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Serum Vitamin D Levels, Disease Activity Score-28 for Rheumatoid Arthritis with C-Reactive Protein (DAS28-CRP), and Cardiac Remodeling Determined by Ventricular Dimensions and Left Atrium Diameter in Patients with Rheumatoid Arthritis: A Prospective Observational Study

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Background: Rheumatoid arthritis (RA) can cause extra-articular manifestations, and the myocardium can be a target. This study aimed to describe structural and functional cardiac echocardiographic variables in RA patients and to evaluate whether vitamin D (VD) levels and inflammation markers, evaluated by Disease Activity Score-28 for Rheumatoid Arthritis with C-reactive protein (DAS28-CRP), are associated with cardiac remodeling (CR) in this population.


Material/Methods: This prospective observational study evaluated 90 patients with RA in Botucatu University Hospital wards from 2014 to 2017. Clinical data were recorded, including demographic information, comorbidities, length of disease, and treatment type. Serum VD and C-reactive protein levels were measured, and the DAS28-CRP was calculated. A transthoracic echocardiography study was performed. The outcome evaluated was CR. This parameter was assessed by left ventricular geometric patterns and left atrium diameter.

Results: We evaluated 90 RA patients. The mean age was 52.9 ± 10.8 years, and 17.8% were male. The length of the disease was 96 (60-180) months. Serum VD levels were 30.7 ± 10.4 ng/mL and the DAS28 was 2.7 ± 0.9 . Regarding the CR parameters, 56.7% had altered left ventricular geometric patterns and 25.8% had enlargement of left atrium diameter. Even in multivariate analysis, the left ventricular geometric patterns were not associated with the VD levels and the inflammation marker used. However, sufficient VD levels protect from left atrium enlargement (OR: 0.905; IC 95%: 0.843-0.973; $P=0.007$).

Conclusions: Low serum vitamin D values, but not inflammation, are associated with CR in patients with RA.

Keywords: 25-hydroxyvitamin D • Arthritis, Rheumatoid • Echocardiography • Heart Atria

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Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by joint destruction [1]. However, extra-articular manifestations are common and usually responsible for reducing RA patients' survival. Compared with the general population, RA patients have a 1.5-fold increase in mortality rate due to cardiovascular (CV) events [2]. The primary CV compromise is due to ischemic heart disease [3]. However, RA can also silently affect myocardial tissue independent of vascular disease [4]. The relationship between RA and cardiac structural changes suggests that some RA patients have the cardiac remodeling (CR) process [3-6]. Cardiac remodeling is characterized as molecular, cellular, and interstitial changes that manifest clinically as changes in size, mass, geometry, and function of the heart [5].

Some cardiac alterations that have been described in RA patients are left ventricular (LV) hypertrophy [6-8] and atrial dilatation [9]. Hypertrophy occurs through an increase in the mass of the LV. The evaluation of LV mass combined with the relative wall thickness (RWT) characterizes 4 geometric echocardiographic patterns: standard, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy. Although alterations in ventricular geometry may be clinically asymptomatic, they significantly enhance the risk of cardiac failure and death [10].

One of the potential mechanisms for cardiac structural changes in RA patients is the pro-inflammatory status [11]. Cytokines such as IL-6 and tumor necrosis factor (TNF)- α , known to exert crucial roles in RA, are associated with cardiac hypertrophy. IL-6 participates in the Janus kinases (JAK)/signal transducer and activator of transcription proteins (STAT) pathways of inflammation and cardiac hypertrophy signaling. In experimental studies, TNF- α induced cardiac hypertrophy and fibrosis, dilated cardiomyopathy, and cardiac dysfunction [3,6,11,12]. Importantly, inflammation is associated with RA activity. This activity can be measured by different parameters, including Disease Activity Score-28 for Rheumatoid Arthritis with C-reactive protein (DAS28-CRP) [13,14].

Another potential mechanism of cardiac alterations in RA is vitamin D (VD) deficiency. The role of vitamin D in cardiovascular disease (CVD) is an emerging topic. This nutrient has a well-described relationship with cardiac structure and function, but it still requires further clinical investigation [15,16].

Although the relationship between VD deficiency and inflammation with cardiac changes is already known, no study has yet evaluated the association between CR, VD status, and inflammation in RA patients. Therefore, this study aimed to describe structural and functional cardiac echocardiographic variables in rheumatoid arthritis patients and to evaluate whether

VD levels and inflammation (evaluated by DAS28-CRP score) are associated with CR in RA patients.

Material and Methods

Ethics Statement

The study was approved by the Ethics Committee of Botucatu Medical School, São Paulo State University, UNESP (protocol: 4135-2012). Written informed consent was obtained from all patients before their inclusion.

Study Design

This prospective observational study was conducted with patients diagnosed with RA and followed by the Rheumatology Service from Botucatu Medical School from 2014 until 2017. The sample size was calculated using the expected difference in the means of the LV mass index (LVMI) from RA and control patients, which was 8.6, and the standard deviation was 15.5 [8]. Considering $\alpha=0.05$ and the desired power of 80%, the estimated sample size was 53 patients. Considering the multiple factors that can influence CR patterns, the sample size was raised to 90 patients. All patients met the 2010 American College of Rheumatology/European League Against Rheumatism criteria for RA to be included [17]. The exclusion criteria were previous coronary artery disease, heart failure symptoms or signs, chest pain, non-sinus cardiac rhythm, and renal and liver failure history.

Vitamin D and C-Reactive Protein Evaluation

A baseline medical history was recorded, and a blood sample was collected. The following clinical variables were analyzed: age, gender, previous diseases, smoking status, RA activity, length of disease, and treatment. Blood samples were taken to determine the 25-hydroxyvitamin D levels by chemiluminescence method [18]; in our laboratory, the normal reference range is 9.5 to 55.5 ng/dL. C-reactive protein (CRP) was assessed using the dry chemistry method.

RA Activity Evaluation

Inflammation was evaluated by grade disease activity calculated by DAS28-CRP score [19]. DAS28-CRP was calculated using tender joint count, swollen joint count, the visual analog scale of the patient's global health, and CRP measurement. The DAS28 cut-off points were considered remission lower than 2.6, low disease activity between 2.6 and 3.2, moderate disease activity between 3.2 and 5.1, and high disease activity if higher than 5 [13,14].

Echocardiographic Evaluation

Cardiac structural and functional evaluation was performed by Doppler transthoracic echocardiogram. Exams were performed by the same researcher using General Electric (GE) Vivid S6 equipment, with a 2.0-3.5 MHz multifrequency ultrasonic transducer and image recording system [20].

Echocardiographic alterations describe various CR findings as previously described changes in size, mass, geometry, and function of the heart [5]. As dysfunction may not be present at early stages, we evaluated cardiac remodeling through morphological parameters, ventricular geometry, and LA dimension [5,21]. Regarding the geometry pattern, 4 types were defined based on LVMI and RWT. The normal value of LVMI was less or equal to 95 g/m² for women and 115 g/m² for men, and normal RWT was less or equal to 0.42. Thus, the 4 types are: normal, concentric remodeling if normal LVMI and high RWT, concentric hypertrophy if high LVMI and high RWT, and eccentric hypertrophy if high LVMI and normal RWT [20]. We used the LA diameter adjusted by body surface area, which was considered increased when its diameter was more than 2.3 cm/m² [22].

Statistical Analysis

All statistical analyses were performed with SigmaPlot software for Windows v12.0 (Systat Software, Inc., San Jose, CA, USA). Data are expressed as the percentage, mean values, standard deviation, or medians, with 25% and 75% percentiles, where appropriate. Comparisons between 2 groups for continuous variables were performed using the *t* test or the Mann-Whitney test. Comparisons between 2 groups for categorical variables were made using the chi-squared test or Fisher's exact test. Multiple logistic regression models were used to evaluate the independent interest variables (VD and DAS28-CRP) for each analyzed outcome adjusted by all factors, with *P*<0.10 in univariate analysis. *P* values lower than 0.05 were considered statistically significant.

Results

A total of 90 patients with RA were included. The mean age was 52.9±10.8 years, and 17.8% were male. Forty-five percent were hypertensive and 25% were smokers. The length of disease was 96 (60-180) months. Serum VD levels were 30.7±10.4 ng/ml, the DAS28-CRP was 2.7±0.9, and 48.9% of the patients received biological agents. Regarding the CR parameters, 56.7% had altered left ventricular geometric patterns and 25.8% had enlargement of left atrium diameter. Regarding types of LV geometric alterations distributions, 24.4% had concentric remodeling, 27.8% had concentric hypertrophy, and 4.4% had eccentric hypertrophy. Forty-five

percent had diastolic dysfunction, but systolic dysfunction was not observed (EF=69.8±2.6).

Geometric Pattern

Table 1 shows the association of demographic and echocardiographic variables with left ventricular geometric patterns (LVGP). The factors related to this outcome were age, arterial hypertension, and diastolic dysfunction. Echocardiographic parameters such as LVMI, LV diastolic diameter (LVDD), and RWT were significantly associated with geometric patterns. However, because these parameters are used to classify the type of geometric alteration, they were not used in the multiple logistic regression described in **Table 2**. As shown in **Table 2**, VD and DAS28-CRP had no association with the alteration of LVGP.

Left Atrium Enlargement

The association between demographic and echocardiographic variables with LA enlargement is shown in **Table 3**. The factors associated were VD level and LVMI. VD serum levels in patients with LA enlargement were 6 ng/mL smaller than in patients with normal atrial diameter. In multivariate analysis (**Table 4**), adjusted by all factors with *P* value <0.1 (age, smoking, and LVMI), the association between VD and LA diameter was maintained (OR: 0.905; IC 95%: 0.843-0.973; *P*=0.007).

Discussion

This study's initial objective was to describe the echocardiographic parameters in RA patients. Summarizing our finding, high-frequency alterations compatible with CR were observed. In our study, more than 50% of patients had altered ventricular geometry. Of those, more than 95% had concentric remodeling and concentric hypertrophy patterns. Ventricular geometry alteration, even asymptomatic, is a marker of progression to heart failure and death [5,23], reinforcing the importance of identifying preclinical echocardiographic alterations.

LA enlargement was found in 27% of our patients and can be considered an early sign of CR and diastolic dysfunction. A study of a cohort of more than 340 hypertensive patients showed that LA enlargement occurred before left ventricular enlargement and that LA measurement can be an early marker for heart failure [24].

Another study objective was to assess the possible correlation of CR findings with the inflammatory status of the patients (assessed by the DAS28-CRP score) and with serum concentrations of VD. Inflammatory status is important because inflammation is an essential mechanistic pathway in CR pathophysiology [25], and VD is an easily measured marker that is

Table 1. Demographic and echocardiographic data of 90 patients with rheumatoid arthritis according to altered geometry patterns.

Variable	Altered geometry patterns		P value
	Yes (n=51)	No (n=39)	
Age (years)	55.4 (±10.2)	49.5 (±10.7)	0.009
Male, n (%)	10.0 (19.6)	6 (15.4)	0.809
Hypertension, n (%)	33.0 (64.7)	8 (20.5)	<0.001
Smoking, n (%)	11.0 (21.6)	12 (30.8)	0.455
LOD (months)	96.0 (60.0-180.0)	108 (60-168)	1.000
Vitamin D (ng/mL)	30.3 (±9.1)	31.3 (±12)	0.656
DAS28-CRP	2.7 (2.4-3.2)	2.5 (1.8-3.4)	0.193
Biological agents, n (%)	24 (47.0)	22 (56.4)	0.505
Corticosteroid, n (%)	35.0 (68.6)	29.0 (74.3)	0.719
LVIM (g/m ²)	100.6 (90.3-110.4)	75.5 (71.3-85.3)	<0.001
LVDD (mm)	47.0 (46.0-48.0)	46.0 (44.0-48.0)	0.027
RWT	0.46 (0.43-0.50)	0.37 (0.36-0.40)	<0.001
EF (%)	70.0 (±2.8)	69.6 (±2.3)	0.433
DD, n (%)	35.0 (68.6)	10 (25.6)	<0.001

LOD – length of disease; DAS28-CRP – Disease Activity Score-28 for Rheumatoid Arthritis with c-reactive protein; LVMI – left ventricular mass index; LVDD – left ventricular diastolic diameter; RWT – relative wall thickness; EF – ejection fraction; DD – diastolic dysfunction.

Table 2. Logistic regression model for the prediction of association between altered geometry patterns, vitamin D levels, DAS28-CRP, and biological agents.

Variable	Altered geometry patterns		P value
	OR	IC	
Vitamin D	0.981	0.935-1.029	0.438
DAS28-CRP	0.948	0.566-1.587	0.838

DAS28-CRP – Disease Activity Score-28 for Rheumatoid Arthritis with c-reactive protein. * This model is adjusted by age, hypertension, and diastolic dysfunction.

increasingly documented to be associated with cardiovascular diseases.

In patients with ventricular geometry alterations, age and arterial hypertension were the only positive associations observed. Evidence indicates a close relationship between senescence and CR, but age is a non-modifiable intrinsic factor [26]. On the other hand, hypertension is known to influence the CR process, which has been demonstrated to be prevalent in patients with RA. In our study, 45% were hypertensive. Hypertension in RA patients may be increased due to the inflammatory process that can increase blood pressure [27], and the therapy itself when using corticosteroids.

We found no association between ventricular geometry alteration with inflammatory activity or VD levels. Unlike our findings, Midtbo et al [11] found that patients with active RA had a higher RWT than patients with RA remission, assessed in the present study using the Simple Disease Activity Index (SDAI) score. One explanation of these results is that the mean DAS28-CRP score of our patients was lower than in the study discussed above, reflecting lower disease activity in our sample. Another explanation for this discrepancy may be the different scores used to assess the inflammatory state (SDAI versus DAS28-CRP). Despite having a good correlation at initial assessment, recent studies have shown that this correlation decreases over time [28]. In addition, a large observational cohort study in Japan showed that DAS28-CRP underestimates

Table 3. Demographic and echocardiographic data of 90 patients with rheumatoid arthritis according to left atrium enlargement.

Variable	Left atrium enlargement		p value
	Yes (n=25)	No (n=65)	
Age (years)	56.2 (±10.1)	51.6 (±10.8)	0.064
Male, n (%)	4.0 (16.0)	12.0 (18.5)	1.000
Hypertension, n (%)	12.0 (48.0)	36.0 (55.4)	0.958
Smoking, n (%)	10.0 (40.0)	13.0 (20.0)	0.093
LOD (months)	96.0 (60.0-180.0)	96 (60.0-180.0)	0.525
Vitamin D (ng/mL)	26.4 (±9.5)	32.4 (±10.3)	0.014
DAS28-CRP	2.7 (2.2-3.0)	2.6 (2.0-3.4)	0.978
Biological agents, n (%)	10.0 (40.0)	36.0 (55.4)	0.284
Corticosteroid, n (%)	18.0 (72.0)	46.0 (70.8)	0.885
LVIM (g/m ²)	101.8 (±17.4)	87.3 (±15.3)	<0.001
LVDD (mm)	47.0 (46.0-48.0)	46.0 (44.0-48.0)	0.534
RWT	0.44 (0.38-0.48)	0.42 (0.38-0.46)	0.417
EF (%)	70.3 (±3.2)	69.6 (±2.3)	0.251
DD, n (%)	14.0 (56.0)	31.0 (47.7)	0.638

LOD – length of disease; DAS28-CRP – Disease Activity Score-28 for Rheumatoid Arthritis with c-reactive protein; LVMI – left ventricular mass index; LVDD – left ventricular diastolic diameter; RWT – relative wall thickness; EF – ejection fraction; DD – diastolic dysfunction.

Table 4. Logistic regression model for the prediction of association between Left atrium enlargement, vitamin D levels, DAS28-CRP, and biological agents.

Variable	Left atrium enlargement		P value
	OR	IC	
Vitamin D	0.905	0.843-0.973	0.007
DAS28-CRP	0.726	0.382-1.380	0.328

DAS28-CRP – Disease Activity Score-28 for Rheumatoid Arthritis with c-reactive protein. * This model is adjusted by age, smoking, and left ventricular mass index.

disease activity and overestimates response criteria compared to DAS28 erythrocyte sedimentation rate [19].

Regarding atrial assessment, age and smoking participated in multivariate analysis because the *P* value was lower than 0.1; however, they were not associated with the atrial dimension. LVMI and VD levels were the only factors statistically associated with LA enlargement. The association between smoking and CR is described as arising from hemodynamic and neuro-hormonal changes, oxidative stress, and inflammation and is usually used as a model to induce CR in animals [29]. However, in our study, this association was not shown. Smoking prevalence and history may explain this fact. LV mass index was associated with atrial dilatation. The mean LVMI in patients with

a remodeled atrium was 101.8 (±17.4) g/m², while in the normal atrium, this mean was 14.5 g/m² lower. A possible cause for this finding is the relationship between LA enlargement caused by the increase in atrial filling pressures secondary to ventricular hypertrophy [30]. Similar results between LA enlargement and LV mass were shown by Lavie [31]. This finding is supported by an evaluation of ventricular geometry patterns showing that concentric hypertrophy is the only pattern related to atrial enlargement.

Despite finding no association with the DAS28-CRP score during the atrial evaluation, an association with VD levels was found. The role of vitamin D role in calcium homeostasis is well established, but its deficiency is emerging as a new risk factor for CVD. Vitamin

D deficiency is prevalent in 5.9-13% of the population [32]. In our study, the mean of VD was 30.73 ng/dL (± 10.42), and when evaluated separately, approximately 36% had values compatible with insufficiency and 11% with deficiency of this nutrient.

Previous studies have established VD as a critical cardiac structure and function regulator. Detecting a nuclear VD receptor in endothelial cells and cardiomyocytes suggests direct involvement of VD in the development and progression of cardiovascular disease [33]. At the practical level, multiple pathways through which VD can act have been described, including inflammatory regulation and CR attenuation [34]. In clinical scenarios, several studies have reported a close association between low levels of VD and CR-associated diseases [33].

However, despite growing evidence, VD supplementation in CVD is still controversial. Some studies suggest that VD supplementation attenuates human ventricular remodeling [35]. However, the toxicity risk is a problem. Despite playing an

essential role in the CV system, VD appears to exert a biphasic “dose-response” curve in cardiovascular pathophysiology and can cause deleterious effects, even at non-toxic doses, as recently demonstrated in experimental models [36].

We should consider some limitations of this study. We only included patients from a single medical center, with a small number of patients. In addition, RA patients can have a range of associated cardiac diseases, including pericardial and myocardial disease, which could have affected the results [37]. However, we emphasize the importance of VD in CR in patients with rheumatoid arthritis and encourage the development of trials with VD supplementation in patients with RA.

Conclusions

In conclusion, low serum vitamin D values, but not inflammation, are associated with cardiac remodeling in patients with RA.

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