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Circulating DHEA-S levels and major cardiovascular outcomes in chronic Chagas cardiomyopathy: A prospective cohort study

Lyda Z. Rojas [a,1], Sergio Alejandro Gómez-Ochoa [b,1], Luis E. Echeverría [c], Paula Katherine Bautista-Niño [d], Lukas Hunziker [e], Michele F. Eisenga [f], Taulant Muka [g,*]

[a] Research Group and Development of Nursing Knowledge (GIDCEN-FCV), Research Center, Cardiovascular Foundation of Colombia, Floridablanca, Santander, Colombia
[b] Public Health and Epidemiological Studies Group, Cardiovascular Foundation of Colombia, Floridablanca, Colombia
[c] Heart Failure and Heart Transplant Clinic, Fundación Cardiovascular de Colombia, Floridablanca, Colombia
[d] Research Center, Fundación Cardiovascular de Colombia, Floridablanca, Santander, Colombia
[e] Department of Cardiology, Bern University Hospital, Bern, Switzerland
[f] Department of Internal Medicine, Division of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[g] Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland

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ABSTRACT

Objective: To analyze the association of circulating dehydroepiandrosterone sulfate (DHEA-S) levels with cardiovascular outcomes in patients with chronic Chagas cardiomyopathy (CCM) diagnosis.
Background: DHEA-S is among the main endogenous steroid hormones. Some studies have suggested a relevant role of this hormone in infections and the setting of CCM. Nevertheless, no study has evaluated the prognostic role of DHEA-S in CCM patients.
Methods: Prospective cohort study. Patients with CCM and reduced ejection fraction were included. We explored the association of DHEA-S levels with NT-proBNP levels and echocardiographic variables using linear regression models. Next, by using Cox Proportional Hazard models, we examined whether levels of DHEA-S could predict a composite outcome (CO) including all-cause mortality, cardiac transplantation, and implantation of a left ventricular assist device (LVAD).
Results: Seventy-four patients were included (59% males, median age: 64 years). After adjustment for confounding factors, high DHEA-S levels were associated with better LVEF, lower left atrium volume, end-systolic volume of the left ventricle and lower NT-proBNP levels. 43% of patients experienced the CO during a median follow-up of 40 months. Increased levels of DHEA-S were associated with a lower risk of developing the CO (HR 0.43; 95%CI 0.21-0.86). Finally, adding DHEA-S to the multivariate model did not improve the prediction of the CO, but substituting NT-proBNP in the model with DHEA-S showed similar performance.
Conclusions: In patients with CCM, higher DHEA-S levels were associated with lower mortality, heart transplantation, and LVAD implantation. Further larger studies are required to confirm our results and assess causality.

1. Introduction

Chagas Disease (CD), an infectious disease caused by the protozoan parasite *Trypanosoma cruzi (T. cruzi),* is currently recognized as the parasitic disease with the highest associated disease burden worldwide [1,2]. Chronic Chagas cardiomyopathy (CCM) is the most common form of chronic involvement leading to a dilated cardiomyopathy with rapidly progressive heart failure [3,4].

Patients with heart failure (HF) secondary to CCM may have a significantly higher mortality risk than other HF etiologies [5]. However, assessing the prognosis of a patient with CCM may be challenging [6]. A relatively under-explored option for risk prediction in CD cardiomyopathy that may prove very useful in this context are serum biomarkers [7]. Nevertheless, few studies have addressed their role in CCM,

* Corresponding author at: Institute of Social and Preventive Medicine (ISPM), University of Bern, Mittelstrasse 43, 3012 Bern, Switzerland.
E-mail address: taulant.muka@ispm.unibe.ch (T. Muka).
[1] Denotes equal contribution.

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which warrants direct confirmation given its unique pathogenesis [8–11].

Sex hormones, such as Dehydroepiandrosterone sulfate (DHEA-S), have been linked with levels of NT-proBNP and shown to predict prognosis in patients with HF [12,13]. For example, dehydroepiandrosterone (DHEA) significantly inhibited B-type natriuretic peptide mRNA in a rat cardiocytes model [14]. Moreover, a more recently published study observed a significant association between DHEA-S levels and NT-proBNP levels in post-menopausal women free of cardiovascular diseases, suggesting a role of this hormone in the risk of cardiovascular disease [15]. Finally, DHEA and DHEA-S have been implicated in the pathophysiology of chronic infectious diseases such as *Mycobacterium tuberculosis* infection, suggesting a relevant link between chronic inflammation and the role of this endogenous steroid hormone [16,17]. However, the impact of DHEA-S in Chagas disease, and specifically in the chronic forms of the disease, remains poorly investigated [18]. We aimed to assess the association of circulating DHEA-S levels and cardiovascular outcomes in patients with CCM diagnosis.

2. Methods

2.1. Study population

This prospective cohort study was conducted between July 2015 to June 2021 at the Heart Failure and Heart Transplant Clinic of Fundación Cardiovascular, in Floridablanca, Colombia. Adult outpatients (> 18 years old) with a positive serological diagnosis of *T. cruzi* infection (positive IgG antibodies) and echocardiographic or electrocardiographic abnormalities consistent with chronic Chagas cardiomyopathy were included. We enrolled only patients with reduced left ventricular ejection fraction (LVEF) defined as a LVEF $\leq$ 40%, including also individuals with implantable devices and refractory heart failure. The study sample was obtained from the CCM patients attending their follow-up evaluations. We excluded individuals with diabetes mellitus, coronary heart disease history, mitral stenosis, or uncontrolled hypertension. The Institutional Committee on Research Ethics approved the research protocol of the study. All patients provided written informed consent for their participation in the study.

2.2. Population for analyses

There were 272 patients with CD diagnosis and serum samples stored in the institutional biobank eligible for the analysis. Among those, 198 were excluded because (i) they were in the indeterminate stage of the disease when the serum samples were collected ($n = 96$), (ii) they had a preserved or mid-range left ventricular ejection fraction defined as a LVEF >40% ($n = 71$), (iii) had an incomplete echocardiographic assessment ($n = 5$) and (iv) had incomplete follow-up ($n = 26$). Therefore, 74 patients with CCM diagnosis were included in the final analysis (Supplementary Fig. 1).

2.3. Measurement of DHEA-S

In the present study, serum DHEA-S levels were assayed from stored serum samples and were quantified in duplicate by a competitive chemiluminescent enzyme immunoassay using the ARCHITECT DHEA-S Reagent Kit. The assay sensitivity is 3.0 μg/dl, while it is expected to have a cross-reactivity of less than 10%. We maintained a consistent methodology across the duration of the study.

2.4. Study outcomes and follow-up

After baseline screening, patients were followed up with a telephone interview and provided a standardized checklist of questions to identify clinical outcomes. Further, clinical records of each patient were revised for additional information and to validate the reported outcomes. The primary composite outcome (CO) included all-cause mortality, heart transplant, and left ventricular assistance device (LVAD) implantation. Follow-up of each participant began on the date of collection of non-fasting blood samples (2015) and ended at the date of all-cause mortality, heart transplant, LVAD implementation, loss to follow-up, or end of the study period on January 2021, whichever came first.

The secondary outcome was myocardial involvement (assessed by NT-proBNP levels [measured using the electrochemiluminescence method, Roche Diagnostics GmbH, Mannheim, Germany], LVEF, global longitudinal strain value [GLS], LA volume index, ESV-LV, EDV-LV, LV mass index, TAPSE, Mitral flow E velocity, E/e' lateral ratio).

2.5. Covariates assessment

Age, sex, social stratum, heart failure (HF) medication, and body mass index (BMI) were included as the main covariates. The social stratum was defined according to the estimated median household income of residents, which was assessed using the patient's ZIP code. On the other hand, use of HF medications was evaluated by a standardized format at the moment of enrollment. The use of each of the following HF medications was considered: Angiotensin-Converting Enzyme Inhibitors (ACEI)/Angiotensin Receptor Blockers (ARB), beta-blockers, and Mineralocorticoid Receptor Antagonists (MRAs).

2.6. Statistical analysis

Categorical variables were presented as numbers and proportions, while continuous variables were reported as medians and interquartile ranges. The Chi-square and Fischer exact test were used to assess differences in categorical variables, while the Mann-Whitney *U* test and the Kruskal-Wallis test were used for continuous variables. Furthermore, we used natural log-transformed values of the DHEA-S concentrations, NT-proBNP levels, and the echocardiographic variables to approximate a normal distribution. The associations of DHEA-S with echocardiographic parameters and NT-proBNP were assessed using multivariable linear regression models. Survival analyses were performed using the Kaplan- Meier method, life table, and Cox Proportional Hazard models to evaluate the association between DHEA-S and CO. At first, a basic model (model 1) adjusted by age and sex was constructed. Next, a second model (model 2) adjusting additionally for BMI, social stratum, and HF medications was developed. We build a third model for survival analysis, including variables in model 2 and including log-natural transformed NT-proBNP values and log-natural transformed LVEF. The collinearity of the models was investigated using the collin command, which provides detailed collinearity diagnostics, including VIF and eigenvalues. We did not find any evidence of collinearity in our analysis (VIF < 2). A p-value <0.05 was considered statistically significant for all tests. All analyses were performed using Statistical Package STATA version 15 (Station College, Texas USA).

2.7. Sensitivity analyses

To explore whether the associations of DHEA-S with the outcomes under study would differ by sex, an interaction term of DHEA-S and sex was tested in model 2. Considering the possibility of a non-linear effect of the DHEA-S levels in the Cox Proportional Hazard models, we included a quadratic term of this variable in model 2 and, if a non-linear effect was observed, we performed an Additive Cox model using the package mgcv in R (R Core Team. 2020). In addition, we analyzed DHEA-S in tertiles. To explore whether the association between DHEA-S and the CO was driven by cardiovascular mortality, we further investigated the association between DHEA-S and cardiovascular mortality. To evaluate the prognostic value of DHEA-S, we quantified the discriminatory ability of the models with and without DHEA-S using Harrell's C statistic and the area under the receiver operating characteristic curve (AUC-ROC).

3. Results

3.1. Population characteristics

Seventy-four patients were included, mainly males (59%) with a median age of 64 (Q1: 58, Q3: 72) years at the time of enrolment. All included patients had a reduced left ventricular ejection fraction (median LVEF 29%, Q1: 21%; Q3: 36%), while the median GLS value was -7.8% (Q1 = -10.7%; Q3 = -5.6%). Most of the patients were receiving an ACEI/ARB (87.8%), beta-blockers (95.9%), or mineralocorticoid receptor antagonists (82.4%) (Table 1 and Supplementary Table 1).

3.2. DHEA-S and severity of CCM

After adjusting for age, sex, BMI, social stratum, and HF medications, log-natural converted DHEA-S values were significantly inversely associated with log-natural converted NT-proBNP levels (per 1-unit increase in natural log-transformed of DHEA-S Coef. -0.62; 95% CI –1.03; -0.21). Similarly, log-natural converted DHEA-S values were also associated with LVEF (Coef. 0.16; 95% CI 0.05; 0.27), but not with GLS values (Coef. -1.13; 95% CI -2.35; 0.10) (Table 2). Finally, DHEA-S values were also significantly associated with some echocardiographic markers of the severity of the myocardial involvement; higher levels of DHEA-S were associated with reduced log-natural converted LA volume indexes (Coef. -0.23; 95% CI -0.43; -0.29) and log-natural converted ESV-LV values (Coef. -0.26; 95% CI -0.51; -0.18), while no association was observed with other markers (Table 2).

Table 1
Baseline characteristics of the cohort of patients with chronic Chagas cardiomyopathy according to the presence of the composite outcome (CO).

	Patients without the CO (*N* = 42)	Patients with the CO (*N* = 32)	Total (*N* = 74)	p-Value
Males	26 (61.9%)	18 (56.2%)	44 (59.5%)	0.624
Age	62.5 (56.0, 66.5)	66.0 (62.0, 74.0)	64.0 (58.0, 71.5)	0.060
BMI	24.6 (21.9, 28.7)	22.0 (19.8, 25.3)	23.5 (21.5, 27.4)	**0.012**
NYHA				**0.001**
I-II	38 (92.7%)	19 (61.3%)	57 (79.2%)	
III-IV	3 (7.3%)	12 (38.7%)	15 (20.8%)	
ACEI/ARB	35 (83.3%)	30 (93.8%)	65 (87.8%)	0.174
Beta-blockers	39 (92.9%)	32 (1.0%)	71 (95.9%)	0.123
MRA	34 (81.0%)	27 (84.4%)	61 (82.4%)	0.701
Diuretics	20 (47.6%)	26 (81.2%)	46 (62.2%)	**0.003**
Digitalis	9 (21.4%)	10 (31.2%)	19 (25.7%)	0.338
Ivabradine	1 (2.4%)	1 (3.1%)	2 (2.7%)	0.845
Antiplatelets	8 (19.0%)	6 (18.8%)	14 (18.9%)	0.974
Anticoagulants	22 (52.4%)	17 (53.1%)	39 (52.7%)	0.949
NT-proBNP (pg/ml)	1480.0 (487.2, 2839.5)	4639.5 (1943.3, 8045.0)	2146.5 (1021.7, 6065.7)	< **0.001**
DHEA-S (μg/dL)	81.2 (50.8, 119.6)	40.3 (25.6, 65.9)	58.7 (35.8, 1.2)	< **0.001**
LVEF (%)	33.5 (24.3, 37.0)	25.0 (19.8, 31.0)	29.0 (21.0, 36.0)	**0.012**
GLS (%)	-9.2 (-10.8, -6.5)	-7.050 (-8.575, -4.7)	-7.8 (-10.6, -5.8)	**0.027**
ESV-LV (ml)	99.0 (71.0, 132.0)	122.0 (88.3, 202.0)	107.0 (76.0, 142.0)	0.145
EDV-LV (ml)	148.0 (120.0, 179.0)	173.5 (141.0, 253.8)	158.0 (121.0, 192.0)	0.173
LV mass index (g/m2)	146.8 (117.7, 173.7)	152.4 (116.8, 191.0)	146.8 (117.4, 184.2)	0.824
TAPSE (mm)	16.0 (11.0, 18.0)	12.0 (10.0, 14.0)	13.5 (10.8, 17.0)	**0.020**
Mitral flow E velocity (cm/s)	70.5 (51.5, 88.3)	77.0 (46.0, 113.0)	73.0 (50.0, 93.0)	0.233
E/e' lateral ratio	9.4 (7.8, 12.4)	10.9 (8.2, 16.9)	9.8 (7.9, 13.4)	0.388
LA volume index (mL/m2)	56.5 (42.5, 70.0)	68.0 (52.5, 84.9)	61.0 (45.0, 77.0)	0.156

BMI: Body-mass index; ACEI/ARB: Association of Angiotensin-Converting Enzyme Inhibitor/Angiotensin Receptor Blocker; MRA: Mineralocorticoid receptor antagonists; LVEF: Left-ventricle ejection fraction; GLS: Global longitudinal strain; LA: Left atrium; ESV-LV: End-systolic volume of the left ventricle; EDV-LV: End-diastolic volume of the left ventricle; TAPSE: Tricuspid annular plane systolic excursion. Bold text represent p-values < 0.05.

3.3. Impact of DHEA-S levels on the composite outcome

During the median follow-up of 40 months (Q1: 23; Q3: 52), 43% of participants reported an event of the CO, with a rate of 0.40 per 1000 person-years (95% CI 0.28-0.56). In model 1, higher DHEA-S levels were associated with a lower risk of developing the CO (per unit increase in naturally log-transformed DHEA-S, HR 0.35; 95% CI 0.18–0.66. P = 0.001). This association remained significant even after adjusting for BMI, social stratum, HF medication,LVEF, and NT-proBNP (HR 0.43; 95% CI 0.21–0.86 P = 0.018) (Table 3).

3.4. Sensitivity analyses

No significant interaction terms by sex were observed in any of the analyses. After adjusting for all covariates, including NT-proBNP value and LVEF, compared to the first tertile of DHEA-S, the HR for CO for tertile 2 and 3 were 0.56 (95% CI 0.22-1.44) and 0.20 (95% CI 0.05-0.75), respectively. The quadratic term of DHEA-S in the Cox Proportional Hazards model was significant (p-value <0.05), suggesting a non-linear association (Supplementary Fig. 2). Therefore, an additive Cox proportional hazards model was fitted, confirming the non-linear trend (Supplementary Fig. 3) and showing that the smoothed value of the DHEA-S remained significantly associated with the CO (effective degrees of freedom: 2.12 [which supports the quadratic nature of the effect], p-value: 0.034). Finally, DHEA-S levels were also significantly associated with cardiovascular mortality (n = 29; 39.2%) after adjusting

Table 2
Association between DHEA-S levels and markers of severity in chronic Chagas cardiomyopathy.

Parameter[a]	Basic model[b]		Adjusted model[c]	
	β (95% CI)	p-Value	β (95% CI)	p-Value
NT-proBNP (pg/ml)	−0.67 (−1.09; −0.24)	**0.003**	−0.62 (−1.03; −0.21)	**0.004**
LVEF (%)	0.17 (0.07; 0.28)	**0.001**	0.16 (0.05; 0.27)	**0.005**
GLS (%)	−1.02 (−2.25; 0.22)	0.106	−1.13 (−2.35; 0.10)	0.071
LA volume index (mL/m2)	−0.14 (−0.30; 0.10)	0.067	−0.23 (−0.43; −0.29)	**0.026**
ESV-LV (ml)	−0.24 (−0.50; 0.03)	0.083	−0.26 (−0.51; −0.18)	**0.036**
EDV-LV (ml)	−0.21 (−0.40; −0.11)	**0.039**	−0.19 (−0.41; 0.03)	0.084
LV mass index (g/m2)	0.01 (−0.06; 0.19)	0.929	0.01 (−0.15; 0.16)	0.984
TAPSE (mm)	0.13 (0.01; 0.26)	**0.033**	0.01 (−0.02; 0.23)	0.099
Mitral flow E velocity (cm/s)	−0.07 (−0.23; 0.09)	0.390	−0.11 (−0.28; 0.05)	0.180
E/e' lateral ratio	−0.14 (−0.03; 0.31)	0.099	0.12 (−0.06; 0.29)	0.196

LVEF: Left-ventricle ejection fraction; GLS: Global longitudinal strain; LA: Left atrium; ESV-LV: End-systolic volume of the left ventricle; EDV-LV: End-diastolic volume of the left ventricle; TAPSE: Tricuspid annular plane systolic excursion.
[a] All parameters are natural log transformed, except for GLS.
[b] Model adjusted by age and sex.
[c] Model adjusted by sex, age,BMI, social stratum, and HF medications.

Table 3
Association of dehydroepiandrosterone sulfate (DHEA-S) levels and clinical outcomes in patients with chronic Chagas cardiomyopathy and reduced ejection fraction ($N = 74$).

	Tertile 1	Tertile 2	Tertile 3	Continuous
Composite outcome				
Cases				
Model 1, HR (95% CI)	1.00	**0.32 (0.14-0.76)**	**0.15 (0.05-0.46)**	**0.35 (0.18-0.66)**
Model 2, HR (95% CI)	1.00	0.48 (0.20-1.15)	**0.21 (0.07-0.63)**	**0.37 (0.19-0.71)**
Model 3, HR (95% CI)	1.00	0.59 (0.24-1.48)	**0.25 (0.08-0.77)**	**0.43 (0.21-0.86)**
Cardiovascular death				
Cases				
Model 1, HR (95% CI)	1.00	**0.33 (0.13-0.81)**	**0.11 (0.03-0.44)**	**0.28 (0.14-0.58)**
Model 2, HR (95% CI)	1.00	0.48 (0.19-1.18)	**0.17 (0.05-0.66)**	**0.34 (0.17-0.68)**
Model 3, HR (95% CI)	1.00	0.56 (0.22-1.44)	**0.20 (0.05-0.75)**	**0.38 (0.18-0.81)**

Model 1: Age and sex.
Model 2: Model 1 + social stratum, body mass index and HF medications.
Model 3: Model 2 + NT-proBNP levels and left-ventricular ejection fraction.
Results significant at *P*-value lower than 0.05 are bold in the table.

for the covariates specified for model 3 (Additive Cox proportional hazards model: Effective degrees of freedom: 2.21, p-value: 0.039. Cox proportional hazards model: HR 0.33; 95% CI 0.16–0.70, $P = 0.018$) (Table 3). Finally, we evaluated the potential additive value of including DHEA-S in a multivariate predictive model. At first, a model including sex, age, BMI, social stratum, HF medications use, NT-proBNP levels, and LVEF showed an AUC-ROC of 0.75 according to Harrell's C concordance statistic. After including DHEA-S levels as a continuous variable, there was no significant increase in the AUC (0.75), neither after including the quadratic term of continuous DHEA-S levels (AUC: 0.76). A model including DHEA-S levels without NT-proBNP value had a similar AUC (0.73) compared to the model including NT-proBNP without DHEA-S levels (AUC: 0.75) p for the difference = 0.198).

4. Discussion

In this study of 74 patients with CCM and a follow-up of more than three years, we found DHEA-S levels to be associated with NT-proBNP, LVEF, and markers of cardiac involvement. Further, DHEA-S levels were significantly associated with the risk of our composite outcome (CO) of mortality, heart transplantation, and LVAD implantation, even after adjusting for prognostic factors such as NT-proBNP levels and LVEF. While we did not find any added value of DHEA-S in predicting CO compared to NT-proBNP in the prognostic prediction model, we found DHEA-S to have similar prediction performance with a model without NT-proBNP.

One of the most relevant findings observed in the present study was the association between DHEA-S levels and adverse cardiovascular outcomes, independently of two strong prognostic biomarkers in the context of CCM, NT-proBNP, and LVEF [11]. Androgens such as DHEA have been inversely associated with NT-proBNP levels in several studies, suggesting an inhibitory effect of androgens in natriuretic peptides, potentially through an epigenetic modulation process [14,19,20]. Nevertheless, this inverse association may also be explained by the direct effect of DHEA on the cardiovascular system, ameliorating the risk of disease and preventing complications [21,22]. There is evidence supporting a potential causal role of DHEA/DHEA-S levels and disease outcomes through different biologically plausible mechanisms, highlighting their influence in traditional cardiovascular risk factors, oxidative stress, PPARα activation, and atherogenesis, among others [23–26]. Our observation of an association between DHEA-S levels and clinical outcomes in HF of chagasic etiology supports the hypothesis of alternative conditions in addition to myocardial stretch and hemodynamic status that may significantly contribute to the risk of complications in these patients.

Previous studies have suggested DHEA's potential protective effect in both humans and murine models of Chagas Disease [18]. In this context, DHEA and DHEA-S seem to have strong antiphlogistic effects, reducing the levels of several pro-inflammatory cytokines and even provide protection from the harmful effects of glucocorticoids; however, the mechanisms behind these associations are still poorly understood [27–30]. Similar to NT-proBNP, evidence supports a direct correlation between DHEA-S levels and LVEF, as observed in our study. For example, in the study of *Jankowska et al.,* which assessed the prognostic impact of anabolic deficiencies in men with heart failure, LVEF and plasma NT-proBNP levels were only related to circulating DHEA-S levels [31]. Similar to our study, DHEA-S levels were observed to be negatively associated with the left atrial volume index ($r = -0.38$, $p = 0.01$) in the study of *Favuzzi et al.*, which evaluated a cohort of patients with heart failure with preserved ejection fraction in Italy [32]. In contrast, the study of *Subramanya et al.* suggested an association between DHEA levels and LV mass in post-menopausal women and men aged 45-84 years without a history of CVD or HF, nevertheless, no association with LV end-systolic volume, as observed in our study, was reported [33]. However, these differences may be explained due to the absence of left ventricular dysfunction in these patients, as patients with HF were excluded from this study. Finally, our study is the first to evaluate an association between DHEA-S levels and GLS values in heart failure patients, showing no association between these two variables. This result may suggest that DHEA-S measurement could be more helpful in assessing prognosis in patients with HF rather than evaluating myocardial involvement patterns or the presence of early myocardial injury, as GLS has been observed to be very sensitive for identifying these conditions but not as good as LVEF as a prognostic biomarker in the setting of HF with reduced ejection fraction [34–36]. Future studies evaluating the potential association between DHEA-S and GLS in patients with preserved LVEF are needed.

Finally, some studies have observed that DHEA-S (the metabolite of DHEA) levels are inversely correlated with disease severity in CCM, highlighting a significantly lower value in patients with severe myocardial dysfunction compared to those with mild-to-moderate disease and those in the indeterminate stage, even after considering the physiological decrease of DHEAs levels with aging [18,37]. The reasons behind this imbalance in DHEAs levels are not entirely known. The elevated concentration of circulating cytokines and immune-endocrine mediators could also play a role, as several studies have observed an inverse association between immunological markers, such as C reactive protein, and DHEA levels [38,39]. It has been hypothesized that certain immunological products can have a direct action at the adrenal glands, inhibiting the steroidogenesis of molecules such as DHEA [40,41]. Furthermore, the potential activation of a polyclonal immune response eliciting a process of autoreactivity seem to also play a central role in this setting [42]. Interestingly, DHEA levels may even play a protective role in the context of Chagas Disease, as some studies in animal models of acute *T. cruzi* infection have suggested that treatment with DHEA could be associated with an improvement of the immune response magnitude and parasite control [43–45].

4.1. Study limitations

Our study suffers from some relevant limitations, highlighting the small sample size, which may explain some of the borderline significant associations. Furthermore, there was no information available regarding smoking and alcohol consumption in this cohort, which could be potential confounders in the association between DHEA-S and HF. In addition, the presence of inflammatory disorders such as osteoarthritis,

which can influence DHEA-S levels and the prognosis of CCM, was not evaluated; therefore, an adjustment of the models for inflammatory conditions or inflammatory biomarkers was not possible. Also, other sex hormones or cortisol were not measured, and thus we could not explore whether the associations we found are independent of these factors. Moreover, DHEA-S levels were estimated using a single serum sample, and the levels of DHEA-S could change over time. However, this would likely shift the results toward the null. Although information regarding the circadian variations in DHEA-S suggests non-significant differences, the samples were collected at a similar time of the day for all patients, potentially mitigating these variations [46,47]. In addition, the potential geographical variations in the immune response to *T. cruzi and* the genotypic differences in the parasite may limit the generalizability of our results to other contexts. Therefore, further research considering different *T. cruzi* strains and ethnic groups is needed. Finally, we must be cautious when assessing the real role of DHEAs in CCM's prognosis, as the presence of an association does not necessarily mean causality. In fact, the association of DHEA-S levels and adverse outcomes may be related to a worse clinical status, and CCM pathophysiological changes may not be the only source of DHEA-S levels variations in these patients [48].

5. Conclusion

Higher DHEA-S values were associated with lower mortality, heart transplantation, and LVAD implantation in patients with CCM. Thus, DHEA-S may have a potential use as a biomarker for assessing the risk of adverse cardiovascular outcomes in patients with this special cardiomyopathy. However, further studies are required to thoroughly evaluate the role of DHEA-S in CD and CCM and the potential mechanisms underlying the observed associations, contributing to a significant improvement in the knowledge of CCM pathophysiology.

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Disclosures

Nothing to disclose.

Subject codes

Cardiomyopathy; Heart Failure; Biomarkers.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.11.054.

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