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Review Article

Vitamin D and Calcium Pharmaceutical Supplements: All we Need to Know to Choose the Right One

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ABSTRACT

Calcium and Vitamin D deficiency is highly prevalent in Pakistan. Both micronutrients have a significant role in human growth and development. Supplementation becomes essential when the available natural sources like food and sunlight, cannot replenish the deficiencies. Nevertheless, it is critical that while prescribing Calcium or Vitamin D supplements, physicians should know the composition and specific application of each supplement. This review explores the different types of Calcium and Vitamin D pharmaceutical supplements available in the market their composition, indication and contraindications. Data of Calcium and Vitamin D supplements has been collected by Pakistani drug sites databases, including 'Drug Infosys (www.druginfosys.com)', 'Dawaee.pk', 'Sehat.com.pk' and 'Medicine Net' by pharmacists and orthopaedists. The commonly prescribed supplements are Cholecalciferol (Vitamin D) and Calcium Carbonate (Calcium). Over time, an increase in market share of Vitamin D and Calcium supplementations is due to their over-the-counter availability, increased physicians' prescriptions, and self-prescribed use by the population. There is a need to develop national guidelines and policies to safeguard the population's health at large.

Keywords: Calcium, Composition, Deficiency, Supplements, Vitamin D, Toxicity.

How to Cite This Article: *Majid H, Zehra N, Khan A, Jafri L, Khan AH. Vitamin D and Calcium Pharmaceutical Supplements: All we Need to Know to Choose the Right One. Pak Armed Forces Med J 2024; 74(3): 884-889. DOI: https://doi.org/10.51253/pafmj.v74i3. 7361*

INTRODUCTION

The bony skeleton is richly composed of minerals, especially Calcium, and the absorption of this vital mineral in the gut is dependent on Vitamin D. Vitamin D is one of the fat-soluble Vitamins and its active form is available in 1,25 dihydroxy Vitamin D, which encourages the intestinal absorption of Calcium.[1] Calcium is an essential mineral because of its role in skeleton mineralization, teeth, nerve conduction, muscle contraction, and blood clotting.[2] Studies have suggested that an adequate amount of Vitamin D is directly proportional to muscle strength.[3] Standard levels of Calcium and Vitamin D prevents Osteoporosis and Osteosarcopenia in the geriatric population.[4] Researches have shown that an adequate amount of Vitamin D during pregnancy can prevent dreaded outcomes like pre-eclampsia, gestational diabetes and preterm delivery.[5] In humans, Calcium homeostasis is tightly controlled by parathyroid hormone (PTH), and Vitamin D. The PTH helps regulate the Calcium flow to and from the bones and Vitamin D facilitating intestinal absorption of Calcium.[5,6]

Vitamin D can be obtained by multiple means and ways, amongst which exposure to the sun is the primary natural way, but the use of sunscreens or having a lifestyle that involves shunning of the sun can lead to Vitamin D deficiency (VDD).[7,8] In terms of fortified food, ghee, oil, and butter are the best resources of this Vitamin. However, due to the growing epidemic of non-communicable diseases or cardiometabolic syndromes, excessive use of fats is often discouraged. Furthermore, the amount of Vitamin D present in these products is low. In contrast, Calcium can be obtained naturally from dairy products like milk, cheese, yoghurt, egg yolk.

Similarly, it can be acquired in small amounts through non-dairy products such as lentils, beans, fish, nuts, and cabbage; however, Calcium from these sources is less bio-available. Moreover, as mentioned previously, the intake of dietary Calcium is low in our population. The RDAs of Calcium and Vitamin D are shown in Table-I.

Literature shows widespread VDD in our population, with a prevalence in 60-90% of people irrespective of age and gender.[7,8] According to the National Nutritional Survey 2018, 62.3% of children under five from Vitamin D deficiency.[9] The efficiency of Calcium absorption is mainly determined by the amount of Calcium taken in the diet. When Calcium intake is severely deficient (<200mg/dl), Vitamin D increases the Calcium absorption from the intestines. It is evident through a survey from 3 different towns of

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Received: 04 Sep 2021, revision received: 23 May 2022; accepted: 24 May 2022

Table-I: Recommended Daily Allowance values for Vitamin D and calcium (International Osteoporosis Foundation Recommendations)

Age	Male	Female	Pregnancy and lactation	Male	Female	Pregnancy and lactation
	Calcium			Vitamin D**		
0-6 months*	200 mg		-	400 IU(10 mcg)		-
7-12 months*	260 mg					
1-3 years	700 mg			600 IU(15 mcg)		600 IU(15 mcg)
4-8 years	1,000 mg					
9-13 years	1,300 mg					
14-18 years			1,300 mg			
19-50 years	1,000 mg		1,000 mg			
51-70 years	1,000 mg	1,200 mg	-			-
71+ years	1,200 mg			800 IU(20 mcg)		

**Adequate Intake (AI)*

*** 1 IU = 0.025 ug*

Karachi that 90%of the females are taking Calcium less than their daily requirement, and VDD is prevalent in the females of those three areas.[10] Unpublished data on healthy medical students (19-21 years of age) in our population showed that daily mean Calcium intake was 862.8±457.8 mg/day, and consumption was significantly lower in females (p-value<0.001).

Calcium and Vitamin D supplements play an essential role in subjects unable to obtain Calcium and Vitamin D from natural sources. It is also essential in high-risk subjects like the elderly and home-bound when there is a lack of sun exposure. Calcium and Vitamin D are usually given together, or combined tablets are prescribed. As it is recorded that Vitamin D supplements are necessary for the active absorption of Calcium from the gastrointestinal tract, especially when the diet has low Calcium content.

However, both are not benign drugs, and prescribing a supplement requires just as much care and consideration as any other drug. There are multiple types of supplements available for paediatric and adult use, which differ in their efficacy and have a different therapeutic application due to the chemical composition of the kind of Calcium and Vitamin D present. Both adults and children need a safe formulation to prevent adverse effects.[11] That is why a physician's understanding of the type of supplements he/she is prescribing is critical for optimising a treatment plan for the correction of deficiency and maintenance of optimal levels, without knowing the detrimental effects of both elements' toxicity. We must know what supplement is available, its potential use, and the RDA we require. Therefore, we performed this study to explore the different types of Calcium and Vitamin D pharmaceutical supplements available in the Pakistani market and their use.

METHODOLOGY

Two persons, a pharmacist and a bone consultant independently searched the Pakistani drug sites databases, i.e., 'Drug Infosys (www.druginfosys.com)', 'Dawaee.pk', 'Sehat.com.pk' and 'Medicine Net (www.medicinenet.com)' to collect the data on pharmaceutical supplements of Vitamin D and Calcium, available in Pakistani markets. This review is divided into two parts; in part one, we have included Vitamin D supplements in clinical use, and in the second part, the Calcium supplements are discussed. The data on the formulation, concentration, and elemental Calcium was collected from each supplement's product labels or the websites mentioned above.

RESULTS

Vitamin D Supplements

A total of 312 preparations of Vitamin D are available in Pakistani market. Out of these 59(15%) formulae are available in injections and 253(81%) are available in oral form. These compositions are ranges from 200 IU to 600000 IU with the price range of 103 Pakistani Rupees (PKR) to 2,700 PKR. Out of the total, 27(10.6%) products of Vitamin D are available in a composition that contains various minerals and Vitamins such as Calcium, magnesium, zinc, Vitamin, Vitamin C, Vitamin B12, Vitamin B6. A few commonly Vitamin D brands are presented in Table-II. The indications and characteristics of Vitamin D analogues are shown below:

Ergocalciferol: Is sourced from botanical source mainly fungi, herbs and plants are the best sources of this Vitamin, and it is less potent then cholecalciferol.[12,13] It is first converted into biologically active form after metabolism in liver and kidney, so shows a time lag of 10-24 hours to function. It is

Table-II: Commonly Available Vitamin D Pharmaceutical Supplements in the Market

Type of Vitamin	Indication	Available as	Amount of Vitamin D available (IU)
Cholecalciferol	Vitamin D deficiency, Hypocalcemia	Oral Drops	10,000,000 IU
		Capsules	200000IU
			50,000IU
			5000IU
		Injection	200,000IU
		Injection	200,000 IU
		Syrup	400 IU
		Tablet	1000 IU
		Capsules	200,000 IU
Alfacalcidol	Chronic kidney diseases, especially end-stage renal failure Osteoporosis Hypoparathyroidism Renal diseases	Injection	80 IU
		Injection	80 IU
		Injection	80 IU
		Capsule	40 IU
		Tablet	40 IU
		Syrup	20 IU
		Tablet	40 IU
		Tablet	40 IU
		Syrup	20IU
Calcitriol	Chronic renal disease Dialysis patients Hypoparathyroidism	Injection	40 IU
		Capsule	20 IU
		Soft capsule	10IU
Ergocalciferol	Hypoparathyroidism, Vitamin D resistant rickets, Familial hypophosphatemia	Capsule	50,000 IU

**International Unit (IU).*

contraindicated in hypercalcemia, Vitamin D toxicity and malabsorption.

Cholecalciferol: (25-Hydroxy Vitamin D) is synthesized via UV radiation of 7-dehydrocholesterol in the skin at a UV wavelength of 290-320nm, with a further thermal isomerization step to form Vitamin D313. It is the first choice of supplement for a healthy individual, as its more potent than ergocalciferol (87%).[12] Moreover, the RDA for Vitamin D is also based on it.

Alfacalcidol: (1-Hydroxy Vitamin D) requires 25-hydroxylation in the liver to become biologically active, showing a time lag of 2-4 hours to function. It has a longer half-life than Calcitriol, so the frequency of dosing is extended. However, it has a lesser impact than Calcitriol on gut Calcium absorption but significantly affects the immune system. It decreases fall risk, and subsequent fractures by increasing muscle strength and neuromuscular coordination.[14]

Calcitriol: (1, 25 dihydroxy Vitamin D) is the biologically active Vitamin D and has the most potent hypercalcemic effect in healthy and renal failure patients. It is given orally, and dose calculation is advised to be done carefully, start with minimum dose to prevent hypercalcemia and titration is recommended based on the serum Calcium, phosphate and parathyroid levels. It is recommended to either prescribe Calcium supplements simultaneously or maintain an adequate dietary Calcium intake.[15]

Vitamin D supplements are available as tablets, capsules, soft-gel capsules, oral drops, syrups and injectable. Oral supplementations are the easiest to take and circumvent the side effects of injections like thrombophlebitis and others. The oral supplementation drawbacks are that the peak effect is delayed after oral Vitamin D supplementation, noncompliance as patients usually forget to take the medication on time every day.

Calcium Supplementation

One hundred and seventy different Calcium supplements are available in the market, out of these 17(10%) supplements also in combination with Vitamin D. The pharmacokinetics of different Calcium supplements are distinctive, hence the indication of these supplements differs. Calcium supplement should be selected based on the amount of elemental Calcium in a supplement, RDA levels of Calcium for that particular age group, and comorbidities of the patients.

Calcium Carbonate: It is the most commonly available and first choice for Calcium supplement. It has the

highest amount of elemental Calcium and is also used as a gastric antacid. The bioavailability is 25-35%, which increases up to 10-30% when taken with food. Hence, it should be taken with food for optimal absorption. Peak plasma time is achieved in 20-60 min in fasting state and up to 3 hours when it is ingested after meals. It also acts as a phosphate binder in hypophosphatemia. That is why it is a drug of choice in patients with hyperphosphatemia.

Calcium Citrate: It is easier to digest than Calcium carbonate and has more bioavailability with 36-37% absorption in an empty stomach and should be taken in a fasting condition for better absorption. It is a supplement of choice in patients with gastric problems, shown in Table-III.

magnesium toxicity, while Calcium lactate can also be used as an antacid.

Calcium Acetate: Its elemental Calcium content is less than carbonate supplements. In fasting, 40% of supplement is absorbed, whereas only 30% is absorbed when taken with meals, so it should be taken in a fasting condition. It binds with dietary phosphate to form insoluble Calcium phosphate, which is excreted in the faeces, making it the preparation of choice in patients with hyperphosphatemia and patients with end-stage kidney disease.

Calcium Chloride: This Calcium salt is necessary to maintain muscular and nervous systems, cardiac function, and mechanism for coagulation of blood.

Table-III: Commonly Available Calcium Pharmaceutical Supplements in the Market

Calcium Compound	Elemental Calcium In Each 1 gm Of Supplement	Indications	Elemental Calcium*
Calcium Carbonate	400 mg	Hypocalcemia Gastric ulcers Hyperphosphatemia Osteoporosis	200 mg, 200 mg 300 mg 130.8mg 177.6 mg 500 mg 600 mg 500 mg
Calcium Citrate	211 mg	Treat hypocalcemia in Gastric problem Achlorhydria (patients taking histamine-2 blockers or proton-pump inhibitors) Gastric bypass Chron's disease Hyperphosphatemia in renal osteodystrophy	136.5 mg 262.5 mg 500 mg 269.2 mg
Calcium Gluconate & Calcium Lactate	93 mg	Treat hypocalcemia in Treatment adjunct in cardiac arrest Hyperkalemia Magnesium poisoning	 93 mg 130.8 mg 46.87
Calcium Acetate	253mg	Treat hypocalcemia in Hyperphosphatemia End stage renal failure Also used as pharmaceutical buffering agent	667mg
Calcium Chloride	273mg	Treat hypocalcemia in Muscular & nervous system related problems Coagulation related problems Malignant arrhythmias Magnesium Poisoning	200mg/ml

**Note: Elemental Calcium is the elemental form of Calcium occurring in supplement*

Calcium Gluconate and Lactate: These supplements have very small amounts of elemental Calcium and require multiple doses, but they are comparatively more soluble than citrate preparations. Calcium gluconate is also utilized to treat hypoglycemia,

Calcium supplements which are not available in the Pakistani market, include Calcium glubionate, Calcium phosphate, and Calcium gluceptate. Calcium glubionate supplements contain 66mg of elemental Calcium in 1g salts. While Calcium phosphate and

gluceptate have 38.7mg per gram, and 82mg elemental Calcium in 1g salts, respectively. All of these supplements are better absorbed on when taken orally.

DISCUSSION

Vitamin D deficiency and inadequate dietary intake of Calcium are widely prevalent in our population. Methods to improved Vitamin D and Calcium status of a population include food fortification and supplementation. Food fortification is a safe and cost-effective intervention for preventing micronutrient deficiencies and has been widely practised in developed countries for well over a century. Edible oil and ghee are the ideal vehicles for Vitamin D fortification, while Calcium can be fortified in wheat flour, milk, yoghurt, cottage cheese, and soya-based beverages. Fortification of edible oil and ghee in Pakistan was started from May 2017, but the coverage is not 100%, as not all edible ghee/oil manufacturers are registered with Food Fortification Program.[16]

Currently, Vitamin D is available in injectable and oral forms. Individuals should be assessed clinically and biochemically, and Vitamin D supplements should only be prescribed if Vitamin D levels are deficient or in certain conditions requiring supplementation.[8] Unmonitored and indiscriminate Vitamin D use can lead to toxicity, which is another negative situation now observed in our country.[17] It has been reported that a loading dose of 50,000 to 60,000 IU of Vitamin D once a week for eight weeks followed by a maintenance dose of 500IU/daily should be administered if the patient is found to be Vitamin D deficient based on clinical as well as laboratory assessment.[12] Alternatively, in severe Vitamin D deficiency mega-doses, 200,000 IU three times a year or 600,000 IU twice a year, followed by a maintenance dose of 400-600 IU Vitamin D. Additionally, Vitamin D supplementation should be cautiously prescribed in patients on thiazide diuretics, which causes reabsorption of Calcium from kidneys and can lead to hypercalcemia.

Elemental Calcium is vital for the mineralization and the growth of the bones. The Institute of Medicine (IOM) and International Osteoporosis Foundation (IOF) suggest that RDA of Calcium is different in both genders according to their age, shown in Table I, which should be covered by food rich in Calcium and supplement if RDA is not met. The best way to get the RDA of Calcium is by a proper diet. Physicians must encourage patients to make a habit of using Calcium and Vitamin D rich foods in their daily diet. Supplements should only be prescribed to those patients who cannot achieve their daily requirements through nutrition. According to IOF 1 glass or 200ml of milk contains 240mg of Calcium, 150 gm of yoghurt has 207mg of elemental Calcium, 50gm of the egg contain 27mg of Calcium, 200mg of cooked lentils contains 40 mg, 200 gm cooked chickpeas, and white beans contain 80mg and 132mg respectively.[18] If the patient cannot take an adequate amount of Calcium through diet, then the supplement can be prescribed. Gender and age-specific RDA should be considered while prescribing Calcium supplements.

At present, we do not have approved national guidelines and are still following the western guidelines to treat our patients. There is a need to educate masses about adequate sun exposure and replenishing vitamins and minerals through diet. Physicians need to enhance their understanding regarding the optimal dosage and the appropriate supplement selection. Inappropriate or excessive supplementation can lead to toxicity, and the patient can develop consequences related to hypervitaminosis D or hypercalcemia, for example, nephrocalcinosis, kidney stones.[19]

With the Vitamin D deficiency (VDD) pandemic declaration, the market share of Vitamin and Calcium supplements has shown a sale upsurge in recent years. Euromonitor's report shows an increased sale of Calcium and multivitamin supplements up to 6.6% globally from 2017 till 2025.[19] Vitamin and Calcium supplements are readily available over the counter, and the majority of the population is taking them with little or no knowledge about their side effects and contraindications. Over recent years' media has played an essential role in creating the awareness of Vitamin D and Calcium deficiency. Awareness is essential but should be done with caution. The Pakistan Electronic Media Regulatory Authority (PEMRA) should make stringent policies and keep a check on such supplements' marketing. A message should be given from media that any supplementation cannot be taken without a proper physician's prescription.

CONCLUSION

This review evaluated the different types of Calcium and Vitamin D supplements available in Pakistan, their utility, and RDAs. Prescribing an optimal supplement at an optimal dosage becomes even more critical when dealing with patients with comorbidities, as different types of Vitamin D and Calcium supplements are recommended in different diseased conditions. This review will serve as a

guide for the physicians while prescribing Vitamin D and Calcium.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

HM & NZ: Data acquisition, critical review, approval of the final version to be published.

AK & LJ: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AHK: Conception, data analysis, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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