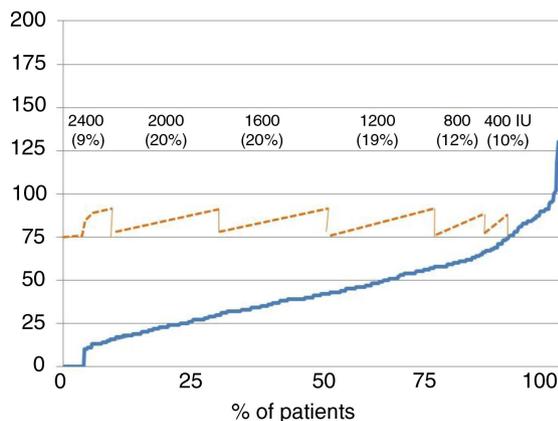
Based on the 25(OH)D levels in a study of 626 patients with a recent fracture, one could theoretically – going out from the starting point that every 100 IU of added vitamin D causes a 2.5 nmol/L increase in the serum 25(OH)D level – tailor the vitamin D supplementation in order to achieve a level  $\geq 50$  nmol/L in everyone (55) (Fig. 6).

In order to achieve a level  $\geq 75$  nmol/L in every patient, one would theoretically have to give a dosage  $>800$  IU per day to at least 80% of the patients, even up to 2,400 IU per day (Fig. 6).

Serum 25(OH)D



Serum 25(OH)D



**Fig. 6.** Required dose of vitamin D to achieve a 25(OH)D level:  $\geq 50$  (top panel) and  $\geq 75$  nmol/L (bottom panel).

If one assumes a standard supplementation of 800 IU vitamin D<sub>3</sub>, this will achieve a 25(OH)D  $\geq 50$  nmol/L in 75% of the patients (Fig. 7).

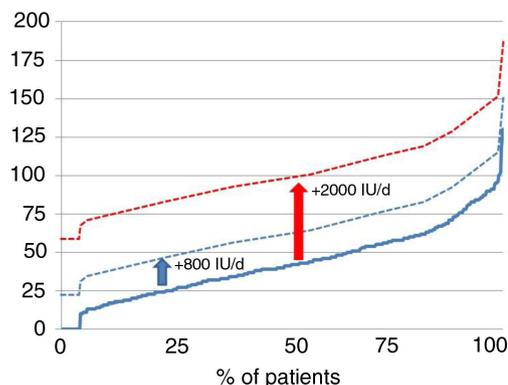
A standard supplementation of 2,000 IU vitamin D<sub>3</sub> would theoretically result in a 25(OH)D  $\geq 50$  nmol/L in 100% of the patients and a 25(OH)D  $\geq 75$  nmol/L in 90% of the patients (Fig. 7).

In addition, there are as yet unidentified sub-groups that require higher dosages of vitamin D<sub>3</sub>, such as patients with a severe vitamin D deficiency with secondary hyperparathyroidism. The first placebo-controlled study on the effect of various daily dosages of vitamin D<sub>3</sub> in healthy post-menopausal women with vitamin D deficiency (25(OH)D  $< 50$  nmol/L) was published very recently. The authors concluded that a dosage of 800 IU per day resulted in an increase of the serum 25(OH)D level to above 50 nmol/L in 97.5% of the women, without further increase after 12 months. These results show that a daily dosage of 800 IU is sufficient for the majority of post-menopausal women with vitamin D deficiency to exceed the threshold of 50 nmol/L, which most guidelines consider the desired threshold value of 25(OH)D (56).

### Calcium intake and cardiovascular disease

Concern has arisen amongst doctors and patients following the epidemiological study by Bolland et al. from 2008 (57). This study found a link between calcium supplementation and an increased risk of myocardial infarction. This study evaluated healthy elderly women who – in addition to an average calcium intake of 860 mg per day – received either a calcium supplement of 1,000 mg per day or a placebo for five years in this randomized controlled trial. A significant problem is therefore the generalizability of the results of this study. Who would prescribe such a high level of calcium to healthy women for such a lengthy period?

Serum 25(OH)D



**Fig. 7.** 25(OH)D level achieved with use of a set dosage of vitamin D supplementation (800 IU and 2,000 IU per day).

There was a slightly increased risk of myocardial infarction in the treated group.

The study by Lewis et al. (58) contradicts this. In this study, 1,460 women aged 70 years or older were given a calcium supplement of 1,200 mg or a placebo. In addition, these women consumed about 950 mg calcium via the diet. In this study, the investigators found no evidence that calcium supplementation causes an increased risk of cardiovascular conditions during an average follow-up of 4.5 years.

Several large observational studies performed more than 10 years ago even show a favorable effect of calcium supplementation such as the IOWA Health Study (59) and the Nurses' Health Study (60). The observed protective effect of higher calcium intake in these studies is probably due to the phenomenon of confounding by indication: healthy women who consume more calcium, will in general have a healthier lifestyle: more exercise, healthier diet, and less smoking.

In a reanalysis of The Women's Health Initiative Study there was a slight increase in cardiovascular events in the intervention group, most noticeable in myocardial infarction (61).

In a recently published prospective (Swedish mammogram) cohort study the use of calcium supplementation was not associated with cardiovascular mortality or ischemic heart disease (62). In women who had a dietary intake of >1,400 mg calcium per day, the use of calcium supplements was associated with a higher all-cause mortality rate (62).

In another recently published prospective observation study an association of calcium supplementation with an increased risk of cardiovascular mortality was found in men but not in women (63).

To summarize, probably because of heterogeneity and limitations in study design, the result of the different studies are contradictory. Some show a cardio protective effect of calcium supplementation. Other studies find an increased risk of myocardial infarction, cardiac mortality, and/or total mortality (but only with a total calcium intake greatly exceeding the usual recommendations). Yet other studies find no significant relation between calcium supplementation and cardiac events. Probably only (well-designed and sufficiently powered) prospective randomized controlled trials with cardiac events as a prespecified primary end point will be able to allow definite conclusions on this subject. After an extensive literature search we have come to the conclusion that as up to now no such studies have been published.

### Calcium intake and drug interactions and adverse effects

It is important to note that oral use of calcium salts can reduce the absorption of bisphosphonates, tetracyclines (doxycycline, minocycline, and demeclocycline),

fluoroquinolones (ciprofloxacin, levofloxacin, norfloxacin, ofloxacin, and moxifloxacin), levothyroxine, fiber-rich food, and levodopa. For these medicines, it is generally recommended to take these at least 2 h before ingestion of calcium salts; for the fluoroquinolones an interval of 4 h is preferable.

As the gastric emptying speed decreases with age and emptying takes longer in certain patients with specific conditions (for example in diabetes patients with gastroparesis due to autonomic neuropathy), it is probably better for all these medicines to maintain a period of 4 h between intake of these medicines and ingestion of calcium salts (longer if indicated, as in the case of gastroparesis).

Calcium could cause constipation, which can form a reason to add a laxative, for example, a magnesium salt or oxide.

### Patient preference

Assuming that therapy compliance is an important subject in the treatment of osteoporosis, any preference by the patient for a certain medication is probably also important. There are very few direct comparative studies on patient preference, also for calcium tablets. Which form of administration of calcium supplementation (tablet or effervescent tablet in solution) does the patient prefer? Do patient-friendly packages combining calcium and vitamin D and bisphosphonate promote therapy compliance? Research performed in the Netherlands used a randomized, open, cross-over trial in 102 patients to compare Calci-Chew D<sub>3</sub>® chewable tablets to CaD® sachets (64). It was determined before the start that patient preference would be the most important primary measure of outcome: 67% preferred the chewable tablet, 19% the sachet, and 15% had no preference (64). The question that arises is how to interpret this: there was no difference in clinical relevant factors such as tolerance, compliance, and adverse effects. Also the actual medication taken was not significantly different: of the 14 days, the chewable tablet was taken an average of 12.8 days and the sachet 13.5 days. One point of criticism on this study is the extent to which these results over a period of 14 days can be extrapolated to the long term, for example a period of 5 years. The tolerability was similar for the two formulations. The authors concluded that patient preference is very important for medication that should be used chronically but also that the design of studies and the interpretation of the data are complicated.

### Practical advice for calcium and vitamin D supplementation

Based on guidelines, optimization of total calcium intake towards a total of 1,000–1,200 mg calcium per day is considered necessary and sufficient in the context of osteoporosis and fracture prevention strategies with drug

treatment. Calcium supplementation can be achieved by diet, mainly milk products (milk, yogurt, or cheese) or calcium-containing tablets. Dietary calcium intake is preferred and 3–4 portions of milk products per day should be advised. If this cannot be achieved, supplementation of calcium should be considered. If a patient consumes 1–2 portions of milk products per day, then the advice is to add 1–2 portions of milk products per day or 500 mg of calcium supplementation. If a patient does not take any milk products, supplementation of 1,000 mg calcium is needed. No adjustment is required if the patient consumes 3–4 portions of milk products per day. In the context of the concern about cardiovascular conditions, calcium supplementation should be individualized.

When considering the choice of calcium supplements one should take into account that fractional calcium absorption is 24% higher for calcium citrate compared to calcium carbonate, probably because of higher dissolution in the ileum, where 65% of the total calcium is absorbed. The effect of proton pump inhibitors on calcium absorption are inconclusive as is the case with the effect of age-related changes in gastric physiology (65). The practical advice concerning vitamin D supplementation as part of osteoporosis treatment is to prescribe a minimum dose of 800 IU per day of vitamin D<sub>3</sub>. This also applies to people in nursing homes and care homes and patients with a recent fracture, irrespective of BMD. Higher dosages could be considered in case of severe vitamin D deficiency with secondary hyperparathyroidism.

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**\*Robert Y. van der Velde**

Department of Internal Medicine  
VieCuri Medical Centre for North Limburg  
Venloseweg 210  
5912 BL, Venlo, The Netherlands  
Email: rvdvelde@viecuri.nl