SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (3); e2020008 DOI: 10.36141/svdld.v37i3.9939

Association of the calcitriol to calcifediol ratio with cardiac involvement in newly diagnosed sarcoidosis

Elias Gialafos[1,6], Lykourgos Kolilekas[2], Effrosyni Manali[3], Spyros Katsanos[5], Paschalis Steiropoulos[4], Elias Tsougos[6], Grigorios Stratakos[1], Mina Gaga[2], Nikos Koulouris[1], Spyros Papiris[3], Ioannis Ilias[7]

[1] 1st Respiratory Medicine Department, Athens Chest Hospital 'Sotiria' Medical School, National and Kapodistrian University of Athens, Greece; [2] 7th Respiratory Medicine Department, Athens Chest Hospital 'Sotiria', Athens, Greece; [3] 2nd Pulmonary Medicine Department, General University Hospital 'Attikon', Medical School, National and Kapodistrian University of Athens, Greece; [4] Department of Respiratory Medicine, University General Hospital, Medical School, Democritus University of Thrace, Greece; [5] 2nd Department of Cardiology, General University Hospital "Attikon", Medical School, National and Kapodistrian University of Athens, Greece; [6] 6th Department of Cardiology, Heart Failure and Preventive Cardiology Section, Ygeia Hospital, Athens, Greece; [7] Department of Diabetes, Endocrinology and Metabolism, Elena Venizelou Hospital, Athens, Greece

Vitamin D (VitD), a well-known regulator of calcium- and phosphate-metabolism has been shown to influence many non-skeletal conditions, including sarcoidosis and cardiovascular diseases; decreasing levels of vitamin are correlated with increased mortality[1]. In sarcoidosis (Sa), granuloma-derived interferon-gamma (among others) stimulates the production - and expresses to a high degree - one alpha hydroxylase, the enzyme that drives hydroxylation of 25(OH)D3 (calcifediol) to $1,25(OH)_2D3$ (calcitriol). The $1,25(OH)_2D3/25(OH)D3$ ratio (VDR) may reflect the efficiency of vitamin D hydroxylase activity [2]. A possible association between VitD metabolites and VDR with Sa severity has not been adequately evaluated. Cardiac involvement in Sa impairs prognosis, even with preserved left ventricular ejection fraction (EF). The aim of this study was to evaluate serum $1,25(OH)_2D3$, 25(OH)D3 and VDR vis-à-vis myocardial involvement in Sa.

In this study, we enrolled 87 newly diagnosed biopsy-proven Sa patients from our outpatient unit between March 2016 and September 2019. These were subjects who were referred for assessment of possible myocardial involvement according to Heart Rhythm Society (HRS) criteria[3]. The diagnosis of Sa was based on the presence of noncaseating granulomas on tissue biopsy specimens and compatible clinical and radiological findings based on the ATS/ERS/WASOG statement[4,5]. Inclusion criteria for this study were: patient age ≥18 years; no supplementation with calcium or vitD, absence of parathyroid dysfunction, kidney and/or liver failure. Exclusion criteria included known collagen vascular disease and cardiac dysfunction related to parathyroid disease, congenital heart disease, coronary artery disease, unrelated to sarcoidosis heart failure, valvular and pericardial disease. Also, patients with current treatment of arterial hypertension and diabetes mellitus were excluded.

All patients had a fasting morning blood collection for determination among others of inflammation markers (C-reactive protein [CRP] and fibrinogen) as well as Serum Angiotensin Converting Enzyme (SACE), Brain Natriuretic Peptide (BNP), Troponin, Parathyroid Hormone (PTH), serum calcium level, serum 25(OH)D3 and $1,25(OH)_2D3$ levels (the latter with Elecsys 25 (OH) D3 and DiaSorin Liaison 1,25 (OH)2 D3 chemilluminescence assays; Hoffman-La Roche AG, Basel, Switzerland and DiaSorin, Sallugia, VC, Italy, respectively) were

Received: 29 May 2020
Accepted after revision: 4 September 2020
Correspondence: Elias J. Giallafos, MD, PhD
Tel: 00306944399924
E-mail: gialaf@yahoo.com

used for the determination of the serum VitD metabolites levels respectively. Clinical parameters and prescribed therapies were recorded for each patient. The Body Mass Index (BMI) was calculated as the ratio of weight (Kg) per height in square (meter^2). Disease stage was assessed on chest X-ray according to the Scadding classification. All patients underwent pulmonary function testing (PFTs) and also baseline cardiac evaluation including cardiac Magnetic Resonance Imaging (c-CMR), in order to detect myocardial involvement according to HRS[4] consensus criteria. The EF and the E/E' ratio (mitral inflow E-wave divided by annular tissue e wave) were obtained from the cardiac echogram as systolic and diastolic function indices, respectively. The study protocol complied with the Declaration of Helsinki, was approved by the institutional ethics committee, and informed consent was obtained from all patients.

Table 1a. Demographic, Clinical and laboratory characteristics of all patients, without (Group A) and with Myocardial Sarcoidosis (Group B). With bold parameters with statistical significance

Parameters	All Patients (N=87)	Group A (n=66)	Group B (n=21)	p-Value
Demographic				
Sex (M)	42.53%	43,94%	38,09%	NS
Age (years)	49.51±11.5	49.67±11.65	49.04±11.49	NS
BMI(kg/m^2)	**27.73±5.17**	**27.09±5.14**	**30.06±4.63**	**0.013**
Hyperlipidemia (Yes)	22.9%	21.21%	28.6%	NS
Smoking (Yes)	20.69%	21.21%	19.05%	NS
Clinical				
Scadding's stage classification (0/1/2/3/4)	3/32/43/7/2	1/25/34/5/1	2/7/9/2/1	NS
Eye Involvement	4,59%	4,54%	4.76%	NS
Skin Involvement	13.79%	13.64%	14.29%	NS
Left Ventricular EF (%)	**62.73±3.85**	**63.26±3.54**	**60.9±4.36**	**0.009**
E/E'	7.47±2.17	7.44±2.18	7.58±2.21	NS
FEV1 (% of Predicted)	94.72±13.63	95.86±12.67	92.42±15.58	NS
FVC (% of Predicted)	97.31±14.36	98.00±12.21	96.94±18.41	NS
FEV1/FVC	80.99±7.26	81.37±7.39	79.83±6.84	NS
DLCO (% of Predicted)	84.08±17.21	84.53±17.27	82.68±17.41	NS
Laboratory				
Urea (mg/dL)	35.79±11.36	35.44±11.69	37.63±9.88	NS
Creatinine (mg/dL)	0.8±0.18	0.76±0.23	0.83±0.15	NS
CRP (mg/dL)	0.5±0.621	0.51±0.64	0.47±0.56	NS
Homocystein (μmol/L)	13.23±6.083	13.53±6.6	12.42±4.12	NS
Fibrinigen (mg/dL)	275.19±60.01	270.79±59.75	287.65±61.49	NS
25(OH)D3 (ng/mL)	**20.44±9.92**	**19.44±9.99**	**24.19±8.84**	**0.039**
1,25(OH) D3 (pg/mL)	24.85±4.57	24.61±4.53	25.9±4.64	NS
VitD Ratio	**1.5±0.77**	**1.6±0.84**	**1.16±0.33**	**0.0001**
PTH (pg/ml)	49.59±24.62	48.64±21.89	52.54±32.74	NS
Serum Calcium (mg/mL)	9.75±0.39	9.77±0.37	9.7±0.44	NS
SACE (U/L)	46.44±22.85	48.13±24.71	41.72±29.52	NS
Log BNP (pg/mL)	1.29±0.35	1.27±0.31	1.37±0.48	NS
Log Troponin (pg/mL)	0.26±0.47	0.24±0.43	0.33±0.57	NS

Table 1b. Stepwise backward logistic linear regression analysis

Variable	B (SE)	Significance	OR (95% CI)
Vitamin D ratio	-1.712 (0.738)	0.020	0.180 (0.042-0.767)
BMI	+0.249 (0.086)	0.003	1.283 (1.083-1.520)
EF	-0.196 (0.077)	0.015	0.821 (0.705-0.956)

SE: standard error; OR: odds ratio; 95% CI: 95% confidence interval

Statistical analyses were performed with SPSS (Version 20.0). Variables in the data set were expressed as mean ± standard deviation. If variables were not normally distributed median and interquartile range (IQR) were used. Dichotomous variables were expressed as frequency and percentage. Differences between continuous variables were tested for statistical significance using Student's t test or Mann-Whitney test. The Chi-squared test or Fisher's exact test were used to analyze categorical data. Further analysis for an association between possible variables (BMI, EF, VDR and 25(OH)D3) and myocardial involvement was done using stepwise backward logistic regression analysis; a two-sided P value <0.05 was considered as being statistically significant.

Table 1a presents baseline demographic, clinical, characteristics, and diagnostic findings in the 87 newly diagnosed Sa patients included in this study. According to the HRS consensus criteria, myocardial involvement was detected in 21 patients (Group B) while the rest formed (Group A). Group B had significantly higher BMI, lower EF, higher 25(OH) D3 and lower VDR (Table 1a). No significant differences were noted between the two groups regarding lung disease severity, other cardiac parameters and indices of inflammation. Logistic regression was performed to ascertain the effects of BMI, EF, VDR on the likelihood that subjects have cardiac involvement (disease stage and SACE levels were not associated with cardiac involvement). The logistic regression model was statistically significant (Chi square=21.257, p=0.0001). The obtained model correctly predicted 80.82% of cases. For each incremental increase in VDR or EF subjects were 5.55 or 1.22 times less likely to exhibit cardiac involvement, respectively, whereas for each incremental increase in BMI subjects were 0.78 times more likely to exhibit cardiac involvement (Table 1b).

Numerous clinical studies with different pathological conditions confirm an association between VitD abnormalities - especially deficiency - and increased morbidity and mortality. This assumption is based on the fact that active VitD metabolites can induce important biological effects at a molecular level in different organs. Mounting evidence suggests that VitD may influence the pathophysiology of heart failure through activation of VitD receptors in the cardiovascular system[6]. The latter interfere with the renin-angiotensin system (RAS), calcium handling, inflammatory status, and especially in cardiac fibrosis (mechanisms that active in myocardial Sa). Also, the complex and integrated regulatory pathways of VitD suggest that efficient regulation of vitD hydroxylation might be more crucial than the concentration of any D metabolite alone. Although several studies have previously reported an association between Sa and VitD, to our knowledge, this is the first one showing an association of myocardial involvement in Sa with a simple measure of VitD metabolites, thus correlating VDR with disease activity and/or possibly severit[7,8]. The exact mechanism of this association is unknown and speculative, however possible mechanisms can be mentioned. Either immunologic mechanisms through VitD metabolites to a sensitized myocardium or/ and the granuloma induced interferon-gamma and interleukin (IL) 2 production interferes with one alpha hydroxylase activity and production of active $1,25(OH)_2D3$, thus counter-regulating granuloma formation. Notably, we found that low VDR was a significant independent factor associated with the presence of cardiac involvement. Also, it is interesting to note the absence of association between pulmonary sarcoidosis with VitD metabolites, most probably due to the presence of mild pulmonary disease and the absence of important disease activity in the majority of patient[9,10]. This study was limited because we could not ascertain the duration of disease until diagnosis; furthermore it was limited by the number of patients studied and the non-inclusion of

newer markers of Sa activity such as of IL-2r or of chitotriosidase.

In conclusion, the role of Vit D metabolites and especially VDR may represent a promising simple informative tool for initially assessing cardiac involvement in Sa; further evaluation with follow-up studies in the future is ongoing.

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