

Calcium and Vitamin D

What does the Evidence say?

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Calcium

Optimal Intake of Calcium

- The recommended dietary allowance (RDA) of calcium intake for postmenopausal Indian women is **> 800 mg per day** (Indian Menopause Society CPG PMO 2020)
- As much as possible (at least half) of the calcium should come from dietary sources
- During clinic visits, we estimate dietary calcium intake with the aim of recommending increased dietary calcium (or calcium supplements) to patients with inadequate dietary intake and preventing excessive calcium supplementation in patients with adequate dietary intake

Calcium Supplements

- Calcium of all types is best absorbed in doses of ~ 500 mg or less. Higher individual doses are associated with a plateau in calcium absorption that may prevent attainment of a positive calcium balance
- **Calcium carbonate** is the cheapest and often a good first choice. It requires stomach acid for absorption and so is best taken with food.
- Individuals who experience GI side effects (dyspepsia, constipation) taking calcium carbonate may benefit from taking multiple small doses, taking it with meals and/ or switching to calcium citrate.

Calcium Supplements

- Calcium carbonate is also poorly absorbed in patients on proton pump inhibitors (PPIs) or H2 blockers. Calcium citrate is a first-line calcium supplement for these patients.
- **Calcium citrate** is absorbed equally well on an empty stomach.
- Calcium citrate is useful for people with achlorhydria, inflammatory bowel disease, and absorption disorders.
- Calcium supplements interfere with absorption of iron, levothyroxine and quinolone antibiotics, so these medications should be taken at different times.

Calcium Supplements - Side effects

- **Safe upper limit** - Total intake of calcium (diet plus supplements) should not exceed **2000 mg/day**, because of possibility of adverse effects
- **Lead** - Natural **calcium carbonate** preparations such as oyster shells contain some lead, but the low lead levels in calcium supplements are unlikely to be a health risk because calcium blocks lead **absorption**

Calcium Supplements - Side effects

Nephrolithiasis

- In general, concern that high **dietary** calcium increases the risk of nephrolithiasis in otherwise healthy patients is unfounded as the incidence of stone formation appears to be reduced in both females and males ([Curran et al 1997](#)) ([Heller HJ et al 2000](#))
- The Women's Health Initiative (WHI) trial reported an increased risk of kidney stones in postmenopausal women who were supplemented with calcium and vitamin D when compared with placebo ([2006](#))
- There is evidence that **intake of supplemental calcium above 1200 to 1500 mg/day** can increase risk of developing kidney stones in at-risk individuals

Calcium Supplements - Side effects

Cardiovascular disease

- Findings of two meta-analyses evaluating calcium or calcium with /without vitamin D supplementation (8 and 9 trials, respectively) raised some concern about an increased risk of MI in patients randomly assigned to calcium vs placebo ([Bolland MJ et al 2010, 2011](#))
- After 24 years of follow-up of 74,245 women aged 30-55 years at baseline who participated in the [Nurses' Health Study](#), women taking more than 1,000 mg/day calcium supplements did not have a higher risk of CVD than those taking no supplemental calcium ([2014](#))
- A large systematic review and meta-analysis by [Chung M et al \(2016\)](#) found no evidence that calcium with or without vitamin D increased CVD risk
- **An expert panel convened by the National Osteoporosis Foundation and American Society for Preventive Cardiology determined, on the basis of moderate-quality evidence, that calcium intakes with or without vitamin D from foods or supplements neither increase nor decrease the risk of CVD or CVD mortality.**

Vitamin D

Optimal Dose of Vitamin D

- Vitamin D deficiency can be considered as a National Nutritional Deficiency pandemic (**IMS CPG PMO 2020**)
- Recommended dietary allowance (RDA) of Vitamin D in adults is **1500-2000 IU daily (US Endocrine Society 2011 RDA adopted by IMS CPG PMO 2020)**
- Skin of those > 70 years of age does not convert vitamin D as efficiently as in younger age. Supplements are necessary for older adults and for people who avoid sunlight.
- In Obesity, HIV infection, patients on glucocorticoids, anticonvulsant, antifungal and antiviral therapy dose is 2-3 times the RDA for age

Optimal Dose of Vitamin D

- In 2010, the Institute of Medicine(IOM) defined the **Safe Upper Limit for vitamin D** as **4000 IU per day**.
- Hypercalcemia has been reported when the dose exceeds 10,000 IU/day
- A **desirable range is between 30 and 60 ng/mL**, although levels up to 100 ng/mL are unlikely to result in Vitamin D toxicity except in granulomatous disorders.

Vitamin D Supplements

- **Ergocalciferol (vitamin D2)**
- **Cholecalciferol (vitamin D3)**
- Vitamin D3 increases serum 25(OH)D more efficiently than Vit. D2.
- Vitamin D2 is not accurately measured in all vitamin D assays
- Vitamin D3 is available in 3 forms

Alfacalcidol (25 hydroxycholecalciferol)

Calcitriol (1,25 dihydroxycholecalciferol)

Cholecalciferol (inactive vitamin D)

Vitamin D Supplements in the Indian Market

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Lhamo, *et al.*: Vitamin D Supplements

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, alfacalcidol and calcitriol as single ingredient products and in combination with calcium and other micronutrients. Most of the supplements contain calcitriol (46.5%) or alfacalcidol (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.

Vitamin D Supplements - Cholecalciferol

- **Initial Dose:** 60,000 IU tablets or capsules weekly for 8 weeks followed by
- **Maintenance dose:** 60,000 IU once a month in summers and twice a month in winters

Vitamin D Supplements - Calcitriol

- Calcitriol is a hormonally-active, synthetic vitamin D analogue
- Systemically, calcitriol binds to vitamin-D receptors in the kidneys, parathyroid glands, intestines, and bones to increase serum blood calcium levels by promoting absorption in the intestines, renal tubular reabsorption, and release from bone.
- Calcitriol has a rapid onset of action with a short half-life of 6 hours

Calcium–Calcitriol: Fixed Dose Combinations (FDC)

- In a recent study by **Dutta *et al* (2018)** 53% of GPs showed a preference for calcium/calcitriol preparations compared with 0% of endocrinologists for the treatment of osteoporosis and vitamin D deficiency.
- Common considerations:
 - Cost and convenience
 - Risk of hypercalcemia
 - Need for monitoring serum and urine calcium

Vitamin D Supplements - Cost and Convenience?

- The **additional cost** resulting from combining calcitriol and calcium may not be useful for the most common indications for which calcium is used - osteoporosis and vitamin D deficiency.
- **For most patients with osteoporosis and vitamin D deficiency, calcitriol/calcium combination therapy would increase costs without tangible benefits—as their renal 1-alpha, hydroxylation is normal.**
- However, for those with impaired activation of vitamin D, calcium–calcitriol FDC offers **both a cost and convenience advantage**. Thus, wherever there is a genuine need for calcitriol therapy, calcium–calcitriol FDCs can be considered and can bring down the cost by up to 31.5%.

Cost and Convenience

Conditions in which Calcium Calcitriol FDC are genuinely indicated:

- Chronic kidney disease (CKD)
- Hypoparathyroidism
- Pseudo hypoparathyroidism
- Vitamin D-dependent rickets
- Hypophosphatemic rickets/osteomalacia
- Prevention and management of steroid-induced osteoporosis

Price Dispersion of Vitamin D Supplements Over Time: An Initiative for Prescriber Education

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Abstract

Objectives: High prevalence of vitamin D deficiency mandates prescribing an appropriate form of vitamin D that allows attainment of sufficiency in a cost-effective manner. We aimed to compare vitamin D products in Indian market in terms of composition and cost in 2020 with 2013 to understand price dispersion over 7 years. **Methods:** Constituents, formulations, and prices of 'branded' and generic vitamin D products were sourced from various drug information compendia and online sources. Price per defined daily dose (DDD), percentage cost variation, and change in prices over 7 years (2020 vs. 2013) was determined. **Results:** There has been a disproportionate increase in the number of brands and cost variation of cholecalciferol and calcitriol in the last 7 years. The percentage cost variation increased almost 10 times for calcitriol and 4.4 times for alfacalcidol tablets and cholecalciferol granules. An analysis of >1,100 products in 2020 showed that the predominant form was calcitriol which was combined with calcium in >90% of the products with huge cost variation (>3000%). Ergocalciferol and cholecalciferol were available in 22 and 15 different strengths respectively. Median price/unit of cholecalciferol (60,000IU) was lower for tablets/capsules compared to other formulations; but with >1000% cost variation. **Conclusion:** A wide cost variation exists with the use of different vitamin D brands and preparations with conventional cholecalciferol tablets and capsules being a low-priced alternative. Quality control measures and strict enforcements of existing regulations are essential to ensure that competitive prices of branded generics are translated into availability and affordability for the population.

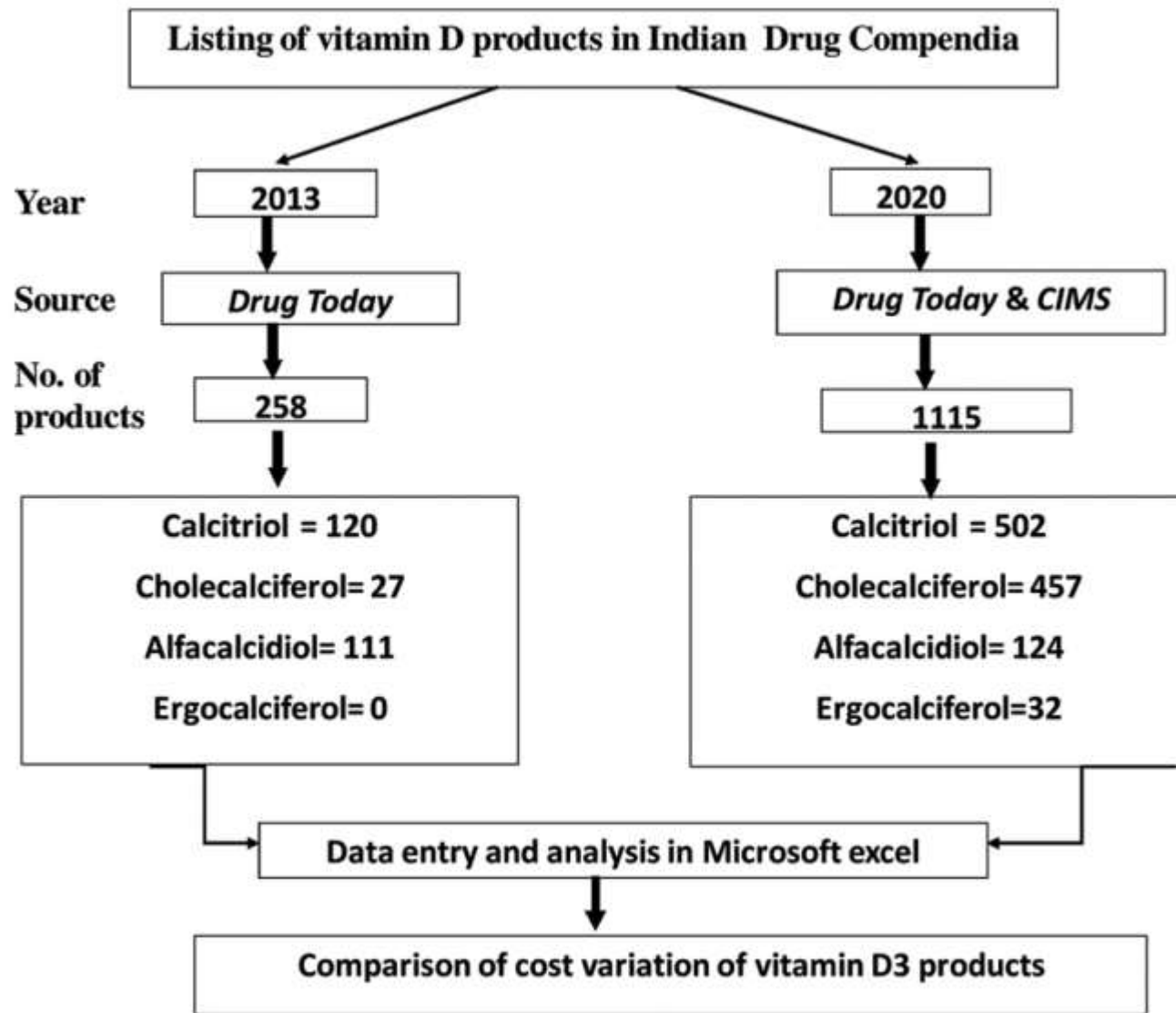


Figure 1: Flowchart for the analysis of vitamin D products in 2013 and 2020

Chugh PK, Dabas A. Price dispersion of vitamin D supplements over time: An initiative for prescriber education. Indian J Endocr Metab 2021;

Vitamin D Supplements - Calcitriol

- The present study showed that calcitriol was the most commonly available D3 analog which was combined with calcium in >94% of the products. These combined supplements were **3 times more expensive** than calcitriol (single-ingredient) tablets and can significantly raise expenditures and risk of adverse reactions; **thus impacting compliance when prescribed for long-term use.**
- **Conclusion: A wide cost variation exists with the use of different vitamin D brands and preparations with conventional cholecalciferol tablets and capsules being a low-priced alternative.** Quality control measures and strict enforcement of existing regulations are essential to ensure that competitive prices of branded generics are translated into availability and affordability for the population.

Vitamin D Supplements - Cost and Convenience ?

- The drug price control order (DPCO) of 2013 fixes the maximum amount that companies can charge for essential medication. The National List of Essential Medicines (NLEM) of 2015 includes calcium.
- The DPCO is a **double-edged sword**—while it allows a reduction in prices when an expensive medication is combined with an essential medicine (e.g., Calcitriol with Calcium) the availability of such combinations also opens up the market for the costlier drugs.

Vitamin D Supplements- Cost and Convenience ?

- Paradoxically, the same mechanism that causes a reduction in prices might end up costing the patient more. The Department of Pharmaceuticals (DoP) data show that the costly + cheap medicine combinations occupy less than 10% of the pharmaceutical market and even in those, the reduction in prices is to the tune of 20% or less.
- **Calcium/calcitriol combination is an exception—46.5% of available preparations contain calcitriol in the form of tablets or capsules of 0.25 mcg.**

Risk of hypercalcemia ?

- Risk is determined by many factors—including
 - the dose of calcium
 - dose of calcitriol
 - baseline dietary calcium intake
 - coexisting use of cholecalciferol
- Most cases of vitamin D toxicity reported in the literature are because of the indiscriminate use of cholecalciferol—often as injectable therapy.
- In a study by **Kaur et al (2015)** in Delhi NCR Vit. D toxicity due to mega doses emerged as an increasingly common cause of symptomatic hypercalcemia

Risk of hypercalcemia ? Need for monitoring serum and urine calcium?

- As shown in a systematic review by [Balk et al \(2017\)](#), the average calcium intake in India is low (400–500 mg/day)
- Given the low calcium intake, high prevalence of vitamin D deficiency of 70%-100% in the general population ([G R, Gupta A 2014](#)) and a low dose of calcitriol in FDCs (0.25 mcg), the risk of hypercalcemia attributable to calcium calcitriol FDCs is likely to be low **as long as the patient does not get high doses of cholecalciferol.**
- In a study of 53 Thai women ([Domrongkitchaiporn S 2000](#)) supplementation of calcium vs calcium calcitriol did not result in an increased risk of calcium oxalate nephrolithiasis.
- The need for monitoring is a direct consequence of the perceived high risk of hypercalcemia with calcitriol therapy but is not required in every patient

Hypercalcemic Crisis in Granulomatous Disorders

- Granulomatous disorders - also tend to have hypercalcemia and hypercalciuria due to extrarenal production of **calcitriol** and consequent increased intestinal absorption of calcium
- Even increased sunlight exposure with consequent endogenous production of Vitamin D can precipitate a hypercalcemic crisis.
- Maintain serum levels of 25(OH) D up to >30 ng/mL.
- In patients of Sarcoidosis / Tuberculosis with osteoporosis, serum and urinary calcium and vitamin D concentrations must be carefully monitored if supplements are required

Take Home Message

- Thus, the onus of **choosing judiciously** the right calcium and Vit D FDC for the right patient falls on the clinician.
- Indiscriminate use of calcitriol should be avoided
- Use of mega doses of cholecalciferol to be avoided
- The clinician should be aware of the potential risks and prescribe supplements only on an individual basis for the requisite duration
- Regulations are required to keep a check on marketing and availability

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A top-down view of various pharmaceuticals including capsules, tablets, and blister packs arranged around a central piece of lined paper. The paper has the words 'THANK YOU' printed in a bold, black, serif font. The background consists of several blister packs containing pills of different colors (green, white, yellow, red and white, brown) and shapes (round, oval, capsule).

THANK YOU