

# Vitamin D in Therapeutics: Past, Present and Future

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## Abstract

In the beginning of 20<sup>th</sup> century vitamin D was classified as a vitamin but later considered as a prohormone (“conditional” vitamin) which influences the expression of more than 200 genes in the human body. Worldwide vitamin D insufficiency affects about 50% of the population and in India about 80% of population has vitamin D level less than normal. In India sunshine is abundant but still Indians are deprived of this sunshine vitamin. Minimal exposure to direct sunlight, staying indoors, use of sunscreen lotions, pollution, clothing, dietary and cooking habits are most important factors for vitamin D deficiency in the Indian population. Serum 25 hydroxyvitamin D level is the initial diagnostic test in patients at risk for deficiency. Treatment with either vitamin D<sub>2</sub> or vitamin D<sub>3</sub> is recommended for patients having deficiency, keeping hypervitaminosis in mind.

**Keywords:** Vitamin D, VDD- Vitamin D Deficiency, 25 Hydroxyvitamin D

## 1. Introduction

In the beginning of 20<sup>th</sup> century vitamin D was classified as a vitamin but later considered as a prohormone (“conditional” vitamin) which influences the expression of more than 200 genes in the human body<sup>1</sup>. Most of tissues in the human body e.g., heart, brain, kidney, pancreas, skin etc., has receptors of vitamin D. Hence deficiency of vitamin D in the human body affect normal functioning of all the organs which contain Vitamin D receptors. Worldwide about 50% of the population is suffering from Vitamin D insufficiency .

An estimated 1 billion people worldwide, across all ethnicities and age groups, have a vitamin D deficiency (VDD)<sup>2</sup>. In India sunshine is abundant but still Indians are deprived of this sunshine vitamin. It is estimated that around 80% of the Indian population has Vitamin D levels less than normal. Surprisingly most of the people are not even aware of Vitamin D deficiency and its consequences. Minimal exposure to direct sunlight (during the period of 10am to 3pm), staying indoors, use of sunscreen lotions,

pollution, clothing, dietary and cooking habits are most important factors for vitamin D deficiency in the Indian population<sup>2</sup>. Vitamin D deficiency is a global concern, still it under-diagnosed and under-treated nutritional deficiency.

Vitamin D is a unique nutrient as synthesized endogenously (skin) and functions as a hormone. Initially it was consider that vitamin D is only responsible for maintaining calcium homeostasis and bone health hence responsible for osteoporosis, but in the last few years, research has established the strong association of vitamin D deficiency in hypertension, heart disease, diabetes, cancer, depression. Vitamin D deficiency plays vital role in improving insulin sensitivity and hence hyperglycaemia can be managed in better way.

## 2. History

In the mid-1600s, Whistler and Glisson independently published scientific descriptions (in Latin!) of rickets, cause of which we now know today by a vitamin D

deficiency. However nobody recognized the vital role of diet or exposure to sunlight in the prevention of this disease. Around 200 years later in 1840 a Polish physician Sniadecki found that rickets occurred in children living in the industrial centre of Warsaw but did not affect children living outside Warsaw. He found that lack of exposure to sunlight in the crowded streets of the city where sunlight is not abundant and there was considerable pollution due to the burning of coal and wood, caused the disease.

In 1918 Sir Edward Mellanby discovered that beagles, which are exclusively placed inside house away from natural sunlight and fed a diet of oatmeal, developed rickets but after the addition of cod liver oil to the food cure the disease successfully. In 1921 he demonstrated "The action of fats in rickets is due to a vitamin or a specific food factor which they contain, probably the fat-soluble vitamin.

In the 1920s and 1930s by Windaus and colleagues in Germany identify the chemical structures of the various forms of vitamin D. In 1928 Windaus was awarded the Nobel Prize in Chemistry "for his research into the structure of the sterols and their connection with the vitamins". In 1936 biologically active form of vitamin D, found in the skin and called D<sub>3</sub>, was characterized and produced from the Ultraviolet (UV) radiation of 7-dehydrocholesterol. Thus vitamin D was considered as a steroid. Later the component in cod liver oil that prevented rickets was identified as vitamin D<sub>3</sub><sup>4</sup>.

### 3. Metabolism

Vitamin D<sub>3</sub> is cholecalciferol and vitamin D<sub>2</sub> is ergocalciferol. On exposure to sunlight Vitamin D<sub>3</sub> is produced in the skin. It is derived from 7-dehydrocholesterol by ultraviolet irradiation of the skin. After ingestion vitamin D both D<sub>2</sub> or D<sub>3</sub>, incorporated into chylomicrons which get absorbed into the lymphatic system and enter the venous blood. Vitamin D that comes from the skin or diet is biologically inert and requires its first hydroxylation in the liver and second one in kidneys to form the biologically active form of vitamin D<sub>1</sub>, 25(OH)D<sub>2</sub>, 1,25(OH)<sub>2</sub>D<sub>2</sub> may be responsible for regulating up to 200 genes which may facilitate many of the health benefits<sup>2</sup>.

### 4. Sources

Vitamin D perhaps the one of the vitamin that gets synthesized in the body in the skin with the help of sunlight. Vitamin D<sub>3</sub> is found in animal food e.g., fatty

fish (e.g., mackerel, salmon and tuna), cod liver oil, milk. Vitamin D<sub>2</sub> is found in vegetal sources like sun-exposed yeast and mushrooms<sup>3</sup>.

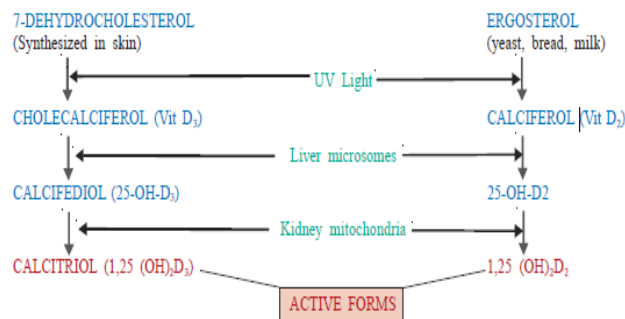


Figure 1. Vitamin D metabolism.

## 5. Deficiency: Definition, Causes and Consequences

In adults, vitamin D deficiency is defined as a serum 25-hydroxyvitamin D level of less than 20 ng per mL (50 nmol per L), and insufficiency is defined as a serum 25-hydroxyvitamin D level of 20 to 30 ng per mL (50 to 75 nmol per L)<sup>5</sup>.

### 5.1 Causes of Vitamin D Deficiency<sup>2</sup>

- Inadequate exposure to sunlight - as major source of vitamin D is exposure to natural sunlight.
- Skin tone- Dark skin people are more prone for deficiency than white tone as dark skin provide natural sun protection.
- Use of sunscreens- reduces vitamin D synthesis in the skin.
- Dietary and cooking factors.
- Obesity- There is an inverse association Body Mass Index (BMI) and serum 25(OH) D level.
- Primary hyperparathyroidism – due to excessive metabolism of 25(OH)D to 1,25(OH)<sub>2</sub>D
- Chronic granulomatous disorders- e.g. tuberculosis, sarcoidosis, and chronic fungal infections.
- Lymphomas.
- Fat malabsorption syndromes.
- Nephritic syndrome- due to loss of vitamin D binding proteins in the urine.
- Drugs – e.g., anticonvulsants, antiretroviral- as these drugs enhance the catabolism of 25(OH)D and 1,25(OH)<sub>2</sub>D.

There are certain groups which are at risk of vitamin D inadequacy<sup>2</sup>-

- Breastfed infants.
- Older adults.
- People with limited sun-exposure.
- Dark skin people.
- Fat malabsorption.
- Obese people.
- People undergoing gastric bypass surgery.

### 5.2 Dietary and Cooking Factors Contributing to High Prevalence of Vitamin D Deficiency in India<sup>3</sup>

- Most Indians are vegetarians and majority of food items rich in vitamin D are of animal origin.
- In India for vegetarians milk is only dietary source of vitamin D but its vitamin D content is very low (2 IU/100 mL in unfortified milk).
- Boiling of milk for longer duration and several times reduces the content vitamin D.
- High prevalence of lactose intolerance.
- Poverty-milk and milk products are unaffordable.
- Low dietary intake of calcium- Most studies indicate that in India calcium intake is much lower than the RDA (Recommended Daily Allowance) stated by the Indian council of medical research. As low calcium intake with vitamin D insufficiency leads to secondary hyperparathyroidism.
- High phytate content in diet- phytates chelate calcium and thus reduce its intestinal absorption.
- Thermal stability of vitamin D is inversely related to temperature and time- Vitamin D is degraded at temperatures above 200°C. As Gas flames and coal stove heat reaches above this temperature.

- Deep frying of foods- When foods are fried, vitamin D in the food comes out into the cooking medium and is thermally degraded.
- Publications -Apart from dietary and cooking factors in most research studies subjects are mostly from lower and upper middle classes and not from poor class<sup>3</sup>.

### 5.3 Consequences of Vitamin D Deficiency

Calcium, phosphorus, and bone metabolism affected result in decrease in the absorption of dietary calcium and phosphorus, leads to increase in parathyroid level which leads to increase in osteoclastic activity and generalized decrease in Bone Mineral Density (BMD) ultimately results in osteopenia and osteoporosis.

In young children mineralization defect in the skeleton leads to variety of skeletal deformities (e.g., bowed legs, knock knees, rachitic rosary etc.) known as rickets. Vitamin D also causes muscle weakness leads to difficulty in standing and walking<sup>2</sup>. Chronic vitamin deficiency in adults leads to osteomalacia, osteoporosis, muscle weakness and increased risk of falls<sup>3</sup>.

Other common complaints in people having vitamin D deficiency are low backache, pain lower extremities, impaired physical function, increased risk of falls<sup>5</sup>.

## 6. Musculo-Skeletal Benefits of Vitamin D

### 6.1 Fracture and Falls

Many studies have shown association between low vitamin D concentrations and increased risk of fractures and falls. Vitamin D receptors are located on the muscle



Figure 2. Benefits of vitamin D.

fibers, which are the first to give response in a fall<sup>2</sup>. It is assumed that vitamin D may increase muscle strength, thereby preventing falls.

A combined analysis of 12 fracture prevention trials found that supplementation with about 800 IU of vitamin D/day decrease incidence of hip and non-spinal fractures by about 20%. BischoffFerrari HA et al researchers of Jean Mayer USDA Human Nutrition research center at Tufts university concludes that risk of fractures and falls reduces at 700 IU and above doses<sup>2</sup>.

## 7. Extra Skeletal Benefits of Vitamin D

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### 7.1 Hypertension

There are various studies which show correlation between blood pressure and vitamin D. According to German national interview and examination survey prevalence of arterial hypertension was also associated with reduced serum 25(OH)D levels<sup>7</sup>.

The third National Health and Nutrition Examination Survey have shown systolic blood pressure and pulse pressure were inversely and significantly correlated with 25(OH)D levels.

Ageassociated increase in systolic blood pressure was significantly lower in individuals with sufficient vitamin D<sup>8</sup>.

The antihypertensive effects of vitamin D is mediated by renoprotective effects, suppression of the RAAS<sup>9</sup>.

### 7.2 Heart Disease

Evidence has been found by several studies that vitamin D has protective effect on heart. This protective effect might be via the renin angiotensin hormone system, or through the suppression of inflammation, or directly on the cells of the heart and bloodvessel walls<sup>10</sup>.

Framingham Heart Study, have shown patients having low vitamin D concentrations (<15 ng/mL) had a 60% higher risk of heart disease than those with higher concentrations. In another study patients with low vitamin D concentrations (<15 ng/mL) were three times more likely to be diagnosed with hypertension than those with high concentrations (>30 ng/mL)<sup>11</sup>.

### 7.3 Type 2 Diabetes

Association between plasma glucose level and vitamin D have been studied by various trials and showed possible correlation between vitamin D and the risk of diabetes. One of the trial of non-diabetic patients having age more than 65 years showed that individuals receiving 700 IU

of vitamin D ( in association with calcium) had a smaller rise in fasting plasma glucose over 3 years versus those who received placebo<sup>12</sup>.

### 7.4 Cancer

Although definitive conclusion cannot be made about the association between vitamin D concentration and cancer risk but results of various studies are indicative of association.

It is theorized that vitamin D decreases cell proliferation and increases cell differentiation, inhibit the growth of new blood vessels<sup>13,14</sup>.

Many studies have shown a possible link between low vitamin D levels and higher risk of colorectal cancer. In the Health Professionals Followup Study (HPFS), subjects with high vitamin D concentrations were half as likely to be diagnosed with colon cancer as those with low concentrations<sup>13</sup>.

Some studies showed that higher vitamin D intake lowers risk for breast cancer<sup>14</sup>.

### 7.5 Depression

A Norwegian trial of overweight subjects determines a correlation between vitamin D and the risk of depression which showed that individuals receiving a high dose of vitamin D, about 20,000 or 40,000 IU weekly had a significant improvement in depressive symptoms after 1 year as compared to those receiving placebo<sup>15</sup>.

### 7.6 Parkinson `s Disease

Recently it is observed that chronic vitamin D deficiency has major role in the pathogenesis of Parkinson's disease<sup>16</sup>.

### 7.7 Autoimmune Diseases

Vitamin D deficiency can be associated with autoimmune diseases e.g., multiple sclerosis, rheumatoid arthritis, and autoimmune thyroid disease<sup>17</sup>.

### 7.8 Influenza

In randomized, controlled trial in a Japanese childrens who received vitamin D of 1200 IU had a 40% lower rate of influenza type A compared with those receiving placebo<sup>18</sup>.

## 8. Diagnosis of Vitamin D Deficiency

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Plasma 25(OH)D or calcidiol (a summation of both D<sub>3</sub>

and D<sub>2</sub> forms) is the most sensitive indicator of vitamin D status. In clinical labs Immunoassays e.g., Enzyme Linked Immunosorbant Assay (ELISA), Radioimmunoassay (RIA), protein binding assays, chemiluminescence immunoassay are used for testing of 25(OH)<sup>3</sup>.

## 8.1 Laboratory and Radiographic Findings that Suggest Possible Vitamin D Deficiency<sup>19</sup>

### 8.1.1 Laboratory

- Elevated parathyroid hormone level.
- Elevated total or bone alkaline phosphatase level.
- Serum calcium and serum phosphorus level.
- 24-hour urine calcium excretion.

### 8.1.2 Radiographic

Useful to detect various spectrum of findings depending upon duration and severity of deficiency

Ranging from osteoporosis to classical findings of rickets or non-traumatic fractures<sup>19</sup>.

## 9. Treatment and Prevention

1 µg of cholecalciferol = 40 IU of vitamin D.

Dose of vitamin D for prophylaxis of deficiency is 400 IU/day and for treatment purpose is 3000 to 4000 IU/day. This is given to prevent and treat rickets in children and osteomalacia in adults.

Alternatively 300,000 to 600,000 IU can be given orally or intramuscularly once in 2-6 months.

Prophylactic treatment can be given in obstructive jaundice, steatorrhoea and other conditions which predisposes to vitamin D deficiency<sup>20</sup>.

## 10. Measures to Correct Vitamin D Deficiency: Supplementation, Food Fortification and Educational Programs

There are various opinions regarding optimal levels of consumption of vitamin D, preferred form of vitamin D for human use and extraskeletal benefits of vitamin D. But in general, Indians need more vitamin D. Vitamin D can be obtained from three sources: Sun exposure

(limitations of which has been discussed earlier), vitamin D supplements and vitamin D fortified foods. There is urgent need to prioritize development of national level programs to make available quality-regulated and affordable vitamin D supplements and vitamin D fortified foods to the Indian population. The government needs to implement measures to educate the Indian population about the current status of vitamin D in India and also the modes to attain vitamin D sufficiency.

## 10.1 Hypervitaminosis D

- As vitamin D is fat soluble vitamin hence hypervitaminosis can occur on excessive intake.
- Hypervitaminosis is diagnosed by detecting elevated 25(OH)D level.
- Hypervitaminosis leads to hypercalcemia, hypercalciuria and hyperphosphatemia.
- Symptoms and signs of hypervitaminosis are Nausea, vomiting, constipation and dehydration – due to hypercalcemia.
- Polyuria and kidney stones–due to Hypercalciuria.
- Other symptoms are headache, metallic taste, pancreatitis.

However vitamin D toxicity is rare and happen after intake of large doses, generally more than 10,000 IU/day for longer duration. If we measured 25(OH)D level in these patients, it is generally within 80 ng/ml to 150 ng/ml or rarely even greater. Hypervitaminosis leads to hypercalcemia. Hypervitaminosis D is not medical emergency but hypercalcaemia needs further evaluation. In case of hypervitaminosis renal function should be monitored<sup>19</sup>.

## 11. Conclusion

Vitamin D is a pro-hormone that influences the expression of more than 200 genes in the human body. Vitamin D is not only important for skeletal system but also beneficial in hypertension, heart disease, diabetes, cancer, depression, Parkinson`s disease. Today vitamin D deficiency is becoming a national and international health concern very rapidly. Serum 25hydroxyvitamin D level is first diagnostic test to be carried out in persons which are prone or suspected for deficiency. For deficient persons, supplementation with vitamin D<sub>2</sub> or D<sub>3</sub> is recommended.

Supplementation with 400 IU/day of vitamin D is indicated. This dose is generally safe for most of peoples and can prevent deficiency of vitamin D. However possibility of hypervitaminosis should be kept in mind.

More research is needed to detect vitamin D deficiency in non-risk individuals and vitamin D benefits in non-skeletal conditions or diseases.

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