

Vitamin D Supplements in the Indian Market

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It is now known that vitamin D deficiency is a worldwide health problem. In our country, as food fortification is lacking, supplementation with pharmaceutical preparations is the only means of treatment of vitamin D deficiency. We aimed to study the composition and availability of various vitamin D preparations in the Indian market, data about which was collected from annual drug compendium. The preparations were assessed for total number, different formulations, constituents and amount of each constituent present in the formulation. Vitamin D₃ is available in the form of cholecalciferol, alfalcidol and calcitriol as single ingredient products and in combination with calcium and other micronutrients. Most of the supplements contain calcitriol (46.5%) or alfalcidol (43%) as tablets (51.1%) and capsules (35.2%). Cholecalciferol, the preferred form for prophylaxis and treatment of vitamin D deficient states, constitutes only 10% of the available market preparations. High market sales of calcium supplements containing calcitriol indicate increasing intake of calcitriol rather than cholecalciferol; which could predispose to toxicity. There is a need for marketing and rational prescribing of the appropriate vitamin D supplement in ostensibly healthy Indian population. Implementation of population-based education and intervention programmes with enforcement of strict regulations could generate awareness and curb unsupervised intake of vitamin D containing dietary supplements. This health challenge mandates effective nutritional policies, fortification and supplementation programmes and partnership between government, healthcare and industry to safeguard the health of Indian population at large.

Key words: Vitamin D, India, vitamin, supplement, nutrition, health

It has been widely accepted that vitamin D deficiency (VDD) is a global health problem that impacts not only musculoskeletal health but also varied acute and chronic diseases^[1]. Low vitamin D has been associated with an increased risk of diabetes mellitus, cardiovascular disease, certain cancers, cognitive decline, autoimmune disorders and pregnancy complications^[2]. It has been estimated that 20 to 80% of US, Canadian and European men and women are vitamin D deficient^[1,3,4]. In Middle East and Asia, VDD is highly prevalent in both children and adults^[1,2,5]. Even in India, numerous studies across various regions of the country indicate that approximately 70-90% of apparently healthy population is vitamin D deficient^[6-9]. Low vitamin D status is prevalent irrespective of age, sex, profession, rural/urban settings or regional distribution^[10,11] (Table 1).

The major source of vitamin D is exposure to sunlight. It has been presumed that Indians are vitamin D sufficient due to adequate sunshine throughout the

year^[6]. However, reduced cutaneous synthesis of vitamin D could be attributed to limited UV exposure owing to increased skin pigmentation, topical application of sunscreen, certain socio cultural practices and urban life style^[6]. Secondary sources include dietary intake of foods naturally rich in vitamin D such as salmon, cod liver oil, sun dried mushrooms or vitamin D fortified foods^[2,28]. In our country, availability, acceptability and cost of these dietary products limits their widespread use by the general population. This complex interplay between lack of adequate sun exposure, deficient intake and effective food fortification strategies makes Asian Indian population particularly susceptible to vitamin D insufficiency/deficiency.

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TABLE 1: VITAMIN D SERUM LEVELS IN DIFFERENT POPULATION GROUPS ACROSS INDIA

Study population	Number of participants	Age mean (SD)	State	Mean 25(OH) D serum levels (ng/ml) (SD)	References
Young adults					
Adults	50	28.15 (4.9) years	Kashmir	11.26 (9.65)	Zargar <i>et al.</i> ^[8]
Adults	90	22-23 years	Punjab and Haryana	18.4 (4.3)	Tandon <i>et al.</i> ^[12]
Urban adults	31	25 (5) years	Delhi	18.87 (4.69)	Goswami <i>et al.</i> ^[13]
Young adults	186	18.6 (13) years	Delhi	12.96 (9.84)	Marwaha <i>et al.</i> ^[14]
Urban adults	642	31.4 (13.4) years	Delhi	7 (4.08)	Goswami <i>et al.</i> ^[15]
Rural adults	57	42-43 years	Delhi	14.56 (9)	Goswami <i>et al.</i> ^[7]
Urban adults	125	45.5 (0.95) years	Tirupathi	13.52 (0.59)	Harinarayan <i>et al.</i> ^[16]
Urban adults	214	26-30 years	Mumbai	12.80 (7.94)	Multani <i>et al.</i> ^[17]
Infants and children					
Exclusively breastfed infants	97	10 weeks	Delhi	12.59 (8.37)	Agarwal <i>et al.</i> ^[18]
Breastfed infants	60	3.0 (0.14) months	Delhi	9.03 (4.63)	Mehrotra <i>et al.</i> ^[19]
Infants	127	3 months	Delhi	6.5 (4.0)	Agarwal <i>et al.</i> ^[20]
Infants, urban area	26	16±4.1 months	Delhi	12.4 (7)	Agarwal <i>et al.</i> ^[11]
Adolescent girls	50	14.7 (0.10) years	Pune	9.36	Khadilkar <i>et al.</i> ^[21]
Adolescents	3089	10-18 years	Delhi	10.4 (0.4)	Marwaha <i>et al.</i> ^[22]
Pregnant and lactating women					
Lactating mothers	342	24.6 (2.8) years	Delhi	7.84 (3.32)	Marwaha <i>et al.</i> ^[23]
Lactating mothers	180		Delhi	10.88 (5.8)	Seth <i>et al.</i> ^[24]
Pregnant women	207	24.0 (4.1) years	Lucknow	14.00 (9.3)	Sachan <i>et al.</i> ^[25]
Pregnant women	42	20-35 years	Mumbai	22.99 (10.93)	Bhalla <i>et al.</i> ^[26]
Pregnant women	559	24 years	Mysore	15.12 (9.6)	Farrant <i>et al.</i> ^[27]
Pregnant women	521	24.6 (2.8) years	Delhi	9.28 (4.88)	Marwaha <i>et al.</i> ^[14]

SD: Standard deviation, 25(OH) D: 25-hydroxy Vitamin D

Thus, vitamin D supplementation in the form of pharmaceutical preparations is one of the most effective ways to prevent and treat VDD in high-risk groups^[29]. We, therefore undertook a study to ascertain that availability and composition of various pharmaceutical preparations of vitamin D in the Indian market.

MATERIALS AND METHODS

This study was conducted to determine the number and composition of the various vitamin D pharmaceutical preparations. Data for the study was collected from an annual Drug Compendium entitled The Drug Today 2013 (October–December 2013 issue) and product labels. The preparations were assessed for total number, different formulations, constituents and amount of each constituent present in the formulation.

RESULTS

Analysis of various vitamin D preparations:

A total of 258 vitamin D formulations are available in the Indian market. Vitamin D is commonly available in two forms: Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Only two preparations

contain vitamin D2 (ergocalciferol). More than 99.9% of the preparations contain vitamin D3 in the form of alfalcidol (25 hydroxycholecalciferol), calcitriol (1,25 dihydroxycholecalciferol) or cholecalciferol (inactive vitamin D). Most of the preparations contain calcitriol ($n=120$, 46.5%) or alfalcidol ($n=111$; 43.02%). Approximately 10% of preparations contain cholecalciferol ($n=27$, 10.5%) (fig. 1, Tables 2 and 3).

Different formulations of vitamin D:

The most common formulation for oral administration is in the form of tablets ($n=132$, 51.1%) and capsules ($n=91$, 35.2%). Though alfalcidol and calcitriol are commonly available as tablets and capsules; cholecalciferol is in the form of granules in sachets ($n=17$, 62.9%). Other dosage forms include syrups and softgel capsules. Though oral administration in the form of drops is commonly recommended for infants and children, adolescents and adults are usually prescribed tablets, capsules or granules for supplementation. While all cholecalciferol preparations are available as a single constituent; more than 75% of alfalcidol preparations also contain calcium ($n=85$, 76.5%). Majority of calcitriol preparations are combined with zinc or zinc sulphate ($n=87$, 72.5%). Vitamin D preparations also contain various other minerals/vitamins

such as magnesium, cupric, boron, methylcobalamin, vitamin E, vitamin K, vitamin C, pyridoxine, folic acid, beta-carotene, glutamic acid, manganese, omega 3 and docosapentaenoic acid. Tablets and capsules contain 10 IU (0.25 µg) -10000 IU (25 mg) of vitamin D and are usually administered on a daily basis. Sachets of cholecalciferol containing granules of vitamin D amount to 60,000 IU of vitamin D are administered weekly. Vitamin D2 (doxercalciferol) preparation is available in tablet form (two formulations) containing 20 IU (0.5 µg) and 100 IU (2.5 µg) respectively (Table 3).

Cost analysis:

Cost analysis reveals that tablets/capsules of alfacalcidol (equivalent to 10 IU of vitamin D) and calcitriol (0.25 µg) commonly costs Indian National Rupees (INR) 5.5 and INR 7, respectively

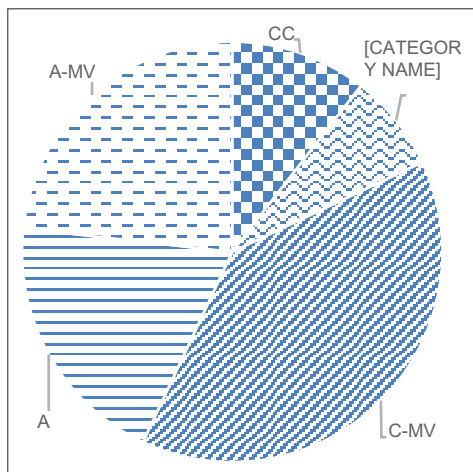


Fig. 1: Various vitamin D preparations available in Indian market. All the available cholecalciferol preparations (CC) (10.5%) contain only vitamin D3. 39 % of calcitriol preparations contain vitamin D3 in combination with minerals /vitamins (C-MV) and 7.5% contain vitamin D3 alone (C). 23.22% of alfacalcidol preparations contain vitamin D3 in combination with minerals /vitamins (A-MV) and 19.8% contain vitamin D3 alone (A)

(Table 4). Whereas, cholecalciferol granules (equivalent to 60,000 IU) costs INR 20. The common treatment regime for VDD is 60000 IU weekly for eight weeks, which costs approximately INR 160. Furthermore, vitamin D given monthly as maintenance therapy for a year would cost INR 240.

DISCUSSION

Vitamin D deficient state has become one of the most prevalent and underdiagnosed medical conditions in the world^[1,30]. Recent evidence suggests that lack of adequate sun exposure is the most important factor for this global pandemic as very few foods naturally contain vitamin D (wild caught salmon and UV exposed mushrooms)^[2]. Analysis in children and adults indicate that dietary sources are grossly inadequate in providing the Recommended Dietary Allowances (RDA) for vitamin D. In our population, cutaneous production of vitamin D is further limited by increased melanin content of skin or sun avoidance by use of sunscreens, extensive clothing cover due to sociocultural practices or staying indoors for most of the day^[6]. Deficient vitamin D status can be corrected either by vitamin D fortification (addition of micronutrients to processed foods) or supplementation (the provision of relatively large doses of micronutrients, usually in form of pills, capsules or syrup). Vitamin D fortification is an effective and passive way to increase vitamin D intake in both general population and vulnerable groups^[31-33]. However, it mandates political commitment and involvement of various ministries (health, agriculture and social welfare) to develop nationwide strategies for a better vitamin D status in the population. In our country, where vitamin D fortification initiative is lacking, supplementation is the only alternative^[34].

TABLE 2: VITAMIN D3 PREPARATIONS AVAILABLE IN THE MARKET

	Alfacalcidol (25 hydroxy cholecalciferol)	Calcitriol (1,25 dihydroxy cholecalciferol)	Cholecalciferol (inactive Vitamin D)	Total
Total number of preparations (%)*	111 (43.02)	120 (46.5)	27 (10.5)	258 (100)*
Number of preparations that contain only Vitamin D3 (%)**	22 (19.8)	9 (7.5)	27 (100)	58 (22.4)*
Number of preparation that contain Vitamin D3 in combination with calcium (%)**	85 (76.5)	26 (21.6)	0	111 (43)*
Number of preparations that contain Vitamin D3 in combination with zinc (%)**	10 (9.0)	87 (72.5)	0	97 (37.6)*
Number of constituents (range)	1-14	1-12	1	1-14
Number of preparations available as tablets (%)**	68 (61.2)	60 (50)	4 (14.8)	132 (51.1)*
Number of preparations available as capsules (%)**	35 (31.5)	53 (44.1)	3 (11.1)	91 (35.2)*
Number of preparations available as injectable (%)	0	2 (1.6)	4 (14.8)	6 (2.3)*
Number of preparations available as sachets (%)	0	0	17 (62.9)	17 (6.5)*

*: Percentage of the total number of vitamin D preparations; **: percentage of the total number of that particular vitamin D preparation

TABLE 3: COMMONLY AVAILABLE VITAMIN D BRANDED PREPARATIONS IN THE MARKET

Brand name	Company	Vitamin D biochemical form	Formulation	Amount of Vitamin D	Available as	Cost (INR)
Rocaitrol	Abott Healthcare Pvt. Ltd.	Cholecalciferol	Capsules	0.25 µg	10 capsules	175.4/17.5*
Calosto	Abott Healthcare Pvt. Ltd.	Calcitriol	Capsules	0.25 µg	15 capsules	198.36/13.22*
Alpha calcirol	Cadila Pharmaceutical Ltd.	Alfacalcidol	Capsules	0.25 µg	10 capsules	48.87/4.8*
Alfarich	Cipla Ltd.	Alfacalcidol	Capsules	0.25 µg	10 capsules	54.30/5.4*
Alfado	GlaxoSmithKline Pharmaceuticals Ltd.	Alfacalcidol	Capsules	0.25 µg	10 capsules	54.30/5.4*
Alfa D3	GlaxoSmithKline Pharmaceuticals Ltd.	Alfacalcidol	Capsules	0.5 µg	10 capsules	268/26.8*
Rocaltrol	Sun Pharmaceutical Industries Ltd.	Calcitriol	Capsules	0.25 µg	10 capsules	123/12.3*
Alphadol	Panacea Biotec Ltd.	Alfacalcidol	Capsules	0.25 µg	10 capsules	169/16.9*
Vitanova SG	Zuventus Healthcare Ltd.	Cholecalciferol	Capsules	60,000 IU	10 capsules	250/25*
Quente D3	Stanley Healthcare	Cholecalciferol	Capsules	60,000 IU	4 capsules	86.25/21.5*
Minroset	Win Medicare Ltd.	Alfacalcidol	Capsules	0.25 µg	10 capsules	56.8/5.6*
Calcit SG	Zudus Cadila Healthcare Ltd.	Alfacalcidol	Tablets	0.25 µg	10 tablets	94.40/9.4#
Vitalcal	Genesis Biotec Inc.	Cholecalciferol	Tablets	60,000 IU	4 tablets	96.00/24#
Hira D3	Hiral Lab Ltd.	Cholecalciferol	Tablets	60,000 IU	4 tablets	80/20#
Calcit SG	Zudus Cadila	Alfacalcidol	Tablets	0.25 µg	10 tablets	94.40/9.4#
Arachitol	Solvay Pharma India Pvt. Ltd.	Cholecalciferol	Injection	600,000 IU	1 injection (2 ml)	34
Fovit D3	Forgo Pharmaceuticals (P) Ltd.	Cholecalciferol	Injection	600,000 IU	1 injection (1 ml)	21.90
D3 UP	Abott Healthcare Pvt Ltd.	Cholecalciferol	Granules	60,000 IU	1 sachet	21
Caldikind	Mankind Pharmaceutical Pvt. Ltd.	Cholecalciferol	Granules	60,000 IU	1 sachet	21
Calotec D3	Lupin Laboratories Ltd.	Cholecalciferol	Powder	60,000 IU	1 g	29
Sorvate	Glenmark	Calcitriol	Ointment	0.0003%	20 g	175
Rosical	Sun Pharma	Calcitriol	Ointment	3 µg	15 g	213

INR: Indian national rupees, *: cost per capsule; #: cost per tablet

TABLE 4: THE COST (IN INDIAN NATIONAL RUPEES) OF VARIOUS DOSAGE FORMS OF VITAMIN D3 PREPARATIONS

	Alfacalcidol (0.25 µg) 10 IU	Calcitriol (0.25 µg) 10 IU	Cholecalciferol (60,000 IU)
Average cost	4.3	5.15	10.10
Modal	5.5	7	20
Cost range of tablets (strength)	0.75-7.5 (10 IU)	3-13.5 (10 IU)	4.9 (5000 IU)
Cost range of capsules (strength)	3-22.6 (10 IU)	4-12.9 (10 IU)	5.9 (1000 IU)
Cost of granules (strength)	16 (60,000 IU)	NA	0.73-23.23 (60,000 IU)

NA: Not available

In our analysis, we found that multiple supplements of vitamin D are available. The two common forms are vitamin D3 (alfacalcidol, cholecalciferol and calcitriol) and vitamin D2 (ergocalciferol). Evidence suggests that cholecalciferol is superior to ergocalciferol in terms of potency, elevating and sustaining 25 (OH) D concentrations and maintaining the storage form of vitamin D^[35,36]. In our analysis, we were not able to ascertain the cause of lack of availability of vitamin D2 preparations in the Indian market. Majority of preparations available in the market contain vitamin D3 (99.9%). About half of the preparations (46.5%) contain calcitriol in the form of tablets or capsules of 0.25 mcg. Calcitriol has a rapid onset of

action with short half-life of 6 h. It is most useful in chronic kidney disease and type I and type II vitamin D deficient rickets (VDDR) with decreased synthesis of calcitriol. Though calcitriol is the most commonly available form, it is not the preferred agent for treatment of nutritional deficiency or stoss therapy (single large oral/ intramuscular therapy). It is associated with a high incidence of hypercalcemia and requires serum calcium monitoring. Furthermore, when calcitriol is used as a supplement, 25(OH) D levels do not indicate clinical vitamin D status. Calcitriol does not build up stores and is an expensive preparation^[37]. Around 43% of the preparations contained alfacalcidol (25 dihydroxy cholecalciferol). It is most commonly available as tablets or capsules of 10 IU, usually in combination with calcium (76.5% of alfacalcidol preparations). Alfacalcidol has a rapid onset of action with a half life of 2-3 weeks. It does not require hepatic 25-hydroxylation, and is therefore most useful in patients with liver disease. Approximately 10% of vitamin D3 preparations are available as cholecalciferol. It is the inactive, unhydroxylated form of vitamin D3, synthesized in skin from 7 dehydrocholesterol. It has a slow onset of action with a half-life of 12-30 days. Thus, it is the preferred form for prophylaxis or treatment of vitamin D deficient states^[37].

Vitamin D can be administered daily, weekly, monthly, or every 4 months to sustain an adequate serum 25 (OH) D concentrations^[38-40]. A high bolus dose of vitamin D (up to 300,000 IU) can be used initially in persons with extreme VDD. Repeated boluses of high-dose vitamin D at 6- to 12-month intervals have been used in a nursing home setting, but a steady-state serum 25(OH) D concentration is likely to be maintained by more frequent, lower doses of vitamin D. An effective strategy to treat vitamin D deficient state in children and adults is to administer 50,000 IU of vitamin D3 once a week for 6-8 weeks respectively^[41,42]. To prevent recurrence, administration of 600 to 1000 IU/day is effective^[43]. In our country, most market preparations contain 60, 000 IU, and are usually recommended for 6 to 8 weeks for obtaining adequate serum 25 (OH) D concentrations. A monthly maintenance therapy is usually required and should be continued for over one year^[44]. Another study suggested that a single high dose of 120,000-180,000 IU of oral cholecalciferol was adequate to elevate 25(OH) D out of the deficiency range. However, maintenance dose is required for sustaining the desired concentration of 25(OH) D^[44,45]. Our analysis suggests that this treatment regime would initially cost approx. INR 160 and a maintenance therapy for a year would cost INR 240. However, the treatment costs are usually higher as calcium supplements are coadministered with vitamin D therapy.

Vitamin D supplementation varies with the RDA, tolerable upper levels in different age groups and in certain circumstances^[46]. The Institute of Medicine (IOM), USA guidelines suggest a vitamin D sufficient level of 20 ng/ml to optimize bone health^[47]. In contrast, US Endocrine Society recommends that serum 25 (OH) D levels of 30 ng/ml (vitamin D sufficiency) should be attained for children and adults to optimize the probability of good health and avoid other risk associated with vitamin D deficient status (Table 5). Furthermore, it is now acknowledged that previously recommended vitamin D intake of 200

IU/day in the American recommended intakes or 400 IU/day in the WHO report are grossly inadequate^[46]. Thus, RDA of 600-800 IU is recommended to maintain adequate levels of vitamin D^[46]. In our country, Indian Council of Medical Research (ICMR) recommends a daily supplement of 400 IU/day of vitamin D for Indians under situations of minimal exposure to sunlight^[34]. However, in light of recent evidence, there is a need to update these guidelines regarding vitamin D intake and supplementation in adults, vulnerable population and susceptible groups^[48-50]. It is now recognized that vitamin D is not as toxic as once thought to be. IOM recommends that up to 4,000 IUs of vitamin D/day is safe for most children and adults. Studies in various populations have shown that adults can tolerate 10,000 IU of vitamin D/day for at least five months without altering their serum calcium or urinary calcium output^[50]. However, in rare cases, vitamin D toxicity can cause hypercalcemia, hyperphosphatemia, nephrocalcinosis, and soft tissue calcification, thus contributing to high risk of mortality^[51].

Studies indicate general and widespread use of dietary supplements across populations^[52,53]. Though these supplements often are used with the intention of attaining health benefits by preventing chronic diseases, cumulative effects of widespread supplement use, together with food fortification, have raised concern regarding exceeding upper recommended levels and, thus, long-term safety^[53]. In case of vitamin D, unsupervised intake of alfalcidol and calcitriol, which are not recommended for vitamin D deficient states, could result in adverse effects/toxicity^[54]. Thus, it is recommended that supplements should only be used with strong medically based cause, such as symptomatic nutrient deficiency disease^[53]. 'Blanket prescription' of these supplements in all patients for prolonged use should be stopped. Physicians need to evaluate the patient's dietary nutrient consumption, intake of any other multivitamin supplement, potential interactions and prescribe them only on an individual basis.

Widespread VDD in the Indian population is a cause for grave concern. Adequate measures are imperative to prevent VDD at the outset. There is a need for educating the masses about sensible sun exposure for vitamin D synthesis and dietary intake of vitamin D rich foods. Fortification of commonly available foods could prevent vitamin D insufficiency in our large

TABLE 5: VITAMIN D STATUS IN RELATION TO 25-HYDROXY VITAMIN D LEVELS

US IOM classification ^{†[30]}	US Endocrine Society classification ^[3]
Severe deficiency: <5	Deficiency: <20
Deficiency: <15	Insufficiency: 21-29
Sufficiency: >20	Sufficiency: >30
Risk of toxicity: >50	Toxicity: >150

Values are given in ng/ml, IOM: institute of medicine

population. There is an urgent need to prioritize development of national level programs to provide regulated vitamin D fortified foods at affordable prices for Indian population at large. As far as vitamin D supplements are concerned, their easy availability and chronic self-administration mandates awareness on the part of the consumer, pharmacist, chemists, physicians and regulatory bodies to prevent misuse and serious harm. As evident by high market sales, high intake of calcitriol in the form of dietary calcium supplement in the general population could result in serious hypercalcemia, calcium stones and metastatic calcification. The prescribing physicians need to be aware of this potential risk and should prescribe supplements only on an individual basis for requisite duration. These supplements should be adequately labeled indicating the amount of each constituent with special instructions/precautions/warnings, if any. Stringent regulations are required to keep a check on their marketing and availability. Adequate legal actions are required for pharmaceutical companies/ drug firms not adhering to regulatory provisions.

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There are no conflicts of interest.

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