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EXPERT OPINION

Replenishment of vitamin D status: theoretical and practical considerations

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In recent years, there have been a very large number of scientific publications concerning various aspects of vitamin D, ranging from physiologic to therapeutic studies. However, despite the multiple discoveries made in this fast-growing scientific research area, numerous issues still remain unresolved [1, 2]. Examples include, though are not limited to, the definition of hypovitaminosis D (this term is used to cover cases of both insufficiency and deficiency), i.e. 20 vs 30 ng/mL; the relationship between 25(OH)D and parathyroid hormone (PTH) (linear vs non-linear and related point of inflection) [3–5]; the referent that should be considered (total vs free determination) [6]; and the utility of screening for hypovitaminosis vs universal supplementation [7].

However, one of the most heatedly debated issues is the question of what comprises appropriate treatment. Indeed, irrespective of the threshold adopted, there is uncertainty regarding the specific vitamin and the dose that should be utilised, for how long, and how to maintain the threshold once it is reached. In the following section, we will address the topic of cholecalciferol supplementation both from a theoretical and a practical point of view.

There has been much debate regarding the modalities by which vitamin D supplementation should be provided and, to discuss this issue, we propose a hypothetical situation. Let us imagine a 53-year-old woman who had her vitamin D status checked during a routine visit for bone problems after 2 years of estrogen deficiency. She reports no particular complaints apart from non-specific weakness and mild hot flushes. Her total 25(OH)D level measured by liquid chromatography tandem mass spectroscopy (a reference method) is 10 ng/mL. How can the desired value of 30 ng/mL be reached, as suggested, for example, by the Italian Society of Osteoporosis, Mineral Metabolism and Bone Diseases, as well as by National Osteoporosis Foundation, International Osteoporosis Foundation, American Association of Clinical Endocrinologists and American Geriatric Society? The target value could be achieved either via daily doses or, alternatively, she could be offered an immediate vitamin D repletion strategy.

There are several important points that should be kept in mind. First, as a rule of thumb, long-term steady-state administration of 100 IU of vitamin D raises serum 25(OH)D concentration by about 1 ng/mL (2.5 nmol/L). Secondly, as a pharmacological principle, it takes four half-lives for a drug to reach its steady-state level. Therefore, considering that serum 25(OH)D falls by half within 2 months, if a person is suddenly deprived of vitamin D, it should take 6 to 8 months for a full steady state of serum 25(OH)D level to be reached.

The point is that if you want to raise a patient's serum 25(OH)D from 10 to 30 ng/mL (i.e. by 20 ng/mL) in the long term, the administration of 2,000 IU of cholecalciferol for 8 months will achieve this 30 ng/mL target in most patients. In order to sustain this level in the long term, the dose must also, of course, be maintained in the long term. However, all osteoporosis medications require, from their initiation, vitamin D sufficiency in order to be effective at achieving their full densitometric and anti-fracture effect [8]. Moreover, there are also situations in which waiting for half a year to optimise the serum 25(OH)D serum level is not desirable. One example

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is the acute-phase reactions following zoledronate infusion. A number of studies have shown that vitamin D replenishment can decrease or even abolish this drug side effect [9]. Also, in this case, a rapid conversion to a state of vitamin D sufficiency is desirable.

The pharmacological principle of a loading dose can be applied to vitamin D so that the target level of serum 25(OH)D can be reached within a few days. Again, from the point of view of basic pharmacology, a loading dose for a drug works out to be the total dose of the drug that would be given to sustain the steady-state concentrations of the drug. In the previous example, the loading dose for vitamin D works out at about 60 times the anticipated daily maintenance dose (2-month half-life = 60 days of doses, that is about 120,000 IU as a loading dose of vitamin D_3). Evidently, from that loading dose onwards, the maintaining dose is required. To return to the hypothetical case, the ideal is to administer 120,000 I.U. as a bolus of vitamin D_3 to raise serum 25(OH)D to its target level of 30 ng/mL, followed by 2000 IU/day from then on to maintain the appropriate levels.

From a pharmacological point of view, about a week after this dose is given as a bolus, the 25(OH)D should be at the same steady level as would be reached after 8 months of 2,000 IU per day. After this dose, the average daily dose should be kept at 2,000 or 14,000 IU once a week as an alternative regimen. In this context, it is important to note that an excess of 150,000 IU of vitamin D administration is very unusual, doses that, according to some authors, may dangerously increase falls and fractures [10, 11].

Cholecalciferol formulations are not available as prescription products in the USA, unlike in many European countries, where a number of formulations and doses of D_3 are on the market. 50,000 IU of ergocalciferol (vitamin D_2) given once a week for 8 weeks may be considered an effective strategy to target vitamin D deficiency [12]. However, since there is no clinical trial evidence that vitamin D_2 is effective [13], vitamin D_3 is considered the most appropriate compound to prescribe to patients [14–16].

There is a long list of possible alternative strategies that have been published, the analytical examination of which is, however, not possible within this short review. A number of studies have, meanwhile, been published that seek to address the issue as to whether the same cumulative dose of cholecalciferol determines different 25(OH)D values if administered on a daily, weekly, or monthly basis. In general, the results reported in these studies are consistent with similar levels reached, independently of dosing frequencies.

There are two problems that should be briefly considered in this context. The first concerns potential toxicity. However, such doses as mentioned above are highly unlikely to cause hypercalcemia, kidney stones, and ectopic calcifications of soft tissues and vasculature, which are the most serious complications. Two patients have been reported in this Journal who suffered from primary hyperparathyroidism and who erroneously took 2,400,000 U (300,000 U/day for 8 days) and 4,500,000 U (300,000 U/day for 15 days) of cholecalciferol, respectively [17]. Intriguingly, the unintentional oversupplementation of vitamin D in these two cases caused only a moderate and temporary increase of serum and urinary calcium that were not associated with clinical signs of toxicity. These findings strongly suggest that the regulatory mechanisms of the human body are able to metabolise supraphysiological levels of vitamin D. On the other hand, the finding of frank hypercalcemia in those receiving vitamin D at the dose prescribed for supplementation and treatment could well be associated with mutations in CYP24A1. The latter polymorphisms were probably the cause of the small epidemic of infantile hypercalcemia in England in the 1950s.

The second point that should be emphasised is the well-known finding that differences are reported in the level of 25(OH)D reached among individuals following similar doses of vitamin D administration by both the oral and the intramuscular routes [16, 18, 19]. Apart from genetic considerations, these differences may be the reflection of variability in absorption, degradation, and distribution [20]. Considering all these variables, it might be surprising that a single fixed dose is nevertheless recommended in international clinical trials. Therefore, apart from administration of the standard initial large bolus of vitamin D, prescribing according to the "one size fits all" logic cannot be justified except for practical purposes. In this context, for example, the guidelines of the American Geriatric Society report that only 51% of patients treated with the recommended dose of vitamin D (1,000 IU) achieve the goal of 30 ng/mL [21].

In conclusion, we believe that a "treat to target strategy" is the most desirable approach in each subject [22]. However, in daily practice, it is difficult to apply in practical terms. There is no risk with the initial bolus administration of 100,000–150,000 IU of vitamin D: it is, in fact, needed in the great majority of cases, since severe vitamin D deficiency, defined as 25(OH)D values less than 10 ng/mL, is not common in the USA and Europe. This latter approach is sound from a pharmacological point of view and very efficiently targets the well known hypovitaminosis D pandemic round the world.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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