Cardiovascular comorbidities in patients with chronic Chagas disease

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Background: The treatment of Chagas disease (DC) is an important challenge for health services, especially when the disease is associated with comorbidities that increase cardiovascular risk, such as hypertension (HA), diabetes mellitus (DM), dyslipidemia, obesity, hypothyroidism and lifestyle habits that compromise the health of the individual. This study aims to describe and understand the demographic characteristics of patients in the chronic phase of CD and the risk factors for cardiovascular diseases.

Methods: This was a descriptive, cross-sectional study of 168 patients with chronic CD with the clinical forms: cardiac, digestive, undetermined and mixed. The presence of HA, DM, dyslipidemia, BMI, hypothyroidism, cardiovascular complications and life habits were evaluated.

Results: The percentage of female patients was 50.6%. The mean age was 60.8±8.5 years. Of these patients, 53.6% had the indeterminate form, 20.8% the digestive form, 19.6% the cardiac form and 6.0% the mixed form. Overweight/obesity was present in 65.5% of the patients, HA in 51.2%, dyslipidemia in 45.8%, DM in 23.8%, hypothyroidism in 6.6% and cardiovascular complications in 5.4%. Regarding life habits, 75.6% were sedentary, 14.3% smokers and 23.8% mentioned alcohol consumption.

Conclusions: Individuals with chronic CD are elderly and present comorbidities related to age and increased cardiovascular risk, which may exacerbate the health status of infected individuals. In the absence of specific treatment for chronic CD it is important to adopt measures that aim at the control of these comorbidities and that favor the quality of life of these individuals.

Keywords: Chagas disease (CD); chronic Chagas disease (chronic CD); cardiovascular comorbidities

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Introduction

Chagas disease (DC) has as etiological agent the protozoan *Trypanosoma cruzi*. It is endemic in 21 Latin American countries and is considered one of the 17 neglected tropical diseases in the world in which it affects about 8 to 10 million people, 3 million in Brazil alone. In addition, it is estimated that there are more than 25 million people living

in an area of transmission risk (1,2).

For years the main form of transmission of CD was the vector, through contact with the feces of the insect vector of the family *Reduviidae*, subfamily *Triatominae*. However, CD control programs in Latin America have caused the Pan American Health Organization (PAHO) to declare some countries free from transmission by the main vector,

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Triatoma infestans. Thus, other transmission mechanisms support CD permanence such as blood transfusions, organ transplants, accidents with contaminated material, congenital (vertical), consumption of food containing the parasite and other triatomine species (1-3).

The interruption of transmission by the main vector and the efforts to detect CD in blood bank screening significantly reduced acute cases in Brazil (4). On the other hand, individuals infected in the past have evolved into the chronic phase of CD and are currently at an advanced age, which favors the appearance of chronic-degenerative comorbidities that increase cardiovascular risk, hinder their treatment by the health services and affect their quality of life, besides providing the worsening of the CD. Among them, hypertension (HA), diabetes mellitus (DM), dyslipidemia, hypothyroidism, overweight and other heart diseases (5-7).

Thus, the objective of the present study was to describe the clinical-epidemiological profile and to identify the risk factors for cardiovascular diseases of individuals with chronic CD attended at the Clinic for Tropical Diseases of the Medical School of Botucatu (HCFMB), São Paulo, Brazil.

Methods

This is a cross-sectional, descriptive, non-experimental and quantitative study. We included patients with diagnosis of CD in its chronic phase, both sexes, assisted at the Clinic for Tropical Diseases of the Medical School of Botucatu, UNESP during 2014 to 2016.

Data were collected through medical interview, regarding age, gender, place of birth, origin, tobacco use disorder, alcoholism, HA, DM, sedentary lifestyle, dyslipidemia, body mass index (BMI) and clinical form.

To classify the tobacco use, patients were grouped into three categories, according to the World Health Organization (WHO), in which "non-smokers" were those who have never smoked or smoked less than 100 cigarettes during their whole life; "ex-smokers" were those who have smoked at least 100 cigarettes during their life, but stopped; and "current smokers" were those who have smoked 100 or more cigarettes during their lives and are still smoking (8).

Sedentary lifestyle was verified through adaptations of the guidelines of the International Physical Activity Questionnaire (IPAQ). The classification of the physical activity level was divided into three categories: "sedentary" when the patients do not perform any physical activity; "active" when they perform any vigorous physical activity more than three times a week for over 20 minutes and; "very active" when they perform any vigorous physical activity more than five times a week for over 30 minutes (9).

To determine the alcoholism degree, the criteria of the WHO were used: "moderate consumption" for those who drink at least two doses of alcohol a day, or more than twice a week; "social drinking" when they drink alcohol in the company of other people and only for socially acceptable reasons and manners; "no consumption" for those who never have consumed alcohol. Other definitions are not reported since our study did not find them (10).

After obtaining anthropometric data (weight and height), weight was classified according to the BMI through parameters established by the WHO with the formula "weight (kg)/height (m²)". The patients were grouped as follows: underweight (BMI <18.5 kg/m²), eutrophic (BMI: 18.5–24.9 kg/m²), overweight (BMI: 25.0–29.9 kg/m²), obesity I (BMI: 30.0–34.9 kg/m²), obesity II (BMI: 35.0–39.9 kg/m²) and obesity III (BMI ≥40 kg/m²) (11).

HA, DM and dyslipidemia diagnoses were conducted by a doctor during monitoring of patients, which were classified according to the presence or absence of the pathology by consulting the Electronic Patient Record.

The definitions of clinical manifestations followed the criteria of the II Brazilian Consensus on Chagas Disease: chronic Chagas heart disease (CCHD), the chronic Chagas gastrointestinal disease (CCGD), indeterminate form of human chronic CD (IFCCD) and the mixed form of chronic CD (MFCCD), when there are clinical symptoms of CCHD and CCGD. Those who were diagnosed with CCHD presented changes in the electrocardiography (ECG) and/or echocardiography and clinical symptoms such as palpitations, arrhythmia, ventricular extrasystole, tachycardia and different degrees of heart block. Those diagnosed with CCGD had radiological changes in the esophagus and colon, through barium enema and esophagus, stomach and duodenum (ESD) contrasted study. Patients with IF had no changes in the ECG, barium enema and ESD exams and no clinical symptoms.

The data were entered in the software Microsoft Office Excel 2013 and analyzed through the Epi-Info[™] software, version 7.2, provided by the Center for Disease Control and Prevention, which enabled descriptive analysis of frequency and association of variables.

All patients underwent serology for confirmation of CD diagnosis through enzyme-linked immunosorbent assay (ELISA), hemagglutination inhibition test (HAI) and

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indirect fluorescent antibody technique (IFAT) with IgG research.

Consent to participate in the study was obtained after information and clarification on the research objectives and signature of the informed consent form. The research was submitted to the Research Ethics Committee of the Medical School of Botucatu, UNESP.

Results

In this study, 168 patients with CD in the chronic phase were included, being 85 (50.6%) women and 83 (49.4%) men. The age of patients ranged from 36 to 89 years old, with a 60.8 ± 8.5 years mean, being 60.1 ± 8.2 for women and 61.5 ± 8.8 years for men. The profile of the patients included is present in *Table 1*. It is worth mentioning that 63.9% of the men were older than 60 years old while the 51.8% women were younger than 60 years old. The clinical manifestations CCHD, CCGD and MFCCD showed percentage of 69.2% in individuals over 60 years old.

Regarding place of birth, the *Figure 1A* shows 125 (74.4%) were born in the State of São Paulo, 22 (13.1%) in the state of Paraná, 11 (6.5%) in the state of Minas Gerais and 10 (6.0%) in other states. Among the patients born in the state of São Paulo, 54 (43.2%) belonged to municipalities from Itapeva microregion, including Itaporanga (17.6%), Taquarituba (9.6%) and Coronel Macedo (5.6%). Considering the current hometown, 70 municipalities were mentioned, but three of them outstand: Itaporanga (22–13.1%), Itaí (14–8.3%) and Taquarituba (12–7.1%) (*Figure 1B*).

The frequency of clinical manifestation was 90.0–53.7% to IFCCD, followed by 35.0–20.8% to CCGD, 33.0–19.6% for CCHD and 10.0–5.9% to MFCCD. There was little difference regarding IFCCD frequency between the sexes; however, for the symptomatic clinical manifestations (CCHD, CCGD and MFCCD) women were affected by the DF (22.0–25.8%) while men were affected by the CCHD (18.0–21.6%). The symptomatic clinical manifestations had frequency in the age group from 60 to 69 years for both sexes, while IF was frequent in the age group from 50 to 59 years.

Considering the BMI, 110 (65.5%) patients were overweight, of which 48 (28.6%) had some degree of obesity. When asked about life habits, 127 (75.6%) do not do any type of physical activity, 24 (14.3%) were smokers and 40 (23.8%) reported consuming alcohol daily or occasionally.

According to Table 2, out of the 168 patients with

chronic CD, 86 (51.2%) had HA as comorbidity, 77 (45.8%) had dyslipidemia, 40 (23.8%) had DM, 11 (6.6%) had hypothyroidism and 9 (5.4%) had some type of cardiovascular complication, such as stroke and myocardial infarction. *Table 3* shows number of comorbidities of the patients included in the study.

It is worth mentioning that, as shown in *Figure 2*, HA, dyslipidemia, hypothyroidism and cardiovascular complications were observed with regular times frequent in patients who had a defined clinical manifestation, except DM. Hence, it is worth highlighting HA and dyslipidemia as frequent comorbidities associated with chronic CD, with 55.8% and 57.1% respectively. The comorbidities such as HA was observed in 40.1% of patients and dyslipidemia was observed in 33.6% and the age range of this group of patients were over 60 years.

Discussion

As aforementioned, CD is a public health problem with many aspects not yet clarified, particularly the cardiovascular risk factors related to the disease. This study observed no significant difference between the sexes, although most men included in the study were diagnosed in blood banks after the donation. Thus, our findings are consistent with data found in the literature, according to which the CD affects men and women indistinctly. On the other hand, some authors suggest that the male prevalence in the CD is significantly lower comparing with women, since women seek health services more often for routine exams and prevention than men; man's diagnosis is fair and less notify than adults woman (12,13).

Regarding age, both sex and the age group found $(60.8\pm8.5 \text{ years})$ were lower than those found by de Almeida *et al.* (2007) and Alves *et al.* (2009), although still within the age group considered young elderly. The mean age of younger individuals (under 60 years) was 53.4 ± 5.6 years, which could mean aging of individuals infected in that age group. Therefore, aging of this population can favor the emergence of comorbidities that affect the quality of life of patients, which can worsen the prognosis if associated with this disease. The association of chronic CD with comorbidities such as HA, DM and dyslipidemia represent a major challenge to public health (7,13,14).

Regarding clinical manifestations of chronic CD, there was predominance (53.5%) of IFCCD for both sexes, which is in agreement with other authors. This may be related to the fact that the study was conducted in patients of an

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Table 1 Epidemiological variables of 168 individuals with chronic Chagas disease (CD)

Variables	Men (n=83)		Women (n=85)		Total (n=168)	
variables	Number	%	Number	%	Number	%
Age group						
30 to 39 years old	0	0.00	1	1.18	1	0.60
40 to 49 years old	9	10.84	5	5.88	14	8.33
50 to 59 years old	21	25.30	38	44.71	59	35.12
60 to 69 years old	39	46.99	31	36.47	70	41.67
70 to 79 years old	13	15.66	9	10.59	22	13.10
80 to 89 years old	1	1.20	1	1.18	2	1.19
Ethnicity						
White	62	74.70	71	83.53	133	79.17
Black	12	14.46	10	11.76	22	13.10
Brown	9	10.84	4	4.71	13	7.74
Clinical manifestation						
Cardiac	18	21.69	15	17.65	33	19.64
Digestive	13	15.66	22	25.88	35	20.83
Mixed	6	7.23	4	4.71	10	5.95
Indeterminate	46	55.42	44	51.76	90	53.57
Physical activity						
Very active	12	14.46	12	14.12	24	14.29
Active	7	8.43	10	11.76	17	10.12
Sedentary	64	77.11	63	74.12	127	75.60
Tobacco use disorder						
Smoker	12	14.46	12	14.12	24	14.29
Former smoker	43	51.81	18	21.18	61	36.31
Non-smoker	28	33.73	55	64.71	83	49.40
Alcoholism						
Daily	2	2.41	2	2.35	4	2.38
Occasionally	29	34.94	7	8.24	36	21.43
Does not consume	52	62.65	76	89.41	128	76.19

outpatient clinic. When compared with the age group, IFCCD was more frequent (67.5%) in patients under 60 years old, while the symptomatic clinical manifestations were more frequent in individuals over 60 years old (69.2%). Although asymptomatic, presence of parasites may trigger inflammatory responses, which contributes to the emergence and aggravation of cardiovascular changes.

These changes and other comorbidities can reduce time and quality of life of infected individuals (5,15-17).

The symptomatic clinical manifestations (CCHD, CCGD and MFCCD) are manifestations of the chronic phase of CD. They may develop late in approximately 30% to 40% of the infected individuals. Among them, CCHD is the most severe manifestation of the disease,



Figure 1 Place of birth (A) and origin (B) of the patients with chronic Chagas disease. Blue circles contain the number of patients per state. Red circles contain the number of patients per city.

with complex physiopathology and big impact on indicators of morbidity and mortality. Our findings are consonant with many authors, who relate the CCHD to men. In this study, CCHD was reported in 21.7% of men and 17.6% of women (6,7,18,19).

CCGD affects approximately 10% of individuals with chronic CD, with digestive manifestations as megacolon and esophageal achalasia. Clinical signs vary from asymptomatic motility disorders to more severe sings such as deglutition disorders, gastroesophageal reflux, chronic constipation and weight loss (20).

When it comes to treating the individual with chronic CD with little active and potentially toxic drugs, the objective must always focus on controlling the symptoms and improving quality of life. Thus, the treatment of comorbidities that affect them can prevent future complications as well as limit the progression of the disease and increase the survival rate of these individuals. The comorbidities evaluated in the study—obesity, HA, DM, dyslipidemia, hypothyroidism, cardiovascular complications, tobacco use disorder, alcoholism and sedentary lifestyle in addition to mortality, can cause irreversible damage and directly affect the quality of life of individuals and, if they happen simultaneously, there may be an increased risk comparing with them separately (21,22).

In Brazil, HA affects approximately 32.5% of the adult population and is directly or indirectly responsible for 50% of deaths caused by cardiovascular diseases. In this study, HA was the most reported comorbidity (51.2%) among individuals with chronic CD, the same found in several studies, such as Silva *et al.* (2010), who found HA in 64% of the individuals studied. According to the Brazilian Society of Cardiology (2016), about 60% of the hypertensive subjects are older adults older than 60 years, similar to the number we found, which was 63.9%. These data suggest that CD may be responsible for blood pressure elevation, especially if it comes along with aging of the individuals (13,23-25).

By evaluating all the clinical manifestations, we noticed that HA was more frequent in IFCCD; however, when the clinical manifestations were individually analyzed, the prevalence was in individuals with CCHD. This prevalence was also found by Bertanha *et al.* (2008) and can be justified by the advanced age of patients with CCHD and more time for the disease evolution. Thus, the incidence of HA with the chronic CD is a factor that must be considered in the follow-up of the individual, since this situation can result in a functional impairment of the cardiovascular system (26,27).

Dyslipidemia was the second comorbidity that most affected individuals with chronic CD, which was found in 41.6% of them, higher than the number found by Alves *et al.* (2009) in a study with individuals with chronic CD at the Clinic Hospital of the University of Campinas. Dyslipidemia along with HA represent important factors of initiation and development of cardiovascular diseases. Another study by Teston *et al.* (2016), found over 50% individuals with changes in lipid levels, with odds 2.6 higher of developing a cardiovascular disease than normal individuals (13,28,29).

In this study, DM frequency was low. There are very few studies that relate DM with chronic CD; however, Campos and Cançado (1962) showed that patients with the IFCCD showed lower insulin response. Oliveira *et al.* (1993) demonstrated parasympathetic denervation and injury in the pancreatic cells. Among the individuals with DM, 75% presented overweight and obesity. This association between excess of weight and DM becomes even more important in the Brazilian population, since according to studies, over half of people are overweight. Therefore, it is suggested that DM is a comorbidity related to modifiable risk factors, and when combined with other comorbidities, it raises the risk of cardiovascular diseases (30-33).

Another important aspect in this study is associated

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Table 2 Comorbidities associated with patients with chronic CD										
Comorbidities	Cardiac (n=33)		Digestive (n=35)		Mixed (n=10)		Indeterminate (n=90)		Total (n=168)	
Comorbialities	Number	%	Number	%	Number	%	Number	%	Number	%
BMI (kg/m²)										
BMI ≤18.5 (underweight)	0	0.00	1	2.86	0	0.00	1	1.11	2	1.19
BMI >18.5 and ≤24.9 (eutrophic)	12	36.36	11	31.43	6	60.00	27	30.00	56	33.33
BMI ≥25.0 and ≤29.9 (overweight)	10	30.30	7	20.00	2	20.00	43	47.78	62	36.90
BMI \geq 30.0 and \leq 34.9 (obesity I)	7	21.21	11	31.43	2	20.00	14	15.56	34	20.24
BMI ≥35.0 and ≤39.9 (obesity II)	4	12.12	4	11.43	0	0.00	3	3.33	11	6.55
BMI ≥40.0 (obesity III)	0	0.00	1	2.86	0	0.00	2	2.22	3	1.79
Hypertension										
Yes	24	72.73	18	51.43	6	60.00	38	42.22	86	51.19
No	9	27.27	17	48.57	4	40.00	52	57.78	82	48.81
Diabetes										
Yes	11	33.33	6	17.14	1	10.00	22	24.44	40	23.81
No	22	66.67	29	82.86	9	90.00	68	75.56	128	76.19
Dyslipidemia										
Yes	20	60.61	19	54.29	5	50.00	33	36.67	77	45.83
No	13	39.39	16	45.71	5	50.00	57	63.33	91	54.17
Hypothyroidism										
Yes	4	12.12	2	5.71	0	0.00	5	5.56	11	6.55
No	29	87.88	33	94.29	10	100.00	85	94.44	157	93.45
Cardiovascular complication	าร									
Yes	1	3.03	3	8.57	1	10.00	4	4.44	9	5.36
No	32	96.97	32	91.43	9	90.00	86	95.56	159	94.64

Table 3 Number of comorbidities in	patients with chronic CD
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Number of comorbidities	Distribution	%			
4 comorbidities	7	4.2			
3 comorbidities	14	8.3			
2 comorbidities	46	27.4			
1 comorbidity	61	36.3			
No comorbidity	40	23.8			



Figure 2 Comparison between the frequency of comorbidities in individuals and clinical manifestation of CD. CD, Chagas disease.

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with excess of weight. This finding may contribute due to the prevalence of HA and dyslipidemia as observed. In this study, over 65% of the individuals were overweight and obese. This demonstrates the importance of adopting strategies aimed at encouraging healthy eating habits and physical activity to control several risk factors for cardiovascular diseases.

Among life habits, tobacco use disorder and alcoholism were not significant (14.3% and 23.8%, respectively). However, sedentary lifestyle was observed in 75.6% of individuals. The evaluation of sedentary lifestyle is very important in the development of cardiovascular diseases. Every year, approximately 3.2 million deaths are caused by insufficient physical activity, a factor already considered as public health priority in the world. According to data from the Brazilian Institute of Geography and Statistics (IBGE), in Brazil, sedentary lifestyle reaches about 80.8% of adults. Only in São Paulo city, Mello et al. (2000) verified a 68.7% rate of sedentary adults (34). In a study conducted in Bambuí, in the state of Minas Gerais, the sedentary lifestyle was observed in 29.8% out of the 1,479 patients with the CD (>60 years old). Similar results to ours were found by Geraix et al. (2007), in a retrospective data collection with CD patients assisted at the same outpatient clinic of our study, which reported that 83.3% were sedentary. It shows that in our study population, many individuals are sedentary. This is really worrying, since the sedentary lifestyle can control cognitive functions negatively, increase the risk of myocardial infarction, as well as be a risk factor for many chronic diseases (17,35-38).

Regarding hypothyroidism, a low frequency was observed in the individuals studied. Hypothyroidism is one of the most common endocrine disorders and is characterized by a deficiency in the production of the thyroid hormone. Its prevalence varies, but it is known that individuals at an advanced age and women are the most affected. Although the symptoms are not specific, we know that hypothyroidism is associated with weight gain, HA and cardiovascular changes, which constitute important comorbidities in the chronic CD (39-41)

There was no association between low frequency of cardiovascular complications and other comorbidities as well as the clinical manifestation of the chronic CD.

Conclusions

Finally, we can conclude that most individuals with chronic CD identified in the outpatient service are older adults,

a particularly vulnerable population both for the CD and the association of comorbidities. These comorbidities, individual or associated, may aggravate the health condition of the individual and cause serious cardiovascular damage. In the absence of a specific treatment for the chronic CD, it is important to adopt measures aimed at the control of these comorbidities and that favor the quality of life of these individuals.

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Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/amj.2018.07.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Consent to participate in the study was obtained after information and clarification on the research objectives and signature of the informed consent form. The research was submitted to the Research Ethics Committee of the Medical School of Botucatu, UNESP (No. 1.576.519/2016).

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