



AN OVERVIEW TO VITAMIN D DEFICIENCY AND TREATMENT IN PREGNANT WOMEN

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ABSTRACT

Vitamin D is a lipid soluble prehormone which has a well known role in regulation of calcium and phosphate homeostasis as well as bone metabolism. Vitamin D deficiency is a common health problem all over the world. In fact, the condition is considered as a pandemia. The most recognized effect of vitamin D is over metabolism of calcium and phosphor and bone mineralization; deficiency causes a clinical presentation called rickets in children and osteomalasia in adults. However, association of vitamin D deficiency with many chronic diseases such as common cancers, cardiovascular diseases, metabolic syndrome, infectious and autoimmune diseases was found in the recent years. The aim of the present review was to present an updated approach to effects of vitamin D deficiency on pregnant women and fetuses as well as treatment of the deficiency which is very common in adults.

Keywords: Vitamin D deficiency, pregnancy, fetal effects

ÖZET

D vitamini kalsiyum fosfat dengesinin düzenlenmesi ve kemik metabolizmasında görevli, yağda çözünen bir pre-hormondur. Dünya çapında D vitamini eksikliği yaygın olarak görülmektedir. Hatta bu durum pandemi kabul edilebilir. En belirgin etkisi kalsiyum ve fosfor metabolizması üzerindedir ve eksikliği çocuklarda rickets ve erişkinde osteomalazi kliniği ile karşımıza çıkar ve bu durum kemik ağrıları ile karakterizedir. Gebelikte D vitamini ihtiyacı artmaktadır. Gebelikte D vitamini eksikliği, preeklampsi, gestasyonel diyabet gibi çeşitli gebelik komplikasyonları ile ilişkilidir. Fetal kemik metabolizması ve gelişimi de D vitamini eksikliğinden olumsuz etkilenir. Geçtiğimiz yıllarda pek çok kronik hastalık, yaygın bazı kanserler, metabolik sendrom, kardiyovasküler hastalıklar, enfeksiyöz ve otoimmün hastalıklarla da D vitamini eksikliği arasında ilişki gösterilmiştir. Bu derlemenin amacı erişkinde yaygın görülen bu durumun, gebelik ve fetus üzerine etkilerini ve güncel tedavi yaklaşımlarını sunmayı amaçlamıştır.

Anahtar Kelimeler: D vitamini eksikliği, hamilelik, fetal etkiler

INTRODUCTION

Vitamin D, one of the lipid soluble vitamins, is a group of sterols with hormone-like functions. Vitamin D has two forms including cholecalciferol (vitamin D3) synthesized in the skin and ergocalciferol (vitamin D2) taken with foods [1,2]. The most important effect of the vitamin is on calcium and phosphore metabolism as well as bone mineralization [3,4]. However, an association between deficiency and insufficiency of vitamin D and many chronic diseases including cancers, cardiovascular diseases, metabolic syndromes, infectious and autoimmune diseases [5,6]. Vitamin D deficiency is a common health problem all over the world. In fact, the condition is considered as a pandemia. In a study conducted in Ankara region of our country detected a quite higher deficiency (51.8%) and insufficiency (20.7%) rate [7]. Deficiency or insufficiency of vitamin D is common among pregnant women and pregnancy is one of the risk factors for vitamin D deficiency [8-10].

DERIVATION OF VITAMIN D IN THE BODY

The skin synthesis about 90-95% of vitamin D in human body and a less portion is taken with diet. Therefore, geographical features, season and incidence angle of the sun-rays affect vitamin D production [11,12]. A study found that vitamin D level of the body was lower in winter season than summer [13].

There are 2 types of vitamin D which have different resources with similar formations and structures in skin synthesis. These are calciferol (vitamin D2) and cholecalciferol (vitamin D3). Calciferol (ergocalciferol) is synthesized from vegetal ergosterole and vitamin D3 (cholecalciferol) is synthesized from 7-dehydrocholesterol (provitamin D3) synthesized in the body as a result of skin exposure to ultraviolet light [14]. The ultraviolet (UV) required for vitamin D formation is UV-B with a wave-

length of 290-315 nm. The most suitable wavelength for synthesis of vitamin D in our country is obtained by sun exposure of the body between 11.00 a.m. and 3.00 p.m. within April to November. Vitamin D which is synthesized in the body is hydroxylated in the liver and 25 (OH) vit D appears. The 25 (OH) vit D is re-hydroxylated in the kidneys and metabolically active form, 1,25(OH) vitamin D appears. Half-life of vitamin D is predicted to be about three weeks [15-17].

About 5% to 10% of vitamin D which is not synthesized in the skin naturally exist in fatty fishes, fish liver, fish oil, liver, egg yolk, mushroom and red meat and cheese in lower amounts. Furthermore, milk, fruit juices, margarines, yoghurt, bread, breakfast cereals have supplemented vitamin D [18].

Food	(IU)
Salmon (105 g)	360
European pilchard (52.5 g)	250
Tuna fish (90 g)	345
1 whole egg	20
Calf's liver (105 g)	15

Table 1: Vitamin D content in foods

Increase in calcium and phosphor levels in serum and tissues inhibit 1-hydroxylase activity whereas parathyroid hormone and lower calcium/phosphor levels increase 1-hydroxylase activity as well as 1,25(OH)2D3 production [19, 20].

EFFECTS OF VITAMIN D IN THE BODY

Vitamin D provides calcium and phosphate uptake by increasing blood level of these minerals and enabling transition from blood to bone matrix for bone mineralization.

Effects of vitamin D on organs include increasing calcium and phosphorus absorption in the intestines, increasing calcium reabsorption in the kidneys and suppressing parathormone, stimulating the immune system in the lymphoid tissue and increasing bone formation through stimulation of osteoblasts in the osseous tissue. Furthermore, it has some functions such as suppressing cellular proliferation in different tissues, suppressing angiogenesis, stimulating insulin production and suppressing rennin production [1,2,21].

ANALYSIS OF VITAMIN D IN THE BODY

Assessment of vitamin D in an individual is performed by analysis of 25(OH) vit D level which has a half life of 2 to 3 weeks and shows vitamin D intake and endogenous production. The biological active form, 1,25(OH)₂D is not suitable for analysis. Because its half life is very short (4 to 6 hours) and levels in the circulation is 1,000-fold lower than 25(OH) vitamin D [22, 23]. Many studies were carried out to identify vitamin D deficiency and insufficiency and to detect normal range of 25(OH) vitamin D level. In the light of these studies; a 25(OH)D level lower than 20 ng/mL is accepted as vitamin D deficiency; 25(OH)D level between 12 and 29 ng/mL is considered as vitamin D insufficiency; sufficient level of vitamin D is accepted as serum levels of 25(OH)D higher than 30 ng/mL (preferred range is between 40 and 60 ng/mL) and vitamin D intoxication is accepted as levels higher than 150 ng/mL [22,23].

There are different methods for analysis of 25(OH)D level in pregnant women. WHO (World Health Organization) and some organizations of USA do not recommend a routine 25(OH)D analysis for pregnant women. American Academy of Pediatrics and Canadian Pediatrics Society suggest a regular analysis of calcium and vitamin D levels in pregnant women [18,24]. The program in our country recommends to start vitamin supplementation without analysis of 25(OH)D level [18].

Hazardous Conditions for vitamin D deficiency

- Chronic kidney disease
- Liver failure
- Malabsorption syndromes (Cystic fibrosis, Irritable Bowel Syndrome (IBS) Chron's disease, obesity surgery, radiation enteritis, ingestion of foods with much fiber)
- Hyperparathyroidism
- Medications (Antiepileptic drugs, glucocorticoids, AIDS therapy, anti-fungal agents, cholestiramine)
- Pregnant and breastfeeding women
- Seniors with a history of falling
- Seniors with a history of non-traumatic fracture
- Obese children and adults
- Granulomatous diseases (Sarcoidosis, tuberculosis, histoplasmosis)
- Some lymphoma types
- Individuals with dark skin color
- Diet deprived from vitamin D resources
- Insufficient exposure to sun light (covered dressing style due to religious or cultural effects, having day-time indoor, use of sun-screen creams, urban or industrial air pollution)
- Geographical conditions of the countries [25,17]

CLINICAL SIGNS OF VITAMIN D DEFICIENCY

Deficiency of vitamin D causes a clinical presentation of rickets in children and osteomalasia in adults. The most significant complaint in osteomalasia is common pain including pelvis, spine and ribs. The pain generally starts from low back area and diffuses to the pelvis, hips, femur, back and ribs. Tenderness and pain may appear by deep palpation of the tibia, sternum, spinous processes, pelvis and ribs as a result of tapering of the osseous cortex. Another clinical sign for osteomalasia

observed in adults is antalgic walking or proximal muscular weakness causing walking difficulty. The patients have difficulty to get up a chair without getting support from their arms and going up and down a ladder [25,26]. The first sign of severe osteomalasia may be a fracture. The typical radiological finding for osteomalasia is diffuse osteopenia and pseudofractures called Looser's zones. Pseudofractures are usually observed on long bones, pubic and ischial rami, ulna, ribs and scapula [23].

Biochemical findings of osteomalasia may include normal or lower serum calcium levels, lower phosphorus levels, higher PTH and ALP levels, lower 25(OH)D levels and normal or higher 1,25(OH)₂D levels. However, if deficiency of vitamin D is dependent to 1-alpha hydroxylase enzyme, lower 1,25(OH)₂D levels as well as normal or higher 25(OH)D levels may be detected [27].

Many prospective and retrospective studies revealed that colon, prostate and breast cancers are more common in conditions with insufficient vitamin D levels [18,23]. Furthermore, vitamin D insufficiency is associated with multiple sclerosis, rheumatoid arthritis, osteoarthritis, type 1 diabetes, hypertension and cardiovascular diseases (cardiac hypertrophy and increase in tendency to thrombosis) [26].

EFFECT OF VITAMIN D ON PREGNANT WOMEN

During the pregnancy, calcium required for development of fetal bone mineralization, development of bone and growth and gain of function of the tissues is provided from the mother through some modifications in maternal vitamin D and calcium metabolism. Approximately 25 to 30 grams of calcium passes from mother to the fetus during the pregnancy (a great portion within third trimester) [26]. For this purpose, absorption of fractioned calcium from the intestines increases by 35 to 60% especially within third trimester [26]. Ionized calcium and phosphorus levels remain constant whereas maternal serum calcium level decreases during pregnancy; and this continues throughout pregnancy. PTH level decreases to 10-30% of PTH level before pregnancy during the first trimester; however it increases to the pre-pregnancy level within second half of the pregnancy [28]. Active vitamin D (1,25(OH)₂D₃) level in the serum increases more than two-fold by progression of the pregnancy. Free 1,25(OH)₂D₃ concentration remains higher during pregnancy, despite the increase in vitamin D binding protein concentration. 1,25(OH)₂D₃ increases absorption of calcium from small intestines of the mother [28,29]. Many studies showed that all aforesaid modifications caused a decrease in mineral density of the bone by 2-4% and this decrease usually appeared on the spine and distal radius [29-33].

CLINICAL EFFECTS OF VITAMIN D DEFICIENCY IN PREGNANT WOMEN

It is known that maternal vitamin D level is important for fetal bone development, formation of dental enamel as well as fetal growth and development during pregnancy. Along with these effects, an association between maternal vitamin D level and neurological development, immune functions and predisposition to chronic diseases (asthma, schizophrenia, Type 1 diabetes) is suggested just after the birth and further periods of life [34].

Deficiency of vitamin D during pregnancy is related to an increased risk for preeclampsia [35-39], gestational diabetes mellitus [40], premature delivery [41,42], deformed fetal skeletal formation as a cause of infantile rickets (softening of the bone causing fractures and deformation) and decreased bone mass [43-45]. Although the underlying pathogenic mechanisms are not well-known, insufficient vitamin D level was associated with maternal immune dysfunction, abnormal angiogenesis and placental implantations [46-50]. Some studies go further and further, although the underlying pathogenic mechanisms are not well-known (It was connected to the reduction of pelvic muscle strength), insufficient vitamin D level was associated with increased cesarian births to [51,52].

A study reported that vitamin D deficiency during pregnancy period of the rats caused ventricular dilatation in fetuses, decrease in "neural growth factor" content, lower activities of the genes which provide neural structure and neurotransmitter formation [53]. Furthermore, studies carried out on rats detected some findings which suggested an association between vitamin D deficiency during pregnancy and schizophrenia-like conditions [54]. Moreover, maternal 25-OH-D vitamin

level during late term of pregnancy was shown to be associated with lumbar spinal bone mineral composition, bone age and bone mineral density of whole body at nine years of age [55]. A study conducted in Canada compared the effects of maternal milk intake and vitamin D intake on growth parameters of the newborns and detected that vitamin D intake was associated with the birth weight and an increase of 11 grams occurred in birth weight per 40 IU vitamin D intake [56]. Another study where intrauterine effects of maternal vitamin D were searched found a correlation between 25-OH-D vitamin level in umbilical cord blood and head circumference at postnatal third and sixth months [57]. It is reported that infants of the mothers with vitamin D deficiency born with lower birth weights of about 200 grams [58]. A recent study from Japan stressed out that “physiological craniotabes “ incidence in newborns was connected with low vitamin D levels and such condition was a result of intrauterine vitamin D deficiency [59].

TREATMENT OF VITAMIN D DEFICIENCY FOR NON-PREGNANT INDIVIDUALS

Endocrine Society recommended different therapeutic strategies for the patients with vitamin D deficiency according to the age and underlying medical conditions in its practice guideline [60] as follows;

For infants and toddlers between 0 and 1 years of age who are vitamin D deficient, 2000 IU/d of vitamin D2 or vitamin D3, or 50,000 IU of vitamin D2 or vitamin D3 once weekly for 6 weeks to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 400-1000 IU/d;

For children between 1 and 18 years of age who are vitamin D deficient, 2000 IU/d of vitamin D2 or vitamin D3 for at least 6 weeks or with 50,000 IU of vitamin D2 once a week for at least 6 wk to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 600-1000 IU/d;

For all adults who have vitamin D deficiency, 6000 IU of vitamin D2 or vitamin D3 are administered daily or 50,000 IU of vitamin D2 or vitamin D3 once a week for 8 weeks to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 1500–2000 IU/d;

For obese patients, patients with malabsorption syndromes, and patients using medications affecting vitamin D metabolism, a higher dose, at least 6000–10,000 IU/d) of vitamin D to treat vitamin D deficiency to maintain a 25(OH)D level above 30 ng/ml, followed by maintenance therapy of 3000–6000 IU/d

Treatment strategy with 50,000 IU of vitamin D twice a month treats vitamin D deficiency or insufficiency without any toxicity and prevents recurrence up to six years [61]. A recent study found that 50,000 IU of vitamin D intake every other week or equivalent intake of 3,000 IU/day of vitamin D was effective to keep 25(OH)D level in the blood between 40 and 60 ng/mL without any toxicity. There is not any hazardous case for increase of vitamin D intake in children or adults except granulomatous conditions such as sarcoidosis and tuberculosis. All adults should intake 2,000 IU/day vitamin D [62]. However, toxicity risk of vitamin D increases in some certain conditions such as granulomatous diseases, genetic disorders or enzyme polymorphism rarely affecting vitamin D metabolism [61].

Recommended doses of vitamin D to prevent deficiency in pregnant and non-pregnant individuals

Institute of Medicine (IOM) recommends to start 400 IU/day vitamin D supplementation for infants during first year of life, 600 IU/day vitamin D supplementation for individuals between 1 and 70 years of age and 800 IU/day vitamin D supplementation for the individuals over 70 years of age to prevent vitamin D deficiency.

The aforesaid doses recommended by IOM may increase 25(OH)D level to 20 ng/ml which is considered sufficient for bone health; however, it is not enough for 30 ng/mL levels suggested by the Endocrine Society. Therefore, the Endocrine Society recommends daily intake of 400-1000 IU (safe up to 2000 IU) of vitamin D per day in infants for first year of life, 600-1000 IU (safe up to 4000 IU) of vitamin D for children and adolescents between 1 and 18 years of age and 1500-2000 IU (safe up to 10,000 IU) for adults over 18 years of age.

However, higher doses may be required for obese individuals, patients with malabsorption syndrome, individuals treated by glucocorticoid

and antiepileptic drugs [61]. Prevention of vitamin D deficiency in pregnant women requires sufficient exposure to sun as well as vitamin D supplementation during pregnancy. IOM specifies that pregnant women should intake 600 IU of vitamin D, daily intake may be increased to 4000 IU for pregnant women with vitamin D deficiency and same dose should be continued during lactation period to maintain health of the mother and the baby [63, 18]. It is reported that daily intake of 600 IU of vitamin D is recommended for pregnant women to keep serum 25(OH) vitamin D level at about 5 nmol/L to prevent deficiency [64,65]. World Health Organization/United Nations Food and Agriculture Organization recommends 5 µg (200 IU) of vitamin D intake per day for pregnant women. However, various studies showed that 800 to 1600 IU/day of vitamin D supplementation during pregnancy period have not achieved normal serum levels of 25-OHD and therefore, daily supplementation of 2000 IU of vitamin D and making vitamin D supplementation as a part of antenatal care were suggested [66,67].

Due to the risk of vitamin D deficiency in pregnant women for both mother and infant health, a project initiated by General Directorate of Mother and Child Care and Family Planning of Ministry of Health recommends a single dose of 1200 IU (9 drops) vitamin D per day for all pregnant women for 12 months between second trimester of pregnancy and postnatal sixth month [63].

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Conflict of Interest

The author declares that he has no conflict of interest