EDITORIAL

Vitamin D Deficiency and Intoxication - A concern either way

Major biologic function of activated vitamin D is to maintain normal blood levels of calcium and phosphorus, thus regulating bone mineralization.[1-3] Research suggests that vitamin D may help in immunomodulation, regulating cell growth and differentiation as well as some diverse unspecified functions.[1,4] Overt vitamin D deficiency leads to hypocalcaemia, secondary hyperparathyroidism and increased bone turnover, which in prolonged and severe cases may cause rickets in children and osteomalacia in elderly.[2,3,5]

While the body naturally produces vitamin D when the skin is exposed to ultraviolet rays, concerns about skin cancer, the heavy use of sunscreens and use of veiled dresses in some communities have contributed to a worrying deficiency in large populations.[5-10] Despite plenty of sunshine, most of Indian population have low level of vitamin D and thus a propensity for bone disease.[11-21] Vitamin D deficiency is also prevalent in Kashmir valley, with a study by Zargar A H *et al* showing about 80% of a healthy cohort has lower than the normal level of this important vitamin, and about 25% of these are severely vitamin D deficient.[22] Deriving from the J & K 2011 Census it can be roughly estimated that about hundred thousand (100,000) elderly people will be severely vitamin D deficient in the valley and will need some form of replacement. These deficient people may be asymptomatic or come to medical attention because of diverse clinical manifestations including aches, bone pain and generalized debility.

Vitamin D repletion in individuals with vitamin D deficiency has been shown to have a positive effect on bone biology, increase in bone mineral density measurements and possibly reduced fracture rates.[23,24] The best way to treat a deficient patient is to fortify the foods (as is done in developed countries) or to give supplements in the form of tablets (long term), sachets (short term) or injections (under medical supervision). Researchers continue to study the most effective dosing regimen for vitamin D supplementation, particularly in the elderly who are at increase risk for falls and fractures, which are a major cause of death. The target for vitamin D supplementation is suggested to be a serum level of 50 nmol/L, which is protective against secondary hyperparathyroidism and decreased bone density.[10,23]

The main vitamin D supplements available in Kashmir are oral vitamin D2 and D3 preparations (contain 200-600 IU) usually in combination with calcium, oral sachets (contain 60,000 IU), and injectable form (contain 3 lac & 6 lac IU). Oral formulations can be purchased by anyone over the counter and at the dose they contain, they are safe. However, vitamin D preparations with doses above 1000 IU are pharmaceutical agents, and should ideally be regulated by a much stricter code by the Drug Administration Committee. This is not the case in Kashmir valley, where higher doses of 300,000 to 600,000 IU are being administered at very frequent intervals with or without a prescription.

In this issue of the journal, Banday K *et al* report yet more cases of vitamin D intoxication presenting as acute kidney injury. The cases bring to fore an important iatrogenic complication of a relatively safe vitamin, which is being misused and given in improper doses. Contrary to what the medical community suggests, many caregivers in the peripheries still use vitamin D in "super-doses". They perhaps wrongly convey that vitamin D can help against everything from cancer and hypertension, to diabetes and stroke. The present sales of vitamin D preparation are staggering at what the requirement is and what is being prescribed. According to a market survey, the present estimate with about 4000 actively functioning registered chemist shops selling at least 20 units of injectable vitamin D 3 monthly, the average sale of vitamin D in the valley is near 80,000 units/month. This is a huge number and many of the people seem to be unnecessarily given an excess of vitamin D.

The side effects of vitamin D, oral or injectable are definite possibilities, but only after prolonged use or with mega-doses.[25,26] Excretion of vitamin D is negligible and hence excessive administration can lead to toxicity. To understand the toxic effects of vitamin D, an understanding of its mechanism of action and inactivation is necessary. The major pathway for inactivation of vitamin D metabolites is an additional hydroxylation step by 24 hydroxylase, an enzyme that is expressed in most tissues. Activated vitamin D mediates its biologic effects by binding to vitamin D receptor (VDR). The affinity of the VDR for 1, 25 (OH) D is approximately three orders of magnitude higher than for other vitamin D metabolites. In normal physiologic circumstances, these other metabolites are not thought to stimulate receptor dependent action. However in states of vitamin D toxicity the markedly elevated levels of 25(OH) D may lead to hypercalcemia by interacting directly with the VDR and by displacing 1, 25(OH) D from vitamin D binding protein, resulting in increased bioavailability. The consequences of vitamin D toxicity are because of hypercalcemia per se.

Vitamin D toxicity generally is usually iatrogenic or due to accidental overdose. Long-term daily vitamin D consumption of

more than 40,000 IU (1000µg) is needed to cause hypercalcemia in healthy persons. Acute vitamin D intoxication with D2 or D3 supplements is a rare event. Symptoms may include weakness, polyuria, intense thirst, weight loss, nausea, vomiting, constipation, difficulty in speaking and confusion. Patient may lapse into coma, while cardiac arrhythmias and renal failure may occur. These effects are due to hypercalcemia induced by increased intestinal absorption and mobilization of calcium from bone. Hypercalciuria and nephrocalcinosis may occur.

Most of the cases of vitamin D toxicity in the western literature have been due to accidental exposure of individuals to vitamin D, most of the times because of higher than the recommended supplementations or faulty food fortification[25-27]. Unintentional vitamin D poisoning has been associated with over fortification of milk[28], adulteration of table sugar[27], and contamination of cooking oil and with use of over-the-counter supplements.[25,26] Over- fortified diet supplement induced vitamin D intoxication in a 58 year old female was reported from USA, in which about 188,640 IU of vitamin D had been accidently added to the daily serving size of six capsules instead of the intended 400 IU. A 2 year old Hispanic boy given an imported vitamin D supplement "raquiferol" reported with hypercalcemia.[29] Lowe H *et al* reported 9 patients presenting with hypercalcemia due to over the counter vitamin supplement "Soladek" imported from the Dominican Republic containing massive amounts of vitamin D.[31] The patients presented with hypercalcemia (10.8-17.2mg/dl), suppressed PTH (3-11ng/L) and elevated vitamin D (94-524ng/ml). Although serum calcium values before ingestion of Soladek were not elevated, most had a disorder that can be associated with hypercalcemia (squamous cell carcinoma-1, pneumocystis or mycobacterial infection-3, lymphoma-1, granulomatous disease-1 hyperthyroidism-2). Hydration helped in most and 2 received intravenous pamidronate.

Deliberate misuse of the injectable form is mostly reported from the Indian subcontinent, where unrestricted use of the medications is a problem.[32,33] Joshi R reported 7 children (aged 7.5 to 25 months) who had received malpractice related high doses of vitamin D injections (900,000 to 400,000,000 IU), for failure to thrive[33]. All of them had hypercalcemia (12-16.8mg/dl) and toxic levels of vitamin D (96-2150 ng/ml), suppressed PTH (<3-8.1 ng/L). Hypercalciuria was found in all patients while nephrocalcinosis was found in 5 patients. All were treated with intravenous fluid, oral prednisolone, while 4 received pamidronate infusion for reducing hypercalcemia. In a case report by Naik M *et al*, a patient who had received a cumulative dose of 21,000,000 IU of injectable vitamin D and presented with acute kidney injury, recovered after hydration and short course oral steroids.[34] Parvaiz K *et al* reported 10 patients seen over a decade who presented with hypercalcemia due to vitamin D overdose.[35] All the patients had hypercalcemia and varying azotemia. Vitamin D was elevated in 9 patients. They stressed to unravel the history of injectable vitamin D intake in patients presenting with hypercalcemia in endemically vitamin D deficient area.

Treatment for vitamin D toxicity includes immediate removal of the exogenous source, intravenous fluid hydration, loop diuretics, glucocorticoids, and a low calcium diet[36]. Glucocorticoids decrease the production of 1,25-dihydroxyvitamin D3, which decreases dietary absorption of calcium. It also prevents calcium from being resorbed in the renal tubules, thereby promoting the urinary excretion of calcium. Exogenous calcitonin can be used; it inhibits bone resorption and blocks release of calcium and phosphate into the serum. The use of bisphosphonates, such as pamidronate, a bone resorption inhibitor through osteoclast mediation is accepted widely for adults, but uses in children have been only anecdotal[36-38]. Hemodialysis can be used to treat hypercalcemia and can lower serum calcium levels rapidly. Because rebound hypercalcemia is predictable after vitamin D intoxication, hemodialysis should be reserved for life-threatening, medically unmanageable indications, such as acute or chronic renal failure and hypercalcemic crisis.

Vitamin D is a beneficial supplement and is safe when used correctly at its recommended doses (200–1000 IU for infants and 2000 IU for all others).[39] However, if a patient presents with hypercalcemia and a history that reveals the use of a vitamin D supplement in higher than the prescribed doses, it should make clinicians consider vitamin D toxicity in the differential diagnosis. It is necessary to educate the people about vitamin D deficiency, as well as the caregivers in the peripheries about the symptoms of acute vitamin D intoxication, and stress about the possible dangers of megadose vitamin D.

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