REVIEW ARTICLE

Vitamin D deficiency: Plethora of Etiological Factors Prevalent in Pakistan

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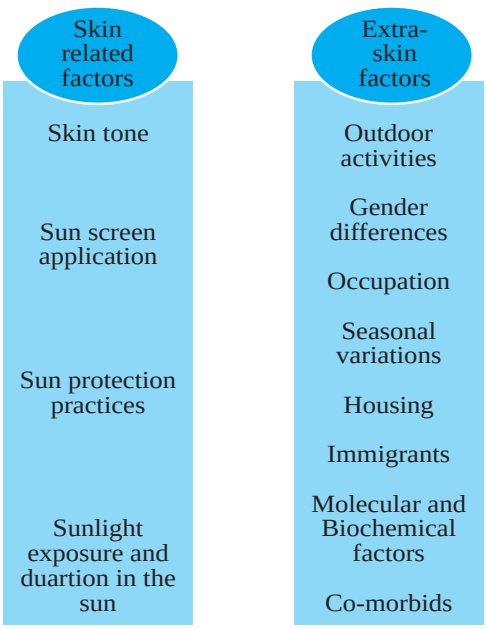
ABSTRACT:
Vitamin D, known as cholecalciferol, is a lipid soluble vitamin. Vitamin D (VD) has tremendous array of functions in the body; especially it plays a vital role in the health of the skeletal tissues. It strictly cannot be regarded as a vitamin since a substantial amount of the vitamin can be produced by the effect of sunlight on the skin. The insufficiency or deficiency of VD is growing worldwide and has assumed a pandemic situation. There are various factors contributory towards the development of vitamin D deficiency. Even in Pakistan, where sun drenched climate prevails, this alarming situation is growing and getting worse day by day. There are copious factors; like pervasiveness of sun protection practices, improper exposure to sun, lesser avenues of outdoor recreational activities, gender hindrances, biological factors etc. Lack of awareness and negligence are making this situation go even grim. In this review, the contributory factors, especially those more widespread in Pakistan are kept in view and are amalgamated in this article. Recent literature from our part of the world and after that from Asia had been preferred so that our population could connect, relate and benefit from it well.
Keywords: Vitamin D deficiency (VDD), Sunlight exposure and vitamin D deficiency, Vitamin D deficiency in Pakistan, Vitamin D deficiency in Asia, Vitamin D deficiency in women.

INTRODUCTION:

Cholecalciferol, renowned as Vitamin D; by the definition cannot be stringently considered as a vitamin, since it can be manufactured by the largest organ of the human body, the skin.[1] Cholecalciferol is a lipid-soluble vitamin. The types of Vitamin D are Vitamin- D_3 or cholecalciferol, regarded as the most active form and Vitamin D_2 or ergocalciferol. Vitamin D has tremendous array of functions to perform in the body, it escalates the absorption of calcium, helps in maintaining the serum profiles of calcium and phosphorus thus enabling the healthy metabolism and mineralization of bones.[2] It influences the bone osteoblasts and osteoclasts and aids in bone growth and remodeling.[3, 4, 5] Thus normal levels eliminate the development of osteomalacia in adults and rickets in pediatric populations. Vitamin D mediates its actions via acting upon nuclear receptors. Other documented roles are regulation of cell proliferation, differentiation and apoptosis[1], immune and neuromuscular functions.[3, 4, 6, 7] Vitamin D obtained from sunlight and the external sources; like food and supplementation is the inactive or inert form. Active form of the vitamin is acquired after successive hydroxylation. Initial hydroxylation occurs in the liver, converting it to 25-hydroxyvitamin D [25(OH)D] or calcidiol. The second one occurs in the kidneys producing the active form 1, 25 dihydroxyvitamin D or calcitriol[3]. Vitamin D is sparse in diet, and unless diet is fortified, cannot replenish the lack of vitamin D. Our diet is proficiently poor in vitamin D, as only fortification of the diet; like butter and milk can provide VD. 25-hydroxy D (25[OH]D) is the form widely used as an indicator of vitamin D level in the body. 25-hydroxy D (25[OH]D) has an advantage of long half-life, 15 days.[8] It gives a fairly good idea about the circulating levels of vitamin D but has no role in reflecting the levels of storage form. On the other hand, the active form, 1, 25 dihydroxyvitamin D or calcitriol is generally not considered to be a good indicator of vitamin D since it has a short half-life, 15 hours and the levels are tightly regulated by endocrine and mineral levels of the body. Vitamin D deficiency (VDD) is now being regarded as a global pandemic, affecting about 1 billion.[9, 10, 11] Pakistan despite of its equatorial position over the globe, has around 20-83% affected. In the review, the author is trying to sum up the factors responsible for VDD preponderant in Pakistan.

Figure-1 shows the factors affecting vitamin D levels in the body.

Figure: 1



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METHODOLOGY:

A comprehensive literature search was being conducted from 1990-2015. The search engines utilized were Google Scholar, Pubmed, HEC Digital Library, Springer link and Medline. The key words used were vitamin D deficiency (VDD), vitamin D deficiency in Pakistan, sunlight and vitamin D, vitamin D deficiency in Asia and vitamin D deficiency in women. In the beginning of literature search exploring with the said keywords about 50 articles were found. By adding vitamin D deficiency in Pakistan, the articles based on Pakistani data related to vitamin D deficiency (VDD) and then with the data of South East Asia were filtered. 35 original articles were found, the articles having foreign data were disregarded and so about 7 articles were filtered out and the rest were used in the write-up. In addition to the keywords that were used, the references of the articles were further elaborated to find more literature. In this piece of review, the preponderant factors of VDD were described, and the etiological reasons more common in our part of the world were explained with the help of Pakistani and Asian literature.

VDD FACTORS ASSOCIATED WITH SKIN:

Skin Tone: The complexion of skin and production of VD are closely linked .[9] Lighter skin tones are found to be associated with greater production of vitamin D (VD) due to the action of ultraviolet radiation (UVR), the vice versa is true for the dark complexioned population. Ultraviolet B (UVB) is the kind of radiation that is involved in the photosynthesis of VD. The melanin in the skin is associated to confer natural sun screen property, and thus greater protection against the penetration of UVR. It has been proven that darker skin tones (Negros) need around 6 times the standard intensity of UVR to produce VD as is produced in lighter skin tone people (Caucasians).[12] Melanin is efficient in absorbing UVB and increased pigmentation of skin containing augmented amount of melanin impedes cutaneous synthesis of VD.[13, 14, 15, 16]

Application of Sun Screen: Pakistan lies in the temperate zone of the world, and thus has a diverse climate from tropical to temperate. In most regions of Pakistan the weather tends to be relatively hot and sunny. Our country has ample sunlight, so for enhancement and maintenance of fair complexion, the use of sunscreens is widespread in our population, especially in women. Use of sunscreen is shown to be beneficial against the harmful effects of skin tan, sunburns, premature aging and the deadly danger of skin cancers. Sunscreens are enriched with para-aminobenzoic acid, which confers its beneficial effects of skin protection. Cutaneous application of sunscreens have also illustrated to reduce the photosynthesis of cutaneous VD_3 which prevents photo isomerization of 7-dehydrocholesterol to previtamin D_3 in skin.[17] Sunscreen protector of SPF 15 reduces about 99% of UVB radiation, thus greatly diminishing VD conversion.[13]

Sun Protection Practices: Sunlight is the major source of vitamin D production. UVB is associated with the cutaneous conversion of VD_3. Any factor that interferes with UVB infiltration of skin, provides hindrance in the production of VD. Sun protection practices and "no exposure to sun at all" is putting the mankind at jeopardy of developing VDD.[18] Some ethnic and religious practices, like observation of veiling are also associated with reduced sunlight exposure and thus VDD.[19, 20] But studies from Bangladesh have proved that veiling has no direct connection with the development of VDD as those who do not observe it are at equal chance of developing VDD.[21, 22, 23, 24, 25]

Sunlight Exposure and Duration in the Sun: Some people, who are better exposed to sun, use sunlight as their source of production of VD_3. UVB with a particular wavelength of 290-320 nm penetrates the skin and is linked with the production of VD. Weather, cloud cover, latitude,[19,26,27] haze, melanin content etc have association with altered productions of VD. The timing to sunlight exposure is also a key factor, the time of the day with most intense UVB radiations is 10 AM to 3 PM. Exposure during these timings have proved to produce a substantial amount of VD. 5-30 minute exposure of face, arms, legs and back with no sun protection practices twice a week is proven to produce ample amount of VD.[3,28,29] Cloud cover diminishes the intensity of UV rays to about 50% and thus its ability to produce VD .[30, 31] UVB does not pass through glass, the exposure to sunlight with glass windows does not confer any good.[3]

EXTRA-SKIN RELATED VDD FACTORS

Outdoor Activites: Healthy outcomes are produced by outdoor recreational activities, like swimming, cycling and outdoor games.[32] It has been shown that home bound subjects are prone to develop VDD.[33,34] Women and elderly are at risk of developing VDD as they have lesser chances of going outdoor.[19] On the other hand, children and younger age group are found to have higher values of VD, seemingly linked with their outdoor playing activities.[35,36,37,38]

Gender Differences: Pakistan regardless of its equatorial location over the globe and sun drenched luminous climate; VDD is prevalent and it is more common in women[21]**.** Alarming statistics show that 90% of premenopausal women have 25-hydroxyvitamin D (25[OH] D) less than 20 ng/ml. Decreased values of VD are associated with negative skeletal outcomes and predisposition of women of child bearing age towards osteopenia and osteoporosis. The literature also supports the effective role of VD in obstetrics, like prevention from premature births, neonatal neurodevelopment insufficiencies etc. Our females, as compared to their male counterparts get lesser avenues of obtaining optimal sunlight and therefore more discriminately develop VDD. Similar facts have been revealed by a study conducted in Karachi that showed VDD to be more common in women as compared to men.[39] This gender discrimination of VD levels is also shown in East African men and women, in which women are shown to have lesser values.[40,41] Studies conducted elsewhere in Asia have also established the fact of high disposition of women towards VDD.[21,22,42,43]

Occupational Behaviour: As with the people with

outdoor recreational and leisure activities, professions coupled with outdoor exposures have proved to provide better UVB exposure,[9,44,45] good exposure to sunlight and thus better values of VD. The proper, appropriately timed better contact of sunlight are allied with superior levels of 25[OH]D and consequently lesser chances of the development of VDD. Occupations like gardeners, delivery boys, daily vendors, all professions related with travelling are less susceptible to develop VDD.[9] Various studies have shown dissimilar serum values of 25[OH]D in groups of people having varying occupations, like in-house bound and outdoor working people.[9,21] The people with internal or domestic chores have shown to exhibit lower serum values of 25[OH]D as compared to those whose activities are outdoors.

Seasonal Variations: Winter season and less intensified sunlight are counterparts and they go hand in hand. In Pakistan, majority of its provinces and cities face some extreme weather like Balochistan, Islamabad, Lahore, interior Punjab and all of Khyber pakhtoon khuwa (KPK). In some parts of Pakistan smog and cloud cover diminishes the sunlight even more, like in Lahore and Sargodha. Such seasons are coupled with lower serum values of 25[OH] D as compared to the values obtained in summer,[46] as in summer there is abundance of sunlight, and photosynthesis of Vitamin D_3 ensues uninterrupted. Many studies document VD sufficiency in hot climates,[47] like a study conducted in Karachi exhibited this seasonal predilection. In winter season, the total sunshine hours get reduced. In Karachi, the total sunshine hours in January are calculated to be 271 hours, as compared to 282 hours in April and 304 hours in May.[39] The total sunshine hours in other diverse areas of Pakistan may have even more fluctuations. The photosynthesis of VD_3 and sunlight can have said to be directly proportional to each other.

Housing: Way of living and housing also plays a key role in the development of VDD. Town of residence, house architecture and avenues for the better aeration and natural light are pertinent factors in this regard. A study conducted had shown that downtown dwellers and thickly populated housing areas have positive links with the lesser amount of sunlight provision, and thus progression towards the development of VDD.[48] A study conducted in Karachi showed VD levels in posh localities like DHA and Clifton to be healthier as compared to Saddar and Gulshan-e-Iqbal, which can be accounted for the better socioeconomic background and literate attributes of the dwellers of the said areas.[49] To cater the wildly rising population, living in apartments seems to be a solution. But apartment dwellers get limited access to air and light. The same fact has been documented by another study, that showed Arabian ladies living in apartments are prone towards VDD than women living in villas.[50]

Immigrants: Substantial data is available that immigrants are at risk of developing VDD. In a study conducted in 1970 in United Kingdom (UK), 25[OH]D levels were first noted to be decreased amongst the immigrants of UK. This can in part be accounted for the total change in climate, sparse chances of obtaining sunlight,[31] and diet. Numerous researches have authenticated that migration to Western countries makes the non-western immigrants predisposed towards VDD as compared to the natives.[51,52] Oslo health study had revealed more than 90% of Pakistani immigrants to have low levels of VD as compared to 14% of their Norwegian counterparts[53]. The immigrants of origin other than Pakistan can also fit in this factual frame, as stated by the Oslo health study. The similar insufficiency can also be found in refugees, as their serum levels of 25[OH]D have validated the same results.[54] Research shows lowest levels of VDD among refugees from any region of the world to be 59% and overall more than 70% of the refugees have VDD.

Molecular Biological Factors: Although alterations in VD status are always allied with the decreased exposure to sunlight, diet, outdoor activities, but it also has positive linkages with molecular factors as well. VDD can also result due to genetic factors, notably the one genetic determinant on which research data is available is rs4588 (Styl) polymorphism, that causes faulty production of vitamin D binding protein. Literature documents the genotype of vitamin D binding protein (DBP) to affect the total 25[OH]D levels.[21] Apart from DBP, incongruity in the genes programming the vitamin D 25- hydroxylase enzyme CYP2R1 and its receptor (VDR) have also been accounted for the development of VDD.[55] rs4588 (Styl) polymorphism in the vitamin D binding protein are found to be consistent with lower levels of VD in one of the studies conducted upon the women of child bearing age in Lahore.[56,57]

Biochemical Factors: Dietetic factors play a vital role in bone homeostasis. Minerals like calcium, phosphorus and some organic factors are integral in maintenance of skeletal tissues. VD, Calcium and parathyroid hormone (PTH) are components of one cycle. Variation/ imbalance in any one can vary the levels of other components in the cycle. These three components are the key factors in normal health of the osseous/skeletal tissues. The absorption of calcium is dependent upon VD. Calcium initiates, maintains and regulates the mineralization of bones and keeps the secretion of PTH in check. The lower levels of calcium causes enhanced release of PTH, and thus PTH reverses the insufficiency of calcium in the serum by demineralization of the bone. Skeletal tissues produce Alkaline phosphatase (ALP), an isoenzyme. The raised serum levels of this isoenzyme are related with certain skeletal diseases, osteoporosis is one of them. The secretion of alkaline phosphatase (ALP) also becomes raised when PTH is trying to revive the insufficient serum calcium levels. Vitamin D deficiency has been linked with altered serum levels of several minerals. Serum Calcium is indispensable in the accrual of bony mineralization. Vitamin D insufficiency is associated with flawed mineralization of bones, secondary hyperparathyroidism and negative musculoskeletal outcomes. VDD and resulting low serum calcium level further augment this vicious cycle of secondary hyperparathyroidism.[57] Low levels of

calcium, phosphates and high levels of Alkaline phosphatase have associations with VDD but any strong positive link is yet to be established.[21] Whereas low levels of calcium and high values of alkaline phosphates (ALP) can be related to severe VDD.[31]

Comorbids: Low levels of VD are associated with comorbid, or it may be said that lower levels of VD struck affecters are at higher risk of contracting other diseases. Bone pain, osteopenia and occult osteomalacia is highly prevalent in Pakistani healthy women, mothers and in their breast fed infants.[31] VDD has also been seen in bed ridden patients, women with obstetric problems and hip fractures.[31] As in other parts of the world, Tuberculosis ranks high in increasing the global illness burden, and as an estimation responsible for 1.5 million deaths annually.[58] It had been documented in a Pakistani research that VDD may precede the onset of tuberculosis. Although it cannot be said that VDD and tuberculosis have direct association with one another. Chronic renal disease patients are at high risk of developing VDD. No association had been found between the development of hypertension and VDD.

Table: 1

Life-stage group	RDA (IU/D)	Serum 25[OH]D level corresponding to RDA
1-70 years	600	20ng/ml
70+ years	800	20ng/ml
0-12 months	400	20ng/ml

CONCLUSION:

Based upon the above described factors, lack of sunlight exposure and enhanced risk of adopting VDD, the author recommends supplementation of the vitamin as prescribed by Institute of Medicine (IOM) in table-1. These values are designed to regulate the serum value of 25[OH]D at 20ng/ml, at which maximum of the bodily needs are met by 97.5% of population[59]. VD supplementation should be advised to masses to exclude the potential deleterious effects VDD may have on our lives.

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