Original Article

The Role of Vitamin D in Body Organ Systems: A Systematic Review

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Abstract

Introduction: The role of vitamin D was used to be focused on mineral homeostasis and bone reuptake. Though, discovery of the role of vitamin D in prevention form a number of diseases including breast and colon cancers, asthma, cardiovascular diseases, inflammatory bowel disease, systemic lupus erythematous, rheumatoid arthritis, type I diabetes, and infectious diseases, enhanced the importance of this vitamin. **Materials and Methods:** In this review article, PubMed, Scopus, Google Scholar, Medline and Embase databases were used and approximately 291 studies were assessed. Inclusion criteria of this study was using searching terms in the title and key words of the studies. 240 studies were discussed and summarized on the role of vitamin D is body organ systems. **Discussion and Conclusion:** Due to the extensive role of vitamin D in body organ systems, it can be considered as a treatment goal in different diseases. Moreover, considering the high prevalence of chronic diseases and vitamin D deficiency, this review article aims to discuss the role of vitamin D in body organ systems and processes such as inflammation, blood coagulation, cancer, and metastasis.

Keywords: Vitamin D, Body Organ Systems, Chronic Diseases

Introduction

Vitamin D plays a vital role in human's health, survival, and fertility in all stages of life [1]. Chemical structure of vitamin D is similar to steroid hormones and vitamin D acts via VDR nucleus receptors as well [2]. Vitamin D is synthesized in the skin and is transferred to the liver through blood circulation where it is turned to calcidiol (25 (OH) D) by 25-hydroxylase enzyme. Then, calcidiol is transferred to kidney where the active for of Vitamin D or calcitriol (1,25 $(OH)_2$ D3) is formed by renal 1-α hydroxylase [3-6]. Circulating level of calcitriol with a half-life of 1-2 month indicated vitamin D status in terms of vitamin D production, absorption, and storage [7]. Fish oil (salmon and sardine), egg yolk, and fortified milk are nutritional sources of vitamin D [8]. Unfortunately, in most cases, the amount of nutritional vitamin D is not sufficient and fortified foods are limited and cannot supply the required amounts of vitamin D. This is the most important issue that leads to epidemic prevalence of vitamin D deficiency especially in European and American countries. In fact, the major source of vitamin D is production of vitamin D when exposed to ultra violet waves of sunlight [9]. Its major function is regulation of calcium and phosphorus homeostasis and bone mineralization, while an extensive distribution of its intracellular receptors have been found in different body tissues [10]. On the other hand, vitamin D increases the intestinal absorption of phosphorus and calcium and decreases their renal excretion and reinforces osteogensis. As a result, vitamin D deficiency is a major factor in the incidence of osteogenic metabolism disorders [11]. Recently, non-calcium related role of vitamin D, especially its anti-inflammatory and immunomodulatory role, has attracted much attention. The beneficial effect of vitamin D and its metabolites in different autoimmunity disorders have been proved in animal studies [12]. Several studies indicate that decreased levels of vitamin D are associated with breast cancer, colon cancer, asthma, cardiovascular diseases, preeclampsia, multiple sclerosis, systemic lupus erythematosus, rheumatoid arteritis, type I diabetes and

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infectious diseases [11, 13, 14]. Vitamin D deficiency occurs in individuals with inappropriate dietary intake or insufficient exposure to ultra-violate B waves (UVB, 290-320 nm) [15]. Serum 25(OH)D level is used as a reliable index to assess vitamin D status [16]. Thus, vitamin D deficiency is affected by a number of factors including age, sex, geographical area, and diet [17]. It is estimated that more than one billion people suffer from vitamin D deficiency all over the world. The elderly and children are at higher risk of vitamin D deficiency [18]. According to NHANES study, the level of vitamin D is sufficient only in 23% of people in the United States [19]. Some studies have evaluated vitamin D status in Iran indicating high prevalence of vitamin D deficiency in Iran ranging from 44.8% to 79.6% [20, 21]. Decreased serum level of Vitamin D_3 induced by antiepileptic medications [22] increases the prevalence of vitamin D deficiency and its complications in both childhood and adulthood [23]. Vitamin D content of breast milk is relatively low [24]. As a consequence, vitamin D deficiency is more common among infants who are only breastfed [25]. In case of maternal vitamin D deficiency, the deficiency is worsened; thus, infants receive formula, fortified milks, nutritional supplements containing vitamin D such as vitamin AD and D and multivitamin drops to compensate this shortage [26].

Due to the high prevalence of vitamin D deficiency in Iran, especially in women, and the role of vitamin D is various physical and mental diseases, this review article is intended to comprehensively assess the role of vitamin D in body organ systems.

Method

Search strategy and selection criteria

This systematic review was conducted based on the methods presented in PROSPERO. The outline protocol includes the evaluation of the effect of vitamin D on different organs in human body.

In this review article, 291 studies were included which consists of original studies, review articles, double-blinded studies, and clinical trials. Following the initial evaluation and exclusion of irrelevant studies and animal studies, 240 relevant studies were used in this article.

Researchers searched valid electronic databases such as Pubmed, Scopus, Google Scholar, Medline, and Embase using Vitamin D, Cardiovascular, Infertility, Immune System, Endocrine System, Musculoskeletal, Nervous system, and Cancer key words. Studies published until 12th February, 2019 were included in this study without any language limitation.

Data Analysis

In this study, researchers evaluated different data and studies with internal consistency analysis and the obtained results.

In this study, the following variables were extracted: Setting, eligibility criteria, details of intervention and control regimens, and study duration. Afterwards, the authors published this study according to the principles of article writing.

Role of Vitamin D in Cardiovascular System

Blood circulation in the vascular system includes vessels and capillaries. To effectively maintain the blood flow, appropriate nutrition including a verity of vitamins is required. Niacin, Vitamin E, Vitamin D, vitamin C, and Vitamin K are among these vitamins. Vitamin D is the most important vitamin affecting the cardiovascular system through various mechanisms. These mechanisms include downregulation of PTH [27], suppression of Renin-Angiotensin-Aldosterone system [28], regulation of proliferation of smooth muscle cells of vessel walls and cardiomyocytes [29], improvement of vasodilation [30], and regulation of coagulation system [31]. Vitamin D controls more than 200 genes which are responsible in cell growth, proliferation, and differentiation. Hence, vitamin D deficiency may lead to ventricular hypertrophy, vessel stenosis or obstruction, heart failure and arrhythmia [32].

- #### Effect of Vitamin D on Hypertension

E, D, and C are fat-soluble vitamins with a very strong anti-oxidant property which neutralizes free radicals and protects body tissues and blood vessels. These vitamins have been effective in preventing from preeclampsia and reducing mean diastolic blood pressure. Yet, Vitamin D is engaged in renin-angiotensin-aldosterone systems and thus modulates blood pressure and prevents from malignant hypertension. Moreover, previous studies have shown that higher levels of 25–hydroxy vitamin D is associated with lower blood pressure, blood sugar and lipid. As a result, vitamin D is more effective in comparison with other micronutrients [33-36]. Wood et al. study (2015) suggested that blood pressure is lower in summer compared with winter which may be caused by higher levels of vitamin D n the summer compared with winters [37]. Loloei et al. study (2013) proved the significant prevalence of vitamin D deficiency in hypertension patients. Moreover, it is suggested that vitamin D deficiency treatment affects hypertension [38].

- #### Effect of Vitamin D on Serum Lipid Profile

Dyslipidemia is defined as an imbalance in blood lipid profile including triglyceride, total cholesterol, LDL, and HDL. It seems that D, C, and E vitamins affect lipid profile parameters due to their antioxidant activity. Wang et al. (2008) indicated that vitamin D supplement leads to better and faster reduction in LDL level of patients with hyperlipidemia who are under atorvastatin treatment [39]. Ford et al. showed in NHANES III study that, 25-hydroxy vitamin D serum level is negatively associated with hypertriglyceridemia; though no relationship was observed with HDL or cholesterol level [40]. A purposed mechanism for the negative association between serum level of 25-hydroxy vitamin D and triglyceride relies on the role of

vitamin D in enhancing the activity of lipoprotein lipase enzyme in adipose tissue [41].

• Effect of Vitamin D on Atherosclerosis

vitamin D deficiency induces PTH secretion, calcium bone resorption and deposition in the vessels, aggregation of collagen fibers and increased risk of cardiovascular diseases. Evidences imply the association between vitamin D deficiency and atherosclerosis. Though, the effectiveness of vitamin D supplements in the treatment of atherosclerosis is not yet clear [42, 43].

• Effect of Vitamin D on Heart Failure

Vitamin D can prevent cardiomegaly and progression of heart failure through regulating blood pressure [44]. Different studies demonstrated that low levels of 25-hydroxy vitamin D is associated with cellular transformation leading to ventricular hypertrophy and dilated cardiomyopathy [34, 45]. Hyperthyroidism patients were evaluated in a study which concluded that treatment with calcium and vitamin D reduces the severity of cardiomyopathy and heart failure symptoms [46]. Kerdegari et al. study (2009) showed that vitamin D_3 improves systolic function of left ventricle in patients with chronic heart failure as well as function class status [47]. Several studies, regarding regulation of inflammation by vitamin D, have showed that vitamin D treatment in patients with chronic heart failure reduced inflammatory cytokines (TNF-α) and elevated anti-inflammatory cytokine (IL-10) in comparison with control group [48].

• Effect of Vitamin D in the Treatment of Cardiovascular Diseases

Although the role of vitamin D deficiency in the incidence of cardiovascular diseases has been shown in many studies, the role of vitamin D supplement in the treatment of cardiovascular diseases is not yet proved [49, 50]. According to the slow nature of pathologic process and treatment of cardiovascular diseases, clarifying the uncertainties require more extensive and long-term studies on human population [49, 51].

Due to the ever growing rate of cardiovascular diseases and its mortality and morbidity rate as well as the undeniable role of vitamin D on cardiovascular health, more accurate measurements and screenings should be performed to treat vitamin D deficiency.

Role of Vitamin D in Inflammation and Cancer

• Effect of Vitamin D on Inflammation

A, B, C, D, E, and K vitamins are engaged in the regulation of metabolism and strengthen the immune system. Moreover, these vitamins play role in reducing muscular and joint pain and inflammation and seem to be vital for skin health. Diaz et al. study on human trophoblast culture medium indicated that 1,25-dihydroxy vitamin D can suppress the induction to produce inflammatory cytokines (TNF-α) and reduce expression of TNF-α producing cells which includes many cells such as macrophages, T-cells, smooth muscle cells, adipocytes, and fibroblasts [52, 53]. Many studies have shown that vitamin D and its analogs are able to inhibit IL-6 production in different cells [54-56]. A study on hemodialysis patients with high PTH suggested that 1,25-dihydroxy vitamin D supplement for 6 months reduced the level of IL-6 [57]. A study showed that calcium and 1,25-dihydroxy vitamin D regulate the expression of adiponectin in peripheral adipose tissue and in particular, high calcium diet induce the expression of anti-inflammatory factors such as IL-5 and adiponectin [58]. Due to the anti-inflammatory role of vitamin D, and the fact that adiponectin is the only adipokine with anti-inflammatory role, there might be a strong positive association between vitamin D and adiponectin [59].

• Effect of Vitamin D on Breast Cancer

Anderson et al. study (2010) showed no relationship between vitamin D dietary intake and risk of breast cancer, although the risk of breast cancer was significantly lower in women taking vitamin D supplement more than 400 units/day in comparison with women who did not take any supplement [60]. Another case control study indicated a negative significant relationship between vitamin D dietary intake and the risk of breast cancer [61]. It is demonstrated in Engel et al. study (2011) that individuals who live in area with highest does of sunlight ultraviolet, higher vitamin D intake is associated with reduced risk of breast cancer [62].

• Effect of Vitamin D on Ovarian Cancer

Ovarian cancer is a common cause of mortality and the most common female reproductive cancer [63]. If diagnosed in early stages, it is curable; though, in most cases, long-term survival is poor due to late diagnosis despite using extensive surgical methods and chemotherapy [64]. BRCA gene is not mutated in most women with ovarian cancer so that they can be diagnosed and treated at an early stage. A biomarker such as tt genotype of VDR gene can be studied and used in their diagnosis and treatment [64-66]. Many studies show the relationship between reduced serum level of 1,25-dihydroxy vitamin D and increased risk of ovarian cancer, breast cancer, and prostate cancer. Vitamin D receptor (VDR) coding gene is related to the risk of incidence of ovarian cancer, breast cancer, and prostate cancer in early stages and metastasis. VDR is an estrogen receptor and estrogen increased VDR gene expression in animal models. Moreover, high levels of estrogen in women is associated with enhanced expression of VDR gene mRNA [67, 68]. Onsory et al. study (2013) indicated that tt genotype of VDR gene has a direct association with ovarian cancer in women [69].

Role of Vitamin D in Endocrine System

• Effect of Vitamin D on Diabetes

Biotin, Zinc and vitamin D consumption in diabetic patients maintains blood insulin level through improving the level of Glucokinase enzyme which is engaged in glucose metabolism. The level of Glucokinase, as a hepatic enzyme, is often very low in diabetic patients. Type I diabetes is caused by autoimmune degradation of pancreatic beta cells leading to absolute insulin deficiency. For progression of type

II diabetes, abnormal function of pancreatic cells, insulin resistance and systematic inflammation are present. Numerous evidences prove the effect of vitamin D on all these pathways [70]. Vitamin D acts thorough activation of 25-hydroxy vitamin D by α1-hydroxylase expressed in beta cells. Vitamin D can directly increase insulin sensitivity by stimulation of expression of insulin receptor or thorough peroxisome proliferated-activator receptor-γ (PPAR-γ), the modulator factor of increasing metabolism of fatty acids in skeletal muscles and adipose tissue [71]. Vitamin D directly activate transcription of insulin receptor [72] and acts as the activator of PPAR-γ [73] and this way increases insulin–medicated glucose uptake [74]. Vitamin D deficiency leads to insufficient secretion of insulin and other pancreatic hormones and glucose intolerance in animal models and humans [75]. The purposed mechanism in this regard is the significant increment in Ca^{2+} concentration is cytosol followed by insulin secretion form Langerhans islet cells [76]. The role of vitamin D in type II diabetes in reported due to alterations in glycaemia control in patients with type II diabetes mellitus in winters which can be partially attributed to reduced serum levels of vitamin D in the winter [77]. Many studies have reported the relationship between the concentration of 25-hydroxy vitamin D and the prevalence of type II diabetes mellitus [78]. It is shown is some studies that the risk of incidence of type II diabetes is higher in the individuals in highest percentile of vitamin D concertation [79-81]. Forouhi et al. study (2008) showed the reverse relationship between 25-hydroxy vitamin D concentration and fasting insulin [82]. Other studies have reported significant improvement of insulin secretion after supplement therapy with different dosages of vitamin D_3 in type II diabetes mellitus and patients or at risk individuals [83, 84]. Epidemiologic evidences suggest that type I diabetes is more common in equator and subaquatic geographical latitudes and a seasonal difference where most cases are diagnosed during autumn and winter and the least cases in the summer [85]. Fish liver oil in the first year of life reduced the risk of type I diabetes in the childhood [86]. Hyppönen et al. study (2001) proved that taking 2000 IU of vitamin D in the first year of life reduced the risk of type I diabetes. Moreover, they reported the three-fold higher risk of type I diabetes in suspected cases of rickets [87]. Though, other studies conducted on vitamin D supplement therapy of neonates and type I diabetes failed to show a relationship between vitamin D supplement therapy and progression of type I diabetes [88, 89].

• Effect of Vitamin D on Thyroid Gland

Group B vitamins and vitamin D are crucial for thyroid gland normal function. Talaei et al. study (2017) reported that 68.7% of the 201 hypothyroidism patients suffered from vitamin D deficiency and their TSH level significantly reduced after taking vitamin D, though taking vitamin D did not affect T_3 and T_4 level [90]. Many studies have reported low level of vitamin D in grave's patients [91, 92]. Mackawy et al. study (2013) demonstrated decreased serum level of vitamin D and a positive significant relationship between level of vitamin D and T_3 and T_4 besides a negative significant relationship between vitamin D and TSH. This study also found that vitamin D deficiency is related to the severity of hypothyroidism [93]. Vitamin D and thyroid hormone both bond to similar steroid receptors. Several polymorphisms are identified in VDR gene making individual prone to thyroid diseases such as Hashimoto thyroiditis or graves [94]. Kinuta et al. study (2000) indicated that serum estrogen suppresses TSH secretion in men by affecting pituitary gland and vitamin D plays a significant role in estrogen production in both men and women [95]. It is proved in a study that vitamin D administration considerably suppresses TSH secretion. Additionally, it is shown that TSH level in the elderly is higher in women compared with men in same age group, indicating that TSHS secretion is regulated by sex hormones, genetic predisposition, or environmental factors. This relationship might be caused by the relationship between vitamin D and TSH level [96, 97].

• Role of Vitamin D in Immune System

C, B_6, E, D_3, and A vitamins and folic acid play an important role in the enforcement of the immune system. As the level of these vitamins elevates, the immune system more aggressively attacks the infections.Vitamin D exerts various effects on immune system cells. Vitamin D inhibits proliferation and differentiation of B cells and immunoglobulin secretion [98, 99]. In addition, vitamin D suppresses T cell proliferation [100] and turns Th_1 phenotype to Th_2 [101, 102]. Moreover, this vitamin affects T cell maturation through preventing from inflammatory phenotype Th_{17} [103, 104] and facilitates T_{reg} induction [105-108]. These effects prevent from inflammatory cytokine (IL-17, IL-21) synthesis by inducing IL-10 synthesis [109]. Vitamin D inhibits the proliferation of monocytes through inflammatory cytokines such as IL-1, IL-6, IL-8, IL-12, and TNF-α. Also, this vitamin reduces the maturation and differentiation of dendritic cells (DCs) by maintaining immature phenotypes through suppressing the expression of co-stimulatory macules, MHC II and IL-12 [110-112]. Inhibition of maturation and differentiation of dendritic cells (DCs) improved immunity tolerance and reduces the rate of autoimmune diseases. Due to the importance of the role of vitamin D in the function of immune system, reduced serum levels of vitamin D is observed in autoimmune diseases [109]. Interferons (INF) are synthesized by plasma dendritic cells. In systemic lupus erythematous (SLE), inductive effect of INF-α in peripheral blood mononuclear cells (PBMCs) increases the expression of interferons. Vitamin D helps to prevent form SLE by reduction of INF expression [113]. Vitamin D deficiency is a common finding in autoimmune diseases. Immune system cells are able to synthesis and response to vitamin D. The effects of vitamin D supplement therapy me be further that its role in calcium homeostasis and bone [109].

In the recent 5 years, numerous prospective studies have reported that high prevalence of vitamin D deficiency in HIV positive patients. A number of studies have stated that

vitamin D deficiency is more common among HIV positive patients compared with healthy individuals [114]. Sufficient vitamin D is not only crucial for bone health, but also for the general health status of HIV positive patients. Improved control of HIV transcription, increased number of CD_4+ T cells, slowed disease progression, improved control of opportunist infections and neurocognitive disorders, and prolonged survival are among benefits of vitamin D supplement therapy [115]. Vitamin D deficiency may be involved in the progression of HIV infection, due to the immunoregulatory role of vitamin D [116].

- Role of Vitamin D in Respiratory System

Long term vitamin D supplement therapy improved FEV_1 in smokers, especially those who suffer from vitamin D deficiency and patients with asthma and COPD [117]. Smoking reduces 1,25-dihydroxy vitamin D synthesis by lung epithelia cells [118] and may affect vitamin D receptors [119]. Smoking leads to proinflammatory state, oxidative stress, and activation of proteases [120, 121]. Theses pathophysiologic changes may maintain even after quitting smoking [122]. Yet, vitamin D can slow down this process [123-125]. Moreover, this process is accelerated in asthma and COPD [120]. Sluyter et al. study (2017) indicated that the effects of vitamin D are only observed in smoker, especially asthma or COPD patients [117].

Hall et al. study (2010) demonstrated that 25-hydroxy vitamin D serum level in below 75 nmol/L in more than 90% of cystic fibrosis (CF) patients. Vitamin D malabsorption is seen in 85-90% of patients with cystic fibrosis due to pancreatic failure [126]. Another reason for vitamin D deficiency in these patients is alteration in liver 25-hydroxylase enzyme and faster clearance of 25-hydroxy vitamin D [127]. Low serum levels of vitamin D may also be caused by reduced level of vitamin D binding protein (DBP) [126]. DBP plays an important role in the regulation of the amount of free vitamin D – for cellular use- and thus maintaining serum concentration of vitamin D [128]. Yosefzadeh et al. study demonstrated that different physiologic and pathologic situations may affect DBP serum level and thus 25-hydroxy vitamin D serum level [129]. In CF patients, vitamin D synthesis is also reduced, while 90-95% of the required amount of vitamin D is supplied by sunlight [126]. Vitamin D deficiency in CF patients is associated with osteopenia and other diseases in the childhood which will progress afterwards. Pulmonary function disorder is exacerbated in adults with CF in case of vitamin D deficiency [130]. Since pulmonary inflammation may occur in these patients even in the absence of infection, it is involved in the progression of their respiratory disease. Due to the role of vitamin D in the down regulation of metalloproteinase and consequent inflammation reduction, and considering the fact that vitamin D deficiency is common among these patients, this deficiency may play a significant role in alteration of immune response [131].

Shamsizadeh et al. study (2018) showed that the level of 25-hydroxy vitamin D is significantly lower in infants with bronchiolitis compared with healthy infants, though its level did not significantly affect the severity of bronchiolitis. Additionally, level of 25-hydorxy vitamin D was significantly and directly affected by infant's age, vitamin D supplement therapy, and breastfeeding [132]. In Moreno-Solís et al. study (2015), the level of 25-hydroxy vitamin D was significantly lower in children with bronchiolitis compared with healthy children [133]. Golan-Tripto et al. study (2013) reported that the level of 25-hydroxy vitamin D is significantly lower in children with bronchiolitis compared with control group [134]. In contrast with the reported results, McNally et al. (2013) failed to report a significant difference in the level of 25-hydroxy vitamin D between healthy children and children with lower respiratory tract infection (including bronchiolitis and pneumonia) [135].

- Role of Vitamin D on Hematopoietic Stem Cells

Folic Acid (B9) and cobalamin (B_{12}) vitamin deficiency directly leads to anemia. Though, Vitamin E, B2, B6, C, and D may indirectly cause anemia which can be considered as auxiliary agents. Vitamin D receptors exist in almost all erythrocyte progenitors in bone marrow [136]. Level of 1,25-dihydroxy vitamin D is hundreds-fold higher in bone marrow compared with plasma [137, 138]. Insufficient level of 25-hydorxy vitamin D reduces the synthesis of 1, 25-dihydroxy vitamin D in the bone marrow and consequently erythropoiesis [139]. 1,25-dihydorxy vitamin D is directly associated with erythropoiesis and, in line with erythropoietin, increases iron storages and retention [137, 139-142]. Erythropoietin stimulate proliferation of hematopoietic cell lines [136]. Vitamin D deficiency in engaged in iron deficiency anemia [143-145].

Hepcidin is an anti-bacterial protein hormone [146, 147] synthesized in the liver and inhibits erythropoiesis [139]. Hepcidin acts as an immune mediator which is responsible for systematic regulation of iron metabolism [146, 148]. Hepcidin reduces plasma concentration and bioavailability of iron by inhibition of ferroportin [146]. Vitamin D is a strong regulator of hepcidin-ferroportin axis in human body [147]. Low vitamin D levels is in favor of hepcidin expression [139]. Increased level of hepcidin is associated with reduced liver iron and transferrin saturation. 25-hydroxy vitamin D concentration is significantly negatively associated with hepcidin and positively associated with iron and hemoglobin concentration [146, 148, 149].

Role of Vitamin D in Behavioral System

- Effect of Vitamin D on Depression

Deficiency in some vitamins and minerals may cause depression presentations. Thus, if depression symptoms are caused by these deficiencies, nutritional supplements will definitely help the patients. Milaneschi et al. study (2010) was conducted over 6 years by participation of 954 individual aging more than 65 years in Italy. They concluded that vitamin D deficiency is a risk factor of depression in the elderly and stated that this association is more strong in the women [150]. 89 geographical zones in the United states were

studies between 1988 to 1994 and it was observed that individuals with vitamin D deficiency are more prone to show depression symptoms in comparison with healthy individuals [151]. Hoogendijk et al. (2000) reported that decreased serum level of vitamin D is significantly associated with depression incidence among 1282 elderly aging 65-95 years. Results of their study showed that vitamin D deficiency is associated with both severe and mild depression [152].

- ### Effect of Vitamin D on Post-Partum Depression

The pattern of post-partum depression in Iran is similar to the developing countries. Psychological support should be provided during pregnancy and just after delivery; since the risk of development or recurrence of psychological disorders is high during this period. Unfortunately, due to cultural factors, all the attention is paid to the neonate and not mother which a reason of high prevalence of post-partum depression in Iran [153]. Presence of 1,25-dihydorxy vitamin D, vitamin D receptor and its activating enzyme (α-hydroxylase) and cytochrome P450 in different parts of central nervous system [154] which catalyzes hydroxylation of calcidiol to active form of vitamin D are among purposed explanation for the role of vitamin D in post-partum depression. Accordingly, brain can locally activate vitamin D which makes the role of vitamin D more probable in brain function [155]. Vitamin D provides a neuroprotective effect through various mechanisms. Calcitriol is responsible for regulation of calcium intracellular and extracellular concentration to prevent toxicity. Several studies have stated the relationship between vitamin D deficiency and depression including that light therapy is beneficial for depression [156]. Some studies have been performed on psychiatric disorders indicating the role of decreased serum level of vitamin D. It is known that vitamin D is engaged in presentation of symptoms of seasonal depression. During winter, due to limited sunlight, serum level of 25-hydroxy vitamin D is reduced and vitamin D supplement therapy recovers the symptoms of seasonal depression [157]. Based on the study of Mohammaddokht et al. (2018), post-partum depression is associated with low serum level of vitamin D and vitamin D supplement therapy during pregnancy may be an effective method to prevent this disorder [158].

- ### Effect of Vitamin D on Sleep Disorders

Deficiency in the level of vitamin B group and Vitamin D and some minerals may cause sleep disorders. According to McCarty et al. study (2014), low serum levels of vitamin D is common in patients with sleep disorders. This may be caused by chronic pains leading to sleep disorder. It was reported in this study that more than 50% of patients with physical pains and sleep disorder suffer from vitamin D deficiency. moreover, this study proved that the primary reason of sleep disorders in most cases, is obstructive apnea or restless leg syndrome [159].

- ### Role of Vitamin D in Nervous System

Vitamin B1, B9, and C as well as Calcium, Magnesium, and Zinc affect memory, learning, and cognitive abilities. Deficiency of these vitamins and minerals will lead to serious disorders in the function of nervous system. Available evidences show that vitamin D is involved in regulation of growth and function of neurons [160]. The role of vitamin D in improvement of function of neurons system is approved by presence of 25(OH)D_3-1α-Hydroxylase enzyme which is responsible for forming active form of vitamin D [155] as well as existence of vitamin D receptors in brain, especially in hypothalamus and dopaminergic neurons in substantia nigra [161, 162]. It is believed that vitamin D has a role similar to neurosteroids in nervous system. Due to the interaction between vitamin D and MARRS receptor, hormonal form of this vitamin is engaged in different intracellular metabolic pathways [163]. Moreover, presence of α1-hydroxylase enzyme and nuclear VDRs in microglia and non-neural cells in central nervous system (CNS) indicates the autocrine and paracrine effects of calcitriol (1,25-dihydroxy vitamin D) on neurons [164]. The role of active form of vitamin D in the nervous system is to change the trend of synthesis and release of neurotrophic growth factors such as nerve growth factor (NGF) which is vital for neural differentiation. Additionally, increased level of glial derived neurotrophic factors (GDNF) is approved. Also, 1,25-dihydoxy vitamin D_3 is an important factor in the synthesis of neural mediators such as acetylcholine through increased expression of the gene of Choline Acetyl transferase (CAT) [165]. Likewise, vitamin D affects the expression of GABA-related genes [166] and stimulation of tyrosine hydroxylase (TH) and biosynthesis of catechol amines [167-171]. The neuroprotective effect of vitamin D includes synthesis of calcium ion (Ca^{2+}) binding proteins and maintaining intracellular calcium homeostasis which is vital for brain cells function [172-174].

Pliz et al. (2008) evaluated the relationship between serum level of vitamin D and mortal stroke in patients who were referred for coronary vessels angiography. Results of their study proved that low serum levels of 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D are independent predictors of mortal stroke. According to this study, vitamin D supplement therapy is an effective method in stroke prevention [175]. Kilkkrinen et al. study (2009) proved that as the serum level of vitamin D increases, the risk of stroke and its mortality in the future 27 years decreases and low vitamin D level is associated with higher risk of stroke [176]. Daubail et al. study (2012) demonstrated a relationship between low serum levels of vitamin D and severity of acute stroke; by treatment of vitamin D deficiency, morbidity of stroke patients will be lessened [177]. Anderson et al. study was performed on 41504 patients and indicated that serum level of vitamin D is strongly related to increase risk of cardiovascular events and consequent stoke [178].

Role of Vitamin D in Reproductive System

The role of vitamin D in fertility has attracted attention in a number of studies [179, 180]. Existence of α1-hydroxylase enzyme and VDRs in these tissues as wells as ovarian cells,

endometrial cells and pituitary gland have been shown. After recognition of this enzyme and vitamin D receptor, their function in ovarian granulosa cells, reproductive system and immune system has been explained [181-183].

- ### Role of Vitamin D in Female Reproductive Health

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of women in reproductive age with a prevalence of 15-20% in infertile women [184]. PCOS is a heterogeneous disease and is among the causes of infertility of women. Some studies purposed low levels of vitamin D as a possible factor in the pathogenesis of PCOS [185-187]. Vitamin D deficiency is reported in 65-87% of women with PCOS which can be due to aggregation of vitamin D in the adipose tissue of obese women and sunlight avoidance especially in women with hirsutism [185]. Irani et al. study (2014) demonstrated that vitamin D modifies the pattern of Anti Mullerian Hormone (AMH) in granulosa cells and FSH sensitivity, and thus affecting ovum evolution; in a way that vitamin D supplement therapy leads to increased inflammatory serum level of receptor for advanced glycation end products (sRAGE) and advanced glycation end products (AGEs) and simultaneous reduction of AMH. This reduced AMH and increased sRAGE levels after D_3 administration acts as an anti-inflammatory factor and thus improving folliculogenesis in PCOS patients [188, 189]. Endometriosis is an estrogen-dependent inflammatory disease and one of the most common chronic gynecologic disease affecting 5-10% of women in reproductive age. In this disease, endometrial cells are implanted in extraurtrine areas [190]. Endometriosis presents itself with signs of abdominopelvic pain, dysmenorrhea, backache, and dyspareunia [191]. Di Rosa et al. study (2012) on the effect of vitamin D on endometriosis indicated that abnormally high levels of vitamin D leads to incomplete removal of endometrial cells transmitting to peritoneal cavity via ovarian reflux [192]. Premature ovarian failure defined as menopause before the age of 40, is affected by serum level of vitamin D and anti Mullerian hormone [193]. Chang et al. study (2014) was conducted to determine the relationship between serum level of vitamin D, estrogen hormone, sex hormone binding globulin (SHBG) and ovarian reserve marker in 73 non-obese fertile and healthy women. Result of this study showed the positive relationship between serum level of vitamin D with total testosterone and free androgen index. Authors purposed that vitamin D can enhance fertility though androgen activity modulation [194].

- ### Role of Vitamin D in Male Reproductive Health

Jensen et al. study (2011) evaluated the relationship between serum level of vitamin D and sperm quality. They reported a positive relationship between the percentage of mobile sperms and level of vitamin D [195]. Many studies show that infertile men with different sperm disorders or normosperm infertile men (OATN) are at higher risks of osteoporosis and proportionately lower levels of testosterone and vitamin D [196]. Ramlau-Hansen study (2011), performed on 307 men in Denmark, demonstrated weaker sperm parameters and androgen concentration is associated with low concentrations of vitamin D [197]. In Yang et al. study (2012), lower BMD in lumbar spine and iliac bones was associated with lower testosterone plasma concentration and there was a strong positive correlation between number, mobility, and morphology of sperms and vitamin D [196].

Low serum concentrations of vitamin D is responsible in reproductive functions such as PCOS, uterine fibrosis, inappropriate sperm parameters and IVF treatment failure. Thus, vitamin D supplement is suggested in the treatment of infertility in women and men [198].

Role of Vitamin D in Musculoskeletal System

Anti-oxidant supplements improve the anti-oxidant body defense and prevent from oxidative pressure, inflammation, and muscle injury. Multiple anti-oxidant supplements are introduced to protect cells from free radicals including: E, C, and D Vitamins, Carotenoids, Flavonoids. In some studies, high prevalence of vitamin D deficiency have been shown in patients with musculoskeletal pains of unknown origin [199]. Mascarenhas et al. study (2004) on pains attributed to vitamin D deficiency performed in the United States, revealed a strong relationship between low serum level of vitamin D and unspecific persistent musculoskeletal pains. Additionally, this study proved that measurement of the level of vitamin D in patients with pain with unknown origin and probably vitamin supplement therapy is required [200]. Also, several studies show that treatment of vitamin D deficiency in women leads to extensive recovery of clinical presentations of skeletal pains and muscular fatigue [201, 202] and it appears that this relationship is stronger in women [201-205]. Khaw et al. study (1992) on 138 women aging 45-65 found that bone density of lumbar spine, neck of femur and intertrochanteric area is directly associated with serum level of vitamin D and is reversely associated with PTH [206]. In Martinez et al. study (1994) on 150 menopause women aging 45-74 years, a direct relationship between bone density on lumbar spine and vitamin D was reported. In this study, in women above 60 years old, a direct relationship was observed with bone density in neck of femur, trochanter, and Ward triangle, as well as lumbar spine [207]. Ooms et al. study (1995) on 330 apparently healthy women aging above 70, a direct relationship between serum level of vitamin D and bone density of neck of femur and trochanter was reported only in serum levels below 12 ng/ml [208]. In Lips et al. study on 7564 osteoporotic menopause women form 25 countries, the effect of vitamin D was evident only on the trochanteric area in serum levels below 10 ng/ml [209]. Moreover, several studies have reported the negative relationship between PTH serum level and bone density, especially in the neck of femur [206, 210-212]. Many studies suggest that there is no relationship between vitamin D serum level and bone density [213-218]. Holick et al. study (1992) on 213 women and 176 men who were home resident, after supplement therapy of one group of them with 500 mg calcium and 700 IU vitamin D, the mineral

density of all bone centers were higher compared with the group who received placebo. Moreover, non-vertebral fracture was less common in comparison with control group [219]. Calcium and vitamin supplement therapy in elderly and menopause women with a history of vertebral fracture, reduces the rate of non-vertebral fractures [220]. Vitamin D supplement therapy in the elderly reduces bone turnover and improved bone density. Similarly, vitamin D and calcium supplement therapy in the elderly reduces the rate of fracture [221]. Osteoarthritis disease gets more severe in case of reduced vitamin D [222]. In Dawson-Hughes et al. study (1997), more than 75 nmol/L vitamin D supplement is recommended. Vitamin D deficiency disturbs immune function in animals and there is an important relationship between pneumonia incidence and nutritional rickets in children [223].

Role of Vitamin D in Gastrointestinal System

Irritable bowel syndrome (IBS) is a chronic debilitating disease with gastrointestinal dysfunction with severe adverse effects on the quality of life [224]. IBS is characterized with abdominal pain, distention, and alterations in normal bowel habits. A novel study assessed the condition of IBS patients and showed that these patients are more prone to vitamin A, E, and D deficiency compared with healthy individuals [224]. Vitamin D active metabolite (1,25-dihydroxy vitamin D_3) plays an important role in the regulation of gastrointestinal system through both paracrine and autocrine methods [224]. 1,25-dihydroxy vitamin D_3 is pivotal and crucial in absorption and function of epithelia cells in the gastrointestinal system. In addition, it has detoxifying and infectious protective features [225]. In comparison with other body cells and tissues, there are more vitamin D receptors in intestinal epithelial cells [226]. Hence, the effect of 1,25-dihydroxy vitamin D_3 in the gastrointestinal system is exerted through gene transcription [227, 228]. In the United States, IBD incidence and hospitalization due to IBD is higher in areas with low sunlight [229]. Different studies on the association between patients with crohn's disease or ulcerative colitis with low serum levels of vitamin D and 25-hydroxy vitamin D is related to crohn's disease activity index (CDAI; there were too few studies to evaluate ulcerative colitis) [230]. Cantorna et al. study (2016) revealed a reverse relationship between serum levels of vitamin D and acute form of crohn's disease and ulcerative colitis [231]. Malone et al. study (2008) reported irritable bowel syndrome (IBS) as a complication of vitamin D deficiency [232]. It is reported in Sprake et al. study (2012) that 95% of IBS patients have low serum levels of 25-hydroxy vitamin D [233]. Dehghanian et al. study (2015) demonstrated that vitamin D supplement therapy significantly increases serum level of 1,25-dihydroxy vitamin D_3 in IBS patients. Additionally, vitamin D supplement therapy significantly reduced severity of clinical presentations of IBS patients and significantly improved their quality of life [234]. Three mechanism including modification of intestinal permeability, alteration in intestinal microflora, and inflammation are purposed in IBS and it seems that the effect of vitamin D on recovery of IBS symptoms occurs through reducing intestinal permeability, inflammation, and alteration of intestinal microflora [235-239]. Furthermore, some studies have shown that vitamin maintains the integrity of junctions and repairing capacity of colon epithelium in hostess of mucus layer. Hence, vitamin D deficiency may endanger mucus layer and increase mucus sensitivity and mucus damage [235-239]. In Ly et al. (2011) reported in their study that bacterial colonies affect both expression and distribution of vitamin D receptors (VDR) in intestinal epithelial cells which shows the dynamic balance between this receptor and bacteria. Thus, vitamin D pathway is a vital modulator of the effect of intestinal flora on inflammatory disorders [240].

Discussion and Conclusion

Recent studies showed that not only vitamin D is a required for osteogensis, and osteoporosis prevention, but also it is involved in several extra-skeletal functions such as regulation of immune system, prevention from cancer, hypertension, inflammatory bowel disease, systemic lupus erythematous, rheumatoid arthritis, type I diabetes, and infectious diseases. Since vitamin D deficiency is more common in the middle east compared with Europe and the United States, evaluation of vitamin D deficiency and factors affecting vitamin D deficiency is vital. There a limited number of studies on the role of vitamin D deficiency in health and approaches to prevent from vitamin D deficiency. Moreover, due to the nature of vitamin D and several factors affecting vitamin D level, as well as disease and complications caused by vitamin D deficiency, evaluation of this issue should be considered among the major priorities of health field. Overall, these evidences indicate the necessity of performing further studies in the future (without the limitations of previous studies) to achieve more reliable results on the role of this vitamin in disease prevention.

References

1. Wagner CL, Taylor SN, Dawodu A, Johnson DD, Hollis BW. Vitamin D and its role during pregnancy in attaining optimal health of mother and fetus. Nutrients. 2012;4(3):208-230.
2. Holick MF, Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr 2004; 79(3): p. 362-71.
3. Hernan, MA, MJ. Olek, and A. Ascherio, Geographic variation of MS incidence in two prospective studies of US women. Neurology 1999; 53(8): p. 1711-8.
4. MF, H, Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004; 80: p. 11.
5. Mathieu C, Adorini L. The coming of age of 1,25- dihydroxy vitamin D(3) analogs as immunomodulatory agents. Trends Mol Med. 2002; 8:174-179.
6. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr 2005; 135: 317-22.
7. Holick M, Vitamin D deficiency: a worldwide problem with health consequences. American Journal of Clinical Nutrition. 2008; 87: 7.
8. Christakos S, Dhawan P, Benn B, Porta A, Hediger M, Oh GT, et al. Vitamin D: molecular mechanism of action. Ann N Y Acad Sci 2007; 1116:340–8.
9. Iyer P, Diamond F. Detecting disorders of vitamin D deficiency in children: an update. Advances in pediatrics. 2013;60(1):89-106.

10. Wagner CL, Taylor SN, Dawodu A, Johnson DD, Hollis BW. Vitamin D and its role during pregnancy in attaining optimal health of mother and fetus. Nutrients. 2012;4(3):208-230.
11. Zhang R, Naughton DP. Vitamin D in health and disease: current perspectives. Nutrition journal. 2010;9(1):65-77.
12. Wacker M, Holick MF. Sunlight and vitamin D: a global perspective for health. Dermato-endocrinology. 2013;5(1):51-108.
13. Bjork A, Andersson A, Johansson G, Bjorkegren K, Bardel A, Kristiansson P. Evaluation of sun holiday, diet habits, origin and other factors as determinants of vitamin D status in Swedish primary health care patients: a cross-sectional study with regression analysis of ethnic Swedish and immigrant women. BMC family practice. 2013;14:129.
14. Leventis P, Kiely PD .The tolerability and biochemical effects of high-dose bolus vitamin D2 and D3 supplementation in patients with vitamin D insufficiency. Scand J Rheumatol. 2009; 38(2):149-153.
15. Haidari F, Zakerkish M, Karandish M, Saki A, Pooraziz S. Association between serum Vitamin D level and glycemic and inflammatory markers in non-obese patients with type 2 diabetes. Iran J Med Sci 2016; 41: 367-73.[Farsi]
16. Amri Maleh P, Firoozjaee A, Hidari B, Malaki S, Bijani A, Heidarnia F. The Relationship between Serum Vitamin D Level and the Outcome of Patients Hospitalized in the Medical Intensive Care Unit. J Babol Univ Med Sci 2017; 19: 13-7. [Farsi]
17. Babaei M, Esmaeili Jadidi M, Heidari B, Gholinia H. The Relationship between Vitamin D Deficiency and Nonspecific Shin Pain in the Elderly; A Case-control Study. J Babol Univ Med Sci 2017; 19: 20-15. [Farsi]
18. Hollick MF, Chen TC. Vitamin D deficiency a worldwide problem with health consequences. Am J Clin Nutr 2008; 87(4): 1080S-6S.
19. Adeyemi OM, Agniel D, French AL, Tien PC, Weber K, Glesby MJ, et al. Vitamin D deficiency in HIV-infected and HIV-uninfected women in the United States. J Acquir Immune Defic Syndr. 2011 Jul 1;57 (3) :197-204.
20. Azizi F, Raees-Zadeh F, MirSaeed-Ghazi AA. Vitamin D deficiency in a population of Tehran's residents. Journal of the Faculty of Medicine 2000; 24:291-303. [Farsi]
21. Hashemipour S, LarijaniB, Adibi H ,et al. Vitamin D deficiency and causative factors in the population of Tehran.BMC Public Health 2004; 4:38-40. [Farsi]
22. World Health Organization. Complementary feeding of young children in developing countries. geneva. 1998.
23. Atiq M, Suria A, Nizami SQ, Ahmed I. Vitamin D status of breastfed Pakistani infants. Acta Paediatr. 1998; 87: 737-740.
24. Glezen WP, Loda FA, Clyde WA Jr. Epidemiologic patterns of acute lower respiratory disease of children in a pediatric group practice. J Pediatr. 1971; 78: 397-406.
25. Cannell JJ, Vieth R, Umhau JC, et al. Epidemic influenza and vitamin D. Epidemiol Infect. 2006; 134: 1129-1140.
26. Theodore C, Sectish Charles G, Prober. Nelson Textbook of Pediatrics. 18th ed. Philadelphia: Saunders. 2007; 1795-1800.
27. Anderson JL, Vanwoerkom RC, Horne BD, Bair TL, May HT, Lappe DL, Muhlestein JB: Parathyroid hormone, vitamin D, renal dysfunction, and cardiovascular disease: dependent or independent risk factors? Am Heart J 2011; 162: 331–339.
28. Li YC, Kong J, Wei MJ, Chen ZF, Liu SQ, Cao LP: 1,25-Dihydroxyvitamin D 3 is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 2002; 110: 229– 238.
29. O'Connell TD, Berry JE, Jarvis AK, Somerman MJ, Simpson RU: 1,25-Dihydroxyvitamin D3 regulation of cardiac myocyte proliferation and hypertrophy. Am J Physiol 1997; 272:H1751–H1758.
30. Carthy EP, Yamashita W, Hsu A, Ooi BS: 1,25-Dihydroxyvitamin D 3 and rat vascular smooth muscle cell growth. Hypertension 1989; 13: 954–959.
31. Borges ACR, Feres T, Vianna LM, Paiva TB: Effect of cholecalciferol treatment on the relaxant responses of spontaneously hypertensive rat arteries to acetylcholine. Hypertension 1999; 34: 897–901.
32. Ohsawa M, Koyama T, Yamamoto K, Hirosawa S, Kamei S, Kamiyama R: 1,25 Dihydroxyvitamin D3 and its potent synthetic analogs downregulate tissue factor and upregulate thrombomodulin expression in monocytic cells, counteracting the effects of tumor necrosis factor and oxidized LDL. Circulation 2000; 102: 2867–2872.
33. Deleskog, A., Ostenson, C.G. Vitamin D and aspects of cardiovascular disease. Journal of Diabetes and Metabolism, 2015; 6, 545.
34. Anderson, J.L., May, H.T., Horne, B.D., Bair, T.L., Hall, N.L., Carlquist, J.F, Group, I.H.C.I.S. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. The American Journal of Cardiology, 2010; 106, 963-968.
35. Witham, M.D., Ireland, S., Houston, J.G., Gandy, S.J., Waugh, S., Macdonald, T.M, Struthers, A.D. Vitamin D therapy to reduce blood pressure and left ventricular hypertrophy in resistant hypertension: randomized, controlled trial. Hypertension, 2014; 63, 706.
36. Vaidya, A., Forman, J.P. Vitamin D and Vascular Disease: The current and future status of Vitamin D therapy in hypertension and kidney. Current Hypertension Reports, 2012; 14, 111-119.
37. Wood, A.D., Secombes, K.R., Thies, F., Aucott, L., Black, A. J., Mavroeidi, A ... Macdonald, H.M. Vitamin D3 supplementation has no effect on conventional cardiovascular risk factors: a parallelgroup, double-blind, placebo-controlled RCT. Abstracts accepted through January, 2015; 12, 1.
38. Loloei S M-KH, Mirjalili MR, Fallahzadeh H, Poursoleiman F. Vitamin D Status in Patients with Hypertension that Covered in Azad Shahr Health Center of Yazd-2013. Yazd Health university Journal. 2013;13(5):9.
39. Wang, T.J., Pencina, M.J., Booth, S.L., Jacques, P.F., Ingelsson, E., Lanier, K. & Vasan, R.S. Vitamin D deficiency and risk of cardiovascular disease. Circulation, 2008; 117, 503-511.
40. Ford ES. Concentration of serum vitamin D and the metabolic syndrom among U.S. adults. Diabetes care 2005; 28: 30.
41. Querfeld U, Hoffmann MM, KLAUS G, et al. Antagonistic effects of vitamin D and parathyroid hormone on lipoprotein lipase in cultured adipocytes. Journal of the American Society of Nephrology 1999; 10: 2158.
42. Reis, J.P., von Mühlen, D., Michos, E.D., Miller, E.R., Appel, L.J., Araneta, M.R., Barrett-Connor, E. Serum vitamin D, parathyroid hormone levels, and carotid atherosclerosis. Atherosclerosis, 2009; 207, 585-590.
43. Fanari, Z., Hammami, S., Hammami, M.B., Hammami, S., Abdellatif, A. Vitamin D deficiency plays an important role in cardiac disease and affects patient outcome: Still a myth or a fact that needs exploration. Journal of the Saudi Heart Association, 2015.
44. Zoccali, C., Mallamaci, F. Does a vitamin D boost help in resistant hypertension control?. Hypertension, 2014; 63, 672-674.
45. Polat, V., Bozcali, E., Uygun, T., Opan, S., Karakaya, O. Low vitamin D status associated with dilated cardiomyopathy. International Journal of Clinical and Experimental Medicine, 2015; 8, 1356.
46. Jung, Y.J., Kim, S.E., Hong, J.Y., Lee, J.H., Park, D.G., Han, K.R., Oh, D.J. Reversible dilated cardiomyopathy caused by idiopathic hypoparathyroidism. Korean Journal of Internal Medicine, 2013; 28, 605- 608.
47. Maryam Kerdegari MG, Mansoor Siavash, Ali Poormoghaddas. Vitamin D Supplementation Effects in Patients with Heart Failure. Journal of Isfahan Medical School. 2010;28(109):8. [Farsi]
48. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure. Am J clin Nutr 2006; 83(4): 754-9.
49. Agarwal, M., Phan, A., Willix, R., Barber, M., & Schwarz, E.R. Is vitamin D deficiency associated with heart failure? A review of current evidence. Journal of Cardiovascular Pharmacology and Therapeutics, 2011; 16, 354-363.
50. Camici, M., Galetta, F., Franzoni, F., Carpi, A., & Zangeneh, F. Vitamin D and heart. Internal and Emergency Medicine, 2013; 8, 5-9.
51. Gepner, A.D., Ramamurthy, R., Krueger, D.C., Korcarz, C.E., Binkley, N., & Stein, J.H. A prospective randomized controlled trial of the effects of vitamin D supplementation on cardiovascular disease risk. PLoS One, 2012; 7, e36617.
52. Diaz L, Noyola-Martinez N, Barrera D, Hernandez G, Avila E, Halhali A, et al. Calcitriol inhibits TNF-alpha-induced inflammatory

cytokines in human trophoblasts. J Reprod Immunol. 2009;81(1):17-24.
53. Popa C, Netea MG, van Riel PL, van der Meer JW, Stalenhoef AF. The role of TNF-alpha in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. J Lipid Res 2007;48(4):751-762.
54. Muller K, Heilmann C, Poulsen LK, Barington T, Bendtzen K. The role of monocytes and T cells in 1,25- dihydroxyvitamin D3 mediated inhibition of B cell function in vitro. Immunopharmacology. 1991;21(2):121- 128.
55. Riachy R, Vandewalle B, Belaich S, Kerr-Conte J, Gmyr V, Zerimech F, et al. Beneficial effect of 1,25 dihydroxyvitamin D3 on cytokinetreated human pancreatic islets. J Endocrinol. 2001;169(1):161-168.
56. Schleithoff SS ,Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a doubleblind, randomized, placebo-controlled trial. Am J Clin Nutr. 2006;83(4):754- 759.
57. Turk S, Akbulut M, Yildiz A, Gurbilek M, Gonen S, Tombul Z, et al. Comparative effect of oral pulse and intravenous calcitriol treatment in hemodialysis patients: the effect on serum IL-1 and IL-6 levels and bone mineral density. Nephron 2002;90(2):188-194.
58. Sun X, Zemel MB. Calcium and 1,25- dihydroxyvitamin D3 regulation of adipokine expression. Obesity (Silver Spring). 2007;15(2):340-348.
59. Diez JJ, Iglesias P. The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur J Endocrinol. 2003;148(3):293-230.
60. Anderson LN, Cotterchio M, Vieth R, Knight JA. Vitamin D and calcium intakes and breast cancer risk in pre- and postmenopausal women. Am J Clin Nutr. 2010; 91(6):1699-707.
61. Kawase T, Matsuo K, Suzuki T, Hirose K, Hosono S, Watanabe M, et al. Association between vitamin D and calcium intake and breast cancer risk according to menopausal status and receptor status in Japan. Cancer Sci. 2010; 101(5):1234-40.
62. Engel P, Fagherazzi G, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F. Joint effects of dietary vitamin D and sun exposure on breast cancer risk: results from the French E3N cohort. Cancer Epidemiol Biomarkers Prev. 2011; 20(1):187-98.
63. Siegel R, Naishadham D, Jemal A. Cancer statistics. CA Cancer J Clin. 2012; 62(1):10-29.
64. Ahonen M, Zhuang Y, Aine R, Ylikomi T, Tuohimaa P. Androgen receptor and vitamin D receptor in human ovarian cancer: growth stimulation and inhibition by ligands. Int J Cancer. 2000; 86(1):40-46.
65. Villena C, Meyberg R, Axt R, Reitnauer K, Reichrath J, Friedrich M. Immunohistochemical analysis of 1,25-dihydroxyvitamin- D3-receptors, estrogen and progesterone receptors and Ki-67 in ovarian carcinoma. Anticancer Res. 2002; 22(4):2261-2267.
66. Gross C, Krishnan A, Malloy P, Eccleshall T, Zhao X, Feldman D. The vitamin D receptor gene start codon polymorphism: a functional analysis of FokI variants. J Bone Miner Res. 1998; 13(11):1691-1699.
67. Jurutka P, Remus L, Whitfield G, Thompson P, Hsieh J, Zitzer H, et al. The polymorphic N terminus in human vitamin D receptor isoforms influences transcriptional activity by modulating interaction with transcription factor IIB. Mol Endocrinol. 2000; 14(3):401-420.
68. Lurie G, Wilkens L, Thompson P, Carney M, Palmieri R, Pharoah P, et al. Vitamin D receptor rs2228570 polymorphism and invasive ovarian carcinoma risk: pooled analysis in five studies within the Ovarian Cancer Association Consortium. Int J Cancer. 2011; 128(4):936-943.
69. Onsory KH BTM, Davoodi B, Heydari AshrafiM, Abdollahi M. The Role of Polymorphism of TaqI in Vitamin D Receptor Gene and Risk of Ovarian Cancer in Women of North India. Journal of Fasa University of Medical Sciences. 2013;3(3):260-5.
70. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. Journal of Clinical Endocrinology & Metabolism. 2007;92(6):2017-29.
71. Pittas AG, Dawson-Hughes B. Vitamin D and diabetes. The Journal of steroid biochemistry and molecular biology. 2010;121(1-2):425.
72. Maestro B, Molero S, Bajo S, Davila N, Calle C. Transcriptional activation of the human insulin receptor gene by 1, 25-dihydroxyvitamin D3. Cell biochemistry and function. 2002;20(3):227-32.
73. Dunlop TW, Väisänen S, Frank C, Molnar F, Sinkkonen L, Carlberg C. The human peroxisome proliferator-activated receptor d gene is a primary target of 1a, 25-dihydroxyvitamin D3 and its nuclear receptor. J Mol Biol. 2005;349(2):248-60.
74. Maestro B, Campión J, Dávila N, Calle C. Stimulation by 1, 25-dihydroxyvitamin D3 of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. Endocrine journal. 2000;47(4):383.
75. Cade C, Norman AW. Vitamin D3 improves impaired glucose tolerance and insulin secretion in the vitamin Ddeficient rat in vivo. Endocrinology. 1986;119(1):84-90.
76. Norman AW, Frankel J, Heldt AM, Grodsky GM. Vitamin D deficiency inhibits pancreatic secretion of insulin. Science (New York, NY). 1980;209(4458):823.
77. Bourlon PM, Faure-Dussert A, Billaudel B. Modulatory role of 1, 25 dihydroxyvitamin D3 on pancreatic islet insulin release via the cyclic AMP pathway in the rat .British journal of pharmacology. 1997;121(4):751-8.
78. Ishii H, Suzuki H, Baba T, Nakamura K, Watanabe T. Seasonal variation of glycemic control in type 2 diabetic patients. Diabetes care. 2001;24(8):1503.
79. Scragg R, Sowers MF, Bell C. Serum 25- hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes care. 2004;27(12):2813-8.
80. Snijder M, Van Dam R, Visser M, Deeg D, Seidell J, Lips P. To: Mathieu C, Gysemans C, Giulietti A, Bouillon R (2005) Vitamin D and diabetes. Diabetologia. 2006; 49(1):217-8.
81. Knekt P, Laaksonen M, Mattila C, Härkänen T, Marniemi J, Heliövaara M, et al. Serum vitamin D and subsequent occurrence of type 2 diabetes. Epidemiology. 2008;19(5):666-71.
82. Forouhi NG, Luan J, Cooper A, Boucher BJ, Wareham NJ. Baseline serum 25-hydroxy vitamin d is predictive of future glycemic status and insulin resistance the medical research council ely prospective study 1990–2000. Diabetes. 2008;57(10):2619-25.
83. Borissova A, Tankova T, Kirilov G, Dakovska L, Kovacheva R. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. International journal of clinical practice. 2003;57(4):258.
84. Boucher B, Mannan N, Noonan K, Hales C, Evans SJW. Glucose intolerance and impairment of insulin secretion in relation to vitamin D deficiency in east London Asians. Diabetologia. 1995;38(10):1239-45.
85. Nguyen LTH, Pham Nguyen DN. The role of vitamin D in protecting type 1 diabetes mellitus. Diabetes/metabolism research and reviews. 2005;21(4):338-46.
86. Stene LC, Joner G. Use of cod liver oil during the first year of life is associated with lower risk of childhoodonset type 1 diabetes: a large, population-based, casecontrol study. The American journal of clinical nutrition. 2003;78(6):1128-34.
87. Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. The Lancet. 2001;358(9292):1500-3.
88. Visalli N, Sebastiani L, Adorisio E, Conte A, De Cicco A, D'Elia R, et al. Environmental risk factors for type 1 diabetes in Rome and province. Archives of disease in childhood. 2003;88(8):695-8.
89. Stene L, Ulriksen J, Magnus P, Joner G. Use of cod liver oil during pregnancy associated with lower risk of Type I diabetes in the offspring. Diabetologia. 2000;43(9):1093-8.
90. Talaei. A GF, Naseri. P, Chehrea. A. The Study the Effect of Vitamin D on Hypothyroidism. Iran South Med J. 2017;20(3):301-7. [Farsi]
91. Yamashita H, Noguchi S, Takatsu K, et al. High prevalence of vitamin D deficiency in Japanese female patients with Graves' disease. Endocr J 2001; 48(1): 63-9.
92. Wang J, Lv S, Chen G, et al. Meta-analysis of the association between vitamin D and autoimmune thyroid disease. Nutrients 2015; 7(4): 2485-98.
93. Mackawy AM, Al-Ayed BM, Al-Rashidi BM. Vitamin D deficiency and its association with thyroid disease. Int J Health Sci (Qassim) 2013; 7(3): 267-75.

94. Vitamin D Deficiency and Thyroid Disease. (Accessed at May 30, 2017 at https:// www.goodhormonehealth.com/VitaminD6mar 10.pdf).
95. Kinuta K, Tanaka H, Moriwake T, et al. Vitamin D is an important factor in estrogen biosynthesis of both female and male gonads. Endocrinology 2000; 141(4): 1317-24.
96. Smith MA, McHenry C, Oslapas R, et al. Altered TSH levels associated with increased serum 1, 25-dihydroxyvitamin D3: a possible link between thyroid and parathyroid disease. Surgery 1989; 106(6): 987-91.
97. Gross HA, Appleman MD, Nicoloff JT. Effect of biologically active steroids on thyroid function in man. J Clin Endocrinol Metab 1971; 33(2): 242-8.
98. Lemire JM, et al. 1 alpha,25-dihydroxyvitamin D3 suppresses proliferation and immunoglobulin production by normal human peripheral blood mononuclear cells. J Clin Invest. 1984; 74(2):657–61.
99. Chen S, et al. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. J Immunol. 2007; 179(3):1634–47.
100. Bhalla AK, et al. 1,25-Dihydroxyvitamin D3 inhibits antigen-induced T cell activation. J Immunol. 1984; 133(4):1748–54.
101. Mattner F, et al. Inhibition of Th1 development and treatment of chronic-relapsing experimental allergic encephalomyelitis by a non-hypercalcemic analogue of 1,25-dihydroxyvitamin D(3). Eur J Immunol. 2000; 30(2):498–508.
102. Boonstra A, et al. 1alpha,25-Dihydroxyvitamin d3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. J Immunol. 2001; 167(9):4974–80.
103. Tang J, et al. Calcitriol suppresses antiretinal autoimmunity through inhibitory effects on the Th17 effector response. J Immunol. 2009; 182(8):4624–32.
104. Daniel C, et al. Immune modulatory treatment of trinitrobenzene sulfonic acid colitis with calcitriol is associated with a change of a T helper (Th) 1/Th17 to a Th2 and regulatory T cell profile. J Pharmacol Exp Ther. 2008; 324(1):23–33.
105. Gregori S, et al. Regulatory T cells induced by 1 alpha,25-dihydroxyvitamin D3 and mycophenolate mofetil treatment mediate transplantation tolerance. J Immunol. 2001; 167(4): 1945–53.
106. Barrat FJ, et al. In vitro generation of interleukin 10-producing regulatory CD4(+) T cells is induced by immunosuppressive drugs and inhibited by T helper type 1 (Th1)- and Th2-inducing cytokines. J Exp Med. 2002; 195(5):603–16.
107. Gorman S, et al. Topically applied 1,25-dihydroxyvitamin D3 enhances the suppressive activity of CD4+ CD25+ cells in the draining lymph nodes. J Immunol. 2007; 179(9):6273–83.
108. Penna G, et al. Expression of the inhibitory receptor ILT3 on dendritic cells is dispensable for induction of CD4+ Foxp3+ regulatory T cells by 1,25-dihydroxyvitamin D3. Blood. 2005; 106(10): 3490–7.
109. Aranow C. Vitamin D and the Immune System. J Investig Med. 2012;59(6):881-6.
110. Piemonti L, et al. Vitamin D3 affects differentiation, maturation, and function of human monocytederived dendritic cells. J Immunol. 2000; 164(9):4443–51.
111. Griffin MD, et al. Dendritic cell modulation by 1alpha,25 dihydroxyvitamin D3 and its analogs: a vitamin D receptor-dependent pathway that promotes a persistent state of immaturity in vitro and in vivo. Proc Natl Acad Sci U S A. 2001; 98(12):6800–5.
112. Szeles L, et al. 1,25-dihydroxyvitamin D3 is an autonomous regulator of the transcriptional changes leading to a tolerogenic dendritic cell phenotype. J Immunol. 2009; 182(4):2074–83.
113. Bennett L, et al. Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. J Exp Med. 2003; 197(6):711–23.
114. Abd Mishani M HM, Najmi M, Baziar N. The role of vitamin D in HIV disease. Iranian Journal of Nutrition Sciences & Food Technology. 2013;7(5):679-88.
115. Spector SA. Vitamin D and HIV: letting the sun shine in. Top Antivir Med. 2011 Feb-Mar;19 (1) :6- 10.
116. Giusti A, Penco G, Pioli G. Vitamin D deficiency in HIV-infected patients: a systematic review. Nutrition. 2011; 3:101-11.
117. John D. Sluyter CAC, Jr., Debbie Waayer, Carlene M. M. Lawes, Les Toop, Kay-Tee Khaw, Robert Scragg. Effect of Monthly, High-Dose, Long-Term Vitamin D on Lung Function: A Randomized Controlled Trial. Nutrients. 2017;1353(9):1-14.
118. Hansdottir, S.; Monick, M.M.; Lovan, N.; Powers, L.S.; Hunninghake, G.W. Smoking disrupts vitamin D metabolism in the lungs. Am. J. Respir. Crit. Care Med. 2010, 181.
119. Haley, K.J.; Manoli, S.E.; Tantisira, K.G.; Litonjua, A.A.; Nguyen, P.; Kobzik, L.; Weiss, S.T. Maternal smoking causes abnormal expression of the vitamin D receptor. Am. J. Respir. Crit. Care Med. 2009, 179.
120. Fischer, B.M.; Pavlisko, E.; Voynow, J.A. Pathogenic triad in COPD: Oxidative stress, protease-antiprotease imbalance, and inflammation. Int. J. Chronic Obstruct. Pulm. Dis. 2011, 6, 413–421.
121. Shapiro, S.D. Proteolysis in the lung. Eur. Respir. J. 2003, 22, 30s–32s.
122. Mortaz, E.; Masjedi, M.R.; Rahman, I. Outcome of smoking cessation on airway remodeling and pulmonary inflammation in COPD patients. Tanaffos 2011, 10, 7–11.
123. Baeke, F.; Takiishi, T.; Korf, H.; Gysemans, C.; Mathieu, C. Vitamin D: Modulator of the immune system. Curr. Opin. Pharmacol. 2010, 10, 482–496.
124. Kim, S.H.; Baek, M.S.; Yoon, D.S.; Park, J.S.; Yoon, B.W.; Oh, B.S.; Park, J.; Kim, H.J. Vitamin D inhibits expression and activity of matrix metalloproteinase in human lung fibroblasts (HFL-1) cells. Tuberc. Respir. Dis. 2014, 77, 73–80.
125. Ke, C.Y.; Yang, F.L.; Wu, W.T.; Chung, C.H.; Lee, R.P.; Yang, W.T.; Subeq, Y.M.; Liao, K.W. Vitamin D3 reduces tissue damage and oxidative stress caused by exhaustive exercise. Int. J. Med. Sci. 2016, 13, 147–153.
126. Hall WB, Sparks AA, Aris RM. Vitamin D deficiency in cystic fibrosis. Int J Endocrinol 2010; 2010.
127. Lark RK, Lester GE, Ontjes DA, Blackwood AD, Hollis BW, Hensler MM, et al. Diminished and erratic absorption of ergocalciferol in adult cystic fibrosis patients. Am J Clin Nutr 2001; 73(3): 602-6.
128. Chun RF. New perspectives on the vitamin D binding protein. Cell Biochem Funct 2012; 30(6): 445 56.
129. Yousefzadeh P, Shapses SA, Wang X. Vitamin D binding protein impact on 25-hydroxyvitamin D levels under different physiologic and pathologic conditions. Int J Endocrinol 2014; 2014: 981581.
130. Green DM, Leonard AR, Paranjape SM, Rosenstein BJ, Zeitlin PL, Mogayzel Jr PJ. Transient effectiveness of vitamin D< sub> 2</sub> therapy in pediatric cystic fibrosis patients. J Cyst Fibros 2010; 9(2): 143-9.
131. Gilbert CR, Arum SM, Smith CM. Vitamin D deficiency and chronic lung disease. Can Respir J 2009; 16(3): 75-80.
132. Ahmad Shamsizadeh RN, Mina Safi, Tahereh Ziaei Kajbaf, Amir Saberi-Demneh, Reza Karbalaei. Assessment of serum 25(OH)D level in infants with bronchiolitis. Tehran University Medical Journal. 2018;75(12):883-93. [Farsi]
133. Moreno-Solís G, Fernández-Gutiérrez F, Torres - Borrego J, Torcello-Gáspar R, Gómez-Chaparro Moreno JL, Pérez – Navero JL. Low serum 25-hydroxyvitamin D levels and bronchiolitis severity in Spanish infants. Eur J Pediatr 2015;174(3):365-72.
134. Golan-Tripto I, Goldbart AD, Loewenthal N, Tal A. 25(OH)Vitamin D insuf ciency in infants with bronchiolitis. Am J Respir Crit Care Med 2013;187:A5906.
135. McNally JD, Leis K, Matheson LA, Karuananyake C, Sankaran K, Rosenberg AM. Vitamin D deficiency in young children with severe acute lower respiratory infection. Pediatr Pulmonol 2009;44(10):981-8.
136. Sooragonda B, Bhadada SK, Shah VN, Malhotra P, Ahluwalia J, Sachdeva N. Effect of vitamin D replacement on hemoglobin concentration in subjects with concurrent iron-deficiency anemia and vitamin D deficiency: a randomized, single-blinded, placebo-controlled trial. Acta haematologica. 2015;133(1):31-35.
137. Sim JJ, Lac PT, Liu IL, Meguerditchian SO, Kumar VA, Kujubu DA, et al. Vitamin D deficiency and anemia: a cross-sectional study. Annals of hematology. 2010;89(5):447-452.
138. Lucisano S, Di Mauro E, Montalto G, Cernaro V, Buemi M, Santoro D. Vitamin D and anemia. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation. 2014;24(1):61-62.
139. Atkinson MA, Melamed ML, Kumar J, Roy CN, Miller ER, 3rd, Furth SL, et al. Vitamin D, race, and risk for anemia in children. J Pediatr. 2014;164(1):153-158 e151.

140. Hall AC, Juckett MB. The role of vitamin D in hematologic disease and stem cell transplantation. Nutrients. 2013;5(6):2206-2221.
141. Blanco-Rojo R, Perez-Granados AM, Toxqui L, Zazo P, de la Piedra C, Vaquero MP. Relationship between vitamin D deficiency, bone remodelling and iron status in iron-deficient young women consuming an iron-fortified food. European journal of nutrition. 2013;52(2):695-703.
142. Meguro S, Tomita M, Katsuki T, Kato K, Oh H, Ainai A, et al. Plasma 25-hydroxyvitamin d is independently associated with hemoglobin concentration in male subjects with type 2 diabetes mellitus. International journal of endocrinology. 2011;2011:362981-362986.
143. Golbahar J, Altayab D, Carreon E, Darwish A. Association of vitamin D deficiency and hyperparathyroidism with anemia: a cross-sectional study. Journal of blood medicine. 2013;4:123-128.
144. Soliman AT, Eldabbagh M, Elawwa A, Ashour R, Saleem W. The effect of vitamin D therapy on hematological indices in children with vitamin D deficiency. Journal of tropical pediatrics. 2012;58(6):523-524.
145. Abdul-Razzak KK, Khoursheed AM, Altawalbeh SM, Obeidat BA, Ajlony MJ. Hb level in relation to vitamin D status in healthy infants and toddlers. Public health nutrition. 2012;15(9):1683-1687.
146. Coates TD. Physiology and pathophysiology of iron in hemoglobin-associated diseases. Free radical biology & medicine. 2014;72:23-40.
147. Bacchetta J, Zaritsky JJ, Sea JL, Chun RF, Lisse TS, Zavala K, et al. Suppression of iron-regulatory hepcidin by vitamin D. Journal of the American Society of Nephrology : JASN. 2014;25(3):564-572.
148. Shin JY, Shim JY. Low vitamin D levels increase anemia risk in Korean women. Clinica chimica acta; international journal of clinical chemistry. 2013;421:177-180.
149. Zughaier SM, Alvarez JA, Sloan JH, Konrad RJ, Tangpricha V. The role of vitamin D in regulating the iron-hepcidin-ferroportin axis in monocytes. Journal of clinical & translational endocrinology. 2014;1(1):19-25.
150. Milaneschi Y, Shardell M, Corsi AM, et al. Serum 25-hydroxyvitamin D and depressive symptoms in older women and men J Clin Endocrinol Metab 2010; 95(7):3225–3233.
151. Ganji V, Milone C, Cody M, et al. Serum vitamin D concentrations are related to depression in young adult US population: the Third National Health and Nutrition Examination Survey, International Archives of Medicine 2010; 3:29.
152. Hoogendijk WJ, Lips P, Dik MG, et al. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Arch Gen Psychiatry 2008;_65: 508–512.
153. Tannous L, Gigante LP, Fuchs BS, Busnello ED. Postnatal depression in southern Brazil: prevalence and its demographic and socioeconomic determinants. BMC Psychiatry 2008; 8(1):22-32.
154. McCann JC, Ames BN. Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction? FASEB J 2008; 22(4):981-1001.
155. Eyles D, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alphahydroxylase inhuman brain. J Chem Neuroana 2005; 29(1):21-30.
156. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357(3):266-81.
157. Lansdowne AT, Provost SC. Vitamin D3 enhances mood in healthy subjects during winter. Psychopharmacology 1998; 135(4):319-23.
158. Mohammaddokht Z, Karimi A, Mardanaian F. Study on effect of serum level of vitamin D in depressant post partum in Isfahan. IJOGI. 2018;21(5):74-9. [Farsi]
159. McCarty DE, Reddy A, Keigley Q, Kim PY, Marino AA. Vitamin D, race, and excessive daytime sleepiness. J Clin Sleep Med 2012; 8(6): 693-7.
160. Magorzata Wrzosek Ju, Micha Wrzosek, Andrzej Jakubczyk, Halina Matsumoto, Pawe Pi¹tkiewicz, Maria Radziwoñ-Zaleska, Marcin Wojnar, Gra¿yna Nowicka. Vitamin D and the central nervous system. Pharmacological Reports. 2013;65:271-8.
161. Khanal RC, Peters TM, Smith NM, Nemere I: Membrane receptor-initiated signaling in 1,25(OH)2D3-stimulated calcium uptake in intestinal epithelial cells. J Cell Biochem, 2008, 105, 1109–1116.
162. Nemere I, Garbi N, Hämmerling GJ, Khanal RC: Intestinal cell calcium uptake and the targeted knockout of the 1,25D3-MARRS (membrane-associated, rapid response steroid-binding) receptor/PDIA3/Erp57. J Biol Chem, 2010, 285, 31859–31866.
163. Brown J, Bianco JI, McGrath JJ, Eyles DW: 1,25-Dihydroxyvitamin D3 induces nerve growth factor, promotes neurite outgrowth and inhibits mitosis in embryonic rat hippocampal neurons. Neurosci Lett, 2003, 343, 139–143.
164. Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D: New clues about vitamin D functions in the nervous system. Trends Endocrinol Metab, 2002, 13, 100–105.
165. Sonnenberg J, Luine VN, Krey LC, Christakos S: 1,25-Dihydroxyvitamin D3 treatment results in increased choline acetyltransferase activity in specific brain nuclei. Endocrinology, 1986, 118, 1433–1439.
166. Féron F, Burne TH, Brown J, Smith E, McGrath JJ, Mackay-Sim A, Eyles DW: Developmental vitamin D3 deficiency alters the adult rat brain. Brain Res Bull, 2005, 65, 141–148.
167. Puchacz E, Stumpf WE, Stachowiak EK, Stachowiak MK: Vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells. Brain Res Mol Brain Res, 1996, 36, 193–196.
168. Reichrath S, Müller CS, Gleissner B, Pfreundschuh M, Vogt T, Reichrath J: Notch- and vitamin D signaling in 1,25(OH)2D3-resistant glioblastoma multiforme (GBM) cell lines. J Steroid Biochem Mol Biol, 2010, 121, 420–424.
169. Robin E, Derichard A, Vallet B, Hassoun SM, Neviere R: Nitric oxide scavenging modulates mitochondrial dysfunction induced by hypoxia/reoxygenation. Pharmacol Rep, 2011, 63, 1189–1194.
170. Rovner AJ, O'Brien KO: Hypovitaminosis D among healthy children in the United States: a review of the current evidence. Arch Pediatr Adolesc Med, 2008, 162, 513–519.
171. Sanchez B, Relova JL, Gallego R, Ben-Batalla I, Perez- Fernandez R: 1,25-Dihydroxyvitamin D3 administration to 6-hydroxydopamine-lesioned rats increases glial cell line-derived neurotrophic factor and partially restores tyrosine hydroxylase expression in substantia nigra and striatum. J Neurosci Res, 2009, 87, 723–732.
172. De Viragh PA, Haglid KG, Celio MR: Parvalbumin increases in the caudate putamen of rats with vitamin D hypervitaminosis. Proc Natl Acad Sci USA, 1989, 86, 3887–3890.
173. Fernandes de Abreu DA, Eyles D, Féron F: Vitamin D, a neuro-immunomodulator: implications for neurodegen-erative and autoimmune diseases. Psychoneuroendocrinology, 2009, 34, 265–277.
174. Tuohimaa P, Keisala T, Minasyan A, Cachat J, Kalueff A: Vitamin D, nervous system and aging. Psychoneuroendocrinology, 2009, 34, Suppl 1, 278–286.
175. Pilz S, Dobnig H, Fischer JE, Wellnitz B, Seelhorst U, Boehm BO, et al. Low vitamin d levels predict stroke in patients referred to coronary angiography. Stroke. 2008;39 9):2611-2613.
176. Kilkkinen A, Knekt P, Aro A, Rissanen H, Marniemi J, Heliövaara M, et al. Vitamin D status and the risk of cardiovascular disease death. Am J Epidemiol. 2009;170 8):1032-1039.
177. Daubail B, Jacquin A, Guilland JC, Hervieu M, Osseby GV, Rouaud O, et al. Serum 25-hydroxyvitamin D predicts severity and prognosis in stroke patients. Eur J Neurol. 2012.
178. Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, et al. Relation of vitamin D deficiency to cardiovascular risk factors, diseases status, and incident events in a general healthcare population. Am J Cardiol. 2010;106 (7):963-968.
179. Lerchbaum E, Rabe T. Vitamin D and female fertility. Curr Opin Obstet Gynecol 2014; 26(3):145–50.
180. Grzechocinska B, Dabrowski FA, Cyganek A, Wielgos M. The role of vitamin D in impaired fertility treatment. Neuro Endocrinol Lett 2013; 34(8):756–62.
181. Evans KN, Nguyen L, Chan J, Innes BA, Bulmer JN, Kilby MD, et al. Effects of 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 on cytokine production by human decidual cells. Biol Reprod 2006; 75(6):816–22.
182. Parikh G, Varadinova M, Suwandhi P, Araki T, Rosenwaks Z, Poretsky L, et al. Vitamin D regulates steroidogenesis and insulin-like growth factor binding protein-1 (IGFBP-1) production in human ovarian cells. Horm Metab Res 2010; 42(10):754–7.
183. Luk J, Torrealday S, Neal Perry G, Pal L. Relevance of vitamin D in reproduction. Hum Reprod 2012; 27(10):3015–27.
184. Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. Int J Womens Health 2011; 3:25-35.

185. Patra SK, Nasrat H, Goswami B, Jain A. Vitamin D as a predictor of insulin resistance in polycystic ovarian syndrome. Diabetes Metab Syndr 2012; 6(3):146–9.
186. Wehr E, Pilz S, Schweighofer N, Giuliani A, Kopera D, Pieber TR, et al. Association of hypovitaminosis D with metabolic disturbances in polycystic ovary syndrome. Eur J Endocrinol 2009; 161(4):575–82.
187. Yildizhan R, Kurdoglu M, Adali E, Kolusari A, Yildizhan B, Sahin HG, et al. Serum 25-hydroxyvitamin D concentrations in obese and non-obese women with polycystic ovary syndrome. Arch Gynecol Obstet 2009; 280(4):559–63.
188. Irani M, Minkoff H, Seifer DB, Merhi Z. Vitamin D increases serum levels of the soluble receptor for advanced glycation end products in women with PCOS. J Clin Endocrinol Metab 2014; 99(5):E886–90. [Farsi]
189. Irani M, Merhi Z. Role of vitamin D in ovarian physiology and its implication in reproduction: a systematic review. Fertil Steril 2014; 102(2):460–8. Serdar E, Bulun MD. Mechanisms of disease endometriosis. N Engl J Med 2009; 360:268-79. [Farsi]
190. Serdar E, Bulun MD. Mechanisms of disease endometriosis. N Engl J Med 2009; 360:268-79.
191. Sahin S, Beji NK. Assessment of quality of life of women with endometriosis. Hum Reprod 2012; 27:263-8.
192. Di Rosa M, Malaguarnera G, De Gregorio C, Palumbo M, Nunnari G, Malaguarnera L. Immuno-modulatory effects of vitamin D3 in human monocyte and macrophages. Cell Immunol 2012; 280(1):36–43.
193. Visser JA, de Joop FH, Laven JS, Themmen AP. Anti-Müllerian hormone: a new marker for ovarian function. Reproduction 2006; 131(1):1–9.
194. Chang EM, Kim YS, Won HJ, Yoon TK, Lee WS. Association between sex steroids, ovarian reserve, and vitamin D levels in healthy nonobese women. J Clin Endocrinol Metab 2014; 99(7):2526–32.
195. Jensen MB. Vitamin D and male reproduction. Nat Rev Endocrinol 2014; 10(3):175–86.
196. Yang B, Sun H, Wan Y, Wang H, Qin W, Yang L, et al. Associations between testosterone, bone mineral density, vitamin D and semen quality in fertile and infertile Chinese men. Int J Androl 2012; 35(6):783–92.
197. Ramlau-Hansen CH, Moeller UK, Bonde JP, Olsen J, Thulstrup AM. Are serum levels of vitamin D associated with semen quality? Results from a cross-sectional study in young healthy men. Fertil Steril 2011; 95(3):1000–4.
198. Irani M, Mirzaei Kh, Maleki N, Entezari E. Effect of vitamin D on fertility health in men and women. IJOGI. 2017;20(3):98-109. [Farsi]
199. Gartner L.M., Greer F.R. Prevention of rickets and vitamin D deficiency: new guidelines for vitamin D intake. Pediatrics. 2003;111:908-10.
200. Mascarenhas R., Mobarhan S. Hypovitaminosis D-induced pain. Nutrition Reviews. Washington: 2004;62:354-60.
201. Torrente de La Jara G., Pecoud A., Favrat B. Musculoskeletal pain in female asylum seekers and hypovitaminosis D3, Bri Med J. 2004;329 (7458):156.
202. Myalgia working group. People with undetermined muscle / bone pain may be severely vitamin D deficient, Atlanta. Drug Week, Pain medicine.2004:504.
203. Aldo B., Nicola D. A woman with bone pain, fracture, and malabsorption. Lancet.1999;347:300.
204. Russell J.A. Osteomalacic myopathy, Department of Neurology, Lahey Clinic Medical Center, Burlington, MA 0.1886.
205. Plotnikoff G.A., Quigley J.M. Prevalence of severe Hypovitaminosis D in patient with persistent, nonspecific musculoskeletal pain, Mayo Clinic Proceedings.December.2003;78:1463-70.
206. Khaw KT, Sneyd MJ, Compston J. Bone density. Parathyroid hormone and 25-hydroxyvitamin D Concentrations in middle aged women. BMJ 1992; 305: 273-77.
207. Martinez ME, del Campo MT, Sanchez-cabezudo MJ, Garcia JA, Sanchez Calvin MT, Torrijos A, et.al. Relations between calcified serum levels and bone mineral density in postmenopausal women with low bone density. Calcif Tissue Int 1994, 55: 253-6.
208. Ooms ME, Lips P, Roos JC, van der Vijgh WJ, Popp-Snijders C, Bezemer PD, et.al. Vitamin D status and sex hormone binding globulin: determinants of bone turnover and bone mineral density in elderly women. J Bone Miner Res 1995; 10: 1177-84.
209. Lips P, Duong T, Oleksik A, Black D, Cummings S, Cox D, Nickelsen T. A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: baseline data from the multiple outcomes of raloxifene evaluation clinical trial. J Clin Endocrinol Metab 2001; 86: 1212-21.
210. Collins D, Jassani C, Fogelman I, suaminathan R. Vitamin D and bone mineral density. Osteoporos Int 1998; 8: 110-4.
211. Sahota O, Masud T, San P, Hosking DJ. Vitamin D insufficiency increases bone turnover markers and enhances bone loss at the hip in patients with established vertebral osteoporosis. Clin Endocrinol (Oxf) 1999; 51: 217-21.
212. Fradinger EE, Zanchetta JR. Vitamin D and bone mineral density in ambulatory women living in Buenos Aires, Argentina. Osteoporos Int 2001; 12: 24-7.
213. Tsai KS, Wahner HW, Offord KP, Melton LJ 3rd, Kumar R, Riggs BL. Effect of aging on vitamin D stores and bone density in women. Calcif Tissue Int 1987; 40: 241-3.
214. Sowers MR, Wallace RB, Hollis BW, Lemke JH. Parameters related to 25-OH-D levels in a populationbased study of women. Am J Clin Nutr 1986; 43: 621-8.
215. Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, et.al Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int 1997; 7:439-43.
216. Tsai KS, Hsu SH, Cheng JP, Yang RS. Vitamin D stores of urban women in Taipei: effect on bone density and bone turnover, and seasonal variation. Bone 1997; 20: 371-4.
217. Kudlacek S, Schneider B, Peterlik M, Leb G, Klaushofer K, Weber K, et al. Austrian Study Group on Normative Values of Bone Metabolism. Assessment of vitamin D and calcium status in healthy adult Austrians. Eur J Clin Invest 2003; 33: 323-31.
218. Sigurdsson G, Franzson L, Steingrimsdottir L, Sigvaldason H. The association between parathyroid hormone, vitamin D and bone mineral density in 70- year-old Icelandic women. Osteoporos Int 2000; 11: 1031-5.
219. Holick MF, Chen TC. Vitamin D3 the synthesis and biologic function in skin. In: Pharmacology of skin, Mukhtar, Hed, editors, USA: CRC press series in pharmacology and toxicology 1992 p.183-202.
220. Nakhjavani M, Fallahian F. Effective dose of calcium and vitamin D in prevention and treatment of osteoporosis. Iranian Journal of Endocrinology and Metabolism. 2001; 3 (4) :285-291.
221. Jones G, Blizzard C, Riley MD, Parameswaran V, Greenaway TM, Dwyer T. Vitamin D levels in prepubertal children in Southern Tasmania: prevalence and determinants. Eur J Clin Nutr 1999; 53:824-9.
222. McKenna MJ. Differences in vitamin D status between countries in young adults and the elderly. Am J Med 1992; 93:69-77.
223. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997; 337:670-6.
224. Antonio Barbáchano AF-B, Gemma Ferrer-Mayorga, Alba Costales-Carrera, María Jesús Larriba, Alberto Muñoz. The endocrine vitamin D system in the gut. Malecular and Cellular Endocrinology. 2016;1-28.
225. Christakos, S., Dhawan, P., Verstuyf, A., Verlinden, L. and Carmeliet, G. Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects, Physiol Rev. 2016; 96, 365-408.
226. Yamamoto, H., Miyamoto, K., Li, B., Taketani, Y., Kitano, M., Inoue, Y., Morita, K., Pike, J.W. and Takeda, E. The caudal-related homeodomain protein Cdx-2 regulates vitamin D receptor gene expression in the small intestine, J Bone Miner Res. 1999; 14, 240-7.
227. Limketkai BN, Bayless TM, Brant SR, Hutfless SM. Lower regional and temporal ultraviolet exposure is associated with increased rates and severity of inflammatory bowel disease hospitalisation. Aliment Pharmacol Ther. 2014; 40:508–517.
228. Govani SM, Higgins PD, Stidham RW, Montain SJ, Waljee AK. Increased ultraviolet light exposure is associated with reduced risk of inpatient surgery among patients with Crohn's disease. J Crohns Colitis. 2015; 9:77–81.
229. Khalili H, Huang ES, Ananthakrishnan AN, Higuchi L, Richter JM, Fuchs CS, Chan AT. Geographical variation and incidence of inflammatory bowel disease among US women. Gut. 2012; 61:1686–1692.

230. Lu C, Yang J, Yu W, Li D, Xiang Z, Lin Y, Yu C. Association between 25(OH)D Level, Ultraviolet Exposure, Geographical Location, and Inflammatory Bowel Disease Activity: A Systematic Review and Meta-Analysis. PLoS One. 2015; 10:e0132036.
231. Cantorna MT. IBD: Vitamin D and IBD: moving towards clinical trials. Nature reviews Gastroenterology & hepatology. 2016; 13:322–323.
232. Malone RW, Kessenich C. Vitamin D deficiency: implications across the lifespan. The Journal for Nurse Practitioners. 2008;4(6):448-54.
233. Sprake EF, Grant VA, Corfe BM. Vitamin D3 as a novel treatment for irritable bowel syndrome: single case leads to critical analysis of patient-centred data. BMJ case reports. 2012.
234. Dehghanian L RA, Hekmatdoost A. Effects of Vitamin D3 Supplementation on Clinical Symptoms in Patients with Irritable Bowel Syndrome and Vitamin D Deficiency: Clinical Trials. Iranian Journal of Nutrition Sciences & Food Technology 18. 2016;11(1):11-8.
235. Assa A, Vong L, Pinnell LJ, Rautava J, Avitzur N, Johnson-Henry KC, et al. Vitamin D deficiency predisposes to adherent-invasive Escherichia coli-induced barrier dysfunction and experimental colonic injury. Inflammatory bowel diseases. 2015;21(2):297-306.
236. Bashir M, Prietl B, Tauschmann M, Mautner SI, Kump PK, Treiber G, et al. Effects of high doses of vitamin D on mucosa-associated gut microbiome vary between regions of the human gastrointestinal tract. European journal of nutrition. 2015 Jul 1. PubMed PMID: 26130323. Epub 2015/07/02. Eng.
237. Cantorna MT, McDaniel K, Bora S, Chen J, James J. Vitamin D, immune regulation, the microbiota, and inflammatory bowel disease. Experimental biology and medicine (Maywood, NJ). 2014;239(11):1524-30.
238. Ooi JH, Chen J, Cantorna MT. Vitamin D regulation of immune function in the gut: why do T cells have vitamin D receptors? Molecular aspects of medicine. 2012;33(1):77- 82.
239. Raftery T, Martineau AR, Greiller CL, Ghosh S, McNamara D, Bennett K, et al. Effects of vitamin D supplementation on intestinal permeability, cathelicidin and disease markers in Crohn's disease: Results from a randomised double-blind placebo-controlled study. United European gastroenterology journal. 2015;3(3):294-302.
240. Ly NP, Litonjua A, Gold DR, Celedón JC. Gut microbiota, probiotics, and vitamin D: Interrelated exposures influencing allergy, asthma, and obesity? Journal of Allergy and Clinical Immunology. 2011;127(5):1087-94.