Effect of strength training and antioxidant supplementation on perceived and performance fatigability of breast cancer survivors – A randomized, double-blinded, placebo-controlled study

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Effect of strength training and antioxidant supplementation on perceived and performance fatigability of breast cancer survivors – A randomized, double-blinded, placebo-controlled study

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Abstract

This randomized, double-blinded, placebo-controlled study aimed to investigate the effect of strength training (ST) combined with vitamin C and E supplementation on perceived and performance fatigability in breast cancer survivors (BCS). Twenty-five BCS were randomly assigned to one of two groups: vitamins (VIT; $n = 12$; 51.0 ± 9.0 years); or placebo (PLA; $n = 13$; 48.2 ± 8.3 years). Both groups performed a 10-week ST protocol, twice a week. VIT was supplemented with vitamins C (500mg/day) and E (180mg/day) and PLA with polydextrose (1g/day), once a day after breakfast. At the beginning and at the end of training period, perceived fatigability was assessed using MFI-20 (general fatigue and physical fatigue). Performance fatigability was assessed during 30 maximal isokinetic knee extension at $120^\circ/\text{s}^{-1}$. General fatigue reduced similarly in VIT ($p = 0.004$) and PLA ($p = 0.011$). Physical fatigue reduced similarly in both, VIT ($p = 0.011$) and PLA ($p = 0.001$). Performance fatigability also decreased similarly in VIT ($p = 0.026$) and PLA ($p < 0.001$). There was no difference between groups in any moment ($p > 0.05$). In summary, antioxidants supplementation does not add any positive synergistic effect to ST on improving perceived or performance fatigability in BCS.

Clinical trial registered in Brazilian Clinical Trials Registry, number RBR-843pth (UTN number: U1111-1222-6511).

Novelty

Strength training with maximal repetitions reduces perceived and performance fatigability of BCS. Vitamins C and E supplementation does not add any positive synergistic effect to ST on reducing fatigability in BCS.

Keywords: Breast cancer; Cancer-related fatigue; Resistance training; Antioxidant supplementation; Performance fatigability; Perceived fatigability.

Introduction

Cancer-related fatigue is a multifactorial condition induced by cancer and/or cancer treatments defined as a persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion, that is not related to recent activity and that interferes with the ability of the cancer survival to perform activity of daily living (Mock et al. 2000). Nearly 75% of all cancer patients experience increased fatigue during treatment (O'Regan et al. 2019). Furthermore, this debilitating fatigue experienced by the majority of cancer survivors may persist for years after completion of treatment (Wang et al. 2014). This persistent fatigue has been associated with decreases in functionality, quality of life, and the ability to respond to work demands (Wang et al. 2014; Wang and Woodruff 2015; Joly et al. 2019). Noteworthy, the increased fatigue could contribute to dysregulation of endocrine activity, via behavioral pathways, causing a cyclical relationship between fatigue, physical inactive and physiological disturbances (Thornton et al. 2010; Berger et al. 2012; Neil-Sztramko et al. 2014)

Although cancer-related fatigue has a multifactorial pathophysiology, several studies have proposed underlying biological pathways of fatigue in cancer (Gutstein 2001; Barsevick et al. 2010; Saligan et al. 2015; Sha et al. 2015; Gerber 2017). According Saligan et al. (2015), cancer-related fatigue is caused by a cascade of events including an increased pro-inflammatory cytokine production, metabolic dysregulation, hypothalamic-pituitary-adrenal axis activation dysfunction, disruption of circadian rhythm, and neuromuscular function abnormalities. Due to cancer and its treatments, mitochondrial function and structure can also be disrupted, impairing energy supply of the cells and increasing the production of reactive oxygen species (ROS) (Yang et al. 2019). Thus,

oxidative stress and mitochondrial dysfunction play an important role in the reduction of contractile function and exercise tolerance, muscle weakness and wasting, in abnormal accumulation of muscle metabolites, and in the reduction of overall functionality (Gilliam and St Clair 2011; Carson et al. 2015; Wang and Woodruff 2015).

Several interventions have already been proposed to attenuate cancer-related fatigue. Non-enzymatic antioxidants could be supplemented with the goal of reducing oxidative stress and consequently perceived fatigue in cancer survivors; however, the use of antioxidants with the purpose of improving muscular function and performance fatigability is still debatable. The supplementation of non-enzymatic antioxidants, such as vitamin C and E, may reduce adverse reactions of the cancer treatment, regulate immune function, reduce muscle weakness and wasting, and improve antioxidant function (Fuchs-Tarlovsky 2013; Assi and Rebillard 2016; Mohandas et al. 2017; Thyagarajan-Sahu and Sahu 2017). Interestingly, despite the uncertainties about antioxidants vitamins, 40% to 60% of all cancer survivors used multivitamins and/or antioxidants supplementations during or after cancer treatment (Miller et al. 2008; Ferrucci et al. 2009; Miller et al. 2009; Luo and Asher 2018).

Otherwise, a recent consensus statement from an international multidisciplinary roundtable discussed strong evidence supporting the use of physical exercise to attenuate cancer-related fatigue both during and after treatment, with a strongest effect for moderate- to vigorous-intensity exercise (Campbell et al. 2019). While exercise type (aerobic vs. strength training) does appear to impact perceived fatigability differently in breast cancer survivors (van Vulpen et al. 2020), exercise interventions emphasized with strength training (ST) may bring additional benefits, such as the improvement of strength, overall functionality, exercise tolerance, and performance fatigability in healthy individuals and breast cancer survivors (Ribeiro et al. 2014; Hanson et al. 2016; Dos Santos et al. 2017). Also, exercise training tends to improve antioxidant indicators, regardless of intensity, volume and population characteristics (de Sousa et al. 2017). Thus, considering the parallel effects of ST and antioxidants supplementation on oxidative stress and

fatigue, it is crucial to understand if the combination between them augments the well-known exercise effects on the reduction of fatigue in breast cancer survivors.

The combination of ST and antioxidants supplementation had already been studied in healthy and elderly subjects (Bobeuf et al. 2010; Bobeuf et al. 2011; Theodorou et al. 2011; Paulsen et al. 2014; Bjornsen et al. 2016; Yfanti et al. 2017; Dutra et al. 2018; Dutra et al. 2019). However, only Dutra et al. (2018) assessed performance fatigability after both ST and antioxidants supplementations. In healthy young women, vitamins supplementation failed to reduce performance fatigability, probably, because it blunts reactive oxygen species produced during exercise and attenuate ST-induced adaptations (Dutra et al. 2018; Dutra et al. 2020). Although the ROS produced during exercise plays an important role in neuromuscular adaptations (Merry and Ristow 2016), breast cancer survivors could benefit from antioxidants supplementation due to increased oxidative stress potential.

Considering that all efforts must be taken to attenuate long-term side effects of cancer and its treatment (Stewart and Wild 2016), it is crucial to assess if the combination of ST and antioxidants supplementation show any potential additional effect in reducing performance-related fatigue compared to ST alone. Therefore, the purpose of this study was to assess the effect of ST and antioxidant supplementation on perceived and performance fatigability in breast cancer survivors. We hypothesized that antioxidants supplementation combined with ST would improve perceived and performance fatigability.

Materials and methods

Participants

Twenty-five breast cancer survivors (BCS) took part in the present study. All volunteers were recruited from community, by word of mouth and advertisements on internet, and from public and private local hospitals. The volunteers must have been women, diagnosed with breast cancer

in the stages I to IIIC according Classification of Malignant Tumors (TNM), who had completed their major cancer treatments six months or more before the beginning of the study protocol. None were participating in regular exercise training at least six months prior of enrollment in the study. Individuals were excluded if they were diagnosed with lymphedema or had cardiovascular, respiratory, muscular, metabolic, or neuroendocrine disorders that would preclude the ability to participate safely in any aspects of the study protocol. To be included in final analyses, compliance had to be at a minimum of 85% (Dutra et al. 2018) and 80% for the supplementation and ST protocol respectively. In the first visit to the laboratory, all individuals completed the Physical Activity Readiness Questionnaire (PAR-Q) (Cardinal 1997; Adams 1999) and an extensive survey regarding clinical characteristics, health limitations and medical history. All participants were fully informed of the purpose, procedures, and possible risks related to participating in the study, and provided a written informed consent. The study was approved by the University Center of Brasília Institutional Ethics Committee and was conducted in accordance with the declaration of Helsinki.

Experimental Design

The experimental design of this study is summarized in figure 1. This randomized, double-blinded, placebo-controlled study with 14-weeks duration is part of a bigger registered clinical trial (UTN number: U1111-1222-6511). BCS were randomly assigned to receive either vitamins (VIT) or placebo (PLA). The randomization process was performed by an independent researcher. All included volunteers received a code and was designated to one of the two. Neither the volunteers nor the main researcher knew the allocation until the end of the study. In the first week, BCS were submitted to nutritional assessment and blood samples collection, in order to quantify plasma ascorbic acid (vitamin C) and serum α -tocopherol (vitamin E). In the second week, BCS performed two session of familiarization with tests and training protocols. Also, in the second week, both groups started the 12-week supplementation with vitamins C and E or placebo. To assess the effect of ST and antioxidants supplementation on perceived and performance

fatigability, self-perceived general and physical fatigue, and fatigue index were assessed before and after the ST protocol, in the third and 14th weeks. Blood samples were collected on week 14. Between the fourth and the 13th weeks, both groups performed a 10-week ST protocol. In the first, fourth, and tenth weeks of ST, the volunteers were submitted to a 3-day dietary record in order to assess possible dietary intake differences between groups and changes during training protocol.

Strength Training Protocol

Both groups performed a 10-week ST protocol, conducted twice per week, with a minimum of 48h between sessions. Six exercises were administered during the study, adapted from (Hagstrom et al. 2016): knee extension, deadlift, leg press, lat pulldown, machine bench press, and trunk flexion. Exercise load varied in a linear periodized fashion (Ratamess et al. 2009). On the first five weeks of ST, BCS performed three sets of 12 maximum repetitions (reps). On the last five weeks of ST, BCS performed three sets of 10 reps. BCS were instructed to perform concentric and eccentric phases in approximately 2 seconds each, without pause between them, as proposed by Dutra et al. (2018). All sets were performed until repetition maximum, according to the definition of Steele et al. (2017), and the loads were adjusted from set to set to maintain the designated number of repetitions. So, the volunteers lifted the most weight they could lift sustaining the repetitions prescribed. Such protocol had already been proved safe for cancer survivors (Schmitz et al. 2005; Ahmed et al. 2006). Rest interval between sets and exercises was 2 minutes. Training was supervised by experienced trainers and all data was recorded in order to calculate the training volume per week, as $\text{loads} \times \text{repetitions} \times \text{sets}$. In the familiarization week, BCS performed two sessions, with 48h between them. The same six exercises were composed by two sets of 12 submaximal repetitions, with 2 minutes rest interval, with an approximately 2-sec duration for concentric and eccentric phases, without pause between them. BCS were asked to perform each set with an intensity between 6 and 8 on the OMNI-Resistance Exercise Scale

(Lagally and Robertson 2006), and the loads were adjusted according that intensity, to guarantee submaximal characteristic of familiarization sessions.

Supplementation protocol

The supplementation protocol was adapted from Dutra et al. (2018). Both groups supplemented during 12 weeks with either vitamins C and E or placebo. Each pill of vitamin contained 250 mg of ascorbic acid (vitamin C) and 90 mg of α -tocopherol (vitamin E), while each pill of placebo contained 500 mg of povidone. Both vitamins and placebo had the same shape and appearance, and were ingested at the same time. Two pills of vitamin C and E (totalizing 500 mg and 180 mg, respectively) were taken after breakfast, for 84 days, till the end of ST protocol. Vitamin E presents low toxicity (Wu and Croft 2007) and seems to be well absorbed during the day, if fasting periods are lower than 12h (Traber et al. 2019). However, the antioxidant effect of vitamin C and its plasma levels seems to maximize when ≥ 500 mg is ingested (Schlueter and Johnston 2011). In addition, a ~ 24 h interval is needed to return to basal levels of vitamin C (Padayatty et al. 2004), what avoids decreases in intestinal absorption and side effects (*e.g.* gastrointestinal distress, nausea and diarrhea) (Schlueter and Johnston 2011). Therefore, all pills were taken at the same time of day to maximize absorption, to avoid side effects and also to avoid mistakes by participants (*e.g.* forgetfulness). Thus, the daily dosage for VIT was 500 mg of vitamin C and 180 mg of vitamin E, while for PLA was 1g of povidone. Doses of vitamin C greater than 500mg/day could be unsafe for cancer patients because it may improve the recurrence risk of lung, head and neck, and colon cancers (Arends et al. 2017; Limon-Miro et al. 2017). So, we used 500 mg of vitamin C in order to minimize the risks and adverse responses during the study (Fleischauer et al. 2003). The blind process was carried out by a certified pharmacy. The supplements ingested by VIT and PLA were differed by codes during the study; the code of each substance was revealed after all experimental and statistical procedures were performed.

Muscle strength

Isokinetic peak torque was measured to characterize muscle strength of groups at the beginning of the study, using an isokinetic dynamometer Biodex System 4 (Biodex Medical Systems, Inc., New York, USA). The volunteers were positioned on the dynamometer seat with Velcro belts fastened to the trunk, pelvis and thigh to avoid extraneous body movements that could affect results. The lateral epicondyle of the femur was used to align the knee rotation axis and the dynamometer rotation axis, allowing free knee extension and flexion from 85° flexion up to full extension. Gravity correction was obtained by measuring the torque exerted by the lever arm and the subject's leg at 30° flexion as well as in a relaxed position. The values of the isokinetic variables were automatically adjusted for gravity with the software Biodex Advantage (Biodex Medical Systems, Inc., New York, USA). Calibration of the dynamometer was carried out according to the manufacturer specifications. For the test, volunteers were asked to cross their arms across the chest. The same researcher carried out the procedures for all subjects and provided verbal encouragement. As part of warm-up, the volunteers performed one set of 10 submaximal knee isokinetic extension at 120°.s⁻¹. Two minutes after warm-up, two sets of four maximal isokinetic knee extensions at 60°.s⁻¹ were used to determine PT, with 2-min rest interval between them (Vieira et al. 2015). PT was recorded as the highest torque achieved in the 2 sets.

Three-day dietary record

In order to investigate if the dietary intake was similar between groups and during the study period, the food consumption was assessed by self-reported food records for 3 days and for 3 times during the training program: one week before the first familiarization session (Pre), four weeks after the training program start (Intra) and during the final week of data collection (Post). As there is evidence that too long recording periods and respondents' fatigue tend to decrease compliance of the diet diaries information (Ortega et al. 2015), a protocol was chosen to investigate potential habitual diet differences in groups before, during and after the intervention, but also to cause the

least discomfort to the participants, since they were already being quite demanded. Thus, macronutrients and vitamins C and E ingested during the experimental protocol were assessed in 3 time points (*i.e.* weeks 1, 4 and 10) by 3-days diet diaries (2 week days and 1 weekend day). A software (Dietbox, Porto Alegre, Brazil) was used to analyze the diet diaries. A registered dietitian instructed the subjects how to properly record mealtime, foods and portions. Information of total energy consumption and quantities of carbohydrates, proteins, fats, vitamin C and vitamin E consumed were calculated using the database of the Brazilian Institute of Geography and Statistics (IBGE) and of the Brazilian food composition table (TACO), for food not registered in the first one. BCS were instructed to avoid consumption of muscle-building supplements, ergogenic aids, coffee, tea, alcoholic beverages, and foods rich in antioxidants. Since the main vitamin C and E sources comes from fruits and vegetables, BCS received a list of substitution aiming to help them to maintain a healthy dietary behavior, even avoiding fruits and vegetables rich in antioxidants. The values of vitamins C (500 mg/day) and E (180 mg/day) ingested as supplement by the participants of the VIT group were intentionally removed from the dietary diary prior to perform analyses, since this would make it impossible to verify potential real differences in the habitual dietary consumption between groups.

Blood samples

Venous blood samples were obtained twice from the upper arm of each BCS by a trained phlebotomist, prior to and after the completion of the ST program. Samples were immediately sent for analysis of ascorbic acid (Vitamin C) and α -tocopherol (Vitamin E). BCS were instructed not to exercise or drink alcohol the day before blood collection (fasting was not compulsory). Blood samples were collected at the same time of the day (afternoon), both before and after training protocol. Samples for plasma ascorbic acid were collected in Vacutainer heparin tubes and assessed by high-performance liquid chromatography (HPLC). Samples for serum α -tocopherol were collected in Vacutainer tubes and assessed by HPLC.

Perceived fatigability

Self-perceived fatigue was measured through MFI-20. This questionnaire was designed to assess levels of fatigue between different time points, subjects, groups, and/or different conditions (Smets et al. 1995). The questionnaire measures fatigue experienced in previous days using 5 different domains: General fatigue, Physical fatigue; Mental fatigue, Reduced Activity, and Reduced Motivation. In the present study, only General Fatigue and Physical Fatigue were used as a wide, global and general indicator of perceived fatigue. The score was calculated in a range of 4-20 points, with 4 being little fatigue and 20 the highest level of fatigue.

Performance fatigability

Performance fatigability was measured through the fatigue index calculated using an isokinetic Biodex System 4 (Biodex Medical, Inc., Shirley NY, USA) dynamometer. BCS were positioned on the dynamometer seat with safety belts fastened to the trunk, pelvis and thigh to avoid extraneous body movements that could affect outcome values. The lateral epicondyle of the femur was used to align the knee rotation axis and the dynamometer rotation axis, allowing free knee extension and flexion from 85° flexion to full extension. Gravity correction was obtained by measuring the torque exerted by the lever arm and the participant's leg at 30° flexion as well as in a relaxed position. The values of the isokinetic variables were automatically adjusted for gravity with the software Biodex Advantage (Biodex Medical, Inc., Shirley NY, USA). The calibration of dynamometer was carried out according to the specifications provided by the manufacturer. For the test, BCS were asked to cross their arms across their chest (Vieira et al. 2015). The same researcher carried out the test procedures for all participants and provided verbal encouragement. As part of warm-up, subjects performed one set of 10 submaximal knee isokinetic extension at 120°.s⁻¹. Performance fatigability was measured two minutes after warm-up, with one set of 30 maximal isokinetic extensions at 120°.s⁻¹ (Correia et al. 2018). Fatigue index was calculated

according Dutra et al. (2018), as the percent drop in torque throughout the set via the following equation, where peak torque was the highest torque achieved during the set and the minimum torque was the mean of the last three repetitions:

$$FI = \frac{(\text{peak torque} - \text{minimum torque})}{\text{peak torque}} * 100$$

In the familiarization week, BCS performed one session composed by one set of 10 submaximal isokinetic extension at $120^{\circ} \cdot s^{-1}$, and one set of four maximal isokinetic extension at $60^{\circ} \cdot s^{-1}$, with two minutes as rest interval between them.

Statistical analyses

Data are presented as mean and standard deviation. Data normality was assessed using the Shapiro-Wilk test. Independent t-tests we used to compare physical and clinical characteristics between groups. A two-way mixed ANOVA was used to analyze potential differences in the dietary intake between-groups (vitamins vs placebo) and within-groups (week 1 vs week 4 vs week 10). Potential differences in training volume per week between-groups (vitamins vs placebo) and within-groups (weeks) were analyzed by a two-way mixed ANOVA. Additionally, a two-way mixed ANOVA was used to analyze potential differences in plasma ascorbic acid, serum α -tocopherol, general fatigue, physical fatigue and fatigue index between-groups (vitamins vs placebo) and within-groups (pre- and post-intervention). The Bonferroni adjustment was used as post-hoc assessment. Partial eta-squared was calculated and reported (η_p^2). Cohen's d was calculated as effect size (ES) within-group for blood concentration of vitamins C and E, general and physical fatigue, and fatigue index in order to estimate the magnitude of the difference within-group according the following criteria: < 0.20 trivial; $0.20 - 0.50$ small; $0.50 - 0.80$ moderate; $0.80 - 1.20$ large; $1.20 - 2.00$ very large. Cohen's d was calculated as follow: $(ES = (\text{mean pre} -$

mean post)/SD pooled). The Statistical Package for Social Sciences (SPSS), version 21.0 (IBM, USA) was used for all analyses. The alpha level was set a priori at 5% ($p < 0.05$).

Results

Thirty-three breast cancer survivors met the inclusion criteria and were randomly assigned to either a VIT ($n = 17$) or PLA ($n = 16$) group. Three BCS declined to participate in the study before or during ST protocol. Five volunteers discontinued participation in the study due to health issues, such as breast reconstruction surgery ($n = 2$), flu ($n = 1$), hyperglycemia ($n = 1$) and knee injury ($n = 1$). Therefore 25 BCS completed all experimental protocols; 12 in VIT and 13 in PLA groups. Flow of participants is presented in Figure 2.

Physical and clinical characteristic of all BCS are presented in Table 1. There was a significant difference observed between groups in age on diagnosis ($p = 0.047$). There were no differences between groups in any other variables ($p > 0.05$).

Dietary intake and training volume

The dietary records in each group and time are exposed in Table 2. There was no difference between groups or between times in any variable ($p > 0.05$).

The training volume per week of each group is presented in Figure 3. There was a significant main effect for time ($F = 76.615$; $p < 0.001$; $\eta_p^2 = 0.769$), but not for group ($F = 0.836$; $p = 0.370$; $\eta_p^2 = 0.035$). Also, there was no significant group by time interaction ($F = 0.400$; $p = 0.934$; $\eta_p^2 = 0.017$). Training volume substantially increased ($p < 0.05$) during weeks in both groups, with no differences between groups ($p > 0.05$).

Blood concentration of vitamins C and E

Changes in plasma ascorbic acid (vitamin C) and serum α -tocopherol (vitamin E) are presented in Figure 4. Regarding vitamin C, there was no significant main effect for time ($F = 0.124$; $p = 0.728$; $\eta_p^2 = 0.005$) or group ($F = 0.508$; $p = 0.483$; $\eta_p^2 = 0.022$). Also, there was no significant group by time interaction ($F = 3.819$; $p = 0.063$; $\eta_p^2 = 0.142$). There was no difference between groups at any time ($p > 0.05$). Also, there was no difference between pre and post intervention in VIT (0.87 ± 0.44 vs. 1.13 ± 0.61 mg/dL; $\Delta = +29.89\%$; $p = 0.123$; ES = 0.50) and in PLA (0.99 ± 0.35 vs. 0.81 ± 0.36 mg/dL; $\Delta = -18.18\%$; $p = 0.260$; ES = 0.51). Although no differences were seen between groups in Vit C blood sample analyses, a moderate effect size of the rise of vitamin C was seen favoring VIT group (+29.89%).

Regarding vitamin E, there was a significant main effect for time ($F = 13.685$; $p = 0.001$; $\eta_p^2 = 0.373$) and for group ($F = 7.701$; $p = 0.011$; $\eta_p^2 = 0.251$). Also, there was a significant group by time interaction ($F = 9.445$; $p = 0.005$; $\eta_p^2 = 0.837$). There was no difference between pre and post intervention in PLA (1.17 ± 0.23 vs. 1.22 ± 0.33 mg/dL; $\Delta = +4.27\%$; $p = 0.656$; ES = 0.18). However, vitamin E increased significantly in VIT (1.20 ± 0.37 vs. 1.78 ± 0.42 ; $\Delta = +48.33\%$; $p < 0.001$; ES = 1.47). There was no difference between groups at pre intervention ($p = 0.804$). Post intervention, vitamin E in VIT was significantly higher than PLA ($p = 0.001$).

Perceived and performance fatigability

General fatigue, physical fatigue and fatigue index data are presented in Figure 5. There was significant main effect for time ($F = 17.895$; $p < 0.001$; $\eta_p^2 = 0.438$), but not for group ($F = 2.618$; $p = 0.119$; $\eta_p^2 = 0.102$) on general fatigue. There was no significant group by time interaction ($F = 0.174$; $p = 0.680$; $\eta_p^2 = 0.008$) and no significant difference between groups at any time point ($p > 0.05$). General fatigue reduced similarly after the experimental protocol in VIT (10.58 ± 3.78 vs. 7.58 ± 3.63 ; $\Delta = -28.36\%$; $p = 0.004$; ES = 0.81) and in PLA (12.23 ± 2.52 vs. 9.77 ± 3.47 ; $\Delta = -20.11\%$; $p = 0.011$; ES = 0.82). There was a significant main effect for time (F

= 20.654; $p < 0.001$; $\eta_p^2 = 0.473$) and for group ($F = 4.912$; $p = 0.037$; $\eta_p^2 = 0.176$) on physical fatigue, while, no significant group by time interaction ($F = 0.316$; $p = 0.580$; $\eta_p^2 = 0.014$) was observed. There was no difference between groups in any time point ($p > 0.05$). Physical fatigue decreased similarly after experimental protocol in VIT (9.33 ± 4.52 vs. 6.33 ± 2.74 ; $\Delta = -32.15\%$; $p = 0.011$; $ES = 0.80$) and in PLA (12.00 ± 2.42 vs. 8.15 ± 2.58 ; $\Delta = -32.08\%$; $p = 0.001$; $ES = 1.54$). There was a significant main effect for time ($F = 20.806$; $p < 0.001$; $\eta_p^2 = 0.475$), but not for group ($F = 0.001$; $p = 0.974$; $\eta_p^2 = 0.000$) on fatigue index, while no significant group by time interaction ($F = 1.256$; $p = 0.274$; $\eta_p^2 = 0.052$) was observed. There was no difference between groups in any time point ($p > 0.05$). Fatigue index decreased similarly after experimental protocol in VIT (52.72 ± 9.32 vs. $48.41 \pm 7.25\%$; $\Delta = -8.18\%$; $p = 0.026$; $ES = 0.52$) and in PLA (54.22 ± 9.81 vs. 47.11 ± 7.20 ; $\Delta = -13.11\%$; $p < 0.001$; $ES = 0.83$).

Discussion

This randomized, double-blinded, placebo-controlled trial aimed to investigate the effect of ST combined with antioxidant supplementation on perceived and performance fatigability in BCS. The main findings of the present study suggested that antioxidants supplementation does not augment the effect of ST on perceived and performance fatigability. Thus, the hypothesis of the present study that vitamins supplementation associated with ST would improve cancer related fatigue more than ST alone was rejected.

In the present study, there was a substantial reduction in perceived fatigue after the ST protocol. The Vit group reduced 28.36% and 32.15% of general and physical fatigue, respectively, while the PLA group reduced 20.11% and 32.08% of general and physical fatigue, respectively. In both perceived and performance fatigability, the effect of the ST varied from a moderate to a large size. According (Meneses-Echavez et al. 2015), exercise programs composed by strength exercises alone could indeed promote a moderate reduction in cancer-related fatigue. Such effect

could be related to improvement in musculoskeletal function, body composition, and physical function (Hanson et al. 2016).

Additionally, the effects of ST on perceived and performance fatigability may be explained by possible physiological effects that include improving in immune function, regulating of HPA-axis activation and metabolic function, reducing insulin resistance and estradiol release, improving oxygen consumption, and increasing muscle strength and antioxidant capacity (Jones et al. 2011; Repka and Hayward 2016; Dieli-Conwright et al. 2018). Correspondingly, the reducing in Fatigue Index after ST protocol in both groups showed an improvement in physical function and exercise tolerance. Although we did not measure some of these variables, they are well-known physiological effects of ST that could, speculatively, explain the improvements in both perceived and performance fatigability in the present study. Noteworthy, BCS in both groups showed, on average, an overweight condition (BMI greater than 25kg/m²). Such condition could increase perceived fatigue in adult women (Lima et al. 2019), due to an overstated release of pro-inflammatory cytokines and amplified production of ROS (Romano et al. 2015). Thus, the effect of ST could be even more positive in overweight survivors, reducing substantially perceived fatigue, as showed in the present study.

Contrary to our expectations, antioxidants supplementation did not promote an additive effect to ST on cancer-related fatigue, even though antioxidant supplementation appears to play an important role in the maintenance of immune system homeostasis during and after anti-cancer treatment (Thyagarajan-Sahu and Sahu 2017). Considering that increased oxidative stress, metabolic dysfunction and immune system dysregulation are all causing factors of cancer-related fatigue (Gilliam and St Clair 2011; Carson et al. 2015; Saligan et al. 2015; Wang and Woodruff 2015; Yang et al. 2019), we hypothesized that vitamins C and E supplementation would augment the effect of ST on perceived and performance fatigability of BCS. Vitamin C scavenges superoxide, hydrogen, peroxide, and hydroxyl radicals, and also protects cellular membranes,

while vitamin E operates in a lipid environment, protecting membranes and lipoproteins against peroxidative damage (Fuchs-Tarlovsky 2013).

In healthy individuals, Bowtell and Kelly (2019) showed that the acute and chronic supplementation of antioxidants derived from fruits seems to enhance exercise performance and to avoid or delay muscle damage induced by high-intensity prolonged activities. Such ergogenic effects may be related to an alteration in vascular function, promoting an increased muscle perfusion, added to an amplified antioxidants capacity that inhibit the generation of ROS in the initial damage process (Bowtell and Kelly 2019). In the other hand, antioxidants supplementation does not seem to add any beneficial effect to ST on performance fatigability in healthy young women (Dutra et al. 2018), and may even be detrimental to ST-induced adaptations in healthy population (Dutra et al. 2020)

In BCS, antioxidants supplementation showed no additional effect to ST in performance and perceived fatigability. A possible explanation for the non-additive effect of antioxidant supplementation observed in the current study could be the initial level of fatigue of the BCS who participated in the study. In this study, the BCS assigned to VIT were not highly fatigued to begin with. All BCS were more fatigued than general population (Schwarz et al. 2003), but only PLA crossed the high-fatigue cutoff score on average (General fatigue > 11) (Singer et al. 2011). According Assi and Rebillard (2016), antioxidants supplementation is effective to improve physical function and quality of life mostly in patients exhibiting low antioxidant status or high levels of ROS in blood.

In contrast with Dutra et al. (2020), in the present study, vitamins C and E supplementation was not detrimental to BCS, since ST induced similar effects on perceived and performance fatigability in VIT compared to PLA, despite the antioxidants supplementation administered to the VIT group. This result suggests that the effect of antioxidants supplementation on ST-induced adaptations could be related to initial antioxidant status and fatigue levels. It is important to note that no BCS had vitamin C deficiency or depletion (Hampl et al. 2004). Furthermore, only BCS

on the VIT group had increased blood vitamins concentration, showing an increased non-enzymatic antioxidant capacity.

The current study has some limitations but also strengths. One of the study major limitation was the lack of a direct measurement of inflammatory markers and oxidative stress. However, the measurement of blood concentration of vitamins C and E does provide valuable information on non-enzymatic antioxidant status. The lack of a standard dietary prescription might have allowed some variation in nutrient intake distribution, both during tests and training protocol. However, subjects were systematically instructed to maintain their habitual dietary intake, and only avoid coffee, tea, alcoholic beverages, and juices rich in antioxidants. Also, the 3-day dietary record was administered to each BCS in order to minimize this shortcoming, with no differences within or between groups observed. Another limitation of the present study was the inclusion BCS diagnosed in different, ages and stages, and submitted to different treatments. However, the absence of difference in muscle strength, muscle function (fatigue index), and perceived fatigue between both groups at the beginning of the study provides some confidence regarding the results. The randomized, double-blinded, placebo-controlled design, examining the effects of antioxidant supplementation used with the goal of augmenting the effects of ST is novel and one of the strengths of this study. In future studies would be also important to evaluate how the initial levels of fatigue and antioxidants impact the adaptations promoted by strength training. Furthermore, the assessment of muscle mass and strength should be considered in future experiments as these parameters are also associated with different neuromuscular adaptations examined in this novel and exciting area of research in exercise oncology.

In summary, ST reduces perceived and performance fatigability in BCS. However, Antioxidant supplementation does not appear to add a positive synergistic effect of the ST on decreases in cancer-related fatigue or muscle fatigability in BCS when compared to the PLA group. Further research is needed to confirm or refute the results of this initial study.

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Conflict of Interest Disclaimer

The authors report no conflicts of interest associated with this manuscript.

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Tables

Table 1 Physical and clinical characteristics of both groups, and difference between them.

Physical and clinical characteristics	VIT (n = 12)	PLA (n = 13)	p
Age (years; mean $\pm$ SD)	51.00 $\pm$ 9.03	48.23 $\pm$ 8.34	0.433
Weight (kg; mean $\pm$ SD)	68.08 $\pm$ 10.57	70.45 $\pm$ 9.92	0.570
Height (m; mean $\pm$ SD)	1.61 $\pm$ 0.07	1.58 $\pm$ 0.05	0.182
BMI (kg/m ² ; mean $\pm$ SD)	26.27 $\pm$ 4.19	28.20 $\pm$ 3.48	0.221
Age on diagnosis (years; mean $\pm$ SD)	46.50 $\pm$ 8.37	39.38 $\pm$ 8.59	0.047
TNM stage			
IA (%)	1 (8.33%)	0	
IB (%)	1 (8.33%)	1 (7.69%)	
IIA (%)	3 (25.00%)	2 (15.38%)	
IIB (%)	4 (33.33%)	4 (30.77%)	
IIIA (%)	1 (8.33%)	3 (23.08%)	
IIIB (%)	2 (16.67%)	0	
IIIC (%)	0	3 (23.08%)	
Treatments			
Chemotherapy (%)	12 (100%)	12 (92.31%)	
Radiotherapy (%)	11 (91.67%)	11 (84.62%)	
Mastectomy (%)	12 (100%)	12 (92.31%)	
Hormonotherapy (%)	8 (66.67%)	8 (61.54%)	
Sessions of CT (mean $\pm$ SD)	13.00 $\pm$ 4.13	11.38 $\pm$ 5.84	0.436
Sessions of RT (mean $\pm$ SD)	26.75 $\pm$ 9.21	23.54 $\pm$ 18.42	0.592
Muscle strength (N.m)	120.54 $\pm$ 17.75	120.56 $\pm$ 23.41	0.998

BMI: body mass index; CT: chemotherapy; RT: radiotherapy.

Table 2 Dietary Record of Each Group by the first, fifth and tenth weeks of the ST (mean $\pm$ standard deviation).

	VIT (n = 12)			PLA (n = 13)		
	1 st week	4 th week	10 th week	1 st week	4 th week	10 th week
Calories (kcal)	1681 $\pm$ 541	1607 $\pm$ 598	1602 $\pm$ 445	1703 $\pm$ 486	1713 $\pm$ 428	1729 $\pm$ 383
Carbohydrate (g/kg/day)	3.0 $\pm$ 1.3	2.9 $\pm$ 1.3	3.0 $\pm$ 0.9	3.3 $\pm$ 0.7	3.2 $\pm$ 0.6	3.5 $\pm$ 0.8
Protein (g/kg/day)	1.1 $\pm$ 0.4	1.1 $\pm$ 0.3	1.0 $\pm$ 0.4	1.0 $\pm$ 0.2	1.1 $\pm$ 0.4	1.1 $\pm$ 0.3
Fat (g/kg/day)	0.9 $\pm$ 0.5	0.8 $\pm$ 0.5	0.8 $\pm$ 0.5	1.0 $\pm$ 0.4	1.0 $\pm$ 0.4	0.9 $\pm$ 0.3
Vitamin C (mg)	106 $\pm$ 74	378 $\pm$ 645	203 $\pm$ 213	83 $\pm$ 71	129 $\pm$ 104	120 $\pm$ 81
Vitamin E (mg)	4.9 $\pm$ 2.7	4.7 $\pm$ 2.0	6.0 $\pm$ 4.5	4.2 $\pm$ 1.4	5.0 $\pm$ 2.5	5.0 $\pm$ 1.9

Figure Captions

Figure 1 Experimental design.

Figure 2 Flow of participants enrolled in the study.

Figure 3. Training volume per week

Figure 4. Blood concentrations of vitamin C (A) and E (B), expressed as mean and standard deviation, before (pre) and after (post) experimental protocol. * Significantly different from pre ($p \leq 0.05$). † Significantly different from PLA post experimental protocol ($p \leq 0.05$)

Figure 5 General fatigue (A), physical fatigue (B) and fatigue index (C), expressed as mean and standard deviation, before (pre) and after (post) experimental protocol.

* Significantly different from pre ($p \leq 0.05$).

Figure 1 Experimental design.

338x190mm (95 x 95 DPI)

Figure 2 Flow of participants enrolled in the study.

220x254mm (146 x 146 DPI)

Figure 3. Training volume per week

201x114mm (300 x 300 DPI)

Figure 4. Blood concentrations of vitamin C (A) and E (B), expressed as mean and standard deviation, before (pre) and after (post) experimental protocol. * Significantly different from pre ($p \leq 0.05$). † Significantly different from PLA post experimental protocol ($p \leq 0.05$)

233x103mm (600 x 600 DPI)

Figure 5 General fatigue (A), physical fatigue (B) and fatigue index (C), expressed as mean and standard deviation, before (pre) and after (post) experimental protocol.

* Significantly different from pre ($p < 0.05$).

295x88mm (300 x 300 DPI)