

Vitamin D and heart failure. Pathophysiology, prevalence, and prognostic association

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INTRODUCTION

Heart failure (HF) is a major public health problem characterized by high mortality, frequent hospitalizations and deterioration in the quality of life, with a prevalence and incidence that is increasing worldwide^{1,2}. Although the prognosis has improved in recent decades thanks to the diagnostic and therapeutic improvement of cardiovascular diseases, the morbidity and mortality of these patients remains high³. All this implies that new objectives and treatment options are still needed.

Vitamin D had traditionally been associated only with bone health, accepting that vitamin D deficiency caused osteomalacia and osteoporosis in adults and rickets in children^{4,5}. However, data obtained in recent years indicate that vitamin D is an important micronutrient for optimal function of many organs and tissues throughout the body, including the cardiovascular system^{6,7}. It has been suggested that vitamin D deficiency may be an important factor both in the genesis of risk factors and cardiovascular disease⁷ as a prognostic marker in HF. Pathophysiological data indicate that vitamin D deficiency may be very harmful for patients with HF and that vitamin D supplementation can be potentially beneficial, although all this is not without controversy⁸.

In this paper, we review the evidence that so far supports the link between vitamin D and HF. We analyze the potential mechanisms through which vitamin D could exert, its cardioprotective effects, the potentially deleterious effects of its deficit and break down the main studies on vitamin D supplementation in patients with HF.

PATHOPHYSIOLOGY OF VITAMIN D AND HEART FAILURE

There is no single established route or a single hypothesis that explains the relationship between vitamin D and HF. The vitamin D receptor (VDR) is a nuclear hormonal receptor that mediates the action of calcitriol through genomic and non-genomic pathways⁹. Cardiomyocytes have VDR, and it is known that calcitriol through VDR also modulates important genes related to cardiovascular health, so they may be influenced by vitamin D¹⁰.

Functional VDRs are expressed in the cell nucleus or adjacent to the T tubules of cardiomyocytes, and also of cardiac fibroblasts. Cardiac hypertrophy has been associated with an increase in the expression of these receptors in these cells. Vitamin D has also been attributed an antiproliferative property mediated by the suppression

of proto-oncogenes such as c-myc, as well as the natriuretic peptide, acting directly on the growth and differentiation of cardiomyocytes. Mice without VDR (knock-out of the VDR gene) show a greater deposition of collagen in their cardiac structures¹⁰.

There are also more complex molecular mechanisms that can explain the relationship between vitamin D and HF. Vitamin D acts on the calcium channels of the cardiomyocytes inducing a rapid intracellular calcium influx¹¹. This intracellular calcium concentration controls long-term growth, proliferation and cell death responses. In addition, by activating the protein C-kinase, it promotes cardiomyocyte relaxation and, therefore, participates in cardiac diastolic function¹² and in cardiac systole through activation of adenylyl cyclase or cyclic adenosine monophosphate. Dysfunction of any of these pathways can cause systolic and/or diastolic ventricular dysfunction, and, therefore, HF.

Several neuroendocrine systems and inflammatory cytokines are involved in the pathophysiology of vitamin D and HF. These are activated to maintain circulatory homeostasis, but in the long term they contribute to increased systemic resistance and ventricular remodeling, developing and worsening HF. Although the renin-angiotensin aldosterone system (SRAA) and the sympathetic nervous system (SNS) have so far been the most important in HF, recently, both at the diagnostic and therapeutic level, counter-regulatory systems such as natriuretic peptides are also being key. In the diagnostic-therapeutic approach of this syndrome^{13,14}.

It has been shown that vitamin D has an intimate relationship with SRAA. Different studies have shown that there is an inverse correlation between vitamin D levels and the activity of SRAA¹⁵⁻¹⁷. The main actions of SRAA include the regulation of vascular tone, volemia, ventricular and vascular remodeling and activation of SNS. The key role of SRAA in the pathophysiology of HF and arterial hypertension is well defined.

The cascade of action and pathophysiology of SRAA is as follows: renin is a protein that acts on angiotensinogen, producing angiotensin I, which is transformed into angiotensin II by the action of angiotensin converting enzyme at the pulmonary and vascular level. Angiotensin II is a potent vasoconstrictor hormone of afferent and efferent renal arterioles, and also promotes the activation of the sympathetic nervous system (also key in



the pathophysiology of HF). The overactivation of SNS and SRAA contributes to the progressive cardiac remodeling that can lead to HF. This hormone in turn also promotes the release of aldosterone from the adrenal cortex, important in electrolyte and volume balance by retaining sodium and water and releasing potassium and magnesium at the renal level¹⁸.

Although one of the main factors that stimulate the release of renin, and therefore SRAA, is the decrease in renal perfusion, experimental studies have shown that after modifying the RVD function in experimental animals with knock-out RVD mice, an increase in the concentration of renin expression with increased mRNA and its protein in the kidney, and plasma angiotensin II, compared to wild-type mice¹⁵. Consequently, these knock-out mice developed more arterial hypertension, left ventricular hypertrophy and an increase in fluid retention. Injection of 1.25 (OH)₂D achieved marked suppression of renin, which was also achieved with the use of the angiotensin-converting enzyme inhibitor, captopril, or angiotensin II receptor antagonist, losartan; which showed the key pathophysiological role of SRAA^{15,19}, demonstrating that the probable cause of this is overstimulation of SRAA²⁰. The role of angiotensin II in increasing fibrosis and cardiac hypertrophy, increasing vascular tone and therefore blood pressure, as well as increasing sympathetic tone, and direct relationship with the symptoms and progression of heart failure in humans, is also clearly established.

Vitamin D deficiency has been linked to an increase in the production and release of inflammatory cytokines, which has an indirect and direct negative effect on the heart and other organs. Inflammatory cytokines induce apoptosis of cardiomyocytes, hypertrophy, fibrosis, cardiac remodeling and negative ionic alterations such as sodium retention and, therefore, fluid retention²¹. It also increases catabolic activity and induces cachexia, which contributes to the progression of HF syndrome²². *In vitro* studies have suggested that vitamin D inhibits inflammatory cytokines such as TNF- α and IL-6, while stimulating anti-inflammatory cytokines such as IL-10²³.

RVDs are also present in the parathyroid gland, and calcitriol suppresses the production of parathyroid hormone (PTH) and prevents the proliferation of parathyroid glands²⁴. When there is a vitamin D deficiency, secondary hyperparathyroidism occurs, which also has deleterious cardiovascular and trophic effects on cardiomyocytes. This increase in PTH levels also leads to an increase in blood pressure due to an increase in arterial stiffness and, therefore, and once again, contributes to cardiac remodeling in HF secondary to hypertrophy, apoptosis and fibrosis of the ventricle^{10,25}.

Another pathophysiological mechanism is the influence of vitamin D on the regeneration of the myocardial extracellular matrix, another route by which it can be harmful for cardiac structure and function. Experimental studies with knock-out RVD mice have shown that the absence of vitamin D is associated with an increase in the expression and activity of myocardial matrix metalloproteinases (MMP), which results in myocardial remodeling, increased collagen deposition and greater fibrosis^{26,27}. Vitamin D modulates the regeneration of the extracellular matrix of the myocardium by acting on the expression of both matrix metalloproteinases (MMPs) that hydrolyse extracellular matrix (ECM) proteins and tissue inhibitors of metalloproteinases (TIMP). In knock-

out RVD mice, the unbalanced expression of MMP/TIMP was characterized by the positive regulation of the MMP-2 and MMP-9 negative metalloproteinases of TIMP-1 and TIMP-3. The imbalance between MMP and TIMP promoted the destruction of myocardial tissue and ventricular remodeling; All this is closely related to the complex processes of initiation and progression of diastolic and systolic HF²⁸. It should also be noted that certain inflammatory cytokines such as TNF- α are also an important regulator of MMP activity, and can contribute to this pathophysiological pathway²⁹.

Coronary artery disease is an important factor for the development of HF, and vitamin D deficiency has been associated with an increase in arteriosclerosis and calcification of the coronary arteries^{1,9,27,30}. This observation is consistent with the inverse objectified relationship between vitamin D levels and coronary artery calcification^{6,30,31}. It is documented that endothelial cells also express RVD, and that vitamin D increases nitric oxide activity *in vitro*³², improves vascular endothelial growth factor production³³ and reduces endothelial platelet aggregation³⁴. Finally, there is evidence that vitamin D deficiency may be an important regulatory factor of the cardiorenal system. As we have previously emphasized, the cardiovascular and renal system are closely related, so that alterations in the functioning of one can progressively deteriorate the other³⁴.

When there is a progression of cardiorenal syndrome, this also implies neurohormonal activation, mainly of the renin-angiotensin system and the sympathetic nervous system, and of inflammatory systemic mechanisms as described previously. This once again influences fibrosis and ventricular remodeling, hydroelectrolytic abnormalities, and cardiac and renal dysfunction; triggering a negative vicious circuit in response to deterioration of the cardiorenal system, with greater neurohormonal activation and inflammatory cytokines, resulting in greater systemic dysfunction.

In the population with chronic kidney disease (CKD), as in the population with HF, the prevalence of hypovitaminosis D is high, and has also been associated with an increased risk of cardiovascular events³⁴. A reduction in enzyme 1- α -hydroxylase activity and the depletion of vitamin D binding proteins to RVD secondary to proteinuria are responsible for patients with CKD having a vitamin D deficiency. Therefore, the close correlation of HF and chronic kidney disease highlights the importance of vitamin D in both pathologies and in the pathophysiology of cardiorenal syndrome.

PREVALENCE OF HYPOVITAMINOSIS D AND HEART FAILURE

Although there is no consensus on the optimal levels of vitamin D, the deficiency of this hormone is defined by most experts as a level of 25-hydroxy-cholecalciferol (25-HCC) below 20 ng/ml^{4,38-42}. To be more specific, according to the consensus uniformly accepted by scientific societies dedicated to bone mineral metabolism, patients are considered to have optimal levels of vitamin D when serum 25-HCC levels are above 30 ng/ml; between 29 and 20 ng/ml it is considered that there is an insufficiency; and below 20 ng/ml the existence of a deficiency is established, which would be severe with 25-HCC figures below 10 ng/ml^{38,41}. Likewise, the theory of the U-shaped relationship between vitamin D levels and any cause of mortality, cardiovascular disease, certain types of cancer, falls and fractures has emerged, and that

Table 1. Prevalence of vitamin D deficiency in heart failure (HF)

First author Year Type of study	Patients (n)	Inclusion criteria	Definition of hypovitaminosis	Average age (years) /women (%)	Prevalence
Gostman I <i>et al.</i> 2012 Prospective	3,009/46,825	Patients ≥45 years with HF vs. control population with 25-HCC measure	25-HCC <10 ng/ml	75.9±10.7/ 64.7/11.3	14.8 ng/ml/16.3ng/ml (28% versus 22%, p<0.00001). In HF group, only 8.8% had 25-HCC >30 ng/ml
Liu L <i>et al.</i> 2011 Prospective	548	HF NYHA II-IV	25-HCC <20 ng/ml	74/61	75% cohort
Kim DH <i>et al.</i> 2008 Cross	8,351	Adults with 25-HCC levels measured	25-HCC <30 ng/ml		74% of the general population. 89% of hypovitaminosis D in patients with HF and ACS
Zittermann <i>et al.</i> 2003 Cross	24/34/34	HF patients NYHA II-IV <50 years vs. ≥50 years vs. control without HF ≥50 years		38.9/64.1/68.9	Both groups with HF had decreased levels of 25-HCC and calcitriol (p<0.001). Reverse correlation of vitamin D levels with severity of HF (assessed by levels of Nt-proBNP)
Shane E <i>et al.</i> 1997 Cross	101	HF NYHA III-IV; transplant consideration	25-HCC ≤9 ng/ml	NE/22	17% of hypovitaminosis D in patients with 25-HCC ≤9 ng/ml and 26% with 1.25 (OH) ₂ D ≤15 pg/ml. Inverse correlation between severity of HF and vitamin D levels

NYHA: New York Heart Association scale; ACS: acute coronary syndrome; Nt-proBNP: N-terminal cerebral natriuretic propeptide; NE: not specified.

vitamin D poisoning is observed with serum levels 25-HCC >150 ng/ml⁴³. Clinical practice guidelines recommend that plasma vitamin D levels should not be routinely measured in the general population and should only be measured in patients from populations considered at risk for this hormone deficiency⁴⁴⁻⁴⁷.

In recent years it has been shown that vitamin D deficiency has probably been underestimated and is much more prevalent than had been recognized. A global prevalence of one billion individuals with deficit and insufficient vitamin D levels is estimated⁴² and it has been described that 40-80% of the adult population has a vitamin D deficit^{48,49}, being of special importance in women in Middle Eastern countries. Numerous risk factors for vitamin D deficiency have been described, such as age, skin hyperpigmentation, hospitalization in institutions, distant latitude of Ecuador, obesity, smoking, nephropathy, hepatopathy or certain drugs such as corticosteroids, phenytoin or phenobarbital⁴⁹. Of particular relevance is the global obesity epidemic in developed countries, which significantly influences the deficit of vi-

tamin D, given the kidnapping that occurs of this hormone in the adipose tissue⁴⁸.

It is also true that a vitamin D deficit has been observed in both the young and apparently healthy population⁵⁰, described in up to approximately 50% of young adults; even in studies carried out in areas with high exposure to sunlight such as the Canary Islands, Israel, Australia, Turkey, India or Lebanon, where 30-50% of children and adults have 25-HCC levels <20 ng/ml⁵¹⁻⁵³.

Likewise, data obtained from the National Health and Nutrition Examination Survey (NHANES) showed a prevalence of hypovitaminosis D of 74% in the general population, significantly increasing the prevalence to 89% when only patients with HF and coronary artery disease were considered. (odds ratio [OR]=3.52; 95% confidence interval [CI]: 1.58-7.84)⁵⁴. Another study, with similar characteristics in which 4,105 subjects from a general population with at least one determination of vitamin D were included, found that only 36% of this cohort had vitamin D levels within normal range. A higher prevalence of heart failure (90% relative and 9% abso-

Table 2. Vitamin D levels and risk of heart failure (HF)

First author Year Type of study	Patients (n)	Inclusion criteria	Average age (years) Sex F (%)	Follow-up	Results
Bansal N <i>et al.</i> 2014 Prospective	6,469	General population free of established CVD (Multi Ethnic Study of Atherosclerosis)	62 53	8.4 years	- Comparison between patients with PTH <65 and ≥65 pg/ml; the latter had 50% (95% CI: 3-20%) higher risk of incidence of HF and 5.3 g (95% CI: 2.6-7.9 g) plus left ventricular mass due to MRI - No association between HF and 25-HCC
Wannamethee SG <i>et al.</i> 2014 Prospective	3,713	General population aged 60-79 years with and without established CVD	68 0	13 years	-In patients with PTH >55.6 pg/ml, risk of de novo CI of 1.66 HR (95% CI: 1.30-2.1) - No association between 25-HCC, calcium or phosphorus levels with a risk of CI (HR=1.07; 95% CI: 0.67-1.71)
Kestenbaum B <i>et al.</i> 2011 Prospective	2,312	Healthy subjects ≥65 years	75 NI	14 years	- In patients with 25-HCC <15 ng/ml, risk greater than 29% (95% CI: 5-55% higher) of mortality from any cause. Every 10 ng/ml less than 25-HCC was associated with a 9% higher relative risk of mortality (95% CI: 2-17% higher) - In patients with PTH ≥65 pg/ml, a risk greater than 30% (95% CI: 6-61%) of incidence of HF
Pilz S <i>et al.</i> 2008 Prospective	3,299	Caucasian patients undergoing cardiac catheterization	63 NI	7.7 years	2.84 HR (95% CI: 1.20-6.74) for death by CI and 5.05 HR (95% CI: 2.13-11.97) for sudden death when comparing patients with severe hypovitaminosis D (25-HCC <10 ng/ml <i>versus</i> patients with optimal levels of vitamin D (25-HCC >30 ng/ml). Inverse correlation with 25-HCC and 1.25 (OH) 2D level levels, and Nt-proBNP (r=-0.190 and -0.255, respectively; p<0.001) and with LVEF (p<0.001)

CVD: cardiovascular disease; NMR: nuclear magnetic resonance; NI: not indicated; HR: hazard ratio; CI: confidence interval; Nt-proBNP: N-terminal cerebral natriuretic propeptide; LVEF: left ventricular ejection fraction

lute) was observed in subjects with vitamin D levels ≤15 ng/ml, and in a follow-up of 1.3±1.2 years of a population over 50 years an incidence of new cases of HF was observed in 2.5% of this cohort. In this study, plasma vitamin D levels was found to have an inverse correlation with HF risk, and the adjusted risk values for HF were 2.01 and 1.3 for values between 16-30 ng/ml. and ≤15 ng/ml, respectively⁷.

A high prevalence of vitamin D deficiency has also been demonstrated in patients with HF evaluated for heart transplantation, as well as its inverse correlation between serum levels of vitamin D and the severity of HF⁵⁵. This relationship has also been objectified by other groups using controls without heart failure⁵⁶ even in

younger patients, which suggests that there is an association between HF and vitamin D deficiency that is independent of age.

Therefore, although there is a high prevalence of hypovitaminosis D in the apparently healthy general population, this deficit seems to be more marked in the population with HF (Tables 1, 2 and 3).

RELATIONSHIP BETWEEN VITAMIN D AND HEART FAILURE

HF is a disease with a high socio-sanitary impact, so a special effort has been made in predicting the risk of developing HF and identifying that population at risk in which a more active primary prevention should be emphasized. Therefore, and given the high morbidity and

Table 3. Prognostic impact of vitamin D deficiency in patients with heart failure (HF)

First author Year Type of study	Patients (n)	Inclusion criteria	Follow-up	Levels of vitamin D	Results
Gruson D <i>et al.</i> 2015 Prospective	170	HF NYHA II-IV with LVEF \leq 35%	4.1 years	NE	- Inverse correlation of levels of 1.25 (OH) $_2$ D with the severity of CI (mean values: NYHA II: 33.3 pg/ml, NYHA III: 23.4 pg/ml, NYHA IV: 14.0 pg/ml; $p < 0.001$) - 1.25 (OH) $_2$ D and its ratio to PTH (1-84) independent predictor of cardiovascular mortality in HF
Gostman I <i>et al.</i> 2012 Prospective	3,009 with HF /46,825 control	Patients \geq 45 years with HF vs. control population with 25-HCC measure	518 days	25-HCC <10 ng/ml	- Higher mortality in patients with HF (HR=1.52; 95% CI: 1.21-1.92; $p < 0.001$) - Reduction of mortality in patients who received vitamin D supplementation (HR 0.68; 95% CI: 0.54-0.85; $p < 0.0001$)
Liu L <i>et al.</i> 2011 Prospective	548	HF NYHA II-IV hospitalized	18 months	NE	- For every 4 ng/ml decrease in 25-HCC, increased risk of death due to combined final objective of death from any cause or heart failure and rehospitalization (HR=1.09; 95% CI: 1.00-1.16) and higher mortality from any cause (HR=1.10; 95% CI: 1.00-1.22) - No significant effect on HF rehospitalization

NYHA: New York Heart Association scale; LVEF: left ventricular ejection fraction; HR: hazard ratio; CI: confidence interval; NE: not specified.

mortality of HF, it is interesting to find prognostic markers in this pathology that can predict mortality. In this regard, attempts have also been made to confirm the association between vitamin D levels and the risk of HF and adverse events through longitudinal studies.

Vitamin D has been associated with the development of HF and as an independent prognostic factor for HF mortality and sudden death in a prospective study of 3,299 Caucasian patients undergoing cardiac catheterization, with a follow-up of 7.7 years on average. When patients with severe hypovitaminosis D (25HCC <10 ng/ml) were compared with patients with optimal levels of vitamin D (25-HCC >30 ng/ml), a hazard ratio (HR) of 2.84 (CI) was obtained. 95%: 1.20-6.74) for death due to HF and 5.05 (95% CI: 2.13-11.97) for sudden death. There was also an inverse correlation between levels of N-terminal cerebral natriuretic propeptide (Nt-proBNP) and serum vitamin D levels, and an inverse association with the NYHA functional class (New York Heart Association)⁵⁷. These findings have also been subsequently corroborated in a study of 2,312 healthy subjects over 65 years of age, where it was observed that patients with 25-HCC <15 ng/ml had a risk greater than 29% (95% CI: 5-55% higher) of mortality from any cause, and that for every 10 ng/ml that decreased 25-HCC increased the relative risk of mortality by 9% (95% CI: 2-17%)²⁰.

To date, data that relate vitamin D levels to the risk of

developing HF are discrepant. On the one hand, an unequivocal association of vitamin D levels with the incidence of HF has not been objectified, but on the other, its association with PTH levels^{20,58,59} has been objectified. Thus, in a study of 6,469 people from a general population free of established cardiovascular disease, with a mean follow-up of 8.4 years, after comparing patients with PTH levels <65 pg/ml and PTH \geq 65 pg/ml, the latter had a 50% (95% CI: 3-20%) of greater risk of incidence of CI and 5.3 g (95% CI: 2.6-7.9 g) more left ventricular mass determined by RNM⁵⁸. Likewise, in a cohort of 3,713 men between 60-79 years with and without cardiovascular disease, it was observed that in patients with PTH levels >55.6 pg/ml, there was an increased risk of de novo HF (HR=1, 66; 95% CI: 1.30-2.1)⁵⁹. These findings were previously demonstrated by Kestenbaum et al. in a study of 2,312 healthy subjects \geq 65 years of age, in which, after a follow-up of 14 years, they observed that patients with PTH \geq 65 pg/ml had a greater risk of 30% (95% CI: 6-61%) of incidence of HF²⁰.

This is interesting given that high levels of PTH generally identify patients with low levels of vitamin D, and the relationship between hypovitaminosis D and PTH levels with HF can be confused. In fact, the progressive deterioration of renal function, physical inactivity, as well as the reduction of calcium absorption, are both causes and consequences of hypovitaminosis D, which in turn

are associated with an increase in PTH levels. Therefore, in the light of the studies previously exposed, it can be extrapolated that it has been shown that there is an independent association of heart failure risk in patients with low vitamin D levels or elevated PTH levels. This is interesting, as some authors consider that it is the levels of PTH that predict cardiovascular disease⁶⁰.

Finally, several studies have been published in recent years in which not only a high prevalence of vitamin D deficiency has been observed in patients with HF, but vitamin D has also been linked as a marker of more severe disease and higher rate of adverse events in patients with heart failure. An inverse relationship between 25-HCC levels and B natriuretic peptide (BNP) levels has been observed in patients with HF^{20,54}, as well as ventricular function⁶¹, reporting as an independent marker of hospitalization due to HF and mortality²⁰.

However, there is also the theory that vitamin D deficiency in patients with HF occurs because these patients have a worse functional class, are weaker and, therefore, have a more sedentary lifestyle, so they have less exposure to sunlight, which conditions a lower production of vitamin D in the skin and lower concentrations of vitamin D⁶². This is called into question in different studies in which, after a multivariate analysis with the quantification of physical activity, an association between vitamin D levels and ventricular dysfunction and mortality due to HF is still observed⁵⁶.

Finally, it is also interesting to comment on the strong association that has been reported among patients with atrial fibrillation and HF (since atrial fibrillation is an important trigger for exacerbation of HF and therapeutic failure) in an observational study in which 180 patients were included. separated into two groups, based on whether they were in sinus rhythm or permanent atrial fibrillation⁵⁶. In the atrial fibrillation group it was observed that plasma levels of vitamin D were significantly lower (11.05 ng/ml *versus* 20 ng/ml; $p < 0.001$), PTH levels were significantly higher (76.7 *versus* 55 pg/ml; $p < 0.001$), and the atrial size was significantly larger (45.03 mm/m² *versus* 42.05 mm/m²; $p < 0.01$) than in the sinus rhythm group. Vitamin D levels (OR=0.854; 95% CI: 0.805-0.907; $p < 0.001$) and atrial size/body surface area (OR=1.077; 95% CI: 1.003-1.156; p were found to be independent predictors of atrial fibrillation < 0.05). In this study, the level of vitamin D was established as a predictive cut-off point for atrial fibrillation at 16.50 ng/ml (76.0% sensitivity and 65.5% specificity, area under curve -AUC- =0.75; 95% CI: 0.67-0.82).

In conclusion, there is experimental and clinical evidence that demonstrates plausible pathophysiological mechanisms and a direct and indirect association between vitamin D with HF and the cardiovascular system. Vitamin D deficiency is very high in patients with HF and could be associated with the prognosis of these patients^{4,6,8,10,17,19,20,24,30,31,35-37}.



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