

Relationship between Vitamin D Deficiency and Cardiovascular Diseases: a review of literature

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Abstract

Background: Vitamin D deficiency is a global health problem. It affected approximately 1 million people worldwide. In Saudi Arabia, it is highly prevalent; ranges from 65 to 100%. Cardiovascular diseases (CVD) estimated 31% of all deaths globally. In Saudi Arabia, CVD estimated among 5.5% of Saudi population. Recent evidences indicate vitamin D deficiency association with several cardiovascular diseases and their risk factors such as obesity.

Objectives: The aim of this review is to highlight the prevalence and association of cardiovascular diseases and vitamin D deficiency. In addition, to establish the role of vitamin D supplements in improvement vitamin D status and prevention cardiovascular diseases.

Review of literature: Vitamin D deficiency and cardiovascular diseases are highly prevalent worldwide. It estimated 30-50% and 31% respectively. Recent evidence suggests that there is a significant association between vitamin D deficiency and cardiovascular diseases. Vitamin D deficiency can lead to CVD through different mechanisms including renin-angiotensin-aldosterone system and parathyroid hormone activity. However, Vitamin D supplementation and exercise improved vitamin D level as well as cardiovascular outcome and lead to significant reduction in systolic and diastolic blood pressure.

Conclusion: Vitamin D deficiency is related to the pathogenesis of wide spectrum of cardiovascular diseases such as hypertension, Myocardial infarction (MI) and heart failure. The potential role of vitamin D supplementation in treatment of cardiovascular diseases, their complications and in prevention of morbidity and mortality have been evaluated by several clinical studies.

Keywords: Cardiovascular diseases, exercise, obesity, parathyroid hormone renin- angiotensin-aldosterone system, Vitamin D deficiency, vitamin D supplements.

1 INTRODUCTION

Cardiovascular disease (CVD) considers as a global health problem and one of the causes of mortality and morbidity worldwide ⁽¹⁾. According to world health organization (WHO), 17.5 million people die each year from CVDs, and it is estimated 31% of all deaths globally ⁽²⁾. In Saudi Arabia, CVD affected approximately 5.5% of Saudi population. It considers the third cause of mortality in this country after traffic accident and senility according to several hospital data ⁽³⁾.

Vitamin D is one of the fat-soluble prohormones. Synthesis of vitamin D depends on exposure of skin to ultraviolet (UV) light or it can be obtained from dietary source such as fatty fish. The two major biological precursors of vitamin D are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). 25 (OH) D considers a main circulating form in blood of vitamin D, and it is used to assess and establish vitamin D level ⁽⁴⁾.

Institute of Medicine (IOM) defines Vitamin D insufficiency as level <20 ng/mL, while the Endocrine Society defines it as level 20-29 ng/mL. The American Society of Geriatric recommends a minimum target of vitamin D level of 30 ng/ml ⁽⁵⁾.

Vitamin D deficiency or insufficiency is very common globally. It considers, as re-emerging public health problem. One billion people approximately have been diagnosed with vita-

min D deficiency or insufficiently worldwide. International research has reported that in the United States, vitamin D deficiency affected from 25% to 57% of the total adults ⁽⁶⁾. In Gulf region especially in Saudi Arabia, it is highly prevalent; it is ranging from 8.4 to 11.6 ng/ml for males and from 8 to 16.6 ng/ml for females ⁽⁷⁾.

Several observational studies have shown inverse relationship between vitamin D status and risk of many of CVD. However, the mechanism underlying this association not fully explained and the role of vitamin D on cardiovascular system considers a novel function and under investigations ⁽⁸⁾.

National Health and Nutritional Examination Surveys (NHANES) and the Framingham Offspring cohort are two of large epidemiological studies, mentioned that there is a significant association between low levels of vitamin D and risk of hypertension, myocardial infarction, and stroke ^{(8),(9)}. These studies have showed that vitamin D plays an important role in regulation cardiovascular metabolism and preventing cardiovascular metabolic risk factors such as hyperlipidemia, obesity and hypertension ⁽¹⁰⁾. In addition, they explained different mechanisms and hypothesis about pathogenesis of cardiovascular diseases caused by vitamin D deficiency. In addition, they demonstrated the key role of vitamin D in regulation of the

renin-angiotensin system and parathyroid hormone that in turn affect blood pressure⁽¹⁰⁾. Low level of vitamin D activating renin-angiotensin-aldosterone system, which leads to ventricular hypertrophy, also when vitamin D becomes low this lead to increase parathyroid hormone, which in turn leads to increase blood pressure⁽¹¹⁾. Moreover, vitamin D level influences the intracellular calcium and indirectly affect cardiac muscle contractility⁽¹²⁾.

Previous study suggested that Vitamin D supplementation

might play an important role in lowering disability and mortality related to cardiovascular diseases. It has been explained that regular exposure to ultraviolet B radiation improves circulating 25(OH) D above a level of 100nmol/l and in turn reduces blood pressure by approximately six mmHg among hypertensive patients with initial level of vitamin D equal 26nmol/l⁽¹³⁾. A recent meta-analysis demonstrated that moderate to high doses of vitamin D supplementation might decrease risk of cardiovascular diseases⁽⁶⁾.

2 OBJECTIVES

The aim of current review is to highlight and determine the prevalence of vitamin D deficiency and to show the association between vitamin D deficiency and cardiovascular diseases. In addition, to establish the role of vitamin D supplements in improvement vitamin D status and prevention cardiovascular diseases.

3 LITERATURE REVIEW

1 Basic vitamin D metabolism

Vitamin D is one of the fat-soluble prohormones. Synthesis of vitamin D depends on exposure of skin to ultraviolet (UV) light or it can be obtained from dietary source such as fatty fish. The two major biological precursors of vitamin D are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol)⁽⁴⁾. Vitamin D3 is formed by converting 7-dehydrocholesterol in the skin to previtamin D3 and this process requires adequate exposure to ultraviolet B (UVB, 290-320 nm). Then, previtamin D is converted immediately to vitamin D in heat-dependent process. Excess UVB rays converts previtamin D3 into inactive metabolites such as tachysterol and lumisterol. Vitamin D2 is a plant-based precursor formed by irradiation of ergosterol exogenously then enters the circulation through diet⁽¹³⁾. Finally, both the precursors of vitamin D are entered the liver and converted to 25-hydroxyvitamin D [25(OH) D] (calcidiol). Additional hydroxylation in the kidneys by alpha hydroxylase enzyme is required to activate it biologically and is converted it to 1, 25-dihydroxyvitamin D [1, 25(OH) 2D] (calcitriol)⁽⁴⁾.

Vitamin D3 reach the target cells either free or with megalin and bind to vitamin D receptor. After that, it will translocate to nucleus in DNA and then heterodimerizes with retinoid X receptor (RXR). Finally, all this complex vitamin D 3-RXR-VDR attach to vitamin D response element (VDRE) and it will stimulate and increase transcription of vitamin D gene. Important vitamin D genes include Vitamin D gene responsible for the classical function of 1, 25(OH) 2D which is mineralization of bone, transport and absorption of calcium and phosphate ions from intestine. Vitamin facilitates and increases entry of calcium into the cells, and activates movement of calcium ion through cytoplasm and converts it into the blood

circulation. In addition, Vitamin D maintains homeostasis by facilitating absorption and inhibiting excretion of calcium and phosphate ions by kidney and these ions are very important for bone mineralization⁽⁸⁾.

2 Definition of vitamin D deficiency

There are different definition for vitamin deficiency and insufficiency regarding the cut-off value for deficiencies and insufficiencies. According to Institute of Medicine (IOM), Vitamin D considers insufficient when vitamin D level <20 ng/mL, while the Endocrine Society defines it as level 20-29 ng/ml. The American Society of Geriatric recommends a minimum target of vitamin D level of 30 ng/ml. Most experts define vitamin D deficiency as a calcidiol level of <20 ng/mL and insufficiency as 21-29 ng/ml⁽⁵⁾.

2.1. Prevalence of Vitamin D Deficiency

Vitamin D deficiency and insufficiently are considered as pandemic problems and they are highly prevalent globally. More than half of population has the level of vitamin D less than 30ng/ml. It is estimated approximately 30% to 50% worldwide⁽¹⁴⁾. Many studies were performed in Kingdom of Saudi Arabia in scattered regions revealed that the incidence of vitamin D deficiency ranges from 65 to 100% among different sectors of populations⁽¹⁵⁾.

One study performed among Saudi children and adults, reported that 30 to 50% of children and adults in Saudi Arabia had vitamin D levels less than 20 ng/ml. Another study done among females in Saudi Arabia revealed that 30% to 50% of Saudi females have vitamin D deficiency⁽¹⁶⁾.

According to the Saudi Health Interview Survey (SHIS), the prevalence of vitamin D deficiency from April to June 2013 among male and female was 40.6% and 62.7% respectively. The most likely factors demonstrating the high prevalence of

low levels of vitamin D in KSA are lack to sunlight exposure and insufficient vitamin D supplementation (17).

In recent evidence, low level of serum 25(OH) D levels has been associated with type two diabetes mellitus and obesity. More than 80% of obese adults have vitamin D insufficiency. In Saudi Arabia, obesity is estimated by 39.3% among cases with diabetes mellitus compared to 18.5% among cases without diabetes. Researches indicated that there is a relationship between low vitamin D levels and development of type-2 diabetes and metabolic syndrome. In addition, vitamin D insufficiency significantly associated with insulin resistance and cardio metabolic risk factors in obese adults. They found that vitamin D supplementation prevents cardiovascular risk factors and improve insulin resistance (18).

One cross-sectional study was done among healthy adults in Riyadh indicated that 29% of the subjects were vitamin D deficient and about 23% insufficient (19). Similarly, in another study done in Qassim, 28% were vitamin D deficient and 39% were insufficient (20). Hussain et al. (19) reported high incidence of vitamin D deficiency among Saudi population and emphasized the female gender as a risk factor.

Many predisposing factors may lead to vitamin D deficiency such as aging, female gender, dark skin, poor exposure to sunlight, seasonal variation and distance from equator. All these must be considered for vitamin D deficiency and insufficiently. So elevating rates of 25(OH) D deficiency mostly caused by lifestyle factors, air pollution and poor exposure to sunlight (21).

3 Vitamin D and Cardiovascular health

Vitamin D plays an important role in improvement overall health and it considers as a key component for maintenance essential function. The active form of vitamin D, 1, 25-dihydroxyvitamin D (1, 25(OH) 2D), acts as a steroid hormone by binding to the vitamin D receptor (VDR). Vitamin D receptor is found in several cells throughout the body, including cardiomyocytes, vascular smooth muscle, and endothelium (22). When vitamin D3 binds to vitamin D receptors in cardiomyocyte and blood vessel, this binding cause rapid influx of calcium into the cell and this will lead to increase intracellular calcium concentration. Calcium in turn activates contractile proteins and elevates formation of prostacyclin, which is potent vasodilator. Therefore, Vitamin D has an essential role in protection and prevention of cardiovascular diseases like hypertension and atherosclerosis (23).

Vitamin D affects the morphological remodeling of cardiac muscle and vascular tissues and results in improvements in flow-mediated dilation and blood pressure. Improved cardiac muscle function has been shown in patients with severe vitamin D deficiency following supplementation with the vitamin. In addition, it regulates the function of calcium channels in cardiac myocyte, causes rapid influx of calcium, and improves contractility (24). Recent studies showed that individuals with low level of serum 25(OH) D are at risk of development of

cardiovascular diseases or are more likely to develop incident CVD (22).

Benefits of vitamin D on cardiovascular system are well explained in several preclinical and clinical studies, which provided evidence that vitamin D has an essential role of protection of blood vessels. It down-regulates the progression of coronary atherosclerosis in patients suffered from angina pectoris. It also decreases inflammatory markers within vessel and improves plaque volume and common carotid intima media thickness in patients with atherosclerosis (25).

4 Vitamin D deficiency and pathogenesis of cardiovascular diseases

Several epidemiological studies reported that the incidence of cardiovascular diseases such as hypertension and coronary heart diseases increased proportion to increasing distance from equator. Recent study done in NHANES III among the 15,088 participants highlighted and demonstrated the association of cardiovascular diseases with vitamin D deficiency. It revealed that vitamin D deficiency significantly was associated with hypertriglyceridemia and obesity (15). See Figure [1] & [2].

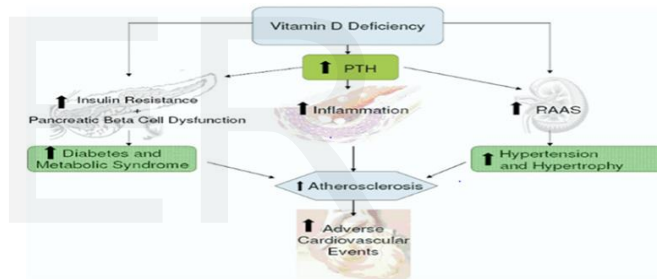


Figure1: Potential Mechanisms for CV Toxicity of Vitamin D Deficiency

Lee J (2008) (14).

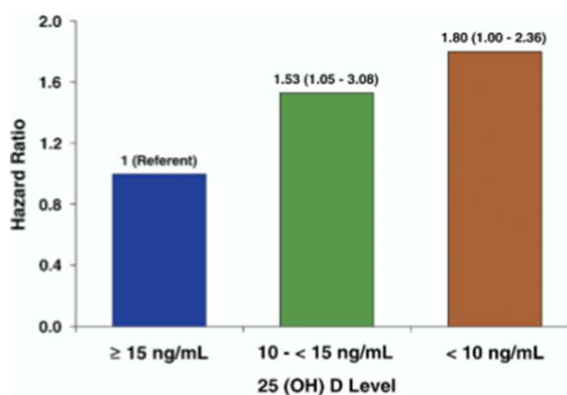


Figure 2: Hazard ratio for CVD by vitamin D level

Lee J (2008) (14).

Obesity is one of the risk factors for heart associated with vitamin D deficiency. There are different hypothesis explained this relation. First, it may be due to accumulation of vitamin D in adipose tissue, leading to reduce circulating 25(OH) D in blood. ⁽²⁶⁾ Second, adipose tissues secrete large amounts of leptin and interleukin 6. High levels of these substances might inhibit synthesis of vitamin D via their receptors. In addition, vitamin D deficiency itself can lead to obesity. Some suggested that vitamin D in adipocyte down regulates active form of adipogenic transcription factors and fat deposition during the phase of differentiation. Therefore, when vitamin D is reduced, it will lead to accumulation of the body fat and impairment of metabolic function ⁽²⁷⁾.

A randomized bi-directional Mendelian study done by Vimalaswaran et al. ⁽²⁸⁾ assessed the association between obesity and low level of vitamin D. They reported that each unit increase of BMI was related with a 1.15% reduction of 25(OH) D after adjustments for typical confounders. The authors explained that obesity estimating approximately for one third of vitamin D deficiency.

A case-control study design was applied among Saudi adults living in the two largest cities, Jeddah and Makkah, to evaluate the relationship between vitamin D status and coronary heart disease (CHD). The results of this study explained that the subjects with low level of serum vitamin D 25(OH)D under 20 ng/mL, were 6.5 times more probable to developed CHD than those with normal vitamin D status (serum 25(OH)D \geq 20 ng/mL) 46% and 3%, respectively ⁽²⁹⁾.

4.1. Arterial hypertension and ventricular hypertrophy

Vitamin D deficiency has been related to hypertension. This fact supported by many observational data. Possible mechanisms explain the correlation between vitamin D level and blood pressure include the inverse relationship between vitamin D levels and the renin-angiotensin-aldosterone system (RAAS) activity. In addition, the role of vitamin D in protection of endothelial function and the prevention of secondary hyperparathyroidism ⁽²⁹⁾.

Renin-angiotensin-aldosterone system

The renin-angiotensin system (RAS) has an essential role in the regulation of blood pressure, electrolyte, and volume homeostasis. One of the important function of angiotensin II is promoting release of aldosterone, which is a steroid hormone formed by the adrenal glomerulosa. Aldosterone has a clear and direct role in pathogenesis of CVD. At the level of the vessels, inflammation, hypertrophic remodeling, oxidative stress and endothelial dysfunction are triggered by aldosterone ⁽³⁰⁾. Angiotensin II is main mediator responsible for adverse vascular remodeling in hypertension. It promotes this function by inducing endothelial dysfunction and vascular permeability. RAAS stimulates accumulation and promoting inflammatory cells inside lumen of blood vessels and this will lead to hyperplasia and hypertrophy of vascular smooth muscles (VSMC) ⁽³¹⁾. So RAAS stimulation considers as a risk of developed hypertension and other CVD ⁽³⁰⁾.

Several animal experiments reported that vitamin D inhibits renin release and expression in juxtaglomerular apparatus and down regulates proliferation of vascular smooth muscle cells (VSMC) that may in turn affect systemic blood pressure ⁽⁴⁾.

Parathyroid hormone

Elevated level of parathyroid hormone (PTH) considers as a hallmark of vitamin D deficiency and is known to be related to myocardial hypertrophy and increase blood pressure. The mechanism that explains the connection between high levels of PTH and hypertension is still unclear and many pathways can trigger it. PTH stimulates RAAS activity and in turn, it will promote renin release and stimulates aldosterone release directly from adrenal glomerulosa ⁽³²⁾. Moreover, PTH stimulates sympathetic activity with extra RAAS activation (elevating levels of renin and aldosterone secretion) and vascular contractility ⁽³³⁾.

A cross sectional study was done by Al-Daghri et al. ⁽³⁴⁾ applied among adolescents and children in both sexes male and female in Riyadh, Saudi Arabia and demonstrated the correlation between low level of vitamin D and cardio metabolic risk factors. The result highlighted that the Vitamin D deficiency was highly prevalent among females compared to males. In addition, it is associated with triglyceride, body mass index (BMI) and blood pressure. The variation of vitamin D deficiency between males and females explained by different hypothesis. One of them that prevalence of sun exposure among males more than in females. Also, there is a significant prevalence of obesity among female more than male ⁽³⁴⁾. In addition, the sex hormones such as estrogen plays an important role in this variation, which interact with vitamin D, could be the cause of the differences in calcium absorption under the same vitamin D conditions ⁽³⁵⁾.

A meta-analysis study involved eleven prospective studies done by Kunutsor et al. ⁽⁴⁾ between 2005 and 2012. This study included 55,816 hypertensive cases out of 283,537 participants with a mean follow-up of 9 years to demonstrate the association between baseline vitamin D status and hypertension risks. The authors reported that baseline serum 25(OH) D levels is significantly have inverse association with incident hypertension risk. Kota, et al. ⁽³⁶⁾ reported that systolic, diastolic and, mean arterial blood pressure was high among individuals experiencing vitamin D deficiency. They proposed that inadequate level of vitamin D is associated with renin-angiotensin-aldosterone system (RAAS) regulation.

The correlation between vitamin D status and incident hypertension examined by several studies. One of them performed in the Harvard School of Public Health (HPFS) and the Nurses' Health Study among men and women with vitamin D deficiency (less than 15 ng/mL) had three to six fold increase risk of developing incident arterial hypertension compared to average vitamin D status with an over 4 years follow up period ⁽⁴⁾. In addition, cohort study applied in United Kingdom

revealed that vitamin D level inversely associated with development many of metabolic risk including hypertension ⁽⁶⁾.

4.2. Myocardial infarction

Myocardial infarction (MI) considers as one of most common causes that lead to morbidity and mortality globally. MI contributes to more than half mortality related cardiovascular diseases (CVD) in the industrialized world. MI is a consequence of coronary occlusion that finally lead to cardiac cells damage and death. In 2008 according to World Health Organization (WHO), it was responsible for 7.3 million deaths out of 17.3 million CVD deaths worldwide ⁽⁴⁾. Recent evidence demonstrated the relationship between vitamin D deficiency and risk of MI. Danish carried out a study among 128 patients diagnosed with ischemic heart disease (IHD) (75 with angina pectoris and 53 with acute MI) and 409-control group. He examined the serum 25(OH) D in both groups and found that vitamin D levels were significantly reduced in patients with MI (24 ng/ml) and angina (23ng/ml) compared to control group (28ng/ml) ⁽³⁷⁾.

There was a study performed in gulf region (Qatar) showed that male with low vitamin D levels had three times more likely to developed MI than male with optimal vitamin D level ⁽³⁸⁾.

There are different possible mechanisms that explain the link between vitamin D deficiency and risk of developed MI. First, vitamin D deficiency accompanied with low intake of calcium possibly can lead to impaired fasting glucose and risk of type 2 diabetes mellitus, which in turn can lead to CVD. Second, low level of 25(OH) D can associate with increase cytokine profile that favors inflammation (e.g. elevated C-reactive protein, IL-6 and reduce IL-10), which can lead to increase MI risk ⁽³⁷⁾.

4.3. Heart failure

Heart failure (HF) is a principle cause of morbidity and mortality in western countries. In several observational studies, vitamin D deficiency and hyperparathyroidism regardless of age and renal function of patient are common in HF patients ⁽³⁹⁾. Low level of serum vitamin D has been correlated to worse cardiovascular outcomes among patient with or without HF. The mechanism that well explains this relation is that low level of serum vitamin D can lead to stimulate RAAS and this will release huge amount of aldosterone. Aldosterone has a clear role in pathogenesis of heart failure, it contributes to myocardial fibrosis. Therefore, in this situation, inhibiting aldosterone release is required to improve outcomes ⁽²⁶⁾.

Liu et al. ⁽³⁹⁾ investigated prognostic role of vitamin D deficiency among 548 patients diagnosed with HF combined with reducing left ventricular ejection fraction (LVEF). They found after multivariable adjustment that the concentration of vitamin D independently predicts endpoint of all causes of death and HF hospitalization. In addition, there was a study done by Pilz et al. ⁽²⁶⁾ involved followed up 3229 patients for

7.7 years. They demonstrated that there was a potent relationship between low level of vitamin D and heart failure.

4.4. Peripheral arterial disease

Approximately 5 million United States US adults affected by peripheral arterial diseases (PAD). PAD associated with increasing risk of cardiovascular mortality and morbidity. Established predisposing factors for PAD are the same of typical atherosclerosis risk factors such as diabetes mellitus, dyslipidemia, hypertension, smoking and impaired renal function. In addition, there are non-traditional cardiovascular risk factors like C-reactive protein (CRP) and fibrinogen have been related to PAD ⁽⁴⁰⁾. Clinical pictures of PAD, including claudication, rest pain, and tissue loss ⁽⁴¹⁾.

Many mechanisms can explain the association between vitamin D deficiency and developed PAD. Low level of serum 25(OH) D is correlated with obesity and hypertension, which in turn can lead to peripheral arterial disease. Therefore, serum vitamin D is inversely associated with rates of PAD ⁽⁴¹⁾. Melamed et al. ⁽⁴²⁾ studied the relationship between vitamin D status and prevalence of PAD and found that the risk of PAD increases by 1.35 for each 10 ng/ml reduction in serum vitamin D after multivariable adjustment.

Melamed et al. ⁽⁴³⁾ interpreted data from (National Health and Nutrition Examination Survey 2001 to 2004) showed vitamin D level among 4839 adults and found that those with optimal level of vitamin D had significantly less prevalence of PAD compared to those with low vitamin D levels.

5 Role of vitamin D supplements in management of cardiovascular diseases

Dietary vitamins supplements used widely and provide the potential role in improvement health. Reduction intake of essential nutrition and micronutrient are associated with many diseases and it is adversely affect global health. Therefore, improvements in diet quality and quantity are important to reach and address these issues; dietary supplements should help the individuals at deficiencies risk by providing all needed requirements. Vitamin D supplementation has a potential role in treatment of cardiovascular diseases and prevents its complications ⁽⁴³⁾.

Commonly, there are three main sources used to treat vitamin D deficiency: sunlight exposure and perform physical activities, exposure to artificial ultraviolet light and oral vitamin D supplementation ⁽¹⁰⁾.

More than 10,000 IU of vitamin D in systematic circulation can be reached by full -body exposure to sunlight for 10 - 15 minutes in summer noon -day or by artificial ultraviolet radiations. Approximately 1-2 exposure to sun per week should maintain vitamin D level in optimal range. Krause et al. ⁽¹⁰⁾ randomized 18 hypertensive patients into two groups to show the effect of ultraviolet exposure on improvement blood pressure by performed skin exposure to ultraviolet A and ultraviolet B. They demonstrated that the systolic and diastolic

blood pressure significantly decreased after 6 weeks of course of therapy in ultraviolet B group. This result ensuring that synthesis of vitamin D in skin regulated blood pressure.

The effect of vitamin D directly on blood vessels have been evaluated by several clinical studies. A cross sectional study was done among 52 subjects with end stage renal disease explained that there is a significant positive correlation between vitamin D level and arterial compliance examined by brachial artery and a negative correlation between velocity and aortic pulse wave. These findings suggested reduced compliance of vessel. In addition, vitamin D down-regulated pro fibrotic markers in vitro by using mesenchymal multipotent cells this indicating that vitamin D may have beneficial effect on vessels when become injured⁽¹¹⁾.

A meta-analysis study including eight randomized trials evaluated the role of vitamin D supplements on hypertension, demonstrated a little and significant reduction in diastolic blood pressure and non-significant reduction in systolic blood pressure compared to control group⁽⁴⁴⁾.

Liu et al.⁽⁴⁵⁾ applied randomized control trail among 548 heart failure patients have 75% vitamin D deficiency to see the effect of vitamin D supplementation in cardiovascular diseases. The result and outcomes of this study described as all causes of morbidity, hospitalization and mortality decrease.

6 Role of exercise in improvement vitamin D status and cardiovascular health

Physical exercise plays an important role in improvement overall health, prevention of many diseases especially life style-related diseases and reduces risk of cardiovascular diseases and cardio metabolic risk factors like obesity. Several data reported that individuals who do regular physical activity have 20% lower risk of cardiovascular diseases comparing to sedentary individuals⁽⁴⁶⁾.

Physical activity decreases risk of CHD by several possible mechanisms. Exercise have anti atherogenic effect, it can improved lipid profile, insulin sensitivity and reduced inflammatory marker⁽⁴⁶⁾. Researcher established that three or more hours a week of exercise like jogging, running or playing basketball might reduce a risk of cardiac attack by 22%⁽⁴⁷⁾. In addition, they found that those who practiced a physical activity have elevated levels of vitamin D as well as higher level of high-density lipoprotein (HDL) which is a good cholesterol⁽⁴⁴⁾.

Al-Othman, A et al.⁽⁴⁸⁾ performed study to examine the role of physical activity and sun exposure in improvement vitamin D status. This study was done among children and adolescents in Saudi Arabia. It showed that there was a positive correlation between physical activity and improvement vitamin D level according to sunlight exposure, this result explained in [figure 3].

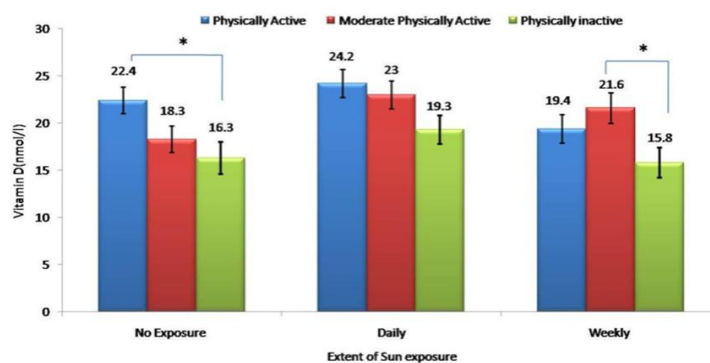


Figure 3: Effect of physical activity on 25(OH) vitamin D levels according to level of sun exposure
Al-Othman A (2017)⁽⁴⁸⁾.

Vitamin D itself have an important role in improvement Physical performance by improving skeletal muscle function. It increases number of type II muscle fiber (fast twitch fiber) which causes a good performance. It also elevates troponin C level in muscles, and increases amino acid uptake by skeletal muscles. In addition, it stimulates mitogen- activated protein kinas pathways, which involve in regulation myocyte proliferation and differentiation⁽²⁴⁾.

Exercise and physical activity are considered as a protective factor of vitamin D level. The National Health and Nutrition Examination Survey (NHANES III) reports revealed that physical activity improved serum vitamin D₃ due to either promoted vitamin D metabolism or increased sun exposure. Exercise can increase vitamin D level by increase vitamin D receptor (VDR) in skeletal muscle, pancreas and adipose tissue⁽⁴⁹⁾.

There are many mechanisms explain increasing VDR during exercise and improve lipid profile that in turn prevent cardiovascular diseases. First, vitamin D inhibits PTH secretion and this will lead to stimulate lipolysis and reduce fat. Second, vitamin D reduces serum triglyceride by lowered hepatic triglyceride formation. Third, vitamin D might improve insulin secretion and insulin sensitivity, which indirectly affecting lipid metabolism. Regular exercise can lead to number of adaptations in skeletal muscle that adjust the muscle to be more efficiently utilize substrates for Adenosine triphosphate (ATP) production and become more resistant to fatigue⁽⁵⁰⁾.

4 CONCLUSION

Vitamin D deficiency is related to several cardio metabolic risk factors like obesity and to the pathogenesis of wide spectrum of cardiovascular diseases such as hypertension, MI and heart failure. It is associated with high level of morbidity and mortality. Vitamin D exerts its cardiovascular effects by reducing the activity of the renin- angiotensin- aldosterone system, lowering blood pressure values, and having an anti-

inflammatory, anti-proliferative, anti-hypertrophic, anti-fibrotic and antithrombotic effect and beneficial modulation of classical cardiovascular risk factors. The potential role of vitamin D supplementation in treatment of cardiovascular diseases, their complications and in prevention of morbidity and mortality have been evaluated by several clinical studies. Further studies are needed to establish optimal vitamin D level and intake, to maintain a healthy vitamin D status in patients with cardiovascular diseases, and to include vitamin D blood tests, genotyping for vitamin D receptor variants as mandatory in evaluating patients with cardiovascular diseases.

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