

# Vitamin D deficiency and diseases: a review from Pakistan

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## Abstract

**Objective:** Vitamin D deficiency is claimed to be associated with many diseases in the world populations. Many studies reported that vitamin D deficiency is quite prevalent in Pakistan. The aim of this review is to describe the current status of vitamin D deficiency in healthy individuals and in different disease conditions in this country. **Methods:** Search engines such as “Google Scholar”, “Medline and PubMed” were used by applying key words such as vitamin D deficiency, vitamin D deficiency and different disease conditions in Pakistani population. **Results:** Total 82 studies were included in which 12 studies showed vitamin levels less than 30 ng/mL in the healthy individuals (male and female) and 70 studies in different disease conditions. It found that about 64.6% healthy subjects had vitamin D levels less than 30 ng/mL. Moreover, 70 studies showed its deficiency in some diseases such as musculoskeletal, bone and periodontal problems, nursing mothers and children, tuberculosis, diabetes, cardiovascular problems and some type of cancers. **Conclusion:** The current status of vitamin D deficiency in healthy population and in several diseases and conditions are thoroughly discussed in this review. This review could be helpful to understand status of vitamin D and different aspects of vitamin D research in this population

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## **Abstract**

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Vitamin D deficiency is claimed to be associated with many diseases in the world populations. Many studies reported that vitamin D deficiency is quite prevalent in Pakistan. The aim of this review is to describe the current status of vitamin D deficiency in healthy individuals and in different disease conditions in this country.

### **Methods:**

Search engines such as “Google Scholar”, “Medline and PubMed” were used by applying key words such as vitamin D deficiency, vitamin D deficiency and different disease conditions in Pakistani population.

### **Results:**

Total 82 studies were included in which 12 studies showed vitamin levels less than 30 ng/mL in the healthy individuals (male and female) and 70 studies in different disease conditions. It found that about 64.6% healthy subjects had vitamin D levels less than 30 ng/mL. Moreover, 70 studies showed its deficiency in some diseases such as musculoskeletal, bone and periodontal problems, nursing mothers and children, tuberculosis, diabetes, cardiovascular problems and some type of cancers.

### **Conclusion:**

The current status of vitamin D deficiency in healthy population and in several diseases and conditions are thoroughly discussed in this review. This review could be helpful to understand status of vitamin D and different aspects of vitamin D research in this population.

**Key words:** Vitamin D, Vitamin D deficiency, Diseases, Pakistani population, Pakistan

### **How did you gather the information you considered in your review?**

The information present in this review article is gathered from online data sources such as “Google Scholar”, Medline and PubMed”.

### **What is the ‘take-home’ message for the clinician?**

The vitamin D deficiency is quite prevalent in Pakistani population and could affect different diseases. Therefore, it is worthwhile to consider the vitamin D levels in the management of such disease conditions which are described in this article.

### **Introduction:**

Vitamin D is an essential micro nutrient for wellbeing of a living individual (1). Sunlight plays an important role in its production in the body (1). It works as a pleiotropic hormone (2). Its deficiency in children is manifested by improper growth of bone commonly known as rickets (3). Previously, vitamin D was considered to only affect bone metabolism and calcium absorption, but later studies found its vital role in many other physiological functions in the body (4). It was found that almost all cell types exhibit vitamin D receptors (VDR) and all vital organs and tissues of the body are benefitted by vitamin D (5). Since past decades, much attention have been diverted to understand its role in different modalities such as diabetes mellitus, cardiovascular disorders, infections especially tuberculosis and some auto-immune disorders such as psoriasis and multiple sclerosis etc (5). Even some types of cancers such as prostate, breast and colon have been correlated with its deficiency (6, 7).

As Pakistan is a developing country and most of its population resides in the villages (8). Its geographical location (30.3753° N, 69.3451° E) makes it a country of proper sun light throughout the year (9). Due to the cultural norms, people wear dresses that cover the whole body. (10). Malnourishment in the villages and imbalanced diet in the urban settings are common problems in this population (11). Due to un-awareness and cultural norms, people could not get proper sun shine, therefore vitamin D deficiency is prevalent in all over the country (13).

This review would be helpful to understand the recent status of vitamin D deficiency in the healthy subjects and in different diseases and conditions in the Pakistani population.

### **Literature search:**

The search engines such as “Google Scholar”, “Medline and PubMed” were used by applying some search key terms; “Vitamin D Pakistan”, “Vitamin D diseases Pakistan”, “Vitamin D deficiency Pakistan”, “Vitamin D tuberculosis Pakistan”, “Vitamin D Children Pakistan”, “Vitamin D rickets Pakistan”, Vitamin D Women Pakistan”, “Vitamin D Cancer Pakistan” and “Vitamin D receptor SNPs Pakistan”.

### **Inclusion and exclusion criteria:**

All relevant studies found by above mentioned research terms were included. However, those studies were excluded which were conducted in Pakistani communities residing outside the country.

### **Status of vitamin D deficiency in healthy individuals:**

The results of a small-scale survey in a randomly selected asymptomatic subjects (n=300) of Karachi showed that 84.3% subjects had vitamin D levels less than 30 ng/mL (14). Female subjects (62.3%) were found more vitamin D deficient as compared to male subjects (55.2%). Another study in 858 subjects (351 males and 507 females) belonged to low income peri-urban community in Karachi (15) showed that 89.9% subjects had vitamin D levels less than 30 ng/mL. Female subjects were again found more vitamin D deficient than male subjects.

A study conducted in 500 subjects (29% males and 71% females) from the capital city Islamabad (13) showed that only 11% subjects had normal vitamin D levels (30 ng/mL).

An interesting study was conducted in the undergraduate medical students of different universities and health professionals to analyze the awareness about sunlight exposure and importance of vitamin D and the symptoms associated with its deficiency such as muscular pain and fatigue (16). The result of this study revealed that the participants were well aware about importance of vitamin D and the sign of its deficiency but most of the participants were found to avoid sun exposure intentionally, and only 8% of the participants knew about minimum sun light exposure to prepare vitamin D. Vitamin D levels were not measured in this study therefore it was difficult to correlate the symptoms such as body pain with vitamin D deficiency.

A similar study was conducted to analyze vitamin D levels in the students of a medical college of Peshawar which showed that 95.19% subjects had vitamin D deficiency. (17)

Another study was conducted to evaluate vitamin D status in 191 randomly selected medical students (86.43% females and 13.57% males) in Karachi which revealed that 96.4% students had low vitamin D levels (<30 ng/mL). (18)

A comprehensive study was conducted in healthy subjects (50 males and 38 females) of Lahore (19). The results showed that the average vitamin D in the 98.86 % subjects was below 30ng/mL. Subjects such as females, physically less active persons, indoor job holders, people with high socioeconomic status along with higher education and subjects having fair skin complexion were found more vitamin D deficient.

Another small-scale study was conducted in 244 (79% females and 21% males) healthy adults (20). Vitamin D deficiency (<30 ng/mL) was present in 76.2% subjects and showed significant correlation with the area of skin exposed to sunlight.

An observational study to assess the prevalence of vitamin D deficiency in healthy male subjects (n=180) was conducted in Hyderabad, Sindh (21). It found that 88.8% subjects had vitamin D deficiency (<30 ng/mL).

A large study was conducted to evaluate the effect of socio-economic conditions, different types of residencies and vitamin D levels in different localities of Karachi (22). A total of 4788 subjects were randomly selected. Results showed that 74% of the subjects had vitamin D deficiency (<30 ng/mL). Post hoc analyses revealed that subjects belonged to densely populated areas with low socio-economic status had significantly lower levels of vitamin D as compared with subjects of middle income and resident of less densely populated areas.

A study to evaluate the vitamin D levels in 305 premenopausal women in different parts of Karachi (23) revealed that 90.1% subjects had vitamin D deficiency (<30 ng/mL). The vitamin D levels were found to be associated with low sun exposure.

A large retrospective data analysis (audit) of 60937 specimens (30.7% male and 69.3% female) from all over the country revealed that 61.1% subject had mean log vitamin D value as 1.14 ng/mL (13.8 ng/mL). The specimen received from Khyber Pakhtunkhwa had lowest levels (11 ng/mL) and the specimen received from Azad Kashmir had highest levels of vitamin D (17.1 ng/mL). Overall results showed prevalence of vitamin D deficiency in all over the country regardless location and gender differences (24).

Another study conducted to assess the vitamin D status in different parts of the country revealed that only 15.3% of 4830 subjects had normal vitamin D levels (25).

### **Vitamin d deficiency in different disease conditions:**

#### **Musculoskeletal, Bone and Periodontal Health**

Vitamin D deficiency is directly associated with some bones and musculoskeletal problems such as rickets, osteopenia, osteomalacia, osteoporosis and osteoarthritis (26). Vitamin D supplementation showed beneficial effects in Musculoskeletal pain proving it to be a sign of Vitamin D deficiency (27, 28). A study conducted in 400 participants with complain of musculoskeletal pain (43.5% males and 55.5% females) with age ranging from 18 to 80 years in a less developed city Swat (29) which showed only 7% of the subjects had adequate levels of vitamin D (>30 ng/mL). Similar results were obtained from a cross-sectional observational study conducted in an outpatient department of Rahim Yar Khan, Punjab (30). About 400 patients with musculoskeletal pain showed that 47% of the subjects had low vitamin D levels (<30 ng/mL). In another study, fibromyalgia and nonspecific musculoskeletal pain were reported with lower levels of vitamin D in female subjects in Karachi (31). Similarly, out of 100 subjects with sign of fatigue, 92 subjects were also found vitamin D deficient (32).

Vitamin D deficiency with poor bone health was observed in premenopausal women (33). It was found that out of 174 subjects, the high bone turnover was present in 36.8% subjects and vitamin D deficiency was observed in 96.9% subjects. A similar study was conducted in 143 postmenopausal women in rural communities to assess bone mineral density by quantitative ultrasound index (QUI) and their dietary habits (34). The results showed that 42% of the women had osteopenia and 29% had an indicative score of osteoporosis. Vitamin D deficiency and low calcium intake in the diet were found more prevalent in this study.

Another study conducted to assess dietary calcium, vitamin D status and bone turnover in 305 women subjects in three towns of Karachi city (35). Overall, 90.5% subjects were found vitamin D deficient and in these, 42.6% subjects had secondary hyperparathyroidism. The 76.7% female subjects had low while, only 23.3% had normal bone turnover.

A survey was conducted to assess the status of calcium and vitamin D deficiency along with awareness about osteopenia and osteoporosis in 252 female subjects in Karachi out of which only 34% subjects had its awareness while 77% subjects had pain in back, legs and joints. (36)

A multicentric cross-sectional study including 291 subjects (39.5% males and 60.5% females) from three big cities (Karachi, Lahore and Islamabad) was conducted (37). Overall 84% subjects had vitamin D levels below the normal limit (30 ng/mL). A significant difference in Vitamin D levels was found on the basis of age and

skin color. Total 147 (48%) subjects had low BMD and out of them 98 (66.6%) had osteopenia. In these total 98 osteopenic subjects, 80 (81.6%) had low vitamin D levels. The vitamin D levels were not significantly different between subjects having low bone mineral density, serum calcium and phosphorus levels.

The association of periodontal health with vitamin D deficiency is quite prevalent worldwide (38). A study conducted in pregnant (n=36) and non-pregnant women (n=35) revealed that pregnant women were more vitamin D deficient than non-pregnant women but no association between vitamin D deficiency and periodontal diseases was found (39). The results of a randomized clinical trial conducted in 85 female of 12 weeks of gestation revealed that after 4000 IU dose of vitamin D on daily basis could not improve the periodontal status and birth weight among the study subjects (40).

The association of vitamin D level with above mentioned disease conditions was not described on the basis of adequately adjusted model, therefore it could not be inferred that only vitamin D deficiency is responsible for above mentioned conditions.

### **Nursing mothers and children:**

Vitamin D deficiency has also been associated with some complications such as poor fetal growth, rickets and neonatal eczema (41). Vitamin D status was assessed in parturient and gravidae in a tertiary care hospital in Karachi (42). Maternal and fetal vitamin D levels were estimated from blood and cord blood respectively. It found that 89% of the subjects were vitamin D deficient (<30 ng/mL) and vitamin D levels were found inversely correlated with maternal blood pressure.

Vitamin D deficiency was also found in the nursing mothers (85.1%) of South Punjab (43). According to the study, most of the mothers used to live in open houses with maximum chances of sun exposure (168.81 minutes/day). Despite of ample sun exposure, the reason of vitamin D deficiency could be clothing style of the females that is very common in the society.

Vitamin D deficiency was also found in healthy infants from 9 to 12 months of age in Rawalpindi (44). The radiological studies of wrists showed that 53.8% of infants had rickets with sub-optimal levels of vitamin D (<30 ng/mL).

The possible reasons of the vitamin D deficiency in pregnant women could be low sun exposure and less physical activity during pregnancy. Clothing style and cultural regulations (not to go outside during pregnancy), may play their role in this condition.

Another study revealed that 99.5% women and 97.3% neonates in Karachi while, 89% of women and 85% of neonates in rural areas of district Jehlum were found vitamin D deficient. (45) Similarly, another study revealed maternal vitamin D deficiency (<30ng/mL) during early pregnancy in 44% (out of 301) of the subjects visiting a tertiary care hospital in Karachi (46). A similar study reported 77% vitamin D deficiency from neonates to children (15 year of age) (47).

Nutritional rickets was observed in 74% children admitted in a health care center in Karachi with the symptoms of severe pneumonia (4). The rickets was more prevalent (79.8%) in age group between 2 to 12 months. Vitamin D status was not measured in this study, but it could be inferred that the children would have severe vitamin D deficiency.

Sub-clinical rickets was also observed in several areas of Pakistan. A study conducted in 189 children with 11 to 16 years of age showed 27% prevalence of sub-clinical rickets in Hazara district, KPK (48). Similarly in Kaghan Valley, 26 students were evaluated for sub-clinical rickets and all were found to have this condition along with vitamin D deficiency and high alkaline phosphatase levels (49).

An interventional study was conducted to evaluate the effect of two oral doses of 200000 IU of vitamin D in the malnourished children of 6 to 58 months age range (50). The results of this interventional clinical study showed significant improvements in the developmental indices in these children as compared with control group.

## Diabetes mellitus:

Vitamin D deficiency has been observed in the onset of diabetes (type 1 and 2) in world populations (51). The active form of vitamin D (calcitriol) after binding with its receptor (VDR) plays an important role in insulin secretion and the insulin sensitivity in the targeted cells (52).

Some observational studies in Pakistani population showed vitamin D deficiency in type 2 diabetic subjects (53, 54). A case control study conducted in a district headquarter hospital Gujranwala, Punjab found that vitamin D levels were significantly lesser in diabetic patients as compared with control group but both groups had vitamin D levels less than 20 ng/mL (55). In another study, vitamin D levels were found negatively associated with blood glucose levels of type 2 diabetic patients in Karachi (56). Similarly, another study showed that 62% of type 2 diabetic patients had elevated levels of HbA1c and poor glycemic control along with vitamin D deficiency (57). A study was conducted by our group found that vitamin D levels were negatively correlated with random blood sugar and HbA1c levels in the diabetic patients. However, vitamin D levels were not significantly different between good and poor glycemic control subjects (58).

Elevated levels of HbA1c represent poor glycemic control and it is a common modality in type 2 diabetic patients (59). A study showed positive association of vitamin D deficiency with poor glycemic control in Pakistani population (60).

A randomized clinical trial was conducted to evaluate the effects of vitamin D administration to improve glycemic control in type 2 diabetic patients at a tertiary care hospital in Lahore, Punjab (61). Patients were divided in to two groups. One group was administered only Metformin 500 mg after dinner while, second group was administered 200,000 IU of vitamin D along with 500 mg Metformin after dinner for six months of period. The result showed improvement in vitamin D levels in the group administered with vitamin D and metformin, but HbA1c levels were not found significantly different after six months between two groups.

Vitamin D deficiency has also been studied with the relevance of dyslipidemia in type 2 diabetic patients (62). A study conducted to evaluate the role of statin use with vitamin D levels showed no significant association with dyslipidemia. But a significant negative association was found between total cholesterol and vitamin D levels suggesting an important impact of vitamin D levels with hypercholesterolemia in the type 2 diabetic patients (63).

Microvascular complications in diabetes such as retinopathy, neuropathy and nephropathy have been associated with vitamin D deficiency in world populations (64). The results of meta-analysis revealed that vitamin D deficiency is associated with the onset of diabetes neuropathy in Caucasians and Asian populations (65). Microvascular complications are prevalent in Pakistani population and Vitamin D deficiency was found to be associated with diabetic retinopathy in type 2 diabetic patients of Peshawar, KPK (66).

## Cardiovascular disorders:

Vitamin D receptors and its metabolizing enzymes are present in the whole cardiovascular system (67). The VDR knock-out mice showed severe impairments in cardiovascular system including cardiac hypertrophy (68). Many observational studies and results of meta-analyses showed vitamin D deficiency is associated with the cardiovascular disorders (69, 70, 71, 72, 73). The studies to probe the association of vitamin D deficiency with cardiovascular events in Pakistani population are very few. A study conducted in patients with first acute myocardial infarction (AMI) showed association between vitamin D deficiency and a genetic variant in the vitamin D binding protein with this event (74). However, another study conducted to evaluate the role of vitamin D and calcium deficiency with hypertension showed weak correlation of these two factors with mean, systolic and diastolic blood pressures (75).

Vitamin D deficiency was also studied with the relevance of cardio metabolic syndrome and found that it was significantly associated with hypertension in Pakistani population (76). High levels of parathyroid hormone (PTH) could be responsible for the development of hypertension (77, 78). One study conducted in Pakistani population showed that PTH levels were significantly associated with variation (R990G) of calcium sensing gene in the vitamin D deficient subjects (79). However, blood pressure was not monitored in this study.

## Cancer:

Many epidemiological studies showed higher prevalence of some type of cancers in those geographical locations which observe less sun exposure throughout the year (80). The 50 ng/mL and 30 ng/mL of vitamin D were found to be associated with 60% and 33% decreased risk of colorectal cancer, respectively, and more than 50 ng/mL of vitamin D was found to have preventive role (81). Other studies also showed that the UVB exposure and vitamin D are associated with lower cancer risk and higher survival from cancer (82).

In Pakistani population, several studies have been conducted to probe the link between vitamin D deficiencies with incidence of some cancers. Breast cancer is a common cancer type in the women of this country (83, 84). Studies conducted in different parts of this country showed negative association of vitamin D levels with breast cancer incidences. In one of the study, 42 newly diagnosed breast cancer subjects were found vitamin D deficient (85). In Lahore, 300 newly diagnosed pre and post-menopausal women belonging to different parts of the Punjab province showed positive association with vitamin D deficiency and the tumor size in breast cancer (86). However, tumor grade and stage were not associated with vitamin D levels in this study. A study conducted in 90 newly diagnosed breast cancer patients in Lahore showed association of breast cancer with low vitamin D levels (87). Another study to understand the onset of breast cancer in women with the relevance of dietary habits, dress style and sun exposure showed that vitamin D deficiency was more prevalent in breast cancer patients (88).

A study to assess the effect of vitamin D supplementation in breast cancer risk showed that the odds of breast cancer were more significant in the subjects which were not taking vitamin D supplement (89). A cross sectional study to evaluate BMI, bone markers and vitamin D status in the newly diagnosed breast cancer patients showed low levels of vitamin D in the subjects (90). Another study conducted in Multan, South Punjab also showed that 90% breast cancer patients had vitamin D deficiency (91).

Instead of breast cancer, vitamin D deficiency has been studied in leukemic patients. One study showed vitamin D deficiency was prevalent in patients of B-chronic lymphoid leukemia (92). Another study showed that after remission-induction chemotherapy, this deficiency was increased as compared with subjects with no chemotherapy (93).

## Tuberculosis:

The first treatment of skin tuberculosis was discovered by lamp arc radiation and the inventor Neils Rayberg Finsen (1890-1904) was awarded by Noble prize for this discovery (94). It is suggested that UV radiation from lamp arc produces vitamin D in the body and facilitates the production of anti-microbial peptides such as cathelicidin to fight against infectious diseases including tuberculosis (95, 96, 97). Many observational studies showed strong association of vitamin D deficiency with tuberculosis in different populations including Pakistani population (98, 99, 100).

Some of the case control studies found severe vitamin D deficiency in patients with pulmonary and extra pulmonary tuberculosis (98, 101, 102, 103, 104, 105, 106, 107). A case control study designed to evaluate the amount of vitamin D, anti-microbial peptide cathelicidin, chemerin and inflammatory marker TNF  $\alpha$  in pulmonary tuberculosis and healthy subjects found significant association was present between vitamin D, cathelicidin, chemerin and TNF  $\alpha$ . (108).

An interventional trial named as SUCCINIT study (Supplementary cholecalciferol in recovery from tuberculosis) was conducted in patients with pulmonary tuberculosis to evaluate the effects of vitamin D supplementation (109). A total of 259 patients with newly diagnosed TB were randomly divided into two groups (Vitamin D group n=132 and placebo group n=129). The vitamin D group was administered by 600000 IU of vitamin D on weekly basis for two weeks along with standard medications while, placebo group was administered by normal saline along with standard medications. The results of this study showed improvement in clinical, radiological and host defense outcomes in the patients of vitamin D group.

Another interventional trial was conducted to evaluate adjuvant effects of vitamin D with anti-tuberculosis therapy (ATT) as compared with ATT alone for 77 days (110). The results showed improvement in some



parameters such as increase in serum vitamin D, calcium, BMI and hemoglobin and decrease in erythrocytes sedimentation rate (ESR), C-reactive proteins (CRP), total white blood count and a 12 days earlier sputum conversion as compared with placebo group.

A similar study also showed early sputum conversion in smear positive pulmonary tuberculosis by the administration of vitamin D (100000 IU) on every fourteenth day for three months (111). The results showed improvement in the vitamin D levels and rate of sputum smear conversion in patients with pulmonary tuberculosis.

CXCL10 is a chemo-attractant factor that is found to be elevated in TB patients (112). Vitamin D levels were found negatively associated with the CXCL10 levels in 119 TB patients in Karachi (113).

### Genetic studies:

Genetic variations in the genes of vitamin D synthesis and its metabolism have been linked with many diseases in the world populations (114, 115, 116).

Vitamin D receptor (VDR) is a type of nuclear receptor that after binding its ligand calcitriol (active form of vitamin D) regulates expression of many genes (117, 118). The variations in the VDR gene have been associated with several disease conditions in different populations (119, 120, 121, 122).

Many studies in Pakistani population showed the association of some diseases with certain types of SNPs in VDR gene. The Apa1 SNP present in the 3' intronic region of VDR may affects the stability of mRNA of VDR (123). Some SNPs in VDR gene were found to be associated with Type 1 diabetes (T1D) (124). Another study was conducted to probe a link between T1D and two SNPs of VDR (Fok1 and Apa1) in children (125). The results of this study showed vitamin D deficiency was prevalent in studied group but no significant association was found of any of these SNPs with T1D. It may be due to very small sample size (44 cases and 44 controls).

SNPs in VDR gene have been studied with the relevance of vitamin D levels in healthy women of Pakistani population (126). Two SNPs (Fok1 and Taq1) were found significantly associated with vitamin D deficiency and insufficiency.

Vitamin D circulates in the body after binding with vitamin D binding protein (VDBP); a type of transporter protein (127). A case control study showed significant association of group-specific 1-2 (Gc 1-2) genotype with the risk of T2DM in the subjects (128). Another study found a significant link between vitamin D deficiency and IF-IF genotype of VDBP gene with acute myocardial infarction (AMI) in Pakistani population (74). Breast cancer is quite prevalent in Pakistani women (83). The analyses of 360,933 breast cancer cases revealed that Asian Pakistani/Indian women had higher frequency of breast cancer than Caucasians (129). Meta analyses of some studies carried out to probe the role of variation in VDR gene with the onset of breast cancer, showed its positive correlation in different world populations (130). Many studies in Pakistani population revealed the association of variations in VDR gene with breast cancer. A case-control study (103 cases and 161 controls) showed the GG genotype of cdx-2 SNP may increase the risk of breast cancer in young females belonged to the Southern Punjab (131). The Tru9I SNP in VDR gene was studied in 228 patients and 503 controls and found that this SNP could be associated with the risk of this disease (132). It found from the same study that the mutant Tru9I was found significantly associated with grade IV carcinoma in the study group.

The b allele of Bsm1 polymorphism of VDR gene showed positive association with breast cancer (133). This study included 463 cases with known BRCA1/2 status and 1012 controls. Sub-group analysis of the study revealed that BRCA1/2 non-carriers and subjects with a family history of breast and/or ovarian cancer had significant association of this allele with this disease condition.

The overall results of many studies showed that the variations in VDR gene are not associated with some disease conditions in Pakistani population. The results of a study conducted by our group showed that only

TT genotype of TaqI polymorphism was significantly associated with T2DM in Karachi, Pakistan (Mahmood et al., unpublished data).

### **Summary:**

Total 82 studies were included in which 12 studies represented vitamin D levels in healthy individuals (Table 1) and 70 studies (Table 2) in different conditions. It found that vitamin D deficiency is prevalent in all parts of the country and about 64.6% healthy subjects had vitamin D levels less than 30 ng/mL. Moreover, 70 studies showed its deficiency in some diseases such as musculoskeletal, bone and periodontal problems, nursing mothers and children, tuberculosis, diabetes, cardiovascular problems and some type of cancers.

Women were found more deficient than men due to the cultural norms and clothing style in this population. Some previous studies in different parts of the world also showed that cultural norms and dress style were associated with vitamin D deficiency in women (134-136).

Limited studies have been conducted to see the association of genetic variations with some diseases. The results of such studies could not establish any significant association with different diseases. This could be due to the small sample size with limited scope of the study.

### **General recommendations:**

The vitamin D levels should be kept at normal range (30 ng/mL) either by vitamin D supplementation or by optimum sun exposure. Sun exposure should be preferred due to its benefits on other physiological functions.

Men, women and children should be encouraged and facilitated to expose themselves in the sun shine. Balanced diet containing dairy products fortified with vitamin D and the use of sea foods should be recommended for child bearing and nursing mothers.

A country wide survey could be conducted to assess the present status of vitamin D in this population and the possible reasons of its deficiency in this population.

### **Limitations:**

Most of the studies did not use appropriate measure of analyses using adequately adjusted statistical models to associate vitamin D deficiency with the disease conditions alongwith different assay types which may affect the results of vitamin D levels.

The results of genetic studies are limited and not conclusive therefore further investigations with large data set are required to infer logical conclusions

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**Table 1: Studies indicating vitamin D status in the healthy individuals of Pakistan**

| Total number of individuals | Male and Female (%)             | Number of individuals with vitamin D levels (<30 ng/ml) |
|-----------------------------|---------------------------------|---|
| 300                         | 65% and 35%                     | 272 (84%)   |
| 858                         | 41% and 59%.                    | 768 (89.5%)   |
| 500                         | 29% and 71%                     | 438 (87.6%)   |
| 104                         | 37.5% and 62.5%                 | 99 (95.2%)  |
| 191                         | 86% and 14%                     | 170 (89.1%)   |
| 88                          | 57% and 43%                     | 87 (98.86%)   |
| 244                         | 21% and 79%                     | 186 (76.2%)   |
| 180                         | 100% male                       | 160 (88.8%)   |
| 4788                        | 29% and 71%                     | 3562 (74.4%)  |
| 305                         | 100% female                     | 275 (90.1%)   |
| 60937                       | 31% and 69%                     | 37233 (61.1%)   |
| 4830                        | 33% and 67%                     | 4091 (84.7%)  |
| Total individuals = 73325   | Overall male 31% and female 69% | Overall = 47341 (64.6%)                                 |

**Table 2: Vitamin D deficiency in different health conditions in Pakistani population**

| Health conditions                            | No. of studies | References       |
|--|----------------|------------------|
| Musculoskeletal, bone and Periodontal health | 09 studies     | 29, 30, 32-38    |
| Nursing mothers and children                 | 11 studies     | 4, 42-59         |
| Diabetes mellitus                            | 08 studies     | 55-58, 60-63, 66 |
| Cardiovascular disorders                     | 07 studies     | 53, 74-79        |
| Cancer                                       | 09 studies     | 85-93            |
| Tuberculosis                                 | 16 studies     | 98-113           |
| Genetic studies                              | 10 studies     | 124-133          |