Vitamin D in Cardiovascular Diseases

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Vitamin D represents a group of secosteroids involved in the calcium and phosphate metabolism. The active form of vitamin D, 1,25-dihydroxylcalciferol, exerts its biological mechanisms via the VDR which acts as a regulator of several target genes.

Keywords: Vitamin D ; Heart Failure ; Cardiovascular

1. Introduction

Vitamin D is a group of secosteroids that physiologically improve the intestinal absorption of calcium and phosphate. The most important compounds of the vitamin D group are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) ^[1]. The first association between vitamin D and cardiovascular diseases was reported by Scragg et al. ^[2], who recognized a seasonality in people suffering from heart disease. In particular, winter was the season when heart diseases were more frequent, possibly due to low levels of vitamin D. Cholecalciferol and ergocalciferol can be taken with food. After food intake, vitamin D2 undergoes two distinct metabolic processes. Firstly, vitamin D2 is metabolized in the liver to 25hydroxyvitamin D, which in the kidney is, subsequently, converted by the enzyme 25-hydroxyvitamin D-1 α -hydroxylase (CYP27B1) to its active form, named 25-dihydroxyvitamin D (calcitriol)^[3]. The endocrine production of calcitriol is regulated by feedback mechanisms involving bone, calcium, and the phosphorus metabolism. Calcitriol production is stimulated by the parathyroid hormone (PTH), released upon the reduction in calcium plasma levels. Calcitriol in turn directly suppresses the PTH gene transcription and the consequent hormone production, thereby increasing serum calcium levels. Furthermore, calcitriol also upregulates gene transcription and protein expression of the calcium-sensing receptor. Moreover, vitamin D regulates its own production by inhibiting CYP27B1 [4]. Additionally, under exposure to sunlight, the skin can synthesize vitamin D, namely, cholecalciferol ^[5]. The amount of sunlight needed to satisfy the vitamin D requirements is dependent on several factors such as skin pigmentation, age, latitude, season of the year, or time of the day ^[6]. Several diseases can be associated with low vitamin D levels. Rickets has long been recognized as a consequence of vitamin D deficiency. Furthermore, low vitamin D levels can be associated with other chronic disorders, such as atherosclerosis, coronary heart disease, arterial hypertension, heart failure [I], type 2 diabetes mellitus [B], cancer (9), and immunological disease (10). Even if a pathogenic link between vitamin D deficiency and these diseases was established, the results of randomized clinical trials (RCT) designed to prove the therapeutic role of vitamin D supplementation have been inconclusive to date. However, it should be pointed out that the involvement of the vitamin D system in the pathogenesis of cardiovascular diseases is quite intricate. Indeed, within this context, a relevant role is also played by the autocrine/paracrine pathways locally activated by vitamin D inside atherosclerotic plagues [11][12]. In particular, it has been shown that vitamin D receptor (VDR) expression in human carotid plaques correlates with a reduction in major adverse cardiovascular events (MACE) [12].

2. Vitamin D and Heart Failure

Both VDR and hydroxylases necessary to form active vitamin D are expressed in ventricular cardiomyocytes. Current in vivo evidence suggests that the loss of the activity of the vitamin D signaling pathway can induce the remodeling of cardiomyocytes and the extracellular matrix, and the administration of the active form of vitamin D can reduce or prevent this remodeling, by acting on anatomical, functional, molecular, and genetic aspects of cardiac hypertrophy and dysfunction that lead to heart failure with preserved ejection fraction (HFpEF). HFpEF is characterized by an increased filling pressure, cardiac hypertrophy, and diastolic dysfunction, with a normal value of ejection fraction. A study conducted on a mice model of hypertension and left ventricular hypertrophy (LVH), induced by a high-salt diet, showed that the group treated with paricalcitol (PC) had reduced LVH with respect to the control group (13%). Moreover, echocardiographic parameters of hypertrophy such as interventricular septum, posterior wall, and left ventricle (LV) mass increases were reduced in the interventional group. Similar echocardiography findings were found in a population with end-stage renal disease and, also in this setting, the administration of PC reduced the cardiac hypertrophy signs ^[13]. To exclude that these

findings were due to a different pressure overload between the two groups, continuous wireless telemetries for seven consecutive days were performed, and no differences were found in the mean arterial pressure (MAP) between the two groups. Molecular markers of heart failure as brain natriuretic peptide (BNP) and atrial natriuretic factor (ANF) were also reduced in the PC group. The mechanism used by vitamin D to improve cardiac function is not fully understood, but the evidence that VDR is expressed on cardiomyocytes suggests an activation of intracellular pathways leading to a modified gene expression. Microarray gene analyses demonstrated that in the PC-group mice, the expression of hypertrophyrelated genes, such as myosin heavy-chain isoform, α -tropomyosin, and NF- κ B, was downregulated ^[13]. Evidence of changes in genetic expression came from another mouse model of cardiac hypertrophy induced by transverse aortic constriction (TAC), where the expression of collagen III, fibronectin, and TIMP-1 (tissue inhibitor-1 of matrix metalloproteases) was reduced by the use of PC or losartan ^[14]. Further evidence suggests that vitamin D pathway activation stimulates calcium uptake, increases contractility in wild-type, but not in VDR knockout mice, and improves diastolic function [15][16]. In VDR knockout animal models, cardiomyocytes develop hypertrophy and cardiomegaly [17][18]. A study conducted on newly diagnosed treatment-naïve hypertensive patients, showed that hypovitaminosis D was a strong predictor of increased left ventricular mass index ^[19]. By interfering with collagen and metalloproteinase production, vitamin D can also affect the heart extracellular matrix. Vitamin D-deficient mice develop cardiomegaly, associated with increased extracellular space and collagen. Moreover, VDR knockout mice express high levels of matrix metalloproteinases, and are also characterized by increased fibrosis and low concentrations of tissue inhibitors of metalloproteinases [20].

3. Vitamin D Supplementations and Cardiovascular Health

The Vitamin D and Omega-3 Trial (VITAL) is a recent RCT that aims to investigate cardiovascular outcomes in patients taking omega 3 or vitamin D3 supplementations in the general populations. The study sample consists of 25.871 patients, including men aged >50 years and women aged >55 years, recruited all over the United States, receiving placebo or a 2.000 IU daily dose of vitamin D. The primary endpoints were decreases in myocardial infarction, stroke, and death from cardiovascular causes tracked for a median of 5.3 years. The VITAL trial did not find any significant benefits in regard to cardiovascular outcomes. Indeed, only a not significant reduction in cardiovascular events was observed in the group treated with vitamin D when compared to the placebo [21]. These results were consistent with the Women's Health Initiative Calcium and Vitamin D Trial (WHI CaD), which found no cardiovascular benefits from daily vitamin D supplementation ^[22]. The DIMENSION trial evaluated the potential impact of a 16-week cholecalciferol supplementation on endothelial function in patients with diabetes. In particular, the eventual improvements referring to vascular biomarkers and reactive hyperemia index were assessed. Vitamin D levels significantly increased in the treatment arm. Nevertheless, a multivariate regression analysis did not detect any effect on endothelial function [23]. A further controlled study aimed to evaluate the possible protective action of vitamin D on markers of heart lesions showed that cholecalciferol, administered before a percutaneous coronary procedure, did not elicit any MACE change in comparison to the control arm ^[24]. In a primary care setting, the authors of the BEST-D trial studied in healthy subjects the effects of a 1-year daily supplementation of cholecalciferol on disease risk and biochemical markers. Similar to the above-mentioned data, the results of this trial were also not encouraging. Indeed, vitamin D supplementation enhanced serum 25(OH) concentrations, but no significant improvements were reported with regard to cardiovascular (CVD) risk factors, blood pressure, arterial stiffness, and blood lipids ^[25]. The D-Health Trial evaluated in more than 21,000 subjects the eventual efficacy of vitamin D supplementation about the prevention of cancer and mortality. In particular, this RCT assessed the effects of either placebo or monthly oral administrations of cholecalciferol during a 5-year period, followed by further 5 years of passive monitoring, based on the access to health records and death registries. The results of this study did not clarify if vitamin D supplementation exerted any protective action on cancer and mortality risks, and the authors concluded that data obtained from observational investigations are not useful to support the utilization of vitamin D in healthy subjects as a protective agent [26]. Moreover, cholecalciferol supplementation did not reduce the cardiovascular risk [27]. Another double blind, placebo-controlled RCT investigated if a 12-week daily supplement of cholecalciferol could be useful in healthy subjects to decrease blood pressure, heart rate, and other CVD risk markers. However, although this treatment increased the serum levels of 25(OH)D, the CVD risk did not improve [28]. A recent meta-analysis evaluated the eventual correlation between serum 25(OH)D levels and CVD incidence. No significant relationship was found, though low vitamin D levels correlated with a 44% increase in the relative risk of CVD (incidence-mortality combined), as well as with an enhanced mortality related to CVD [29]. Another meta-analysis included 21 RCTs to evaluate the cardiovascular benefits of a vitamin D supplementation over one year, regardless of calcium supplementation. The primary endpoint was a combination of MACEs. Secondary endpoints included the eventual changes involving myocardial infarction, stroke, or cerebrovascular accidents, cardiovascular mortality, and all-cause mortality. According to this meta-analysis, vitamin D supplementation did not elicit any significant changes in MACE, single cardiovascular endpoints (myocardial infarction, stroke, cardiovascular mortality), or all-cause mortality [30]. The above studies are consistent with the evidence that vitamin D supplementation does not seem to induce relevant benefits for cardiovascular health. The occurrence of acute toxic effects of vitamin D supplementation are quite rare, because vitamin D toxicity can be induced only by very high dosages. The toxic effects of vitamin D may include hypercalcemia, that can promote cardiac arrhythmias sustained by a shortened QT interval ^[31].

4. Potential Impact of Calcium and Phosphate on Cardiovascular Risk

Because vitamin D is a key factor in the regulation of calcium/phosphate absorption and metabolism, it is quite logical that a relevant association can occur between changes in the levels of these metabolites and the overall cardiovascular risk [62]. Indeed, several experimental and clinical studies suggest that calcium, phosphate, and vitamin D can play an important role in the pathogenesis of cardiovascular diseases. Since calcium, phosphate, and vitamin D are closely connected, they constitute a biological axis that should be considered with regard to all these three components and their reciprocal relationships.

However, their coordinated roles in the development and progression of cardiovascular disorders have not yet been clearly elucidated. In fact, within the very complex scenario of the global cardiovascular risk, rationally designed clinical trials have so far failed to shed light on the real consequences of calcium/phosphate/vitamin D deficiencies or supplementations [63].

5. Conclusions

Vitamin D represents a group of secosteroids involved in the calcium and phosphate metabolism; an adequate food intake and sunlight exposition are necessary to reach sufficient levels of vitamin D. Different diseases can be associated with low levels of vitamin D, that are not only related to bone and calcium metabolism diseases. Indeed, current evidence suggests a direct involvement of hypovitaminosis D in cardiovascular diseases. Both in vitro and in vivo animal models showed that vitamin D deficiency can cause or worsen endothelial dysfunction, favoring the onset and progression of atherosclerotic plaque.

Endothelial dysfunction and RAAS modulation have been shown to be implicated in the development of arterial hypertension due to vitamin D deficiency in animal reversible models, where the reintegration of vitamin D restored or improved the cardiovascular

impairment. Vitamin D deficiency in animal models is also related to heart hypertrophic remodeling, characterized by biochemical and echocardiographic changes similar to the

findings of the HFpEF. Even if the association between hypovitaminosis D and cardiovascular disease is well established in animal models, several trials and meta-analyses performed to prove eventual cardiovascular benefits of vitamin D supplementation in humans have been inconclusive, thereby never reaching significant results referring to MACE. Further studies are, thus, needed to eventually prove the supposed benefits of vitamin D supplementation.

References

- 1. Holick, M.F. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin. Proc. 2006, 81, 353-373.
- Scragg, R.; Jackson, R.; Holdaway, I.M.; Lim, T.; Beaglehole, R. Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: A community-based study. Int. J. Epidemiol. 1990, 19, 559–563.
- 3. Holick, M.F. Environmental factors that influence the cutaneous production of vitamin D. Am. J. Clin. Nutr. 1995, 61 (Suppl. 3), 638S–645S.
- 4. Christakos, S.; Dhawan, P.; Verstuyf, A.; Verlinden, L.; Carmeliet, G. Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. Physiol. Rev. 2016, 96, 365–408.
- 5. Cashman, K.D.; Kiely, M. EURRECA-Estimating vitamin D requirements for deriving dietary reference values. Crit. Rev. Food Sci. Nutr. 2013, 53, 1097–1109.
- Terushkin, V.; Bender, A.; Psaty, E.L.; Engelsen, O.; Wang, S.Q.; Halpern, A.C. Estimated equivalency of vitamin D production from natural sun exposure versus oral vitamin D supplementation across seasons at two US latitudes. J. Am. Acad. Dermatol. 2010, 62, 929.e1–929.e9299.
- 7. Wang, T.J. Vitamin D and Cardiovascular Disease. Annu. Rev. Med. 2016, 67, 261-272.
- 8. Krul-Poel, Y.H.; Ter Wee, M.M.; Lips, P.; Simsek, S. Management of endocrine disease: The effect of vitamin D supplementation on glycaemic control in patients with type 2 diabetes mellitus: A systematic review and meta-analysis.

Eur. J. Endocrinol. 2017, 176, R1-R14.

- 9. Fleet, J.C.; DeSmet, M.; Johnson, R.; Li, Y. Vitamin D and cancer: A review of molecular mechanisms. Biochem. J. 2012, 441, 61–76.
- 10. Hewison, M. An update on vitamin D and human immunity. Clin. Endocrinol. 2012, 76, 315–325.
- 11. Carbone, F.; Montecucco, F. The role of the intraplaque vitamin d system in atherogenesis. Scientifica (Cairo) 2013, 2013, 620504.
- Carbone, F.; Satta, N.; Burger, F.; Pagano, S.; Lescuyer, P.; Bertolotto, M.; Spinella, G.; Pane, B.; Palombo, D.; Pende, A.; et al. Vitamin D receptor is expressed within human carotid plaques and correlates with pro-inflammatory M1 macrophages. Vasc. Pharmacol. 2016, 85, 57–65.
- Bodyak, N.; Ayus, J.C.; Achinger, S.; Shivalingappa, V.; Ke, Q.; Chen, Y.S.; Rigor, D.L.; Stillman, I.; Tamez, H.; Kroeger, P.E.; et al. Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in Dahl salt-sensitive animals. Proc. Natl. Acad. Sci. USA 2007, 104, 16810–16815.
- Meems, L.M.; Cannon, M.V.; Mahmud, H.; Voors, A.A.; van Gilst, W.H.; Silljé, H.H.; Ruifrok, W.P.; de Boer, R.A. The vitamin D receptor activator paricalcitol prevents fibrosis and diastolic dysfunction in a murine model of pressure overload. J. Steroid Biochem. Mol. Biol. 2012, 132, 282–289.
- 15. Green, J.J.; Robinson, D.A.; Wilson, G.E.; Simpson, R.U.; Westfall, M.V. Calcitriol modulation of cardiac contractile performance via protein kinase C. J. Mol. Cell. Cardiol. 2006, 41, 350–359.
- 16. Walters, M.R.; Ilenchuk, T.T.; Claycomb, W.C. 1,25-Dihydroxyvitamin D3 stimulates 45Ca2+ uptake by cultured adult rat ventricular cardiac muscle cells. J. Biol. Chem. 1987, 262, 2536–2541.
- 17. Weishaar, R.E.; Kim, S.N.; Saunders, D.E.; Simpson, R.U. Involvement of vitamin D3 with cardiovascular function. III. Effects on physical and morphological properties. Am. J. Physiol. 1990, 258 Pt 1, E134–E142.
- 18. Chen, S.; Law, C.S.; Grigsby, C.L.; Olsen, K.; Hong, T.T.; Zhang, Y.; Yeghiazarians, Y.; Gardner, D.G. Cardiomyocytespecific deletion of the vitamin D receptor gene results in cardiac hypertrophy. Circulation 2011, 124, 1838–1847.
- Magurno, M.; Crescibene, D.; Spinali, M.; Cassano, V.; Armentaro, G.; Barbara, K.; Miceli, S.; Hribal, M.L.; Perticone, M.; Sciacqua, A. Vitamin D and Subclinical Cardiovascular Damage in Essential Hypertension. Endocrines 2021, 2, 13.
- 20. Rahman, A.; Hershey, S.; Ahmed, S.; Nibbelink, K.; Simpson, R.U. Heart extracellular matrix gene expression profile in the vitamin D receptor knockout mice. J. Steroid Biochem. Mol. Biol. 2007, 103, 416–419.
- Manson, J.E.; Cook, N.R.; Lee, I.M.; Christen, W.; Bassuk, S.S.; Mora, S.; Gibson, H.; Gordon, D.; Copeland, T.; D'Agostino, D.; et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. N. Engl. J. Med. 2019, 380, 33–44.
- 22. Hsia, J.; Heiss, G.; Ren, H.; Allison, M.; Dolan, N.C.; Greenland, P.; Heckbert, S.R.; Johnson, K.C.; Manson, J.E.; Sidney, S.; et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation 2007, 115, 846–854.
- Dalan, R.; Liew, H.; Assam, P.N.; Chan, E.S.; Siddiqui, F.J.; Tan, A.W.; Chew, D.E.; Boehm, B.O.; Leow, M.K. A randomised controlled trial evaluating the impact of targeted vitamin D supplementation on endothelial function in type 2 diabetes mellitus: The DIMENSION trial. Diabetes Vasc. Dis. Res. 2016, 13, 192–200.
- Aslanabadi, N.; Jafaripor, I.; Sadeghi, S.; Hamishehkar, H.; Ghaffari, S.; Toluey, M.; Azizi, H.; Entezari-Maleki, T. Effect of Vitamin D in the Prevention of Myocardial Injury Following Elective Percutaneous Coronary Intervention: A Pilot Randomized Clinical Trial. J. Clin. Pharmacol. 2018, 58, 144–151.
- 25. Hin, H.; Tomson, J.; Newman, C.; Kurien, R.; Lay, M.; Cox, J.; Sayer, J.; Hill, M.; Emberson, J.; Armitage, J.; et al. Optimum dose of vitamin D for disease prevention in older people: BEST-D trial of vitamin D in primary care. Osteoporos. Int. 2017, 28, 841–851.
- Neale, R.E.; Armstrong, B.K.; Baxter, C.; Duarte Romero, B.; Ebeling, P.; English, D.R.; Kimlin, M.G.; McLeod, D.S.; O'Connell, R.L.; van der Pols, J.C.; et al. The D-Health Trial: A randomized trial of vitamin D for prevention of mortality and cancer. Contemp. Clin. Trials 2016, 48, 83–90.
- 27. Legarth, C.; Grimm, D.; Krüger, M.; Infanger, M.; Wehland, M. Potential Beneficial Effects of Vitamin D in Coronary Artery Disease. Nutrients 2019, 12, 99.
- Seibert, E.; Lehmann, U.; Riedel, A.; Ulrich, C.; Hirche, F.; Brandsch, C.; Dierkes, J.; Girndt, M.; Stangl, G.I. Vitamin D3 supplementation does not modify cardiovascular risk profile of adults with inadequate vitamin D status. Eur. J. Nutr. 2017, 56, 621–634.
- Gholami, F.; Moradi, G.; Zareei, B.; Rasouli, M.A.; Nikkhoo, B.; Roshani, D.; Ghaderi, E. The association between circulating 25-hydroxyvitamin D and cardiovascular diseases: A meta-analysis of prospective cohort studies. BMC Cardiovasc. Disord. 2019, 19, 248.

- Barbarawi, M.; Kheiri, B.; Zayed, Y.; Barbarawi, O.; Dhillon, H.; Swaid, B.; Yelangi, A.; Sundus, S.; Bachuwa, G.; Alkotob, M.L.; et al. Vitamin D Supplementation and Cardiovascular Disease Risks in More Than 83,000 Individuals in 21 Randomized Clinical Trials: A Meta-analysis. JAMA Cardiol. 2019, 4, 765–776.
- 31. De la Guía-Galipienso, F.; Martínez-Ferran, M.; Vallecillo, N.; Lavie, C.J.; Sanchis-Gomar, F.; Pareja-Galeano, H. Vitamin D and cardiovascular health. Clin. Nutr. 2021, 40, 2946–2957.

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