Scandinavian Journal of Clinical & Laboratory Investigation, 2012; 72(Suppl 243): 60–64

ORIGINAL ARTICLE

Interaction between Vitamin D and calcium

PAUL LIPS

Department of Internal Medicine, Endocrine section, VU University medical center, Amsterdam, The Netherlands

Abstract

A low calcium intake aggravates the consequences of vitamin D deficiency. This suggests an interaction between vitamin D and calcium intake, which is the subject of this review. The active vitamin D metabolite, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) binds to the vitamin D receptor (VDR) in the intestinal cell and stimulates the active calcium transport from the intestine to the circulation. Vitamin D is not needed for the paracellular transport of calcium, which depends on the calcium gradient. Active calcium absorption decreases when the serum 25-hydroxyvitamin D (25(OH)D) concentration is <20 nmol/L. Studies in the VDR null mouse have demonstrated that bone mineralisation can be restored without vitamin D by a diet very high in calcium and lactose. Both calcium and vitamin D metabolites can decrease the secretion of parathyroid hormone (PTH) through the calcium sensing receptor and the VDR respectively. With an increasing serum 25(OH)D concentration up to 100 nmol/L or higher serum PTH is still decreasing. A high calcium intake increases the half life of 25(OH)D. In patients with primary or secondary hyperparathyroidism, the half life of 25(OH)D is shorter. Similar interactions between calcium intake and vitamin D status have been shown in rat experiments, generally indicating that a high calcium intake is good for the vitamin D economy. Clinical trials with vitamin D and/or calcium to decrease fracture incidence generally have shown that trials with vitamin D and calcium had better results than calcium or vitamin D alone. The effects of these trials also depend on baseline calcium intake, baseline vitamin D status, age and residence. Trials in institutionalized persons had better results than in independently living elderly. These results confirm that an interaction exists between calcium and vitamin D.

Introduction

Since the early 20th century it is known that vitamin D facilitates the absorption of calcium and can cure rickets. A predisposing factor for rickets is a low calcium intake. This suggests that there is an interaction between vitamin D and calcium. One may ask the following questions:

1. Can calcium compensate for vitamin D deficiency?
2. Can vitamin D compensate for low calcium intake?
3. Do calcium and vitamin D have additive effects?

The active interplay between calcium and vitamin D is needed to prevent skeletal disease. Clinical rickets or osteomalacia occurs more easily when vitamin D deficiency is coupled to low calcium intake or low calcium absorption. This occurs for example in coeliac disease. While rickets may occur in the growing skeleton after a few months, it usually takes a long time, several years for osteomalacia to develop in the adult skeleton. Vitamin D deficiency and low dietary calcium intake both may cause secondary hyperparathyroidism leading to bone resorption and contributing to the pathogenesis of osteoporosis [1]. In this review vitamin D dependent and vitamin D independent calcium absorption will be discussed. Subsequently, the skeletal disease in the vitamin D receptor knock-out mouse will be presented. Secondary hyperparathyroidism can be suppressed by calcium and by the active vitamin D metabolite, 1,25-dihydroxyvitamin D. A vitamin D threshold has been sought for calcium absorption, for parathyroid hormone secretion, for bone mineral density and bone turnover and for physical performance. The calcium intake may be a determinant for the turnover of vitamin D metabolites and high calcium intake may have a vitamin D sparing effect. These subjects will be discussed in this review paper. The interaction between vitamin D and calcium can also be deducted from clinical trials with vitamin D without or with calcium to prevent osteoporotic fractures.

Correspondence: Paul Lips, Department of Internal Medicine, Endocrine section, VU University medical center, Amsterdam, The Netherlands. E-mail: P.Lips@vumc.nl

ISSN 0036-5513 print/ISSN 1502-7686 online
DOI: 10.3109/00365513.2012.681960

Calcium absorption

The active vitamin D metabolite, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) stimulates the active calcium transport through the intestinal wall. The active metabolite binds to the vitamin D receptor in the intestinal epithelial cell, subsequently the calcium binding protein CaBP-9K is synthesized and the calcium channels TRPV6 and TRPV5 are activated. Calcium can enter the cell from the intestinal lumen and is transported through the cell by the calcium binding protein and transferred to the interstitium by an ATP mechanism [2]. This active transport mechanism has a maximum. Besides the active transport, paracellular transport takes place by diffusion. The paracellular transport depends on the calcium gradient, i.e. on calcium intake. In case of vitamin D deficiency, the active transport is lower and diffusion becomes more important especially when calcium intake is high.

Clinical vitamin D deficiency with a risk for rickets and osteomalacia occurs at low serum concentrations of 25-hydroxyvitamin D (25(OH)D). This was shown in an Australian study in 319 patients with serum 25(OH)D concentration below 40 nmol/L. In these patients calcium absorption was measured by an isotope technique and the active vitamin D metabolite, $1,25(OH)_2D$, was measured as well as bone turnover parameters, hydroxyproline excretion and alkaline phosphatase. It turned out that $1,25(OH)_2D$ and calcium absorption became low when serum 25(OH)D concentrations was below 20 nmol/L. At these concentrations hydroxyproline excretion increased as well as serum alkaline phosphatase [3]. A relationship between serum 25(OH)D concentration and calcium absorption was not found in a study in pre- and postmenopausal women. However, a positive correlation existed between serum $1,25(OH)_2D$ concentration and calcium absorption and this relationship was somewhat stronger when serum 25(OH)D concentration was low [4]. The roles of calcium and vitamin D for skeletal mineralisation have been extensively studied in the VDR-null mouse. The VDR-null mouse is characterized by alopecia, decreased longitudinal growth and rickets, altered immunity, hypertension and cardiac hypertrophy, increased risk for chemically induced cancer and altered emotional behaviour [2]. Rickets in this mouse cannot be cured by $1,25(OH)_2D3$ and not by a high calcium diet. However, when a very high calcium and lactose diet ("rescue diet") is given to the VDR-null mouse the rickets is cured and the bone becomes well mineralized. This shows that vitamin D is not essential for bone mineralization while the problem of low calcium absorption can be overcome with a special diet to facilitate passive diffusion [5]. The VDR-null mouse has a human analogue i.e. patients with mutations leading to inactivation of the vitamin D receptor. This causes vitamin D dependent rickets type 2 or hereditary vitamin D resistant rickets associated with alopecia and severe rickets. This rickets can be cured by calcium infusion or by a very high calcium diet [6].

Suppression of secondary hyperparathyroidism

The activity of the parathyroid glands can be decreased by calcium and vitamin D metabolites. Calcium can bind to the membrane bound calcium sensing receptor in the parathyroid cell, suppressing parathyroid hormone (PTH). The active vitamin D metabolite $1,25(OH)_2D$ binds to the nuclear vitamin D receptor in the parathyroid cell and suppresses parathyroid hormone. The active metabolite increases serum calcium by increasing active calcium absorption in the intestine and the increased serum calcium concentration suppresses PTH. In clinical trials and in epidemiological studies, usually a negative relationship is found between serum 25-hydroxyvitamin D and parathyroid hormone. This suggest a direct negative feedback by 25(OH)D on the parathyroid cell. This could be possible when 25(OH)D is further hydroxylated in the parathyroid cell to $1,25(OH)_2D$. The 1α-hydroxylase has been demonstrated in many cell types of many organs and probably is also present in the parathyroid cell. This could explain the negative correlation between 25(OH)D concentration and parathyroid hormone. The different negative feedback mechanisms are shown in Figure 1. The relationships between the serum concentrations of 25(OH)D and PTH and other parameters of bone metabolism have been extensively studied in the Longitudinal Aging Study Amsterdam (LASA). The LASA study is an ongoing epidemiological study on the determinants of healthy aging in a representative sample of the older Dutch population. In this population 48 % of the participants had a serum 25(OH)D concentration lower than 50 nmol/L. A significant negative correlation between serum concentrations

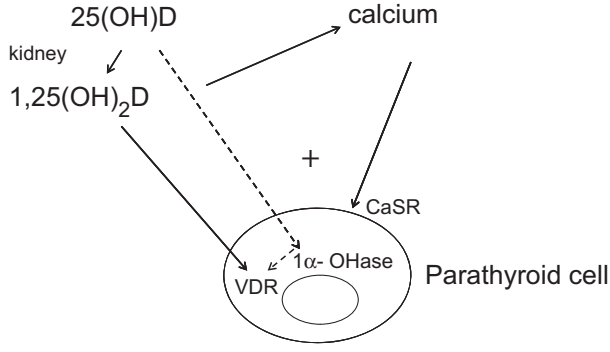

Figure 1. Negative feedback on parathyroid cell by $1,25(OH)_2D$, by 25(OH)D after conversion by the 1α-hydroxylase, and by calcium.

of 25(OH)D and PTH was observed but there was no clear threshold [7]. This means that serum PTH concentration still decreased when serum 25(OH)D concentrations were higher than 100 nmol/L. Similar observations were made in the NEMO study (Network in Europe on Male Osteoporosis) in a cohort of aging males from Lyon and another cohort of aging males from Ghent (NEMO, unpublished data). While a clear threshold for serum PTH concentrations was not observed, suppression of bone turnover parameters serum osteocalcin concentration and urine-deoxypyridinoline excretion was possible up till a threshold serum 25(OH)D concentration of about 40 nmol/L [7]. Similarly, bone mineral density of the total hip and the trochanter increased with serum 25(OH)D concentration up till a threshold of 50 nmol/L. Physical performance measured with three tests, a walking test, 5 chair stands and a tandem stand, increased with serum 25(OH)D concentration up till a threshold of 60 nmol/L. The effect of calcium supplements on the concentrations of serum PTH and serum $1,25(OH)_2D$ has been studied on the short and long term. A long term study was done in 248 postmenopausal women receiving 0, 1,000 or 2,000 mg calcium per day for three years. The sserum PTH concentration was suppressed about 15 % and that of serum $1,25(OH)_2D$ more than 20 % [8]. A short term study showed that increasing the calcium intake from 800 to 2,400 mg per day in volunteers caused a decrease of serum PTH concentration of 30 % during 24 hours [9]. The relationship between vitamin D status, calcium intake and serum PTH was studied cross-sectionally in 2,310 Icelandic adults. When serum 25(OH)D concentration was lower than 25 nmol/L calcium intake influenced serum PTH concentration significantly [10]. In that case a calcium intake of more than 1,200 mg led to a suppression of serum PTH concentration of about 20 % compared with a calcium intake lower than 800 mg per day. However, this effect of calcium intake decreased when serum 25(OH)D concentration was higher than 25 nmol/L and disappeared when serum 25(OH)D concentration was higher than 45 nmol/L. The investigators concluded that calcium intake had little or no effect on serum PTH concentration when serum 25(OH) D concentration was higher than 45 nmol/L. This study clearly shows the interaction between vitamin D status and calcium intake.

Influence of calcium on vitamin D economy

Experiments in rats on different calcium intakes showed that there was a relationship between calcium intake and the half life of serum 25(OH)D concentration. When calcium intake was higher, the half life of 25(OH)D was longer, indicating a vitamin D sparing effect. Serum 25(OH)D concentration decreased faster in rats with a very low calcium intake than in rats with a high calcium intake [11]. In patients with primary hyperparathyroidism or secondary hyperparathyroidism after gastrectomy serum $1,25(OH)_2D$ concentration showed a relationship with the half life of serum 25(OH)D;. the higher the $1,25(OH)_2D$ concentration the shorter the half life of 25(OH)D [12]. The authors concluded that high concentrations of $1,25(OH)_2D$ and PTH in these circumstances stimulated the breakdown of 25(OH)D. More recently the effect of dietary calcium on the synthesis of $1,25(OH)_2D$ and the metabolism of 25(OH)D was studied in rats. The authors observed that increasing the dietary calcium content from 0.1 to 1.0 % led to an increase of 25(OH)D concentration from 22 to 85 nmol/L. However, the $1,25(OH)_2D$ concentration was much higher in the rats on a low calcium and low vitamin D diet than in the rats with either a low vitamin D and high calcium diet or rats with a high calcium and high vitamin D diet [13]. When studying the kidney tissue of these rats they observed that the 1α-hydroxylase or CYP27B1 mRNA was induced by low calcium diet. On the other side CYP24 was stimulated by a high vitamin D diet. These studies show that a high calcium intake has a vitamin D sparing effect.

Clinical trials with calcium and/or vitamin D supplements

The interaction between calcium and vitamin D is also visible in the results from randomized clinical trials with calcium and/or vitamin D with fractures as mean outcome criterion. One of these trials was done in France in 3,270 nursing home residents who received either vitamin D3 800 IU/day and calcium 1200 mg/day vs double placebo. In this trial there was a significant decrease in the incidence of hip fractures and other non-vertebral fractures after 18 months [14]. A trial performed in Amsterdam in 2,578 elderly persons who received vitamin D3 400 IU/day or placebo did not show a decrease of hip fractures or other non-vertebral fractures [15]. These trials were quite different in many aspects. In Lyon the patients had a mean age of 84 yr while in Amsterdam this was 80 yr. The baseline calcium intake was 514 mg/day in Lyon and more than 1,000 mg/day in Amsterdam. The interventions were very different. The effect of treatment on serum PTH concentration was a decrease of 50 % in Lyon and 15 % in Amsterdam. The gain in BMD was 6 % in Lyon and 2 % in Amsterdam [16]. The different outcomes may be due to the different centres, different baseline circumstances and different interventions. Calcium may be needed besides vitamin D for a successful treatment. However, another trial in the United Kingdom with vitamin D3 100,000 IU/4 months vs

placebo in persons older than 65 yr showed a significant decrease in fracture incidence in the vitamin D group vs the placebo group. In this trial calcium was not added [17]. Also in another trial from the UK in older persons with a previous fracture 4 groups received either vitamin D3 800 IU/day or placebo and calcium 1,000 mg/day or placebo in a factorial design. This study did not show any difference in fracture incidence between the calcium group, the calcium and vitamin D group, the vitamin D group and the placebo group (Record Trial Group), [18]. In the last 20 years altogether 18 trials with vitamin D with or without calcium were performed and five of these showed a significant decrease of fracture incidence. Two trials showed an increase of fracture incidence and both of these were performed with high dose of vitamin D once yearly [19].

Many meta-analyses were performed with different conclusions according to different inclusion criteria. The meta-analysis of Boonen et al. [20] compared trials with vitamin D alone with trials combining vitamin D and calcium. Only the latter trials showed a significant decrease of hip fracture risk with a risk ratio of 0.82 (95 % CI 0.71–0.94). The meta-analysis of Tang et al. [21] compared trials with calcium only with trials using calcium and vitamin D. In the meta-analysis both groups of trials showed a significant decrease of fracture incidence, 10 % with calcium alone and 13 % with calcium and vitamin D. A sensitivity analysis was performed and this showed that trials in institutionalized elderly showed better results than those in the community. The trials with a low baseline 25(OH)D concentration showed a better outcome than those with a normal serum 25(OH)D concentration at baseline. Trials in patients with a low dietary calcium intake showed better outcome than those in patients with a normal dietary calcium intake. A vitamin D dose of 800 IU/day or more gave better results than lower vitamin D doses. Results in persons of 70–79 years and especially more than 80 years gave better results than in persons of 50–69 years. Lastly, compliance played a very important role. These trials and meta-analyses show a clear interaction between baseline calcium intake, calcium supplements, baseline vitamin D intake and vitamin D supplements.

Conclusion

It is possible to live without the active vitamin D metabolite $1,25(OH)_2D$ and vitamin D receptor. However, this requires a very high calcium intake as only passive diffusion of calcium in the intestine can supply the calcium for bone mineralization in this situation. An adequate vitamin D status makes calcium intake more flexible. A low calcium intake causes a high turnover of vitamin D metabolites, due to higher production of $1,25(OH)_2D$ and higher breakdown of vitamin D metabolites. A low calcium intake causes or aggravates vitamin D deficiency while a high calcium intake is vitamin D sparing. Clinical trials with vitamin D with or without calcium sometimes show contradicting results. The effect size and significance regarding a decrease of fracture incidence depend on baseline calcium intake, baseline vitamin D status, calcium and vitamin D supplement doses, age, housing situation and compliance. Meta-analyses on vitamin D for fracture prevention suggest that a combination of vitamin D and calcium is more effective than vitamin D alone. When prescribing vitamin D or calcium supplements one should remember the interaction between calcium and vitamin D.

Questions and Answers

M Fikagawa, *Japan*

As a nephrologist, I am concerned that a higher calcium load may lead to deterioration in renal function. Has this perhaps been looked at in previous clinical trials?

P Lips

In most trials an exclusion criterion on renal function was set at a serum creatinine concentration of 150 μmol/L. There might be an issue of high calcium intakes. The meta-analyses from Poland and Australia raised some concerns about cardiovascular disease and the same would apply for renal disease.

M Hewison, *USA*

I wonder if you could speculate on the way that calcium was modulating the action of vitamin D in the kidney. It would be interesting to know if the same mechanism could apply in extra-renal sites of vitamin D metabolism.

P Lips

I was also surprised at the very large effect reported in the study from Australia. I do not know whether the effect is through PTH or if it is a direct effect on the kidney.

J-D Ringe, *Germany*

I think the study from Poland raised a very dangerous issue, because in the pathogenesis of atherosclerosis, a disease of lipids and cholesterol, with plaque formation, the plaques will calcify regardless of the intake, because there is always enough calcium. Normally supplementation with calcium, does not increase the serum calcium concentrations. Calcium is in a steady state and the rest goes into the kidney.

P Lips

The effects, if real, are small. We studied people in nursing homes, giving them vitamin D in three different regimes, 600 U/day, 4,000 U/week or 18,000 U/month and after 4 months added calcium. The calcium had no additive effect on PTH but lead to a small significant increase in serum calcium concentrations, which may lead to some deleterious effect.

J-D Ringe

If you say that calcium may be dangerous, it follows that vitamin D could be dangerous, since it increases calcium absorption! It is an anomaly if you say that vitamin D is protective of CVD when it increases calcium.

Declaration of interest: The author report no conflicts of interest. The author alone is responsible for the content and writing of the paper.

References

[1] Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocrine Rev 2001;22:477–501.

[2] Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HG, Lieben L, Mathieu C, Demay M. Vitamin D and human health: lessons from vitamin D receptor null mice. Endocr Rev 2008;29:726–76.

[3] Need AG, O'Loughlin PD, Morris HA, Coates PS, Horowitz M, Nordin BE. Vitamin D metabolites and calcium absorption in severe vitamin D deficiency. J Bone Miner Res 2008;23:1859–63.

[4] Aloia JF, Chen DG, Yeh JK, Chen H. Serum vitamin D metabolites and intestinal calcium absorption efficiency in women. Am J Clin Nutr 2010;92:835–40.

[5] Panda DK, Miao D, Bolivar I, Li J, Huo R, Hendy GN, Goltzman D. Inactivation of the 25-hydroxyvitamin D 1 alpha-hydroxylase and vitamin D receptor demonstrates independent and interdependent effects of calcium and vitamin D on skeletal and mineral homeostasis. J Biol Chem 2004;279:16754–66.

[6] Liberman UA, Samuel R, Halabe A, Kauli R, Edelstein S, Weisman Y, Papapoulos SE, Clemens TL, Fraher LJ, O'Riordan JL. End-organ resistance to 1,25-dihydroxycholecalciferol. Lancet 1980;1:505–6.

[7] Kuchuk NO, Pluijm SM, van Schoor NM, Looman CW, Smit JH, Lips P. Relationships of serum 25-hydroxyvitamin D to bone mineral density and serum parathyroid hormone and markers of bone turnover in older persons. J Clin Endocrinol Metab 2009;94:1244–50.

[8] Elders PJM, Lips P, Netelenbos JC, van Ginkel FC, Khoe E, van der Vijgh WJF, van der Stelt PF. The long term effect of calcium supplementation on bone loss in perimenopausal women. J Bone Miner Res 1994;9:963–70.

[9] McKane WR, Khosla S, Egan KS, Robbins SP, Burritt MF, Riggs BL. Role of calcium intake in modulating age-related changes in parathyroid function and bone resorption. J Clin Endocrinol Metab 1996;81:1699–1703.

[10] Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G. Relationship between serum parathyroid hormone levels, vitamin D sufficiency and calcium intake. JAMA 2005;294:2336–41.

[11] Clements MR, Johnson L, Fraser DR. A new mechanism for induced vitamin D deficiency in calcium deprivation. Nature 1987;325:62–65

[12] Davies M, Heys SE, Selby PL, Berry JL, Mawer EB. Increased catabolism of 25-hydroxyvitamin D in patients with partial gastrectomy and elevated 1,25-dihydroxyvitamin D levels. Implications for metabolic bone disease. J Clin Endocrinol Metab 1997;82:209–12.

[13] Anderson PH, Lee AM, Anderson SM, Sawyer RK, O'Loughlin PD, Morris HA. The effect of dietary calcium on 1,25$(OH)_2$D3 synthesis and sparing of serum 25(OH)D3 levels. J Steroid Biochem Mol Biol 2010;121: 288–292.

[14] Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier PJ. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med 1992;327:1637–42.

[15] Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. Ann Intern Med 1996;124:400–406.

[16] Ooms ME, Roos JC, Bezemer PD, van der Vijgh WJF, Bouter LM, Lips P. Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial. J Clin Endocrin Metab 1995;80:1052–1058.

[17] Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 supplementation on fractures and mortality in men and women living in the community: randomized double blind controlled trial. BMJ 2003;326:469–72.

[18] Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS et al; RECORD Trial Group. Oral vitamin D3 and calcium for secondary prevention of low trauma fractures in elderly people: a randomised placebo-controlled trial. Lancet 2005;365:1621–8.

[19] Lips P, van Schoor NM. The effect of vitamin D on bone and osteoporosis. Best Pract Res Clin Endocrinol Metab 2011;25:585–91.

[20] Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative meta-analysis of randomized controlled trials. J Clin Endocrinol Metab 2007;92: 1415–23.

[21] Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet 2007;370:657–66.