Effects of Nonlinear Training with Resistance Exercise on Breast Cancer Survivor with Lymphedema and Hypothyroidism during Adjuvant Hormone Therapy: A Case Study

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Abstract

Exercise is considered capable of optimizing the immune system and minimizing the side effects of adjuvant and neoadjuvant therapies in cancer (BC) survivors. Despite these findings, the effects of nonlinear resistance training (NLRT) on breast cancer (BC) survivors with lymphedema have not yet been elucidated. Thus, the aim of this study was to evaluate the effects of 12 weeks of NLRT, three times a week, on lipid and hormonal profiles, body composition and anthropometric indices, muscle strength and endurance, aerobic performance, and blood pressure (BP) and mean arterial pressure (MAP) in a BC survivor with lymphedema and hypothyroidism under hormone therapy. A 43 years old female, diagnosed with an invasive ductal and triple positive (PR+ and RE+) BC three years ago, lymphedema two years ago and hypothyroidism 9 years ago, under use of Tamoxifen (20 mg/day) for 3 years (hormonotherapy) and Euthyrox (25 mg/day) for 9 years, was assessed before and after each resistance training. There was improvement in lipid and hormonal profiles, anthropometric indices, upper and lower limb strength and endurance, and resting BP and MAP. Although there was no difference in physical fitness in a 6-minute walk test, the heart rate decreased during this test. The application of NLRT for 12 weeks was beneficial and safe in a BC survivor undergoing hormone therapy.

Keywords

Breast cancer; Lymphedema; Hypothyroidism; Resistance training

Introduction

Population statistics indicate that breast cancer (BC) is the most frequently diagnosed type and the one that most causes deaths among women worldwide. From 2008 to 2012, the incidence of new cases and mortality from BC among women worldwide increased by about 20% (from 1.4 million to 1.7 million) and 14% (from 458 thousand to 522 thousand), respectively [1]. The cause of BC is multifactorial and includes genetic and environmental factors [2]. Other factors responsible for the development of BC would be the presence of other chronic diseases, such as hypothyroidism [3], which may make treatment, recovery and survival of this population even more difficult.

Although the cancer treatment has progressed along with the increase in the prevalence of this disease, the survivors of BC present many health impairments, due to the direct effects of cancer and side effects of its treatments (surgery, chemotherapy, radiotherapy and hormone therapy) [4]. Surgery leads to the risk of lymphedema, which can affect up to 30% of cases of mastectomy and/or quadrantectomy accompanied by axillary lymphadenectomy [5]. This is a chronic progressive disease that weakens the physical condition, harming the activities of daily life and favoring the occurrence of depression, frequently associated with anguish and social isolation [6]. In addition, hormone therapy may lead to an increase in body fat, osteopenia, decreased libido, depression and sleep disturbance, among other consequences [4,7].

Resistance exercise training (RT) is increasingly recognized as an important therapeutic intervention in the health of survivors of BC [8], even in patients with lymphedema [9]. To date, RT interventions have been based on traditional protocols, where the same exercise set is performed in the same order and with constant intensities for long periods. Nonlinear periodized RT (NLRT) with more frequent alterations of intensity and volume of training has been used to minimize boredom, avoid excess injuries [10], potentiate strength gains [11] and improve metabolic health in other special populations [12].

However, to date the use of NLRT has not yet been investigated in populations of BC survivors with or without lymphedema and in populations with hypothyroidism. As lymphedema and hypothyroidism are frequent in BC survivors [3,5], it would be very relevant to know the effects and safety of the use of NLRT protocols in these populations. It is in this sense that the present study reports the effects of the application of a 12-week NLRT protocol on anthropometric, cardiovascular, metabolic, inflammatory and physical fitness variables of a surviving BC patient with lymphedema and hypothyroidism under treatment with hormone therapy.

Material and Methods

The study was previously approved by the Research Ethics Committee of the Federal University of Uberlândia (1,776,712). The volunteer agreed to participate in the study and signed a free informed consent form before starting the intervention. The preparation of the text of this study was done according to the recommendations of CARE (Case Report Guidelines).

Case description

Table 1 presents a description of the clinical history of the study volunteer since the diagnosis of breast cancer. Due to the chronology of the larger study to which this case belongs, the patient was invited to participate in the present study only in May 2016, after recovery of the shoulder movement, when her health was stable.
Procedures

The participant was submitted to measurements of body composition, lymphedema (cirtometry), biochemical variables (plasma lipid and inflammatory profile, salivary IgA and thyroid hormones), resting blood pressure, resting heart rate (HR) and physical fitness (strength, upper and lower extremity muscle resistance, and aerobic capacity) at baseline and after 12 weeks of intervention. All evaluations were performed respecting a minimum period of 48 hours of abstinence from any physical effort. A familiarization of the tests of one maximal repetition (1RM) was done initially and all training sessions were conducted at the same time (8:00-9:00 AM) to avoid circadian variations. In addition, the participant was instructed to maintain dietary habits but to abolish the intake of thermogenic foods and ethanol, to do not wear compression sleeves to the upper limbs and to absent from lymphatic drainage sessions throughout the period of the intervention. These strategies were used to avoid possible interferences of other factors that were not induced by the intervention protocol itself.

Anthropometry and lymphedema assessments

Body composition (lean and fat mass) was evaluated using a quadrupolar bioimpedance device (InBody230™, InBody, Seoul, Korea). The evaluations were performed after a 10-hour fast. Cirtometry of the right and left (control) arms to compare the swelling of lymphedema was made before and after the intervention, with the use of an anthropometric tape (Sanny™, São Bernardo do Campo, SP, Brazil) and measuring the perimeter 5 cm below (forearm) and 15 cm above (arm) of the olecranon [13].

Biochemical assessments

The collection of blood samples and saliva were made in the Laboratory of Clinical Analysis of the Federal University of Uberlândia (Uberlândia, MG, Brazil), after 12 hours of overnight fasting, at the beginning and after 12 weeks of resistance training. Blood samples were used for counting white blood cells and quantification of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), thyroid stimulating hormone (TSH), free thyroxine (T4), interleukin-1 receptor antagonist (IL-1Ra), interleukin-4 (IL-4), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α). Saliva samples were used to evaluate the immunoglobulin A (IgA) content. The white cell count (leukogram) was performed on an automated hematology analyzer (XE-2100™, Sysmex, São José dos Pinhais, PR, Brazil) using specific kits (Advanced Biochemical Compounds, Radeberg, Germany). Kits. Serum levels of TGC, TC, HDL-C, and LDL-C were measured on an automated analyzer (BIO 2000™, Bioplus, Barueri, SP, Brazil). Blood levels of TSH and T4 were measured by immunochromiluminescence assays (Elecys, Roche Diagnostics, IN, USA) using specific kits (BioDiagnostic™, IN, USA) with a sensitivity of 0.2 μg/dL for T4.
and 0.08 μIU/mL for TSH. Serum cytokine profile was determined by Enzyme Linked Immunosorbent Assay (ELISA™, BD Pharmigen, San Diego, USA) in 96-well plates, where the samples were incubated with capture and detection antibodies to IL-1RA, IL-4, IL-6, TNF-α and IgA, according to the manufacturer’s recommendations (BD Biosciences, San Jose, CA, USA). Reactions were revealed by the addition of 3,3',5,5'-tetramethyl benzidine (TMB) and interrupted by the addition of 4M H2SO4, with spectrophotometer readings at 450 nm. The final concentration of each analyte was duly corrected for the dilution factor used in each assay.

Cardiovascular and physical fitness assessments

HR, and systolic (SBP) and diastolic (DBP) blood pressures were measured after 15 minutes of rest by the OMRON M4-1 (Omron Healthcare Europe BV™, The Netherlands) digital blood pressure meter. The measurement was done three times and only values that did not differ by more than 4.5 mmHg were accepted. The values considered were the mean of the second and third measurements and the mean values of three non-consecutive days.

The strength was assessed by the one-repetition maximum (1RM) test, according to previously described conditions [14]. The localized muscular resistance (LMR) was assessed by using a 50% 1RM condition. The aerobic fitness was assessed by the 6-minute walk test (6’WT). The 1RM and LMR tests were performed in all exercises (with the exception of 1RM of abdominal exercise), always with alternation of the body segment order, ie, an exercise for superior members (SM) was always followed by an exercise for inferior members (IM). 48 hours after the completion of the 1RM test, the participant performed the LMR test, which consists of performing the largest possible number of repetitions (up to concentric failure) with 50% of the weight found in the 1RM test with full and standardized amplitude of motion. The strength and the muscular endurance of SM and IM were both assessed by the load of 1RM of the bench press and the leg press, respectively. The 6’WT was performed on a 200 m track and during the test the participant used the RS800™ (Polar Electro, Kempele, Finland) cardio-frequency meter to record the HR every minute to determine the maximum distance walked, the participant was verbally oriented to walk as far as possible and at the highest speed she could reach for 6 minutes [15].

Training protocol

The physical training program, consisting of resistance exercises, was adapted and periodized in a non-linear way [10] (strength, hypertrophy and resistance work) on the same day, to consider the specifics of the volunteer (low physical fitness and early muscle fatigue). The activities of the first two weeks were adaptive and comprised exercises of subjectively low intensity (<50% of 1RM), consisting of two series and performed three times a week on nonconsecutive days. Following the adaptation, the patient began the training, which included performing the exercises (leg press, bench press, knee flexion, front pull, machine rowing and abdominal) in the order and sequence shown in Table 2. The loads were adjusted daily, with increments of 5 to 10%, to the extent that the participant exceeded the range of established repetitions.

Results

A description of the clinical history of the study volunteer since the diagnosis of breast cancer is presented in Table 1.

Table 2 presents the order of exercises, per day, from muscle stimuli, as described in the previous section.

Table 3 presents the anthropometric values before and after 12 weeks of periodized physical training, which included performing the exercises (leg press, bench press, knee flexion, front pull, machine rowing and abdominal) in the order and sequence shown in Table 2. The loads were adjusted daily, with increments of 5 to 10%, to the extent that the participant exceeded the range of established repetitions.

Table 4 presents the biochemical and immunological profiles before and after 12 weeks of intervention with periodized physical

| Table 2: Order of exercises, per day, from muscle stimuli. |
|-----------------|-----------------|-----------------|
|                | 1st Day         | 2nd Day         | 3rd Day         |
| 1. Strength     | Leg press       | Knee Flexion    | Rowing Machine  |
| 2. Hypertrophy  | Bench Press     | Front Pull      | Abdominal       |
| 3. Resistance   | Rowing Machine  | Leg press       | Knee Flexion    |
|                 | Abdominal       | Bench Press     | Front Pull      |

Note: *Strength: 3 sets of 4-6 repetitions at 85% 1RM with 2-3 minutes rest between sets. 
*Hypertrophy: 3 sets of 8-12 repetitions at 70% 1RM with 1-1.5 minutes rest between sets. 
*Resistance: 3 sets of 15-20 repetitions at 60% 1RM with 45 seconds rest between sets.

<table>
<thead>
<tr>
<th>Table 3: Values of anthropometric variables of the participant after 12 weeks of periodized physical training.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Weight (kg)</td>
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<tr>
<td>Height (m)</td>
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<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
</tr>
<tr>
<td>Fat Free Mass (kg)</td>
</tr>
<tr>
<td>Arm (lymphedema) circumference (cm)</td>
</tr>
<tr>
<td>Arm (control) circumference (cm)</td>
</tr>
<tr>
<td>Forearm (lymphedema) circumference (cm)</td>
</tr>
<tr>
<td>Forearm (control) circumference (cm)</td>
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</tbody>
</table>

Note: *BMI: body mass index; arm circumference, measured 15 cm above the olecranon; forearm circumference, measured 5 cm below the olecranon.
Table 4: Biochemical and hematologic changes of the participants.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre</th>
<th>Post</th>
<th>Change</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets (10^3/µL)</td>
<td>196</td>
<td>184</td>
<td>-12</td>
<td>-6.12</td>
</tr>
<tr>
<td>Neutrophils (10^3/µL)</td>
<td>2.04</td>
<td>2.37</td>
<td>+0.33</td>
<td>+16.18</td>
</tr>
<tr>
<td>Lymphocytes (10^3/µL)</td>
<td>1.32</td>
<td>1.42</td>
<td>+0.1</td>
<td>+7.58</td>
</tr>
<tr>
<td>Eosinophils (10^3/µL)</td>
<td>0.13</td>
<td>0.14</td>
<td>+0.01</td>
<td>+7.69</td>
</tr>
<tr>
<td>Basophils (10^3/µL)</td>
<td>0.02</td>
<td>0.038</td>
<td>+0.018</td>
<td>+90</td>
</tr>
<tr>
<td>Monocytes (10^3/µL)</td>
<td>0.32</td>
<td>0.34</td>
<td>+0.02</td>
<td>+6.25</td>
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<tr>
<td>Total cholesterol (mg/dL)</td>
<td>196.4</td>
<td>182</td>
<td>-14.4</td>
<td>-7.33</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>122</td>
<td>104</td>
<td>-18</td>
<td>+14.75</td>
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<tr>
<td>LDL-C (mg/dL)</td>
<td>138</td>
<td>112</td>
<td>-26</td>
<td>-18.84</td>
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<tr>
<td>HDL-C (mg/dL)</td>
<td>44</td>
<td>50</td>
<td>+6</td>
<td>13.64</td>
</tr>
<tr>
<td>TSH (mg/dL)</td>
<td>11.51</td>
<td>8.9</td>
<td>-2.61</td>
<td>-22.68</td>
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<tr>
<td>T4 (mg/dL)</td>
<td>1.09</td>
<td>1.17</td>
<td>0.08</td>
<td>+7.34</td>
</tr>
<tr>
<td>IL-1Ra (pg/mL)</td>
<td>113.24</td>
<td>97.07</td>
<td>-16.17</td>
<td>-14.28</td>
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<tr>
<td>IL-4 (pg/mL)</td>
<td>28.03</td>
<td>59.82</td>
<td>+31.79</td>
<td>+113.42</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>110.54</td>
<td>122.55</td>
<td>+12.01</td>
<td>+10.86</td>
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<tr>
<td>TNF-α (pg/mL)</td>
<td>350.49</td>
<td>342.61</td>
<td>-7.88</td>
<td>-2.25</td>
</tr>
</tbody>
</table>

Note: LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TSH: Thyroid stimulating hormone; T4: Thyroxine; IL-1Ra: Interleukin-1 receptor antagonist; IL-4: Interleukin-4; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor alpha.

Table 5: Changes in the physical fitness of the participants.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre</th>
<th>Post</th>
<th>Change</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Variables</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>65.72</td>
<td>68.7</td>
<td>+2.98</td>
<td>+4.53</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>122.31</td>
<td>113.48</td>
<td>-8.83</td>
<td>-7.22</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>73.17</td>
<td>69.02</td>
<td>-4.15</td>
<td>-5.67</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>89.55</td>
<td>83.84</td>
<td>-5.71</td>
<td>-6.38</td>
</tr>
</tbody>
</table>

| Physical Fitness Variables |    |    |        |          |
| Distance walked in 6'WT (m) | 603.6 | 600.3 | -3.3 | -0.55    |
| Area under the HR x time curve in 6'WT (au) | 692.5 | 671.5 | -21 | -3.03    |
| 1RM Bench Press (kg) | 20 | 31 | +11 | +55.00 |
| 1RM Leg Press (kg) | 75 | 140 | +65 | +86.67 |
| LMR Bench Press (rep) | 17 | 35 | +18 | +105.88 |
| LMR Leg Press (rep) | 28 | 48 | +20 | +71.43 |

Note: HR: Heart rate; HR (bpm): Resting heart rate (beats per minute); PAS: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; 6'WT: 6-minute walk test; au: Arbitrary units; 1RM: one-repetition maximum test; rep: Repetitions; LMR: Localized muscular resistance.

Table 4: Biochemical and hematologic changes of the participants.

Table 5: Changes in the physical fitness of the participants.

training. Reduction in t-C, LDL-C, TGC, TSH, platelets and TNF-α, and increase in lymphocytes, eosinophils, basophils, monocytes, HDL-C, T4, IL-1Ra, IL-4 and IL-6 can be observed.

Discussion

Few studies have tested the safety of application of long-term RT in BC survivors with lymphedema [9,16,17] and to date no study has tested the application of NLRT and/or even RT in BC survivors with other diseases such as hypothyroidism, which is the condition of the volunteer of the present study. The case reported here falls within this context and is, undoubtedly, very significant, given the frequent presence of comorbidities parallel to the deleterious clinical state in BC survivors, [3,3] especially because the NLRT was able to improve body composition, cardiovascular variables and lipid, inflammatory and thyroid profiles, as well as to promote greater muscular strength and resistance of upper and lower limbs and to improve cardiovascular effort in aerobic activity.

Although the changes observed were discrete, they are very relevant, since this type of population presents resistance and restriction to the increase of lean mass and decrease of body fat, even with physical training and dietary control [18]. Survivors of BC who undergo hormone therapy have a blockade in the production of estrogen and progesterone, which means they are forced into menopause [19]. In addition, this state favors osteopenia [20] and favors the gain of body fat [19,21]. In the case of the volunteer in this study, the consequences are accentuated by the presence of hypothyroidism, which reduces resting energy expenditure, lipolysis and gluconeogenesis, increases weight gain and cholesterol levels [22], and produces down-modulation of the immune responses [23]. Despite the limitation of the decline in body fat content (-1 kg), this change is an important protective factor against vascular disease and cancer recurrence [24].

A very important anthropometric change observed in the study was the reduction in the circumference of the arm with lymphedema. Although the reduction in the difference of these circumferences is primarily involved in the increase of the local lean mass in the limb without lymphedema, the TR can also provide a better control of...
lymphatic function [25]. The mechanism involved would be similar
to the positive effects that TR has on the venous return of the
triceps sural muscle [26]. Muscle contraction of the upper limbs in
a BC survivor with lymphedema may result in an improvement in
the repercussion of lymphatic fluid from lymphedema and lead to
reduction of swelling [27].

Biochemical modulations after training also draw attention due
to their benefits. Changes in the lipid profile (increase in HDL-C and
decrease in t-C and LDL-C) occur primarily because of increased
muscle volume, which improves the lipolysis efficiency in both rest
and exercise periods [28]. In the immunological profile, previous
studies have shown that physical training increases the counts of
immune cells [29,30]. Although the mechanism by which physical
training generates lymphocytosis is not yet clear, it is possible that it is
due to the reduction of cortisol levels caused by hormonal adaptation
to physical training [31]. Another possibility is that an immune
response improvement is due to increase in the thyroid hormones
production in response to exercise [32], since thyroid hormones
increase the activity of polymorphonuclear [33] and dendritic cells,
and lymphocytes [34]. The increase in neutrophils in particular
is very important for this population, since they are the main cells
that fight and protect the body against the growth and recurrence of
cancer [35,36].

In addition, increases in the levels of anti-inflammatory
cytokines, such as IL-4, IL-6 and IL-1Ra, as well as reduction in the
level of the proinflammatory cytokine TNF-α have been observed. In
BC survivors, high levels of proinflammatory cytokines are common
and frequently associated with other clinical conditions [37], such as
pain and insulin resistance [38,39]. However, physical training may
improve the pro-inflammatory/anti-inflammatory cytokines ratio,
mainly by decreasing fat mass and increasing lean mass, which leads
to increased expression of anti-inflammatory cytokines [40].

The role of physical training in specialized thyroid metabolism
is also not very clear. In a recent study involving overweight men, there
were no changes in T3, T4 and TSH levels after eight weeks of aerobic
or moderate resistance training [41]. It is possible that the influence
of physical exercise on sympathetic stimulation and the production
of hormones by the thyroid gland depend on the duration, intensity
and method of exercise application, as well as on diet. The decrease
in TSH found in the patient is justified by the increase in blood levels
of T4, which controls the TSH release by negative feedback and by
intermediation of thyrotropin releasing hormone (TRH) [42,43]. In
addition to promoting regulation of TSH levels, the increase in T4
will also raise the formation of its derivative, triiodothyronine (T3)
[43]. T3 is responsible for the increase in the formation of mRNAs
responsible for the synthesis of several proteins, the passage of amino
acids by cell membranes, the activity of mitochondrial Na⁺, K⁺-
ATPase and the basal metabolic rate [22,43]. Thus, the changes in the
thyroid profile of the volunteer are compatible with an improvement
in thyroid function in the regulation of metabolism, leading to
reduction in body fat content, improvement of blood lipid profile and
increase in muscle mass [22].

The hemodynamic changes at rest and during 6'WT observed
in the volunteer need to be analyzed in the light of the diversity of
results obtained in studies on the influence of RT on cardiovascular
performance in individuals without cancer incidence [41-46]. It is
clear that the intensity of the applied RT, as well as the BP profile of
the studied population, can influence the magnitude of the responses
[47,48]. In hypertensive individuals, it seems that the RT has a greater
hypotensive effect in relation to the normotensive ones [47]. In this
sense, the reduction of SBP, DBP and MAP, and the increase in HR,
found in this study, may be due to particularities of the pathological
condition of the volunteer. In this sense, it is worth highlighting the
decrease in cardiovascular effort, measured by HR, during the 6'WT.
A meta-analysis on the subject showed that, after RT protocols,
walked distance increased, but without hemodynamic changes [46]
differently from that of the volunteer in this study. The decrease in
HR during the 6'WT may be due to an increase in the strength and
muscular resistance of the lower limbs, which could minimize the
physical and, consequently, cardiac effort, since in this type of patient
there is a predominance of a critical state of fatigue [49]. However,
it should be emphasized that any hypothesis is limited, due to the
absence of studies involving RT with cardiovascular variables and the
absence of control of the multiple pathways that involve the
hemodynamic changes in the study.

The present study presents its own limitations. The first is that
it is a case study and, therefore, the results found here are limited
to the participant studied, although the clinical frame presented by
the participant of this study is common among BC survivors [3,5].
The second limitation is that the lymphedema evaluation method
was by circumference measurement and not by water displacement
volumetry, which is usually considered the gold standard in this
kind of assessment. However, circumference measurements are
inexpensive and, when applied correctly, also yield valid and reliable
results [50]. Finally, randomized controlled trials of TRNL in BC
survivors should be encouraged in order to verify the additional
effects over traditional methods of physical training.

In summary, high intensity periodized resistance training was
effective in improving body composition, aerobic fitness, muscle
strength and biochemical profile of a breast cancer survivor with
lymphadenopathy and hypothyroidism during hormone therapy.

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