

A Review of Vitamin D in Pakistani Population

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Abstract

Vitamin D is a secosteroid which has an important function in bone metabolism and immunomodulation. Decreased levels of vitamin D are associated with many critical diseases like cardiovascular, cancer, diabetes, tuberculosis and osteoporosis. Low vitamin D can cause obesity and restrict bone growth and bone health in children and adults. Despite being near to equator, Pakistani citizens suffer from low vitamin D levels making them prone to many diseases and there is no guidelines for the treatment of vitamin D deficiency in general and diseased population of Pakistan. This review highlights the prevalence of vitamin D in different disease as well as healthy groups of Pakistani citizens through literature search. Further it also reviewed the literature available on knowledge of clinicians about vitamin D deficiency and its affects.

Key words: Vitamin D, Pakistan, level, deficiency.

Introduction

Vitamin D is a hormone precursor involved in variant functions as calcium homeostasis, immune modulation, and anti-inflammatory process. Phytoplankton species (*Emiliani huxleii*) as old as 750 million years ago, were the source of vitamin D production catalyzed by UVB rays.¹ Vitamin D insufficiency is a common finding worldwide. Levels vary in different areas depending on the demographic features, food fortifications, geographical locations, sun seeking behavior and seasons. It has been reported that a billion people globally have low serum vitamin D levels² but majority are asymptomatic, making it clinically difficult to detect.

A large population of Pakistan is suffering from vitamin D insufficiency which may be occurring due to low intake of vitamin D rich food or less sun exposure or other co-morbidities like cancer, diabetes, osteoporosis and cardiac problems. There is scarce data on vitamin D

deficiency/ insufficiency and its consequences, on Pakistani population.

Vitamin D Physiology

Vitamin D is a secosteroid found in two major forms i.e. vitamin D₂ and vitamin D₃. Vitamin D₂ is also known as Ergocalciferol which is present in plants, and a few fish, while vitamin D₃ also known as Cholecalciferol, is synthesized in the skin when exposed to the sunlight. There are two ways to fulfill vitamin D₃ requirements; one is through foods rich in vitamin D₃ such as mushrooms and sea foods and the other is by exposing skin to the UV light.² The time required to produce sufficient vitamin D₃ from the skin depends on the strength of the UVB rays, the time spent in the sun and the amount of pigment present in the skin.²

Synthesis of Vitamin D₃

The synthesis of vitamin D₃ starts in keratinocytes and dermal fibroblasts. A precursor of vitamin D, 7-Dehydrocholesterol (7-DHC), is secreted on skin surface³ and is converted by UVB radiations (290–315 nm) into pre-cholecalciferol (pre-D₃). Pre-cholecalciferol forms cholecalciferol (D₃) after undergoing thermal isomerization. Cholecalciferol is absorbed in the skin and blood and is transported to the liver by a transporter α -2 globulin vitamin D-binding protein, VDBP.⁴ In the liver, Cholecalciferol is converted into prohormone calcidol 25(OH) through an enzyme called vitamin D 25 hydroxylase.⁴ Calcidol is converted into calcitriol (1,25(OH)₂D) in the kidneys. Plasma calcitriol is transferred to targeted organs by the help of vitamin D binding proteins (VDBP).³ Calcitriol is also synthesized by immune cells like monocytes and macrophages, where it acts as a cytokine.⁴ Calcitriol is a

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RJ and FG have done the conceptualization of project. RJ collected data by reviewing and did literature search. Statistical analysis, writing, drafting and revision of the manuscript was done by RJ and FG.

potent ligand of the vitamin D receptor and mediates the majority of physiological actions of vitamin D.⁴

Role of Vitamin D3

Vitamin D and osteoporosis is caused by decrease in bone mineral density due to low calcium and vitamin D3 in the body. Its prevalence is high in Pakistan. A study from Peshawar on 1000 post menopausal women reported osteoporosis in 55% aged between 45-54 years and this increased to 97% in those aged between 75-84 years.⁵ A previous survey reported 50% females from rural areas of Peshawar to be having low bone mineral density and low vitamin D3 status resulting in osteoporosis.⁶ Another study on rural women from Peshawar reported osteoporosis/osteopenia in 75.6% with possible causes being low dietary intake of vitamin D3 and lack of sun exposure due to covering their body by "burqas".⁷ A community based survey in Karachi on 305 premenopausal females aged above 18 years (mean age 31.97±8.0 years) showed vitamin D3 deficiency in 90.5%.⁸

Vitamin D3 supplementation prevents bone loss, but this supplementation needs to be supported with increased calcium intake otherwise only vitamin D3 does not affect bone density and improve fractures caused by osteoporosis.⁷

Vitamin D Status in Neonates and Children

Vitamin D deficiency in mothers results in serious health issues in off springs like improper skeletal and brain development, diabetes, asthma and schizophrenia.⁹ Its deficiency in childhood results in diseases like rickets, slow brain development and low immunity.⁹

In Pakistan, vitamin D deficiency is seen in all age groups. A study on 349 pregnant women from Karachi having mean age 28.52±3.4 reported vitamin D deficiency in 70% with their 203 neonates also vitamin D deficient. Within the group, 155 neonates had mothers who were vitamin D deficient.⁹ Another study from Karachi on 50 pregnant females reported 46% to be vitamin D deficient with 88% of their newborns also deficient in vitamin D. This study highlighted maternal vitamin D was significantly dependant on sun exposure ($p < 0.007$) and diet ($p < 0.01$).¹⁰

Breast fed infants can also suffer from vitamin D deficiency if their mothers are deficient in vitamin D. A study from Islamabad on 75 infants (4-12 months) reported 66.6% to be vitamin D deficient with 41% mothers also deficient.¹¹ Rickets was reported in 85.3% breast fed children as compared to 40% formula fed based on x-rays, serum calcium, phosphorus and alkaline phosphatase levels.¹²

Vitamin D and Cancer

In Asian countries, the role of vitamin D in breast, colon and prostate cancer has been widely studied. A study from Shaukat Khanam Hospital, Lahore on breast cancer patients assessed the relation of vitamin D

with grade and stage of tumor and found no significant relationship.¹³ Another study from Karachi in newly diagnosed leukemia patients (acute myeloid leukemia and acute lymphoblastic leukemia) aged 1-60 years, concluded that insufficiency of vitamin D was evident in majority of patients which was further reduced after remission when compared with untreated group.¹⁴

Vitamin D and Tuberculosis

Tuberculosis represents a major health issue in developing countries including Pakistan. Although there are various reasons of drug resistant tuberculosis and late sputum smear conversion.¹⁵ A study on 100 TB patients reported a significant difference between vitamin D levels and sputum smear conversion time ($p < 0.001$).¹⁵

A randomized double blind multi centre placebo control trial on 259 smear positive patients aged ≥16 years concluded that high doses of vitamin D3 supplementation could lead to marked clinical and radiological recovery in TB patients along with immunity boosting in vitamin D deficient patients.¹⁶

Role of Vitamin D in Cardiac Diseases and Diabetes

Over 25-33% of all deaths in Pakistan are related to heart diseases or diabetes.¹⁷ A study from Lahore on non diabetic subjects (88) reported 98.5% to be vitamin D deficient and showed strong negative correlation between vitamin D3 level and LDL levels and a strong positive correlation between vitamin D3 level and HDL levels.¹⁷

Another case control study from Aga Khan University Karachi on adult diabetic patients showed significant association between vitamin D levels of diabetic and non diabetic patients. Almost 63% cases were vitamin D deficient while rest had insufficient levels. Direct association was seen between socioeconomic status and vitamin D levels.¹⁸

Vitamin D in General Population

Vitamin D levels in general asymptomatic population of Pakistan have also been studied extensively. A study from Islamabad on 737 people (mostly women=76.2%) showed 71.5% to be vitamin D deficient. Within gender, more females were deficient (56.2%) than males.¹⁹ Another study from Islamabad reported 82.8% prevalence of vitamin D deficiency and concluded inadequate sun exposure as the possible cause.²⁰ A study from Karachi on healthy adults aged 16-62 years reported 77.7% females being vitamin D deficient with majority (76.6%) exposing only face and hands to sun for 1-2 hours.²¹ Another study in 30-80 years reported 57.7% to be vitamin D deficient with significant association between low vitamin D levels and glomerular filtration rate.²²

A study from Karachi on 54 participants working indoor or outdoor areas reported 98% indoor participants to be vitamin D deficient/insufficient and showed a strong relation between sun exposure and

vitamin D levels ($p < 0.01$).²³ A study from Sargodha showed vitamin D deficiency in 36% population irrespective of the gender but found significant difference in vitamin D levels of those working indoor and outdoor.²⁴ A study from Lahore on healthy asymptomatic

adults found 25% to be vitamin D deficient while 73.7% had insufficient levels. They attributed this to sedentary lifestyle, low sun exposure and low vitamin D intake²⁵ (Table-1).

Table 1: Frequency of serum vitamin D levels in various cities of Pakistan.

City	Sample Size (n)	Mean Age Years	±SD	Frequency of Serum Vitamin D Levels					
				Deficient (%)	Cut Off (ng/ml)	Insufficient (%)	Cut Off (ng/ml)	Sufficient (%)	Cut Off (ng/ml)
Islamabad	737	36.3(15-75)	----	71.5	----	11.3	----	17.2	----
Islamabad	351	46.03(13-65)	16.8	82.8	<20	-----	20-30	17.2	>30
Karachi	300	48(30-80)	-----	57.7	<20	26.6	20-30	15.7	≥30
Karachi	244	33.62(16-62)	12.6	76.2	<20	14.8	20-30	9.0	≥30
Sargodha	100	36.8(14-58)	-----	36	<20	10	21-29	54	>30
Lahore	80	47.2(40-60)	6.3	25	<10	73.7	10-29	1.3	>30

Table 2: Prevalence of 25(OH) vitamin D3 in Pakistan.

Ref	Place & Study Site	Study Year	Method Used	Number Tested	Deficiency <10ng/ml	Insufficiency 10-29ng/ml	Sufficiency >30ng/ml
19	FGSH, Islamabad	2014	Information not provided	351 both sexes	291	-----	60
23	Clinics, Sargodha	2013	ILMA	100 both sexes	36	10	54
10	Shifa Falahee, Shifa International Hospital, Islamabad	2013	Information not provided	75 infants	56 infants	9 infants	10 infants
				75 mothers	71 mothers	2 mothers	2 mothers
--	Hayatabad Medical Complex, Peshawar	2013	CMIA	260 females	208	39	13
18	Kulsum International Hospital, Islamabad	2012	ECLIA	737 both sexes	527	83	127
8	Liaquat National Hospital, Karachi	2012	ECLIA	349 mothers	243 mothers	106	-----
				349 neonates	203 neonates	-----	146
13	University of Karachi, National Institute of Blood Disease and Bone Marrow Transplantation, Department of pathology and Haem Oncology	2012	CMIA	86 (Leukemia) both sexes	27	55	04
16	University of Health Sciences, Lahore	2012	ELISA	88 both sexes	86	02	-----
5	Khyber Teaching Hospital, Peshawar	2011	ECLIA	107 (Post Meno) females	-----	99	08
7	Community, Karachi	2011	ECLIA	305 (Post Meno) females	276	16	13
21	Metropolis, Karachi	2011	RIA	300 both sexes	173	80	47
12	Shaukat Khanam Memorial Cancer Hospital, Lahore	2011	ELISA	180 females	86 breast cancer	4 breast cancer	-----
					69 control	17 controls	04 controls
24	Shaikh Zayed Medical Complex, Lahore	2010	ELISA	80 both sexes	20	59	01
15	Agha Khan University Hospital, Ojha Institute of Chest Diseases and Dow University Hospital, Karachi	2010	ECLIA	250 (TB) both sexes	-----	250	-----
20	Hospitals, Karachi	2007	ECLIA	244 both sexes	186	36	22

ECLIA: Electro chemiluminescence immuno assay, ELISA: Enzyme linked immune assay, RIA: Radio immune assay, ILMA: Immunoluminometric assay, CMIA: Chemiluminescent microparticle assay

Vitamin D and Obesity

There is an increasing number of obese population in Pakistan which is attributable to unhealthy foods and sedentary lifestyle. Genetic variation in vitamin D receptor have been correlated with body mass measurements²⁶ however, there is not much data on relation of vitamin D with obesity. In a genetic study on 100 subjects (50 obese, 50 non obese) between 18-45 years. vitamin D receptor, FOK 1 gene was mutated (ff=3) in 6% obese and was not mutated (ff=0) in any non obese person. Larger sample size was recommended to confirm this variation.²⁶

Knowledge of Clinicians about Vitamin D and its Management

A survey on 400 practicing clinicians in Karachi showed only 62% knew the dietary sources for vitamin D, 85% for active form of vitamin D, 27% for conditions favorable for sunlight absorption and only 45% knew about importance of sun exposure for the production of vitamin D.

Signs and symptoms, risk factors and diseases leading to vitamin D deficiency were known to 66%, 82% and 83% clinicians, whereas 63% were not aware of importance of vitamin D in cellular processes (such as immune system, anti proliferation etc) other than bone and muscle. Only 35% and 52% had knowledge about how to manage and treat (non affording) patients with vitamin D deficiency respectively.²⁷

Critical Analyses on Vitamin D Status

Vitamin D status is assessed by the measuring its storage form 25(OH) D which has a half life of 3 weeks rather than active form 1,25(OH) vitamin D which has a short half life of 6 hours.

It is unfortunate that most of the studies conducted in Pakistan published had no information regarding the time span between blood withdrawal and vitamin D test performance, questioning the variability in the results.

Vitamin D deficiency causing bone disease is linked with serum 25(OH) vitamin D levels of < 10 ng/mL worldwide.²⁸ Most of the data from Pakistan has reported a deficiency of < 20 ng/mL. Sub optimal levels (10-30ng/mL) of vitamin D are termed as *vitamin D insufficiency*. Defining vitamin D deficiency/insufficiency on the basis of 25(OH) D levels is still a matter of debate. Optimal levels of vitamin D are ≥ 30 ng/mL, however this cut off is applied regardless of age group and gender. Since every age has its own vitamin D requirement therefore, it is possible that optimal levels might differ. A large Pakistani population based study with age interval and gender is required to define the cut off levels for different age groups and diagnose deficient

or insufficient individuals who have no evidence of disease.

Scientists describe worldwide that "Population reference ranges for vitamin D vary widely depending on ethnic background, age, geographic location and the sampling season."²⁸ In northern latitude locations in particular, the level of vitamin D in 73% of the population is less than 20 ng/mL during winter season.²⁹ Thus, it is also important to determine geographical, seasonal, age, gender variations in 25(OH) vitamin D levels before describing vitamin D cut off levels. The cut off used by researchers in Pakistani population is given in Table-2.

Conflict of interest: None declared.

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