Analysis

Web of industry, advocacy, and academia in the management of osteoporosis

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Re: Bias, Bones and Vitamin D

Dear Editor,

We read with interest the article by Andrew Grey and Mark Bolland (1), regarding the role of calcium/vitamin D treatment in the field of osteoporosis. The authors raise significant scientific and ethical issues in their article, that warrant a statement reflecting the other side of this issue, a view that we think is held by many unprejudiced scientists working on this field worldwide.

Regarding the scientific part of this article, the authors claim that there is a lack of sufficient evidence for calcium/vitamin D supplementation on fracture risk reduction, and the main reasons for this phenomenon mainly lie on a complex association between ‘’big pharma” academic organization and media propaganda. In the end of their article, the authors classify results of many randomized controlled trials (RCTs) as beneficial, neutral or even harmful. without allowing for the challenges of conducting nutritional RCTs, many of which are unique to nutritional studies (2), and that could well confound their results. For example, an informative ‘’nutritional RCT” (that could be included in a systematic review) would use a single form of the nutrient, include a low exposure control group, ensure adequacy in dosing (by documenting therapeutic levels achieved), and optimization of co-nutrient status (3).

Based on the findings and interpretations of previous pioneer RCTs regarding
calcium/vitamin D supplements for osteoporosis (4-14), we would like to emphasize specific points that could affect interpretation of the portfolio of evidence in this field:

1) Trials have used different forms of vitamin D (D2 or D3) (4,5,11,13) , +/- calcium (4,5,9,10,13,14), and various routes of administration(4-10,13,14) . From a pharmacokinetic view, a large bolus of 50,000 or 100,000 IU of vitamin D would rapidly (in a few days) be absorbed, much would be excreted, and become undetectable in the serum (2,15), and several supplementation trials used this type of bolus administration, with further potential for reduction in efficacy due to induction of vitamin D catabolic mechanisms (16).

2) Most trials reported on the attained serum concentrations of 25-(OH) vitamin D post-supplementation (4, 5, 7-9, 11) as a surrogate marker in a small study cohort subgroup (in a total of 5-10% of study participants). Moreover, serum 25(OH)Ds were measured at a single time point and could not be considered as having attained therapeutic levels..

3) A low exposure group was absent in most studies (4, 5, 7-9, 11), though many scientists believe that supplementation with vitamin D in populations with lower baseline concentrations should be more effective, but supplementation of replete subjects (2, 3) will not.

4) Vitamin D efficacy depends on optimal provision of other relevant nutrients such as calcium, e.g. high calcium intakes prevent and heal rickets in vitamin D deficiency, even though vitamin D deficiency causes rickets; similarly, vitamins A and K, and magnesium intakes, affect vitamin D efficacy, but no RCTs examined adjusted for these variables .

5) It is crucial to underline the low adherence to intervention that often did not exceed 40-50% in previous RCTs. Using an ‘intent-to-treat’ analysis is of course the gold standard for evaluating the effectiveness of treatment, but we should mention that it gives no information on the efficiency per se of a molecule compared to a ‘per protocol’ analysis

Thus, RCTs can fail due to design problems and, by chance, as in any other field and in this context, a significant number of the trials cited by Grey and Bolland reported high dropout rates, which could well affect their outcomes. The potential benefits of supplementation with calcium and vitamin D operate through at least two different ways: i) beneficial calcium effects are not seen in serum values, but at the cellular level, with demonstrable increases in bone mineral density, an effect that has been established by a plethora of experimental (17) and clinical studies(18,19) so far.

ii) 25-OHVitamin D has to attain therapeutic levels, but these were not been attained at least not in most study participants, in most of the RCTs analysed in this article; similarly, many subjects had baseline values that demonstrated adequate nutrient status, so that supplementation trial outcomes might have been different in deficient populations, as exist in the majority of populations worldwide. Overall, we support the case that, in focusing on nutritional health effects, RCT interpretation needs to be made using 'nutritional' rather ‘’pharmaceutical” criteria and this stricture also applies to systematic reviews or meta-analyses (2,3) .

Regarding the ethical aspects of work on osteoporosis, we believe that the vast majority of researchers in this field have strong scientific, rather than financial, motivation. We would welcome discussion on any aspect of work in this difficult field, provided that it is accepted that it is studies and not research workers that are biased. We strongly favour continuing scientific debate that strives for carefully balanced views and avoids suggestions of personal lack of integrity, because we do not see the world in such stark terms – right versus wrong, since we think that the biology in this area is more complicated than is currently appreciated.

The debate should go beyond the politically correct and media-attractive phantasm of a scientific reasoning based mainly on conflicts of interest with the major financial groups rather than motivated by the quest for knowledge and health.The role of calcium and vitamin D supplements requires further investigation and we encourage further such work –just as we also appreciate the need for continued vigilance in ensuring correctly designed, objectively analysed, and fully reported, RCTs in this important area.

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Competing interests: No competing interests

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