Update on vitamin D: pros and cons

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Summary

Controversies on vitamin D currently represent a challenging topic in mineral metabolism research. In particular, current guidelines on vitamin D supplementation did not report consistent recommendation and the issue related to beneficial *vs* harmful effects of loading vitamin D doses did not lead to any firm universal conclusion. Finally, serum and clinical outcomes of vitamin D supplementation, particularly as far as extra-skeletal effect of the hormone, need to be further investigated.

KEY WORDS: vitamin D; supplementation; skeletal; extraskeletal.

Among hormones deputed to regulation of mineral metabolism, vitamin D currently stands out as a key topic in clinical patients' management, as well as in many scientific research areas. Many studies focused on the beneficial effects of the hormone on skeletal and extra-skeletal health, and controversial results rose as far as virtually any topic in the field (1-5). As the only agreement seems to be on the recognition of serum 25-hydroxy-vitamin D [25(OH)D] as the indicator of vitamin D status, the two major clinical guidelines advocate for different serum threshold of optimal vitamin D status (20 *vs* 30 ng/ml) (6, 7). As a consequence, the need for vitamin D supplementation, the dose and serum 25(OH)D achievements challenge the scientific debate on vitamin D, as well. Suggested daily intake of vitamin D varies according to age, sex and baseline 25(OH)D serum levels (6-8). The administration of a loading dose in case of documented vitamin D deficiency has been suggested by most (6, 8) but not all (7) experts. Several studies have evaluated the efficacy and the response of serum 25(OH)D to large doses of vitamin D, particularly in the elderly (9, 10). The use of different loading doses and time schedules of administration have been investigated in order to obtain an equivalent cumulative dose, compared to the daily dose, and to rapidly achieve the target 25(OH)D serum levels in deficient patients (9, 10). Data from different studies showed a similar pharmacokinetic profile, with a rapid improvement in serum vitamin D and a subsequent decline when a loading vitamin D_3 dose is administered orally (9-11). Concerns were instead raised about the potential benefit of loading doses of vitamin D in terms of both skeletal and non-skeletal outcomes (11, 12). Two studies reported potential negative effects of high vitamin D doses on skeletal health and different mechanisms were hypothesized but not demonstrated so far (11, 12). Among them, 25(OH)D serum levels fluctuation has been associated with the harmful effect of high doses, and this point brings back to the need for a continuous maintaining dose after the loading dose is administered, as clinical guidelines have suggested (6, 8). Data from our group have also demonstrated as the high dose intramuscular administration could be considered when a slow but continuous increase in 25(OH)D serum levels is the goal of treatment and with the scope to avoid any possible serum fluctuation (10).

As far as extraskeletal effects, a number of studies reported a negative association between vitamin D serum levels and many health outcomes (1). As a variety of extraskeletal tissues were found to express the vitamin D receptor, increasing evidence reported a high frequency of vitamin D deficiency in a large number of chronic conditions, such as diabetes, cardiovascular and autoimmune diseases, sarcopenia, and cancer (1). Cross-sectional and observational studies described an association between low vitamin D levels and an increased risk of such diseases and intervention studies were carried out to investigate the effect of vitamin D intake on these conditions, as well as on all-cause mortality (2-4, 13, 14). Given the substantial heterogeneity in study populations, design, confounding factors and clinical outcomes, the relevant studies on the field did not show consistent results. In this context, results from clinical studies investigating the inter-relationship between vitamin D and falls, represent a nice example of the open debate on the multi-organ effect of vitamin D (14, 15). A number of meta-analyses indeed were performed seeking the effect of vitamin D supplementation on falls (13, 14). Among the most referenced ones, the meta-analysis from Bishoff-Ferrari et al. reported a good efficacy of a daily 700-1000 IU dose of vitamin D in reducing the risk of falls in the elderly, particularly in association with 25(OH)D serum levels above 60 nmol/l (13). On the contrary, Bolland et al. recently showed in a trial sequential analysis the absence of any effect of vitamin D supplementation, with or without calcium, on falls (14). The evidence of such inconsistency strongly recalls the need for randomized controlled trials specifically powered to evaluate whether a low-cost intervention, as vitamin D supplementation, could have effect on reducing the risk of fall in the older people.

Interventional studies on vitamin D were also carried out targeting cardiometabolic outcomes and showed that moderate-high doses of vitamin D may have beneficial effect in reducing cardiovascular risk (15), insulin sensitivity (2, 3), as well as systemic inflammation associated with type 2 diabetes (16). Data on all-cause mortality showed an inverse association between

circulating 25(OH)D and death, while a recent meta-analysis on intervention trials concluded that vitamin D_3 seems to decrease mortality in elderly independent and institutionalized people (4, 17).

Pros and cons positions demonstrate as vitamin D represents an active research area, and regardless data showing the absence of any significant evidence, many issues on the field are worthwhile to be further investigated. As vitamin D deficiency can be easily assessed and rapidly managed, a key point for clinical studies is currently to assess the actual prevalence of the disorder among different cohorts of patients, as well as the efficacy of the supplementation. More data from longitudinal, specifically designed and randomized, placebo-controlled studies will be therefore of utmost importance to target these issues. Clinical management of vitamin D deficient patients will benefit from future research as far as establishing who needs to be treated, which are the best regimen and treatment goals in terms of both vitamin D serum levels and clinical outcomes to be pursued.

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