CLINICAL IMPLICATIONS OF VITAMIN D DEFICIENCY IN ADULTS

Ibtesam Mohammed Mandili[1*], Ibrahim Abdu Alsubaihi[2], Hamed Arif Hejazi[3], AbdulAziz Muslet Al Mutairi[4], Abdullah Abdulelah Alanazi[5], Razan Adel Alghamdi[6], Shatha Awad Alraddadi[7], Alhulwah Saiq Alkuwikybi[8], Khalid Mohammad Alqahtani[9], Nadyah Saud Aloufi[10], Yaser Yahya Qattan[11], Mohammad Bakhiader [12]

ABSTRACT

This review highlights the critical aspects of vitamin D deficiency in adults, focusing on the metabolism, biological functions, and health implications. Vitamin D, available as cholecalciferol (D3) and ergocalciferol (D2), is pivotal for bone health and the regulation of calcium and phosphorus metabolism. Although sunlight exposure can synthesize vitamin D, dietary sources and supplements are crucial due to the skin cancer risks associated with UV exposure. The activation process of vitamin D involves conversion into 25-hydroxyvitamin D in the liver and subsequently into the active form, 1,25-dihydroxyvitamin D, in the kidneys. This active form interacts with the vitamin D receptor (VDR) in various tissues, influencing over 200 genes. Deficiency in vitamin D is linked to skeletal diseases like rickets and osteomalacia, and it is associated with potential risks for non-skeletal diseases, including cardiovascular diseases, diabetes, and certain cancers. The review emphasizes dietary intake and supplementation as key strategies for preventing and treating vitamin D deficiency, advocating for a balanced approach to ensure adequate vitamin D levels to support overall health and mitigate disease risks.

Keywords: Vitamin D deficiency, cholecalciferol, ergocalciferol, bone health, supplementation

[1*]Al Naeem Primary Healthcare Center, King Fahad General Hospital, Jeddah, Saudi Arabia
[2] Al Bareq Primay Healthcare Center, Aseer, Saudi Arabia
[3] Department of Orthopaedic, Al Noor Specialist Hospital, Mecca, Saudi Arabia
[4] Riyadh Third Health Cluster, Ministry of Health, Riyadh, Saudi Arabia
[5] Department of Emergency Medicine, Al Iman General Hospital, Riyadh, Saudi Arabia
[6] Ghulail Primary Healthcare Center, King Abdulaziz Hospital, Jeddah, Saudi Arabia
[7] Primary Healthcare, King Abdulaziz Hospital, Jeddah, Saudi Arabia
[8] Emergency Nursing Department, North Medical Tower Hospital, Arar, Saudi Arabia
[9] Department of Urology, Abha Maternity and Children Hospital, Abha, Saudi Arabia
[10] Virtual Consultation, Eastern Health Cluster, Al Khobar, Saudi Arabia
[11] Department of Psychiatry, Al-Amal Mental Health and Addiction Treatment Hospital, Jeddah, Saudi Arabia
[12] Department of Psychiatry, Al Thager Hospital, Jeddah, Saudi Arabia

[*]**Corresponding Author:** Ibtesam Mohammed Mandili
[*]Al Naeem Primary Healthcare Center, King Fahad General Hospital, Jeddah, Saudi Arabia

DOI:

INTRODUCTION

Vitamin D exists in two main forms, cholecalciferol (D3) and ergocalciferol (D2), both essential for bone health (1). The primary way to obtain vitamin D3 is through the skin's production when exposed to ultraviolet light. However, both D3 and D2 can also be sourced from consuming natural and fortified foods as well as dietary supplements. Despite sunlight being a significant source of vitamin D, oral consumption is considered more crucial for preventing and treating vitamin D deficiency (2). Due to the risk of skin cancer from sun exposure, it is not recommended as a strategy to combat vitamin D deficiency. When calculating the necessary oral intake to prevent and address this deficiency, it is important to account for both accidental and purposeful sun exposure. Thus, the suggested daily intake of vitamin D through diet is particularly aimed at individuals lacking sun exposure; those with adequate exposure to the sun require less (3).

Vitamin D undergoes two crucial hydroxylation processes to become activated. Initially, it is converted into 25-hydroxyvitamin D (25OHD) in the liver by the enzyme 25-hydroxylase (CYP2R1), a step that depends on the availability of the original vitamin D. Subsequently, in the kidneys, 1α-hydroxylase (CYP27B1) transforms it into the hormonally active form, 1α, 25-dihydroxy vitamin D (1,25(OH)2D), a process tightly controlled by parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) (1). This hormonally active form circulates throughout the body, binding to the vitamin D receptor (VDR) in various locations, notably the intestine, where it enhances the absorption of calcium and phosphate. These minerals are critical for the mineralization of the bone matrix during all life stages. Additionally, vitamin D is activated in tissues outside the kidney, where it binds locally to VDR, an action known as the paracrine/intracrine effect. Unlike the renal process, this local effect is not governed by calciotropic hormones but by cytokines specific to each tissue, and it also depends on the availability of substrates (3). This complex mechanism of vitamin D's action has been a significant focus of both basic and clinical research for the last thirty years.

The 2011 report from the Institute of Medicine (IOM) established a definitive causal relationship between vitamin D intake and bone health. A severe lack of vitamin D can lead to rickets in children and osteomalacia in adults. Furthermore, in adults, it can result in reduced bone mass and increase the risk of fractures in the elderly due to bone fragility. While vitamin D deficiency has been linked to a range of health issues, including infections, autoimmune diseases, cardiovascular diseases, diabetes mellitus, falls, and cancer, the evidence supporting a causal connection to these non-skeletal diseases remains inconsistent and not definitive (1, 4).

METHODOLOGY

This study is based on a comprehensive literature search conducted on February 25, 2023, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the clinical implications of vitamin D deficiency in adults. There were no restrictions on date, language, participant age, or type of publication.

DISCUSSION

Vitamin D is essential for human health, obtained through sun exposure and dietary sources. Despite the ability to synthesize vitamin D from prolonged sunlight exposure, the maximum attainable level is approximately 60 ng/mL. The production of cutaneous vitamin D3 is influenced by a variety of factors, including skin color, sunscreen use, the time of day, season, geographic latitude, altitude, and air pollution (5).

Circulating levels of 25(OH)D are the best marker for vitamin D status due to its stable half-life and correlation with disease states. Vitamin D is vital for regulating serum calcium and phosphorus levels, enhancing the absorption of these minerals from the diet, and thereby playing a key role in bone health. Without adequate vitamin D, dietary calcium and phosphorus absorption is significantly reduced (6). Vitamin D receptors are found in numerous cells, highlighting its broad biological impacts beyond mineral metabolism (7). The active vitamin D form enhances calcium and phosphorus absorption in the intestines and contributes to bone remodeling by interacting with receptors on osteoblasts and preosteoclasts, promoting bone formation and resorption. It also affects calcium reabsorption in the kidneys. The presence of VDRs in many body tissues and cells, including the brain and immune cells, which can produce 1,25(OH)2D depending on the availability of 25(OH)D, underscores the importance of maintaining adequate vitamin D levels for overall health (8).

Vitamin D deficiency

Vitamin D deficiency is a global issue associated with various health problems, including an increased risk of diseases like type 1 diabetes, cardiovascular diseases, certain cancers, cognitive decline, depression, pregnancy complications, autoimmune diseases, and allergies (9). The diagnostic criteria for vitamin D status are presented in **Table 1** (10).

Table 1. categorizes vitamin D status according to the concentration of 25-hydroxyvitamin D3 in the blood, measured in nanograms per milliliter (ng/ml) (10).

Vitamin D status	**25(OH)D3 concentration (ng/ml)**
Severe Deficiency	0-10
Deficiency	10-20
Insufficiency	20-30
Optimal Concentration	30-80
Risk of Toxicity	> 100

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) suggests that a 25(OH)D serum level below 20 ng/mL is linked to increased bone turnover, bone loss, and potentially mineralization defects compared to levels of 20 ng/mL or higher. This deficiency correlates with higher risks of frailty, nonvertebral and hip fractures, and overall mortality, with worse outcomes observed at levels below 20 ng/mL. Therefore, ESCEO recommends a minimum serum 25(OH)D level of 20 ng/mL in the general population and patients with osteoporosis for optimal bone health, and at least 30 ng/mL to significantly reduce fracture risk in elderly individuals at high risk of falls and fractures (11).

Causes of vitamin D deficiency

Vitamin D deficiency can be due to various causes, typically categorized into two main types, deficiency due to insufficient ultraviolet B (UVB) radiation exposure **(Table 2)** and deficiency linked to medical or physical conditions **Table 3** (8).

Table 2. UVB-Related vitamin D deficiency causes (8).

Factor	**Impact on Vitamin D Synthesis**
Aging	Limits UVB-mediated vitamin D synthesis due to reduced 7-dehydrocholesterol.
Sun Exposure	Decreased opportunity for vitamin D formation due to lifestyle or geographical limitations.
Skin Pigmentation	Reduced efficiency of vitamin D production in darker skin tones due to higher melanin.
Environmental	UVB absorption by ozone and zenith angle variations affect vitamin D synthesis.
Sunscreen Use	Prevents formation of previtamin D3 by blocking UVB radiation.

Table 3. Medical/physical conditions related to vitamin D deficiency (8).

Condition	**Impact on Vitamin D Synthesis/Absorption**
Fat Malabsorption	Impairs vitamin D absorption due to its fat-soluble nature in conditions like Crohn's disease, cystic fibrosis, and after certain surgeries.
Medication Effects	Interferes with vitamin D metabolism, leading to osteomalacia in long-term use of drugs like antiepileptics and rifampicin.
Chronic Kidney Disease	Reduces capacity to produce 1,25-dihydroxyvitamin D, affecting parathyroid hormone regulation in advanced stages or dialysis patients.
Obesity	Sequestration of vitamin D in body fat leads to lower serum levels despite normal production.

Vitamin D intake in different conditions, organs

The multifaceted role of vitamin D across diverse health conditions underscores its significance beyond mere skeletal health, illuminating its impact on pulmonary function, pregnancy outcomes, sepsis recovery, organ transplant success, cancer

prevention, and diabetes management, as evidenced by extensive research and scientific documentation.

Lung

The immunomodulatory, anti-inflammatory, and anti-infective effects of vitamin D are particularly beneficial for individuals with respiratory conditions, including community-acquired infections, acute respiratory failure, and lung transplant recipients, showcasing therapeutic benefits in respiratory disease treatment and prevention (12, 13).

Pregnancy

Vitamin D supplementation during pregnancy is associated with reduced risks of gestational diabetes, low birthweight, and preeclampsia. Achieving higher serum levels of vitamin D (20 to 50 ng/mL) through supplementation correlates with improved outcomes, highlighting the importance of maintaining adequate vitamin D levels during pregnancy (14-20).

Sepsis

In the context of sepsis, vitamin D plays a crucial role in enhancing antibacterial responses. High-dose supplementation can quickly increase vitamin D levels and circulating cathelicidin, reducing inflammatory cytokine levels, which may offer therapeutic advantages in sepsis management (21).

Organ transplantation

Low levels of vitamin D in organ transplant recipients are linked to prolonged hospitalization and increased mortality rates. The immunobiological effects of vitamin D may help reduce the risk of infections and long-term bone disorders in this population, suggesting a role for supplementation in improving post-transplant outcomes (22).

Cancer

While early research suggested a potential for vitamin D in cancer prevention, recent studies and meta-analyses have provided mixed results regarding its efficacy in reducing cancer incidence. However, vitamin D supplementation has been associated with reduced cancer mortality, indicating a need for further research to clarify its role in cancer prevention and management (23-26).

Diabetes

Vitamin D deficiency is more prevalent among individuals with type 1 diabetes mellitus (T1DM) and is linked to increased risks of the disease in offspring. Supplementation during critical periods may lower the risk of T1DM. For type 2 diabetes mellitus (T2DM), vitamin D supplementation has not consistently been shown to reduce incidence, but specific subgroups, such as those with very low vitamin D levels, might benefit (22, 27-29).

Musculoskeletal impact

Vitamin D deficiency leads to several musculoskeletal issues, including secondary hyperparathyroidism, increased bone turnover, and bone loss. This can result in reduced bone mineral density (BMD), contributing to osteomalacia and an elevated risk of fractures from low-impact trauma. Rickets in children, characterized by symptoms such as rachitic rosary and bowing deformities of the legs, underscore the critical need for adequate vitamin D levels during early development. Moreover, vitamin D deficiency is linked to proximal muscle weakness, further emphasizing its role in musculoskeletal health (30).

Osteoporosis

A significant health concern, particularly among the elderly, osteoporosis is exacerbated by vitamin D deficiency, which compromises intestinal calcium absorption and disrupts calcium balance. This leads to diminished bone mineral content and density, heightening the risk of fractures and impacting the morbidity and mortality of older individuals. Strategies to maximize bone mineral content through adequate calcium and vitamin D intake, coupled with regular exercise from childhood, are crucial for reducing fracture risks later in life, especially as the bone remodeling is disrupted by menopause and aging (8).

Beyond the skeleton

Observational studies have highlighted the nonskeletal benefits of maintaining serum 25(OH)D levels above 28 to 32 ng/mL, linking higher levels to decreased risks of various diseases, including certain cancers, mental disorders, infectious diseases, cardiovascular disease, type 2 diabetes, and autoimmune disorders. This suggests that optimal health benefits may be achieved by maintaining 25(OH)D levels within the range of 28 to 40 ng/mL (30).

Autoimmune diseases

Vitamin D has been recognized as a natural immune modulator, with epidemiological, genetic, and basic science studies suggesting its role in the pathogenesis of autoimmune diseases like type 1 diabetes mellitus, multiple sclerosis (MS), rheumatoid arthritis (RA), and Crohn's disease. For MS, high levels of 25(OH)D have been associated with a reduced risk of the disease and its

progression, with high doses of vitamin D3 shown to be safe and potentially beneficial in reducing specific markers of disease activity (30). RA studies suggest that vitamin D can modulate immune responses, potentially reducing disease severity by dampening T cell activity and lymphokine production (31). Similarly, vitamin D deficiency is common in Crohn's disease, exacerbating the risks of osteopenia and osteoporosis due to malabsorption (30).

Cardiovascular disorders

The inverse relationship between 25(OH)D and 1,25(OH)2D levels with coronary artery calcifications and myocardial infarction incidence highlights vitamin D's role in cardiovascular health. Vitamin D supplementation can attenuate the inflammatory response following acute coronary events and is associated with lower risks of hypertension and metabolic syndrome, partly through the regulation of the renin-angiotensin-aldosterone axis (32).

Neurologic disorders

Vitamin D's capacity to influence neural health is evident through its neuroprotective role, including the promotion of remyelination and amyloid-beta clearance, which are crucial in conditions like Alzheimer's disease. The developmental impacts of vitamin D deficiency, such as the potential link to autism risk and disruption in brain development, underscore the importance of adequate vitamin D levels for neural function and health (8).

Treatment and prevention of vitamin D deficiency

The prevention and treatment of vitamin D deficiency necessitate a comprehensive strategy that leverages sunlight exposure, dietary enhancements, and targeted supplementation. Sunlight remains a pivotal natural source for vitamin D synthesis, with recommendations for moderate exposure tailored to minimize skin cancer risk while ensuring adequate vitamin D production. The limited natural dietary sources of vitamin D underscore the importance of fortified foods in augmenting population vitamin D status (18,19). Supplementation guidelines suggest a daily intake of 600 to 800 international units (IU) to support bone health, with higher doses (1000-2000 IU) recommended for those with lower serum 25(OH)D levels to achieve and maintain optimal levels above 30ng/mL. Specific regimens, such as 50,000 IU of vitamin D2 weekly, are advised for treating established deficiencies, with maintenance dosages to prevent recurrence (33, 34). The role of vitamin D during pregnancy and lactation is critical, with supplementation significantly improving vitamin D status in mothers and their newborns (35). Special considerations for obese individuals and those on certain medications indicate a need for adjusted vitamin D dosages to meet increased requirements, favoring vitamin D3 for its efficacy in maintaining serum 25(OH)D levels (7). Safety protocols highlight the importance of monitoring intake to prevent vitamin D intoxication, with a threshold of 10,000 IU daily deemed safe for healthy adults, ensuring serum 25(OH)D levels do not exceed 200 ng/mL to avoid toxicity. This multifaceted approach emphasizes the importance of maintaining adequate vitamin D levels through balanced sun exposure, dietary intake, and judicious supplementation, ensuring broad health benefits while mitigating the risk of deficiency and toxicity, as illustrated by references (8).

Recommendations

To effectively address vitamin D deficiency, a comprehensive approach involving public education, dietary recommendations, and tailored supplementation guidelines is crucial. Public health initiatives should focus on increasing awareness of vitamin D's benefits, promoting the consumption of vitamin D-rich foods, and advocating for safe sun exposure practices. Regular screening for at-risk populations, along with education for healthcare providers on the latest research and treatment protocols, can enhance patient care. Additionally, ongoing research into vitamin D's broader health impacts and policy efforts, including food fortification, are essential for improving public health outcomes. This multifaceted strategy aims to ensure optimal vitamin D levels across diverse populations, supporting bone health and potentially mitigating the risk of various non-skeletal diseases.

CONCLUSION

Vitamin D deficiency in adults has widespread health implications, affecting bone integrity and potentially influencing non-skeletal diseases. Addressing this deficiency through dietary sources, supplementation, and safe sun exposure is essential. Future research should further explore vitamin D's role in health and refine management strategies, ensuring optimal vitamin D levels to enhance bone health and possibly reduce the risk of various diseases.

REFERENCES

1. Ross AC, Taylor CL, Yaktine AL, Del Valle HB. Committee to review dietary reference intakes for vitamin D and calcium. Food and Nutrition Board. 2011.

2. McKenna MJ. Differences in vitamin D status between countries in young adults and the elderly. The American journal of medicine. 1992;93(1):69-77.
3. McKenna MJ, Kilbane M. Vitamin D deficiency. Endocrinology and Diabetes: A Problem Oriented Approach: Springer; 2022. p. 245-56.
4. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. The Journal of Clinical Endocrinology & Metabolism. 2011;96(1):53-8.
5. Hossein-nezhad A, Holick MF. Optimize dietary intake of vitamin D: an epigenetic perspective. Current Opinion in Clinical Nutrition & Metabolic Care. 2012;15(6):567-79.
6. DeLuca HF. Overview of general physiologic features and functions of vitamin D. The American journal of clinical nutrition. 2004;80(6):1689S-96S.
7. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. The American journal of clinical nutrition. 2006;84(1):18-28.
8. Galesanu C, Mocanu V. Vitamin D deficiency and the clinical consequences. The Medical-Surgical Journal. 2015;119(2):310-8.
9. Vieth R. Why "Vitamin D" is not a hormone, and not a synonym for 1, 25-dihydroxy-vitamin D, its analogs or deltanoids. The Journal of steroid biochemistry and molecular biology. 2004;89:571-3.
10. Matyjaszek-Matuszek B, Lenart-Lipińska M, Woźniakowska E. Clinical implications of vitamin D deficiency. Menopause Review/Przegląd Menopauzalny. 2015;14(2):75-81.
11. Rizzoli R, Boonen S, Brandi M-L, Bruyère O, Cooper C, Kanis JA, et al. Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Current medical research and opinion. 2013;29(4):305-13.
12. Vos R, Ruttens D, Verleden SE, Vandermeulen E, Bellon H, Van Herck A, et al. High-dose vitamin D after lung transplantation: a randomized trial. The Journal of Heart and Lung Transplantation. 2017;36(8):897-905.
13. Leclair TR, Zakai N, Bunn JY, Gianni M, Heyland DK, Ardren SS, et al. Vitamin D supplementation in mechanically ventilated patients in the medical intensive care unit. Journal of Parenteral and Enteral Nutrition. 2019;43(8):1037-43.
14. Palacios C, Kostiuk LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane Database of Systematic Reviews. 2019(7).
15. Holick MF. A call to action: pregnant women in-deed require vitamin D supplementation for better health outcomes. The Journal of Clinical Endocrinology & Metabolism. 2019;104(1):13-5.
16. Fogacci S, Fogacci F, Banach M, Michos ED, Hernandez AV, Lip GY, et al. Vitamin D supplementation and incident preeclampsia: A systematic review and meta-analysis of randomized clinical trials. Clinical Nutrition. 2020;39(6):1742-52.
17. Akbari S, Khodadadi B, Ahmadi SAY, Abbaszadeh S, Shahsavar F. Association of vitamin D level and vitamin D deficiency with risk of preeclampsia: A systematic review and updated meta-analysis. Taiwanese Journal of Obstetrics and Gynecology. 2018;57(2):241-7.
18. McDonnell SL, Baggerly KA, Baggerly CA, Aliano JL, French CB, Baggerly LL, et al. Maternal 25 (OH) D concentrations≥ 40 ng/mL associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center. PloS one. 2017;12(7):e0180483.
19. Wagner C, Baggerly C, McDonnell S, Baggerly K, French C, Baggerly L, et al. Post-hoc analysis of vitamin D status and reduced risk of preterm birth in two vitamin D pregnancy cohorts compared with South Carolina March of Dimes 2009–2011 rates. The Journal of steroid biochemistry and molecular biology. 2016;155:245-51.
20. Rostami M, Tehrani FR, Simbar M, Bidhendi Yarandi R, Minooee S, Hollis BW, et al. Effectiveness of prenatal vitamin D deficiency screening and treatment program: a stratified randomized field trial. The Journal of Clinical Endocrinology & Metabolism. 2018;103(8):2936-48.
21. Quraishi SA, De Pascale G, Needleman JS, Nakazawa H, Kaneki M, Bajwa EK, et al. Effect of cholecalciferol supplementation on vitamin D status and cathelicidin levels in sepsis: a randomized, placebo-controlled trial. Critical care medicine. 2015;43(9):1928.
22. Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M,

Tmava Berisha A, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. European journal of clinical nutrition. 2020;74(11):1498-513.
23. McDonnell SL, Baggerly C, French CB, Baggerly LL, Garland CF, Gorham ED, et al. Serum 25-hydroxyvitamin D concentrations≥ 40 ng/ml are associated with> 65% lower cancer risk: pooled analysis of randomized trial and prospective cohort study. PloS one. 2016;11(4):e0152441.
24. Keum N, Giovannucci E. Vitamin D supplements and cancer incidence and mortality: a meta-analysis. British journal of cancer. 2014;111(5):976-80.
25. Lappe J, Watson P, Travers-Gustafson D, Recker R, Garland C, Gorham E, et al. Effect of vitamin D and calcium supplementation on cancer incidence in older women: a randomized clinical trial. Jama. 2017;317(12):1234-43.
26. Chatterjee R, Erban JK, Fuss P, Dolor R, LeBlanc E, Staten M, et al. Vitamin D supplementation for prevention of cancer: the D2d cancer outcomes (D2dCA) study. Contemporary clinical trials. 2019;81:62-70.
27. Federico G, Genoni A, Puggioni A, Saba A, Gallo D, Randazzo E, et al. Vitamin D status, enterovirus infection, and type 1 diabetes in Italian children/adolescents. Pediatric diabetes. 2018;19(5):923-9.
28. Rasoul MA, Al-Mahdi M, Al-Kandari H, Dhaunsi GS, Haider MZ. Low serum vitamin-D status is associated with high prevalence and early onset of type-1 diabetes mellitus in Kuwaiti children. BMC pediatrics. 2016;16(1):1-7.
29. Mäkinen M, Mykkänen J, Koskinen M, Simell V, Veijola R, Hyöty H, et al. Serum 25-hydroxyvitamin D concentrations in children progressing to autoimmunity and clinical type 1 diabetes. The Journal of Clinical Endocrinology & Metabolism. 2016;101(2):723-9.
30. Hossein-nezhad A, Holick MF, editors. Vitamin D for health: a global perspective. Mayo clinic proceedings; 2013: Elsevier.
31. Zhang R, Naughton DP. Vitamin D in health and disease: current perspectives. Nutrition journal. 2010;9:1-13.
32. Cigolini M, Iagulli M, Miconi V, Galiotto M, Lombardi S, Targher G. Serum 25-hydroxyvitamin D3 concentrations and prevalence of cardiovascular disease among type 2 diabetic patients. Diabetes care. 2006;29:722-4.
33. Mocanu V, Galesanu C, Vieth R. Bread as a vehicle vitamin D fortification: application to nursing home residents. Handbook of Food Fortification and Health: From Concepts to Public Health Applications Volume 2. 2013:179-93.
34. Demetriou ET, Travison TG, Holick MF. Treatment with 50000 IU Vitamin D2 every other week and effect on serum 25-Hydroxyvitamin D2, 25-Hydroxyvitamin D3, and total 25-Hydroxyvitamin D in aclinical setting. Endocrine practice. 2012;18(3):399-402.
35. Hollis BW, Wagner CL. Vitamin D and pregnancy: skeletal effects, nonskeletal effects, and birth outcomes. Calcified tissue international. 2013;92:128-39.