HIGHER ORAL VITAMIN D DOSES REDUCE NONVERTEBRAL FRACTURE RISK

Several investigators have assessed the efficacy of oral vitamin D for prevention of nonvertebral fractures with variable results. Two meta analyses published in 2007 indicated that vitamin D may not have a significant reduction in fracture risk or may only do so in combination with calcium. Another meta analysis conducted in 2007 revealed that calcium with or without vitamin D may reduce fractures by 12%. This issue of CLIPS briefly summarizes a meta analysis that evaluated the use of oral vitamin D for nonvertebral fractures. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Background
- Variable results have been published documenting the benefit of oral vitamin D in the prevention on nonvertebral fractures.
- Increasing doses of vitamin D have been associated with fracture reduction; specifically, a positive trend has been reported between 25-hydroxyvitamin D levels and hip bone density and lower extremity strength.
- A reduced effect of oral vitamin D administration may be observed if there is a low adherence to the treatment regimen, insufficient oral vitamin D dosage, or use of ergocalciferol (vitamin D2).

Study objective
- To determine the efficacy of oral vitamin D supplementation on fracture reduction in patients ≥ 65 years by reviewing the evidence-based high-quality, double-blinded, randomized clinical trials and recent meta analyses.

Study inclusion criteria
- Randomized controlled clinical trials were included if patients received oral vitamin D supplementation (cholecalciferol or ergocalciferol) with a minimum follow up of 1 year.
- The primary outcome measure was the relative risk (RR) of a first or repeated nonvertebral fracture or hip fracture in patients receiving vitamin D with or without calcium supplementation compared to those receiving placebo or calcium monotherapy.
- The effect of the vitamin D dose was calculated by the received dose of supplemental vitamin D and the cross product of dose and percentage of adherence.
- The results of the trial were stratified according to the amount of oral vitamin D supplementation received (≤400 IU daily or 482-770 IU daily).
- Studies (n=12) meeting the inclusion criteria included 42,279 patients with a mean age of 78 years; women comprised 89% of the study population.
  - Calcium supplementation (500-1200 mg daily) was administered concomitantly with vitamin D supplementation in 7 trials.

Evidence supporting the use of oral vitamin D for prevention of nonvertebral fractures
- Pooled analyses revealed a beneficial effect of vitamin D for any dose of vitamin D used to prevent nonvertebral fractures (RR 0.86, 95%CI, 0.77 to 0.96).
- Patients who received the lower dosage (≤ 400 mg daily) of vitamin D did not experience a beneficial effect (RR 1.02; 95% CI, 0.92 - 1.15).
- Patients who received a higher dose of vitamin D (≥ 400 IU daily) did experience benefit from oral vitamin D therapy (RR 0.80; 95% CI, 0.72 – 0.89).
  - Higher dose vitamin D resulted in a 20% reduction in nonvertebral fracture risk.
  - The associated risk differences was 1.1% between groups (95% CI, 0.6-1.5%; p<0.001, NNT 93 for 12-84 months (95% CI, 66-160).
  - No significant differences were found between ergocalciferol compared to cholecalciferol (p=0.07).
  - Addition of calcium therapy to appropriate levels of vitamin D does not appear to enhance the effects of vitamin D.

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Evidence supporting the use of oral vitamin D for prevention of hip fractures
- Eight high-quality clinical trials were included with 40,886 patients.
- Pooled analyses revealed a possible benefit of vitamin D for hip fracture prevention (RR 0.91; 95% CI, 0.78-1.05).
- Low dose vitamin D (≤ 400 IU daily) did not result in clinically significant reductions in hip fracture reduction (RR 1.09, 95% CI 0.90-1.32).
- Significant reductions in hip fractures were observed with vitamin D doses >400 IU daily (RR 0.82; 95% CI 0.69-0.97).
  - Administration of higher dose vitamin D resulted in an 18% reduction in hip fracture risk.
  - Pooled risk difference for hip fracture reduction was 0.6% (0.23%-0.96%; p=0.02); NNT= 168 (95% CI, 104-440) for 12-84 months.

Summary
- Significantly fewer fractures occur with higher doses of vitamin D.
- Significant fracture reductions were not observed with lower dose vitamin D administration.
- Supplemental oral vitamin D therapy resulted in a 20% and 18% reduction in nonvertebral and hip fracture, respectively.
- Cholecalciferol is more effective than ergocalciferol for fracture reduction.
- Current evidence does not support the use of low dose oral vitamin D with or without calcium supplementation for hip or nonvertebral fracture prevention.

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