Vitamin D and the prevention of falls and fractures: a never ending story?

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Vitamin D has a relevant role on skeletal metabolism and calcium homeostasis, however conflicting results have been provided about the preventive effect of vitamin D supplementation on musculoskeletal outcomes. Evidence for a new meta-analysis incorporating the data of more recent randomized controlled trials raises questions whether vitamin D supplementation can reduce the risk of falls and fractures. However, these conclusions should be interpreted with caution.

Refers to: *Bolland MJ, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analyses, and trial-sequential analyses. Lancet Diabetes Endocrinol 2018; published online Oct 9. http://dx.doi.org/10.1016/S2213-8587(18)30265-1.*

Vitamin D has a pivotal role in skeletal health and in the maintenance of a normal calcium homeostasis[1]. It is, therefore, not surprising that vitamin D supplements are widely used for the prevention of rickets in children and to improve bone strength and reduce the risk of fractures in the elderly population. While the causal links between severe vitamin D deficiency (e.g. 25OH vitamin D levels of 25-30 nmol/L) and rickets or osteomalacia are well established (as well as the preventive role of vitamin D supplementation in this setting), less clear information is available from either randomized controlled (RCT) studies or meta-analyses about the role of vitamin D supplementation on the maintenance of bone mineral density (BMD) and the prevention of osteoporotic fractures in postmenopausal women or elderly individuals[1]. Indeed, evidence for most observational studies in these populations indicates that even a milder vitamin D deficiency (e.g. 25OH vitamin D between 25-50 nmol/L) may result in secondary hyperparathyroidism, increased bone loss and fractures[1]. Consistent with this view, a 2014 Cochrane Review indicated that there is high quality evidence that vitamin D plus calcium reduces the risk of any type of fracture[2], while a large meta-analysis showed a small albeit significant benefit of vitamin D supplementation in BMD at the femoral neck, particularly in those subjects with 25OH vitamin D levels below 50 nmol/mL[3]. However, more recent systematic reviews reported conflicting results[4], so that new RCTs have been now conducted in the past few years, leading Bolland and coauthors to perform an up-dated meta-analysis aimed to reassess the efficacy of vitamin D supplementation on fractures, falls, and BMD[5]. Their results failed to demonstrate a positive effect of vitamin D in preventing fractures or falls, or have clinically meaningful effects on BMD. In the opinion of the Authors, these findings suggest that there is little justification to use vitamin D supplements to maintain or improve musculoskeletal health and that there is no justification for more trials of vitamin D supplements with musculoskeletal outcomes.

However, these conclusions should be interpreted with caution, due to the large heterogeneity of the studies and the inadequacy of many of the considered RCTs to exclude a possible role of vitamin D supplementation on the outcomes selected in the metanalysis. In fact, most of the RCTs were largely underpowered to answer the question of fracture prevention and were not specifically designed to assess the role of vitamin D supplementation on the prevention of falls and fractures as a primary endpoint. In up to 50% of these studies both outcomes were not considered and information about falls and fractures was only included among the safety profile.

Ideally, a RCT aimed at assessing the efficacy of vitamin D supplementation on bone loss, falls and fractures should be performed in at risk populations with hypovitaminosis D, should be conducted with adequate doses of vitamin D, so that normal 25OH vitamin D levels could be achieved by most if not all participants, and, most importantly, should be of sufficient duration (e.g. 2 years or more) to obtain a more clear view on the prevention of fractures (Box 1). All the above characteristics were not completely achieved by most of the studies considered by Bolland and co-authors in their metanalysis (Box 1). Indeed, in 32% of selected RCTs, patients were taking less than 1000UI/die of vitamin D, while daily doses up to 800-1000U have been demonstrated to be required to maintain vitamin D levels above >75 nmol/L, which is considered a safe cut-off for the skeleton[6], since up to 30% of patients with vitamin D levels between 50 and 75 nmol/L show histomorphometry feature of osteomalacia[6]. Therefore, it is not surprising (and it is indeed of note) that in the 42% of the included RCTs adequate levels of vitamin D have been not reached. This also pertains to some of the larger RCTs with a major impact on the results of the metanalysis[7,8]. In example, in the large Vitamin D Assessment (ViDA) RCT, that was not designed for assessing the effect of vitamin D on the risk of fractures, adequate 25OH vitamin D levels (above 75 nmol/L) were obtained in only 33% of the individuals[8]. Likewise in two other RCTs[9,10] intermittent supplementation regimens of ergocalciferol (100000UI four-monthly orally or 300000UI annual intramuscular injections) were used, that are actually not recommended, since have been related with oscillations in 25OH vitamin D levels (that are not maintained above the normal threshold during the entire treatment period) and with a paradoxical increase in the risk of falls and fractures. Remarkably, these 3 studies altogether weighted more than half of the whole meta-analysis.

Several other confounders may have influenced the results of the meta-analysis. First, the majority of patients were community dwelling subjects (85%) and most of them (75%) were not selected for underlying illness with lack of information on the presence of comorbidities that may influence *per se* the risk of falls and fractures, irrespective of vitamin D status. Second, only the 25% of the included trials have been conducted in association with calcium supplementation. This might have confounded the results, particularly of studies performed in those Countries where reduced dietary calcium intake is common, since this can neutralize the possible positive effect of vitamin D on BMD and fractures[2]. Third, as the Authors themselves noted, smaller studies of shorter duration should be interpreted very cautiously, and indeed

52% of the selected RCTs were performed in less than 200 patients, while 68% had an overall length of less than 1 year. This consideration renders any clear-cut conclusion on the effect of vitamin D supplementation on the risk of fracture very questionable. Finally, a consistent proportion of these RCTs did include patients with normal or nearly normal 25OH vitamin D levels. Albeit the slight BMD improvement in favour of vitamin D observed in pooled analysis was not considered as a clinically meaningful effect by the Authors of this metanalysis, this does not exclude that more relevant effects of vitamin D supplementation can be achieved in patients with low vitamin D levels and particularly in high risk categories such as postmenopausal women or elderly institutionalized individuals.

In conclusion, albeit the results of Bolland and coauthors are of clinical relevance and do not support the widespread use of vitamin D supplementation for musculoskeletal health in community dwelling individuals, this does not lessen the important role of vitamin D supplementation in subjects with a poor vitamin D status (particular in elderly patients or other categories at risk of bone loss, falls and fractures), as well as its additive use in osteoporotic patients under treatment with antiresorptive or osteoanabolic agents.

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BOX 1. Required criteria for trials assessing vitamin D effects on musculoskeletal outcomes

Criteria	Description
1. Population included	High risk populations*
2. Baseline 25OH Vit D. levels	Below 75 nmol/L (possibly below 50 nmol/L)
3. Duration	At least 2 years for bone mineral density and fractures
4. Vitamin D dosages	Cholecalciferol doses above 1000UI per/day (daily or monthly regimens)#
5. Calcium intake/supplements	Calcium supplements in case of reduced calcium intake (below 1000 mg/day)
6. Target vitamin D levels	Above 75 nmol/L (during the study)
7. Comorbidities	Register major comorbidities

**e.g. institutionalized patients, or subjects with BMD levels within osteopenic range.*

 # according to the baseline 25OH vitamin D levels, consider the use of a cumulative high dose for the rapid achievement of normal vitamin D status during the entering phase of the study.

RCTs rated for fracture outcome (n=36) in the metanalysis by Bolland *et al.* (Lancet Diabetes Endocrinol. 2018) and meeting the above criteria