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B-type natriuretic peptide and anthropometric measures in a Brazilian elderly population with a high prevalence of *Trypanosoma cruzi* infection

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ABSTRACT

B-type natriuretic peptide (BNP) is a diagnostic and prognostic tool in heart failure and also in Chagas disease, which is caused by the protozoan *Trypanosoma cruzi* and has cardiomyopathy as a main feature. BNP lipolytic actions and *T. cruzi* infection in the adipose tissue have been recently described. We aim to investigate the relationship between BNP and anthropometric measures and whether it is influenced by *T. cruzi* infection. We measured BNP, body mass index (BMI), waist circumference (WC), triceps skin-fold thickness (TSF) and performed serological, biochemical and electrocardiographic exams in 1398 subjects (37.5% infected with *T. cruzi*) in a community-dwelling elderly population in Bambui city, Brazil. Linear multivariate regression analysis was performed to investigate determinants of BNP levels. BNP levels were significantly ($p < 0.05$) higher in *T. cruzi*-infected subjects than in the non-infected group (median = 121 and 64 pg/mL, respectively). BMI, WC and TSF in infected subjects were significantly lower than those in non-infected subjects (24.3 vs. 25.5 kg/m2; 89.2 vs. 92.4 cm; and 14.5 vs. 16.0 mm, respectively). There was an inverse relationship between BNP levels and BMI ($b = -0.018$), WC ($b = -0.005$) and TSF ($b = -0.193$) levels. Infected and non-infected groups showed similar inverse relationships between BNP and BMI ($b = -0.021$ and $b = -0.015$, respectively). In conclusion, there was an inverse relationship between BNP levels and the anthropometric measures. Despite the actions in the adipose tissue, *T. cruzi* infection did not modify the associations between BNP and BMI, suggesting that body mass does not modify the accuracy of BNP in Chagas disease.

1. Introduction

B-type natriuretic peptide (BNP), a 32-amino-acid peptide member of the natriuretic peptide (NP) family, is released by ventricular cardiomyocytes under high pressure and volume overload states. Vasodilation, diuresis, natriuresis, and inhibition of the activities of the renin–angiotensin–aldosterone and the sympathetic nervous systems are among its hemodynamic actions. In clinical practice, BNP plasmatic measurement is used both as a diagnostic tool for exclusion of heart failure [22] and as a predictor of coronary heart disease, stroke, and other cardiovascular outcomes [11]. An additional but less well-studied function of BNP is its action as a promoter of lipolysis in the adipose tissue, which has generated speculation regarding its involvement in the biological mechanisms of obesity and cardiac cachexia [4,15,33]. Population-based studies performed in North America, Europe and Asia have shown that body mass index (BMI) is inversely related to BNP levels, and, consequently, obese individuals have lower BNP levels than lean ones, even in the presence of heart failure [8,9,21,38]. Few studies have addressed the influence of other measures of adiposity on BNP levels that may be important in the application of the peptide as a diagnostic or prognostic tool [9,34].

Cardiomyopathy is the main feature of Chagas disease [6], a disorder caused by the protozoan *Trypanosoma cruzi*, endemic in South America and Central America. It is characterized by heart block, ventricular arrhythmia, and heart failure with left ventricular systolic and/or diastolic dysfunction. Left ventricular systolic and diastolic dysfunctions are associated with higher BNP levels [2,30]. Recently, a large community-based study showed that there was a graded and strong cross-sectional relationship between BNP

Abbreviations: BNP, B-type natriuretic peptide; NP, natriuretic peptides; BMI, body mass index; WC, waist circumference; TSF, triceps skin-fold thickness; *T. cruzi*, *Trypanosoma cruzi*; ECG, electrocardiogram; EDTA, ethylenediaminetetraacetic acid; MEIA, microparticle-based immunoassay; NPAr, natriuretic peptide type-A receptor; cGMP, cyclic guanosine monophosphate; NPCr, natriuretic peptide clearance receptors; NT-proBNP, amino-terminal fraction of B-type natriuretic peptide.

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levels and *T. cruzi* infection in old age and that BNP is an independent predictor for the 10-year mortality rate in infected elderly [17]. In addition, adipose tissue has been described as an important target organ for *T. cruzi* infection [25]. To our knowledge, the effect of *T. cruzi* infection on the relationship between BNP and BMI or other anthropometric measures is unknown.

We aimed to investigate the relationship between BNP and anthropometric measures (BMI, waist circumference and triceps skin-fold thickness) in a large community-dwelling elderly population in Brazil. An additional objective was to examine whether *T. cruzi* infection has an influence on these associations.

2. Materials and methods

2.1. Study population

The study was conducted in Bambuí city (~15,000 inhabitants), which is situated in the southeastern Brazil and is one of the oldest known endemic areas for Chagas disease. The procedures used in the Bambuí Cohort Study of Aging have been described in detail elsewhere [18]. Briefly, the baseline cohort population comprised all residents who were 60 years old or older on January 1, 1997, and who were identified by means of a complete census conducted in the city. A total of 1606 (92.2%) of the 1742 eligible residents participated. The present study is based on the baseline data collection, performed in 1997, comprising standardized interviews, blood tests, blood pressure measurements, and electrocardiogram (ECG).

Participants signed an informed consent form and authorized death-certificate verification. The Bambuí Cohort Study of Aging was approved by the ethics board of the Fundação Oswaldo Cruz, Rio de Janeiro, Brazil.

2.2. BNP measurement

Blood samples for the measurement of BNP were collected in tubes containing ethylenediaminetetraacetic acid (EDTA). BNP was measured using a microparticle-based immunoassay (MEIA/AxSYM, Abbott Laboratories). The lower limits of detection and the average inter-assay coefficients of variation were less than 15 pg/mL and 12%, respectively. Subjects were asked to fast for 12 h prior to an early-morning (6:30–8:30 AM) phlebotomy. The samples were aliquoted and stored at −80 °C until used.

2.3. Body mass index and the other anthropometric measures

Anthropometric measures used in the analysis were BMI, waist circumference and triceps skin-fold thickness. Two high-precision digital scales (range 0–150 kg × 0.1 kg) were used for the measurement of weight (kg) and height (cm). BMI was calculated using the conventional formula of weight in kilograms divided by the square of the height in meters. A CMS Portable Stadiometer kit (CMS Weighing Equipment Ltd., London) was used for measurements of the waist circumference (WC) at umbilicus height and triceps skin-fold thickness (TSF) (mm). The reliability of these measurements was determined by repeating them in a 5% cohort of all of the study participants [19]. All measures were performed with individuals wearing light clothing and no shoes.

2.4. Trypanosoma cruzi infection

Infection with *T. cruzi* at baseline was assessed by concurrently performing a hemagglutination assay (Biolab Mérieux SA, Rio de Janeiro, Brazil) and two enzyme-linked immunosorbent assays (Abbott Laboratories, Inc., North Chicago, IL; and Wiener Laboratories, Rosario, Argentina). The agreement (Cohen's kappa) among these assays was 0.989 ($p < 0.001$). Seropositivity in all three examinations was the criterion for the presence of infection; absence of infection was defined as consistent seronegativity.

2.5. Other measures

The following other measures that had been previously described as being associated with BNP levels were included in this study: age, sex, systolic blood pressure, diabetes mellitus, creatinine, and possible old myocardial infarction [24,37,39]. In addition, the ECG abnormalities related with Chagas disease that have already been associated with increased BNP levels in Bambui cohort population were considered in the analysis [17]. Systolic blood pressure was defined as the mean of two out of three measurements using standard protocols. Fasting blood glucose and creatinine levels were assessed by traditional enzymatic methods. Diabetes was defined as a 12-h-fast glucose ≥126 mg/dL and/or the use of insulin or oral hypoglycemic agents. Electrocardiographic variables were verified by 12-lead ECGs digitally recorded at rest using standardized procedures. ECGs were analyzed by experienced cardiologists at the ECG Reading Center (EPICARE Center, Wake Forest University School of Medicine, Winston-Salem, NC) and classified according to the Minnesota code criteria [29]. ECG abnormalities considered in this study were possible history of myocardial infarction (Minnesota codes 1.3.x and 4.1.x, 4.2, 5.1, or 5.2), complete intra-ventricular block (Minnesota code 7.1, 7.2, 7.4, or 7.8) and frequent ventricular premature beats (Minnesota code 8.1.2 or 8.1.3).

2.6. Statistical analysis

Verification of the normal distribution of continuous data was accomplished by construction of histograms and normal plots. Variables with a skewed distribution were log-transformed. Continuous variables were described by the mean and standard deviation or the median and the inter-quartile range. Participant characteristics, stratified by *T. cruzi*-infection, were compared by the Student's *t*-test, Pearson's chi-square test or the Mann–Whitney two-sample rank-sum test for differences between means, frequencies or medians, respectively. Multivariable linear regression models were performed to assess the association of log BNP with anthropometric measures (BMI, waist circumference and triceps skin-fold thickness) adjusting to age, sex, Chagas disease, systolic blood pressure, diabetes mellitus, log-transformed serum creatinine levels, possible history of myocardial infarction, complete intra-ventricular block and frequent ventricular premature beats on an ECG for the whole population and for *T. cruzi* infected and non-infected groups separately. Afterwards, we compared the regression coefficients of infected persons with non-infected persons (Ho: $B_{CHD} = B_{non\text{-}CHD}$, where B_{CHD} is the regression coefficient for infected and $B_{non\text{-}CHD}$ is the regression coefficient for non-infected) [1]. All tests were two-sided and a significance level of 5% was used. Statistical analyses were conducted using STATA 10.1 statistical software (Stata Corporation, College Station, TX).

3. Results

Of the 1606 cohort subjects enrolled, 1398 participants (87.1%) for whom complete data on all study variables were available were included in this analysis. Exclusion criteria included the absence of blood tests for BNP concentration and/or *T. cruzi* infection ($n = 132$), missing data for any other variable in the study ($n = 59$), and inconclusive results for *T. cruzi* infection ($n = 17$). The subjects included in the analysis were younger than those who were excluded (mean ages were 68.9 years (standard deviation (SD), 7.0) and 72.4 years (SD, 9.3), respectively; $p < 0.001$).

Table 1
Characteristics of total and *Trypanosoma cruzi*-infected and non-infected participants.

Characteristics	Total (*n* 1398)	*Trypanosoma cruzi* infection		*p*-Value
		Yes (*n* = 524)	No (*n* = 874)	
Age, mean (SD)	68.9 (7.0)	69.2 (6.9)	68.6 (7.0)	0.108
Female sex, *n* (%)	850 (60.8)	396 (67.9)	454 (56.5)	<0.001
BNP in pg/ml, median (IQR)	80 (43–148)	121 (63–204.5)	64 (34–112)	<0.001
Body mass index in kg/m², mean (SD)	25.0 (4.9)	24.3 (5.0)	25.5 (4.8)	<0.001
Waist circumference in cm, mean (SD)	91.2 (11.2)	89.2 (11.2)	92.4 (11.0)	<0.001
Skin-fold thickness in mm, median (IQR)	15.5 (10.2–22.4)	14.5 (10.2–22.2)	16.0 (11.0–23.0)	0.042
Systolic blood pressure in mm Hg, mean (SD)	137.4 (22.4)	135.5 (22.90)	138.6 (22.0)	0.012
Diabetes mellitus, *n* (%)	200 (14.3)	55 (10.5)	145 (16.6)	0.002
Serum creatinine in mg/dL, median (IQR)	0.85 (0.75–0.99)	0.85 (0.76–0.98)	0.85 (0.75–0.99)	0.601
Potential prior myocardial infarction, *n* (%)	57 (4.1)	29 (5.5)	28 (3.2)	0.036
Intraventricular block, *n* (%)	191 (13.7)	144 (27.5)	47 (5.4)	<0.001
Frequent premature beats, *n* (%)	90 (6.4)	53 (10.1)	37 (4.2)	<0.001
Pathological Q wave, *n* (%)	57 (4.1)	29 (5.5)	28 (3.2)	0.024

p-Value: Student's *t*-test, Pearson's chi-square test and the Mann–Whitney two-sample rank-sum test for differences between means, frequencies and medians, respectively.

The baseline prevalence of *T. cruzi* infection was 37.5%, comprising 524 and 874 participants in the *T. cruzi*-infected and non-infected groups, respectively. Females were predominant in both groups (67.9% and 56.5%, respectively). The median BNP level was 80 pg/mL (interquartile range (IQ) 43–148), with significantly higher values in the *T. cruzi*-infected than in the non-infected group (median BNP 121 pg/mL (IQ, 63–204.5) versus 64 pg/mL (IQ 34–112), respectively). Regarding the anthropometric measures, BMI was significantly lower in the *T. cruzi*-infected than in the non-infected group (24.3 (SD 5.0) versus 25.5 (SD 4.8), respectively). Waist circumference (89.2 cm (SD 11.2) versus 92.4 cm (SD 11.0)) and triceps skin-fold thickness (14.5 mm (IQ 10.2–22.2) versus 16.0 mm (IQ 11.0–23.0)) were significantly lower in infected than in non-infected individuals. Overall participant characteristics and characteristics for each group are depicted in Table 1.

We found an inverse relationship between BNP levels and BMI, which was independent of age and sex ($B = -0.024$; 95% CI −0.034 to −0.013; $p < 0.001$). This association remained highly significant in the fully adjusted model ($B = -0.018$; 95% CI −0.028 to −0.008; $p < 0.001$). We also found an inverse association between waist circumference and BNP levels in the age–sex adjusted model ($B = -0.008$; 95% CI −0.013 to −0.004; $p < 0.001$) and in the fully adjusted model ($B = -0.005$; 95% CI −0.010 to −0.001; $p < 0.05$). Furthermore, an inverse relationship between BNP levels and triceps skin-fold thickness was also found in both univariate and adjusted models ($B = -0.193$; 95% CI −0.306 to −0.081; $p < 0.01$)

Both *T. cruzi*-infected ($B = -0.021$; 95% CI −0.039 to −0.005; $p = 0.013$) and non-infected ($B = -0.015$; 95% CI −0.028 to −0.003; $p = 0.017$) subjects showed a significant inverse association between BNP levels and BMI. Statistically significant associations between BNP levels and waist circumference ($B = -0.009$; 95% CI −0.017 to −0.002; $p = 0.017$) and triceps skin-fold thickness ($B = -0.328$; 95% CI −0.517 to −0.139; $p = 0.001$) were verified among *T. cruzi*-infected subjects; however, this association was not statistically significant in the non-infected group ($B = -0.003$; CI −0.008 to 0.002; $p = 0.222$ and $B = -0.105$; CI −0.246 to 0.362; $p = 0.145$, respectively). In addition, the differences of the regression coefficients between the infected and non-infected groups were not statistically significant for any of the anthropometric measures considered in the present analysis (*p*-values = 0.562, 0.178 and 0.390 for BMI, waist circumference and log triceps skin-fold, respectively). See Fig. 1 for crude correlations between log BNP and the anthropometric measures among infected and non-infected individuals.

4. Discussion

The results of this cross-sectional study of community-dwelling elderly with a high prevalence of *T. cruzi* infection showed an inverse relationship between BMI and BNP levels. This association was independent of age, sex, systolic blood pressure, diabetes mellitus, blood creatinine, and selected ECG abnormalities previously reported as being associated with increased BNP levels. Most important, our results showed for the first time that this inverse association is also present in elderly individuals infected with *T. cruzi*.

Population-based studies have demonstrated an inverse relationship between BNP and BMI [9,34,38]. This relationship seems to be consistent throughout diverse clinical contexts, such as acute dyspnea in the emergency department [21] and ambulatory patients with metabolic syndrome [37]. A recent review performed by our group showed low BNP levels in obese subjects, even when they presented with heart failure [4]. Lower BNP levels have been proposed to maintain the diagnostic accuracy of the peptide in obese patients [8]. To the best of our knowledge, none of these studies specifically addressed the relationship between BNP and BMI in elderly subjects.

The findings of an inverse association between BNP and BMI are considered paradoxical because higher BMI levels are associated with a pressure and volume overload in the heart, which should lead to increased BNP secretion by cardiomyocytes. Most likely, there is a connection between the recently described action of NP as potent activators of lipolysis in adipocytes, their role in the perpetuation of obesity states and the paradoxically low levels of BNP in obese subjects [32]. Binding of NP to the trans-membrane type-A receptor (NPAr) in adipocytes leads to increased levels of cyclic guanosine monophosphate (cGMP) and the activation of human phospholipase and perilipin A. This activation ultimately results in the hydrolyzation of triglycerides into non-esterified fatty acids and glycerol [33]. NP clearance receptors (NPCr) are also highly expressed in human adipose tissue and could contribute to increased clearance and the consequent low levels of circulating NP in obesity. However, the fact that the biologically inactive amino-terminal fraction of BNP (NT-proBNP), which is not degraded by NPCr, is also decreased in obese persons weakens this hypothesis [31]. Hence, alternative explanations for the reduced levels of BNP in obese subjects involve increased degradation of NP by neutral endopeptidases, which are zinc metallo-peptidases widely expressed in the vasculature, or by the action of phosphodiesterases, which are biological regulators of cGMP activity [23].

BNP has an important role in diagnosis and prognosis of various cardiac abnormalities, such as heart failure [5] and coronary disease [14,20]. In the elderly, BNP is an independent predictor of mortality from heart failure [12,28] and from non-cardiac conditions [3,36,40]. BMI is also a predictor of overall mortality in the elderly: underweight and obese older subjects are at greater risk of death than normal weight and overweight persons [7]. BMI also predicts

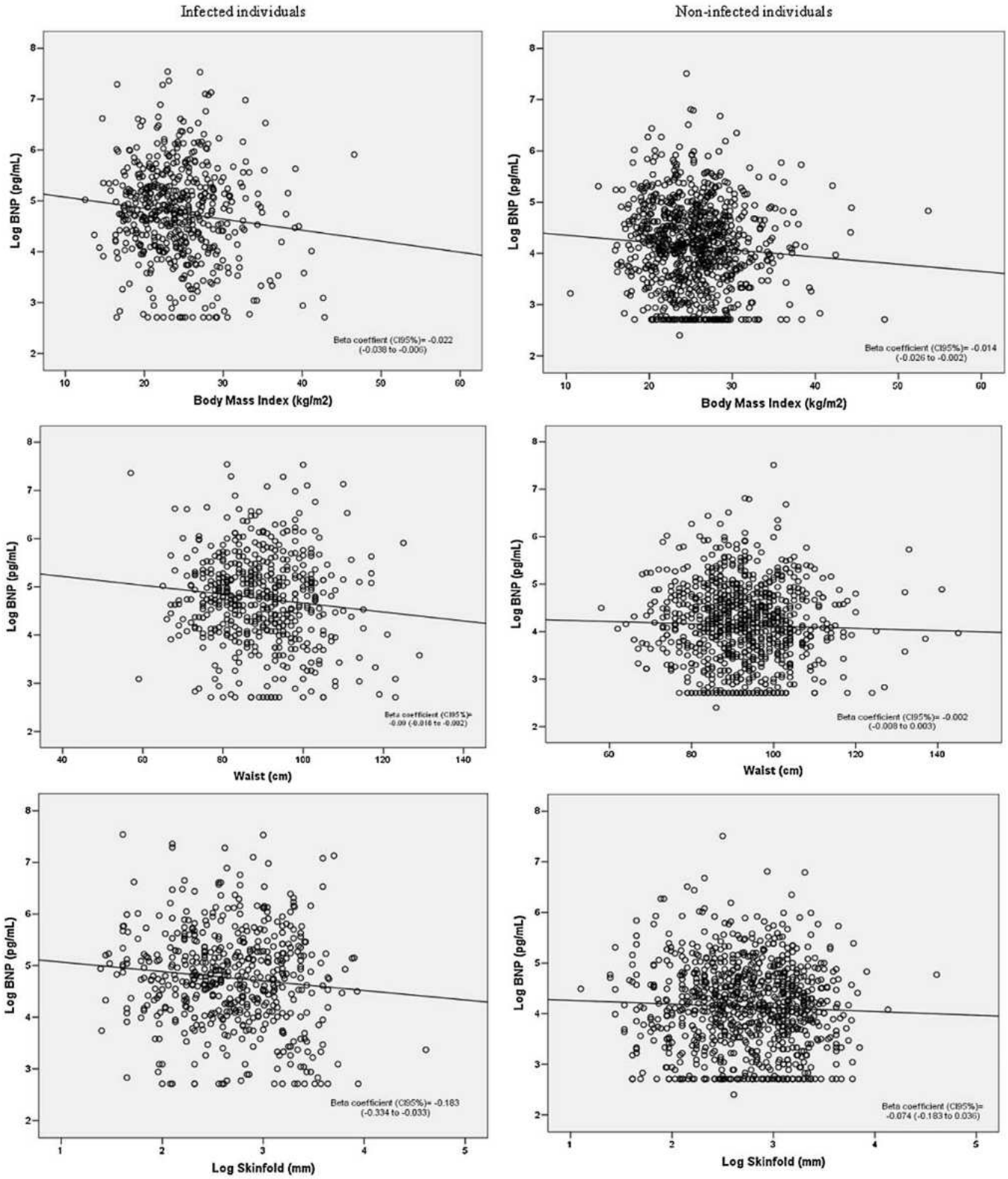

Fig. 1. Correlation between log-transformed B-type natriuretic peptide (BNP) levels and body mass index, waist circumference and log-transformed skin-fold thickness among individuals infected and non-infected with *Trypanossoma cruzi*.

mortality in subjects with heart failure, with lower mortality rates in the overweight and obese categories, a phenomenon called obesity paradox [27]. Thus, it is appropriate to consider whether the relation between BNP and BMI affects the prognostic role of BNP. In subjects with Chagas disease, increased BNP levels are independent predictors of mortality in both clinical settings and in the community [17]; however, the influence of BMI on this association warrants further investigation.

Adipocytes are an important target of *T. cruzi* infection and a reservoir from which parasites can be reactivated during periods of

immunosuppression [25,26]. Furthermore, individuals with Chagas disease and chronic heart failure with high NP levels have low leptin levels that are independent of BMI levels [13]. We sought to determine whether there is a connection between natriuretic peptides, the inflammatory phenotype induced by infection in the adipocytes and the consequences on adipocytokines. The denervation of the sympathetic nervous system induced by *T. cruzi* in both the heart and the adipose tissue [10] can also be related to energy stores, metabolic profile and BMI in Chagas disease. We found an inverse relationship between BNP and waist circumference and skin-fold thickness, which are measures of visceral and subcutaneous fat mass, respectively [16]. Few population-based studies have investigated the relationship between BNP levels and these markers of fat mass [9,34,35]. Our results are consistent with the findings of an Asian cohort, which detected that these two components of fat mass were inversely related to BNP levels [34]. Conversely, the results of another large-based population cohort with individuals aged 30–65 years found only lean mass to be inversely related to BNP [9]. Apparently only infected subjects showed a significant inverse association between BNP and visceral and subcutaneous fat mass after stratification to Chagas disease. Further analysis demonstrated that there was no difference in the *B* coefficient between the infected and non-infected groups. These controversial results indicate the need for larger studies regarding the issue.

The major strengths of this study include the composition and size of the population based sample, the standardized measurement of parameters, and the inclusion of cardiovascular disease risk factors and several other factors previously described as being associated with BNP levels. The high prevalence of *T. cruzi* infection makes the Bambuí Cohort unique for studying the influence of BMI and body composition for the potential prognostic clinical use of BNP in Chagas disease. However, this study was limited by its inability to make conclusions on the temporal relationship between BNP levels and anthropometric measures, owing to its cross-sectional nature.

5. Conclusions

In conclusion, our results showed an inverse relationship between BNP levels and BMI, waist circumference, and triceps skinfold thickness. This finding is probably related to BNP metabolic actions that have already been demonstrated by experimental studies. We also found that *T. cruzi* infection does not modify the nature of these associations.

Conflict of interest statement

The authors do not have any conflicts of interest. All authors have approved the final article.

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Glossary

Trypanosoma cruzi: protozoan which is endemic in South America and Central America.
Chagas disease: disease caused by the infection by *Trypanosoma cruzi*. The main clinical characteristics are the cardiomyopathy and the gastrointestinal disorders. In some cases, there is serological infection, but not clinical manifestations (indeterminate form).
Chagas disease: disease caused by the infection by *Trypanosoma cruzi*. The main clinical characteristics are the cardiomyopathy and the gastrointestinal disorders. In some cases, there is serological infection, but not clinical manifestations (indeterminate form).
Acute coronary syndrome: lack of adequate blood supply for the myocardium due to partial or complete obstruction of the coronary arteries. It results in two main clinical manifestations: angina and myocardial infarction.
Complete intra-ventricular block: disorder of the electrical conduction in the heart.
Frequent ventricular premature beats: disorder of the electrical conduction in the heart characterized by the occurrence of a premature beat. It is considered frequent when it occurs at least six times in a minute.
Dyspnea: feeling or sensation of heavy and difficult breath.
Heart failure: clinical syndrome resultant of the inappropriate blood ejection and/or filling of the heart.