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The role of calcium and vitamin D in the management of osteoporosis

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Abstract

The role of calcium and vitamin D supplementation in the treatment of osteoporosis has been extensively studied. The aim of this paper was to reach, where possible, consensus views on five key questions relating to calcium and vitamin D supplementation in the management of osteoporosis. Whereas global strategies that target supplementation to the general population could not be justified in terms of efficacy and health economics, there is a clearer rationale for supplementing patients who are at increased risk of osteoporosis and those who have developed osteoporosis, including those already taking other treatments for osteoporosis. The combination of vitamin D with calcium may be beneficial in terms of efficacy and, perhaps, for optimising adherence.

Keywords: Calcium; Osteoporosis; Vitamin D; Menopause; Fracture

Introduction

Osteoporosis is a chronic, progressive bone disease in which bone resorption exceeds bone formation, leading to a reduction in bone mineral density and disruption of bone micro-architecture. Patients with osteoporosis have an increased risk of fractures that occur with stresses which would not normally cause fracture in a non-osteoporotic individual. The incidence of osteoporosis increases with age and occurs most frequently in postmenopausal women because the decrease in ovarian oestrogen associated with the menopause accelerates bone loss and increases bone remodelling [1]. Many studies have investigated the effect of vitamin D and calcium supplements on osteoporosis and fracture risk in postmenopausal women. A round table discussion was held between experts in order to reach a consensus on a number of issues regarding the use of dietary supplements of vitamin D and calcium in the prevention and treatment of osteoporosis. The panel considered five specific questions that have arisen in the light of recent publications casting doubt on the benefit of supplementation for postmenopausal women [2–5]. The conclusions reached were based on a consideration of available evidence.

Is there a rationale to supplement postmenopausal women with calcium and vitamin D?

In order to address this question it is necessary to consider threshold intakes of vitamin D and calcium below which skeletal health is compromised. Ideally, this should be based on the establishment of the relationship between nutrient intake and a measurable index of skeletal health. For vitamin D it is possible to determine a plausible threshold in that many studies have characterised a relationship between low circulating levels of 25-hydroxyvitamin D (25[OH]D) and increased secretion of parathyroid hormone (PTH) which in turn, induces bone loss in the elderly through increased bone resorption [6–8].

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Published estimates of the level of circulating 25(OH)D required to maintain normal levels of PTH range between 30 and 100 nmol/l [9]. This in turn means that estimates of vitamin D insufficiency within populations vary greatly depending on the threshold used. In a study of 8532 postmenopausal, osteoporotic European women, 79.6% were found to have vitamin D insufficiency where the serum 25(OH)D threshold was considered to be 80 nmol/l, and 32.1% if the threshold was set at 50 nmol/l [10]. In one study, PTH fell by 35% in subjects with baseline 25(OH)D levels between 27.5 and 39.9 nmol/l after 8 weeks of supplementation, by 26% in those with levels between 40 and 49.9 nmol/l, but there was no significant change in PTH in those with 25(OH)D levels superior to 50 nmol/l, despite a 66% increase in the vitamin D metabolite [11]. After discussion of current evidence it was agreed by the panel that 80 nmol/l may be an overestimate and that 50 nmol/l was a more conservative and acceptable threshold.

The situation regarding an acceptable threshold for dietary calcium intake is far less clear, and recommendations range from 400 to 1500 mg daily. There is little evidence to suggest that countries with lower dietary calcium intakes are at higher risk of osteoporotic fracture, and there are few long term studies to address this issue within populations that take appropriate account of the slow adaptation to changes in dietary intake. For these reasons, it was agreed that there is insufficient evidence to support the widespread supplementation of the dietary intakes of women in the general population who are not at increased risk of osteoporosis.

In contrast, the majority of studies that have investigated the effects of combined calcium and vitamin D supplementation in postmenopausal women have shown a reduction in fracture risk, providing that sufficient patient compliance (75–80%) was reached [3,7,12–14].

The panel's consensus was that supplementation with calcium and vitamin D should be recommended in women at increased risk of osteoporosis and those who have developed osteoporosis. In the case of vitamin D, the dose given should be enough to ensure that circulating levels of 25(OH)D reach the threshold of 50 nmol/l.

Is it appropriate to use various doses or regimens of calcium and vitamin D depending upon age?

Since calcium and vitamin D supplementation should be targeted to those individuals at increased risk of fracture and since age is a very important determinant of fracture risk, a target for intervention is the elderly, particularly those over 65 years. The need for dietary supplementation with calcium and vitamin D may be increased in the elderly for a number of reasons. Dietary intake of calcium and vitamin D generally falls in the elderly. In addition, endogenous production of vitamin D decreases due to a combination of decreasing exposure to sunlight and age-related changes in the dermis which diminish the capacity for cutaneous synthesis of vitamin D [15,16]. Intestinal absorption and renal tubular re-absorption of calcium both decrease with age, as does the ability to adapt to a low calcium diet [1,17]. It was therefore agreed that individuals over 65 years should be considered for supplementation without the need to assess their status beforehand. In addition, younger women with dietary insufficiency and/or an increased risk of fractures should also receive appropriate supplementation following assessment of their status. It was agreed, therefore, that from a health economic perspective, supplementation of vitamin D in addition to calcium can be justified in women less than 65 years with proven calcium insufficiency as a combination of vitamin D and calcium could reduce bone turnover. In terms of dosage, it is plausible that those at greatest risk may benefit from higher doses than those at lower risk.

Vitamin D supplementation must be sufficient to ensure that serum 25(OH)D values reach the threshold level, otherwise it will not confer the desired benefit. Studies investigating the anti-fracture efficacy of different dosing regimens of vitamin D have shown that 400 IU per day was not sufficient to have an effect on fracture rate [18]. Oral doses of >700–800 IU taken daily or 100,000 IU taken quarterly both showed a positive anti-fracture effect, whereas an intramuscular dose of 300,000 IU annually showed inconsistent efficacy [18,19]. This suggests that supplementation is most effective in osteoporotic patients if given orally either daily or quarterly, and if given daily, should be in excess of 700–800 IU daily [20].

Is there any interest to adding calcium to vitamin D supplementation or adding vitamin D to calcium supplementation?

Many studies have shown that persistence and compliance with supplementation regimens can be low, and that poor compliance impairs efficacy [3,21]. It is necessary therefore, from both an efficacy and a health economic perspective, to ensure that any dosing regimen is designed with this in mind. Where medically appropriate, combination treatments may improve treatment compliance by reducing the number of medications which patients need to take.

Current evidence suggests the role that calcium and vitamin D play in fracture prevention is not attributable to calcium alone [4,22] and a meta-analysis of data from 9 randomized clinical trials, including a total of 53,260 patients, found that where the effects of supplementation with vitamin D alone were explored (in a total of 9038 patients), this was not sufficient to significantly reduce the risk of hip fracture in postmenopausal women [6]. However the same study found that combined supplementation with vitamin D and calcium reduced the risk of hip fracture by 25% (95% CI: 4–42) and the risk of non-vertebral fracture by 23% (95% CI: 1–40) compared to supplementation with vitamin D alone. The meta-analysis estimated the number needed to treat (NNT) to prevent one adverse outcome to be 276 (95% CI: 165–843) for hip fractures and 72 (95% CI: 35–834) for non-vertebral fractures [6].

These results support a previous meta-analysis which has shown a reduction of 19% (95% CI: 4–32) for hip fracture and of 13% (95% CI: 3–22) for any non-vertebral fracture [23].

Two recent studies, the RECORD study and the Women's Health Initiative (WHI), both of which were included in the meta-analysis by Boonen et al. [6], have reported results which appear to show that combined vitamin D and calcium supplementation is not effective in fracture prevention [3,21]. However, the WHI

study did not target individuals at high fracture risk, and in both studies the adherence was poor. The RECORD trial did not assess vitamin D levels or PTH response so it is unknown whether subjects had vitamin D insufficiency. In addition, the number of fractures within this trial was low and together with the poor adherence, suggests that the study was underpowered.

The WHI, whilst not showing a reduction in the risk of fractures with supplementation (1000 mg calcium, 400 IU vitamin D_3 daily), did find significantly greater preservation of hip bone mineral density in women in the treatment group compared to those taking a placebo. Importantly, the WHI trial was carried out in healthy postmenopausal women with an average calcium intake above 1000 mg per day, 80% of whom were under 70 years old. It is also important to note that in this study, personal supplementation of calcium (up to 1000 mg/day) and vitamin D_3 (up to 600 IU/day raised up to 1000 IU/day) was allowed. In addition, vitamin D status at baseline was unknown in all but 1% of individuals, so it is not possible to judge the level of vitamin D insufficiency with certainty in this study population. The administered dosage of vitamin D in this study was 400 IU, a dose shown in other studies to be insufficient to have an effect on fracture rate [18,24,25]. Finally, treatment compliance (defined as use of 80% or more of the assigned study medication) was low, estimated as less than 60%. Importantly, when analysis was carried out on only those subjects who were compliant, a significant (29%) reduction in hip fracture risk compared to the placebo group was found. Compliance in the various trials could explain the difference in the number needed to treat (NNT) reported in 2 recent meta-analyses, one including mainly high quality randomized controlled trials [18] and the other one including additional studies with lower compliance, such as the RECORD and WHI trials [6]. In the former meta-analysis, NNT was 45 (95% CI: 28–114) and 27 (95% CI: 19–49), for hip and any non-vertebral fracture, respectively.

Given the low cost of vitamin D and calcium supplements, compared to the high economic burden of osteoporotic fractures, combined supplementation can be economically justified. This case becomes even stronger if supplementation is targeted primarily to those at increased risk in whom the NNT figures given above would be lower still.

It was concluded that in order to reduce fracture risk, combined supplementation should be administered to those at increased risk of fracture at doses adjusted depending on baseline levels, but potentially in the region of 800 IU of vitamin D and 1000–1200 mg of calcium daily.

Should particular caution be taken when supplementing postmenopausal women with calcium and/or vitamin D?

The risks of calcium and vitamin D supplementation and side effects are not well reported from clinical trials. The current recommendation for vitamin D intake in the United States is 400 IU for adults aged between 51 and 70 years and 600 IU for adults of 70+ years old. The Commission of the European Communities recommends 400 IU daily for people over 65 years [26]. An acceptable upper limit for vitamin D intake has been set at 2000 IU/day. The "no observed adverse event level" is 10,000 IU daily and the "lowest observed adverse event level" is 40,000 IU/day [27]. The level at which vitamin D intoxication occurs is unknown, but is likely to be considerably higher than the above mentioned doses. High dose supplementation carries a risk of hypercalcaemia with subsequent impairment of kidney function.

Predisposing factors for expression of vitamin D intoxication include high calcium intake, hypercalcaemia, idiopathic hypercalciuria, sarcoidosis, overproduction of vitamin D metabolites, reduced vitamin D binding and hyper responsivity to vitamin D [28–30].

There are no specific warnings or precautions for use of vitamin D and calcium specifically relating to postmenopausal women. To the contrary, increased prevalence of albuminuria, which is a risk factor for chronic kidney disease progression, has been reported with decreasing levels of 25(OH)D [31]. Some caution may be required in the treatment of patients with cardiovascular disease as the effect of cardiac glycosides may be accentuated by supplementation with vitamin D and calcium. However, calcium and vitamin D supplementation does not influence coronary or cerebrovascular risk in generally healthy postmenopausal women [32]. The use of calcium supplements may give rise to mild gastro-intestinal disturbances non consistently detected such as constipation, flatulence, nausea, gastric pain, and diarrhoea [3,4].

Should anti-osteoporotic treatments be used in combination with calcium and vitamin D?

The vast majority of evidence for efficacy of anti-osteoporotic treatments is based upon combining treatment with calcium and vitamin D supplementation [33–39]. Vitamin D deficiency in humans and animals has been shown to reduce the response to some treatments for osteoporosis. In addition, animal studies have shown that the efficacy of bisphosphonates was blunted when the animals were exposed to a vitamin D deprived diet [40] It is concluded therefore that anti-osteoporotic treatments should be used in combination with calcium and vitamin D supplementation. Little evidence is available regarding the combination of anti-osteoporotic treatments with calcium alone or vitamin D alone.

Conclusion

Supplementation with calcium and vitamin D can be justified both in terms of efficacy and health economics in women at increased risk of osteoporotic fracture, including those who have not yet sustained a fracture. Women can be considered to be at increased risk of fracture if they are over 65 years of age, or; if osteopenic and/or with proven calcium and/or vitamin D insufficiency when they are younger. Evidence suggests that for the greatest reduction in fracture risk, women at increased risk should be given both calcium and vitamin D supplements, in the order of 1000–1200 mg calcium (depending on baseline status) and 800 IU vitamin D daily. Patient adherence is essential for efficacy. Combining vitamin D and calcium into one supplement is recommended as this may increase patient adherence, which in turn improves overall efficacy. In conclusion, combined vitamin D and calcium supplementation

is recommended for all women at increased risk of fracture, including those also taking other anti-osteoporostic treatments.

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