VITAMIN D
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Vitamin D supplementation: better daily or by bolus?

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Vitamin D is a pre-hormone and a dietary nutrient required for the normal function of specific physiological processes. Adequate levels of vitamin D are essential for the proper regulation of calcium-phosphorus homoeostasis and maintenance of the musculoskeletal system [1]. Recent findings have also highlighted some "extra-skeletal" properties of vitamin D [1,2]. Among these an important regulatory activity in the immune system has emerged [2].

Humans are able to synthesise vitamin D_3 through photochemical conversion. Ultraviolet B radiation leads to the conversion of 7-dehydrocholesterol to cholecalciferol by the skin. Several factors limit this process. These include the thickness of the stratum corneum (MORE often with advancing age), the angle of the earth's axis (which limits the amount of UVB useful for the production of vitamin D), and other environmental factors such as air pollution, cloudiness, etc [3,4]. Alternatively, vitamin D, in the form of vitamin D_3 (cholecalciferol), of animal origin and vitamin D_2 of plant origin (ergocalciferol), can be obtained from the diet or dietary supplements [5,6]. This source of vitamin D is essential when exposure to sunlight or the skin's response to ultraviolet radiation is insufficient, as in the elderly. Vitamin D, whether as D_3 or D_2, requires a two-step activation process to become biologically active. Vitamin D is transported in the bloodstream bound to a specific plasma protein: vitamin D binding protein (VDBP). Afterwards, within a few hours of synthesis or dietary absorption, vitamin D is hydroxylated in the liver, forming 25(OH)D (calcifediol). The next step is further hydroxylation largely, but not exclusively, by the kidney, forming $1,25(OH)_2D$ (calcitriol), the biologically active form of vitamin D [1]. To date, serum levels of 25(OH)D are the best indicator for assessing vitamin D status. It is now widely recognised that low levels of vitamin D (< 20 ng/mL) have detrimental effects on skeletal and extra-skeletal health [1].

In fact, among the various national and international scientific societies there is broad consensus on this threshold in the definition of vitamin D insufficiency [7]. Many epidemiological studies have shown that vitamin D deficiency is extremely widespread at all latitudes, especially among the elderly [8]. Quite a few observational studies have linked low serum vitamin D levels to the development or exacerbation of many chronic diseases. However, interventional studies on extra-skeletal health are still inconclusive, even though they have often been influenced by methodological problems [1,9]. Furthermore, there is still no consensus on the best supplementation scheme (dose, treatment frequency and duration).

Actually, in clinical practice, a wide variety of supplementation schemes have been proposed, often guided solely by the physician's preference. Supplementation schemes ranging from a few drops per day to mega-doses of vitamin D given over time, in some cases every six months, are used. The lack of uniformity of these regimens can be explained, at least in part, by the paucity of comparative pharmacokinetic data for the different treatment regimens. However, it has recently emerged that a daily dose, often considered less effective, is instead MORE efficient than boluses (at the same cumulative dose) in restoring normal 25(OH)D levels or increasing them (Fig. 1) [10]. Although this last study had no pre-determined clinical objective and was conducted on healthy subjects, who were followed for just a short time, it did provide valuable information on the pharmacokinetics of vitamin D. The explanation for this phenomenon should be sought in the different anabolism-catabolism of vitamin D in relation to any supplementation scheme. Vitamin D boluses rapidly saturate the hepatic 25-hydroxylase, which is responsible for the conversion of vitamin D_3 and D_2 into 25(OH)D, with the resulting induction of the 24-25-hydroxylase, the enzyme responsible for the catabolism of vitamin D to 24-25(OH) D (inactivated form) [11]. In other words, 25-hydroxylase saturation would limit the conversion of cholecalciferol boluses

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Giovanni Adami and Angelo Fassio declare that they have received funding or have contracts or other forms of financing in place with Theramex, Amgen and Neopharmed.

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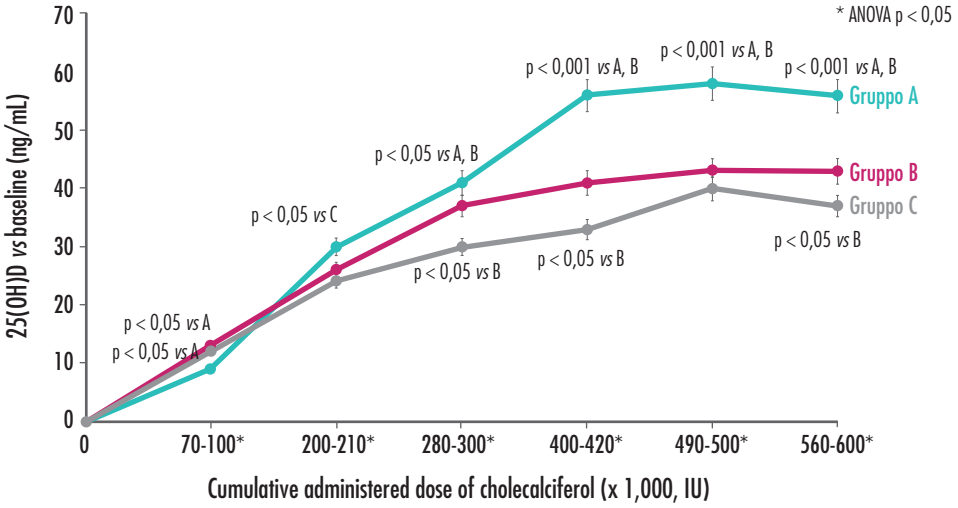

FIGURE 1.
Pharmacokinetics from different treatment regimens in vitamin D deficient patients. Blue line 10,000 IU daily, orange line 50,000 IU weekly, grey line 100,000 IU biweekly(from Fassio et al., 2020, mod.) [10].

to the semi-active form, resulting in fewer biological effects.

This hypothesis is supported by long-term clinical studies which suggest that the treatment schedule itself (i.e., bolus vs fractionated administration) may have a different impact on the efficacy of the treatment and the clinical outcome studied. For example, a recent meta-analysis of more than 40,000 individuals published in the prestigious JAMA Network Open journal showed that only daily doses of vitamin D and not intermittent doses alone were able to reduce the risk of fragility fracture. Specifically, not particularly high doses (400-800 IU daily) reduced the risk of hip fracture by 16% (RR, 0.84; 95% IC, 0.72-0.97) [12].

The evidence supporting the improved efficacy of the daily regimen in restoring normal 25(OH)D levels is therefore growing and increasingly convincing. In addition, it is interesting to note that several studies have shown daily administration schemes to be more promising in terms of both skeletal and extra-skeletal effects. A meta-analysis of randomised clinical trials of more than 11,000 patients published in 2017 showed that vitamin D supplementation is in fact able to significantly reduce the risk of acute respiratory infections (aOR, 0.88; 95% CI 0.81-0.96). The effect was particularly evident in patients taking daily or weekly doses (aOR, 0.81; 95% CI 0.72-0.91), whilst it was not apparent in patients treated with vitamin D boluses (aOR, 0.97; 95% CI 0.86-1.10) [13]. In addition, the protective effect of vitamin D supplementation was, as foreseeable, particularly strong in vitamin D-deficient patients (aOR, 0.30; 95% 0.17-0.53 in patients with pre-study 25(OH)D <10 ng/mL) but, surprisingly, patients with levels ≥ 10 ng/mL also had a tangible benefit from vitamin D supplementation (aOR, 0.75; 95% IC 0.60-0.95 in patients with pre-study 25(OH)D ≥10 ng/mL) [13]. In practical terms, daily vitamin D supplementation in patients with very low vitamin D levels (<10 ng/mL) is able to prevent 70% of infections. This translates into an NNT (number of patients you need to treat to prevent an event) of just 4 individuals. This shows an extraordinarily high efficacy considering that the NNT of the influenza vaccination is between 10 and 50 individuals [14]. Furthermore, the discussion on the efficacy of vitamin D in preventing and treating SARS-CoV-2 infection is also highly topical. To date there are robust epidemiological findings available showing here are robust epidemiological findings available showing that vitamin D deficiency is an important risk factor for contracting SARS-CoV-2 and for developing complications related to COVID-19 [15]. Indeed, it has been noted that over 70% of patients with COVID-19 have insufficient vitamin D levels 16 and that patients with severe respiratory failure have LOWER 25(OH)D levels than patients with non-severe COVID-19 [16]. Nevertheless, there is still little evidence to support the efficacy of vitamin D supplementation in preventing or treating COVID-19. Particularly, randomised clinical trials of daily vitamin D supplementation strategies have not yet been published.

The potential extra-skeletal immunomodulatory effect of vitamin D could be due to direct activity of the 25(OH)D precursors, cholecalciferol and ergocalciferol, on im-

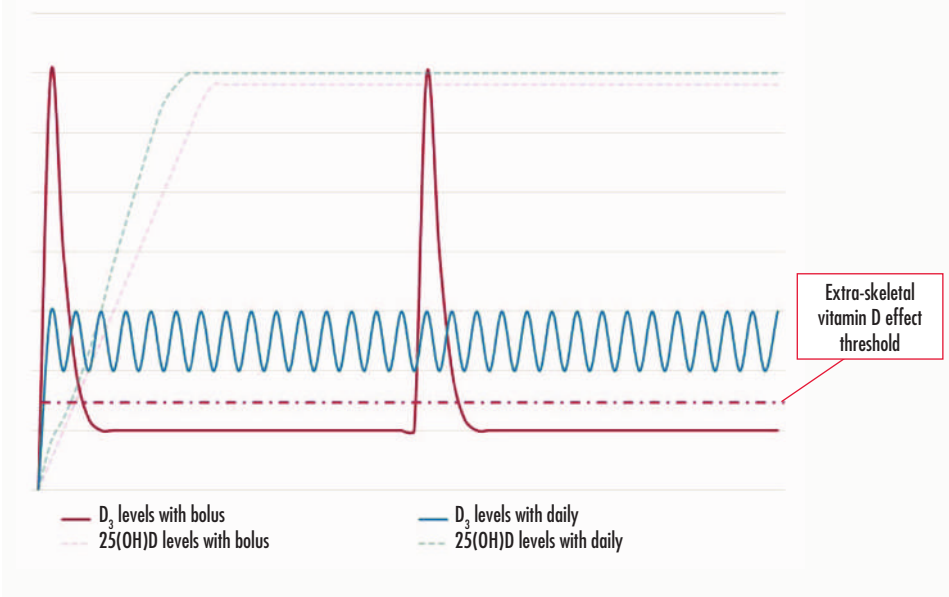

FIGURE 2.
Graph showing the extra-skeletal vitamin D threshold-effect hypothesis and the effects of bolus and daily administration on vitamin D and 25(OH)D levels.

mune cells [2]. After exposure to a foreign pathogen, T-lymphocytes express the vitamin D receptor, which, in the presence of adequate levels of vitamin D_3 or D_2, transduces a signal for lymphocyte proliferation and activation of adaptive immunity.
This particular immunological effect, which has been widely documented in vitro, is mediated by 'inactive' vitamin D precursors and not by the forms biologically active on mineral and bone metabolism. Therefore, this effect appears to be independent of 25(OH)D concentrations, but MORE closely linked to the availability of vitamin D_3 and D_2 in the bloodstream. Daily doses could therefore have the distinct advantage of maintaining stably high levels of vitamin D in the circulation by constantly stimulating immune T cells. On the other hand, bolus administrations are rapidly converted to 25(OH)D with circulating D_2 and D_3 levels dropping rather quickly [17]. Figure 2 shows the hypothesized different effect on extra-skeletal effects of vitamin D bolus compared to daily administration. In conclusion, we believe that there is now pharmacokinetic, pharmacodynamic and clinical evidence to justify the preferential choice of the daily supplementation strategy over the bolus strategy.

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