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Vitamin D Deficiency in Patients Hospitalized for Heart Failure Living in the Tropics

Lucian Batista de Oliveira (ID), MD, MSc[1],
Mariana Andrade de Figueiredo Martins Siqueira (ID), MD[1],
Rafael Buarque de Macedo Gadêlha (ID), MD[2], Jessica Garcia (ID), MD, MSc[2], and
Francisco Bandeira (ID), MD, PhD[1]

[1]Division of Endocrinology and Diabetes, Agamenon Magalhães Hospital, University of Pernambuco (UPE), Faculty of Medical Sciences, Recife, PE, Brazil
[2]Division of Cardiology, Agamenon Magalhães Hospital, University of Pernambuco (UPE), Faculty of Medical Sciences, Recife, PE, Brazil

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Correspondence to
Lucian Batista de Oliveira, MD, MSc
Division of Endocrinology and Diabetes, Agamenon Magalhães Hospital, University of Pernambuco (UPE), Faculty of Medical Sciences, Estrada do Arraial Street, 2723 – Casa Amarela, PE 52070-230, Brazil.
Email: lucian.batista@upe.br

ABSTRACT

Background and Objectives: Vitamin D, as a steroid hormone, has multiple effects on human body and its deficiency has been associated with an increased risk of heart failure (HF) and unfavorable outcomes. The present study investigated the prevalence of vitamin D deficiency (VDD) and its relationship with cardiometabolic parameters in patients hospitalized for HF living in the city of Recife (latitude 8° South).

Methods: Analytical cross-sectional study, with men and women aged 40–64 years. The HF group was recruited during hospitalization due to decompensation. A matched control group was recruited from the general endocrine clinics. Vitamin D status was assessed by measuring serum 25-hydroxyvitamin D (25OHD), considering deficiency when 25OHD <20 ng/mL (<50 nmol/L).

Results: A total of 243 patients were evaluated (HF group: 161, control group: 82). Lower serum 25OHD levels were observed in the HF group (25.2±9.4 vs. 30.0±7.7ng/mL; p<0.001), as well as a higher prevalence of VDD (27.3% vs. 9.8%; prevalence ratio, 2.80; 95% confidence interval, 1.38–5.67; p=0.002). In patients with HF, VDD was associated with diabetes mellitus (65.9% vs. 41.0%; p=0.005) and female sex (65.9% vs. 44.4%; p=0.015). In the subgroup with VDD, higher values of hemoglobin A1c (7.9% [6.0–8.9] vs. 6.2% [5.7–7.9]; p=0.006) and dyslipidemia were also observed.

Conclusions: We found higher rates of VDD in patients hospitalized for HF and this was associated with deleterious laboratory metabolic parameters.

Keywords: Heart failure; Vitamin D; Vitamin D deficiency; Lipids; Diabetes mellitus

INTRODUCTION

Vitamin D has multisystemic effects, at both genomic and non-genomic levels.[1,2] With its role recognized in the context of bone health since the beginning of the 20th century, based on evidence on the pathogenesis of rickets, the observation of its ubiquitous activity led to the development of studies that assess its importance in non-skeletal health, including its potential role on cardiovascular diseases.[1,3-5]

Dietary sources of vitamin D are scarce for most people around the world, therefore cutaneous synthesis is the main way to obtain it naturally.[1] Ultraviolet B irradiation converts the substrate 7-dehydrocholesterol, present in the skin, into pre-vitamin D3.[1,2] In tropical regions, sufficient sun exposure is able to provide vitamin D synthesis throughout the year, while in high latitude regions cutaneous synthesis of vitamin D may be markedly decrease during the winter months.[6,7] However, there are other factors that influence the capacity for endogenous synthesis and activation of vitamin D, such as genetic polymorphisms, skin phototypes, lifestyle and age.[1,6,7] Even in individuals with high sun exposure and living in tropical regions, high prevalence of vitamin D deficiency (VDD) has already been observed, with an association with some parameters of cardiometabolic risk.[8] In the context of heart failure (HF), some data indicates that low serum levels of vitamin D imply a greater risk of the disease, as well as of ventricular remodeling and the association of unfavorable outcomes.[5,9]

Considering the relevance of HF in the context of public health and the numerous factors that may contribute to its emergence and prognosis, as well as the multisystemic actions of vitamin D and the gaps that still exist regarding its role in cardiovascular health, the objective of the present study was to evaluate the prevalence of VDD and its relationship with clinical cardiometabolic, echocardiographic and laboratory parameters in middle-aged patients with HF living in a low-latitude tropical region (8° South).

METHODS

Study population and variables

An analytical cross-sectional study, with men and women aged 40 to 64 years, consecutively selected in a tertiary hospital, located in a Brazilian city with latitude of 8° south. Patients with HF, hospitalized during the data collection period (July 2021 to October 2022), who had a previously confirmed diagnosis of the disease (by clinical, laboratory and echocardiographic parameters) and who were admitted due to decompensation, were included. The exclusion criteria were as follows: individuals with a diagnosis of genetic diseases of bone metabolism or lipodystrophies, who were using vitamin D supplementation, with a history of alcoholism or currently smoking, with severe liver or kidney diseases, with decompensated thyroid dysfunctions, in chronic use of glucocorticoids, with active malignant neoplasms (except non-melanoma skin cancer), with major depression, or with physical or cognitive limitations that prevented them from participating in the study.

Data was obtained through a primary (direct approach to the patient) and secondary (information contained in the medical record) data source.

The patients underwent a complete physical examination, fasting blood analysis and echocardiogram. Abdominal circumference was measured in a standardized way, using a flexible and inelastic millimeter measuring tape. Handgrip strength (HGS) was obtained using a digital dynamometer (Instrutherm, São Paulo, SP, Brazil), taking into consideration the best result of three different measurements with the dominant hand. Biochemical tests were measured using a Cobas® e 601 analyzer (Roche, Basel, Switzerland), with serum 25-hydroxyvitamin D (25OHD) and parathyroid hormone (PTH) were obtained by chemiluminescence.

We considered VDD if serum 25OHD <20 ng/mL (<50 nmol/L), insufficiency between 20–30 ng/mL (50–75 nmol/L) and sufficiency if 25OHD ≥30 ng/mL (≥75 nmol/L).[10] The other categorical variables included sex, presence of diabetes mellitus (DM), left ventricular ejection fraction (LVEF) classification (HF with preserved ejection fraction when LVEF ≥50%, HF with mildly reduced ejection fraction when LVEF 41–49%, HF with reduced ejection fraction when LVEF ≤40%),[11] New York Heart Association functional classification (NYHA-FC) of HF (I–II or III–IV),[11] presence of coronary ischemia, HGS classification (reduced if <16 kg in women or <27 kg in men, according to the European Consensus on Sarcopenia),[12] history of smoking, history of alcohol consumption and chronic statin use. The quantitative variables evaluated were age, body mass index (BMI), hemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR, according to the Chronic Kidney Disease Epidemiology Collaboration formula),[13] sérum PTH, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, waist-to-height ratio and LVEF.

A control group of individuals without HF and who did not use vitamin D supplementation was selected from the endocrine outpatient clinics of the same institution, for comparison with the HF group regarding 25OHD levels and the prevalence of VDD. Groups were matched for sex, age and BMI. The control group was not evaluated for other metabolic and laboratory parameters.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences® version 21 software (IBM Corp., Armonk, NY, USA).

Qualitative variables were presented using frequencies and proportions and compared using Pearson's chi-square test.

Quantitative variables were evaluated for distribution normality using the Kolmogorov-Smirnov test. Those with normal distribution were expressed as mean ± standard deviation and compared using Student's t-test (parametric). Those that did not have a normal distribution were expressed using medians and the interquartile range and compared using the Mann-Whitney U test (non-parametric).

In all tests, 95% confidence intervals (CIs) were used, rejecting the null hypothesis of equality and considering statistical significance when p value <0.05.

Ethical considerations

This study was approved by the ethics committee of the institution where it was carried out (submission certificate of ethical appreciation number 47175121.4.0000.5197) and participants provided a written informed consent form.

RESULTS

A total of 243 patients were studied, 161 with HF and 82 in the control group (**Table 1**). There were no statistically significant differences between the groups regarding age, sex and BMI. Patients with HF had lower serum 25OHD levels than controls (25.2±9.4 vs. 30.0±7.7ng/mL; p<0.001).

Patients with HF had a higher prevalence of VDD compared to the control group (27.3% vs. 9.8%; prevalence ratio [PR], 2,80; 95% CI, 1.38–5.67; p=0.002), as presented in **Figure 1**. Vitamin D insufficiency (serum 25OHD 20–30 ng/mL) was found in 44.7% of patients with HF, and 28% presenting with serum 25OHD above 30 ng/mL.

Analysis of subgroups with and without VDD among individuals with HF

Tables 2 and **3** detail the metabolic parameters evaluated in patients with HF, comparing the subgroups with and without VDD.

Figure 1. Prevalence of vitamin D deficiency in HF patients and controls. The bar chart shows the percentages of vitamin D deficiency in the HF and control groups, in addition to illustrating the PR and 95% CI.
25OHD = 25-hydroxyvitamin D; CI = confidence interval; PR = prevalence ratio.
*Pearson's chi-square test.

VDD was associated with female sex (65.9% vs. 44.4%; p=0.015) and diabetes mellitus (65.9% vs. 41.0%, p=0.005). There were no differences between the groups with and without VDD regarding NYHA-FC (p=0.571), classification of LVEF (p=0.860) or presence of coronary ischemia (p=0.986). Likewise, there were no associations between VDD with reduced HGS (p=0.368), statin use (p=0.680) or with a history of smoking (p=0.687) or ethanol ingestion (p=0.161) (**Table 2**).

Table 1. General characteristics of the study patients

Characteristic	HF (n=161)	Controls (n=82)	p value
Sex			0.393*
Male	80 (49.7)	36 (43.9)	
Female	81 (50.3)	46 (56.1)	
Age (years)	57.0 (51.0–61.0)	55.0 (49.8–60.0)	0.126†
BMI (kg/m²)	27.5 (23.6–30.9)	28.3 (24.9–31.4)	0.078†
25OHD (ng/mL)	25.2±9.4	30.0±7.7	<0.001‡

Values are presented as median (interquartile range) or number (%). The p value results that demonstrate a statistically significant difference between the compared groups are highlighted in bold.
BMI = body mass index; 25OHD = 25-hydroxyvitamin D; HF = heart failure.
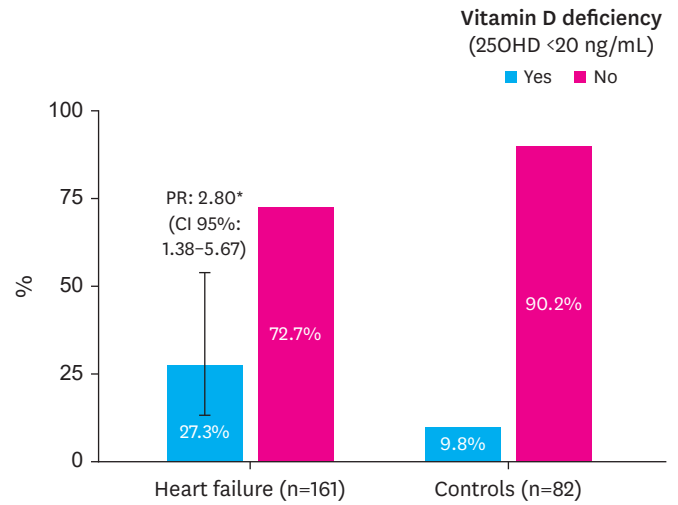*Pearson's chi-square test; †Mann-Whitney U test; ‡Student's t-test.

Table 2. Characteristics of heart failure patients with or without vitamin D deficiency (comparison of categorical variables)

Characteristic	HF (n=161)	Vitamin D deficiency (<20 ng/mL)		p value
		Yes (n=44)	No (n=117)	
Sex				**0.015***
Male	80 (49.7)	15 (34.1)	65 (55.6)	
Female	81 (50.3)	29 (65.9)	52 (44.4)	
Diabetes	77 (47.8)	29 (65.9)	48 (41.0)	**0.005***
LVEF classification				0.860*
Reduced	61 (37.9)	18 (40.9)	43 (36.8)	
Mildly reduced	25 (15.5)	6 (13.6)	19 (16.2)	
Preserved	75 (56.6)	20 (45.5)	55 (47.0)	
NYHA-FC				0.571*
I–II	68 (42.2)	17 (38.6)	51 (43.6)	
III–IV	93 (57.8)	27 (61.4)	66 (56.4)	
Ischemic HF	88 (54.7)	24 (54.5)	64 (54.7)	0.986*
Reduced HGS	97 (60.2)	29 (65.9)	68 (58.1)	0.368*
History of smoking	70 (43.5)	18 (40.9)	52 (44.4)	0.687*
Alcohol ingestion	84 (52.2)	19 (43.2)	65 (55.6)	0.161*
Statin use	102 (63.4)	29 (65.9)	73 (62.4)	0.680*

Values are presented as number (%). The p value results that demonstrate a statistically significant difference between the compared groups are highlighted in bold.
HF = heart failure; LVEF = left ventricular ejection fraction; NYHA-FC = New York Heart Association functional classification; HGS = handgrip strength.
*Pearson's chi-square test.

Table 3. Comparison of quantitative data from heart failure patients with or without vitamin D deficiency

Characteristic	HF (n=161)	Vitamin D deficiency (< 20 ng/mL)		p value
		Yes (n=44)	No (n=117)	
Age (years)	57.0 (51.0–61.0)	58.0 (53.0–60.0)	57.0 (50.5–61.0)	0.519[†]
BMI (kg/m²)	27.5 (23.6–30.9)	27.1 (24.3–31.2)	26.4 (23.0–30.6)	0.471[†]
HbA1c (%)	6.3 (5.8–8.3)	7.9 (6.0–8.9)	6.2 (5.7–7.9)	**0.006[†]**
eGFR (mL/min/1.73m²)	72.9±26.5	65.6±29.5	75.7±24.9	**0.031[*]**
PTH (pg/mL)	31.8 (22.6–52.5)	46.8 (29.8–68.9)	28.6 (21.3–44.7)	**<0.001[†]**
Total colesterol (mg/dL)	164.2±46.8	178.9±46.3	158.8±46.0	**0.015[*]**
HDL-colesterol (mg/dL)	36.6±12.6	38.3±16.6	36.0±10.9	0.391[*]
LDL-colesterol (mg/dL)	98.0 (71.0–125.6)	105.0 (76.0–140.0)	95.4 (70.1–120.0)	0.064[†]
Triglycerides (mg/dL)	119 (82–161.5)	116.0 (70.5–161.8)	119.0 (82.0–163.0)	0.863[†]
Waist-to-height ratio	0.61±0.09	0.61±0.09	0.61±0.09	0.965[*]
LVEF (%)	47.0 (34.0–60.0)	46.5 (34.0–58.0)	48.0 (34.0–60.5)	0.733[†]

Values given are the median (interquartile range) or mean±standard deviation. The p value results that demonstrate a statistically significant difference between the compared groups are highlighted in bold.
BMI = body mass index; HbA1c = hemoglobin A1c; eGFR = estimated glomerular filtration rate; PTH = parathyroid hormone; HDL = high density lipoprotein; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; HF = heart failure.
[*]Student's t-test; [†]Mann–Whitney U test.

Table 4. Comparison between subgroups with heart failure who had vitamin D deficiency vs. sufficiency

Characteristic	Valid sample (n=89)	Vitamin D status		p value
		Deficiency (<20 ng/mL) (n=44)	Sufficiency (>30 ng/mL) (n=45)	
Age (years)	58.0 (53.0–61.0)	58.0 (53.0–60.0)	57.0 (50.5–61.5)	0.773[†]
BMI (kg/m²)	26.7 (23.6–30.8)	27.1 (24.3–31.2)	25.2 (22.7–30.4)	0.350[†]
HbA1c (%)	6.4 (5.8–8.4)	7.9 (6.0–8.9)	6.1 (5.7–6.5)	**0.002[†]**
eGFR (mL/min/1.73m²)	67.7±28.0	65.6±29.5	69.7±26.6	0.490[*]
PTH (pg/mL)	34.9 (23.9–62.9)	46.8 (29.8–68.9)	28.4 (20.0–49.5)	**0.003[†]**
Total colesterol (mg/dL)	178.9±46.3	178.9±46.3	141.7±39.7	**<0.001[*]**
HDL-colesterol (mg/dL)	35.8±14.1	38.3±16.6	33.4±10.9	0.100[*]
LDL-colesterol (mg/dL)	94.2 (71.0–121.4)	105.0 (76.0–140.0)	84.0 (68.3–104.6)	**0.007[†]**
Triglycerides (mg/dL)	112.0 (77.0–157.0)	116.0 (70.5–161.8)	112.0 (78.0–140.0)	0.463[†]
Waist-to-height ratio	0.60±0.09	0.61±0.09	0.60±0.08	0.679[*]
LVEF (%)	46.0 (34.0–60.5)	46.5 (34.0–58.0)	43.0 (30.5–61.5)	0.967[†]

Values given are the median (interquartile range) or mean±standard deviation. The p value results that demonstrate a statistically significant difference between the compared groups are highlighted in bold.
BMI = body mass index; HbA1c = hemoglobin A1c; eGFR = estimated glomerular filtration rate; PTH = parathyroid hormone; HDL = high density lipoprotein; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction.
[*]Student's t-test; [†]Mann–Whitney U test.

There was a statistically significant association between VDD and higher blood levels of HbA1c (7.9% [6.0–8.9] vs. 6.2% [5.7–7.9]; p=0.006), total cholesterol (178.9±46.3 mg/dL vs. 158.8±46.0 mg/dL; p=0.015) and PTH (46.8 pg/mL [29.8–68.9] vs. 28.6 pg/mL [21.3–44.7]; p<0.001), as well as with lower eGFR means (65.6±29.5 mL/min/1.73 m² vs. 75.7±24.9 mL/min/1.73 m²; p=0.031). There was no association between VDD and age (p=0.519), BMI (p=0.471), HDL-cholesterol (p=0.391), triglycerides (p=0.863), LVEF (p=0.733) or waist-height ratio (p=0.965), with a trend towards an association between this hormone deficiency and higher levels of LDL-cholesterol (p=0.064) (**Table 3**).

When comparing patients with vitamin D sufficiency (25OHD ≥30 ng/mL) with those with VDD (25OHD <20 ng/mL), the continuity of the statistically significant association between lower mean eGFR and VDD was not observed (p=0.490), as shown in **Table 4**. Regarding lipid parameters, the comparison of these two subgroups showed an association between higher levels of LDL-cholesterol and VDD (105.0 mg/dL [76.0–140.0] vs. 84.0 mg/dL [68.3–104.6]; p=0.007) (**Figure 2**).
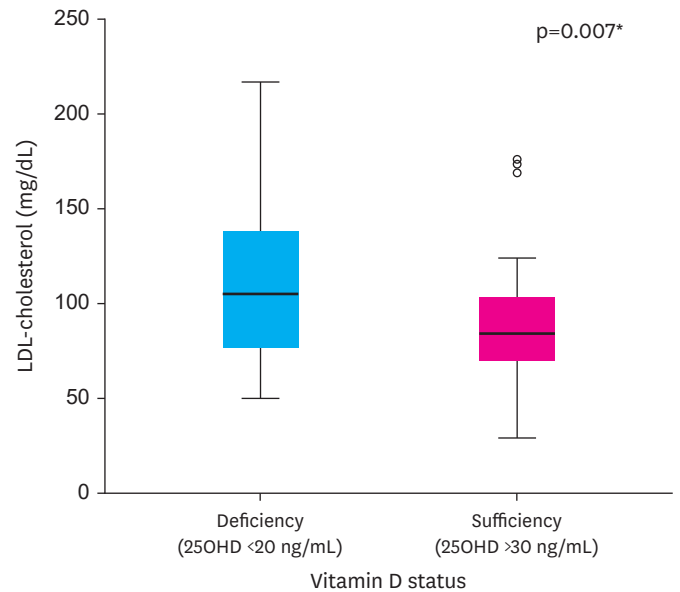

Figure 2. Comparison of LDL-cholesterol rates between patients with vitamin D deficiency and sufficiency. Boxplot illustrating the comparison between subgroups of patients with heart failure who have vitamin D deficiency and sufficiency. Boxes extend from the first to the third quartiles. The horizontal lines inside the boxes represent the median. Vertical lines represent maximum and minimum values within the interquartile range of 1.5. The spheres represent outliers. There was a statistically significant difference between the LDL-cholesterol rates of the two subgroups (p=0.007).
25OHD = 25-hydroxyvitamin D; LDL = low density lipoprotein.
[*]Mann-Whitney U test.

DISCUSSION

Our findings demonstrated a higher frequency of VDD in patients with HF who live in a low-latitude region, being associated with higher glycemic levels and lipid alterations.

Data from different populations shows high prevalence of VDD around the world.[14-16] In temperate regions, the frequency of VDD can double in winter, when compared to the summer months.[15] In Brazil, a country with a tropical climate in most of its territory, a study with 2,264 individuals aged 50 years or more showed a prevalence of VDD of 16%, with lower serum 25OHD observed in regions of higher latitudes.[16] There is, however, a great heterogeneity between the existing epidemiological data in Brazil, evidenced by the different target populations of these studies.[17] Our study demonstrated that HF was associated with higher prevalence of VDD in patients living in the city of Recife (latitude 8º South). One of the possible explanations for the lower levels of vitamin D in patients with HF is the lower sun exposure in outdoor activities,[18] as a result of the loss of functionality.

Despite the scarcity of data, current literature supports that VDD can contribute to the pathophysiology of HF. The vitamin D receptor is expressed in the cardiovascular system, with preclinical studies indicating that calcitriol—the active form of vitamin D—is capable of inhibiting cardiomyocyte hypertrophy and proliferation, reducing the release of natriuretic peptides and optimizing calcium uptake and myocardial contractility, decreasing filling pressures.[15,19] Regarding epidemiological data, a Mendelian randomization study pointed out that higher levels of 25OHD may be responsible for reducing the risk of HF.[20] A meta-analysis of randomized clinical trials, encompassing a total of 465 patients (235 exposed to vitamin D and 230 controls), demonstrated that vitamin D supplementation can improve cardiac function in patients with HF, decreasing end-diastolic diameter and increasing LVEF.[9] Our study found no association between VDD and HF parameters (NYHA-FC, LVEF or ischemic etiology). However, our analysis was limited to patients hospitalized due to chronic HF decompensation, where there may be acute changes in symptoms and ejection fraction due to hospital management.

The hyperactivation of the renin-angiotensin-aldosterone system, one of the main pathophysiological mechanisms of HF, enhances the urinary and fecal excretion of calcium and magnesium, contributing to PTH elevations in individuals with this cardiac condition. PTH levels also seem to increase by the action of aldosterone on mineralocorticoid receptors present in the parathyroids.[21,22] In this context, there are also two causes of secondary hyperparathyroidism, common in patients with HF: VDD and CKD.[21] Corroborating these mechanisms, our study found an association between VDD and higher levels of PTH and lower eGFR. Likewise, a meta-analysis by Xing et al.,[18] who evaluated bone health in patients with HF, observed significantly lower serum 25OHD levels in patients with HF, in addition to markedly increased serum PTH.

Previous studies have shown an association between VDD and dyslipidemia, especially higher levels of total cholesterol, LDL-cholesterol and triglycerides, but not with significant changes in HDL-cholesterol.[23,24] This corroborates our findings, except for triglyceride values (for which there was no statistically significant difference between patients with or without VDD). In this scenario, vitamin D supplementation has been shown to have beneficial effects in serum lipid parameters, as shown by a systematic review and meta-analysis.[24]

Similarly, relationships between VDD and the presence of DM or worse glycemic control have also been observed in different scenarios,[25,26] which is in line with our findings. As for the role of vitamin D supplementation in diabetes control, data in the literature are conflicting.[27,28] A meta-analysis of 24 studies with 1,528 individuals indicated that supplementation was able to reduce fasting glycemia, insulin resistance and HbA1c.[27] On the other hand, a systematic review and meta-analysis with 20 studies and 2,703 participants pointed out that such supplementation was effective only in reducing insulin resistance, without significant reduction in HbA1c and fasting glycemia.[28]

We found no associations between VDD and BMI or abdominal obesity, as demonstrated in population-based studies.[29,30] This lack of association may be linked to changes in body composition caused by HF, with regard to edemigenesis and lean, bone and fat mass.[11,12,21]

As limitations of the present study we highlight its cross-sectional design, since a longitudinal evaluation would allow demonstrating how changes in serum 25OHD levels could impact cardiometabolic parameters linked to HF. We also did not assess HGS and other laboratory metabolic parameters in the control group. The main strengths of this study refer to the lack of data on the prevalence of VDD in patients with HF, especially during decompensation requiring hospitalization, as well as the fact that it was conducted in individuals who live with abundant sunlight availability.

In conclusion, we found higher rates of VDD in patients hospitalized with HF and this was associated with deleterious laboratory metabolic parameters.

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ORCID iDs
Lucian Batista de Oliveira
https://orcid.org/0000-0002-6930-0664
Mariana Andrade de Figueiredo Martins Siqueira
https://orcid.org/0000-0002-7774-9269
Rafael Buarque de Macedo Gadêlha
https://orcid.org/0000-0001-5149-3990
Jessica Garcia
https://orcid.org/0000-0002-4067-9527
Francisco Bandeira
https://orcid.org/0000-0003-0290-0742

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: de Oliveira LB, de Figueiredo Martins Siqueira MA, Garcia J, Bandeira F; Data curation: de Oliveira LB, de Figueiredo Martins Siqueira MA, de Macedo Gadêlha RB; Formal analysis: de Oliveira LB, Garcia J, Bandeira F; Funding acquisition: de Oliveira LB, de Figueiredo Martins Siqueira MA, de Macedo Gadêlha RB, Garcia J, Bandeira F; Investigation: de Oliveira LB, de Figueiredo Martins Siqueira MA, de Macedo Gadêlha RB, Bandeira F; Methodology: de Oliveira LB, Garcia J, Bandeira F; Project administration: de Oliveira LB, Bandeira F; Resources: de Oliveira LB, de Figueiredo Martins Siqueira MA, de Macedo Gadêlha RB, Bandeira F; Software: de Oliveira LB, Bandeira F; Supervision: de Oliveira LB, Bandeira F; Validation: de Oliveira LB, Garcia J, Bandeira F; Visualization: de Oliveira LB, de Figueiredo Martins Siqueira MA, de Macedo Gadêlha RB, Bandeira F; Writing - original draft: de Oliveira LB, de Figueiredo Martins Siqueira MA, de Macedo Gadêlha RB, Garcia J; Writing - review & editing: de Oliveira LB, Bandeira F.

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