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DRIVING UP THE DOSE: IMPLICATIONS FOR HIGH-DOSE VITAMIN D THERAPY

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Vitamin D is a unique nutrient and secosteroid hormone, in that it can be given either as a daily, weekly, or monthly supplement to correct vitamin D status owing to the long circulating half-life (approximately 2 to 3 weeks) of its major metabolite, 25-hydroxyvitamin D (25[OH]D) (1,2). There has been a great deal of interest in prescribing high-dose vitamin D for rapid correction of vitamin D status and/or as an adjunctive treatment for other diseases which may be modified by vitamin D therapy (3); however, there is no universally accepted regimen (4). In the United States, high-dose bolus vitamin D is typically given as a capsule of 50,000 IU of vitamin D_2 or vitamin D_3. Both forms of vitamin D are available over the counter or by prescription, though only vitamin D_2 is U.S. Food and Drug Administration (FDA) approved (despite evidence that high-dose vitamin D_3 may be more effective in raising serum 25[OH]D concentrations) (5). However, intramuscular high-dose vitamin D has not been widely available due to variability in the potency of different vitamin D preparations and is not currently FDA approved (6).

In this issue of *Endocrine Practice*, Masood et al (7) report the evaluation of high-dose oral or intramuscular vitamin D_3 therapy in patients with vitamin D deficiency (serum 25[OH]D <20 ng/mL). They randomized 100 subjects to a bolus dose of 200,000 or 600,000 IU orally or intramuscularly. By 2 months, 87.5 and 93.8% of subjects who received intramuscular vitamin D_3 (200,000 and 600,000 IU, respectively) achieved serum 25(OH)D concentrations above 20 ng/mL, whereas only 70.6 and 83.3% of subjects who received oral vitamin D_3 (200,000 and 600,000 IU, respectively) achieved 25(OH)D concentrations above 20 ng/mL. After 6 months, greater than 80% of the subjects who had received a single dose of 600,000 IU of vitamin D_3 intramuscularly maintained serum 25(OH)D concentrations above 20 ng/mL, whereas less than one-third of the subjects who received the bolus oral dose or the

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lower intramuscular dose of 200,000 IU had 25(OH)D concentrations above 20 ng/mL. A repeated bolus dose of vitamin D was given at 2 or 4 months for subjects who failed to achieve 25(OH)D concentrations >30 ng/mL at those time points; however, this did not improve the rate of vitamin D sufficiency. The investigators reported no differences in adverse events in response to the high-dose bolus of vitamin D.

High-dose vitamin D therapy, termed Stoss therapy, originated in Germany in the late 1930s for the rapid repletion of vitamin D status in the treatment or prevention of rickets. Since that time, high-dose vitamin D therapy has evolved as a strategy not only for rapid repletion in rickets but as a treatment and maintenance regimen in conditions potentially modifiable by vitamin D, including cystic fibrosis, chronic kidney disease, and infections (8,9). Though clinical trials of high-dose vitamin D in various disease states have been mixed (3), as the role of vitamin D in health continues to be defined, other conditions in which rapid repletion of vitamin D status may be beneficialhave emerged, including infection, inflammation, and anemia (10).

With the widespread distribution of CYP27B1 (the enzyme that converts 25[OH]D to 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]) throughout the body, including in immune cells, there has been much attention given to extraskeletal functions of vitamin D. One such function is the role of vitamin D in enhancing immunity, with increasing evidence for anti-inflammatory properties of vitamin D (11). It has been demonstrated that vitamin D can upregulate expression of the antimicrobial peptide cathelicidin through intracrine/paracrine activation of 25(OH)D to the active, hormonal 1,25$(OH)_2$D in macrophages in response to a pathogenic stimulus. Given the intracrine/paracrine activation of 25(OH)D, it follows that adequate serum concentrations are needed to support the local activation of vitamin D. Therefore, high-dose vitamin D therapy, as a useful tool to rapidly replete vitamin D status, may support immune function in the context of an acute or chronic infection (12).

Recent evidence also suggests that vitamin D may favorably influence anemia, particularly in the context of inflammation, by decreasing pro-inflammatory cytokines and the antimicrobial peptide hepcidin (the hormonal regulator of systemic iron concentrations). Under pro-inflammatory conditions, hepcidin is elevated, resulting in decreased iron absorption and sequestration of iron in macrophages, which may leave insufficient iron available to support hemoglobin synthesis and erythropoiesis. Vitamin D has been found to directly suppress hepcidin expression and downregulate hepcidin-stimulatory pro-inflammatory cytokines, which may help to improve anemia (13,14). Therefore, in the context of inflammation and conditions where anemia is prevalent, including chronic kidney disease, cardiovascular disease, and critical illness, high-dose vitamin D supplementation may be beneficialin rapidly repleting and maintaining 25(OH)D concentrations and may serve as a complement to other treatment regimens to improve anemia. However, trials evaluating the dosing and frequency of administration are needed to determine the optimal efficacy of high-dose vitamin D therapy in improving anemia and supporting immunity.

While high-dose vitamin D may be a promising therapy in certain conditions, there are other circumstances in which bolus high-dose vitamin D may have limited efficacy, including in lactating mothers, where daily vitamin D is necessary to provide adequate daily amounts of

vitamin D in breast milk for the infant (15). In addition, patients with hypercalcemic disorders such as hyperparathyroidism and those with chronic granulomatous disease prone to elevated extrarenal production of $1,25(OH)_2D$ may have increased risk of hypercalcemia when given high-dose vitamin D for a prolonged period of time. Caution should be exercised, and pre-existing conditions that could be exacerbated by high-dose vitamin D therapy should be evaluated when considering high-dose vitamin D therapy. Patients should be screened for hypercalcemia and hyper-calciuria prior to high-dose vitamin D therapy, and urinary and serum calcium levels should be monitored during vitamin D treatment so as to avoid toxicity. There are some data that very high-dose vitamin D therapy may increase the risk of fractures; however, the cause of this is not known (3).

High-dose vitamin D therapy is effective in rapidly raising 25(OH)D concentrations and has historically been used to treat rickets. Implications in other disease states are continuing to be elucidated, though actions in immunity and anemia appear promising. Further research is needed to establish the optimal dosing regimens in various groups. This paper by Masood et al (7) demonstrates the efficacy and safety of both oral and intramuscular administration of high-dose cholecalciferol in correcting vitamin D deficiency in the large majority of patients by 2 months. The results presented in this paper indicate that intramuscular administration of vitamin D_3 may provide a more sustained increase in 25(OH)D concentrations compared to oral administration. However, intramuscular injections have the limitation of potential discomfort of administration, and the bioavailability of the vitamin D may be affected by the vehicle of the preparation. Despite these limitations, intramuscular formulations, though not commonly used in the United States, may offer an effective alternative route of administration where nonadherence is a concern or in populations at risk for vitamin D malabsorption or in those intolerant of oral medications. Future research on long-term maintenance strategies post–bolus dosing will be helpful in determining optimal dosing regimens to support the actions of vitamin D in various health conditions.

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