Oral calcidiol is a good form of vitamin D supplementation

Piergianni Biondi
Jessica Pepe
Federica Biamonte
Marco Occhiuto
Martina Parisi
Chiara Demofonti
Valeria Baffa
Salvatore Minisola
Cristiana Cipriani

Department of Internal Medicine and Medical Disciplines, “Sapienza” University of Rome, Rome, Italy

Address for correspondence:
Cristiana Cipriani
Department of Internal Medicine and Medical Disciplines
“Sapienza” University of Rome, Rome, Italy
E-mail: cristiana.cipriani@gmail.com

Summary

Vitamin D supplementation represents an important topic in the field of metabolic bone disease. Calcidiol, the 25-hydroxy-vitamin D [25(OH)D], is the form of vitamin D most recently introduced in clinical practice. Advantages of the use of calcidiol derive from the pharmacokinetic properties and are related to the possibility of use in patients with liver disease, obese patients, patients with intestinal malabsorption, secondary hyperparathyroidism associated with chronic kidney disease as well as to avoid any possible toxic effect when high doses are used. The ADDI-D study demonstrated the efficacy and safety of calcidiol at the daily dose of 20 or 40 μg and 125 μg/week. In particular, the daily dose of 40 μg can be suggested as an alternative in severely deficient patients, as it has demonstrated to ensure higher vitamin D levels, compared to the 20 μg/day and the weekly 125 μg dose. The last can be an option when issues with compliance to the supplementation are present.

KEY WORDS: vitamin D; calcidiol; supplementation; hypovitaminosis D.

Vitamin D deficiency is a very common condition in the elderly and in young adults, with many clinical consequences, mostly in relation to the role of the hormone in the regulation of skeletal and calcium metabolism and in many other systems. The classical actions of vitamin D include regulation of mineral homeostasis of the skeleton by promoting calcium and phosphorus absorption in the gut to ensure adequate serum concentrations and mineralization of bone. Among non-classical target tissues, the parathyroid glands, the neuromuscular and immune system, heart, vessels, cancer cells, and gastrointestinal tissues have been studied (1, 2). The association between vitamin D deficiency and increased risk of many chronic conditions has been extensively described in observational studies investigating the effect of the hormone on the aforementioned “classical” and “non-classical” target organs (2, 3). Available evidence indicates that 25(OH)D serum levels > 30 ng/mL (75 nmol/L) are desirable in all subjects, particularly patients at high risk for falls and fracture, and before the initiation of bone-active drugs (4). Conversely, intervention studies on the extra-skeletal effects of vitamin D supplementation showed so far inconsistent results.

In general, the issue of vitamin D supplementation is one of the most important in the clinical management of deficient states, particularly as far as form, doses and dose schedule to be used. The two main forms of vitamin D employed for supplementation are cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). In particular, oral cholecalciferol demonstrated in many studies to be superior to ergocalciferol in rapidly and safely increase vitamin D serum levels in deficient and insufficient patients (5, 6). Both the pro-hormones are biologically inactive and hydroxylated in the liver to 25-hydroxy-vitamin D [25(OH)D], or calcidiol. The second hydroxylation occurs primarily in the kidney to form the physiologically active 1,25-dihydroxy-vitamin D [1,25(OH)2D], or calcitriol. As far as recommendation on dose regimes, a daily administration of 1,500-2000 IU of cholecalciferol is warranted in adult deficient patients (4). Also, the use of loading doses, followed by a daily or monthly regimen after the threshold for sufficiency is reached, is recommended for severely deficient patients (4, 7).

Among other precursors of vitamin D employed in clinical practice, calcidiol is the most recently introduced for treatment of hypovitaminosis D (8). Pharmacokinetic studies demonstrated the hydrophilic properties of calcidiol, as well as a shorter half-life (10-13 days) in comparison with cholecalciferol (9). These data suggest the possible advantage of calcidiol, compared to cholecalciferol, in the management of deficient states in patients with liver disease, obese patients (where there is a lower trapping of calcidiol vs cholecalciferol in the adipose tissue), as well as to avoid any possible toxic effect when high doses are used (10). Also, conditions associated with intestinal malabsorption can represent an indication for calcidiol use, as it is better absorbed than cholecalciferol. The use of calcidiol in the setting of secondary hyperparathyroidism associated with chronic kidney disease has also been advocated, as high PTH levels can inhibit the liver cytochrome and eventually reduce the synthesis of calcidiol (11). Finally, data on the immunological effect of calcidiol vs cholecalciferol suggest a possible use in patients at high risk of infections (12).

As far as dose regimen, studies have shown that daily, weekly or monthly administrations of calcidiol are safe and effective in increasing and maintaining optimal 25(OH)D
serum levels (8, 13). Corresponding doses are as follows: daily 15-20 μg, weekly 105-140 μg, and monthly 500 μg. The daily dose of 20 μg and the monthly dose of 140 μg demonstrated to be more effective and rapid than the corresponding cholecalciferol doses in enhancing serum 25(OH)D levels in healthy postmenopausal women (13). Similar results were observed for the 140 μg bolus (13). As far as clinical outcomes, calcidiol showed beneficial effect on muscle performance, lower extremity function and blood pressure (14).

There are few data on the long-term skeletal effects of calcidiol and few studies have compared different therapeutic regimens in terms of effect on vitamin D status and bone metabolism.

The ADDI-D (Administration of Different Doses of calcidiol) study is a multicenter, randomized, open label study designed at evaluating the effects of three different regimens of oral calcidiol in post-menopausal women aged 55 and older with baseline serum 25(OH)D levels < 30 ng/mL (15). A total of 87 women were randomized to 3 different dose regimens, as follows: calcidiol 20 μg/day (27 subjects); calcidiol 40 μg/day (28 subjects); calcidiol 125 μg/week (29 subjects) (15). Follow-up time was 90 days, with monitoring visits performed once a week for the first month and at 60 days. All regimens resulted in a significant increase in serum levels of 25(OH)D at the end of the treatment period. The average serum levels of 25(OH)D were similar at any time point in the group placed on 20 μg/day and the one on 125 μg/week, while patients on 40 μg/day had almost doubled levels (15). Adequate vitamin D levels [25(OH)D concentration > 30 ng/mL] were observed in all subjects after 14 days, with a further increase thereafter, and a plateau between 30 and 90 days. Concomitantly, there was a significant increase of serum vitamin D binding protein levels up to 4 weeks. No safety issue (hypercalcemia, hypercalciuria) was registered in the observation period and serum 25(OH)D maintained in the range 30-100 ng/mL. Bone markers, 1,25(OH)2D and FGF-23 remained within the normal range for the duration of the study with no statistical difference between the groups, while PTH levels significantly decreased equally in the 3 groups at 90 days. Results from the ADDI-D study further clarify the role of calcidiol in improving vitamin D status and define alternative regimens to be used in clinical practice. In particular, the daily dose of 40 μg can be suggested as an alternative in severely deficient patients, as it has demonstrated to ensure higher vitamin D levels, while the weekly 125 μg dose can be an option when issues with compliance to the supplementation are present.

In conclusion, calcidiol has demonstrated to be effective in rapidly and safely improve vitamin D status and maintain adequate vitamin D serum levels with positive effect on the vitamin D target organs. To this end, different dose regimens have been suggested by the studies, showing that the daily 20 μg or 40 μg can be good options, while the weekly 125 μg and the monthly 500 μg may be used to improve compliance. More data from randomized controlled trials are needed in order to clarify the skeletal effect of calcidiol, particularly on fracture risk, as well as the effect on non-skeletal tissues.

References