



Case Report

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 hormonotherapy. 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 hormonotherapy.

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.

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Table 1: Clinical timeline of the study volunteer.

Dates	History and Relevant Medical Interventions		
05/2014	Patient: female, caucasian, 43 years old, BMI = 22.88 kg/m ² , non-smoking, non-consumer of alcoholic beverages, with previous diagnosis of hypothyroidism, with no family history of breast cancer.		
04/2007	Diagnosis of hypothyroidism. Intervention done by endocrinologist: daily insertion of Euthyrox (25mg / day). Treatment remains until the present.		
Dates	Summary of Initial and Follow-Up Visits	Diagnostic Tests	Interventions
07/2013	Consultation with a mastologist due to complaints of pain, swelling and sensibility in the right breast.	Self-examination by breast touch (own patient).	Referred to mammography.
08/2013	Return to the mastologist for mammography evaluation; Confirmation of multifocal ductal carcinoma in the right breast (Scarff-Bloom-Richardson grade II).	Staging.	Immunohistochemical analysis; 25 sessions of radiotherapy.
10/2013	Positive results for estrogen (ER ⁺) and progesterone receptors (PR ⁺); Radiation therapy caused nausea, weakness, insomnia, and local fibrosis; End of radiation therapy.	Mammography and reassessment of staging.	Biopsy of the sentinel lymph node.
10/2013	Presence of metastasis in the sentinel lymph node.	Classification of the carcinoma in WHO stage III.	Oncologists indicated subcutaneous mastectomy with removal of the areola and right breast nipple and right lymphadenectomy levels I and II (10 lymph nodes).
11/2013	There were no complications in the mastectomy; There were no compromises and / or nerve damage in lymphadenectomy; Good surgical recovery and stabilization of the clinical picture.	Image evaluation; Routine biochemical exams.	The patient was referred to eight cycles of adjuvant chemotherapy, the first four cycles with Doxorubicin (60 mg/m ²) + Cyclophosphamide (600 mg/m ²) and the last four cycles with Docetaxel (100 mg/m ²)
01/2014	Chemotherapy; Lipid profile changes, hair loss, nausea, early fatigue, insomnia, muscle weakness, nocturnal blood pressure changes, and body weight loss.	Routine blood exams; Anthropometric evaluation (weight and height).	At the end of chemotherapy, the patient is referred to hormone therapy with Tamoxifen TM (20 mg/day); Supplementation of vitamin D.
04/2014	Start of hormone therapy; Symptoms of climacteric; Perception of increased circumference of the right arm.	Evaluation of right arm by Cirtometry.	Referral to lymphoscintigraphy.
05/2014	Confirmation of the presence of lymphedema; Presence of depression symptoms.	Psychological evaluations and follow-up by social worker	Referral to lymph therapy (manual lymphatic drainage, skin care, compression (by bandaging or gloves) and <i>myolymphokinetic exercises</i>).
08/2014	Improvement of the clinical picture of lymphedema	Right arm cirtometry.	The patient was instructed by the oncologist to continue the treatment.
09/2014	Interruption of complete lymph therapy, due to the lack of resources of the public hospital, with maintenance only of lymphatic drainage.	Cirtometry; Support from social workers.	Medical recommendations for insertion into physical exercise as a complementary therapy to the control of lymphedema, hypothyroidism and blood biochemical alterations.

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 abstention 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 (InBody230TM, 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 (SannyTM, 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 (TGC), 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-2100DTM, Sysmex, São José dos Pinhais, PR, Brazil) using ABX (Advanced Biochemical Compounds, Radeberg, German) kits. Serum levels of TGC, tC, HDL-C, and LDL-C were measured on an automated analyzer (BIO 2000TM, Bioplus, Barueri, SP, Brazil). Blood levels of TSH and T4 were measured by immunochemiluminescence assays (Elecsys, Roche Diagnostics, IN, USA) using specific kits (BioDiagnosticTM, 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_r 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 12, expressed as gross values, gross change (Pre - Pos) and percentage change (%). After 12 weeks, the participant presented increase of fat free mass and reduction of fat mass. In addition, there was a decrease in the circumference of the arm with lymphedema.

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.

Stimuli	1 st Day	2 nd Day	3 rd Day
1. Strength ^a	Leg press	Knee Flexion	Rowing Machine
	Bench Press	Front Pull	Abdominal
2. Hypertrophy ^b	Knee Flexion	Rowing Machine	Leg press
	Front Pull	Abdominal	Bench Press
3. Resistance ^c	Rowing Machine	Leg press	Knee Flexion
	Abdominal	Bench Press	Front Pull

Note: ^aStrength: 3 sets of 4-6 repetitions at 85% 1RM with 2-3 minutes rest between sets.

^bHypertrophy: 3 sets of 8-12 repetitions at 70% 1RM with 1-1.5 minutes rest between sets.

^cResistance: 3 sets of 15-20 repetitions at 60% 1RM with 45 seconds rest between sets.

Table 3: Values of anthropometric variables of the participant after 12 weeks of periodized physical training.

Variables*	Pre	Post	Change	% Change
Weight (kg)	59.7	59.65	-0.05	-0.08
Height (m)	1.61	1.61	0	0
BMI (kg/m ²)	23.03	23.01	-0.02	-0.08
Fat Mass (kg)	21.5	20.5	-1	-4.65
Fat Free Mass (kg)	38.2	39.2	+1	+2.62
Arm (lymphedema) circumference (cm)	30.5	29	-1.5	-4.92
Arm (control) circumference (cm)	28.5	28	-0.5	-1.75
Forearm (lymphedema) circumference (cm)	27.5	27	-0.5	-1.81
Forearm (control) circumference (cm)	23	24	+1	+4.34

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.

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

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.

Variables	Pre	Post	Change	% Change
Cardiovascular Variables				
HR _r (bpm)	65.72	68.7	+2.98	+4.53
SBP (mmHg)	122.31	113.48	-8.83	-7.22
DBP (mmHg)	73.17	69.02	-4.15	-5.67
MAP (mmHg)	89.55	83.84	-5.71	-6.38
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_r (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.

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.

Table 5 presents the values of cardiovascular and physical fitness variables. Regarding the cardiovascular variables, there was decrease in SBP, DBP and MAP and increase in HR_r. Regarding physical fitness variables, there was increase in load and repetition in the 1RM and LMR tests in SM (bench press) and IM (leg press). In addition, the area under the HR curve as a function of walking time decreased after 12 months of intervention.

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, [3,5] 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 blockage 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 [44-46]. 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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