

## Time to Do Something for Vitamin D Deficiency; A Review

Mehrnoush Kosaryan<sup>1,\*</sup>; Mandana Zafari<sup>1</sup>; Aili Aliasgharian<sup>1</sup>; Masomeh Mosawi<sup>1</sup>

<sup>1</sup>Thalassemia Research Center, Hemoglobinopathy Institute, Mazandaran University of Medical Sciences, Sari, IR Iran

\*Corresponding author: Mehrnoush Kosaryan, Thalassemia Research Center, Hemoglobinopathy Institute, Mazandaran University of Medical Sciences, Sari, IR Iran. Tel: +98-1133343010-15, Fax: +98-1133344506, E-mail: mekowsarian@gmail.com

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**Context:** Vitamin D deficiency is a common nutritional disorder in Iran. Vitamin D is an essential health factor from birth onward. This study was conducted to summarize epidemiologic researches regarding vitamin D deficiency in different parts of the country and to conclude if food fortification is necessary.

**Evidence Acquisition:** The study was designed in Thalassemia Research Center, Sari, Iran. It was a narrative review on the current situation of vitamin D deficiency in Iran. Related literature of the studies, in Farsi and English, conducted in the recent decade were explored. Data source of the study was Medline, SID, PubMed, Scopus, Request, Web-of-knowledge, Springer, Ovid, and Google Scholar.

**Results:** Twenty five cross-sectional researches were found regarding vitamin D status in Iran from 2003 to 2013. There was also a Meta-analysis conducted in 2008. The total amount of 25(OH) D3 was measured mostly by radio immune assay (RIA) method. Most of the studies were done on adults. Definition of vitamin D deficiency was based on cut off of the kit in most studies; however in some studies the serum parathyroid hormone (PTH) was measured and cut off for diagnosis based on increased PTH. Maximum rate of sever vitamin D deficiency was reported as 47% in 2011.

**Conclusions:** Vitamin D deficiency is very frequent in Iran. Dealing with a national important nutritional problem is important. One way is to fortify suitable foods or edible products such as milk or cooking oil. Increasing public awareness about the problem and motivating people to do something on their expense is another option. In the current case taking vitamin D supplements on a regular basis, daily, weekly, or any other routines which could be available and cost effective may solve the problem. For people above one year old it is recommended to take 300'000 IU (as intramuscular injection or oral dose) of vitamin D as a starting dose, then 50,000 IU oral dose every three months.

**Keywords:** Vitamin D2; Vitamin D3; Calciferol; Deficiency; Prevention; Fortification

### 1. Context

Vitamin D is an essential health factor from birth onward or even before that. The most famous role of vitamin D is the health of bones (1). Vitamin D deficiency in infants and children could end in nutritional rickets which is the softening of growing bones. Muscular weakness, bone pain and deformities are symptoms and signs in mild cases. However, convulsion and even death could be the consequences of advanced and severe cases (2). The same pathology in grown up people is named Osteomalacia. Affected persons have bone and muscle pain and also weakness, which deteriorate their quality of life and physical performance (2). Taking vitamin D has other benefits such as reducing the prevalence of type II diabetes mellitus in children (2, 3). More recently the beneficiary role of vitamin D in other immune mediated diseases such as Asthma and Urticaria is found (2, 4). Systemic Lupus Erythematosos (5), multiple sclerosis (2), and even some cancers such as lung, prostate and ovarian cancer are also addressed (1, 2). Children with vitamin D deficiency are more prone to various infections including tuberculosis (2). Vitamin D supplements are routinely

dispersed free of charge by healthcare centers for all infants under one year. Pregnant and lactating women also get prescriptions for extra vitamins (6). Some adults take vitamin supplements as over the counter medications (7). Vitamin D deficiency (insufficiency) is a common nutritional disorder in Iran (8). Related research goes back to many years ago. One strategy to prevent vitamin D deficiency is regular administration of vitamin supplements. However, in many countries food fortification is also carried out. There are no national programs for food fortification with vitamin D in Iran. In order to summarize epidemiologic researches regarding vitamin D deficiency in different parts of the country, this study was conducted in Thalassemia Research Center, Sari, Iran. Also, the literature for con and pros evidences regarding the universal fortification of food with vitamin D3 was reviewed.

### 2. Evidence Acquisition

It was a narrative review on the current status of vitamin D deficiency in Iran in December 2013. The following keywords were also employed to search the literatures regarding the food fortification programs, both in Farsi

and English languages: vitamin D2, vitamin D3, calciferol, deficiency, insufficiency, Osteomalacia, rickets, prevention, treatment, fortification, iodine, iron, supplements, and Iran. Data sources of the current study were Medline, SID, PubMed, Scopus, Request, Web-of-knowledge, Springer, Ovid, and Google scholar. The recent decade epidemiological studies on vitamin D and iron fortification, and the last 25 year research literatures on iodine deficiency were included.

### 3. Results

Twenty five cross-sectional researches were found regarding vitamin D status in Iran from 2003 to 2013. These papers were evaluated according to STROBE check list. There was also a Meta-analysis conducted in 2008 by Heshmat et al. Table 1, indicating 25(OH) D3 mostly measured by radio immune assay (RIA) method. Most studies were conducted on adults, however some included pediatric age. Definition of vitamin D deficiency was based on the cut off of the kit in most studies; however, in some of the serums Parathyroid Hormone (PTH) was measured and the cut off for diagnosis was based on the increased PTH, Table 1. Maximum rate of severe vitamin D deficiency was reported by Neyestani et al. as 47% in 2011.

Vitamin D in nature comes in two forms D2 and D3. Human body can produce vitamin D2 in the skin; however, needs sunshine with enough time and intensity (1). In many countries exposure to sun light is the main source of vitamin D. Factors such as skin tone, adiposity, age, latitude, season, and time of day are important. Because of concerns over skin cancer risk, more sun exposure as a public health strategy to improve vitamin D status is not recommended. Holick argued that since the prevalence of skin cancers did not decrease during the recent three decades and prevention of sun exposure was promoted. The College of Australian Dermatologists and the Cancer Council suggest a balance between avoiding an enhance risk of skin cancer and achieving sufficient UV radiation to preserve enough vitamin D levels (2). Vitamin D3 is naturally found in fish and fish oil. Both forms are hydroxylated to 25(OH) vitamin D in the liver, and then with passage through kidneys another hydroxylation takes place. Interestingly, some foods such as meat, fish, and eggs have vitamin D in nature as the hydroxylated vitamin D metabolite 25-hydroxy vitamin D [25(OH) D3]. On the other hand, it is not identified whether 25(OH) D3 originates in foods or a supplement has the same force on vitamin D compared with vitamin D3 (cholecalciferol). To clarify the issue, Cashman et al. performed a Randomized Controlled Clinical Trial (RCT) to assess the relative effect of oral supplementation with 25(OH) D3 compared with vitamin D3 to raise the total serum 25-hydroxyvitamin D [25(OH) D] in adults. They found that supplementation with 25(OH) D3 resulted in four to five times higher serum 25(OH) D concentrations compared with supplementation with vitamin D3. The authors completed that the capacity of foods rich in 25(OH) D3 to recover vitamin

D status may have been underestimated (9). None of the vegetables is a good source of vitamin D. Industrially made vitamin D2 (Ergocalciferol) is produced by exposing ergosterol from yeast to UVB light. Vitamin D3 (cholecalciferol) is produced from 7-dehydrocholesterol in a similar way from wool fat, as a starting material, followed by purification (10).

#### 3.1. Metabolism of Vitamin D in Body

As already mentioned, both ergocalciferol and cholecalciferol molecules pass the liver where are being hydroxylated in the 25th position. The resulting molecule known as "25(OH) vitamin D" is an active hormone that increases calcium absorption (10). These molecules undergo the second hydroxylation when they pass kidneys, and the final product is known as 1, 25 (OH) 2 vitamin D (calcitriol). This latter compound is the most active form for physiology of vitamin D in the body (1). This metabolite not only regulates calcium and phosphorus metabolism but can motivate the pancreas to create insulin and to down regulate the renal production of rennin (2). The poor absorption of calcium causes a reduction in serum-ionized calcium levels. This is directly renowned by the calcium sensor in the parathyroid glands, resulting in an enhance in the appearance, production, and discharge of PTH (2); PTH conserves calcium by rising tubular reabsorption of calcium in equally the proximal and distal convoluted tubules (2). Circulating vitamin D, the parent compound, likely plays an important physiological role with respect to the vitamin D endocrine/autocrine system, as a substrate in many tissues, not originally thought to be important (11).

#### 3.2. Diagnosis of Vitamin D Deficiency

Clinical: Clinical symptoms of nutritional rickets and Osteomalasia are somewhat similar and include ache and pains, weakness, and fatigue. In advanced cases of rickets, which are rare nowadays, bone deformities, tetany, laryngospasm, and even paralysis may occur (1, 2).

Laboratory: In the past, physicians used to ask for bone radiographs, and blood tests for calcium, phosphorus, and alkaline phosphates. Nowadays measurements of vitamin D3 or its products are available. The most frequently measured vitamin D metabolite is 25(OH) vitamin D3. The method is RIA (Radio Immune Assay) with the normal serum of > 12.5 nmol/L, and also by Chemiluminescence Method, with normal serum level of > 10 ng/mL. In order to diagnose vitamin D deficiency status, a measurement of serum calcium, phosphorus, and alkaline phosphatase is also popular. There is another diagnostic level for vitamin D deficiency based on the compensatory raise of parathormone hormon (PTH) (measured by Immunoradiometric assay (IRMA), kits manufactured by Bio source Europe SA, Belgium), reported as 30 ng/mL (29) 1,25dihydroxy vitamin D is also measurable but is not popular in Iran.

**Table 1.** Data Extracted from the Selected Papers <sup>a</sup>

	Authors	Year of Study	Year of Publication	Place of Study	Case No.	Adult	Pediatric	Without	Mild	Mod.	Severe	Design of study	Lab. Method	According to the kit	PTH rise
1	Reiszadeh F, et al. (12)	2001	2003	Tehran	1172	×	×		91%			×	RIA	×	
2	Hashemipour S, et al. (13)	-	2004	Tehran	1210	×			14.2%	57.6%	9.5%	×	RIA		×
3	Moradzadeh, et al. (14)	2004	2005	Bushehr, Mashhad, Shiraz, Tabriz, Tehran	5329	×			27.2%	42.8%	5.1%	×	RIA		×
4	Rahimi A, et al. (15)	2004	2005	Tabriz	252	×			33.6%	15.5%	15.1%	×	RIA		×
5	Shahla A, et al. (16)	2003	2005	Urmia	162	×		18%	25%		57%	×	-		×
6	Heydarpour R, et al. (17)	2004	2006	Isfahan	318	×			19.8%	18.6%	7.9%	Cross-sectional	RIA		×
7	Salek, et al. (18)	2006	2007	Isfahan	513		×		3%		0	×	RIA		×
8	Maghbooli, et al. (19)	2002	2007	Tehran	552	×			66.8%			×	RIA		×
9	Sahargahi B, et al. (20)	2004	2007	Islam abad gharb	155	×		8.4%	18.7%		72.9%	×	Chemiluminescence method		×
10	Heshmat R, et al. (8)	2001	2008	Bushehr, Mashhad, Shiraz, Tabriz, Tehran	5232	×					44%	Meta-analysis	RIA		
11	Neyestani T.R, et al. (21)	2005	2008	Tehran	90	×			33.3%	33.3%	10%	×	HPLC-CPBA-RIA		×
12	Salek M, et al. (22)	2005	2008	Isfahan	88	×			26.1%			Cross sectional	RIA		×
13	Hossein nezhad A, et al. (23)	2008	2009	Tehran	646	×			72.3%			×	IDS		×
14	Hossein nejad A, et al. (24)	2009	2009	Tehran	646	×			72.3%			Cross-sectional	IDS		×
15	Rahnavard Z, et al. (25)	2001	2010	Bushehr, Mashhad, Shiraz, Tabriz, Tehran	2396	×			25.8%	39.2%	3.9%	×	ELISA/EIA		×
16	Asemi Z, et al. (26)	2008	2010	Kashan	147	×			60.57		32.21	×	RIA		×
17	Ardestani P, et al. (27)	-	2010	Isfahan	530		×		26%		3%	×	RIA		×
18	Talaei et al. (28)	2009	2011	Arak	420	×			84%			×	RIA		×
19	Hovsepian S, et al. (29)	2010	2011	Isfahan	1111	×			19.6%	23.9%	26.9%	×	RIA		×
20	Kaykhaei MA, et al. (30)	2010	2011	Isfahan	993	×			94.7%			×	-		×
21	Nikooyeh B, et al. (31)	2009	2011	Tehran	90	×		26.7%	34.4%		38.9%	Randomized clinical trial	HPLC		×
22	Abbasian M, et al. (32)	2010	2012	Shahrood	284	×			60.2%		1.1%	×	IDS		×
23	Neyestani TR, et al. (33)	-	2012	Tehran	1111		×		21%	26%	48%	×	IDS		×
24	Baradaran A, et al. (34)	2010	2012	Markazi province	259	×			48%			×	ELA		×
25	Kashi Z, et al. (35)	2010	2011	Sari	351	×	×	87.5%				Coss sectional study	ELA		×

<sup>a</sup> Abbreviations: RIA, Radio Immune Assay; CPBA, Competitive Protein-Binding Assay; HPLC, High Performance Liquid Chromatography; IDS, Immunodiagnostic System; ELISA, Enzyme-Linked Immunosorbant Assay; EIA, Enzyme Immunoassay; ELA, Enzyme-Labelled Antigen.

Prevention and Treatment: Prevention of rickets and Osteomalacia is by daily intake of 400 IU (1). Previously the recommended dose of vitamin D to prevent rickets was said to be 200 IU/day (1). Treatment of both diseases is by administration of 600,000 units of vitamin D as a single intramuscular injection or taking the same dose as oral preparation (36). There are researches regarding different responses of body to different doses and routs of administration, but practically results are the same. Heal-

ing of bones starts about 4 weeks after treatment.

The Result of Maternal Vitamin D Supplementation Through Lactation on the Vitamin D Condition of the Breastfed Infant: The vitamin D content of human milk is related to the lactating mother's vitamin D status. In a lactating mother supplemented with 400 IU/day of vitamin D, the vitamin D content of her milk ranges from < 25 to 78 IU/L. Infants who are completely breastfed but who do not get supplemental vitamin D or sufficient sunlight

contact are at improved risk of increasing vitamin D insufficiency and/or rickets. Infants with darker pigmentation are at superior risk of vitamin D deficiency, a fact explained by the larger risk of insufficiency at birth and the decreased vitamin D content in milk from women who are deficient themselves (1). Even though vitamin D concentrations can be improved in milk of lactating women by using great vitamin D supplements, such high-dose supplementation in lactating women must be validated and confirmed to be secure in larger population. Recommendations to universally supplement breastfeeding mothers with high-dose vitamin D are not complete yet. Therefore, it is essential to give supplements to the infant. Infant formulas have 400 units of vitamin D in one liter. All infants who are consuming less than a liter per day of the formula have to take supplement vitamin D (1).

**Vitamin D Supplements:** Vitamin D supplements (as D2 or D3) are available in all types of medication. Drop, syrup, tablets, capsules, pearls, and injecting forms and usually are not expensive. Even water soluble solution for intra venous administration is made for the patients with lipid malabsorption (36). Unfortunately the cost of vitamin supplementation is not covered by medical insurances in Iran. However, more costly interventions which could be prevented by vitamin administration are being covered. Use of calcitriol is recommended for hypoparathyroidism, chronic renal failure, and vitamin D resistant rickets, but not for nutritional rickets.

**Necessity to Add Calcium Supplements to Vitamin D supplements:** Some authors still debate that rickets is a state of calcium deficiency, which is true in a sense. Since the first and the best known function of vitamin D are to absorb calcium from the intestine, there should be enough intake of calcium as well. In a vitamin D-lacking condition, only 10%-15% of the nutritional calcium and 50%-60% of dietary phosphorus are engrossed (2). Therefore, supplementation of diet with calcium is advisable. In case of doubts, oral calcium salts as tablets are advisable. Calcium carbonate as 500 mg tablets has 200 mg of elemental calcium. Calcium D tablets are fortified with 200 IU vitamin D3, which is preferred to the former compound. There is also a more potent form of calcium preparation as an effervescent tablet with 500 mg elemental calcium. There are also calcium suspensions with different concentrations of elemental calcium (37). There are other calcium supplements in the market. Some have magnesium or zinc as a co supplement. It is noteworthy that calcium suspension has a little elemental calcium in each 5 mL that is a very low dose. For persons with greater need to calcium there is effervescent calcium preparation with 500 mg of elemental calcium per tablet.

**Universal Food Fortification:** Vitamin D is a fat soluble vitamin. It is tasteless and odorless and inexpensive (38). The most suitable food would be cooking oils and or dairy products. Shelf life of cooking oils are longer. There is a discussion about the form of vitamin D that should be used for food enrichment or supplements (39). Early

clinical studies suggested that cholecalciferol is superior to ergocalciferol in sustaining higher serum 25(OH) D concentrations. Tripkovic et al. (40) conducted a systematic review and the meta-analysis of 10 randomized controlled trials in humans that considered the serum 25(OH) D retort to ergocalciferol compared with cholecalciferol. The authors established a significant mean difference of 15 nmol/L change in serum 25(OH) D that favored cholecalciferol compared with that of the ergocalciferol supplementation. When the authors examined the studies of bolus dosing of vitamin D, they also established a better increase in serum 25(OH) D concentrations with cholecalciferol compared with ergocalciferol (40). These findings propose that cholecalciferol might be the preferred form of vitamin D to be used in supplements or food fortification (9). There are also some concerns about universal fortification which is the risk of vitamin D intoxication in some populations who probably get vitamin D from other sources as well. Previously, the maximum allowed dose of vitamin D was 1000 IU for infants under one year old, and 2000 IU/day for older infants, however, toxic level was reported in children that took as high as 50,000IU/day of vitamin D2 (2).

Examples of Salt Fortification With Iodine and Iron Fortification of Flour in Iran: Ministry of Health and Medical Education had at least two successful experiences in food supplementation in the past. Epidemiologic data regarding goiter and iodine deficiency goes back to 1969 and then in 1990 ended up in salt fortification with iodine (41). The second and more recent food fortification concerns were adding iron and folic acid to the wheat flour. A pilot study was conducted in Shahinshahr Isfahan and Booshehr in 2001 then extended to other areas (42).

#### 4. Conclusions

One of the key points in cross-sectional studies is the sample size. Sample size depends on some factors including accepted rates of type 1 and type 2 errors, and anticipated frequency of subjects in question. In the current study it was the estimated prevalence of vitamin D deficiency (43). Sample size was too small regarding the reported frequencies in some studies (15, 20, 21, 26, 31, 34). On the other hand the biggest screened number was 5'329 subjects (14). This sample size was too big indeed. Problems with too big sample sizes include long time, high cost, and probability of human errors. Another important point in cross-sectional studies is the random sampling (43). In some papers it was not mentioned properly in detail or sampling was not random at all (44, 45). A meta-analysis was done in 2001, however it was published in 2008 (8). Such a delay, made many others to do the same researches. Even well after 2008 many papers were published concerning the same issue and all emphasized on the importance of the consequences (23, 28-30, 32-34). Heshmat et al. reported that 44% of the studied subjects had severe vitamin D deficiency. Result of this Meta-analysis was enough to start a national for-

tification program. However none are done yet (8). Larijani et al. conducted a clinical trial by adding vitamin D to milk in Tehran (46). They recommend fortifying milk with vitamin D. In the industrialized countries vitamin D is added to Milk, (47) cheese, (48) other dairy products (both regular-fat and low-fat), (49) margarine, (47) oil spread, (49) orange juice, (50) and bread (51).

As a practice in the 1930s in Canada and the United States, fortification of vitamin D reduced the risk of osteoporosis in the elderly, and in important advantages to grow thin children (for growth and development) and pregnant women (52). The fortification level of vitamin D in the related studies varied from 2.5 to 125 µg/day; the most common doses were between 5 and 25 µg/day. The fortification level for each food depended on the intake and characteristics of that food. Some studies showed positive effect of vitamin D fortification on concentration of 1-25 OH. The result of Meta-analysis study on vitamin D fortification showed that the lowest (2.5 µg/day) and the highest (125 µg/day) doses of vitamin D can end the smallest (2 nmol/L) and the largest (97 nmol/L) improvements in 25OH. This study showed no reported toxicity by the foods fortified with 100 µg/day vitamin D (49).

Dealing with a national important nutritional problem theoretically has more than one solution. One way is to fortify suitable foods or edible products such as milk or cooking oil. There are also other possible ways such as increasing public awareness about the problems and motivating people to do something on their own expenses. In this case taking vitamin D supplements as a regular basis would be advisable. Daily, weekly, or any other routines which could be available and cost effective may solve the problem.

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