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for CLINICAL and
ECONOMIC ASPECTS
of OSTEOPOROSIS
and OSTEOARTHRITIS



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Calcium and Vitamin D in the Management of Osteoporosis

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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. This meeting was organised by the Group for the Respect of Ethics and Excellence in Science (GREES) and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). The panel considered five specific questions on this issue in the light of recent publications that have cast doubt on the benefit of supplementation for postmenopausal women. The conclusions reached were based on a consideration of available evidence as summarised below:

IS THERE A RATIONALE TO SUPPLEMENT POSTMENOPAUSAL WOMEN WITH CALCIUM AND VITAMIN D?

In order to address this question it is necessary to consider deficiency 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. Published estimates of the level of circulating 25(OH)D required to maintain normal levels of PTH range between 30 and 100 nmol/l. In a study of 8,532 postmenopausal, osteoporotic European women, 79.6% were found to have vitamin D insufficiency if the serum 25(OH)D threshold was considered to be 80 nmol/l, and 32.1% if the threshold was 50 nmol/l. The panel agreed 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 1,500 mg daily. Dietary intake of calcium varies greatly from country to country and ranges from less than 300 mg per person per day in Thailand to over 1,200 mg in Iceland. There is little evidence to suggest that countries with the lower dietary 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 calcium and vitamin D supplementation in postmenopausal women have shown a reduction in fracture risk, providing that sufficient patient compliance (75-80%) was reached. The panel's consensus was, therefore, that supplementation with calcium and vitamin D should be recommended in women at increased risk of osteoporosis, those who are osteopenic 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 a threshold of 50 nmol/l.

IS IT APPROPRIATE TO USE VARIOUS DOSES OR REGIMENS OF CALCIUM AND VITAMIN D DEPENDING UPON THE AGE OF THE SUBJECT?

The need for dietary supplementation with calcium and vitamin D may be increased in the elderly for a number of reasons. The dietary intake of calcium and vitamin D generally falls in the elderly, as does the efficiency of endogenous production of calcitriol. Intestinal absorption and renal tubular re-absorption of calcium both decrease with age, as does the ability to adapt to a low calcium diet.

Age is a very important determinant of fracture risk. Having agreed that calcium and vitamin D supplementation should be targeted to those individuals at increased risk of fracture, the elderly, particularly those over 65 years are a clear target for supplementation. It was agreed therefore that individuals over 65 should be considered for supplementation without the need to assess their status beforehand. However younger women with insufficiencies and/or increased risk of fractures should also receive appropriate supplementation following assessment of their status. Calcium levels can be checked very simply and at very low cost but this is not the case for 25(OH)D levels. It was therefore agreed that, from a health economic

perspective, supplementation of vitamin D in addition to calcium can be justified in women under 65 with proven calcium insufficiency, as a combination of vitamin D and calcium could reduce bone turnover. In terms of dosage, it is highly plausible that there is a gradient of risk, which is mirrored by a gradient of optimal dosage. Thus, those at greatest risk may benefit from higher doses than those at lower risk.

Many studies have shown that persistence and compliance with supplementation regimes can be low, and that poor compliance reduces or eliminates efficacy. It is therefore necessary from both an efficacy and a health economic perspective to ensure that any dosing regimen is designed with this in mind. It was agreed that vitamin D supplementation must be sufficient to ensure that 25(OH)D reaches the threshold level, otherwise it will not confer the desired benefit. Studies investigating the anti-fracture efficacy of different dosing regimens of vitamin D showed that 400 IU per day was not sufficient to have an effect on fracture rate and it would be better to combine vitamin D with calcium. Oral doses of >700 IU taken daily or 100,000 IU taken quarterly both showed a positive anti-fracture effect, whilst an intramuscular dose of 300,000 IU annually showed inconsistent efficacy. This suggests that supplementation is most effective in osteoporotic patients if given orally either daily or quarterly, and if given daily, should be at least 700-800 IU daily.

IS THERE ANY INTEREST TO ADDING CALCIUM TO VITAMIN D SUPPLEMENTATION OR ADDING VITAMIN D TO CALCIUM SUPPLEMENTATION?

Current evidence suggests that whilst calcium plays a role in fracture prevention when combined with vitamin D, this effect is not attributable to calcium alone. A meta-analysis of data from randomized clinical trials found that supplementation with vitamin D alone was not sufficient to reduce the relative risk of hip fracture in postmenopausal women. However, combined supplementation with vitamin D and calcium reduced the risk of hip fracture by 28% and the risk of non-vertebral fracture by 23% compared to supplementation with vitamin D alone. Two recent studies appear to contradict this finding (the RECORD study and Women's Health Initiative), but importantly, neither study targeted individuals at increased risk of fractures. 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 adherence poor, suggesting that the study was poorly powered.

The clinical trial of the Women's Health Initiative 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. Vitamin D status at baseline was unknown in all but 1% of individuals and vitamin D dosage was 400 IU, a level shown in other studies to be insufficient to have an effect on fracture rate. In addition compliance was low, estimated as less than 60%. Nevertheless, analysis carried out on only those subjects who were compliant did find a significant reduction in hip fracture risk.

It was concluded that in order to reduce fracture risk, combined supplementation should be administered 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. However, this supplementation should be targeted to those identified at higher fracture risk than the populations studied in these two trials.

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. An acceptable upper limit for vitamin D intake has been set at 2,000 IU per day. The “no observed adverse event level” is 10,000 IU per day and the “lowest observed adverse event level” is 40,000 IU per day. The level at which vitamin D intoxication occurs is unknown, but is likely to be considerably higher than the above mentioned doses.

There are no warnings or precautions for use of vitamin D and calcium specifically relating to postmenopausal women. Supplementation with vitamin D and calcium should be undertaken with caution in individuals with renal insufficiency. High dose supplementation carries a risk of hypercalcaemia with subsequent impairment of kidney function. Special caution is also 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. The use of calcium supplements may give rise to mild gastro-intestinal disturbances such as constipation, flatulence, nausea, gastric pain, and diarrhoea.

SHOULD ANTI-OSTEOPOROTIC TREATMENTS BE USED IN COMBINATION WITH CALCIUM AND/OR VITAMIN D?

The vast majority of evidence for efficacy of anti-osteoporotic treatments is based upon combining treatment with calcium and vitamin D supplementation. 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. It is therefore concluded that anti-osteoporotic treatments should be used in combination with calcium and vitamin D supplementation. Little evidence has been provided regarding the combination of anti-osteoporotic treatments with calcium alone or vitamin D alone.