

Vitamin D deficiency, skin, and sunshine: A review

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Abstract

The sunshine vitamin - "Vitamin D" is a subject of interest that attracted researcher's attention in the past few decades. Vitamin D is a fat-soluble vitamin and also a nutrient which increases the calcium absorption and plays an important part in the maintenance of body's immune system and bone formation. However, the deficiency of Vitamin D, also known as hypovitaminosis D, will affect various body parts such as the brain, heart, muscle, immune system, and bones. Thus, the deficiency leads to severe conditions such as osteopenia, osteoporosis, rickets (in children), hypertension, fractures and falls in adults, cancers, diabetes, autoimmune diseases, infections, and neurological disorders. An effective approach for the deficiency prevention is the thorough understanding of Vitamin D sources, Vitamin D serum levels, and deficiency symptoms, linked with different pathological conditions, requirement and maintenance in the body, sunlight exposure duration, and effective treatment dose. Therefore, the present review will lay an emphasis on the role of Vitamin D, the reasons for its deficiency, available sources, and treatment options reported so far.

Key words: Skin, sunlight, Vitamin D, Vitamin D₂, Vitamin D₃

INTRODUCTION

Nowadays, Vitamin D deficiency affects 50% of the population worldwide. The main reason for its deficiency is the change of lifestyle, i.e. increase in sunscreen use and environmental factors such as reducing the time for exposure to sunlight, which is required for ultraviolet (UV) B rays to induce the production of Vitamin D in the skin. The people who are having black skin require more exposure to the skin for the production of Vitamin D as compared to the white ones.^[1] Insufficient Vitamin D will lead to the condition of hypovitaminosis D and the latter is linked with numerous conditions of the body; these are cancer, heart diseases, Type 2 diabetes, probability of stress fractures, autoimmune disease, influenza, and depression.^[2]

Vitamin D - Synthesis and Metabolism

Vitamin D is available in two forms: Vitamin D₃ (cholecalciferol) and Vitamin D₂ (ergocalciferol). Vitamin D₃ is a natural occurring form and produced in skin cells from 7-dehydrocholesterol

underneath the UV light, and Vitamin D₂ is produced from the natural sterol, i.e. ergosterol.

Vitamin D₃ is metabolized in a two-step non-catalytic process favored by UV light and level of skin pigmentation, into 25-hydroxyvitamin D (25OHD) and then to 1,25-dihydroxyvitamin D (1,25(OH)₂D) which is a hormonal form and increases the intestinal calcium absorption, while Vitamin D₂ is metabolized to 25(OH)D in the liver and then to 1,25(OH)₂D in the kidneys from ergosterol,^[3,4] as shown in Figure 1. The presence of melanin in the skin cells limits the Vitamin D₃ production by blocking the UV rays which affect in the synthesis process. Hence, wearing full sleeves clothes and use of sunscreen too confine its production. In our body, some tissues such as breast, macrophages, colon,

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prostate, brain, and others have the enzyme which helps in the $1,25(\text{OH})_2\text{D}$ formation.^[4,5] The production of $1,25(\text{OH})_2\text{D}$ in non-calcium regulating tissues is helpful in controlling the cellular differentiation and cell growth and reduces the risk of cells to transform further into a malignant state.^[6]

Production of Vitamin D inhibits the cancer cell growth and induces the condition of apoptosis.^[6,7] $1,25(\text{OH})_2\text{D}$ plays an important role in the kidneys by inhibiting the production of renin^[8] and possesses an immune modulatory activity on activated B and T lymphocytes as well as monocytes.^[9,10]

Vitamin D - Levels and Functions

Vitamin D dose of 30 ng/mL or 75 nmol/L or 800–1000 IU Vitamin D_3 is required to maintain its level in adults, and <12 ng/mL or 30 nmol/L shows deficiency of Vitamin D. Sunlight exposures are required so that UV B rays can induce Vitamin D production in the skin in a natural way. Various levels and functions of Vitamin D are depicted in Figure 2.

VITAMIN D SOURCES

There are numerous sources available for Vitamin D such as direct sunlight, diet sources (animal and natural sources), and Vitamin D supplements available in the market.

Sunlight

Sunlight is also called as sunshine vitamin because direct exposure to sunlight leads to Vitamin D formation in the skin cells. Sunlight is one of the natural ways to prevent the deficiency of Vitamin D and skin required sunlight exposure production of Vitamin D. Numerous factors such as skin pigmentation, topical use of sunscreen, age, latitude, zenith angle of sun, duration of sunlight exposure, length of the clothes, and head covering as per the religious culture and season of a year influence the Vitamin D production in the skin.^[11,12]

Diet Sources

Vitamin D can be obtained from both animal and natural sources as shown in Figure 3. There are different animal sources such as salmon fish, mackerel fish, and cod liver oil.^[13] Natural sources of Vitamin D are obtained from milk, fruit juices, breads, yogurts, and cheese.

Vitamin D Market Supplements

Vitamin D is obtained from supplements available in the market. Multivitamins generally contain 400 IU, 800 IU, and 1000 IU Vitamin D, but nowadays various supplements containing only Vitamin D are available in different IU,

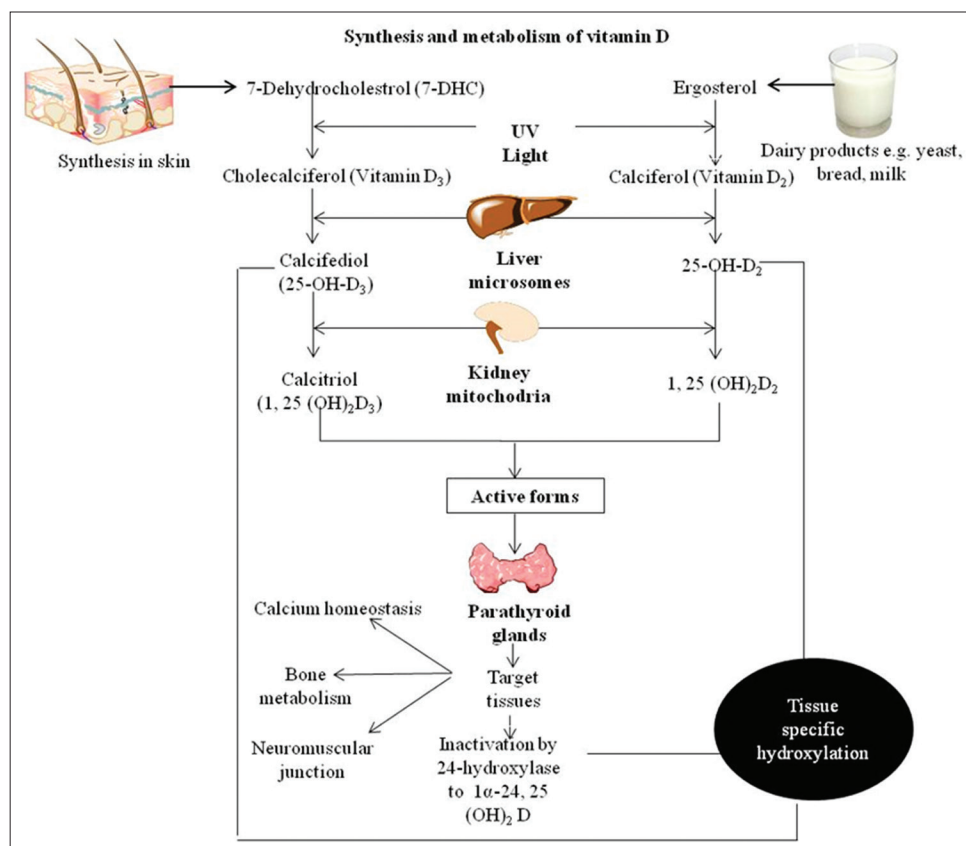


Figure 1: Synthesis and metabolism of Vitamin D

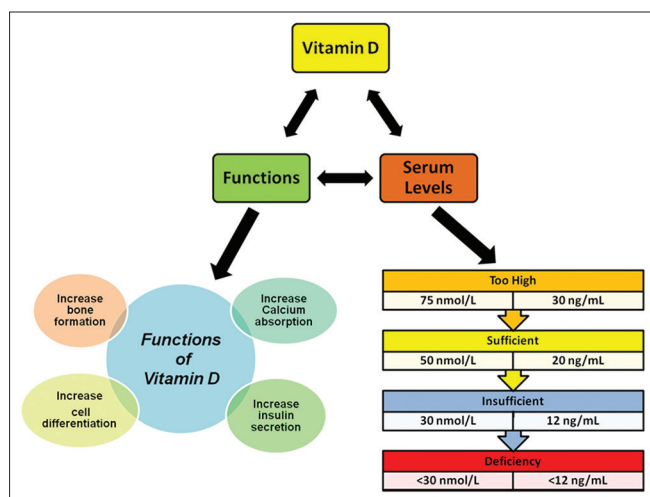


Figure 2: Various levels and functions of Vitamin D

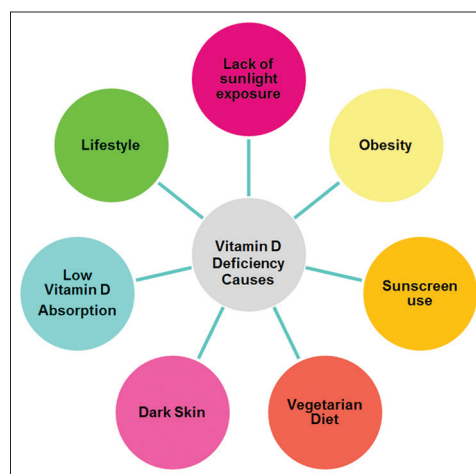


Figure 5: Causes of Vitamin D deficiency in the body

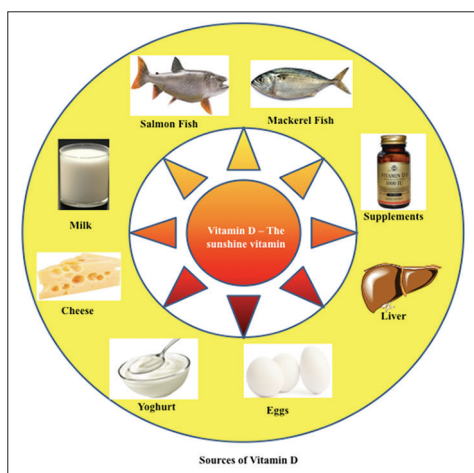


Figure 3: Sources of Vitamin D

Table 1: Diseases occur due to Vitamin D insufficiency in adult male, female, and child

Adult male	Adult female	Child
Depression	Schizophrenia	-
Lung disease	Tuberculosis	-
	Asthma	Asthma
Obesity	Malabsorption	-
Liver disease	-	-
Osteoporosis	Osteoporosis	-
Osteomalacia (bone pain)	Osteomalacia	Reduced bone mass
-	Renal failure	-
-	Muscle weakness	-
-	Osteoarthritis	Rickets

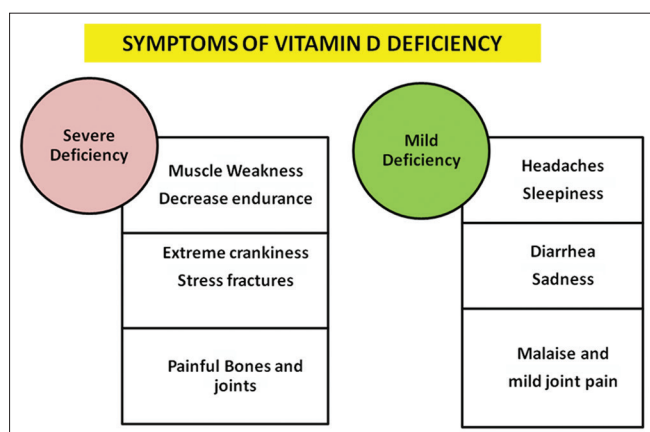


Figure 4: Symptoms of Vitamin D deficiency

such as 400 IU, 1000 IU, 2000 IU, 4000 IU, 5000 IU, and 50000 IU Vitamin D3.^[14]

DEFICIENCY OF VITAMIN D AND ITS SYMPTOMS

Insufficient Vitamin D from the sources or its deficiency will lead to different types of diseases in different age groups and gender, as shown in Table 1. For maintenance of Vitamin D status in the body, only natural source is not sufficient, and there is a requirement of both sunlight and Vitamin D fortified rich food.

The daily Vitamin D supplement for breastfed infants is 400 IU from mother's milk to prevent rickets in the body and for the maintenance of bones and calcium levels. Adults too are facing high threat of Vitamin D insufficiency with an increase in age. With aging, their skin is not able to synthesize sufficient Vitamin D. Moreover, they limit themselves indoors with less exposure to sunlight and less dietary intake of animal sources. As a whole, this leads to

Table 2: Treatment available for Vitamin D deficiency

Serum 25(OH) D	Treatment	Loading dose	Duration	Maintenance therapy
<30 nmol/L (deficiency)	Cholecalciferol Fultium D ₃ 20,000 units	2 capsules (40,000 units)	Once a week for 7 weeks	Patients with documented Vitamin D deficiency and unrectifiable cause are recommended maintenance therapy Patients with high risk are asked for lifestyle modifications which if not possible is shifted to an on-going maintenance dose
	Fultium D ₃ 3,200 units	1 capsule daily	Up to 13 weeks	
	InVita D3 oral solution 25,000 IU/ml (1 ml ampoules) For adults with swallowing difficulties	50,000 IU/week (2 ampoules)	6 weeks	
30–50 nmol/L (insufficiency)	Colecalciferol as fultium D ₃ 20,000 units	1 capsule (20,000 units)	Once a week for 7 weeks	
	Fultium D ₃ 3,200 units	1 capsule daily	Up to 6 weeks	
>50 nmol/L (sufficient)	Reassurance and lifestyle advice recommended			
>250 nmol/L (potentially toxic)	Very rare except in conditions such as liver disease, renal disease, primary hyperparathyroidism, and inflammation			

weakness, reduced mineral density, musculoskeletal pain, osteoporosis, and high chances of fractures and falls.^[15] Lately, this deficiency linked with several health issues such as Type-2 diabetes, sleep disorders, cancer, fractures, cardiovascular diseases, muscle weakness, painful joints, and asthma and their symptoms from mild-to-severe will prevail, as shown in Figure 4.

REASONS - VITAMIN D DEFICIENCY

There are a number of reasons for Vitamin D deficiency. Some main causes are limited sun exposure, vegetarian diet, darker skin, lifestyle, and obesity, as shown in Figure 5. The reasons for these causes are discussed as follows:

1. People who spend their time indoors or wear clothes that cover a large portion of the skin will have more chances of Vitamin D deficiency due to lack of sunlight exposure.
2. People who are vegetarian having more chances of Vitamin D deficiency because a major Vitamin D source is based on animal such as fish, egg yolks, and fish oil.
3. The people who are having dark skin and a higher level of melanin reduce their ability to form previtamin D₃. As with sunlight exposure, melanin competes with provitamin D₃ form available and limits its photolysis to form previtamin D₃.
4. Obesity is another major cause of Vitamin D deficiency because it is fat-soluble and easily absorbed from blood by fat cells.^[10]

PREVENTION AND TREATMENT OF VITAMIN D DEFICIENCY

Sunlight is one of the major Vitamin D sources which will help the skin to produce sufficient Vitamin D usually required for bone formation and its strengthening, reduce inflammation,

boost up the immunity, and give protection against cancer of the skin. Sunlight emits the high-energy UV photons which will penetrate into the layer of epidermis and photolyze the provitamin D₃ to previtamin D₃. The latter isomerizes to form Vitamin D₃ in 2–3 days.

Daily exposure to sunlight for 10–30 min twice a week is very helpful in Vitamin D production in 10–3 PM without sunscreen. Peoples who are having fair skin should get exposure to the sun in the cooler months.^[16]

People should sit in open for Vitamin D production from sunlight exposure because getting sunlight through a glass window will block the UV B rays as glass window absorbs the same and will not allowed to reach to the skin.

Furthermore, the use of sunscreen must be avoided during sunlight exposure for 10–30 min because the sun protection factor present in the sunscreen blocks the UV B ray absorption capability of the skin which is going to affect the production of Vitamin D.^[17]

Some natural occurring foods which are Vitamin D source are raspberries, blueberries, and pomegranates. Some milk products such as cheese and yogurt are also rich in Vitamin D. Almond milk is having 100 IU Vitamin D which is a healthy alternative source of cow's milk. These foods are rich in antioxidants and essential fats which will protect the skin damage from the sun and strengthen the skin cells and protect them from sun damage. Mushroom is also one of the sources of Vitamin D₂ which will produce with UV B rays from sunlight. Some fishes such as salmon, trout, mackerel, tuna, and eel are a very rich source of Vitamin D.^[18]

Vitamin D deficiency can be overcome by taking cholecalciferol, which is available in the form of suspension, capsule, sachet, and injectable form. Cholecalciferol is also

Table 3: Different delivery system available for the treatment of Vitamin D deficiency

Route	Delivery System	Approach	Remarks	Uses	Reference
Transdermal	Combinations of nanoparticles and microneedles	Vitamin D3 encapsulation in Poly (lactic-co- glycolic acid) (PLGA) nanoparticle and coated on solid microneedles	Better release profile in comparison to ointment base	In Vitamin D deficiency	[22]
	Polymeric microneedle (MN) arrays	Biodegradable bilayered MN arrays contained nano-microparticles	Triphasic release with sustained profile	Targeted delivery of Vitamin D	[23]
	Self-assembled vesicular structures	Alpha-tocopheryl phosphate and di-alpha-tocopheryl phosphate (two phosphorylated forms of Vitamin E)	Increase in skin absorption	Targeted delivery of Vitamin D	[24]
	Oil-in-water nanoemulsion	Lipophilic Vitamin D encapsulation in fish oil	Increased bioavailability when encapsulated in comparison to nonencapsulated Vitamin D	In Vitamin D deficiency	[25]
Oral	Nanostructured lipid carriers (NLCs)	Octyl octanoate used as a substitute for miglyol	Increased Vitamin D3 intestinal absorption	Fortifying Food beverages	[26]
	Nanostructured lipid carriers (NLCs)	NLCs are stable in gastric fluid and released Vitamin D3 (more than 90%) in simulated in testinal fluid	Enhancement in oral bioavailability	In Vitamin D deficiency	[27]
	Oil in water emulsions	Lipophilic vitamins solubilized due to mixed micellar formation	Poor <i>in vitro</i> – <i>in vivo</i> correlation	In Vitamin D deficiency	[28]
Oral	Nanocapsules	pH-regulated Gemini amino acid surfactant vesicles	Fabrication of assembled micelles and vesicles based on their interaction	Nutritional supplement	[29]
	Bile salts lipase polymeric film infused minitabket	Enhanced cholecalciferol diffusion from the bioactive association platform	Better <i>in vitro</i> and <i>in vivo</i> performance	Increased delivery of cholecalciferol	[30]
Oral	Oil in water nanoemulsion	Preparation of nanoemulsions with long chain triglycerides	Effect of carrier oil on bioavailability of Vitamin D3 was evaluated	Nutraceuticals	[31]
	Protein based microspheres	Water soluble proteins obtained from egg white, i.e., bovine protein beta-lactoglobulin and lysozyme used to increase bioavailability of Vitamin D	Improved Vitamin D release and stability	Oral delivery of Vitamin D	[32]
Oral	Oil in water nanoemulsions	Encapsulation of lipophilic nutraceutical lipophilic nutraceutical for stable formulation	Stable formulation at ambient temperature	Oral delivery of Vitamin D	[33]
	Nanoemulsions	Improvement in drug solubility and drug dissolution rate	Increased Vitamin D3 absorption in the nanoemulsion form	Treatment of asthma	[34]

(Contd...)

Table 3: (Continued)

Route	Delivery System	Approach	Remarks	Uses	Reference
Oral	Carboxymethyl Chitosan-soy protein isolate complex nanoparticles	Simple ionic gelation method used for carboxymethyl chitosan and soy protein isolate	Controlled release of drug	Nutraceuticals	[35]
	Poly(lactic acid) (PLA) microspheres	Solvent evaporation technique was used for preparation of PLA microspheres	Near-to-zero-order steady drug release pattern over 10 weeks	Diabetic periodontitis	[36]
	Multifunctional hydroxyapatite and poly (D, L-lactide-co-glycolide) nanoparticles	Drug desorption and slow delivery is due to degradation pattern of PLGA	Nanoparticles are active fillers of bony defect	Localized delivery	[37]
	Casein micelles	Casein as a protein self-assembled to incorporate Vitamin D using ultra high pressure homogenization method which provided stability to it against thermal and oxidative degradation	Increased bioavailability	Nutraceuticals	[38]
Injectable	Beta-glucuronides	Conjugation of active molecules in a β -conformation link to increase the water solubility of compound	Greater gene upregulation of the Vitamin D-dependent 24-hydroxylase gene (Cyp 24)	Inflammatory bowel diseases	[39]
	Microsphere	Poly (lactic-co-glycolic acid) microspheres loaded with cholecalciferol (CL)	Zero-order release kinetics was observed	Vitamin D deficiency	[40]
	Hydrogel	ABA triblock copolymers of Vitamin D-functionalized polycarbonate and poly (ethylene glycol)	Enhanced accumulation in the tumor tissue	Metastatic colorectal cancer	[41]
	Cationic liposomes	Cationic liposomes that are adsorbed on anionic hollow microspheres via electrostatic interaction for co-delivery of 1,25(OH) 2D3 and doxorubicin	Synergistic anticancer effect	For cancer treatment	[42]
Topical	Propellant-free foam	Incorporation of lipophilic cholecalciferol and hydrophilic salicylic acid in one system	Non-irritant dermal product	Psoriasis	[15]
	Nanospheres	Hydrolysis and photodegradation of Vitamin D3 prevented by polymeric nanospheres	Enhanced delivery of Vitamin D3	Skin delivery and stability of Vitamin D3	[43]
	Solid lipid nanoparticles	Epidermal and dermal targeting due to the solid lipid nanoparticles	Decreased the epidermal thickness and increased melanocyte count as compared to marketed formulation, Daivobet	Psoriasis	[44]

(Contd...)

Table 3: (Continued)

Route	Delivery System	Approach	Remarks	Uses	Reference
	PEGylated liposomes	PEGylation increased the liposomal stability as well as skin penetration	Accumulation of drug in skin	Delivery through skin	[45]
	Liposome	Liposomes in gel state found to be favorable for epidermal targeting of calcipotriol	Increased penetration and delivery regulated through skin	Skin delivery	[46]
	Nanoemulsion gel	Incorporation of clobetasol propionate (CP) and calcipotriol (CT) in single formulation	High penetration and low skin irritation potential	Psoriasis	[47]

included in many fixed-dose combinations of calcium and vitamins as shown in Table 2.^[18,19]

A combination of sunlight exposure, nutrition, food, and supplements is required for sufficient Vitamin D level in humans throughout the year.^[20,21] Different delivery systems reported for the treatment of Vitamin D by numerous scientists are shown in Table 3.

CONCLUSION

In today world, Vitamin D deficiency is increasing day by day due to unawareness of the peoples regarding sun exposure and Vitamin D-enriched food intake. This deficiency is common in all age groups, and various factors aggravate the condition and lead to insufficiency. Exposure to sunlight is having the major role in providing sufficient amount of Vitamin D. Everyone should sit in the sun at least for 15 min daily without applying sunscreen so that UV B rays reach to the skin and Vitamin D production will be there. Some plant and animal sources are also there in which a sufficient amount of Vitamin D is present such as fishes, mushroom, and milk products. Different dosage forms are available in the market for the treatment of the hypovitaminosis D such as tablets, capsules, injectables, suspensions, sachets, transdermal patches, nanostructured lipid carriers, and emulsions.

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