Vitamin D supplementation and mortality

In this issue of *Lancet Diabetes & Endocrinology*, Neale and colleagues *(insert REF this volume Lancet DE)* present findings from D-Health, a population-based double-blind placebo-controlled vitamin D_3 intervention trial in older Australian adults (n=21,315). It is the largest study to date that assessed the effect of vitamin D supplementation on mortality as the primary outcome. No significant reduction in all-cause mortality or from cancer and CVD was found. For cancer mortality, Hazard Ratio point estimates for ITT and per-protocol analyses were numerically higher in the intervention group, but 95% CIs were wide and crossed 1. Further analyses showed no effect modification according to predicted vitamin D status (i.e., plasma concentration of 25 hydroxy vitamin D (25(OH)D)) and BMI. Explorative analyses excluding the first 2 years of follow-up found a marginally significant higher hazard ratio for cancer mortality in the vitamin D treated group, but no significant effect on all-cause mortality.

Research has shown a role of vitamin D in a wide range of physiological systems and biological responses, including calcium and phosphate homeostasis and skeletal health, immune function, cell cycling and differentiation. In observational studies, low vitamin D status, is associated with increased risk of adverse health outcomes, both chronic and acute[1, 2]. Associations of health outcomes with 25(OH)D, which has little biological activity, may seem counter intuitive. Pre-clinical research has shown expression of the vitamin D receptor in wide range of tissues and local conversion of into 25(OH)D into the active metabolite $1,25(OH)_2D$, with auto- and paracrine effects. Involvement of vitamin D in multiple mechanisms determining mortality risk is therefore plausible. However, intervention trials other than with musculoskeletal health outcomes are less consistent than observational studies and often do not confirm beneficial effects of increasing vitamin D intake or status[1, 2]. This is partly ascribed to the complex nature of vitamin D metabolism, the confounding effects of vitamin D supply from other sources (i.e., supply through sun-exposure and from food and supplements), body composition and alterations of vitamin D metabolism with acute and chronic illness. Vitamin D status is therefore influenced by factors associated with overall health and lifestyle and thus causality and reverse causality are difficult to distinguish.

There is no international consensus about the 25(OH)D threshold for vitamin D sufficiency for non-skeletal outcomes, but most advisory bodies consider a 25(OH)D concentration ≥50 nmol/L sufficient[3] and many intervention studies aimed to increase 25(OH)D above this concentration. The effect of interventions may depend on baseline and post-supplementation vitamin D status, with benefits particularly found in populations with a high prevalence of low 25(OH)D[4, 5].

The findings of the D-health study are highly relevant for population policy, due to its population-based design, large scale and long duration- supplementation was provided for 5 years and the mean follow-up was 5.7 years. Retention and compliance were high. With monthly dosages of 60,000 IU per month (corresponding to 2,000IU/d), the intervention exceeded the Australian recommendations[6] (https://www.nrv.gov.au/nutrients) and those of most other countries[3]. No screening for vitamin D status took place but modelling of bloods collected in subset of the placebo group showed a mean (SD) 25(OH)D concentration of 77±25 nmol/L and a predicted baseline concentration ≥50 nmol/L in 76% of participants. This may have influenced the outcomes of the trial.

The findings of the D-health study are largely consistent with prior intervention trials [7] and 2 other mega-trials with vitamin D supplementation as mono or co-intervention reporting mortality and cancer outcomes. The US based VITAL trial[8] and the New Zealand ViDa trial[9] included participants of similar ages and also in these trials the majority of participants were vitamin D sufficient at baseline. The VITAL trial however found a significant reduction in cancer mortality in the last 3.3 years of the trial[8].

Together, these findings do not suggest that vitamin D supplementation influences all-cause mortality in mostly vitamin D replete older populations. However, the most important caveat in these intervention studies is the lack of data in participants with a 25(OH)D below 50 nmol/L, who are most likely to benefit. Further, longer follow-up may be required to adequately investigate the effects on conditions that develop over decades, rather than years. It is anticipated that 10-year mortality rates from D-Health will be reported in future. For population-based policy, potential adverse effects also need to be considered. Although similar rates of adverse event were reported in the intervention and placebo group, suggesting no short-term effects, a substantial proportion of participants achieved 25(OH)D concentrations exceeding 125 nmol/L. Both the European Food Safety Authority and US

Institute of Medicine caution against the potential adverse effects of sustained plasma concentrations above 125 nmol/L, although findings of adverse effects are inconsistent and strong empirical data are lacking[10].

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