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Effects of resistance training on health indicators in breast cancer survivors

Efeitos do treinamento resistido sobre indicadores de saúde de sobreviventes de câncer de mama

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ABSTRACT
The present study aimed to investigate the effects of resistance training on health indicators in breast cancer survivors. Twenty-two women with a history of mastectomy and lymphadenectomy completed 12 weeks of training. Strength, body mass index, body composition, hematological, and biochemical aspects, and erythrocyte membrane stability were performed before and after the training. In all exercises, there were significant gains in maximal strength and strength endurance. Moreover, there was a decrease in body fat percentage, an increase in lean mass percentage, a reduction in erythrocytes, platelets, and hemoglobin, as well as desirable changes for all lipid profile variables. Altogether, these findings highlight the multidimensional impact of resistance training on the health of breast cancer survivors and reveal the need for constant monitoring of this public.

Keywords: Breast neoplasms. Holistic health. Physical exercise.

RESUMO
O objetivo deste estudo foi investigar os efeitos do treinamento resistido sobre indicadores de saúde em sobreviventes de câncer de mama. Vinte e duas mulheres com histórico de mastectomia e linfadenectomia completaram 12 semanas de treinamento. Avaliações de força, índice de massa corporal, composição corporal, aspectos hematológicos, bioquímicos e de estabilidade de membrana eritrocitária foram realizadas antes e depois do período de treinamento. Em todos os exercícios, ocorreram ganhos significantes de força máxima e resistência de força. Além disso, houve diminuição do percentual de gordura corporal, aumento do percentual de massa magra, redução de eritrócitos, plaquetas e hemoglobina, bem como mudanças desejáveis para todas as variáveis de perfil lipídico. Em conjunto, esses achados destacam o impacto multidimensional do treinamento resistido sobre a saúde de sobreviventes de câncer de mama e revelam a necessidade de monitoramento constante desse público.

Palavras-chave: Exercício físico. Neoplasias da mama. Saúde holística.

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INTRODUCTION

The mortality rate in breast cancer (BC) patients has decreased over the past decades due to various factors, such as information campaigns, early diagnosis, technological development, and advances in treatment. The five and ten-year survival rates are already around 90% and 80%, respectively[1]. Moreover, projections from the World Health Organization indicate that if there is a 2.5% reduction in BC mortality per year worldwide, more than 2 million deaths will be avoided between 2020 and 2040[2].

Such an outlook has demanded from policymakers and the scientific and professional communities an in-depth understanding of the characteristics and needs of women breast cancer survivors (BCS)[1]. Therefore, spaces and practices that encourage wellness, scientific studies with innovative approaches, and interdisciplinary rehabilitation programs deserve increasing encouragement because of their great potential to impact the community. After all, in addition to greater longevity, it is essential to consider the living and health conditions of this population[3,4].

Because of the disease and the treatments used, these women usually deal with local and systemic side effects in the short, medium, and long term[3,5]. Among other problems, BCS are subject to excessive fatigue and reduced physical fitness[3,5], damage to anthropometric characteristics[6], metabolic syndrome[7], and changes in cell membrane composition[8]. Furthermore, compared to women without a history of cancer, BCS show a higher risk of depression[9] and mortality from cardiovascular diseases[10].

Given this challenging scenario, physical activity, understood as a modifiable lifestyle factor, has stood out in the combat against side effects[11]. However, while aerobic modalities have historically been predominant in exercise oncology, only more recently has resistance training (RT) been explored as an essential therapeutic intervention[12]. Furthermore, interventions with resistance training have been mainly based on linear protocols, presenting limited variations over the weeks[13,14].

The scarcity of studies involving BCS, and the prescription of non-linear RT (NLRT) draws attention, mainly because the alternations of intensity, volume, and density (ratio between effort and interval) have been used satisfactorily in other populations[15]. A significant gap exists, especially concerning holistic approaches involving different health indicators.

Considering the interfaces of all this context, we emphasize the need to develop and improve resistance exercise in rehabilitation and health promotion processes. Thus, this study aimed to investigate the effects of NLRT on physical performance, anthropometry, and hematological, biochemical, and biophysical chemical aspects of BCS.

METHODS

PARTICIPANTS AND EXPERIMENTAL DESIGN

Twenty-two women BCS (51.7 ± 9.2 years of age) were recruited, adhering to the following inclusion criteria: 1) female gender; 2) history of mastectomy and lymphadenectomy; 3) completion of chemotherapy and/or radiotherapy at least six months before the study; 4) no involvement in any exercise program in the past six months; 5) medical clearance to participate in the RT; 6) absence of musculoskeletal disorders and/or limitations that would make it impossible to perform the exercises of the training program; 7) no smoking and no consumption of alcoholic beverages. The volunteers would be excluded from the sample if they did not meet all these criteria and, once selected, they failed to attend 75% or more of the training sessions.

This introductory and interventional study was conducted between July 2017 and June 2018, following the Resolutions 466/212 and 510/2016 National Health Council guidelines and the principles of the Declaration of Helsinki. It was also approved by the ethics committee of the Federal University of Uberlândia (CAAE 57837416.5.0000.5152/2016) and registered in Clinical Trials (NCT04479098). All volunteers were informed about the procedures and associated risks and signed an Informed Consent Form.

The research has a total duration of 14 weeks for each participant. There were 12 weeks of training and two weeks of evaluations - the latter conducted before (pre-NLRT) and after the NLRT (post-NLRT). In both cases, the same order of execution was respected (day 1: anthropometry; day 2: blood draws; day 3: maximal strength [MS] tests; day 4: interval; day 5: strength endurance [SE] tests).

ANTHROPOMETRIC ASPECTS

To determine anthropometric aspects, the volunteers were barefoot, wearing light clothing, and fasting for 12 hours. We measured body mass (kg) and height (m) on a scale with a stadiometer (Filizola®), and the results were used to calculate the body mass index (BMI) (kg/m2). The percentage of body fat (% BF) and the percentage of lean body mass (% LM) were measured by tetrapolar bioimpedance (InBody®).

HEMATOLOGICAL AND BIOCHEMICAL ASPECTS

The participants respected 12 hours of fasting without moderate and/or vigorous physical activities for the blood collection. On the side contralateral to the breast surgery, experienced professionals collected peripheral blood samples by venipuncture directly into vacuum tubes (BD Vacutainer®) containing EDTA for hematological analyses and into tubes without anticoagulant for biochemical analyses.

Using an automated analyzer (Abbott®), erythrocytes count, platelet count, hemoglobin concentration, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), and white blood cell count was determined.

Total cholesterol (t-C), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), and triglyceride (TGC) levels were quantified using specific commercial kits and an automated analyzer (Roche®). The t-C/HDL-C and LDL-C/HDL-C ratios were also calculated.

OSMOTIC STABILITY OF ERYTHROCYTES

The osmotic stability test[16] was conducted in a series of duplicate microtubes (Eppendorf®) containing 1.5 mL of NaCl in concentrations ranging from 0.1 to 0.9 g/dL. Initially, the microtubes were incubated at 37 °C in a thermostatic bath for ten minutes. After pre-incubation, we added 10 μL of blood to each microtube. After homogenization, the microtubes were incubated at 37 °C for 30 minutes. Then, the microtubes were centrifuged at 1,600 x g for 10 minutes, and the supernatant was subjected to absorbance reading at 540 nm (A_{540}) in a UV-VIS spectrophotometer (Hach®).

The plot of A_{540} as a function of NaCl concentration (X) was fitted by sigmoidal regression according to the Boltzmman equation:

$$A_{540} = \frac{A_{max} - A_{min}}{1 + e^{(X - H_{50})/dX}} + A_{min}$$

where A_{max} and A_{min} represent, respectively, the maximum and minimum plateaus of A_{540}; H_{50} is the NaCl concentration that releases 50% of the hemoglobin molecules from the erythrocyte's population; and dX represents a quarter of the variation of NaCl concentration responsible for promoting 100% of hemolysis. The salt concentration at the curve's starting point defines the variable H_0, which is the salt concentration required to initiate hemolysis in vitro and can be calculated by the formula $H_0 = H_{50} + 4dX/2$. When *in vitro* lysis reaches its maximum plateau, the salt concentration defines the variable H_{100}, which represents the salt concentration required to promote total lysis of the RBC and is calculated by the formula $H_{100} = H_{50} - 4dX/2$.

MECHANICAL STABILITY OF ERYTHROCYTES

To determine the kinetics of erythrocyte mechanical lysis[16], aliquots of a suspension composed of 250 μL of blood and 49.75 mL of 0.9 g/dL NaCl solution were subjected to mechanical aggression by a spinning propeller under the command of a rotor at 8,000 rpm for periods of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 and 6 minutes. Every 30 seconds of agitation, 1mL aliquots of suspension were removed, added to mini tubes (Eppendorf®), and centrifuged for ten minutes at 1,600 x g (Hitachi®). After centrifugation, the supernatants were carefully removed with an automatic pipette and subjected to an A_{540} reading in a UV-VIS spectrophotometer (Hach®).

The chart of absorbance of A_{540} by time was fitted to the hyperbola from the Michaelis-Menten equation:

$$A_{540} = \frac{A_{mmax} t}{t_{1/2} + t}$$

where Ammax is the maximum plateau of A_{540}, representing the maximum amount of hemoglobin released upon lysis of the entire red cell population; and t1/2 is the time interval required for the release of 50% of the total hemoglobin present in the erythrocyte sample ($A_{mmax}/2$).

MAXIMUM STRENGTH AND STRENGTH ENDURANCE

The one repetition maximum (1RM) test determined the MS. The protocol involved a specific warm-up, with eight repetitions with an estimated 50% of 1RM, a two-minute interval, and another series of three repetitions with an estimated 70% of 1RM. After that, a maximum of five attempts were completed, with a five-minute interval between them, to determine the maximum load[17].

Forty-eight hours after completing the 1RM tests, the volunteers returned to the laboratory for the SE tests. The protocol adopted required the execution of the most significant number of repetitions possible with 50% of 1RM until concentric failure[17,18].

On both occasions, the volunteers were supervised by physical education professionals; and, for validation of the attempts, the correct technique of movement execution was required. The tests were performed in all the exercises that made up the training program, except for the abdominal exercise, which was performed only with body mass throughout the intervention.

NON-LINEAR RESISTANCE TRAINING

The NLRT lasted 12 weeks, with a weekly frequency of three sessions (Monday, Wednesday, and Friday) and with exercises such as leg press, supine, knee flexion, pull-down, rowing, and abdominal. The prescription was organized so that, during the same week, no workout was similar to another. In addition, each session had different stimuli from different combinations of volume, intensity, and density (Table 1).

The intensity (kg) was increased between 5% and 10% whenever the maximum number of repetitions was reached in all series of a given exercise. The training program was conducted under the supervision of physical education professionals with proven experience.

Table 1. Non-linear resistance training protocol (per week)

	1st week training	2nd week training	3rd week training
I			
High Intensity	Leg press	Knee flexion	Rowing
Low Volume	Supine	Pull-down	Abdominal¥
II			
Moderate intensity	Knee flexion	Rowing	Leg press
Moderate volume	Pull-down	Abdominal¥	Supine
III			
Low Intensity	Rowing	Leg press	Knee flexion
High Volume	Abdominal¥	Supine	Pull-down

I - 3 sets, 4 to 6 repetitions, approximately 85% of one repetition maximum (1RM), 120 to 180 seconds apart; II - 3 sets, 8 to 12 repetitions, approximately 70% of 1RM, 60 to 90 seconds apart; III - 3 sets, 15 to 20 repetitions, approximately 60% of 1RM, 45 seconds apart. ¥ The abdominal exercise was performed exclusively by the body mass.

STATISTICAL ANALYSIS

The Shapiro-Wilk test was applied to investigate the regularity of the data. For comparing pre-NLRT vs. post-NLRT, we adopted the paired t-test (parametric data) or Wilcoxon test (non-parametric data) and a significance level of $p < 0.05$. Statistical analyses were performed in Prism GraphPad® 7.0 and Origin Pro® 9.0.

RESULTS

Table 2 presents the physical performance data and anthropometric characteristics of pre-NLR and post-NLR training. After 12 weeks of training, there were significant gains in MS and SE in all exercises, including upper limb exercises. Although no significant difference was observed for BMI, there was a decrease in % BF and an increase in % LM.

Table 2. Effects of non-linear resistance training on maximal strength, strength endurance, and anthropometry in female breast cancer survivors

(Continued)

	pre-NLRT	post-NLRT	*p*
Maximum Strength			
Leg press (kg)	130 (43.2)	200.5 (59.6)	0.000*
Supine (kg)	22 (6.4)	33 (8.6)	0.000*
Knee flexion (kg)	10 [3.3]	14 [3]	0.000*
Pull-down (kg)	28.3 (6.1)	36.3 (10)	0.001*
Rowing (kg)	33.5 (7)	42.1 (7.7)	0.000*

(Conclusion)

	pre-NLRT	post-NLRT	*p*
Strength Endurance			
Leg press (reps)	19.5 [10]	33.5 [12.5]	0.000*
Supine (reps)	20 (7)	29.8 (8.5)	0.001*
Knee flexion (reps)	20 [10]	40 [15.5]	0.000*
Pull-down (reps)	24.6 (7.8)	43.8 (9.3)	0.000*
Rowing (reps)	20.6 (5.3)	33.9 (6.5)	0.000*
Anthropometry			
BMI (kg/m^2)	26.5 (5.2)	26.7 (5.2)	0.090
Percentage of body fat	39.2 (7.4)	38.1 (7.2)	0.004*
Percentage of lean mass	57.3 (7)	58.3 (7)	0.008*

TR - non-linear resistance training; BMI - body mass index; reps - number of repetitions. Values are presented as mean (standard deviation) for parametric data and as median [interquartile range] for non-parametric data. * $p < 0,05$.

Table 3 details the effects of NLRT on the other health indicators analyzed in this study. Significant changes occurred in all biochemical aspects, with increased HDL-C and reduced t-C, t-C/HDL-C, LDL-C, LDL-C/HDL-C, VLDL, and TGC. Among the hematological aspects, there was a significant reduction in erythrocytes, hemoglobin, and platelets. In turn, the biophysical-chemical parameters of the erythrocyte membrane's osmotic stability and mechanical stability did not show any significant differences in comparing pre-NLRT vs. post-NLRT.

Table 3. Effects of non-linear resistance training on hematological, biochemicals, and biophysical chemical aspects in women breast cancer survivors

(Continued)

	pre-NLRT	post- NLRT	*p*
Hematological aspects			
Erythrocyte (10^6/mm^3)	4.8 (0.4)	4.6 (0.3)	0.007*
Hemoglobin (g/dL)	13.8 (1)	13.4 (0.7)	0.015*
Hematocrit (%)	41.2 (3.2)	40.3 (2.2)	0.063
MCV (fL)	86.4 (5)	87.1 (4.3)	0.129
MCH (pg)	29 (1.7)	29.1 (1.7)	0.676
MCHC (g/dL)	33.7 (0.8)	33.4 (1.1)	0.089
RDW (%)	13.3 [1.1]	13.7 [1.2]	0.582
Platelets (10^3/mm^3)	214.7 (48.2)	201.6 (37.9)	0.026*
Leukocytes (10^3/mm^3)	5.3 (1)	5.5 (1.1)	0.193
Biochemical aspects			
t-C (mg/dL)	204 [23]	194.5 [22.5]	0.014*

(Conclusion)

	pre-NLRT	post- NLRT	*p*
HDL-C (mg/dL)	48.6 (8.5)	55.3 (8,5)	0.000*
t-C/HDL-C	4.4 (1.1)	3.7 (0.8)	0.000*
LDL-C (mg/dL)	125.2 (28.2)	110.8 (21.9)	0.003*
LDL/HDL-C	2.6 [1.2]	2 [0.6]	0.000*
VLDL (mg/dL)	31.5 (12.7)	28.3 (10.1)	0.045*
TGC (mg/dL)	157.3 (63.7)	141.6 (50.4)	0.045*
Osmotic stability			
A_{max} (ΔOD)	1.18 (0.09)	1.15 (0.06)	0.296
A_{min} (ΔOD)	0.01 [0.22]	0.01 [0.21]	0.949
H_0 (g/dL NaCl)	0.46 (0.02)	0.47 (0.01)	0.136
H_{50} (g/dL NaCl)	0.44 (0.01)	0.44 (0.01)	0.058
H_{100} (g/dL NaCl)	0.41 (0.02)	0.42 (0.01)	0.060
dX (g/dL NaCl)	0.01 (0.00)	0.01 (0.00)	0.490
Mechanical stability			
A_{mmax} (ΔOD)	0.70 [0.11]	0.67 [0.08]	0.063
$t_{1/2}$ (s)	66.58 [48.36]	55.88 (15.05)	0.222

RT - non-linear resistance training; MCV - mean corpuscular volume; MCH - mean corpuscular hemoglobin; MCHC - mean corpuscular hemoglobin concentration; RDW - red cell distribution width; t-C - total cholesterol; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; VLDL - very-low-density lipoprotein cholesterol; TGC - triglycerides; Amax - maximum absorbance plateau of 540 nm in the osmotic stability test; Amin - minimum absorbance plateau of 540 nm in the osmotic stability test; H0 - salt concentration at the starting point of the curve; H50 - NaCl concentration releasing 50% of the hemoglobin molecules from the erythrocyte population; H100 - salt concentration at the point when the *in vitro* lysis reaches its maximum plateau; dX - one-quarter of the variation of NaCl concentration responsible for promoting 100% of hemolysis; Ammax - maximum absorbance plateau of 540 nm in the mechanical stability test; t1/2 - time interval required for the release of 50% of the total hemoglobin present in the erythrocyte sample. Values are presented as mean (standard deviation) for parametric data and median [interquartile range] for nonparametric data. *p < 0,0

DISCUSSION

The present study adds new theoretical and practical perspectives to exercise in oncology and health promotion. In response to an NLRT protocol, in which diversified volume, intensity, and density stimuli were worked in all sessions, women BCS demonstrated significant gains in MS and SE, including for upper limb exercises. In addition, desirable changes occurred in body composition and lipid profile parameters. Surprisingly, there was a reduction in erythrocytes, hemoglobin, and platelets. Altogether, these findings highlight the need to monitor this population constantly and their preserved responsiveness to exercise. That is the first study to present multidimensional results on physical performance, anthropometry, hematological, biochemical, and biophysical chemical aspects in BCS submitted to NLRT.

By reaching satisfactory levels of attendance (> 75%) and confirming the viability of this type of exercise for BCS, the present study established a model capable of confronting the physical and cognitive impairments generally observed in this population[1,9]. Moreover, the safety demonstrated throughout this supervised training program contradicts the false belief that BCS and women with a history of surgical treatment should not practice resistance exercises involving upper limbs. From the practical point of view, considering all the necessary care, this knowledge favors the organization and implementation of interdisciplinary actions by different health professionals at various levels of care.

Since physical inactivity is associated with higher risks of secondary cancer development and mortality[19], breaking this vicious circle stands out, therefore, as a starting point in the scenario of rehabilitation and health promotion of BCS, opening room for other benefits. Due to the peculiar nature of resistance exercise, the possibilities of managing this population are amplified. This is because, when compared to aerobic exercise, RT has a certain specificity of stimuli and responses on the morphology and function of the musculoskeletal system, facing problems such as low bone mineral density and sarcopenia[12].

The gains in MS and SE are significant for women with a history of mastectomy and lymphadenectomy, such as those who participated in this study. After all, localized muscle weakness, loss of range of motion, and lymphedema are common complaints among this public[5]. Besides strength being a key component of physical fitness related to health, the TRNL can trigger positive repercussions on the activities of daily living, functional independence, and quality of life of BCS[3,20].

It is worth noting that training can be designed in different approaches, representing a decisive factor for the success of the intervention. Thus, the variables that formed the present study - such as the broad intensity range (60%-85% 1RM), choice and order of exercises (alternating between upper and lower limbs), weekly frequency, and muscle mass involved - were carefully selected based on previous recommendations directed at BCS[12,21].

The NLRT model proposed here also generated a reduction in % BF and an increase in % LM, although without significant changes in BMI. These are satisfactory outcomes since the functions performed by adipose tissue and skeletal muscle are increasingly in evidence[22]. In work by Dieli-Conwright et al.[23], BCS women also participated in a supervised training program, but with the RT being performed for 16 weeks, in circuit style and combination with aerobic activities. In addition to changes in body composition, the results demonstrated the benefits of exercise on adipose tissue macrophage profile and inflammatory cytokine release.

The fact is that adipokines and myokines are already recognized for their autocrine, paracrine, and endocrine effects, therefore, for their ability to modulate pro-inflammatory or anti-inflammatory environments[22]. Therefore, aligned with these proposals available in the literature, the changes achieved in the present study highlight the positive impact of 12 weeks of NLRT on the health promotion of BCS. The variations in the load components within the same session were considered precisely to optimize the time-effectiveness ratio, modulate energy expenditure, avoid performance plateaus, and stimulate different muscle recruitment patterns[21].

Surprisingly, there was a reduction in hemoglobin levels and the erythrocyte and platelet counts, contrary to data such as those of Herrero et al.[24], who did not demonstrate any interference of RT on hematological aspects in women's BCS. in the present study, the changes observed would be relatively expected only if the volunteers were in more acute and rigorous phases of treatment when the incidences of thrombocytopenia[25] and anemia are high[26]. However, since even in the face of significant changes, the values remained within the reference range, these are results that do not preclude the participation of BCS in NLRT programs, but that alert us to the need for constant monitoring of this population.

Biochemical aspects well establishes that lipid imbalances are essential in developing metabolic syndrome[7] and cardiovascular diseases in BCS[10]. Aware of this, Abbasi et al.[27] have recently investigated the effects of physical exercise on the lipid profile of BC patients, but they found that the training used was unable to generate benefits on t-C, TGC, HDL-C, and LDL-C. In the 12-week NLRT model in the study, we obtained a significant increase in HDL-C, a crucial lipoprotein in reverse cholesterol transport,[28] and a decrease in t-C, t-C/HDL-C, LDL-L, LDL-C/HDL-C, VLDL-C, and TGC levels. Those results underscore the decisive role that exercises type and protocol play concerning the health outcomes achieved.

There were no significant changes in the biophysical chemical parameters, revealing a scenario contrary to those observed in aerobic activities with healthy, physically active men [29,30]. Although the populations and modalities were different, these previous findings show the possible effects of exercise on cell membrane properties. Thus, future research may investigate the responses generated by other models of NLRT, including in more extended training programs. Since cholesterol concentration in blood is closely associated with membrane composition and functionality[16], it is possible that differences of greater magnitude in the lipid profile led to changes in the osmotic and mechanical stability of erythrocytes.

Since BC already represents the leading cause of global cancer incidence in the female population, safe, non-pharmacological, efficient, and low-cost strategies deserve ample attention in BCS disease prevention and health promotion settings. Because it is an attractive option for the public budget, RT favors allocating funds to other public health spheres. It is a modality that can be promoted indoors or outdoors, in hospitals, parks, and residential condominiums, democratizing its access for women with different socioeconomic conditions.

Evidence-based information with high applicability, such as this study, is decisive for professionals from different areas (medicine, nursing, physiotherapy, physical education, nutrition, psychology) to improve their performance and conduct interdisciplinary strategies. That generates prospects of higher quality in monitoring BCS, promoting health and quality of life for the public.

CONCLUSION

The changes observed after the training period indicate the preserved responsiveness of BCS to exercise—the changes in some hematological aspects alert to the need for constant monitoring of this population. The benefits on MS, SE, body composition and lipid profile attest to the multifactorial positive impact of NLRT on health, thus highlighting it as an approach of great potential. Finally, because of low implementation and maintenance costs, the supervised practice of NLRT presents itself as an excellent cost-effective alternative for public and/or private healthcare systems.

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