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Editorials

Reducing the risk of fractures with calcium and vitamin D

The combination is more effective than vitamin D alone

Conflicting evidence exists on the role of vitamin D, either alone or in combination with calcium, in reducing fractures. Some studies have shown a reduction in the risk of fractures, others have shown no effect, and one recent study found an increased risk of hip fracture.[1] The best dose to use, which patients benefit most, and which fractures are most amenable to such treatment remain a clinical dilemma.

In the linked study (doi:10.1136/bmj.b5463), the DIPART (vitamin D Individual Patient Analysis of Randomized Trials) group reports an individual patient data analysis aimed at identifying factors that influence the efficacy of vitamin D or vitamin D plus calcium in reducing fractures. The study also assessed the influence of dosing regimens and the coadministration of calcium. The study looked at seven randomised controlled trials (n=68 517)—six were individually randomised and one was cluster randomised.[2] It found that trials using vitamin D (low or high dose) combined with calcium reduced the overall risk of fracture (hazard ratio 0.92, 95% confidence interval 0.86 to 0.99), but that only low dose (10 µg) vitamin D combined with calcium reduced the risk of hip fracture (0.74, 0.60 to 0.91). They found no association between fracture history and treatment response, or any association with age, sex, or hormone replacement therapy. In addition, vitamin D alone, irrespective of dose, had no effect on fracture risk.

These findings are important because this is one of the few individual patient data analyses to show that vitamin D alone, irrespective of dose, does not reduce the risk of fracture. In contrast, it found that combined calcium and vitamin D reduced the overall risk of fracture, but that only low dose vitamin D with calcium reduced the risk of hip fracture.

The DIPART group's analysis supports recent meta-analyses that have examined study level data rather than individual patient level data.[3 4] One of the recent meta-analyses based on study level data found that although a combination of calcium and vitamin D prevented the overall risk of fracture, it was only significant in people living in institutions. The conclusions were mainly driven by a large French study, which the DIPART study did not include.[5]

Another recent study level meta-analysis by Bischoff-Ferrari and colleagues of 12 randomised controlled trials of non-vertebral fractures (n=42 279) and eight trials of hip fracture (n=40 886) looked at oral vitamin D, with or without calcium.[6] It concluded that prevention of non-vertebral fractures with vitamin D was dose dependent. Ten of the included studies were not included in the DIPART group's review and two of the studies that were included in the DIPART group's review were not included in Bischoff-Ferrari and colleagues' review. Furthermore, in two studies of higher dose vitamin D that were included in the DIPART group's study, compliance with treatment was poor. Bischoff-Ferrari and colleagues' analysis adjusted for compliance by multiplying the dose by the percentage of adherence to estimate the mean received dose for each trial. The DIPART group made no such adjustment, which may explain the contrasting conclusions between the two meta-analyses.

For many years, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) were believed to have equivalent effects on the human body, even though differences in the metabolism of these two forms were seen in animals 25 years ago. Some studies have suggested that supplemental vitamin D_2 is less effective than vitamin D_3 in humans[7]; however, in the meta-analysis by Bischoff-Ferrari and colleagues, subgroup analyses suggested that vitamin D_3 may be better at reducing fractures than vitamin D_2. In contrast, the results of the DIPART study were similar regardless of whether the potency of vitamin D_2 was considered to be 100% or 50% of vitamin D_3. The optimal concentration of the main circulating form of vitamin D, 25-hydroxyvitamin D, is still debated. Recent consensus has suggested that serum concentrations of 70-80 nmol/l are needed for normal health.[8] However, few vitamin D studies have measured 25-hydroxyvitamin D concentrations, and in those that have such high values are rarely achieved. In addition, the different assays used to measure vitamin D have a limiting effect.[9]

More recently there has been interest in the relation between vitamin D and muscle function. Vitamin D has direct effects on muscle strength modulated by specific vitamin D receptors in human muscle tissue.[10] It is postulated that supplementation may increase muscle strength, thereby reducing the risk of falls and subsequent non-vertebral fractures. In a recent meta-analysis, supplementation with 700-1000 IU of vitamin D a day reduced the risk of falling in older people by 19%, and to a similar degree to active forms of vitamin D.[11] In combination with calcium, vitamin D reduced first falls by 27% at 12 months (relative risk 0.73, 0.54 to 0.96) and 39% at 20 months, with a 28% decrease in body sway.[12] Thus, the reduction of non-vertebral fractures may be related more to the effects of vitamin D on reducing falls than to its direct effects on bone.

What are the implications of current evidence in clinical practice? Although the evidence is still confusing, there is growing consensus that combined calcium and vitamin D is more effective than vitamin D alone in reducing non-vertebral fractures. Higher doses are probably necessary in people who are more deficient in vitamin D, and treatment is probably more effective in those who maintain long term compliance. Further studies are needed to define the optimal dose, duration, route of administration, and dose of the calcium combination.

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Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials
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