

Hypercalcemia and a “no observed adverse effect level” intake of vitamin D

There are many reasons why the diagnosis of vitamin D toxicity in the recent case report by Auguste and colleagues¹ was probably wrong and the result of a red herring. The patient had been taking 8000–10 000 IU of vitamin D daily for 2.5 years, during which time serum creatinine levels were not an issue. When the patient’s serum 25-hydroxyvitamin D was first measured, it was 241 nmol/L, consistent with the patient’s reported long-term vitamin D intake but almost double the top of the reference range for people not taking a supplement.² However, the serum 1,25-dihydroxyvitamin D level was exceptionally high, along with serum calcium and creatinine levels.

The Institute of Medicine specifies 10 000 IU/d as the “no observed adverse effect level” — an intake that is not advisable, but not considered objectively harmful either.² Doses of vitamin D higher than 10 000 IU/d have been used in clinical trials that achieved higher 25-hydroxyvitamin D values and for longer duration, yet there was not one case of hypercalcemia, and certainly no kidney damage reported from among the hundreds of those study participants.^{3–9}

The case report described by Auguste and colleagues is not consistent with any previous clinical experience with vitamin D intake. What is unusual is the high serum 1,25-dihydroxyvitamin D level, because even in the most extreme cases of vitamin D toxicity, with 25-hydroxyvitamin D exceeding 2000 nmol/L, the total serum 1,25-dihydroxyvitamin D was only modestly increased.¹⁰ The primary cause of the renal impairment in the case report of Auguste and colleagues was something beyond the vitamin D intake: either a tumour or sarcoidosis.

Auguste and colleagues speculate that the patient might have been unusually susceptible to vitamin D because of a mutation in the *CYP24A1* gene that encodes for the breakdown enzyme of 25-hydroxyvitamin D and 1,25-

dihydroxyvitamin D.¹ But if that were the case, the condition would not have required 2.5 years of vitamin D supplementation to manifest itself, and it could not have been resolved within a few months. Since several genetic defects can impair the *CYP24A1* enzyme, the diagnosis is suitably screened for with a biochemistry laboratory test, the ratio of 25-hydroxyvitamin D to 24,25-dihydroxyvitamin D concentrations.¹¹ That test was conducted for my research group at the same hospital laboratory that Auguste and colleagues used for their own 25-hydroxyvitamin D results.¹² It is not likely that a rare *CYP24A1* defect is pertinent to this case report, because of the duration of vitamin D intake, the elevated 1,25-dihydroxyvitamin D and the recent onset of symptoms.

The high serum 1,25-dihydroxyvitamin D levels, hypercalcemia-related renal impairment and recent onset are entirely consistent with published case reports on sarcoidosis.^{13,14} The only difference was that, in those cases, serum 25-hydroxyvitamin D levels were normal. The high 1,25-dihydroxyvitamin D in the case report of Auguste and colleagues¹ is not a sign of vitamin D toxicity and is likely a consequence of sarcoidosis.^{13–15} The renal biopsy used by Auguste and colleagues does not rule out sarcoidosis.¹⁶ The hydroxychloroquine they used to treat the patient is not a conventional treatment for vitamin D toxicity, but it is a first-line treatment for sarcoidosis.^{13–15} Although the case reported by Auguste and colleagues was probably not a primary disease of vitamin D toxicity, it is important to limit sources of vitamin D in patients with sarcoidosis.

The lesson here is that it is common for patients to take dietary supplements in amounts that may raise test values beyond the laboratory’s reference range. But an abnormally high laboratory value does not in itself justify a diagnosis of toxicity. The consequence of accepting the false clue of a high vitamin D level was that it curtailed further effort to establish the true cause of the problem.

Reinhold Vieth PhD

Professor emeritus, Departments of Laboratory Medicine and Pathobiology, and Nutritional Sciences, University of Toronto, Toronto, Ont.

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Competing interests: Reinhold Vieth receives patent royalties from Ddrops (vitamin D supplement).