ECRONICON OPEN ACCESS

EC MICROBIOLOGY
Review Article

Overview of Extra-Musculoskeletal Roles of Vitamin D

Hanan Ahmad AbuAhmad[1]*, Wafaa Abdulkaliq Almehmadi[2], Faez Mohammadhasan A Zagzoug[3], Faten Saud Aljehani[4], Saeed Mohammed Alqahtani[5], Mohammad Zain Raddadi[6], Hajer Marei Mohammed Rabaiy[7], Murtadha Hussain Buquryan[8], Ruba Mohammed Amin Khan[9], Reem Emad Gommosani[10], Maria Mohanmed Al-Shehab[11], Shahad Ahmad Bamani[12], Ali Mohammed F Alshehri[13] and Fatimah Yahya Alshabbi[13]

[1]East Jeddah Hospital, Almatar Alqadeem Primary Healthcare, Jeddah, Saudi Arabia
[2]Alnawaryiah Primary Health Care Center, Makkah, Saudi Arabia
[3]Medical Service Center University, Jeddah, Saudi Arabia
[4]Althaghr Hospital, Jeddah, Saudi Arabia
[5]Aseer Central Hospital (Ach), Aseer, Saudi Arabia
[6]Al-Fath Primary Health Care, Medina, Saudi Arabia
[7]Obhur Primary Health Care, Jeddah, Saudi Arabia
[8]Jordan University of Science and Technology, Jordan
[9]King Abdulaziz University, Jeddah, Saudi Arabia
[10]Alshera Primary Health Care, Jeddah, Saudi Arabia
[11]Primary Healthcare, Saihat, Saudi Arabia
[12]King Abdulaziz Hospital, Jeddah, Saudi Arabia
[13]Ahad Rofidah General Hospital, Asir, Saudi Arabia

***Corresponding Author:** Dr. Hanan Ahmad AbuAhmad, Family Medicine Consultant, East Jeddah Hospital, Almatar Alqadeem Primary Healthcare, Jeddah, Saudi Arabia.

Received: November 19, 2022; **Published:** November 22, 2022

Abstract

Introduction: Vitamin D is critical in the musculoskeletal system because it maintains calcium and phosphate balance and dynamics. Vitamin D deficiency has been well-known for decades, and it causes various musculoskeletal diseases such as rickets, osteoporosis, etc. However, in the past two decades, vitamin D was found to strongly influence multiple other systems, such as the immune system, respiratory system, cardiovascular system, and cancer. Vitamin D plays a specific role in immune activation for combating various infections and pathologically undoing some autoimmune conditions. Vitamin D acts on immunocytes unidirectionally to modulate the immune system via stimulatory or suppressive actions and offers better immunological outcomes. Apart from calcium metabolism disorders, vitamin D deficiency may also lead to various acute and chronic diseases such as type 2 diabetes mellitus, cancers, and cardiovascular diseases. Therefore, it is essential to understand the role of vitamin D in the extra-musculoskeletal field.

Aim of the Study: The aim of the present review is to understand the various extra-skeletal role of vitamin D.

Methodology: The review is the comprehensive research of PUBMED since the year 1989 to 2021.

Conclusion: Deficiency and insufficiency of Vitamin D is now a well-recognized global health problem. A multitude of studies suggests that deficiency of Vitamin D not only affects bone health but also has negative effects on the endocrine system, cardiovascular system, and respiratory systems leading to acute and chronic illnesses in the long term, such as cancer, type 2 diabetes mellitus, mental illness, neuropsychiatric disorders, neurocognitive dysfunction, infertility, an adverse outcome in pregnancy and childbirth. This suggests and justify the enhanced recommendation to children and adult in their diet and increasing the level of vitamin D via supplements and appropriate sun exposure.

Keywords: *Vitamin D Deficiency; Osteoporosis; Vitamin D; 25-Hydroxyvitamin D; Fractures; Cancer; Type 2 Diabetes Mellitus; Autoimmune Diseases; Cardiovascular Diseases; Infectious Diseases*

Introduction

Phytoplanktons have been producing vitamin D for more than 500 million years. Vitamin D is known to be the oldest of all the hormones produced in the body. Earlier, the major function of Vitamin D in early life forms was to protect the ultraviolet-sensitive macromolecules like DNA, RNA and protein from sunlight so they could undergo photosynthesis. With evolution, the role of vitamin D changed as marine animals moved to land and became vertebrae with skeletons. The skeleton structure needed calcium homeostasis maintenance which was the major physiological problem faced earlier compared to that of ocean creatures (rich in calcium). The presence of vitamin D ensured this calcium homeostasis by intestinal absorption of calcium from diet and maintained the calcified skeleton of mammals. However, to this date, having sufficient dietary requirements of vitamin D, either from sunlight or dietary source, is crucial. Over a long period of time, Vitamin D evolved into a hormone that plays an important role in the skeletal and extra-skeletal health of humans. It is known to regulate approximately 2000 genes. The upregulation of vitamin D shows differences, not only in ethnical but in gender too. The difference in skin pigmentation is of evolutionary importance. Humans living at latitudes, far from the equator, are light-skinned and tend to produce more vitamin D compared to dark-skinned humans. Gender differences are also seen; females having a lighter tone than males reflect more light and need a higher amount of vitamin D, especially during pregnancy and lactation [1-3].

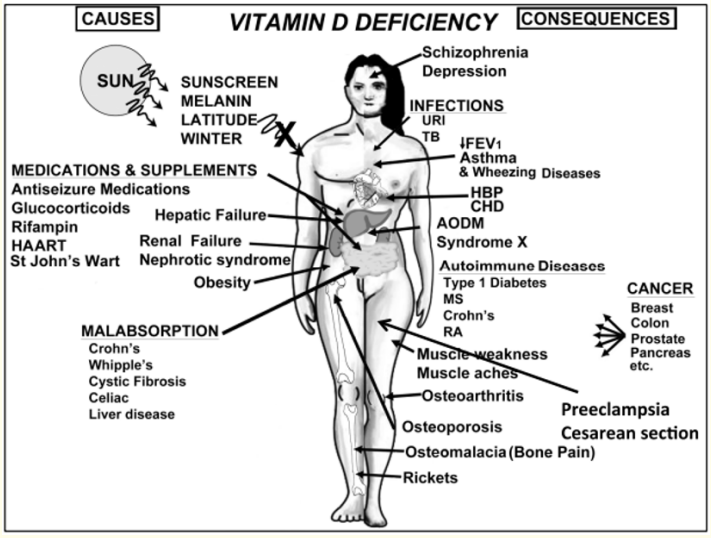

Figure 1: *Depicting various extraskeletal effects of vitamin D deficiency [5].*

Various sources of vitamin D

The main sources are:

- Sunlight
- Supplements (Multivitamin, Vitamin 3, Drisdol (vitamin D2) liquid, Vitamin D2 - Ergocalciferol)
- Diet (Cod liver oil, egg yolk, milk, mackerel, salmon, cheddar cheese, butter, breakfast cereals, yogurt, mushroom, fortified orange juice) [4].

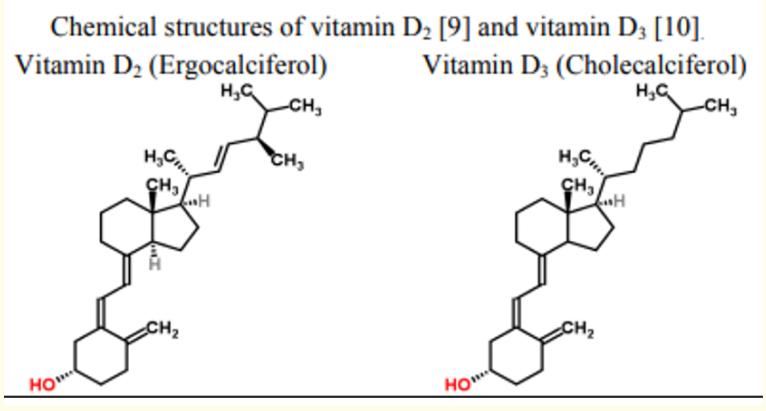

Figure 2: *Chemical structures of vitamin D2 and vitamin D3 [5].*

Metabolism [6]

Vitamin D via dietary or supplemental intake or cutaneous synthesis

↓

Transported to fat (Stored in lover)
First Activation - hydroxylation to 25-hydroxyvitamin D [25(OH)D]
(Major circulating form of vitamin D)

↓

In kidneys → 25-hydroxyvitamin D is metabolized to 1,25-dihydroxy vitamin D [1,25(OH)2D] (systemically circulating active) by mitochondrial enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) and is regulated by various factors such as fibroblast growth factor 23 (FGF-23), serum phosphorus, calcium and parathormone (PTH)

↓

Enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) is also expressed in various tissues such as the parathyroid gland, placenta, prostate, macrophages, keratinocytes, T-lymphocytes, dendritic cells, and several cancer cells which explains the extra-skeletal role of vitamin D.

↓

Destruction of 1,25(OH)2D – own rapid destruction by inducing 25-hydroxyvitamin D-24-hydroxylase (CYP24A1) → multistep catabolism of both 1,25(OH)2D and 25(OH)D into water-soluble metabolites (calcitroic acid) [6]

Figure A

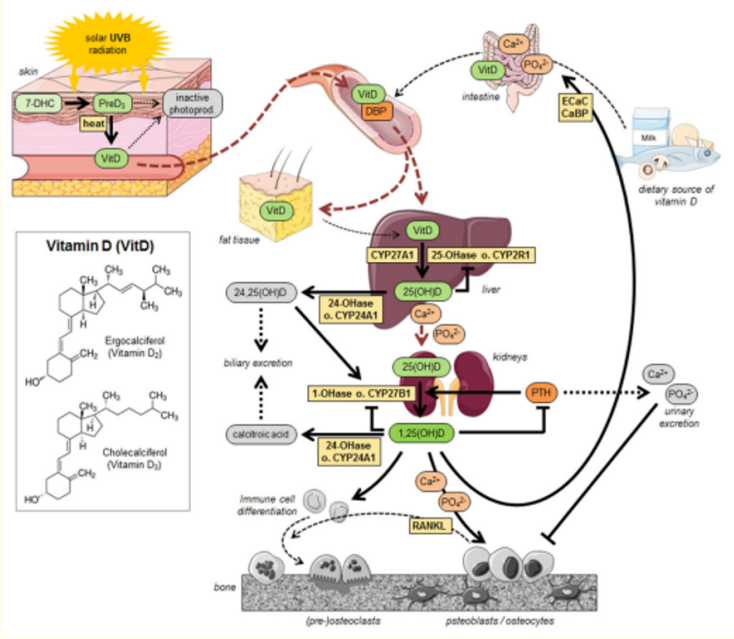

Figure 3: *Schematic representation of admission and metabolism of vitamin D. Vitamin D is supplied by cutaneous synthesis or diet intake. The bloodstream takes it into the liver, where its chemical structure is changed by hydroxylation. Then it is sent to the kidneys for another hydroxylation. Finally, the active metabolite 1,25(OH)D circulates through the body in order to be effective [6].*

Vitamin D deficiency and various extra muscular implication

Cancer

Population living at higher latitudes have lower UV exposure and therefore, there is low production of Vitamin D, which is known to be associated with an increased risk of various types of cancers such as bladder, breast, colon, cervical, endometrial, gastric, esophageal, lung, ovarian, rectal, pancreatic, renal, and vulvar cancer and Hodgkin's and non-Hodgkin's lymphoma. According to many case-cohort studies, there is an inverse association between the incidence of cancer, mortality from these cancers, and 25(OH)D, but these studies have certain limitations since a low level of 25(OH)D is also associated with factors causing cancer such an obesity (Fatty storage of 25(OH)D) and lack of physical activities (less outdoors exposure to the sun) [4,5,7].

Anti-carcinogenic effects of vitamin D can be explained by the fact that vitamin D and its metabolites reduce the incidence of cancer by inhibiting tumor angiogenesis, allowing mutual adherence of cells, increasing intercellular communication through gap junctions, and contact inhibition that is tight physical contact with adjacent cells causing inhibition of proliferation. The metabolites of vitamin aid in maintaining a normal gradient of calcium in the epithelium of colon crypts, decreasing the proliferation of non-cancerous high-risk epithelial cells in the colon, mitosis inhibition in epithelial cells of breast, terminal differentiation, and apoptosis induced by the pulsatile release of calcium ion from stored of the endoplasmic reticulum. It also promotes cyclin-dependent kinase (CDK) inhibitor synthesis and influences several growth factors needed for cell division [9].

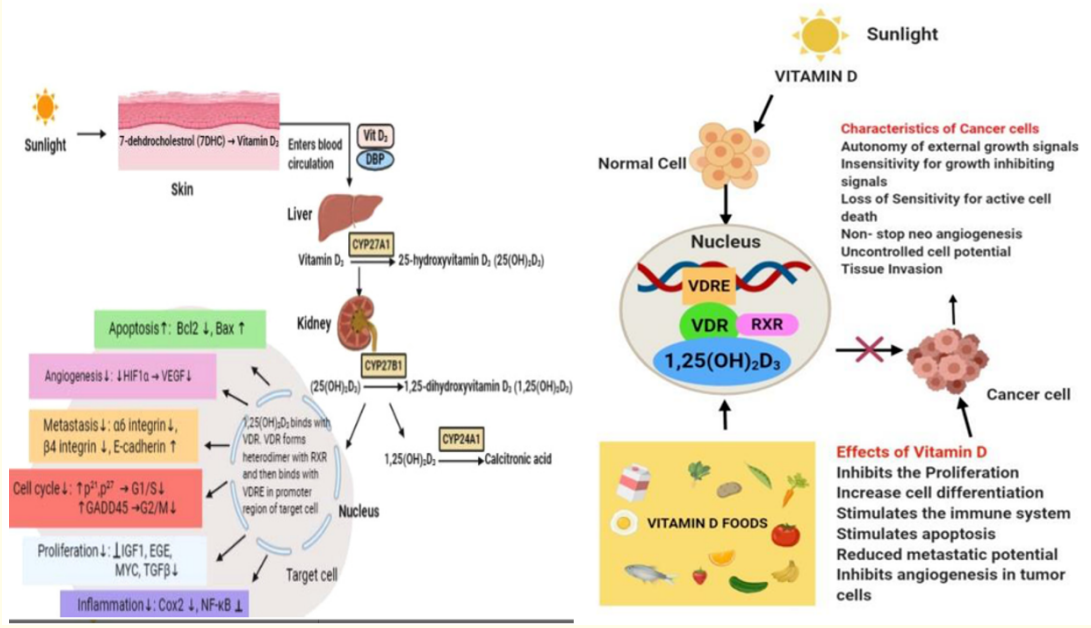

Figure 4: *Vitamin D in events of signal transduction and possible anti-cancer mechanism of vitamin D [8].*

Cardiovascular system

Most of the prospective studies suggest that there is an inverse relationship between 25(OH)D serum levels and cardiovascular risk. A prospective Intermountain Heart Collaborative Study (40,000 participants) suggests that 25(OH)D < 15 ng/mL compared to 25(OH)D > 30 ng/mL was associated with a higher increase in the prevalence of hypertension, hyperlipidemia and peripheral vascular disease, myocardial infarction, coronary artery diseases, heart failure, stroke [5,10].

There are various cardiovascular pleiotropic effects of Vitamin D. It activates its nuclear receptor in cardiomyocytes and vascular endothelial cells and regulates the renin-angiotensin-aldosterone system, energy expenditure, adiposity, and pancreatic cell activity. Vitamin D deficiency is commonly seen associated with the following left ventricular hypertrophy, vascular dysfunction, arterial stiffening, and worsened status of hyperlipidemia, diabetes, and hypertension, altogether leading to significant morbidity and mortality [11].

The vitamin D receptor and 1-a-hydroxylase, which converts vitamin D into the hormonal 1,25-OH, are found in cardiovascular tissues. The experimental models lack Vitamin D receptor highlight and its tissue-specific activity. For example, knockout of vitamin D receptor leads to an increase in ventricular mass, dyshomeostasis of cardiac metalloproteinases and fibroblasts atrial natriuretic peptide levels, and thereby promotes the formation of a fibrotic extracellular matrix. This also leads to ventricular dilation, followed by impaired electromechanical coupling [11].

Immune system

According to many ecological studies, there is a relation between latitude and the prevalence of certain autoimmune diseases. This indicates the role of sunlight and vitamin production in type 2 diabetes mellitus, Crohn's disease and multiple sclerosis, rheumatoid arthritis, and inflammatory bowel diseases [12,13].

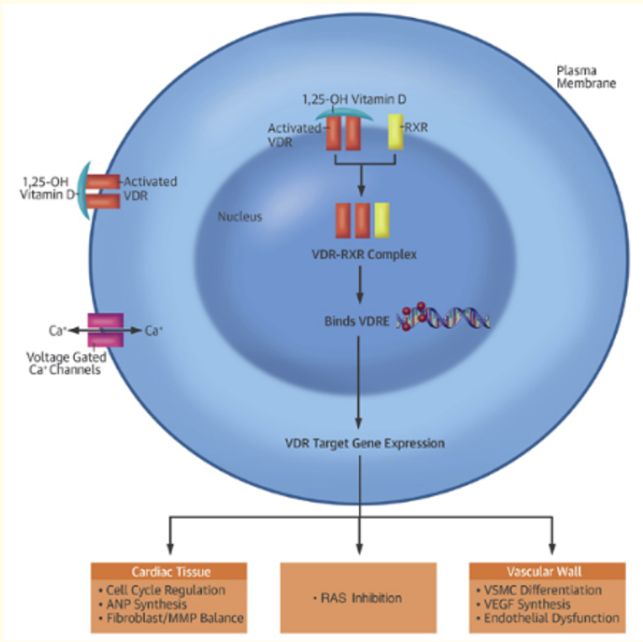

Figure 5: *Mechanism of vitamin D deficiency and increased risk of cardiovascular disease [11].*

Mechanism of vitamin D in immune system [12,13]

Non-skeletal function - Metabolism of 25-hydroxyvitamin D [25(OH)D] to 1,25 dihydroxy vitamin D 1,25(OH)2D

↓

When an infective agent like mycobacterium tuberculosis stimulate monocyte or macrophage through its toll-like receptor 2/1 (TLR2/1)

↓

The expression of vitamin D receptor (VDR) and the 25-hydroxyvitamin D-1-hydroxylase (1-OHase) upregulated by lipopolysaccharide (LPS) signal

↓

When the level of 25(OH)D is more than 30 ng/mL, it provides the substrate to 1-Phase, converting it to 1,25(OH)2D

↓

On the nucleus, 1,25(OH)2D increases the expression of cathelicidin → peptide, promoting innate immunity and causing the destruction of infectious agents/microbes.

↓

Monocytes/macrophage producing 1,25(OH)2D acts on activated A and B lymphocytes → regulate cytokine and synthesis of immunoglobin. 143 147

↓

The local production of 1,25(OH)2D prevents the expression and synthesis of parathormone, while in the kidney, the production of 1,25(OH)2D production → enters circulation.

↓

Downregulate production of renin from kidney

↓

In pancreas → Stimulation of insulin secretion in β-islet cells.

Figure B

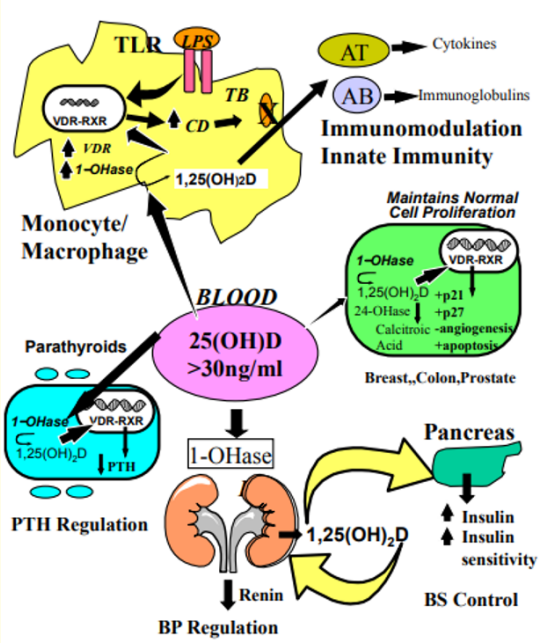

Figure 6: *Showing role of vitamin D in immune system [5].*

The above mechanism shows the association of vitamin D and its role in the pathophysiology of the autoimmune system. Regulation of chemokine production, differentiation of immune cells for self-tolerance, and counteracting autoimmune inflammation may also be associated with vitamin D. There is an inhibition of the adaptive immune system and enhancement of innate immunity by the interaction between antigen-presenting cells and lymphocytes.[12,13] By the proliferation of dendritic cells and an increased quantity of Th2 lymphocytes, vitamin D can exert anti-inflammatory and immunoregulatory responses. Enzymes needed to produce 1,25(OH)2D and vitamin D receptor is also present in immune cells, which is why certain polymorphism in the Vitamin D receptor gene can affect the risk of autoimmune diseases, their activity, and onset [12].

Immune cells have both the enzymatic machinery to produce Vitamin D receptors and 1,25(OH)2D. This explains the fact that certain polymorphisms in the Vitamin D receptor gene affect the risk for multiple autoimmune diseases, the time of onset of disease, and disease activity [13].

Infectious diseases

The effects of vitamin D on the regulation of the immune system explain its role in fighting various infectious diseases. Vitamin D stimulates and enhances innate immunity and fights against various microbes, such as influenza, viral upper respiratory tract infection, and tuberculosis. Since the 20th century, cod liver oil has been given as a supplement to tuberculosis patients, and later they were treated with heliotherapy (sun exposure). Niels Ryberg Finsen, 1903 was awarded the Nobel prize for his contribution to the treatment of the disease lupus vulgaris (tuberculosis of the skin) with concentrated light radiation. Vitamin D is identified as an active component in cod-liver oil, which is used to treat lupus vulgaris. Hence it was concluded that calciferol in an adequate dose could cure lupus vulgaris. With the increased use of antibiotics in the recent era, this old treatment modality is long forgotten, but recent studies suggest a major role of vitamin D in reducing the risk of various infectious diseases [14-17].

Mechanisms of vitamin D as an anti-infectious agent

Pathogen-associated molecular patterns (PAMPs) of microbes can be sensed by monocytes and macrophages since microbes use their toll-like receptors (TLRs). These toll-like receptors induce vitamin D receptors and CYP27B1, causing serum concentration dependant local production of 1,25(OH)2D 145 228, which in turn enhance innate immunity and produce antimicrobial peptides such as cathelicidin, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase producing reactive oxygen species and reactive nitrogen species by autophagy and enzyme nitric oxide synthase (iNOS) [15,18].

Conclusion

Deficiency and insufficiency of Vitamin D is now a well-recognized global health problem. Various multitude studies suggest that deficiency not only affect bone health but also have negative effects on the endocrine system, cardiovascular system, and respiratory systems leading to acute and chronic illness in the long term, such as cancer, type 2 diabetes mellitus, mental illness, neuropsychiatric disorders, neurocognitive dysfunction, infertility, an adverse outcome in pregnancy and childbirth. This suggests and justifies the enhanced recommendation to children and adults in their diet and increasing the level of vitamin D via supplements and appropriate sun exposure.

Bibliography

1. Holick MF., *et al*. "Phylogenetic and evolutionary aspects of vitamin D from phytoplankton to humans". *Vertebrate Endocrinology: Fundamentals and Biomedical Implications* 3 (1989): 7-43.
2. Yoshida T and Stern PH. "How vitamin D works on bone". *Endocrinology and Metabolism Clinics* 41.3 (2012): 557-569.
3. Jablonski NG and Chaplin G. "The evolution of human skin coloration". *Journal of Human Evolution* 39.1 (2000): 57-106.
4. Holick MF. "Vitamin D deficiency". *New England Journal of Medicine* 357.3 (2007): 266-281.
5. Wacker M and Holick MF. "Vitamin D-effects on skeletal and extraskeletal health and the need for supplementation". *Nutrients* 5.1 (2013): 111-148.
6. Wintermeyer E., *et al*. "Crucial role of vitamin D in the musculoskeletal system". *Nutrients* 8.6 (2016): 319.
7. Grant WB. "Ecological studies of the UVB–vitamin D–cancer hypothesis". *Anticancer Research* 32.1 (2012): 223-236.
8. Varghese JE., *et al*. "Therapeutic effects of vitamin D and cancer: An overview". *Food Frontiers* 2.4 (2021): 417-425.
9. Garland CF., *et al*. "The role of vitamin D in cancer prevention". *American Journal of Public Health* 96.2 (2006): 252-261.
10. Anderson J L., *et al*. "Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population". *The American Journal of Cardiology* 106.7 (2010): 963-968.
11. Al Mheid I and Quyyumi AA. "Vitamin D and cardiovascular disease: controversy unresolved". *Journal of the American College of Cardiology* 70.1 (2017): 89-100.
12. Antico A., *et al*. "Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature". *Autoimmunity Reviews* 12.2 (2012): 127-136.
13. Vogel A., *et al*. "Genetic association of vitamin D receptor polymorphisms with primary biliary cirrhosis and autoimmune hepatitis". *Hepatology* 35.1 (2002): 126-131.

14. Vazirnia A and Liu PT. "Vitamin D and the innate immune response". In Vitamin D and the Lung Humana Press, Totowa, NJ (2012): 59-84.

15. Yamshchikov AV., *et al*. "Vitamin D for Treatment and Prevention of Infectious Diseases; A Systematic Review of Randomized Controlled Trials". *Endocrine Practice* 15.5 (2009): 438-449.

16. Martineau AR. "Old wine in new bottles: vitamin D in the treatment and prevention of tuberculosis". *Proceedings of the Nutrition Society* 71.1 (2012): 84-89.

17. Battersby AJ., *et al*. "Vitamin D in early childhood and the effect on immunity to Mycobacterium tuberculosis". *Clinical and Developmental Immunology* (2012).

18. Hewison M. "An update on vitamin D and human immunity". *Clinical Endocrinology* 76.3 (2012): 315-325.

Volume 18 Issue 12 December 2022