Osteoporosis International (2019) 30:2521–2522
https://doi.org/10.1007/s00198-019-05164-7

LETTER TO THE EDITOR

Calcifediol or vitamin D to optimize vitamin D status: Reply to letter of M Sosas

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Received: 6 September 2019 / Accepted: 9 September 2019 / Published online: 14 October 2019

We appreciate Sosa's interest [1] in our review [2]. First, we agree that an optimal calcium intake and vitamin D status is necessary for all elderly subjects especially during treatment with active anti-osteoporosis drugs [3]. For most patients, this will imply a supplement of calcium and vitamin D in line with the rules of EBM [4]. We also agree that this conclusion is based on RCTs using supplements of vitamin D_3 (cholecalciferol) and not 25-hydroxyvitamin D or calcifediol. However, we disagree with Sosa's rather categorical statement that only cholecalciferol and not calcifediol should be used in these situations. We did not claim [2] that calcifediol is superior to vitamin D for most osteoporotic patients. We just compared the relative potency of both compounds as to guide clinicians when they consider using calcifediol. We found that calcifediol is about 3-fold more potent than vitamin D itself when given to osteoporotic patients with a rather poor vitamin D status, whereas its potency is greater in case of supplementation of subjects with a higher baseline 25OHD. For all subjects combined, Sosa is correct that calcifediol is between ~ 1.1- to 12-fold more potent than vitamin D [2]. The reason for this great inter-individual variation is unclear. Genetic factors, kinetics of several hepatic 25-hydroxylases, and metabolic conditions probably all contribute to this variability [2]. Indeed, recent mouse data clearly demonstrated that hepatic *Cyp2r1* expression and activity are severely impaired in case of obesity [5], starvation, or type 1 and type 2 diabetes, with involvement of PPAR-gamma-coactivator-1α, estrogen-related receptor, and glucocorticoid receptor [6, 7]. Therefore, we raise the question of which vitamin D metabolite (vitamin D or calcifediol) is best suited to achieve a set target level of serum 25OHD—high enough to be efficient for skeletal or extra-skeletal actions but not exceeding a maximal target for the large majority of subjects. Our review clearly concluded that the post-supplementation increase in serum 25OHD is not linear with increasing dose of vitamin D, whereas this was clearly much better when using calcifediol. The old and more recent data on the regulation of CYP2R1 help to explain this difference in efficacy [2]. Contrary to what Sosa suggests, calcifediol is not a drug that is totally different from vitamin D itself, as 25OHD is the obligatory intermediate step before the inactive vitamin D can be transformed into the active hormone [$1,25(OH)_2D$], whether produced in the kidney or locally in many tissues [3]. There are increasing arguments that serum 25OHD should not exceed of 50 ng/l (125 nmol/l) as such concentrations are associated with accelerated bone loss [8] and increased risks of falls and fractures [9–11]. Therefore, clinicians should be well aware of the optimal dosing of vitamin D or calcifediol. We also agree that in some conditions, calcifediol is superior to vitamin D for correction of vitamin D deficiency, especially in case of genetic disorders [12–14], for gastrointestinal diseases or after bariatric surgery [15]. Only further research will clarify whether calcifediol may be better (or not) than vitamin D itself to rapidly and reliably reach the optimal target concentration of serum 25OHD and vitamin D-related health outcomes.

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Compliance with ethical standards

Conflict of interest None.

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