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Medical Sciences

VITAMIN D AND ITS RELATIONSHIP WITH CARDIOVASCULAR DISEASES

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ABSTRACT:
VITAMIN D DEFICIENCY HAS BEEN ASSOCIATED WITH DISEASES SUCH AS RICKETS, OSTEOMALACIA, OSTEOPOROSIS, SKIN DISEASES AND CARDIOVASCULAR DISEASE. VITAMIN D DEFICIENCY IS ASSOCIATED WITH INCREASED INFLAMMATION, INCREASED EXPRESSION OF INFLAMMATORY CYTOKINES, ENDOTHELIAL CELLS AND DYSFUNCTION OF VASCULAR SMOOTH MUSCLE CELLS AND DECREASED VDR EXPRESSION AND ACTIVITY, WHICH MAY LEAD TO THE DEVELOPMENT OF VASCULAR DISEASES, SUCH AS ATHEROSCLEROSIS, ANEURYSMS, VASCULAR CALCIFICATIONS, AND ARTERIAL HYPERTENSION. ALTHOUGH THERE IS EVIDENCE THAT VITAMIN D DEFICIENCY IS ASSOCIATED WITH CARDIOVASCULAR DISEASE, A CAUSAL RELATIONSHIP HAS NOT BEEN IDENTIFIED YET.

KEY WORDS: VITAMIN D DEFICIENCY, ATHEROSCLEROSIS, CARDIOVASCULAR DISEASE.

INTRODUCTION

Vitamin D is a fat-soluble vitamin found in some food sources, produced non-enzymatically under the skin, following sun exposure, and metabolized in the liver and kidneys by involving cytochrome P450 enzymes[7]. Vitamin D plays a crucial role in mineral

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homeostasis and skeletal health and, as a steroid and immunomodulatory hormone, vitamin D regulates the body's immune response[8].

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. In 2015, the World Health Organization (WHO) estimated that CVD were responsible for over 17.7 million deaths, representing a total of 31% of global deaths[9]. One of the most important ethiological factors for CVD is atherosclerosis, characterized by lipid deposition and subsequent accumulation of T cells and macrophages, as a result of the response to endothelial injury[10]. In these processes, reactive oxygen species play a pivotal role, as they can cause lipid oxidation, such as low density lipoprotein (LDL) and polyunsaturated fatty acids, which are deposited in the vascular wall, directly damage cellular components and further promote inflammation by activating several pro-atherogenic transcription factors[11].

Vitamin D deficiency has been associated with diseases such as rickets, osteomalacia, osteoporosis, skin diseases and cardiovascular diseases[12]. Some studies have demonstrated the presence of vitamin D receptors in many tissues and have suggested plausible vitamin D pathways that may be linked to cardiovascular disease. Associations between low levels of serum 25-hydroxy vitamin D [25 (OH) D] and increased risk of cardiovascular disease have been shown by several observational studies[13].

THE LINK BETWEEN VITAMIN D AND CARDIOVASCULAR DISEASE

Vitamin D deficiency leads to increased inflammation, increased expression of inflammatory cytokines, and decreased expression and activity of VDR (vitamin D receptor). This leads to increased signaling of the downstream inflammatory signaling cascades, with loss of collagen, fibrosis, increased oxidative stress, increased inflammation, increased

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sensitivity to infections and decreased protective mechanisms[14]. Finally, all these processes induce various cardiovascular diseases, such as cardiomyopathy, ventrcular hypertrophy, myocardial infarction, heart failure, cardiac fibrosis and rhythm abnormalities[15]. Therefore, vitamin D supplementation may decrease these mediators and slow down cardiovascular disease progression and development[16].

In rats, diets low in vitamin D resulted in higher systolic pressure and lower calcium concentration, after which supplementation with vitamin D analogues led to the reversal of these effects[17].

There has also been evidence that vitamin D can regulate matrix homeostasis, which may lead to a critical situation in inflammatory diseases and aneurysms, where matrix destabilization is significant[18].

Vitamin D deficiency may lead to the development of vascular diseases, such as atherosclerosis, aneurysms, calcification, and hypertension[19]. Because vitamin D deficiency is associated with the pathogenesis of vascular disease development and progression, vitamin D supplementation may be useful for prevention of CVD and their complications[20].

Although there is evidence that vitamin D deficiency is associated with more cardiovascular disease, a causal relationship has not yet been identified.

MYOCARDIAL INFARCTION, CARDIAC HYPERTROPHY AND CARDIOMYOPATHY

Myocardial infarction has been associated with vitamin D deficiency, regardless of season[21]. Low plasma vitamin D levels are independently associated with poor inhospital outcomes and at one year in patients with acute myocardial infarction[22].

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Hyperlipidemia is a risk factor for CVD, and serum vitamin D has an inverse association with total cholesterol levels, low density lipoprotein (LDL), homocysteine, triglycerides, and a positive association with high density lipoprotein (HDL). Vitamin D supplementation may be protective against CVD[23].

Vitamin D deficiency is associated with increased inflammation, pro-inflammatory cytokines and atherosclerosis, and supplementation with vitamin D can reduce these factors. Hence the idea of the implication of vitamin D deficiency in the appearance of myocardial infarction, but the role of vitamin D in both the pathogenesis of myocardial infarction and the pathogenesis of atherosclerosis needs to be further studied[24].

VDR gene polymorphisms or genetic variations could be a positive predictor for myocardial infarction[25]. The cardioprotective effect of VDR activation is attributed to the inhibited endoplasmic reticulum, attenuated mitochondrial insufficiency, decreased autophagy dysfunction and reduced cardiomyocyte apoptosis[26].

Cardiac hypertrophy of the left ventricle (LVH) and myocardial performance are associated with low levels of vitamin D[27]. Diabetes is a risk factor for LVH[28]. LVH reversal in diabetic rats treated with vitamin D and attenuation of TNF-α expression by inhibiting nuclear factor-kappa beta signaling suggest the role of vitamin D in LVH reversal[29].

Cardiomyopathy. The pathogenesis of dilated cardiomyopathy (DCM) is usually idiopathic. Various studies have reported vitamin D deficiency-induced hypocalcemia in infants and hypoparathyroidism-induced hypocalcemia in adults as the cause of DCM and

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HF[30]. Low levels of maternal vitamin D have been suggested as a cause for childhood hypocalcemia. Improvement of clinical symptoms after supplementation with vitamin D and calcium for the treatment of hypovitaminosis and hypocalcemia highlights the importance and protective role of vitamin D in cardiomyopathy[31].

Low circulating levels of vitamin D have been correlated with cardiac steatosis. Furthermore, complete deletion of the animal VDR gene, as well as deletion of the myocyte-specific VDR gene, are associated with impaired cardiac structure and function[32].

Obesity is a chronic inflammatory disease associated with low levels of vitamin D. Low levels of vitamin D associated with obesity may be due to increased total clearance of vitamin D and increased consumption of vitamin D in the fight against inflammation associated with obesity[33]. Chronic inflammation of obesity is a risk factor for diabetes and together they are risk factors for heart disease, such as cardiomyopathy, coronary artery disease, myocardial infarction, fibrosis, arrhythmias and HF[34].

HEART FAILURE, RHYTHM ABNORMALITIES AND CARDIAC FIBROSIS

Heart failure. Vitamin D deficiency is associated with increased inflammation and inflammatory cytokines, such as TNF-α, interleukin (IL)-6 and interleukin-1beta (IL-1β), involved in mediating heart disease and heart failure[35]. Vitamin D supplementation reduces these cytokines in chronic heart failure[36].

Low levels of vitamin D and hypoparathyroidism are associated with remodeling of cardiomyopathy and worsening of heart failure[37]. Improvement and beneficial effects of vitamin D on the structure and function of LV in the VINDICATE study (Vitamin D treatment with patients with chronic heArT insufficiency), in patients with heart failure and decreased renin activity with short-term supplementation of vitamin D, suggest the therapeutic role of vitamin D[38].

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Rhythm anomalies. Vitamin D deficiency is associated with cardiac fibrosis, which is a hallmark of arrhythmias. Low levels of vitamin D are associated with heart failure and atrial fibrillation in patients with heart failure[39]. Low levels of vitamin D are significantly associated with increased left atrial fibrosis in patients with paroxysmal rhythm abnormalities, as well as with the recurrence of rhythm abnormalities after cryoablation and post-coronary artery bypass graft surgery[40].

Cardiac fibrosis and remodeling. Negative regulation of the activity of TGF-β1, SMAD3, CTGF and PARP1 / SIRT1 / mTOR pathways with vitamin D suggests the protective role of vitamin D against fibrosis[41]. Inflammation plays a major role in post-infarction remodeling, and vitamin D, as an anti-inflammatory agent, can play a crucial role[42]. Because vitamin D deficiency is associated with the development of hypertrophy and cardiac fibrosis, VDR genomics may play a role in the development of cardiac fibrosis. The cardioprotective effects of VDR activators and modulators suggest the potential therapeutic role of vitamin D[43].

CONCLUSIONS

Vitamin D deficiency is associated with cardiovascular disease, including coronary heart disease, myocardial infarction, heart failure and cardiac fibrosis, cardiomyopathy. Increased inflammation in diabetes and/ or obesity lowers the circulating levels of vitamin D, thus increasing the risk of cardiovascular disease. Vitamin D supplementation alleviates inflammation and pro-inflammatory cytokines and thus may play a therapeutic role in the treatment of cardiovascular disease.

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