



## Review Article

2021 | Volume 7 | Issue 1 | Pages 1-11

## ARTICLE INFO

Open Access

## Received

October 14, 2020

## Revised

December 01, 2020

## Accepted

January 07, 2021

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**Keywords**

Vitamin D deficiency  
Metabolism  
Nutrition  
Consequences  
Interventions

**How to Cite**

Siddique MT, Hafeez A, Mearaj S, Abbas S. Overview of Vitamin D, its status and consequences: Challenges and prospects for Pakistani population: A Review. *Biomedical Letters* 2021; 7(1):1-11.

## Overview of Vitamin D, its status and consequences: Challenges and prospects for Pakistani population: A Review

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**Abstract**

Vitamin D, like other vitamins, is an essential micronutrient required for proper human metabolic function. It refers to a group of compounds, the most important of which are D<sub>2</sub> (ergocalciferol) and D<sub>3</sub> (cholecalciferol). Vitamin D is acquired from two main sources, synthesis in lower layers of the skin triggered by exposure to the sun (90%) and through diet (10%). Vitamin D levels can be determined by measuring 25(OH)D concentration in the serum and deficiencies are responsible for a wide range of issues including bone related problems, depression, diabetes, autoimmune disorders, cardio and respiratory problems, infections, autism and obesity. Synthesis in the body can be affected by a variety of factors including skin color, age, lifestyle, clothing, weather and even general health illiteracy. In terms of diet, the staple foods of the Pakistani population are generally deficient in vitamin D. As a result, a significant proportion of the Pakistani population, in particular women and children, suffer from vitamin D deficiency. The various challenges that need to be addressed to overcome this issue are discussed, along with potentially employable strategies such as food fortification (for example by micro and nano encapsulation technologies) and bio fortification.



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## Introduction

Vitamins are organic molecules which are essential micronutrients required by the body in a specific quantity for proper functioning and body development. Vitamin D helps in maintaining the calcium and phosphorous level in blood. It also plays a very important role for pregnant and lactating women as bones of their fetus and newborns, respectively, grow very rapidly during this time. Overall, 13 vitamins have been identified. Among these, vitamin A, D, E and K are fat soluble while vitamin B and C are water soluble. Vitamin D is one of the most vital micronutrients that are required by the human body. It exists in two bioequivalent forms, i.e., D2 and D3, also known as ergocalciferol and cholecalciferol, respectively, and have similar metabolism pathway. Vitamin D2 is produced by some plants, including yeasts and mushrooms, in response to certain ultraviolet (UV) radiations. Food processors have attempted to increase the vitamin D2 level in mushrooms on commercial scale through UV irradiation. D3 is the biologically active form of vitamin D which is biosynthesized in humans and animals. In this case, cholesterol is converted into the active form D3 in the presence of UV radiations. Humans also obtain vitamin D3 by consuming animal-based food products. For instance, egg yolk, liver, cheese, fatty fish are good sources of vitamin D3 for humans. As vitamin D is fat soluble, when in excess, it tends to accumulate in the body. Therefore, it is not necessary to take it on daily basis. It is estimated that more than one billion people are affected by vitamin D deficiency all over the world [1]. Its deficiency is more rampant in the developing countries, thereby, negatively affecting the health of millions of people. Particularly, it ranked as one of five most prevalent health issues among the children [2]. As biosynthesis of vitamin D in animals and plants is directly linked to the presence of sunlight, its level in the humans is also affected by certain factors including environment, lifestyle and nutrition. Objectives of this review are to describe the primary (sunlight, diet) and secondary (lifestyle and environment) factors affecting vitamin D status. In addition, strategies and suggestion to improve the vitamin D status in Pakistani population are also discussed. In particular, technology-based approaches including the use of micro and nano-encapsulated vitamin D for the fortification of food and feed are highlighted.

## Determination of Vitamin D status

According to the Institute of Medicine, the status of vitamin D can be determined by the 25(OH)D level of serum. When the serum 25(OH)D concentration of an individual is less than 30nmol/L, such an individual is considered to be vitamin D deficient [3]. Moreover, if the concentration is <19nmol/L, it is considered as deficient level. The 25(OH)D range of 20-29nmol/L is considered as insufficient level [4], as shown in **Table 1**.

**Table 1:** classification of vitamin D status by 25(OH) D concentration.

Vitamin D status	25(OH) D con.
Deficiency of vitamin D	Less than 19nmol/L
Insufficiency of vitamin D	20-29nmol/L
Sufficiency of vitamin D	30nmol/L or above
Intoxication of vitamin D	More than 150nmol/L

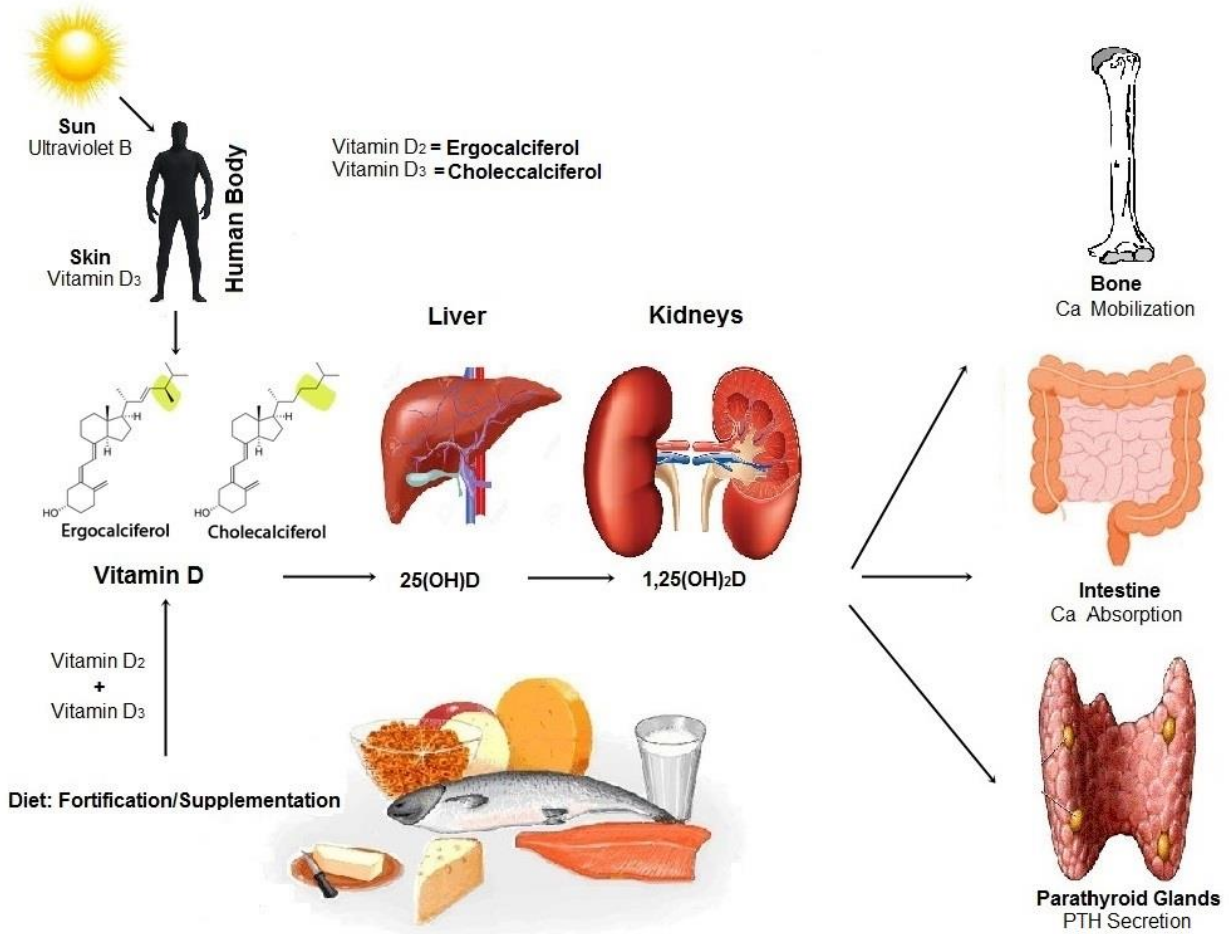
## Biosynthesis and Metabolism of vitamin D

The endogenous synthesis of vitamin D depends upon the exposure of the body to ultra-violet (UV) light. The precursor of vitamin D, 7-dehydrocholesterol when exposed to UV-light, absorbs energy and converts itself into the precursor of pre vitamin D3. This pre-vitamin D3 undergoes several nonenzymatic thermal reactions which results in the rearrangement of molecule bonds, consequently, producing the vitamin D3[5]. Small amount of vitamin D (D2 and D3) both are also produced from diet (Fig. 1). It is naturally present in very few foods that we consumed. Vitamin D level is rich in fatty fish such as salmon fish, beef liver, cheese, milk, mushroom, and egg yolk.

Vitamin D undergoes two steps of hydroxylation for fully activation. It is transported to the liver for the conversion of 25-hydroxyvitamin D 25(OH) D, which is the main storing and circulating form of vitamin D. In case, the transport of 25(OH) D to the liver is interrupted certain liver associated health issues may arise. It is to be estimated that, 92% of chronic liver disease is caused by the vitamin D deficiency. Its deficiency occurs when the 25(OH)D concentration level in serum is less than 25nmol/L [6]. 1, 25-hydroxyvitamin D (1, 25(OH) 2 D), the active form of vitamin D, is formed when 25(OH) D is transported to kidney under the influence of parathyroid hormone. Due to paracrine and endocrine activity, (1, 25(OH)2 D) is released into the circulatory system, thereby,

reaching the target cells [7] (**Fig. 1**). To regulate the calcium, phosphate and alkaline phosphatase, parathyroid hormone interacts with special nuclear receptor, i.e., vitamin D receptor (VDR), which allow the normal development and mineralization of healthy

skeleton. The VDR expression has been identified in many cells (blood cells) and organs which indicates that adequate vitamin D level is critical for the maintenance and functioning of tissues [8].



**Fig. 1:** Schematic Diagram of Biosynthesis and Metabolism of Vitamin D.

## Consequences of Vitamin D deficiency in humans

Deficiency or insufficiency of vitamin D in pregnant and lactating women during this time period result in the appearance of Low Body Weight (LBW) of fetus and newborns, respectively [9]. Similarly, neonates born with vitamin D deficiency are at risk of poor growth, rickets and infantile eczema. These conditions are mainly associated with children born to mother having low levels of vitamin D, and more likely to develop rickets [10, 11].

As Vitamin D promotes bone mineralization by absorbing calcium and phosphorous from birth to death, people of all age groups are affected by the

vitamin D deficiency. Calcium and phosphorus are important for the development of musculoskeletal and maintenance of bone density mass.[12] Without vitamin D only 10-15% calcium and 65% phosphorous will be absorbed. The interaction of calcitriol with vitamin D receptor enhances the absorption of calcium 30-40% and phosphorus up to 80% in blood[13]. Symptoms of Vitamin D deficiency include muscle pain, muscle weakness and fatigue [14]. Vitamin D level influences the muscle mass, performance, balance, thereby reducing the risk of falling in older ages [15]. It helps to maintain the calcium and phosphorous level by absorbing them from the intestine, otherwise, several bone diseases occur including osteoporosis, osteoporotic fractures

and osteomalacia (decrease in bone mineralization) [11, 16-18]. Beside these general health issues caused by the vitamin D deficiency, occurrence of several diseases is also linked to the lower vitamin D levels in the humans, as follows.

### ***Breast cancer***

Vitamin D deficiency is also linked to breast cancer [19]. It is one of the leading cancer which cause mortality in women [20]. Low level of 1, 25 (OH) 2D, the active form of vitamin D, is found to play a role in certain pathways responsible for triggering the cancers. On the other hand, it is observed that circulating vitamin D play a significant role in reducing the breast cancer. Enzyme CYP27B1 present in renal tubules activates 1, 25(OH) 2D in the epithelial breast cells, which has a role in the development of normal cells, consequently, stopping the growth of cancer cells at this location. Active form of vitamin D induces apoptosis and differentiation, and inhibits proliferation of cells and angiogenesis in normal and malignant breast cells [21].

### ***Depression***

Vitamin D receptors are present on specific target tissue, such as, hippocampus, thalamus, prefrontal cortex and limbic system and substantia nigra, indicating the role of vitamin D in the maintenance of mood and cognitive functions [22-24].

### ***Diabetes I and II***

Low vitamin D level is correlated to type-I and II diabetes [25, 26]. Type-I diabetes is insulin dependent issue which is caused due to the autoimmune destruction of pancreatic  $\beta$  cells. Epidemiologically, association of vitamin D intake showed reduced risk of type I diabetes [27]. Worldwide data showed that the occurrence of type I diabetes was more frequent in populations living at higher latitudes [28].

In type II diabetes, insulin is not effectively utilized by the target cells such as adipose tissue, skeletal and muscular tissue. Pancreatic  $\beta$  cells continually produce insulin which is not used by cells lead to increase level of insulin in bloodstream called hyperinsulinemia. This condition is associated with obesity, glucose intolerance, dyslipidemia and hypertension and collectively we called it Metabolic syndrome [29]. Epidemiological studies shows that

vitamin D level have direct relation with metabolic syndrome and type II diabetes [30].

### ***Auto immune diseases***

Calcitriol (active form of Vitamin D) activates the inflammatory and immune cells which are responsible for differentiation, activation and proliferation of the cells in human. Calcitriol is involve in various pathways such as up regulation of the anti-inflammatory pathways and down regulation of the immune system and inflammatory cells [31, 32].

### ***Infections***

Both invitro and in vivo studies showed that, vitamin D affects innate and adaptive immune response. Antigen presenting cells have an enzyme CYP27B1 which metabolize vitamin D to calcitriol. It act as transcription factor by binding to the nucleus of receptor, for antimicrobial peptides, cathelicidin and beta defensins which lead to enhanced phagocytosis, chemotactic and anti-microbial activity [33, 34].

### ***Cardio-vascular and respiratory disease***

Vitamin D has role in cardio and respiratory diseases [35]. Vitamin D paly important role in cardiovascular health by the regulation of blood pressure, cardiac function and endothelial function of smooth and muscle cells [36]. A large number of studies showed that vitamin D plays a key role in inflammatory airway diseases such as asthma, allergic rhinitis and chronic rhino sinusitis by acting on immune cells such as T cells, macrophages, dendritic cells and B cells that are involved in parthenogenesis of these diseases [37].

### ***Autism***

Autism has also linked with vitamin D level [38]. Different studies demonstrated that deficiency of vitamin D during pregnancy, increased the onset risk of Autism Spectrum Disorder (ASD). Genetic polymorphism study shows that, allele AA\A of GC rs4588 is responsible for ASD in children, which encodes vitamin D binding protein [39].

### ***Obesity***

Increased risk of Obesity cause vitamin D [40]. Vitamin D is a fat soluble, almost 34% is able to store



in adipose tissue and thus prevent from being available in circulation for further processing and its level decrease in obese person [41].

## Sources of Vitamin D

Vitamin D is produced under the influence of sun light exposure and small amount is produced through the dietary sources. For sufficient serum 25(OH) D concentration, outdoor activities are better than dietary intake [42].

### *Sun light*

Sunlight is the major source of vitamin D synthesis in humans as almost 90 % of vitamin D is made from sunlight. Approximately, 5-30 minutes body exposure to sun for at least 2 times a week is enough to synthesize vitamin D through skin [43]. Best ultraviolet B (UVB) penetration time in skin is from 10am to 2pm. After 2pm ultra violet A (UVA) level increases which may cause skin cancer [43]. In addition, UV penetration also depends upon season, latitude and altitude, use of sunscreen, and skin color. The penetration of UVB photon (UVBP) into skin depend upon the melanin concentration, blockage of UVB rays by windows, screens and type of clothing. To get normal vitamin D level, sun exposure to arm, face and feet for half an hour is enough rather than exposing the whole body. For one hour of exposure to sun light, 6 IU of vitamin D are biosynthesized by one cm<sup>2</sup> of skin [44]. Our body possess vitamin D hormone which is activated when body is exposed to sunlight. In the skin, 7 – dehydrocholesterol compound is present which changes its conformation when UVB radiation of wavelength 280-350nm passes through the epidermis and dermis layer of skin. Such modification results in the formation of previtamin D3. Melanin in the skin reduces the UVB penetration and competes the production of previtamin D3 synthesis. Over prolonged exposure of UVB, previtamin D3 is converted into vitamin D. Melanin is not only absolute barrier for the reduction of vitamin D in body, but some decline of vitamin D in body depend upon the clothing such as woven clothing which does not permit the UVB rays, smog, light blocking pollution, indoors activities and winter time when radiation is not enough to penetrate to form vitamin D [45]. There are certain social, cultural and physical factors which effect the synthesis of vitamin D by the sunlight.

### *Skin color*

Vitamin D status vary among people of the same country and having same environmental factor because of varying level of penetration of UVB rays due to different melanin concentration in body. Skin pigmentation is accumulation of melanin (brown pigment) in our epidermis of skin [46]. Melanin and acetylcholine both are released from melanocytes, melanin act as a sunscreen which absorb UV radiation and prevent it from reaching other parts of body through skin, while acetylcholine have role in body temperature regulation [47].

### *Aging*

Vitamin D status in humans is also dependent on aging as older people lose capability to biosynthesize vitamin D even in the presence of abundant UVB radiations. Contrary to that, vitamin D is synthesized more efficiently in young individuals [48]. Vitamin D is produced when UVB act on 7- dehydrocholesterol, 7- dehydrocholesterol abundantly located in epidermis of skin. With the passage of time concentration of 7- dehydrocholesterol changes and as result low synthesis of vitamin D occurred. Ability to produce vitamin D from the skin decreases up to 50% from the age of 10 kid year to 70 year elder [49] . Currently, it is assumed that elderly people confined to indoor environments are at high risk of vitamin D deficiency [50]. A study in Italy found that elders involved in outdoor activities (cycling, gardening, fishing and walking) have 25% higher (OH)D concentration than those who stayed indoors [51]. Other factors, which may negatively affect vitamin D synthesis in elderly people is the reduced absorption of dietary sources, vitamin D binding protein DBP transport the vitamin D to the blood after its synthesis. DBP synthesis is also reduced due to low rate of synthesis of hepatic protein in elderly ones. This shows that poor biosynthesis, decreased absorption of dietary vitamin D and decreased DBP synthesis reduced the vitamin D level in elderly.

### *Lifestyle and Workplaces*

Vitamin D status varies among people having different indoor and outdoor activities due to the difference of sun light exposure. Workers such as farmers, gardeners and forestry workers had low chance of cancer that are associated with UVB and vitamin D[52]. A study conducted in India reported that level of 25(OH) D in serum of rural population

was higher than that of urban workers [53]. Beyond the time required to be spent in sun exposure, vitamin D deficiency was also reported due to pollution in the urban dwellers of highly dense areas. In addition, soaring temperature in summer is also responsible for keeping people indoors and covering their bodies [54].

#### *Clothing*

Low vitamin D status in certain populations is also linked to clothing style which act as a barrier in UVB absorption, thereby, negatively affecting the vitamin D biosynthesis. Pakistan is a Muslim country where women mostly put on concealing dresses. Such costumes prevent UVB radiation to penetrate the skin, thus, influencing the status of vitamin D in women. It is suspected that this is the major cause of vitamin D deficiency in Pakistani women. Unfortunately, no specific study targeting the veiled women in Pakistan is conducted which may provide a clear link between clothing style and vitamin D status. However, a study was conducted in India (that share border with Pakistan and mostly have almost same environmental and climatic condition) showed that rickets is three to four times more common in Muslim children than Hindus wearing less concealing veils [55]. Veils are the plausible explanation for low vitamin D status.

#### *Other Environmental Factors*

There are certain other environmental factors which could affect the vitamin D status in humans. Clouds are more likely to decrease the intensity of UVB radiation up to 99% when completely overcasting the Earth [56]. Fog also attenuates the UVB rays to reach the Earth. In places where snow falls, people are found to be deficient in vitamin D. This could be due to the reflection of UVB rays which are necessary for the synthesis of vitamin D through skin [57, 58]. Furthermore, areas lying above 37° latitude receive low intensity of UVB radiations, consequently, decreasing the biosynthesis of vitamin D<sub>3</sub> [59]. Major air pollutants, i.e., Ozone, Carbon monoxide, Sulfur dioxide, Nitrogen dioxide and Particulate matter absorb and scatter UVB radiation resulting in the decreased biosynthesis of vitamin D in humans [60]. For instance, 50% of UVB radiations are found to be attenuated in highly polluted areas of China and India by air pollution [61]. As these pollutants are in abundance in urban area atmosphere, vitamin D biosynthesis is highly affected in the urban population than that of people living in rural areas.

#### *Lack of knowledge about vitamin D significance*

One of the main reasons of deficiency of this vital vitamin D is the lack of knowledge about the importance of vitamin D, risk associated with its deficiency and sources. People usually avoid sunlight to prevent their skin from getting tanned. Literacy cannot be ignored among the factors linked to the vitamin D deficiency. A study conducted in Hong Kong concluded that training about health literacy is more important than simply imparting knowledge about the importance of vitamin D [62]. Another study, conducted in UAE, showed that only 43% were aware that main source of vitamin D is sunlight and 34% were familiar with the vitamin D deficiency [63].

#### *Dietary sources*

Only 10 % of body requirement of vitamin D is fulfilled by the dietary sources such as fish, milk, cereals, liver etc. The populations deprived of enough sun exposure, either due to geography or lifestyle are more dependent on dietary sources to meet their vitamin D requirement. However, due to food insecurity, stapled diet is unable to meet the required vitamin D level. Nowadays, variety of vitamin D enriched processed food and supplements are available in the market to overcome the vitamin D deficiency in body [2].

Vitamin D deficiency is a global problem which affects millions of people from America to Africa, Europe to Middle East and Asia. Despite the availability of abundant sun light in South Asia (India, Pakistan) and its neighboring countries including Turkey, Japan, China, the vitamin D deficiency is very common in these areas [19-21]

### **Nutritional Factors affecting vitamin D levels in Pakistani population**

Our dietary sources contain very low vitamin D content. Commonly, milk and milk products are the main dietary source for vitamin D. Unfortunately, concentration of vitamin D in natural milk is very low (2IU/100ml). Although vitamin D is stable during cooking at up to 200 °C, excessive boiling (2-3 rounds of boiling) of milk-based beverages (tea and coffees) in Pakistan further decrease the vitamin D content. Therefore, these beverages have no significant contribution towards maintaining the required levels of vitamin D and calcium in humans. These issues warrant that milk and milk products should be

fortified with vitamin D. However, fortification of milk is very rare in Pakistan as such food products are more expensive and unaffordable to the socioeconomically deprived groups of society. Another concern is adulteration of milk and milk product.

## Vitamin D deficiency and Pakistan

Pakistan is a country in South Asia and crossroads to Middle East and South Asia. Despite of abundant sun light vitamin D deficiency is prevalent in Pakistan and its neighboring countries, like India, Bangladesh, and China [14]. Only few studies are published which highlight the vitamin D status in Pakistani population. A high prevalence of vitamin D deficiency in women as compared to men is attributed to their lifestyle, such as, traditional clothing (veiled). In these clothing, body get very little exposure to sun light. This issue is further aggravated as majority of women are usually restricted to stay at home. Consequently, women of different age groups are at higher risk of developing vitamin D deficiency.

For instance, a study conducted in 5 Pakistani cities (Lahore, Sialkot/Gujranwala, Rawalpindi/Islamabad, Abbottabad, Peshawar with sunshine range of 2044 - 3094 hours annually) to investigate the serum vitamin D levels showed that 53.5% of citizens are vitamin D deficient as their serum 25(OH) D level was less than 19nmol/L. Furthermore, 31.2% of participants had insufficient level of serum 25(OH) D, ranging from 20 to 29nmol/L. Additionally, 15.3%

participants had normal level of serum 25(OH) D, i.e. 30nmol/L [64].

Another study was conducted in Lahore to determine the vitamin D level in childbearing mothers (**Table 2**). Three groups of women were selected: students at the University of Punjab campus, staff and student of Madrasas (Islamic institutes) and the women working in offices, hospitals and domestic settings (maids). Screening of 215 samples was conducted from January 2012 to July 2012. Of these two hundred and fifteen women, 134 were aged between 15-30 years and 81 were aged between 31-45 years. Out of 215, 156 women were vitamin D deficient while 37 had insufficient level of 25(OH)D and only 22 had a normal 25(OH)D level in serum [65].

A study conducted in 3 localities (downtown and suburb) of Karachi city (population: 16.2 million, census 2017) in Pakistan having 99% of muslim women concluded that vitamin D deficiency was more prevalent in women as compared to male population. Moreover, vitamin D levels were higher in women living in the downtown than those in the suburb. Alarmingly, the 90.5% women were VDD, while 5.2% were insufficient and 4.3% had sufficient level of serum 25(OH) D [66].

Another study was conducted on 600 individuals (300 males and 300 females) in Faisalabad, the fifth largest city of Pakistan with abundant sunshine. Results revealed that 77.5% of individuals under study were vitamin D deficient while 18% had insufficient levels of vitamin D, and only 4% were categorized as vitamin D sufficient [67].

**Table 1:** Determination of vitamin d level in different individuals.

S#	Total Individual	No. of Deficient Individual	No. of Insufficient Individual	No. of Normal Individual	Reference
1	1595* 3235**	899* 1696**	188* 1020**	218* 519**	Riaz, H, et al. 2016
2	215**	156**	37**	32**	Junaid, Kashaf, et al. 2015
3	305**	275**	17**	13**	Khan, Aysa Habib, et al. 2012
4	300* 300**	465	108	27	Masood, et al. 2010

*Note:* MALE= \*, FEMALE=\*\*

## Interventions to improve the vitamin D status in Pakistan

### Fortification: Food

Fortification is a process where micronutrients such as trace elements and vitamins are added to the staple food. In a conventional fortification system, exogenous vitamin D is added to dairy and other regular food products to increase its level in the human

body. Dairy products including fluid milk, cheese, yogurt are reportedly fortified with vitamin D [68]. To prevent vitamin D deficiency, developed countries, i.e., Canada and America are focused on the development of vitamin D enriched foods and supplements. In addition, these countries are carefully regulating the vitamin D level in food to prevent toxicity associated with overdose of vitamin D [69]. Although vitamin D food fortification is a popular strategy to overcome its deficiency, maintaining the vitamin stability and desired sensory characteristics of

fortified food is highly challenging. For instance, vitamin D is sensitive to light and adversely affected by acidic environments [70]. To overcome these issues, researchers have developed micro and nano-encapsulated vitamin D. Recently, researchers have developed vitamin D fortified yogurt using Nano liposome technology. Encapsulation of vitamin D is accomplished by utilizing variety of specialized structures including liposomes [71], emulsions [68], coacervates.

In response to rickets in children industrialized countries added vitamin D through fortification to fluid milk or margarine [72]. A study conducted in Finland where milk and fats contribute 60% of daily vitamin D intake, fortified liquid milk and margarine helped to reduce the vitamin D deficiency in Finnish Defense forces men (age 18-28 years) in winter from 19% in January 2003 to 5% in January 2004 [73]. Wheat, rice, milk, legumes and vegetables are the major components of a diet being consumed by Pakistani population. Unfortunately, these foods lack diversity and are deficient in vitamin D levels, thus, undermining the provision of recommended daily allowance (RDA) of vitamin D.

### ***Bio fortification***

It is an induced process through which the concentration and bioavailability of nutrients is increased in crops. In this approach nutrient content is modified at the pre-harvest level rather than post-harvest processing. Bio fortification is achieved through both conventional and recombinant technology (genetic engineering). Plants and animal both are bio fortified with vitamins. However, there is a huge research gap in the development of vitamin D fortified crop plants. For example, quantification and function of vitamin D is unknown in plants. Additionally, there is no information regarding the mode of vitamin D binding with proteins in plants. Moreover, there is lack of knowledge about the relationship of calcium and vitamin D, and vitamin D receptor in plants [74]. (Black et al., 2017). Metabolic engineering strategies for enhancing vitamin D content in plant have not been yet reported [75].

Bio fortification of vitamin D In animal products have been successfully achieved to overcome this problem. In this process, fish, poultry and livestock feed can be enriched with vitamin D, thereby, increasing the vitamin level in their products (fish, beef, chicken and eggs). The reports from the last decade illustrated that bio fortification of hens

through vitamin D enriched feed resulted in the increased level of vitamin D in the eggs [76, 77]. These reports were further confirmed by other researchers, indicating that vitamin D was efficiently transferred from the vitamin enriched feed into the egg yolk [78, 79].

### **Challenges and Recommendations**

Although South Asian countries including Pakistan get maximum sunshine the whole year, the main reason for vitamin D deficiency in Pakistani women is the inadequate exposure of body to sun light. All this is due to culture and religious beliefs as women preferably stay at home and observe Islamic dress code, consequently, getting minimum exposure to sunlight. Furthermore, slum houses and indoor activities (work, studies) contribute towards the reduced body exposure to sunlight resulting in the decreased synthesis of vitamin D. Unfortunately, to overcome these challenges, governments have done little to educate people and to introduce vitamin D fortification programs [80]. Another primary reason for vitamin D deficiency is malnutrition (chronic and acute) [81]. Beside adequate exposure to sun light, usage of fatty fish, vitamin D supplements and fortified food including beverages may help to overcome vitamin D deficiency. It is to be estimated that 400IU (10 $\mu$ g) of vitamin D for one quarter liter of milk is enough to overcome its deficiency. The major problems in Pakistan regarding vitamin D status are: (1) increased population and urbanization, (2) illiteracy in general and lack of health education in particular, (3) no awareness about exposure of sunlight to permissible limit, (4) work and lifestyle, (5) lack of preference towards fortified foods, and (6) lack of coherent nutrition policy on national level.

### ***Population and urbanization control***

Due to increasing population, resources have become limited, consequently, nutritional status of large population is compromised. Furthermore, capacity of people to buy fortified foods is also shrinking. Due to uncontrolled urbanization, people have limited access to housing, job, health and educational facilities. Concomitantly, people living in such conditions are at higher risk of health issues related to vitamin D deficiency. Therefore, mass migration towards cities should be discouraged and all the basic facilities should be provided in countryside. It will improve the nutritional level of micronutrient including vitamin D.



***Provision of education***

In Pakistan, around 58% of its population is illiterate. People don't receive any formal health education. Therefore, such people need awareness about the benefits of sunlight exposure and its role in the synthesis of vitamin D in body. They should be educated about the importance of vitamin D and health consequences associated with its deficiency. Additionally, people should be convinced to consume vitamin D rich foods (egg, milk, fish, cereals, liver etc.). As low socioeconomic status of people in Pakistan is major hurdle in getting balanced diet, they should be educated about the significance of vitamin D fortification in order to improve the acceptability of fortified foods and supplements among the people.

***Work and lifestyle***

In Pakistani society, women spent most of their time at home due to home bound work routines. To overcome this limitation, outdoor recreational activities should be promoted for women and children to combat the vitamin D deficiency. They are also encouraged to spend some time in the open spaces at home to get sunlight exposure for vitamin D biosynthesis.

***Fortified food and supplement***

Supplements are the best option to achieve optimal level of vitamin D where no or little concept of fortification of food. Public experts, government effort and policy makers should take some initiative to promote the use of fortified food which must enriched with vitamin D and have low cost and non-toxins, which not for mineralization of bone but also prevent from several chronic disease and cancer forms. Food technologists and processors are working hard to increase the acceptability of fortified foods by improving their sensory characteristics, such as aroma, flavor, color, texture and overall appearance. To further improve the stability and sensory characteristics of fortified foods researchers have introduced micro and nanoencapsulation techniques. These techniques might improve the overall acceptability of vitamin D fortified foods among consumer.

***Formulation and implementation of national nutrition policy***

Globally, many countries have legislation on food standard that provide guidance for food fortification

on mandatory and voluntary basis. This should be mandatory at government level to maintain the optimal level of vitamin D status among the population. In Pakistan, to overcome this problem, authorities and legislative bodies should focus on the fortification of most commonly consumed foods (wheat, rice, milk) with vitamin D. Certain policies should be enacted which restrict the sale of unhealthy items or ingredients which are not rich in with vitamins and minerals.

**Conclusion**

In conclusion, we believe that there is urgent need of research studies from Pakistan on the current status of vitamin D and their association with other diseases. Control of vitamin D deficiency is possible by increasing outdoor activities and adopting healthy lifestyle. Also, vitamin D status can be improved through consumption of vitamin D rich foods, vitamin D fortified staple foods, and supplements. Comprehensive strategies to prevent vitamin D deficiency among Pakistani population are highlighted.

**Conflict of interest**

The authors declare no conflict of interest.

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