Vitamin D at the crossroad of prediabetes, sarcopenia, and risk of falls

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In this issue of *The Lancet Healthy Longevity*, Tetsuya Kawahara and colleagues[1] report results of an ancillary study of the Diabetes Prevention with active Vitamin D (DPVD) multicentre, randomised, placebo-controlled trial in Japan investigating the effect of active vitamin D (eldecalcitol 0·75 µg per day) on the prevention of type 2 diabetes among adults with prediabetes. Specifically, the effects of eldecalcitol versus placebo on sarcopenia occurrence were evaluated.[1] Significantly increased muscle handgrip strength and stable muscle mass (decreased in the placebo group) were reported after the use of eldecalcitol, together with a significantly lower fall risk.[1] These findings are of clinical interest as they add interventional prospective well-controlled evidence, at least in a selected population, to the argument of vitamin D being a potential tool in preventing sarcopenia and falls for individuals who are linked to fracture risk and disabilty, particularly in older people.[2]

The ubiquity of vitamin D receptor supports the assumption that vitamin D should be considered a pleiotropic hormone.[3] Although the association between vitamin D deficiency and several extra skeletal endpoints has been consistently reported, evidence on the systemic effect of vitamin D supplementation is conflincting or inconclusive[4] due to lack of control, observational nature, number, and heterogeneity of patients involved in terms of vitamin D deficiency at baseline (vitamin D supplementation is not likely to have any effect in repleted people), ethnicity, use of food fortification, age, and weight.[5]

Among vitamin D extraskeletal endpoints, muscle has been widely studied being strictly linked to bone and antifracture actions. Association studies suggest that vitamin D deficiency could negatively affect skeletal muscle.[4] However, meta-analyses report that vitamin D supplementation either slightly improves or has no effect on muscle strength, which in the older population is linked to falls.[2] Despite conflicting meta-analyses results, standard doses of vitamin D might likely reduce risk of falls in deficient older adults, whereas infrequent larger bolus doses could increase fall risk in relation with too high vitamin D serum concentration.[2] Moreover, low vitamin D is linked to type 2 diabetes incidence, control, and complications, although vitamin D supplementation has substantial diabetes preventive effect in only non-obese people with severe vitamin D deficiency at baseline.[6,7]

Kawahara and colleagues[1] studied a specific population (ie, people with prediabetes), and this is remarkable as focus on specific populations, at least theoretically, allows to investigate treatment outcomes in a relatively small study group at high risk of vitamin D deficiency.[6] However, besides the obvious difficulty of extending the findings to the general population, the study has limitations that hamper, at least in part, its effect in clinical practice. Infact, sarcopenia—the specific topic of the study—does not have a universally accepted definition whether or not it is associated with being overweight.[8] Moreover, as in other vitamin D interventional studies, there are issues concerning doses, schedule, type of vitamin D, prevalence of hypovitaminosis D at study entry and completion, and confounding variables such as age and BMI. In fact, eldecalcitol is an active form of vitamin D used only in Japan and China, which, like calcitriol, can increase serum and urinary calcium as also seen in some patients of the study.[1,9] Therefore, testing the effect of cholecalciferol or calcifediol on sarcopenia will have an added value as these are the most currently used forms of vitamin D.[9]

The observed effect of vitamin D was possibly due to pharmacological rather than substitutive treatment. A single dose of active vitamin D was used, and about 50% of patients were not vitamin D deficient according to guidelines[10] and 25 (OH) vitamin D concentrations did not change during the study,[1] therefore, not being helpful for biochemical monitoring of treatment. Studies with inactive vitamin D could help better understand the possibility of effectively preventing sarcopenia but also allowing personalisation of the dose and understanding if the protective effect might take place at a threshold level of the hormone.

Finally, patients enrolled in the study were of different ages and some of them were also overweight. This heterogeneity of the enrolled population reinforces the concept of the trial focusing more on pharmacological

effects of an active vitamin D analog than on the anti-sarcopenic effect of physiological replacement of vitamin D.

In conclusion, the study suggests that pharmacological use of vitamin D could be beneficial in patients with prediabetes against sarcopenia and risk of falls. The intrinsic limitations of controlled trials like this in terms of selection bias and confounders could possibly be overcome by institution of national and international registries for people treated with every form of vitamin D that should record its doses and levels on treatment and skeletal and extraskeletal outcomes.[3]

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1 Kawahara T, Suzuki G, Mizuno S, et al. Active vitamin D treatment in the prevention of sarcopenia in adults with prediabetes (DPVD ancillary study): a randomised controlled trial. *Lancet Healthy Longev* 2024; published online March 1. https://doi.org/10.1016/S2666-7568(24)00009-6.

2 Giustina A, Bouillon R, Dawson-Hughes B, et al. Vitamin D in the older population: a consensus statement. *Endocrine* 2023; **79:** 31–44.

3 Giustina A, Lazaretti-Castro M, Martineau AR, Mason RS, Rosen CJ, Schoenmakers I. A view on vitamin D: a pleiotropic factor? *Nat Rev Endocrinol* 2024; published online Jan 22. https://doi.org/10.1038/s41574-023-00942-0.

4 Bouillon R, Marcocci C, Carmeliet G, et al. Skeletal and extraskeletal actions of vitamin D: current evidence and outstanding questions. *Endocr Rev* 2019; **40:** 1109–51.

5 Giustina A, Adler RA, Binkley N, et al. Controversies in vitamin D: summary statement from an international conference. *J Clin Endocrinol Metab* 2019; **104:** 234–40.

6 Tecilazich F, Formenti AM, Giustina A. Role of vitamin D in diabetic retinopathy: pathophysiological and clinical aspects. *Rev Endocr Metab Disord* 2021; **22:** 715–27.

7 Pittas AG, Kawahara T, Jorde R, et al. Vitamin D and risk for type 2 diabetes in people with prediabetes : a systematic review and meta-analysis of individual participant data from 3 randomized clinical trials. *Ann Intern Med* 2023; **176:** 355–63.

8 Donini LM, Busetto L, Bischoff SC, et al. Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement. *Obes Facts* 2022; **15:** 321–35.

9 Bilezikian JP, Formenti AM, Adler RA, et al. Vitamin D: dosing, levels, form, and route of administration: does one approach fit all? *Rev Endocr Metab Disord* 2021; **22:** 1201–18.

10 Sempos CT, Heijboer AC, Bikle DD, et al. Vitamin D assays and the definition of hypovitaminosis D: results from the First International Conference on Controversies in Vitamin D. *Br J Clin Pharmacol* 2018; **84:** 2194–207.