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Association of anthropometric variables with therapy-induced cardiotoxicity in women with breast cancer: a pilot study for a randomized clinical trial

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Abstract

Background Doxorubicin (DOX) has been widely used in the treatment of breast cancer, but it is directly associated with late-onset cardiovascular disease (CVD). Whether anthropometric, food intake or other risk factors together with DOX-based chemotherapy can increase the risk of developing cardiotoxicity remains uncertain. We examined the association between anthropometric variables with doxorubicin-induced cardiotoxicity in women with breast cancer.

Methods Twenty-six women (53.7 ± 9.6 y) undergoing DOX-based chemotherapy (408.3 ± 66.7 mg/m^2) participated in the study. We collected data on body composition (bioimpedance), dietary intake (24 h) and cardiac function (echocardiographic assessment of left ventricular ejection fraction, LVEF). All measurements were taken at baseline, one month of treatment completion and one-year follow-up after start of treatment. DOX-induced cardiotoxicity was defined as ≥ 10% absolute decrease in LVEF. Thus, the participants were then grouped as DOX-induced (DIC) or non-DOX-induced (non-DIC) cardiotoxicity. Data are shown as mean ± SD (standard deviation). We performed comparisons between the two groups using Student's t-test for independent samples or Generalized Estimating Equations (groups + 3 evaluation time points) with Bonferroni post-hoc test. Lastly, the correlations were analyzed using Pearson correlation; $p < 0.05$ for all tests.

Results At baseline the participants' body mass index (BMI) was 29.9 ± 7.9 kg/m^2 and LVEF was 67.4 ± 6.2%. Seven of them (26.9%) developed therapy-induced cardiotoxicity (ΔLVEF − 3.2 ± 2.6%; $p < 0.001$). Postmenopausal status and family history of CVD were more prevalent in the DIC group than non-DIC group. We found no consistent BMI changes in the groups over time. Interestingly, the non-DIC group showed a small increase in visceral fat at treatment completion and increased waist circumference at one-year follow-up compared to baseline. These same changes were not seen in the DIC group. We also observed a pattern of correlation of some anthropometric variables with

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LVEF: the more unfavorable the body composition the more pronounced the LVEF decrease at one-year follow-up, though not associated with cardiotoxicity.

Conclusions Our study did not provide sufficient evidence to support that anthropometric variables, food intake or other risk factors increase the risk of developing cardiotoxicity. However, there are apparent trends that need to be further investigated in larger samples.

Keywords Doxorubicin, Body composition, Food consumption, Cardiotoxicity

Background

Breast cancer is the second most common cancer and a leading cause of death among women worldwide [1]. Current survival rates have increased with improved diagnosis and treatment [2]. However, population-based studies have demonstrated that breast cancer survivors are more likely to develop late-onset cardiovascular disease (CVD) [3] which has been associated with anticancer therapies [4]. Furthermore, anticancer therapy has been identified as an independent risk factor for the development of CVD similarly to other risk factors including obesity and smoking [4]. Of the cost-effective antineoplastic agents available for the treatment of breast cancer, doxorubicin (DOX) has been directly associated with late-onset cardiac dysfunction, including arrhythmias, ischemic and thrombotic events and heart failure [4, 5].

Cardiac dysfunction related to the use of antineoplastic agents, also known as cardiotoxicity, occurs when these agents affect the heart resulting in ventricular systolic dysfunction and is chiefly characterized by a decrease in left ventricular ejection fraction (LVEF) [6]. In light of growing evidence showing that antineoplastic agents are associated with the development of CVD, cardio-oncology guidelines have been set out [7] proposing new diagnostic and clinical concepts. However, antineoplastic agents have been associated with a wide variety of clinical manifestations of cardiovascular toxicity. It is challenging to predict or estimate the degree of DOX-induced cardiac dysfunction in patients with breast cancer [7]. There are several methods for the assessment of cardiac function. Global systolic longitudinal strain (GLS) is a major method of measuring cardiac function through echocardiography and an early marker of subclinical or clinical cardiotoxicity in patients undergoing chemotherapy [8].

It is thus crucial to identify factors that can potentially increase the risk of CVD as an effect of anticancer therapy or not to be able to predict cardiovascular outcomes in patients undergoing treatment [9]. Current cardio-oncology guidelines recommend all patients undergoing anticancer therapy to maintain an ideal body weight due to an increased risk of cardiac dysfunction associated with therapy [7]. Body mass index (BMI) is a metric commonly used to define and classify obesity. However, nutritional assessment of patients with cancer should include body composition measurements, especially abdominal fat deposition, because they are directly associated with increased risk of CVD [10, 11]. In addition, these patients should follow a balanced diet (including macronutrients and micronutrients) as it creates a favorable environment for chemotherapy.

To deepen our understanding on the association between body weight, DOX-based therapy and cardiotoxicity, this study aimed to examine the association between anthropometric variables, food consumption and cardiac function in women with breast cancer undergoing systemic chemotherapy with DOX. Secondarily, we investigated the relative risk (RR) for each potential risk factor to be associated with cardiotoxicity. We hypothesize that there is an association between poor body composition (increased relative or absolute body fat, reduced muscle mass, high deposition of visceral adipose tissue) and unbalanced food consumption with therapy-induced cardiotoxicity in women with breast cancer undergoing DOX treatment.

Methods

This study following the principles of the Declaration of Helsinki. We performed a prospective cohort study between January 2019 and December 2020 at the medical oncology outpatient clinic of *Hospital Santa Rita* (HSR) in the city of Porto Alegre, southern Brazil. Cardiac imaging assessments were carried out at *Hospital São Francisco*. Both hospitals belong to *Santa Casa de Misericórdia Hospital Compound* in Porto Alegre. This study was approved by the research ethics committees of *Instituto de Cardiologia do Rio Grande do Sul/Fundação Universitária de Cardiologia* (protocol nr. 3,119,951) and *Santa Casa de Misericórdia Hospital Compound* (protocol nr. 3,061,585).

Sample characteristics

We used convenience sampling due to specific characteristics of volunteers (disease status) as well as special circumstances associated with the COVID-19 pandemic. Our sample comprised female patients over 18 years of age with pathologic diagnosis of primary breast cancer and indication of adjuvant or neoadjuvant anthracycline-based chemotherapy (adriamycin/doxorubicin). Patients with metastatic cancer at diagnosis; prior cancer chemotherapy or radiation therapy; and/or indication of

non-anthracycline chemotherapy regimens (docetaxel and cyclophosphamide) were excluded. Those patients with established CVD, including acute myocardial infarction, stroke, coronary artery disease or valvular heart disease, were also excluded.

Unfortunately, half of this study was conducted under special circumstances due to the COVID-19 pandemic which affected our ability to evaluate a larger sample of volunteers. Participants who were already being followed up completed their assessments by the end of the year 2020. The last patient evaluated completed the study protocol in December 2020. Brazil was hit hard by the pandemic and we decided to terminate the study in the beginning of 2021.

Study flowchart

All volunteers were asked to sign a free informed consent form to participate. The study participants were evaluated at three time points: before starting anthracycline-based therapy (baseline); one month after the last dose of anthracycline (one month of treatment completion); and one year after the beginning of treatment (one-year follow-up). We collected data on demographic and clinical characteristics from medical records and some variables were self-reported, including menopause status, skin color, and level of education; body composition (anthropometric and bioimpedance measurements); dietary intake (24-hour dietary recall [24 h]) and cardiac function (echocardiographic assessment of left ventricular ejection fraction [LVEF] and global systolic longitudinal strain [GLS]) at the three time points evaluated.

Anthracycline-based chemotherapy cycles were repeated every 21–28 days. The participants were provided outpatient care at the clinic according to the local protocol and the Brazilian Ministry of Health guidelines [12].

Anthropometric variables

Body composition assessments were performed in a consultation room at the clinic for the comfort and convenience of the volunteers. Bioelectrical impedance analysis (BIA) and anthropometric methods were used to measure body composition. Body weight and height were measured using a digital scale with a portable stadiometer (Sanny©). Body circumference measures (neck, waist, abdomen, hip and calf) were taken with a two-meter inelastic tape (Cescorf©) with a precision of 0.1 cm. Anatomy landmarks followed the guidelines proposed by the International Society for the Advancement of Kinanthropometry (ISAK) and standardized measurement methods [13].

BIA measurements were taken when participants were not during their menstrual period (if applicable). They were instructed not drink alcohol 48 h prior to testing; not drink tea, coffee or mate infusion 24 h prior to testing; not consume any foods or drinks three hours prior to testing; urinate at least 30 min prior to testing; and remove all metal objects (rings, chains, bracelets, piercings and earrings). All measurements were taken using a tetrapolar device (Omron© HBF-514 C) following a protocol as proposed by Gallagher et al. [14]. Data were collected for total body weight, BMI, body fat percentage (BF%), skeletal muscular mass percentage (MM%) and visceral adipose tissue (VAT). Classification and acceptability of the data collected were based on the procedure described in the manual for the BIA equipment (Omron© HBF-514 C).

Dietary intake assessment

We assessed dietary intake using the 24-hour recall (24 h) for three non-consecutive days at all time points evaluated (baseline, one month of treatment completion and one-year follow-up). We collected information for the first 24 h in a face-to-face visit and then through phone or video interview for all other 24 h.

Dietary information was collected using the multiple-pass 24 h method as recommended [15]: (1) a quick list, when the participants were asked to remember and report all foods and beverages consumed on the day prior to the interview; (2) a list of non-reported food items, when they were asked about sweets, coffee and soft drinks consumed; (3) times and places where they consumed the food and beverage items listed; (4) details about the method of food preparation and amounts consumed; (5) final review to make sure all food items consumed throughout the day were reported. We chose to use the 24 h for dietary assessment to minimize recall bias and consequently errors in calculating dietary intake as it assesses foods consumed on the day prior to the interview.

We calculated dietary calorie and macronutrient and micronutrient intakes using Dietbox© v6.6.1. Mean and dispersion measures were calculated for each macronutrient and micronutrient based on values obtained in every 24 h. The analysis of nutrient intake adequacy was based on the Dietary Reference Intakes [16].

Cardiac function assessment

Skilled evaluators from the study hospitals performed all echocardiographic assessments using an ultrasound device (Philips Epiq 7c). The primary outcome of this study was LVEF calculated using the Simpson method as recommended by the American Society of Echocardiography [17]. GLS measurements were made in the apical views in at least three heartbeats with two-dimensional imaging and frame rates between 40 and 80 frames/second.

The primary outcome was subclinical or clinical cardiac dysfunction defined as an absolute decrease in LVEF by ≥10% [8] or a relative decrease in GLS by ≥15% [18, 19] compared to baseline following the first cycle of DOX chemotherapy.

Lifestyle assessment

We assessed the following lifestyle variables at baseline to rank potential risk factors for doxorubicin-induced cardiotoxicity: physically active (those engaging in physical activity for at least 150 min per week) [20]; smoking (current smokers were those smoking≥5 cigarettes/day for more than 15 days) [21]; and consistent excessive alcohol use (defined as a consumption≥14 units of alcohol per week) [22].

Statistical analysis

We used mean and standard deviation or medians and interquartile range for quantitative variables and absolute and relative frequencies for categorical variables. We calculated median age and used it as a cutoff (below and above median) as an analysis factor. We performed Student's t-test for paired samples to compare variation of the means within the group and the Mann-Whitney test when the data was not normally distributed. For comparison of proportions, we applied Pearson's chi-square or Fisher's exact tests. For comparison of variables over time, the Generalized Estimating Equations (GEE) method with Bonferroni post-hoc test was used. We calculated the relative risk (RR) as the ratio of the absolute risk of exposed and the absolute risk of non-exposed and related 95% confidence intervals to validate RR. We assessed any associations between numerical variables using Pearson or Spearman correlation coefficients. The significance level was set at 5% ($p<0.05$). All analyses were performed using SPSS v27.0.

Results

Sample characteristics

Table 1 shows the characteristics of the sample studied. A total of 26 volunteers participated in the study, median age of 56 years and mean age of 53.7±9.6 years (range 33–63 years). Most were overweight (29.9±7.9 kg/m^2) and postmenopausal (n=18/26; 69.2%) at baseline. The most commonly used regimen was neoadjuvant therapy with a cumulative DOX dose of 408.3±66.7 mg/m^2. The participants showed normal cardiac function at baseline: LVEF was 67.4±6.2% and GLS was −22.1±2.6.

Cardiotoxicity and risk factors

Seven participants (26.9%) developed subclinical or clinical cardiac dysfunction (decrease in LVEF by ≥10% or decrease in GLS≥15% compared to baseline) within one year of DOX treatment (Table 2). To examine

Table 1 Demographic and clinical characteristics of the study participants (n=26)

Age (years) – mean ± SD	53.7 ± 9.6
Skin color – *n* (%)	
white	24 (92.3)
brown	1 (3.8)
black	1 (3.8)
Level of education – mean ± SD	
Incomplete primary education	1 (3.8)
Completed primary education	7 (26.9)
Completed secondary education	13 (50.0)
Completed higher education	5 (19.2)
Family history of breast cancer – mean ± SD	
No	11 (44.0)
Yes	14 (56.0)
Breast cancer molecular subtype – mean ± SD	
Luminal A (ER + or PR+/HER2-/Ki-67 < 14%)	3 (12.0)
Luminal B (ER + or PR+/HER2-/Ki-67 ≥ 14%)	9 (36.0)
Luminal HER* (ER + or PR+/HER2+)	4 (16.0)
HER2+ (ER- and PR-/HER2+)	1 (4.0)
Triple negative (ER-/PR-/HER2-)	8 (32.0)
Family history of CVD – mean ± SD	
No	8 (30.8)
Yes	18 (69.2)
BMI (kg/m^2) – mean ± SD	29.85 ± 7.85
Comorbidities – *n* (%)	
Arterial hypertension	13 (50.0)
Type 2 diabetes mellitus	4 (15.4)
Dyslipidemia	2 (7.7)
CV drug use – *n* (%)	
Antihypertensive agents	13 (50)
Diuretics	6 (23)
Anticoagulant agents	3 (11.5)
Statins	6 (23)
Antidiabetic agents	4 (15.3)
Smoking status† – *n* (%)	
Never smoked	22 (84.6)
Former smoker	1 (3.8)
Current smoker	3 (11.5)
Sedentary lifestyle – *n* (%)	
No	3 (11.5)
Yes	23 (88.5)
Excessive alcohol use† – *n* (%)	
No	24 (92.3)
Yes	2 (7.7)
Menopausal status – *n* (%)	
Premenopausal	8 (30.8)
Postmenopausal	18 (69.2)
Type of treatment – *n* (%)	
Adjuvant	10 (38.5)
Neoadjuvant	16 (61.5)
Other type of treatment‡ – *n* (%)	
Radiotherapy (No/Yes)	21 (84.0) / 5 (19.2)

Table 1 (continued)

Endocrine therapy + trastuzumabe (No/Yes)	22 (84.6) / 4 (15.4)
Total cumulative dose of DOX – mean ± SD	408.3 ± 66.7

BMI, body mass index; CVD, cardiovascular disease; CV, cardiovascular; DOX, doxorubicin. ER, estrogen receptor; PR, progesterone receptors. * Luminal HER is also known as a subtype of Luminal B positive for HER2 defined as "+++ by immunohistochemistry" or "++ by silver-enhanced in situ hybridization" [50]. † See definition in Lifestyle Assessment section. ‡ Radiotherapy was started only after DOX treatment completion and endocrine therapy was administered in four Luminal HER patients

any potential associations between nutritional status and DOX-induced cardiotoxicity (DIC), they were then grouped as DIC or non-DIC (non-DOX-induced cardiotoxicity).

We compared demographic characteristics, clinical and pathological features of breast cancer and prior history of CVD between the two groups based on the development of subclinical or clinical cardiac dysfunction (DIC vs. non-DIC). Table 2 shows differences found in menopausal status, family history of CVD, and lifestyle factors (sedentary) between the two groups.

Body and dietary assessments at three time points

Table 3 summarizes anthropometric changes over the course of DOX treatment. The non-DIC group showed increased visceral fat at the completion of treatment and increased waist circumference at one-year follow-up compared to baseline. These same changes were not seen in the DIC group.

As for dietary changes, a comparison of the two groups did not show no major changes in total calorie intake (Table 3). Both groups showed reduced carbohydrate intake [p(time) = 0.020] at the completion of treatment, which may have been compensated by an increased consumption of total lipids [p(time) < 0.001]. In addition, carbohydrate and total lipid intake returned to baseline values in both groups at one-year follow-up. Similarly, we found increased neck circumferences at the completion of treatment, but they returned to baseline values at one-year follow-up.

Table 4 illustrates potential correlations between anthropometric variables, dietary intake and LVEF. We found a consistent pattern for all anthropometric variables, i.e., the higher the measures of body composition the greater the decrease in LVEF at one-year follow-up compared to baseline, but not for dietary intake (total calories, carbohydrates, proteins, lipids, dietary cholesterol, saturated fat and sodium).

Additional analysis

We calculated the relative risk (RR) for each potential risk factor and related 95% CIs. Although the RR calculated for some variables seemed associated with cardiotoxicity, the associations were not verified in the analysis of 95% CIs for the following variables: age > 56 years (RR 1.82, 95% CI 0.51; 6.53); menopausal status (RR 1.11, 95% CI 0.27; 4.56); history of CVD (RR 1.11, 95% CI 0.27; 4.56); physically inactive (RR 0.50, 95% CI 0.11; 2.35); smoking (RR 2.20, 95% CI 0.63; 7.65); excessive alcohol use (RR 2.00, 95% CI 0.42; 9.42); arterial hypertension (RR 1.14, 95% CI 0.32; 4.12); type 2 diabetes (RR 2.20, 95% CI 0.63; 7.65).

Discussion

In the present study we examined the association of anthropometric variables with DOX-induced cardiotoxicity in women with breast cancer undergoing treatment. We found that 26.9% of the participants developed cardiac dysfunction having a decrease in LVEF by ≥10% or a decrease in GLS by ≥15% at one-year of follow-up of anthracycline-based chemotherapy. But we found no evidence supporting an association of anthropometric variables or food intake with therapy-induced cardiotoxicity. Thus, we reject our initial hypothesis that poor body composition and/or unbalanced food consumption is potentially associated with the development or the severity of DOX-induced cardiotoxicity. Yet, this is a pilot study conducted in a small sample of 26 volunteers and our results should be interpreted with caution.

Until recently cancer was not considered to be related to CVD. However, current data show these conditions share several risk factors, which suggests a common biological pathway [23]. Obesity and visceral adiposity have been directly associated with increased risk of CVD in both the general population and cancer survivors [24]. Yet, they may develop as a result of cancer treatment affecting body composition, specifically leading to increased central adiposity and reduced fat-free mass [25]. But our results did not demonstrate a clear association of poor body composition with therapy-induced cardiac dysfunction. A possible explanation is the small sample used in this study largely because of special circumstances and restrictions imposed due to the COVID-19 pandemic. In addition, food consumption showed no variation in macronutrient and total calorie intake between the groups over time.

A population-based study and a meta-analysis reported that obesity assessed by BMI was an independent risk factor for therapy-induced cardiotoxicity in women with breast cancer undergoing anthracycline and/or trastuzumab treatment [26, 27]. A significant proportion of the participants in our study were overweight (n = 6/26) or obese (n = 11/26) as well as physically inactive (n = 24/26). Regarding their body composition, there was an absolute change in body weight with consequent change in BMI over time. Those women who developed cardiac dysfunction showed reduced BMI compared to baseline immediately after treatment completion while those without cardiac dysfunction showed increased BMI. A similar

Table 2 Doxorubicin-induced cardiotoxicity and potential risk factors

	DIC (*n* = 7) *n* (%)	non-DIC (*n* = 19) *n* (%)	*p*-value
LVEF (%)	-13.2 ± 2.6	2.4 ± 4.9	**< 0.001**[t]
Age (years)	55.9 ± 11.9	52.9 ± 8.9	0.505[t]
Less than 56 (median)	3 (42.9)	12 (63.2)	
≥ 56 (median)	4 (57.1)	7 (36.8)	
Menopausal status			**0.007**
Premenopausal	2 (28.6)	6 (31.6)	
Postmenopausal	5 (71.4)	13 (68.4)	
Family history of CVD			**0.007**
No	2 (28.6)	6 (31.6)	
Yes	5 (71.4)	13 (68.4)	
Sedentary lifestyle			**< 0.001**
No	1 (14.3)	1 (5.3)	
Yes	6 (85.7)	18 (94.7)	
Smoking status[†]			0.453
Never smoked	5 (71.4)	17 (89.5)	
Current smoker or former smoker	2 (28.6)	2 (10.5)	
Alcohol use[†]			0.125
No	6 (85.7)	18 (94.7)	
Alcohol abuse	1 (14.3)	1 (5.3)	
Arterial hypertension			0.092
No	3 (42.9)	9 (47.4)	
Yes	4 (57.1)	10 (52.6)	
Type 2 diabetes mellitus			0.453
No	5 (71.4)	17 (89.5)	
Yes	2 (28.6)	2 (10.5)	
Dyslipidemia	0 (0.0)	2 (10.5)	0.180
CVD drug use			
Antihypertensive agents	4 (57.1)	7 (36.8)	0.344
Anticoagulant agents	0 (0.0)	1 (5.3)	0.070
Statins	1 (14.3)	4 (21.1)	0.754
Antidiabetic agents	2 (28.6)	1 (5.3)	0.219
Cancer staging I-II	7 (100.0)	15 (78.9)	0.549

DIC, DOX-induced cardiotoxicity; non-DIC, non-DOX-induced cardiotoxicity; LVEF. left ventricular ejection fraction; CVD, cardiovascular disease; CV, cardiovascular; [†] see definition in *Lifestyle assessment*; [t] Student's t-test for independent samples. All other variables were tested using Pearson chi-square test ($p < 0.05$)

pattern was seen for BF% and VAT. However, the women in the DIC group showed increased MM% soon after treatment completion compared to baseline. This finding is not clinically relevant and can be associated with changes in eating habits during a stressful life event or a special concern to maintain or excessively increase calorie intake to avoid weight loss [28].

To further the analysis of body composition, we included a dietary assessment in this study. We found the participants changed their eating habits over a period of 12 months, especially regarding macronutrient and micronutrient intake (mostly average consumption of calories, carbohydrates, lipids and sodium) though without marginal significance. From the diagnosis of cancer and the beginning of chemotherapy they became more concerned about their diet and make changes to include more healthy foods and less processed foods and chemical additives. However, they struggled to maintain healthy eating habits over the course of treatment due to emotional distress and side effects of treatment as cancer patients undergoing chemotherapy are likely to present symptoms such as nausea, vomiting, taste changes, among others [29]. A meta-analysis on different methods for assessing changes in weight, body composition and lifestyle among women with breast cancer reported quantitative and qualitative changes compared to women with no breast cancer. This finding provides insights and help understand the changes in this patient population [30].

We compared body composition and dietary variables between DIC and non-DIC groups and found no significant changes at the completion of treatment regardless of cardiotoxicity, i.e., cancer treatment did not affect body composition and dietary variables. In contrast, a recent study demonstrated that, different from the classic relationship between obesity and increased CV risk, a reduction in BMI—though not in waist circumference—was associated with a decrease in LVEF over the course of anthracycline-based treatment among women with breast cancer. The authors reported that every 1 kg/m^2 reduction in BMI was associated with a 0.4% decrease in LVEF [31].

Evidence has shown that the associations between BMI and cardiotoxicity or even cancer mortality are usually nonlinear [26]. Although severe obesity has been clearly associated with lower survival rates, studies have showed a U-shaped association between BMI and unfavorable outcomes. A probable explanation is that BMI likely incompletely captures key measures of body composition, especially when skeletal muscle is not assessed. Fat and lean body mass can be measured using computed tomography, dual-energy radiograph absorptiometry (DEXA), A-mode ultrasound, BIA, and other technologies [32]. Although our results assessed by BIA did not show any differences in fat or lean mass between the groups (DIC and non-DIC), we found a delayed moderate correlation at the one-year follow-up from baseline between muscle mass and LVEF (0.467; $p = 0.033$) and a moderate inverse correlation between visceral fat and LVEF (–0.502; $p = 0.020$). Even though these findings are irrespective of cardiotoxicity, they affect quality of life and thus have significant clinical relevance. In relation to adiposity, some mechanisms by which overweight or obesity promote anthracycline-induced cardiotoxicity involve adiponectin downregulation [33, 34], which has been demonstrated in obese patients [35]. In addition, adiponectin-KO mice showed exacerbated left ventricle

Table 3 Anthropometric and dietary variables

	DIC ($n=7$)			non-DIC ($n=19$)			*p*-value (group)	*p*-value (time)	*p*-value (interaction)
	Baseline DOX treatment	**Completion of DOX treatment**	**One-year follow-up**	**Baseline DOX treatment**	**Completion of DOX treatment**	**One-year follow-up**			
Body weight (kg)	83.2 ± 24.3	82.0 ± 21.5	81.7 ± 21.0	72.6 ± 15.7	74.0 ± 15.9	73.4 ± 17.0	0.314	0.994	0.271
BMI (kg/m^2)	32.6 ± 9.3	32.2 ± 8.8	31.8 ± 8.3	28.9 ± 6.7	29.6 ± 6.3	28.2 ± 5.6	0.389	0.676	0.208
Low weight (*n*)	0	0	0	0	1	0	---	---	---
Normal weight (*n*)	3	3	3	6	3	5	---	---	---
Overweight (*n*)	0	0	0	6	7	7	---	---	---
Obesity I (*n*)	0	1	0	4	5	3	---	---	---
Obesity II (*n*)	3	1	3	2	1	1	---	---	---
Obesity III (*n*)	1	2	1	1	2	1	---	---	---
Fat mass (%)	42.5 ± 11.7	40.8 ± 8.6	41.4 ± 10.5	39.4 ± 8.0	39.6 ± 8.2	38.8 ± 6.5	0.628	0.646	0.408
Muscle mass (%)	23.8 ± 3.6	25.6 ± 3.3	25.4 ± 4.2	26.0 ± 2.6	26.6 ± 3.9	26.0 ± 2.4	0.429	0.054	0.059
Visceral fat (rating)	11.4 ± 5.2	10.4 ± 4.5	10.9 ± 5.0	8.9 ± 3.7	**9.5 ± 3.6***	8.5 ± 2.4	0.375	0.581	**0.007**
Neck circumference (cm)	36.7 ± 4.4	37.7 ± 4.8	36.2 ± 5.3	34.9 ± 2.9	35.6 ± 3.6	34.8 ± 2.8	0.330	**0.027**	0.425
Waist circumference (cm)	103.7 ± 16.9	102.8 ± 14.4	99.8 ± 16.7	96.2 ± 14.2	97.7 ± 14.4	**100.3 ± 10.0***	0.513	0.898	**0.002**
Total calorie intake (kcal)	1378.6 ± 362.8	1499.5 ± 352.6	1467.8 ± 361.9	1601.2 ± 467.5	1321.9 ± 424.3	1623.4 ± 434.2	0.569	0.350	0.122
Carbohydrates (g)	55.4 ± 10.1	50.3 ± 3.2	54.3 ± 4.7	54.4 ± 10.0	53.0 ± 7.7	55.5 ± 5.2	0.636	**0.020**	0.559
Proteins (g)	19.0 ± 3.7	17.5 ± 2.9	19.1 ± 4.7	18.4 ± 4.8	17.8 ± 4.0	16.7 ± 3.9	0.340	0.594	0.233
Lipids (g)	25.6 ± 8.7	32.2 ± 3.4	26.7 ± 5.4	27.3 ± 9.0	29.2 ± 5.9	26.7 ± 7.5	0.868	**< 0.001**	0.088
Cholesterol (g)	336.4 ± 217.1	238.9 ± 133.0	289.5 ± 168.3	266.9 ± 171.0	223.8 ± 156.1	238.9 ± 160.4	0.227	0.529	0.906
Saturated fat (g)	13.3 ± 6.9	20.2 ± 7.9	15.6 ± 5.4	17.9 ± 8.3	16.9 ± 8.3	18.7 ± 8.0	0.578	0.336	0.072
Sodium (mg)	2123.1 ± 868.4	2734.2 ± 1479.9	1881.7 ± 891.4	1966.9 ± 1142.5	1510.5 ± 933.4	1683.7 ± 847.4	0.085	0.133	0.148

DIC, DOX-induced cardiotoxicity; non-DIC, non-DOX-induced cardiotoxicity; BMI, body mass index. Data expressed as mean ± standard error or absolute value (n). Generalized estimating equations (GEE) method with Bonferroni post-hoc test was used; * $p<0.05$ versus baseline within the group

Table 4 Correlation between anthropometric and dietary variables with left ventricular ejection fraction variation at the completion of doxorubicin treatment and one-year follow-up

Baseline variables	Δ LVEF	
	Completion of DOX treatment – baseline	One-year follow-up – baseline
Anthropometric measures		
Body surface	−0.384 ($p=0.070$)	**−0.541 ($p=0.011$)**
Body weight	−0.326 ($p=0.130$)	**−0.509 ($p=0.018$)**
BMI	−0.212 ($p=0.331$)	**−0.475 ($p=0.029$)**
Fat mass	−0.154 ($p=0.482$)	−0.421 ($p=0.057$)
Muscle mass	0.316 ($p=0.142$)	**0.467 ($p=0.033$)**
Visceral fat	−0.151 ($p=0.491$)	**−0.502 ($p=0.020$)**
Neck circumference	−0.138 ($p=0.530$)	**−0.579 ($p=0.006$)**
Waist circumference	−0.201 ($p=0.358$)	−0.423 ($p=0.056$)
Dietary intake		
Total calories	−0.324 ($p=0.132$)	−0.039 ($p=0.868$)
Carbohydrates	0.137 ($p=0.532$)	0.400 ($p=0.072$)
Proteins	−0.276 ($p=0.203$)	−0.233 ($p=0.310$)
Lipids	−0.021 ($p=0.925$)	−0.336 ($p=0.137$)
Cholesterol*	−0.144 ($p=0.513$)	−0.201 ($p=0.382$)
Saturated fat*	−0.292 ($p=0.176$)	−0.028 ($p=0.904$)
Sodium*	0.084 ($p=0.702$)	−0.149 ($p=0.519$)

LVEF, left ventricular ejection fraction; DOX, doxorubicin; BMI, body mass index; Pearson "r" correlation except for (*) where Spearman "r" correlation was used ($p<0.05$)

contractile dysfunction after doxorubicin injection, whereas exogenous adiponectin improved doxorubicin-induced left ventricular dysfunction in wild-type and adiponectin-KO mice [33]. While increased adiposity, mostly visceral, created an unfavorable environment for cardiac performance in our sample—a decrease in LVEF regardless of cardiotoxicity—, skeletal muscle played a role that is consistent with the current focus on inflammatory and immunological pathways for both the cardiac environment and overall cancer survival rates [32]. Skeletal muscle secretes myokines including interleukin (IL)-6, IL-8, IL-15, and leukemia inhibitory factor [36]. Therefore, higher muscle mass may decrease the impact of systemic inflammation [37] and suppress tumor growth [38]. Several studies have suggested that systemic inflammation may lead to ongoing muscle loss in cancer patients and has been associated with cancer survival [39]. Besides, skeletal muscle is a limiting factor in oxygen consumption associated with cardiac performance and is a secondary factor contributing to a decrease in LVEF [40]. Significant reductions in resting cardiac and skeletal muscle energy and increased skeletal muscle degradation have been demonstrated in patients with breast cancer after the administration of anthracycline chemotherapy [41]. Collectively, this evidence shows the importance of preserving muscle mass for improving survival and quality of life of patients undergoing chemotherapy.

As for the volunteers' lifestyle habits, those who developed cardiotoxicity showed at least two risk factors associated, including sedentary behavior, being a current or former smoker and/or excessive alcohol use. Besides, four of these women had a BMI > 30 kg/m^2. Our research group showed in an animal model that exercise training is a cardioprotective approach against DOX-induced cardiomyopathy, especially prior to DOX exposure [42]. The cardioprotective effects of aerobic exercise training are mediated by preserving sympathetic vagal function and improving DNA repair capacity of peripheral blood mononuclear cells [43]. As for smoking, considering the association between smoking and breast cancer risk [44] and that active smoking—or environmental tobacco exposure—is associated with approximately 80% increase in the risk of ischemic heart disease [45], it is expected that women with breast cancer undergoing chemotherapy who are smokers would more likely develop cardiotoxicity. In fact, Jin et al. [46] showed that smoking was associated with reduced LVEF during anthracycline chemotherapy (OR 1.91; 95% CI 1.24 to 2.95; $p=0.003$). Likewise, heavy alcohol use is associated with an increased risk of cardiotoxicity compared to low alcohol intake among these women [47].

Although we were not able to demonstrate that body composition plays a role on the development of DOX-induced cardiotoxicity, health providers should be aware that excess weight gain is not only a stressor but also an additional risk for CVD, diabetes and arterial hypertensin in individuals with cancer [7, 48]. Furthermore, BMI is not the only measure to assess CV risk, but other measures of body composition should be considered to screen those individuals more likely to benefit from CV prevention care [24].

Our study presents some limitations. The measures adopted during the COVID-19 pandemic, such as non-hospital patient care management, social distancing and other care-related restriction measures, significantly affected participation in our study. Losses derived from deaths during treatment and patient refusal to participate as data collection involved physical contact were also issues faced during that highly unusual time caused by the pandemic. Therefore, the small sample size was the main limitation of this study that may have affected its power to verify our primary hypothesis concerning the association between changes in body composition and development of DOX-induced cardiac dysfunction. Many variables showed a relative risk associated with cardiotoxicity, but the great variability resulting from a small sample affected 95% CIs and did not allow to confirm an association of the risk factors evaluated. Another important limitation of our study is the lack of further information on lifestyle habits and nutritional survey. These women were in a fragile state while undergoing chemotherapy and dealing with uncertainties during the COVID-19 pandemic and thus we were careful not to overwhelm them with long questionnaires and surveys.

Conclusions

To the best of our knowledge, only one study in the literature used BIA to assess the correlation between body composition measures and cardiac dysfunction in women with breast cancer undergoing antineoplastic treatment [49]. Despite its small sample, the present study provides insights on the value of BIA as a non-invasive, objective method to assess body composition. Likewise, food consumption showed no association with the outcomes evaluated.

The comparison of body composition between the two groups of participants (DIC and non-DIC) at the completion of DOX treatment did not support the hypothesis that this measure plays a role on the development of cardiac dysfunction. Further studies with larger samples are needed to support our findings.

Abbreviations

BF%	Body fat percentage
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CVD	Cardiovascular disease
DOX	Doxorubicin
GLS	Global systolic longitudinal strain
ISAK	International Society for the Advancement of Kinanthropometry
LVEF	Left ventricular ejection fraction
MM%	Skeletal muscular mass percentage
RR	Relative risk
VAT	Visceral adipose tissue

Supplementary Information

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Supplementary Material 1

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Author contributions

K.M. was involved in conception and design of the study, data collection, data analysis and interpretation, as well as drafting the manuscript. M.I.G.S. worked on the conception and design of the study, and data collection. T.C., A.L., P.C., and O.C. were involved in patient's recruitment and data collection. F.C. and D.R. performed and analyzed echocardiography exams. A.Z. worked on conception and design of the study. A.M.L. and N.N. made data analysis and interpretation, as well as critical review of manuscript. N.M.L. was involved in all steps of manuscript. Also, all authors have read and approved the manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

This study following the principles of the Declaration of Helsinki. This study was approved by the research ethics committees of Instituto de Cardiologia do Rio Grande do Sul/Fundação Universitária de Cardiologia (protocol nr. 3,119,951) and Santa Casa de Misericórdia Hospital Compound (protocol nr. 3,061,585). Also, all volunteer participants read and signed a free informed consent form.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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