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Editorial

**VITAMIN D SUPPLEMENTATION FOR MUSCULOSKELETAL HEALTH OUTCOMES IN ADULTS  
– THE END OF THE BEGINNING?**

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A new study published in *Lancet Diabetes & Endocrinology*[1], in strengthening findings from the authors' previous work, may signal the end to further trials of vitamin D for skeletal outcomes in persons who have not been shown to be vitamin D deficient. However, measuring vitamin D status is technically difficult [2], and the best assays are often not available to clinicians due to cost. Even when measured accurately, vitamin D levels

can be challenging to interpret given seasonal changes that vary from person to person reflecting sun habits, skin type and diet. Add to this that vitamin D supplements are eminently affordable and safe to most people across a broad dose range. Taken together, this has led to a culture looking to provide universal supplementation which falls short of evidence based medicine. Despite vitamin D being a threshold nutrient for adult bone health, most doctors have experienced the temptation or pressure to use a one dose fits all approach for vitamin D. Health professionals are generally not thanked for repeated vitamin D measurements to tailor the exact dose required in the individual person.

The take home message of the study[1] is - in our opinion - not that we should write off vitamin D. Rather, the message is that we can now refrain from initiating new vitamin D trials for bone in non-targeted populations. For non-skeletal effects too, prior reviews[3], [4] have found no strong evidence that vitamin D is effective. The evidence base available consisted of mainly observational data comparing groups of patients whose differences in vitamin D levels could parallel the health effects rather than cause them. However, large vitamin D trials with non-skeletal outcomes are ongoing and will be completed soon; these will add intervention data to the existing inconclusive –findings from observational studies for these outcomes.

Many past meta-analyses have indicated that the effect of vitamin D alone on the risk of fractures, falls and bone mineral density is minimal in the general population[5]–[9] Thus the latest paper from Bolland and colleagues simply represents the most up-to-date and comprehensive exposition of findings documented several times previously: In 2014, Bolland et al. performed their first *trial sequential meta-analysis* on vitamin D to test the hypothesis that additional trials would already be futile in terms of their ability to alter the conclusion regarding the efficacy on fracture and a number of other outcomes such as falls and bone mineral density[7]. Specifically, conducting new trials was found to be statistically highly unlikely to alter the conclusion that any relative risk reduction, if present, was below fifteen percent. However, additional trials have run to completion in the interim period and nineteen additional studies with various outcomes were reported in 2016 or later and included in the new analysis. Here the authors revisited the fracture outcomes and also addressed change in bone mineral density (BMD). The findings essentially confirmed their conclusions from 2014 while further narrowing the futility range to 5% for total fractures. For hip fractures specifically, the relative risk with vitamin D supplementation was 1.12 (95% CI 0.98-1.21). Taken together, the authors conclude that supplementation did not reduce the risk of falls and fractures or elicit consistent effects on BMD.

The most ominous message at first glance is that analyses did not demonstrate *any variation* in efficacy attributable to differences in mean baseline vitamin D levels between the studies, nor did they identify any other significant statistical heterogeneity in effect, though the studies were far from uniform in study population or

approach. How much should we make of this lack of statistical heterogeneity for effects when stratified by mean study vitamin D levels? Unfortunately, very few subjects came from the four vitamin D trials with average baseline vitamin D levels of 25 nmol/L or lower so it is difficult to prove or refute a meaningful clinical effect here. Accordingly, the authors concede that trials in a low baseline vitamin D population could indeed have produced different results- we simply do not have the data to support a definitive conclusion.

How does this study change our clinical practice? Much less than media reports would suggest. Critically, the study focused on vitamin D as sole supplementation, and not on supplementation with calcium and vitamin D combined, an approach for which there is evidence, including from Bolland and colleagues[10], of modest antifracture efficacy, but not of great enough magnitude to justify use as sole treatment for fracture prevention. For funders, the study certainly negates the business case for additional vitamin D trials for skeletal effects in persons with normal or unmeasured vitamin D status. Though new trials were added, the analysis essentially reiterates the point of trial futility made by the authors in their prior analysis. In this, the report only confirms our existing expectation as clinicians that the effects of vitamin D supplementation on the skeleton are small in the average adult and probably restricted to those who lack it.

What the study does not do is change the evidence base for calcium or for vitamin D treatment in patients who are deficient in these nutrients. Nor does it affect recommendations in glucocorticoid treated subjects or in patients receiving medical treatment for osteoporosis, this latter situation usually requiring supplementation to comply with licensing stipulations ensuring calcium and vitamin D repletion.

### **Contributors**

Both authors contributed equally to the editorial.

### **Conflict of interest**

The authors declare that they have no conflict of interest.

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