Vitamin D and calcium in patients with osteoporosis following the Women's Health Initiative

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Summary

Age-related structural and neurochemical changes occurring in the central nervous system have been related to changes in some rhythmometric parameters. In spite of their clinical importance, only a few studies ha
ve investigated the modifications over time of serum electrolytes in senescence.

KEY WORDS: vitamin D deficiency, osteoporosis, muscle function, vitamin D and calcium supplements.

Introduction

Prevention and treatment of osteoporosis with vitamin D and calcium have recently been challenged after publication in the New England Journal of Medicine on the large scale trial in the Women s Health Inititative (1). While this paper was negative, other new positive data on vitamin D have become available. In this article, new data on vitamin D deficiency and its consequences will be discussed, among others the relationship between vitamin D deficiency and muscle weakness. In addition, the effects of treatment with vitamin D and calcium on the incidence of osteoporotic fractures will also be discussed. Vitamin D and calcium as additional treatment in patients with osteoporosis is the last subject of this review.
Vitamin D deficiency causes a lower degree of mineralization of the bone and in the long term osteomalacia in case of long-standing vitamin D deficiency. The earlier stage is characterized by secondary hyperparathyroidism associated with bone loss which may lead to osteoporotic fractures (2). Vitamin D also has effects outside the skeleton specially on muscle tissue. Vitamin D deficiency causes muscle weakness which may lead to falls (3). Vitamin D deficiency has also been related to a higher sensitivity for auto-immune disease such as multiple sclerosis or diabetes mellitus type 1, higher sensitivity for some infectious diseases such as tuberculosis and occurrence of certain types of cancer (4). In this review the emphasis is on the effects of vitamin D on bone and muscle tissue.

Longitudinal Aging Study Amsterdam

The Longitudinal Aging Study Amsterdam (LASA) is an epidemiological cohort study in the older Dutch population in Amsterdam, Zwolle and Oss and the surrounding rural communities. This representative sample of the Dutch population collects data on aging with respect to cognition, emotion, social life and physical function since 1992. The consequences of vitamin D deficiency for the skeleton and for physical function have been investigated in LASA.
In 1996, serum concentration of serum 25-hydroxyvitamin D (25(OH)D) was assessed in participants of LASA who were 65 years or older. Serum 25(OH)D was lower than 25 nmol/l in 13% and between 25 and 50 nmol/ in 35%. Currently it is assumed that serum 25(OH)D should be higher than 50 nmol/l and this was the case in LASA in 52% of the participants (5).
The relationship between serum 25(OH)D and the serum concentration of parathyroid hormone (PTH) was negative as can be expected and serum PTH was maximally suppressed when serum 25(OH)D was higher than 80 nmol/l. It should be questioned whether the increase of serum PTH with a decreasing 25(OH)D concentration should be considered as a physiological compensatory mechanism or as a pathological phenomenon. When the 25(OH)D decreases below 50 nmol/l, the increase of serum PTH becomes steeper. A negative relationship was observed between serum 25(OH)D and the urinary excretion of deoxypyridinolin, a measure of bone resorption, but the excretion of deoxypyridinolin only increased significantly when serum 25(OH)D was below 25 nmol/l. A positive relationship between serum 25(OH)D and the speed of sound through the heel was found, and the speed of sound increased significantly until serum 25(OH)D was higher than 50 nmol/l (6).

Vitamin D status in Europe

The vitamin D status in the European population varies between poor to adequate. Most surveys show that serum 25(OH)D levels are higher in Scandinavian countries followed by Western Europe and lower in the Mediterranean countries (7,8).
This was confirmed in the MORE study by measurement of serum 25(OH)D in a central laboratory facility in postmenopausal women from many countries. The serum 25(OH)D levels in Norway and Sweden were 86-89 nmol/l on average. Serum 25(OH)D was 64-67 nmol/l in Western Europe and 55 nmol/l in Italy (9).
An Italian population survey showed that vitamin D deficiency (serum 25(OH)D < 25 nmol/l) occurred in more than 60% of the women between 60 and 80 years (10). On the other side a

study in Norway on latitude 70 showed that the minimum serum 25(OH)D was higher than 37.5 nmol/l (11).
An explanation was that the mean vitamin D intake was high, around 10 g or 400 IU per day, caused by the consumption of cod liver oil and fish.

Vitamin D status in immigrants

In Western Europe, vitamin D deficiency occurs in immigrants from non-western countries. Studies in general practices in Amersfoort and The Hague showed vitamin D deficiency in 82% of the women. Fatigue and muscle weakness were common complaints (12,13).
A lesson of the month in the British Medical Journal in 2004 reported severe vitamin D deficiency in 11 female asylum seekers who had many aspecific complaints (14). Rickets and osteomalacia often occur in immigrants from non-western countries. Special risk groups are the pregnant non-western women as emerged from a recent study in midwives practices in The Hague (15).

Determinants of vitamin D status

Determinants of vitamin D status are sunshine exposure and the negative factors skin pigmentation, sunscreen use, clothing and advanced age as this is associated with decreased synthesis of vitamin D in the skin (2). Obesity is usually associated with lower serum 25(OH)D levels but the explanation is not completely certain (5). Urbanisation was a clear risk factor in LASA with lower serum 25(OH)D in Amsterdam than in the other cities and rural communities in the Netherlands. Air pollution can be a cause and this has also been reported from India. Artificial ultraviolet light as from a tanning bed can increase serum 25(OH)D. Nutrition, i.e. consumption of fatty fish, fish oil and foods to which vitamin D has been added such as margarine are important. Calcium-rich nutrition can mask vitamin D deficiency and it can also decrease the vitamin D requirement (2). Consumption of vitamin D containing medication or multivitamins can increase serum 25(OH)D.

New data on vitamin D deficiency and the consequences for the locomotor system

Last years, new data have become available on the importance of vitamin D for bone mineral density and muscle function.
In a large American survey, NHANES III, a positive relation existed between serum 25(OH)D and bone mineral density, and BMD increased with increasing serum 25(OH)D to more than 80 nmol/l (16). Based on this, a serum 25(OH)D higher than 80 nmol/l is advised in the USA by some groups. In the same study a relationship was observed between physical function and serum 25(OH)D. The time period in which a walking test and 5 chair stands were done decreased with increasing serum 25(OH)D (17). In this study, the most important effect was seen when serum 25(OH)D increased to 40-50 nmol/l, thereafter the time gain was marginal. In LASA, a similar relationship was found between serum 25(OH)D and the physical performance score consisting of walking test, 5 chair stands and a tandem stand. After correction for age and sex and other confounding variables physical performance increased significantly till a serum 25(OH)D of 50 nmol/l (18).
Vitamin D and calcium may decrease the number of falls as seen in a meta-analysis in which regular vitamin D3 was compared to active vitamin D metabolites either with or without calcium.

Effects of vitamin D with or without calcium on fracture incidence

A clinical trial in French nursing homes in 1992 led to the conclusion that vitamin D3 800 IU/day and calcium 1200 mg/day in comparison to placebo decreased fracture incidence with about 25% regarding hip fractures as well as other non-vertebral fractures (19). A clinical trial in Amsterdam in 1996 with vitamin D3 400 IU/day in comparison to placebo did not lead to a decrease of fracture incidence (20).
Differences between the studies in Lyon and Amsterdam were mean age, in Lyon 84 years and in Amsterdam 80 years, the residence, nursing home in Lyon, mixed residence in Amsterdam, calcium intake 514 mg/day in Lyon and more than 1000 mg/day in Amsterdam, and also the intervention, vitamin D and calcium in Lyon, and vitamin D alone in Amsterdam.
In Amsterdam the amount of calcium in nutrition was much higher, the reason why a calcium supplement was not included. The effect of supplementation with vitamin D and calcium resulted in Lyon in a decrease of serum PTH of 50% and in Amsterdam a decrease of 15%. The bone mineral density increased 6% in Lyon in comparison to 2.2% in Amsterdam (2).
In order to compare the baseline serum 25(OH)D in both studies, a cross-calibration was done. This led to the conclusion that the baseline serum 25(OH)D was much lower in Lyon, i.e. vitamin D deficiency was more severe in Lyon than in Amsterdam (21). The differences in calcium intake and in vitamin D status and the difference in supplementation caused higher contrasts between treated and non-treated group in Lyon than in Amsterdam. Probably compliance was much better in Lyon because medication in a nursing home was supplied under tight supervision, while in Amsterdam most participants were independent and there was less control on the intake of the vitamin D supplement.
Another positive study was performed in England where the participants received 100 000 IU vitamin D3 once per 4 months by mail (22). The intake of the supplements was to be confirmed by means of a reply card. In this study the incidence of osteoporotic fractures decreased with about 25%.
In Denmark, a pragmatic study compared vitamin D3 400 IU and calcium 1000 mg per day with improvements in the home and around (23). In this study, there were 15% less fractures in the treated group than in the control group. On the other side, there are many negative trials.
In general, vitamin D and calcium together leads to a larger decrease of serum PTH than vitamin D alone. Supplementation with vitamin D 800 IU/day appears to be somewhat more effective than 400 IU/day. These factors are important with regard to the effects on fractures.
The RECORD Study, published in 2005 reported supplementation of vitamin D3 800 IU/day and calcium 1000 mg/day for the secondary prevention of fractures in older people (24). There were four groups in this study: placebo, calcium alone, vitamin D alone and the combination of calcium and vitamin D. There was no difference in fracture incidence considering all fractures as well as hip fractures alone between the four groups. The baseline serum 25(OH)D was not so low in this study, 38 nmol/l, and the compliance was 50% after the first year and 47% after the second year.
Recently, a randomized trial was done in the framework of the Women s Health Initiative in more than 36000 women between 50 and 79 years (1). The treatment was calcium 1000 mg/day and vitamin D3 400 IU/day in comparison to placebo and the follow up was 7 years. The bone mineral density in the hip increased 1% and the intention-to-treat analysis did not show a

significant difference in the incidence of hip fractures or all fractures between the treated group and the placebo group. However, the per-protocol analysis in patients who in fact used the medication (high compliance) showed a significant reduction in the number of hip fractures (68 vs 99, hazard ratio 0.71).
The most important side effect was a slight increase in the incidence of renal stones. As a consequence of this trial, one may ask the question what is the sense of the prescription of calcium and vitamin D for the prevention of fractures, and as an additional treatment in patients with osteoporosis who are treated with bisphosphonates or other medication. The fact that randomized trials with vitamin D with or without calcium with fractures as an endpoint are sometimes positive and at other times negative means that the effect of calcium and vitamin D is relatively weak in comparison with bisphosphonates for example. Factors influencing the outcome are among others the baseline serum 25(OH)D level, the lower the greater the effect, the vitamin D dose, calcium intake and the use of calcium supplements, and compliance being higher in nursing homes than in independently living elderly.
A problem is a possible interaction in frail elderly: they are usually vitamin D deficient or insufficient and they have a low compliance.

Vitamin D3 and calcium as additional treatment in patients with osteoporosis

The addition of vitamin D3 and calcium to the treatment in patients with osteoporosis may lead to the following remarks: in all megatrials with bisphosphonates, raloxifene, teriparatide and strontium, vitamin D3 and calcium were added to the treatment to guarantee sufficient intake. There are no data on treatment with these compounds without addition of vitamin D and calcium. On the other side, the calcium intake with nutrition is much lower in most countries than in the Netherlands. In practice, this means that calcium should be added up to the recommended daily allowance of 1000-1200 mg/day.
Supplements should be prescribed to all patients who use less than 4 dairy consumptions per day. In the MORE trial it was studied whether vitamin D insufficiency at the start of the trial influenced the increase of BMD. It appeared that the increase was somewhat higher when serum 25(OH)D was lower at the onset, but the difference was not significant (25). On the other side, a Japanese study in 24 postmenopausal women who were treated with alendronate 5 mg/day had a different outcome. Suppression of bone resorption with alendronate was insufficient when serum 25(OH)D was low and there was a significant relationship between the increase of BMD and baseline serum 25(OH)D leading to the conclusion that vitamin D deficiency was a reason for non-response to bisphosphonates (26).
In practice, one should prescribe vitamin D 1 dd 400 IU to patients who do not go outside in the sunshine. The latter applies to most patients older than 65 years of age.

Conclusion

Treatment of vitamin D deficiency or insufficiency in patients with serum 25(OH)D lower than 50 nmol/l is important for optimal bone mineral density and muscle function, and the prevention of falls and fractures. Risk groups such as immigrants and pregnant women should get more attention. Patients with osteoporosis should take sufficient vitamin D and calcium. Guidelines for Osteoporosis should not be modified in this respect.

References

1. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SAA, Black HR, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354:669-83.
2. 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.
3. Bisschoff-Ferrari HA, Dawson-Hughes B, Willett CW et al. Effect of vitamin D on falls: a meta-analysis. JAMA. 2004;291:1999-2006.
4. Nagpal S, Na S, Rathnachalan R. Noncalcemic actions of vitamin D receptor ligends. Endocr Rev. 2005;26:662-687.
5. Snijder MB, van Dam RM, Visser M, Deeg DJ, Dekker JM, Bouter LM, Seidell JC, Lips P. Adiposity in relation to vitamin D status and parathyroid hormone levels. A population-based study in older men and women. J Clin Endocrinol Metab. 2005;90:4119-23.
6. Lips P, Pluijm SMF, Smit JH, Van Schoor NM. What is the optimal level of serum 25-hydroxyvitamin D for bone health in older people? Results from the Longitudinal Aging Study Amsterdam. ASBMR 2005. J Bone Miner Res. 2005;20:S90 (abstract).
7. McKenna M. Differences in vitamin D status between countries in young adults and the elderly. Am J Med. 1992;93:69-77.
8. Wielen vd RPJ, Lowik MRH, Berg vd H, Groot de LCPGM, Haller J, Moreiras O, Staveren v WA. Serum vitamin D concentrations among elderly people in Europe. Lancet. 1995;346:207-210.
9. Lips P, Duong T, Oleksik AM, Black D, Cummings S, Cox D, Nickelsen T for the MORE Study Group. A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: baseline data from the multiple outcomes of raloxifene evaluation clinical trial. J Clin Endocrinol Metab. 2001;86:1212-1221.
10. Isaia G, Giorgino R, Rini GB, Bevilacqua M, Maugeri D, Adami S. Prevalence of hypovitaminosis D in elderly women in Italy: clinical consequences and risk factors. Osteoporosis Int. 2003;14:577-82.
11. Brustad M, Sandanger T, Aksnes L, Lund E. Vitamin D status in a rural population of northern Norway with high fish liver consumption. Public Health Nutr. 2004;7:783-9.
12. Grootjans-Geerts I, Wielders JP. A pilot study of hypovitaminosis D in apparently healthy, veiled, Turkish women: severe vitamin D deficiency in 82%. Ned Tijdschr Geneeskd. 2002;146:1100-1.
13. Wuister JD, Van der Meer IM, Huisman W, Lutjenhuis MJTh. Herontdekking vitamine D tekort: gegevens uit de Schilderswijk. Epidemiol Bull. 2002;37:8-11.
14. Torrente de la Jara G, Pecoud A, Favrat B. Musculoskeletal pain in female asylum seekers and hypovitaminosis D3. BMJ. 2004;329:156-57.
15. Van der Meer IM, Karamali NS, Boeke JP, Lips P, Middelkoop BJC, Verhoeven I, Wuister JD. High prevalence of vitamin D deficiency in pregnant non-western women in The Hague. Am J Clin Nutr. 2006;84:350-3.
16. Bisschoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxyvitamin D levels and bone mineral density: a population-based study of younger men and older adults. Am J Med. 2004;116:634-9.
17. Bisschoff-Ferrari HA, Dietrich T, Orav EJ, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower extremity function in both active and inactive persons > 60 yr. Am J Clin Nutr. 2004;80:752-8.
18. Wicherts IS, Van Schoor NM, Boeke AJP, Lips P. Vitamin D deficiency and neuromuscular performance in the Longitudinal Aging Study Amsterdam (LASA). ASBMR 2005. J Bone Miner Res. 2005;20:S35 (abstract).
19. 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 elderly women. N Engl J Med. 1992;327:1637-1642.
20. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supple-mentati-on and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. Ann Intern Med.

1996;124:400-406.
21. Lips P, Chapuy MC, Dawson-Hughes B, Pols HAP, Holick MF. An international comparison of serum 25-hydroxyvitamin D measurements. Osteoporos Int. 1999;9:394-397.
22. Trivedi DP, Doll R, Khaw KT 2003 Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ. 326:469-474.
23. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community-dwelling residents. A pragmatic population-based 3-year intervention study. J Bone Miner Res. 2004;19:370-8.
24. The RECORD Trial Group 2005. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet. 2005;365:1621-1628.
25. Antoniucci DM, Vittinghoff E, Blackwell T, Black DM, Sellmeyer DE. Vitamin D insufficiency does not affect bone mineral density response to raloxifene. J Clin Endocrinol Metab. 2005;90:4566-72.
26. Ishijima M, Yamanaka M, Tokita A, Kurosawa H. Vitamin D insufficiency impairs the effect of alendronate for the treatment of osteoporosis in postmenopausal women. J Bone Miner Res. 2005;20: S296 (abstract).