Central Asian Journal of Medical and Pharmaceutical Sciences Innovation **2**(4): 128-140 (2022)

REVIEW PAPER

The physiology of vitamin D and its involvement in cardiovascular diseases

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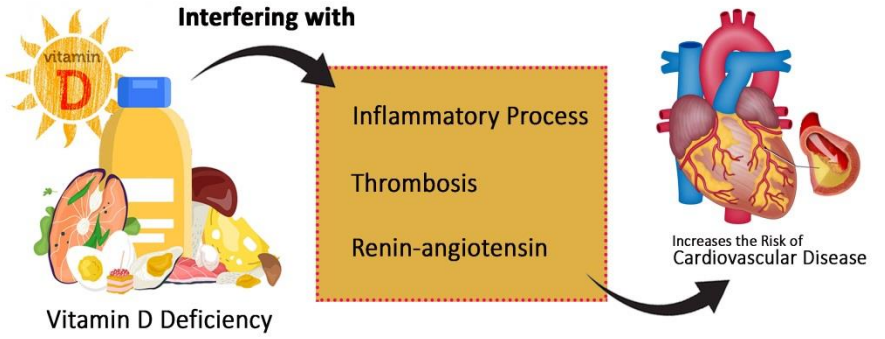
Highlights

- Cardiovascular disease is a leading reason for global mortality.
- Cardiovascular diseases can be influenced by environmental factors and genetic factors.
- Vitamin D deficiency increases the risk of cardiovascular disease.

Graphical Abstract



Article Info

Receive Date: 28 June 2022
Revise Date: 22 July 2022
Accept Date: 07 August 2022
Available online: 19 August 2022

Keywords:
Cardiovascular diseases
Vitamin D
Thrombosis
Cardiomyocytes

Abstract

Cardiovascular diseases (CVD) is a leading reason of global mortality. The most common causes of CVD-related deaths are ischemic heart disease, congestive heart failure, and stroke. Cardiac ischemia is correlated with coronary artery stenosis, which disrupts blood flow to the muscle of heart, also recognized as coronary artery disease. A stroke is also caused by a sudden blockage of blood flow to the brain or a rupture of blood vessels, both of which block blood flow to the brain tissue and deprive the brain of glucose and oxygen. Cardiovascular diseases can be affected by ethnicity, gender, lifestyle, genetic factors, and so on. Vitamin D, now known as a neurosteroid, have a main role in the body's physiological activities. Vitamin D is a fat-soluble vitamin that could be synthesized in the skin and act as a hormone. Vitamin D deficiency increases the susceptibility to vascular disease and ischemic stroke in people. Vitamin D may have a main role in cardiovascular disease by interfering with various mechanisms such as inflammation, thrombosis, renin-angiotensin system, etc. The aim of this study was to describe the important cardiovascular diseases and the physiology of vitamin D and its role in cardiovascular diseases.

10.22034/CAJMPSI.2022.04.02 **E-ISSN: 2783-0993**

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Introduction

Cardiovascular disease (CVD) is a leading reason for global mortality. This disorder affects a wide range of abnormalities such as the heart organs and the arteries that supply it, as well as some other organs such as the brain (1). Cardiovascular diseases accounted for less than 10% of global deaths at the beginning of the twentieth century, up from 30% in 2001. Most of these deaths were in countries with low-income. These diseases were suggested to be the leading cause of global mortality by 2020 (2). The most common causes of CVD-related deaths are congestive heart failure, ischemic heart disease, and stroke (3).

The term ischemia means insufficient blood supply to the tissue due to dilation of blood vessels. Cardiac ischemia is associated with coronary artery stenosis, which impairs blood flow to the muscle of heart, also known as coronary artery disease. Blood clots, atherosclerosis, or plaque buildup can cause coronary artery stenosis. Complete blockage of the arteries stops the blood supply to the heart and eventually leads to myocardial infarction (4). Coronary artery disease is associated with many factors including ethnicity, gender and age. Lifestyle and nutrition could also enhance the risk of this disease. In this disease, lipoproteins can accumulate in the intima of the coronary arteries. LDL penetrates the damaged endothelium, and after oxidation, the leukocytes are absorbed into the intima and can eventually be cleared by macrophages to form foamy cells. Eventually, lesions called fatty streaks form that play a main role in atherosclerosis. Due to the familial accumulation of this disease and the onset of the disease at a young age, this disease can also be the result of genetic factors. The genes on 9p21.3 can be considered risk factors for this disease, two of the most important of which are CDKN2A and CDKN2B (5).

Annually, 22 million people worldwide suffer from stroke, and 50% of stroke survivors suffer from chronic disabilities, unable to carry out their daily activities, and about 25% of cases also result in death (6, 7). Stroke is triggered by a sudden blockage of blood flow to the brain (ischemic) or rupture of blood vessels (hemorrhage), both of which block blood flow to the brain tissue and deprive the brain of glucose and oxygen (8). Ischemic stroke is the most common type of stroke, which accounts for 87% of cases and is the goal of most medical researchers. Obstruction caused by ischemic stroke in 45% of cases is due to the generation of a clot in a blood vessel in the neck or brain, which is called thrombosis, or the clot moves from another part of the body, such as the heart, to the brain, it is known embolic case and includes 20% (9, 10). Other factors such as hyperfusion also have a role in the progress of ischemic stroke (10).

Vitamin D with the chemical formula C27H44O, now known as an evolutionary neurosteroid, plays an important role in the central nervous system. Evidence shows that this vitamin modulates the development of brain and maintains the function of mature brain. Vitamin D is categorized as a fat-soluble vitamin and it could be synthesized and act as a hormone (11). This vitamin is chiefly produced from 7-dehydrocholesterol under ultraviolet light exposure to the skin and could also be provided through nutritional compounds. It is necessary that the vitamin D passes two stages of hydroxylation to become the active hormone calcitriol. This vitamin is first converted in the liver by 25-hydroxylase to 25-hydroxyvitamin D which enters the bloodstream and so in the kidney is transformed to the activated form of calcitriol using 1-α-hydroxylase (12). Calcitriol is considered as the greatest activated vitamin D metabolite and it has been approved by FDA whose neurotrophic and neuroprotective impacts are increasingly being identified. The deficiency of vitamin D increases the susceptibility to the vascular disease and ischemic stroke in people. Vitamin D can show its involvement in cardiovascular diseases by interfering in various mechanisms such as inflammation, thrombosis, Renin-Angiotensin System, etc. The aim of this study was to describe the important cardiovascular diseases and physiology of vitamin D and its involvement in cardiovascular diseases.

Ischemic heart disease

Ischemia refers to an absence of adequate blood supply to a single tissue due to obstruction of the blood vessels that supply the area. Ischemia is defined as the lack of blood and oxygen to a tissue such as the heart. Ischemic heart disease is correlated with coronary artery stenosis, which results in impaired blood flow to the

heart muscle and causes disorders. This disease is also known as coronary heart disease (CHD). Narrowing of the coronary arteries can be caused by contraction or blood clots. Of course, this happens mainly due to atherosclerosis or plaque accumulation. With complete blockage of blood flow to the heart muscle, this tissue is destroyed, leading to myocardial infarction (MI). Angina pectoris, which is the discomfort syndrome caused by a lack of blood supply to the heart muscle, is characterized by symptoms such as discomfort in the chest, arms, shoulders and jaw. The severity of the syndrome increases with stress or emotional factors, while administration of nitroglycerin as well as rest can improve the condition. This syndrome is often a symptom of CHD; however, it is also seen in some diseases such as uncontrolled hypertension, hypertrophic cardiomyopathy and valvular disease (13-15). Coronary heart disease has a different prevalence depending on ethnicity, geographical factors, age, and even gender and genetic factors (Figure 1). Studies in different areas have been reviewed with respect to diet, lifestyle, and heart disease, and the results have shown that high cholesterol levels increase the risk of disease, and this is consistent in different races (16).

An international epidemiological study was done on the occurrence of coronary artery disease over a 10-year period in different races. This study was performed on 15 million people in the age range of 25-64 years (17). Another epidemiological study in this area was the INTERHEART study. The study investigated the role of various risk factors in myocardial infarction in different races. This study was focused in different countries in Europe, Africa, Asia, etc. (18). Another study was conducted on Japanese immigrant men compared to Japanese natives. The results of this study showed that cholesterol levels are higher in immigrant men than in native men (19). Another study in the United States found that the prevalence of coronary artery disease was much higher in older people than in younger people. It was also found that in the UK about half of all deaths associated with heart disorders are due to coronary artery disease (20). Statistics from the American Heart Association in 2016 show that in the United States, 15.5 million subjects more than 20 years suffer from coronary heart disease, which is less common in women than men. In India, the disease has received much attention and its prevalence in rural communities is less than urban population (21, 22).

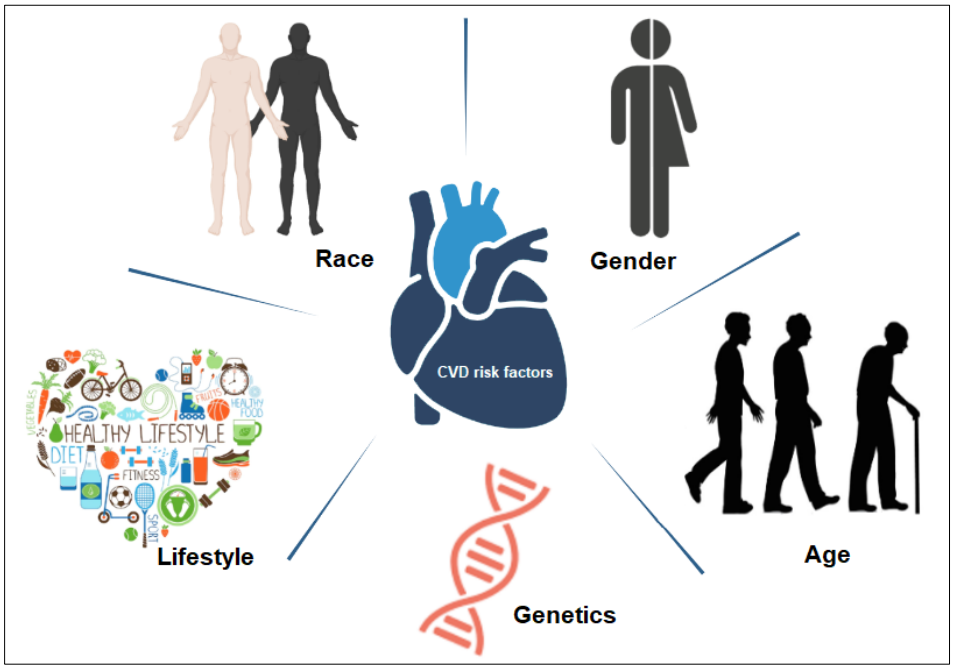

Figure 1. Cardiovascular disease risk factors. Some factor including race, gender, age, lifestyle, and genetic factors could affect the risk of cardiovascular disease.

The cause of coronary artery disease is atherosclerosis or atherosclerotic blockage of the coronary arteries. With endothelial dysfunction, it begins with the lipoprotein accumulation in the intima of the coronary arteries. LDL can penetrate damaged endothelium. After oxidation, LDLs can cause leukocytes to be absorbed into the

intima of the coronary arteries. These could be cleared by macrophages to produce foamy cells. Eventually, lesions called fatty streak are produced, which are the first bodies to form in atherosclerosis. Signals are then generated that cause smooth muscle cells to be attracted to the fatty streak. These cells can produce extracellular matrix proteins such as collagen. Matrix proteins produced by smooth muscle cells could attach to lipoproteins and stabilize their presence in the intima (23, 24).

Due to the familial accumulation of coronary artery disease and the onset of the disease at a young age, the possibility of genetic involvement is highlighted. One of these diseases is familial hypercholesterolemia, which is a single gene disorder and is correlated with mutations in LDL receptors. The disease is correlated with the pathogenesis of coronary artery disease. Genetic analysis has shown that chromosome 9p21.3 locus is correlated with a higher risk of coronary heart disease. It has been shown that 369 genetic variants are correlated with the risk of this disease, 30 of which are accumulated on chromosome 9. Two important genes, including CDKN2A and CDKN2B, belong to the family of cyclin-dependent kinases and are involved in cell cycle control and can be involved in TGF-β function and subsequently play a role in coronary artery disease (25, 26). There is a non-coding RNA in tissues prone to atherosclerosis called the ANRIL antisense as well as CDKN2B-AS. The role of ANRIL in controlling gene expression is well known. Research has shown that varieties associated with coronary artery disease risk play a role in influencing the expression of CDKN2A, CDKN2B, and ANRIL genes. The presence of genetic variants in the regulatory areas of genes correlated with coronary artery disease could impair the transcription factors binding (27-29).

Coronary artery disease is a complex disease that arises from the interaction of environmental and genetic factors. The risk of this disease increases with a family history. Genes correlated with this disorder are divided into three groups: causing, susceptibility, and linked genes. The first group of genes are directly responsible for the disease and have a very high value in predicting the disease and mutations in them are involved in the disease pathogenesis. The first group of genes is involved in familial hypercholesterolemia. The disease is triggered by mutations in some gene such as LDLR, PCSK9, ApoB100, etc. (22, 30). Case-control studies have also presented the correlation of many single nucleotide variations with coronary heart disease which can alter the risk of developing the disease. Two of these genes include USF1 and α-lymphotoxin (31, 32). The first gene, USF1, encodes the transcription factor and controls the genes that metabolize lipids and glucose. Mutations in this gene can cause familial combined hyperlipidemia, which is a risk factor for heart attack and premature coronary artery disease. Lymphotoxin α is also involved in immune and inflammatory responses and may be associated with myocardial infarction. The last category of genes is those that have been identified in myocardial infarction and coronary artery disease using protein assay methods and even genome-based techniques. These genes can be considered as biomarkers of the disease. These genes include fusin, ECGF1, PIM2, etc. (33).

Stroke

After obstruction during ischemic injury, two areas of damage called the central nucleus and penumbra form in the brain tissue. The central region, which is exposed to decreased blood flow, undergoes the phenomenon of necrotic cell death. While in the infarcted or penumbra area, apoptotic cell death occurs, where the lateral blood flow compensates for some degree of hypoxia and efforts are made to prevent the spread of damage in this area (34, 35). Brain neurons are dependent on oxygen and glucose from blood flow to function properly and are more vulnerable to glial and vascular cells (36). Neurons temporarily lose their function when exposed to hypoxia-ischemia, and if this disorder persists, it can lead to permanent damage and cell death (37). Ischemia is generally classified into two types: global and focal; Focal ischemia is limited to a specific area, while global ischemia is widespread. Focal ischemia occurs as a result of decreased blood flow and subsequent reduction of oxygen and glucose in certain parts of the brain. In this type of ischemia, there might be no complete blood flow to the central nucleus, but there is usually some flow coming from nearby vascular areas. Most models of focal cerebral ischemic stroke involve blockage of one of the main cerebral blood vessels, including the middle

cerebral artery. Middle cerebral artery occlusion decreases cerebral blood flow in both the cortex and striatum, but the extent and distribution of decreased cerebral blood flow (CBF) are associated with the time of vascular occlusion, the site of occlusion along the middle cerebral artery, and the amount of collateral blood flow to the cerebral artery (38, 39). Global ischemia happens when CBF has decreased in large areas or the entire brain. In global cerebral ischemia, the entire brain area is deprived of blood supply, which can occur following carotid artery occlusion. This phenomenon leads to neuronal damage to different areas of the brain, depending on their sensitivity. Clearly, if global ischemia persists indefinitely, all neurons will be destroyed (40). There is also a multifocal type of ischemia that produces an irregular pattern of CBF. Delayed injury is expected because the reduction in blood flow after ischemia takes time to spread (41). This ischemia causes a decrease in metabolism, cerebral edema, and an infarct similar to unilateral obstruction of the middle cerebral artery. Multifocal ischemia can be caused by injecting embolic material into the blood vessels of the brain (42).

Stroke including hemorrhagic stroke and ischemia involves 13.7 million individuals worldwide each year and is the second reason of death with 5.5 million deaths/year (43). Of these, about 2.6 million are women and 2.9 are men (44). Krishnamurthi et al. also conducted research on the relationship between gender and the prevalence of stroke, which ultimately revealed that stroke is more common among men than women worldwide (45). On average, 1 in 4 adults will have a stroke during their lifetime. More than 80 million people worldwide have survived a stroke, and secondary prevention strategies are important for stroke survivors because they are at risk again (46). The occurrence and frequency of ischemic stroke have evolved over time. The incidence of ischemic stroke worldwide was 9.5 million in 2016.

In 2017, 2.7 million subjects died of ischemia. The incidence of stroke and its mortality and disability increased between 1990 and 2005, while the incidence of the disease decreased from 2005 to 2013, although it was not statistically significant. Possible reasons for changing the prevalence of stroke mortality were stated improving prevention and better diagnosis of stroke (47). In the Western world, more than 70% of people who have a stroke are over 65 years old. Women and men over the age of 55 had similar age-related risk factors for stroke, but this rate was higher in men aged 55-75 and older (44). Interestingly, the epidemiological trend of ischemic stroke varies according to a country's income level. For example, prevalence, mortality, and mortality-to-prevalence rates are lower in high-income countries. This decrease may be due to differences in age population, health status, life expectancy, and health care standards (48). Statistical results show that the highest rate of stroke occurred in East Asia and then Eastern Europe, while the lowest rate was in Central Latin America. Three months after an ischemia, 15 to 30% of survivors are forever disabled, and 20% of them need intensive care to survive. Disorders due to stroke can include partial paralysis and problems with memory, thinking, language, and movement (49).

Unchangeable risk factors for ischemia comprise sex, age, and genetic factors. The effect of age on the risk of ischemic stroke varies with the development condition of a country. For instance, the prevalence of stroke after the age of 49 in developed countries has increased more sharply compared to developing countries (50). Between the ages of 20 and 64, the incidence of ischemic stroke almost doubled from 1990 to 2013, which is also associated with a 37.3% increase in stroke disability. Also, in relation to gender, as mentioned in the previous articles, the prevalence of ischemic stroke in men (133 cases per 100,000 individuals/year) compared to women (99 cases per 100,000 individuals/year) was higher in a study conducted in 2013 (51). Genetic background is also known to be a central risk factor for ischemia, and researchers have estimated a 37.9% chance of inheriting ischemic stroke. With the exception of a few important but rare disorders, such as mutations in the autosomal dominant Notch3 gene, most pedigrees do not match with Mendelian simple inheritance, and evidence suggests that stroke is a complex multifactorial disorder that Interacts with environmental factors (52).

Variations in genes including ACE, APOE, eNOS, and beta-fibrinogen have also been described to elevate the stroke risk. Several modifiable risks have been identified that were common to 91.5% of people with ischemic stroke in different geographical areas, ages, and genders. These factors include a history of hypertension, low regular exercise, high ratio of apolipoprotein B to apolipoprotein A1, obesity, improper diet,

psychological factors such as depression and stress, smoking, and heart problems including myocardial infarction and atrial fibrillation, consumption of alcohol, and diabetes. Among these factors, hypertension or hypertension greater than 160/90 mmHg was identified as the most important risk (53). Moreover, several other possible risks for ischemic stroke have been reported, including severe inflammation, infectious and inflammatory diseases of the gums, and kidney disease. Interestingly, some studies have revealed an association between elevated risk of stroke and exposure to air pollution (54).

Physiology of vitamin D

Vitamin D is accessible in two forms, D3 (calciferol) and D2 (ergocalciferol). A number of animal food sources including fatty fish, fish liver oil and egg yolks provide vitamin D3 and plant sources such as olive oil also supply vitamin D2 in the body. The active form of vitamin D3 is made during a series of reactions in various tissues of the body. In the first stage of these reactions, 7-dehydrocholesterol in the skin epidermis becomes a precursor of vitamin D3 due to ultraviolet radiation of the sun with a wavelength of 215-315 nm. Vitamin D made in the skin, as well as vitamin D in food sources, is biologically inactive, and to convert it into its active form, the vitamin D precursor enters the bloodstream and binds to the protein that binds to this vitamin and is transported to the liver. The precursor of vitamin D3 in the liver is converted to 25-hydroxyvitamin D3 via the 25-hydroxylase enzyme.

This form of vitamin D3, the most abundant form of vitamin D3, is found in the bloodstream and due to its high half-life in the blood (15 days), it is considered as an indicator of the vitamin D3 status in the body. Then 25-hydroxyvitamin D3 is transmitted to the kidney through circulation, where it is converted to 1 and 25 dihydroxy vitamin D3, which is the activated form of vitamin D. The parathyroid hormone, which is secreted during calcium deficiency in the body, activates the enzyme 1-alpha hydroxylase and as a result, it is considered as an increase in the vitamin D3 production, but increasing the body's calcium by reducing the parathyroid hormone results in a reduce in the production of vitamin D3. In addition to parathyroid hormone, other hormones including glucocorticoids, calcitonin, growth hormone and sex steroids also control the vitamin D production.

If the activated form of vitamin D3 is sufficiently available, another hydroxylase enzyme called CYP24A1 in the kidneys hydroxylases the 25-hydroxy vitamin D3 as well as 1 and 25-dihydroxy vitamin D3 in carbon 24, resulting in production of metabolites 24 and 25 di hydroxyvitamin D3, and also 1, 24 and 25 tri hydroxyvitamin D3 and it seems to play a role in preventing the accumulation of toxic levels of 25-hydroxyvitamin D as well as 1 and 25 hydroxyvitamin D. It should be noted that various factors such as lack of pigmentation in the skin, aging, use of sunscreen, full body coverage, decreased physical activity, reducing sunlight and increasing latitude reduces vitamin D synthesis (55). There is still no comprehensive scientific agreement on the serum level of vitamin D and the individual's state of health. Most researchers believe that the 25-hydroxy vitamin D level should be more than 50 nmol per liter, but others believe that it should be more than 75 and even 100 nmol per liter (56).

A Scientific Committee of the American Institute of Medicine has reported that a serum concentration equal to or less than 30 nmol per liter of -25 hydroxyvitamin D3 is recognized as a vitamin D deficiency and it is necessary to receive nutritional supplements in people with these conditions. According to the committee, the serum concentration of 30 to 50 nanomoles per liter is considered inadequate for bone health and general body health, but concentrations equal to or greater than 50nanmol/L are considered sufficient amounts for the health of the individual and cover the body's needs in 97.5% of the world population to this vitamin. It should also be noted that amounts greater than 125 nanomoles per liter of 25-hydroxyvitamin D3 are toxic to the body and have undesirable effects such as calcification of bones, soft tissues and blood vessels and hypertension (57).

Vitamin D has many non-genomic and genomic functions in the cell. The genomic functions of this vitamin are mediated through its attachment to the vitamin D receptor (VDR). Vitamin D receptors are found in almost all types of tissues throughout the body. VDR is a member of the intranuclear steroid receptor family, in which

the binding of vitamin D to it in the nucleus separates the receptor from the hormone-response element (HRE) and the receptor-hormone complex interacts with the RXR retinoid receptor to procedure a heterodimer. So, this heterodimer binds to one of the vitamin D response elements (VDRE) in DNA, and with the use of other regulatory proteins as a transcription factor, it can express different genes associated with many cellular procedures such as calcium homeostasis, cell cycle regulation, immune system regulation, oxidative stress, and inflammation. There is ample evidence that vitamin D decreases the expression of L-type calcium channels and elevates the expression of calcium pumps, sodium/calcium exchangers, and calcium buffers such as calbindin and prealbumin play a role in reducing the concentration of calcium within the cell and maintaining its homeostasis. Vitamin D also increases the expression of a stress-sensitive transcription factor, Nrf2, and Klotho anti-aging protein (58).

It has long been known that in addition to the delayed genomic effects, steroid hormones, including vitamin D, have non-genomic effects that these effects are exerted through membrane receptors. With its effect on membrane receptors, vitamin D directly and rapidly activates messaging pathways through secondary messengers such as inositol triphosphate (IP3), calcium, cGMP and MAP kinases, and affects the function of various ion channels and protein kinases within the cell through the phosphorylation process (59).

Mechanism of action of vitamin D on cardiovascular function

The types of cells and cellular pathways in the heart and arteries could be influenced by vitamin D. One of these pathways is inflammation. Immune cells as well as the inflammatory process are very important in cardiovascular diseases. Vitamin D can control immune and inflammatory responses. Therefore, this vitamin will be able to maintain inflammatory responses at the physiological level. In infectious conditions, increased release of cytokines is observed in innate immune responses, and the role of vitamin D in these conditions is generally anti-inflammatory.

Proinflammatory cytokines including interleukin-1, interleukin-2, interleukin-6, interleukin-23, interferon-gamma, and TNF-α reduce and anti-inflammatory cytokines such as interleukin-4 and interleukin-10 increase. Vitamin D could prevent the production of interleukin 6 and TNF-α by a special mechanism. Vitamin D may also modulate Toll-like receptor inflammation through epigenetic processes (60). Vitamin D can modulate the immune system by inhibition of the growth and response of TH17 and TH1 cells and supporting TH2 and Treg. Due to plaque formation by cytotoxic T cells in mice lacking apoE, it is therefore highly correlated with atherosclerosis. Various studies show that vitamin D deficiency contributed to the pathogenesis of atherosclerosis and inflammatory responses associated with cardiovascular disease by affecting immune cells, the release of interleukins, as well as the inflammatory process. A clinical study showed that taking vitamin D for 1 year could reduce the concentration of interleukin 6 in overweight people (61). Knocked-out mice showed that vitamin D could regulate the renin-angiotensin (RAS) system. Deletion of LDL and vitamin D receptors in mice can lead to atherosclerosis. This occurs through disruption of the VDR pathway of macrophages and increased local RAS. Inhibition of renin expression by vitamin D occurs through cAMP involvement.

In laboratory models that lacked the VDR gene, renin gene expression and angiotensin II production increased, which in turn could lead to cardiac hypertrophy and hypertension (Figure 2). In this model, pancreatic RAS is also increased and this problem is solved with vitamin D treatment. In animal models that lacked the CYP27B1 gene, renin levels also increased, as did blood pressure and heart atrophy, which was resolved with vitamin D treatment (62).

Endothelial cell function was improved by activation of VDR by vitamin D, which occurred by reducing the generation of reactive oxygen species by reducing the expression of angiotensin II type 1 receptor expression. Clinical studies show that blood pressure and renin activity are inversely related to vitamin D concentration (63, 64).

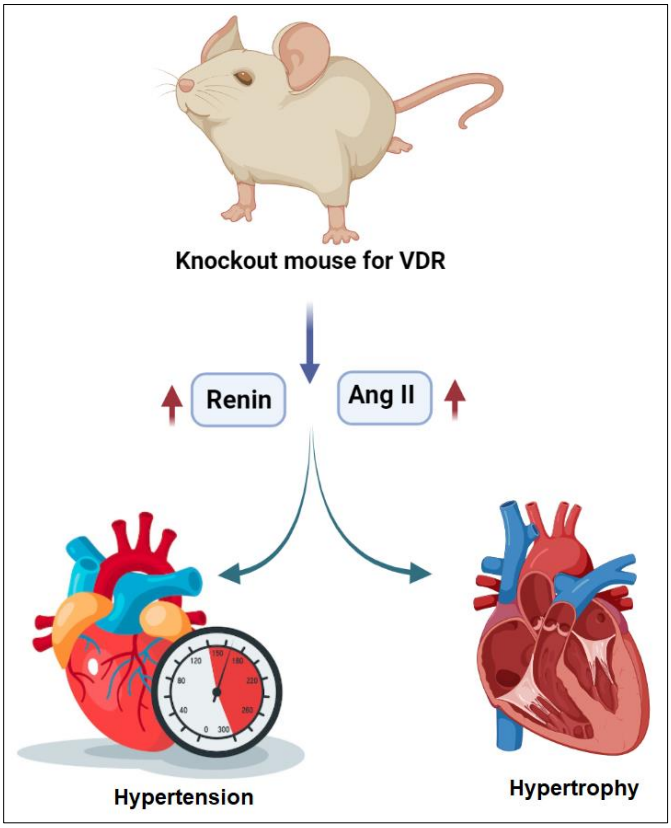

Figure 2. CVD in mouse model lacking the VDR gene. Lacking VDR gene results in increased renin gene expression and angiotensin II production, which in turn could lead to cardiac hypertrophy and hypertension.

Studies have revealed that vitamin D influences the thrombosis procedure. An experimental study displayed that vitamin D in cultured monocyte cells could reduce tissue factor levels and increase thrombomodulin expression (65). In another study, calcitriol and paricalcitol, which are vitamin D analogues, decreased the expression of thrombospondin-1 and plasminogen activator inhibitor-1 and elevated the expression of thrombomodulin. Since the first two substances (thrombospondin-1 and plasminogen activator inhibitor-1) have a role in thrombus formation and increased expression of the third substance (thrombomodulin) can reduce thrombosis, vitamin D can thus play its antithrombotic role (66). Knocked-out mouse models were able to confirm in vitro studies. In these mice lacking the VDR gene, a prothrombotic status was identified because antithrombin and thrombomodulin decreased while tissue factor expression increased (67).

Another anti-thrombotic mechanism of vitamin D is characterized by decreased platelet activation by endothelial cells (68). Vitamin D receptors are expressed by cardiomyocytes and show their function through interaction with this vitamin. Studies display that the deficiency of vitamin D leads to improper cardiac remodeling, which eventually leads to hypertrophy and fibrosis. Ventricular hypertrophy was obtained in mice lacking the VDR gene (69). This animal model is correlated with elevated parathyroid hormone and blood pressure, and these causes heart atrophy, and the role of vitamin D is not yet entirely understood. In an animal model in which the VDR gene was deleted in cardiomyocytes, vitamin D showed an antihypertrophic effect in cardiomyocytes while having little effect on fibrosis (70).

Conclusion

Cardiovascular disease is one of the leading causes of death in the world. People with ischemic heart disease continuously experience fear, anxiety, and depression from heart damage and the expectation of death throughout their lives. Also, the physical limitations created, the progressive symptoms of the disease, and the subsequent development of mental disorders during the treatment process, can reduce the quality of life of this group of heart patients. These diseases are influenced by several factors including ethnicity and race,

geographical factors, lifestyle, genetic factors, and so on. Deficiency of vitamin D is a risk factor for this group of disorders. This vitamin can participate in the processes involved in cardiovascular diseases by various mechanisms. For example, by interfering with the inflammatory process, thrombosis, and the renin-angiotensin system cause the disease. In fact, vitamin D deficiency triggers these processes. Therefore, compensating for deficiency of vitamin D in the body may protect people from cardiovascular disease.

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How to cite this paper:
Ozdemir B, Khan A, Farooq Rashid R. The physiology of vitamin D and its involvement in cardiovascular diseases. Cent Asian J Med Pharm Sci Innov 2022; 2(4): 128-140.