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We thank Dr. Annweiler and Dr. Corvaisier for their remarks about our article entitled "Daily or intermittent vitamin D supplementation in patients with or at risk of osteoporosis: Position statement from the GRIO" [1]. We also consider, like our colleagues, that taking into account the patient choice of a dosing schedule for any preventive long-term treatment should be the rule, especially when efficacy and safety are comparable whatever the mode of supplementation (i.e. daily or intermittent). However, despite similar efficacy of daily and intermittent vitamin D supplementation on improving circulating 25(OH)D concentration [2], clinical efficacy and perhaps safety of both regimens are different. Indeed, the benefits of vitamin D supplementation in vitamin D-deficient/insufficient patients in RCTs (mostly sub-group analyses) were almost exclusively observed with daily supplementation (briefly reviewed in [1]). This may be explained by long-lasting stimulation of inactivating pathways with intermittent dosing but not with daily low dose, the 24 hydroxylation that leads to inactive metabolites ($24,25(OH)_2D$ and $1,24,25(OH)_3D$), and the secretion of FGF23 which inhibits calcitriol secretion [3]. Furthermore, some studies showed an increased risk of falls and fractures with high intermittent vitamin D doses while moderate daily doses decreased the incidence of falls (reviewed in [1]). Mortality was also increased in the vitamin D groups of two recent mega-trials, which tested the effect of 60,000 IU vitamin D3/month versus placebo [4,5].

The major justification for intermittent vitamin D supplementation is a supposed enhanced adherence. However, this hypothesis has been challenged in recent consensus [6] and clinical practice guideline [7] papers co-signed by numerous renowned vitamin D experts who did not find evidence for a better adherence with intermittent supplementation. We know however that pharmaceutical formulation can significantly impact patient preference/adherence. For example, studies showed that solid (tablets) vitamin D products were clearly preferred to liquid forms (drinkable vials) taken at a similar interval (i.e. monthly) [8]. In our opinion, the only defensible reason to be reluctant to daily vitamin D dosing in France is the lack of pharmaceutical forms compatible with a convenient and well-accepted daily supplementation that are reimbursed by the French Health insurance.

According to studies, efficacy and safety have greater relative importance than dosage form for the preference/adherence to a given treatment [9], a point that should be favourable to daily vitamin D dosing. If both the clinicians and the consumers become aware and convinced of the clinical advantages of daily vitamin D supplementation that are now well established, preference for this dosing schedule should strongly increase in France, especially if new better attractive licensed products of pharmaceutical grade (1000, and 2000 IU soft capsules, tablets, or pills) become available and reimbursed. Waiting for that, we encourage an intermittent dosing with the lowest available and reimbursed "higher" dose using short interval (currently 20,000 IU soft capsules weekly or fortnightly) for those who are reluctant to take several drops daily or to pay for the only available solid pharmaceutical daily dosage (1000 IU soft capsule).

Disclosure of interest

JCS: Viatris, Crinex, DiaSorin, Roche Diagnostics, Amgen.

BC: Alexion, Amgen, Aptissen, Besins, Expanscience, Lilly, Kyowa-Kirin, Novartis, Theramex, UCB, Viatris.

MEP declares that she has no competing interest.

References

[1] Pickering ME, Souberbielle JC, Boutten A, et al. Daily or intermittent vitamin D supplementation in patients with or at risk of osteoporosis: position statement from the GRIO. Joint Bone Spine 2025;92:105858.
[2] Zhuang Y, Zhu Z, Chi P, et al. Efficacy of intermittent versus daily vitamin D supplementation on improving circulating 25(OH)D concentration: a Bayesian network meta-analysis of randomized controlled trials. Front Nutr 2023;10:1168115.
[3] Griffin G, Hewison M, Hopkin J, et al. Perspective: vitamin D supplementation prevents rickets and acute respiratory infections when given as daily maintenance but not as intermittent bolus: implications for COVID-19. Clin Med (Lond) 2021;21:e144–9.
[4] Thompson B, Waterhouse M, English DR, et al. Vitamin D supplementation and major cardiovascular events: D-Health randomised controlled trial. BMJ 2023;381:e075230.
[5] Joseph P, Pais P, Gao P, et al. Vitamin D supplementation and adverse skeletal and non-skeletal outcomes in individuals at increased cardiovascular risk: results from the International Polycap Study (TIPS)-3 randomized controlled trial. Nutr Metab Cardiovasc Dis 2023;33:434–40.
[6] Giustina A, Bilezikian JP, Adler RA, et al. Consensus statement on vitamin D status assessment and supplementation: whys, whens, and hows. Endocr Rev 2024;45:625–54 [bnae009].
[7] Demay MB, Pittas AG, Bikle DD, et al. Vitamin D for the prevention of disease: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2024;109:1907–47 [dgae290].
[8] Rothen JP, Rutishauser J, Walter P, et al. Oral intermittent vitamin D substitution: influence of pharmaceutical form and dosage frequency on medication adherence: a randomized clinical trial. BMC Pharmacol Toxicol 2020;21:51.
[9] Stewart KD, Johnston JA, Matza LS, et al. Preference for pharmaceutical formulation and treatment process attributes. Patient Prefer Adherence 2016;10:1385–99.

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