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Vitamin D deficiency and heart failure

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Abstract

Vitamin D is principally known for its role in calcium homeostasis, but preclinical studies implicate multiple pathways through which vitamin D may affect cardiovascular function and influence risk for heart failure. Cross sectional studies demonstrated that prevalence of HF is increased in patients with Vitamin D deficiency or parathyroid hormone (PTH) plasma level increase, whereas longitudinal studies showed enhanced risk of developing new HF in patients with Vitamin D deficiency. In addition, in patients with established HF, low plasma levels of Vitamin D are associated with worsening clinical outcome. Yet, clinical studies did not definitively demonstrate a benefit of Vitamin D supplementation for preventing HF or ameliorating clinical outcome in patients with established HF.

Aim: The aim of this review was to summarize evidence on the role of Vitamin D deficiency in heart failure (HF), from pathophysiological mechanisms side.

Introduction

With the improvement of care in the prevention of high blood pressure (hypertension), smoking, and dyslipidaemia, coupled with technological advances in the diagnosis and treatment of cardiovascular diseases (CVDs), there was a decline in the mortality rate due to CVD in the elderly; however, CVD is the leading cause of morbidity and mortality in the world and the most chronic disability .[1] Vitamin D is a steroid hormone belonging to the group of lipid-soluble vitamins.[3] It is estimated that nearly 30–50% of the world population suffers vitamin D deficiency . Rickets, the skeletal disease associated with vitamin D deficiency, has long been recognized. More recently, however, a broad range of chronic conditions has been associated with vitamin D deficiency, including HF, coronary heart disease, type 2 diabetes mellitus (T2DM).[3] Heart failure (HF) is a complex syndrome secondary to inherited or acquired structural or functional heart abnormalities, and remains a leading cause of mortality and morbidity worldwide.[2] Approximately 10 millions of patients in Europe are affected by chronic HF and, despite substantial advances in therapeutic options over the last years, no substantial changes in prognosis have been observed, with survival rate at 5 years after diagnosis of 35-50% .[2] Several mechanisms are involved in the pathogenesis of HF, including hemodynamic abnormalities, neurohormonal activation, enhanced inflammation and micronutrients

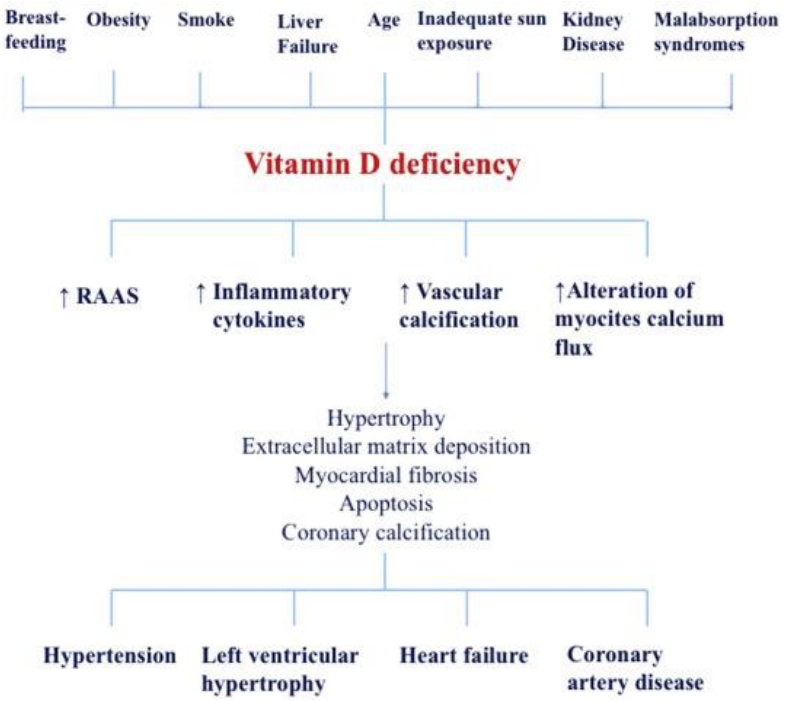
availability , that explains the suboptimal impact of current therapies on clinical outcome.[2] Vitamin D is an important micronutrient with a significant role in autocrine and paracrine regulation of cellular functions and in growth and differentiation of several organs, including the heart.[2] In fact, Vitamin D deficiency is associated with increased incidence of hypertension, myocardial infarction (MI), HF and stroke.[2]

Method

The instruments used for data collection were the copy of the cardiological research protocol used in the cardiology outpatient clinic of the study sites, the Mini-Mental State Examination, the Geriatric Depression Scale, and the Health ABC scale, to calculate risk of HF.

Result

Observational data point toward a relationship between vitamin D deficiency and mortality in patients with established HF. In a cross-sectional analysis of patients referred for cardiac catheterization, severe 25-OHD deficiency (<10 ng/ml) was associated with a 2.8-fold adjusted risk of death from HF and 5-fold adjusted risk of sudden cardiac death. Finally, low 25-OHD status has also been associated with reduced exercise capacity and greater limitation on the Kansas City Cardiomyopathy Questionnaire in patients with HF.



Discussion:

Vitamin D is a secosteroid that exists in two major forms: Vitamin D2 (or ergocalciferol) and Vitamin D3 (or cholecalciferol).[2] Vitamin D can be derived from sunlight (UV-B)-induced production in the skin (80%) and from dietary intake.[2] The formation of active Vitamin D3 metabolite requires two steps, the first in the liver to form 25-hydroxyvitamin D3 (25(OH)D or calcifediol) and the second in the kidney to convert calcifediol in 1,25-dihydroxivitamin D (1,25(OH)2D or calcitriol).[2] The 25(OH)D is primarily dependent on Vitamin D supply, with serum levels higher than calcitriol and with longer half-life (~ 3 weeks) compared to Vitamin D and calcitriol (both with few hours half life).[2] Therefore, 25(OH)D concentrations should be measured to assess Vitamin D status.[1] Vitamin D exerts its action binding Vitamin D receptor (VDR), expressed on at least 36 different tissues including cardiac muscle, vascular smooth muscles, endothelium and lymphocytes.[2] VDR forms a heterodimer with the retinoic acid receptor, and this heterodimeric complex acts on gene transcription of Vitamin D response elements , that consists of a large number of target genes.[2] Recent studies also showed that Vitamin D metabolites might act through non-genomic pathways, using an alternative binding site on VDR .[2] Vitamin D acts as a negative regulator of renin-angiotensin-aldosterone system (RAAS) and several studies showed a relationship between low Vitamin D levels and increased RAAS activity.[2] Both VDR knockout and 1α-hydroxylase knockout mice exhibit elevated renin, angiotensin II, and aldosterone levels compared to wild-type animals.[2] In both models, dietary 1,25-OHD supplementation suppresses RAAS levels.[2] Vitamin D inhibits renin gene expressional at the transcriptional level.Consistently, VDR knockout mice show increased RAAS activity, leading to hypertension, cardiac hypertrophy, increased water intake and sodium retention.[2]

Vitamin D may act directly on growth and differentiation of cardiomyocytes inhibiting their proliferation.[2] This anti-proliferative property may be due to the suppression of proto-oncogene c-myc and of natriuretic peptide.[2] VDRs are also expressed on cardiac fibroblasts, and VDR knockout mice show collagen deposition.[2] By a non-genomic pathway, the functional form of Vitamin D acts on calcium channels in cardiac myocytes

inducing a rapid influx of calcium.[2] Experimental animal studies showed that calcitriol, through the phosphorylation of protein kinase C, promotes myocytes relaxation, thus participating in the homeostasis of diastolic function , and enhances myocyte contractility through adenylate cyclase and cyclic adenosine monophosphate (cAMP) pathways.[2] The effects of Vitamin D on CV system are additionally mediated through elevated parathyroid hormone (PTH) levels.[2] The active Vitamin D form enhances the production and activity of the TRPV6 (Transient Receptor Potential channel Vanilloid type) ion channel and calbindin calcium binding protein in the intestinal epithelium to promote calcium absorption.[2] In addition, 1,25(OH)2D increases renal calcium reabsorption as well as calcium reabsorption from the skeleton together with PTH.[2] Besides, VDRs are present in the parathyroid gland and 1,25(OH) suppresses production of PTH and prevents proliferation of parathyroid glands.[2] Consequently, Vitamin D deficiency is associated with elevated PTH concentration, that exerts a trophic effect on cardiomyocytes with an increase in total cellular mass and arterial stiffness , that is associated with development of left ventricular (LV) hypertrophy in patients with elevated PTH levels. [2]

Conclusion

Vitamin D is a vital nutrient involved in multiple pathophysiological pathways relevant to HF. Thus, it is conceivable that vitamin D plays a significant role in cardiovascular homeostasis and cardiac remodeling. There is also preclinical and observational evidence suggesting that vitamin D deficiency is associated with worse HF outcomes.

Future work

Wider studies encompassing multiple regions and different ethnicities investigating Vitamin D and its correlation with Heart failure should be conducted to assess the role of Vitamin D and its effect in reversing Cardiac Failure , as Vitamin D deficiency is dependent upon geographical location as well as amount of sunlight and skin type, comparing the results can draw a link or help establish the protective role of Vitamin D in these different populations and to raise a larger sample group.

References

1. Porto, C., Silva, V., da Luz, J., Filho, B. and da Silveira, V. (2017). Association between vitamin D deficiency and heart failure risk in the elderly. *ESC Heart Failure*, 5(1), pp.63-74.

2. D'Amore C, e. (2019). *Vitamin D deficiency and clinical outcome in patients with chronic heart failure: A review. - PubMed - NCBI*. [online] Ncbi.nlm.nih.gov. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28954706 [Accessed 4 Dec. 2019].

3. Marshall Brinkley, D., Ali, O., Zalawadiya, S. and Wang, T. (2017). Vitamin D and Heart Failure. *Current Heart Failure Reports*, 14(5), pp.410-420