

# The potential influence of atherogenic dyslipidemia on the severity of chronic Chagas heart disease

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## SUMMARY

**Introduction:** chronic Chagas heart disease (CCHD) is the most common manifestation of American Trypanosomiasis, causing about 50,000 deaths annually. Several factors bear correlation with the severity of CCHD. However, to our knowledge, the assessment on the contribution of major cardiovascular risk factors (CRF), such as hypertension and atherogenic dyslipidemia (AD) to CCHD severity is scarce, despite their well-established role in coronary artery disease, heart failure and stroke.

**Objective:** to explore the potential relationship of blood pressure and AD with the clinical profile of patients with CCHD.

**Methods:** we performed a cross-sectional study in *T. cruzi* seropositive patients categorized according to a standard CCHD classification. All individuals were subjected to complete clinical examination. Autoantibodies induced by *T. cruzi* were assessed by ELISA.

**Results:** we observed that Atherogenic index (AI) levels rose significantly in relation to the severity of the CCHD stage, with CCHD III cases showing the highest values of AI. Furthermore, those patients with globally dilated cardiomyopathy with reduced ejection fraction showed higher levels of AI. In regard to autoantibodies, anti-B13 also showed relation with the severity of the disease.

**Conclusion:** we observed that AI correlated with CCHD stages and contributed, in association with anti-B13 antibodies and age, to the prediction of systolic heart failure.

**Keywords:** Chagas disease, Chagas cardiomyopathy, dyslipidemias.

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## INTRODUCTION

Chronic Chagas heart disease (CCHD) is the most common manifestation of American Trypanosomiasis.<sup>1</sup> It has been described recently that *T. cruzi* infection might be a risk factor for high blood pressure<sup>2</sup> and that it might induce cholesterol homeostasis disruption.<sup>3</sup> In this respect, Nagajyothi et al.<sup>4,5</sup> have observed in an experimental murine model that *T. cruzi* infection promotes an important decrease of serum levels of low-density lipoprotein-cholesterol (LDL-c) and triglycerides (TG). On the other hand, even though both hypertension and atherogenic dyslipidemia (AD) are well-known risk factors for coronary artery disease, heart failure and stroke, their influence on the severity of CCHD is not known. Accordingly, we ex-

plored the potential relationship of blood pressure and AD with the clinical profile of patients with CCHD.

## METHODS

We performed a cross-sectional study in 177 adult patients with Chagas disease, subjected to a complete clinical examination and stratified according the CCHD classification of Storino et al.<sup>6</sup> Exclusion criteria comprised: family history of early heart disease, obesity, metabolic syndrome, diabetes or peripheral arterial disease, history of established coronary artery disease or other cardiac diseases and any other systemic complaints. Individuals treated with anti-*T. cruzi* compounds, immunosuppressive or hypolipemiant drugs were not included.

Auto-antibodies with a pathological role in Chagas disease anti-p2 $\beta$  (*T. cruzi* ribosomal protein), and anti-B13, were measured by immunoassay (ELISA) as described previously.<sup>6</sup> The index of the optical density of autoantibodies in relation to the negative control (IODN) was determined. An IODN $\leq$ 1 was considered negative.

As regards to AD, the atherogenic index (AI) was calculated by dividing the logarithm of the ratio triglycerides/high-density lipoprotein (HDL-c).<sup>7</sup>

The study was approved by the Ethics Review Board of the Universidad Nacional del Litoral. Informed consent was obtained from all participants.

Data were analyzed by using MedCalc version 12.2.1. Normal distributions of the continuous variables were tested by Kolmogorov-Smirnov method. The data are expressed as means $\pm$ SD or median and interquartile range. Groups were compared in relation to age, antibody levels, and CCHD stages. Chi-square test or Fisher's exact test were used for categorical variables, whereas the one-way ANOVA was used to compare means. A p value < 0.05 was considered significant.

## RESULTS

The features of CCHD patients by group are summarized in Table 1. Individuals with CCHD stage III were older than the remaining ones (p<0.001). There were no between-group differences in sex distribution. Regarding cardiovascular risk factors (CRF), 53 patients had essential hypertension, all of them under drug-therapy. Patients from CCHD stages I and II were being treated with monotherapy (13 with angiotensin-converting enzyme inhibitors and 18 with cardio selective  $\beta$ 1-blockers). All the cases of CCHD III with hypertension received combined therapy of enalapril plus  $\beta$ -adrenergic antagonist drugs. In relation to AD, age and sex were not related to serum lipid levels, although a weak correlation between AI and systolic blood pressure was found (r=0.2, p=0.03). Multiple comparisons for total-cholesterol, LDL-c, HDL-c, triglycerides and AI by the CCHD stratification showed that AI levels rose significantly in relation to the severity of the CCHD stage, with CCHD III cases showing the highest values of AI (p<0.001).

Among patients with cardiac impairment (n=67), 32 presented globally dilated cardiomyopathy with reduced ejection fraction. These 32 were older than the remaining patients (p=0.03) and showed higher levels of AI (p<0.001).

As for auto-antibodies, we observed that anti-B13 was not associated with CRF; however, their levels were higher in CCHD III individuals, especially in those with systolic heart failure (p=0.003). In relation to anti-p2 $\beta$  immuno-

globulins, they were inversely correlated with AI (r=-0.214; p=0.004), while showing no between-group differences.

Lastly, we performed a multiple binary logistic regression to assess the impact of age, hypertension, treatment with selective  $\beta$ 1-blockers, AI, and anti-B13 in the prediction of systolic heart failure. The Wald criterion yielded that age (OR: 2.08, 95CI 2.03-2.13, p=0.004), AI (OR 2.45, 95CI 2.18-2.59, p=0.001) and anti-B13 (OR: 2.19, 95CI 1.59-7.64, p=0.04) contributed to the prediction of globally dilated cardiomyopathy with reduced ejection fraction (Hosmer & Lemeshow test Chi-squared 10.36, p=0.94).

## DISCUSSION

Both hypertension and AD are two major CRF which have been associated with the development of cardiovascular diseases. A recent mouse study showed that *T. cruzi* induces a disruption of cholesterol homeostasis which may play an important role in the development of different disorders seen in Chagas disease.<sup>8</sup> In our study, we observed that AI increased as disease severity progressed, reaching its highest values in CCHD III cases.

A study by Diez C et al.<sup>9</sup> exploring the implication of smoking, alcoholism, hypertension and autoimmune response in individuals with CCHD, reported that the concomitant presence of the three CRF was associated with increased auto-antibody levels and disease severity. In the present sample, in which a higher number of patients with accompanying hypertension were present, CRF were not associated with an increase in anti-p2 $\beta$  or anti-B13. Anti-p2 $\beta$  did correlate inversely with AI, whereas anti-B13 appeared related to CCHD stages, as previously.<sup>6</sup>

## CONCLUSION

In conclusion, we observed that AI correlated with the CCHD stages and contributed, in association with anti-B13 antibodies and age, to the prediction of systolic heart failure. Despite the cross-sectional design, the present study underscores some aspects of the complex interaction between cardiovascular risk conditions and the host immune response against the parasite likely to be involved in the progression of CCHD.

## RESUMO

Influencia de la dislipidemia aterogénica en la gravedad de la miocardiopatía chagásica crónica

**Introducción:** la miocardiopatía chagásica (MCC) es la manifestación más común de la tripanosomiasis americana, causando cerca de 50.000 muertes al año. Varios facto-

**TABLE 1** Features of chronic Chagas heart disease, patients by group. Quantitative variables are expressed as means  $\pm$  SD.

	Chronic Chagas Heart Disease			p
	CCHD I (n=65)	CCHD II (n=65)	CCHD III (n=47)	
Age	51.6 $\pm$ 12.9	52.2 $\pm$ 11.8	57.4 $\pm$ 10.11	<0.001
Sex (n)				
Male	35	32	24	NS
Female	30	33	23	
Hypertension (n)	11	20	22	<0.001
Systolic blood pressure (mmHg)	120 $\pm$ 10.33	125.5 $\pm$ 11.7	134 $\pm$ 9	<0.01
Diastolic blood pressure (mmHg)	77.2 $\pm$ 8.44	82.4 $\pm$ 8.2	93.4 $\pm$ 9.2	<0.01
Antibodies				
IODN-p2 $\beta$	4.631 $\pm$ 2.328	4.785 $\pm$ 3.021	4.607 $\pm$ 2.98	NS
IODN-B13	5.085 $\pm$ 3.097	5.055 $\pm$ 2.591	7.372 $\pm$ 3.3465	<0.05
Serum lipids (mmol/L)				
Total cholesterol	4.31 $\pm$ 0.38	4.19 $\pm$ 0.42	4.11 $\pm$ 0.45	NS
HDL-c	1.01 $\pm$ 0.06	1.09 $\pm$ 0.10	1.02 $\pm$ 0.1	NS
TG	1.09 $\pm$ 0.18	1.14 $\pm$ 0.19	1.19 $\pm$ 0.16	NS
LDL-c	2.69 $\pm$ 0.36	2.71 $\pm$ 0.41	2.67 $\pm$ 0.38	NS
Atherogenic index	0.11 $\pm$ 0.05	0.15 $\pm$ 0.06	0.22 $\pm$ 0.066	<0.05

NS: Not significant

CCHD: chronic Chagas heart disease.

Comparison among CCHD groups showed that CCHD III cases were older<sup>1</sup> and presented higher proportion of patients with hypertension.<sup>2</sup> The CCHD I group showed lower levels of systolic<sup>3</sup> and diastolic<sup>4</sup> blood pressure, whereas CCHD III showed increased levels of anti-B13<sup>5</sup> and Atherogenic Index.<sup>6</sup>

res se asocian con la gravedad de MCC. Sin embargo, la evaluación de la contribución de los principales factores de riesgo cardiovascular (FRC), como la hipertensión y la dislipidemia aterogénica (DA), a la gravedad de la MCC es escasa, a pesar de su papel bien establecido en la enfermedad arterial coronaria, insuficiencia cardíaca y accidente cerebrovascular.

**Objetivo:** explorar la posible relación de la presión arterial y la DA con el perfil clínico de los pacientes con MCC.

**Método:** estudio transversal en pacientes con serología positiva para *T. cruzi* categorizados de acuerdo a la clasificación estándar de MCC. Se realizó en todos los pacientes un examen clínico-cardiológico completo. Los autoanticuerpos inducidos por *T. cruzi* se evaluaron mediante ELISA.

**Resultados:** se observó que los niveles de índice aterogénico (IA) aumentaron significativamente en relación con la gravedad de la etapa de la MCC, siendo que los pacientes pertenecientes al grupo MCC III mostraron los más altos valores de IA. Por otra parte, los pacientes con miocardiopatía dilatada global con fracción de eyección reducida mostraron mayores niveles de IA. En lo que respecta a autoanticuerpos, anti-B13 también mostró relación con la gravedad de la enfermedad.

**Conclusión:** observamos que el IA se correlacionó con las etapas de MCC y contribuyó, en asociación con anti-

cuerpos anti-B13, a la predicción de insuficiencia cardíaca sistólica.

**Palabras clave:** enfermedad de Chagas, miocardiopatía chagásica, dislipidemias.

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