Effects of combined resistance and aerobic training program on myoelectric activity of Vastus Lateralis in patients with breast cancer during adjuvant chemotherapy period

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Abstract. – OBJECTIVE: Chemotherapy and/or radiation are normally the predominant therapies administered to cancer patients. Commonly, patients express complaints of fatigue during adjuvant treatment. Furthermore, regular practice of physical exercise during adjuvant treatment seems to have positive effects. The aim of this study was to investigate the effects of combined muscle strength, and a supervised aerobic training program on myoelectric activity of Vastus Lateralis during isometric test in patients with breast cancer undergoing adjuvant chemotherapy.

PATIENTS AND METHODS: Thirty-two women with breast cancer (20 patients in the training group and 12 patients as controls) undergoing adjuvant chemotherapy participated in the study. They took part in a 6-week training period. A muscle-strength program included isometric contraction and electrical muscle stimulation (EMS). Aerobic training program consisted of supervised intermittent cycling exercise and home-based walking exercise. The outcome measures were Root Mean Square (RMS), Mean Power Frequency (MPF), Maximal Voluntary isometric Contraction (MViC), and Endurance Time (ET) of Vastus Lateralis, before and after the training period in the two groups.

RESULTS: Compared to controls, a significant increase in MViC (*p*=0.001) and ET (*p*=0.005) in quadriceps accompanied by a significant decrease in RMS (*p*=0.007) and a significant increase in MPF (*p*=0.002) has been obtained in the training group.

CONCLUSIONS: Supervised muscle strength and supervised aerobic training programs enhanced muscle activity and muscular performance in women with breast cancer during adjuvant chemotherapy treatment and optimized the decrease of muscular fatigue.

Key Words:
Multimodal training, Breast cancer, Myoelectric activity, Fatigue perception.

Introduction

Cancer-related fatigue (CRF) is among the most distressing symptoms in breast cancer patients during and after chemotherapy[1]. CRF is associated with the disease itself and with cancer treatment[2] and is not relieved by rest or sleep[3]. CRF affects up to 70% of cancer patients during chemotherapy[4]. Actually, patients who receive chemotherapy cannot avoid damage that occurs to healthy tissues and cells and leads to side effects or symptoms such as fatigue[5]. Data[6,7] examined changes in neuromuscular function as potential contributors to CRF, including comorbidities, supportive care medication, systemic and local cancer treatments, and tumor-derived factors[8]. Indeed, during adjuvant chemotherapy, patients with breast cancer reduce their daily energy expenditure[9], which is associated with a loss of muscle mass[10,11].

Otherwise, Monga et al[6] have shown that systemic rather than local muscle membrane changes occurred due to radiation therapy. Indeed,

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variation in the above membrane cytoarchitecture may produce a disequilibrium of electrolyte gradients across the cell membranes and thus cause K^+ accumulation in the extracellular medium (plasma). This mechanism leads to a decline in neuromuscular efficiency, as well as enhanced fatigue. Both chemotherapy and radiotherapy have been shown to alter the integrity of the sarcolemma, sarcoplasmic (SR), and mitochondrial membranes, leading to disturbances in the mechanism of muscle force generation and recycling of calcium by the SR and Ca^{2+}-ATPase system, that led to a failure of excitation-contraction coupling[12].

Elsewhere, the decline in neuromuscular has been shown to be aggravated by the lack of physical activity during cancer treatment. Indeed, prolonged bed rest and treatment with high-dose corticoids result in a substantial loss of muscle mass, reduction of plasma volume, and cardiac output that further impair exercise capacity[13]. Furthermore, immunosuppression with cyclosporine may result in loss of capillary density, exercise ability[14], and mitochondrial myopathy[15], leading to decreased muscle strength and endurance. Recently, Ge et al[16] reported that low skeletal muscle mass and/or low muscle quality had a significant association with poor long-term survival and increased risk of complications in cancer patients.

Attempts to treat and prevent cancer-related fatigue with drugs have not been successful[17,18]. However, previous studies[19] have demonstrated that the majority of CRF side effects are controlled by regular physical activity. Currently, aerobic and strength physical exercises are considered to be important tools in the treatment of cancer, not only for the rehabilitation of patients but also for decreasing potential lifestyle risk factors for cancer, which are closely related to the progression of the disease[20]. In this context, Berretta et al[21] pointed out that many complications induced by cancer treatment, such as cardiovascular and respiratory impairments, metabolic disturbances, musculoskeletal problems, weakness, and cancer-related fatigue could be improved with physical activities programs.

Flodgren et al[22] have shown that aerobic and resistance exercise improved physical fitness, body composition, and chemotherapy completion rate without causing lymphedema or significant adverse events during adjuvant chemotherapy. Moreover, Andersen et al[23] have shown that supervised multimodal exercise intervention for six weeks, comprising heavy resistance and high-intensity cardiovascular training, massage, relaxation, and body awareness training, can generate a significant decrease in self-reported CRF in cancer patients undertaking chemotherapy.

Battaglini et al[24] also observed a significant decrease in muscle fatigue and an improvement in muscular strength in women with breast cancer undertaking adjuvant chemotherapy. Nonetheless, no investigation has studied the effects of training on muscle performance and myoelectric activity during isometric strength.

The aim of our investigation was to study the effects of multimodal strength and aerobic training programs, on myoelectric activity and performance of the Vastus Lateralis during isometric test in patients with breast cancer undertaking adjuvant chemotherapy.

Patients and Methods

Patients

A randomized controlled trial was conducted to investigate the effects of combined muscle strength, and a supervised aerobic training program on myoelectric activity of Vastus Lateralis during an isometric test in patients with breast cancer undergoing adjuvant chemotherapy. The sample size was determined based on the main dependent variable measured in this study, the root mean square of electromyography signal. Given the pioneering nature of this study, a high effect size of 0.80 was chosen arbitrarily, and a power of 80% (α=0.05) was fixed. With an allowance of 10% of the dropout rate, the sample size calculated using software (G*Power 1.3.9.4, Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany) was 24 patients (12 patients in each group). Patients were recruited from the Medical Oncology Department "Salah Azaeiz" of the Salah Azaiez Oncologic Hospital in Tunisia. The inclusion criteria were women aged from 18 to 65 years, with no known history of chronic respiratory, cardiac, or neuromuscular disease, diagnosed with non-metastatic breast cancer (stage I-IIIA), who have had a mastectomy and are in the process of adjuvant chemotherapy (postoperative). The chemotherapy session lasts 3 hours and is carried out in the hospital every three weeks. The protocols used are FEC 100 (5 Fluouracil, Epirubicin, Cyclophosphamide) alternated with Docetaxel.

The exclusion criteria were malnutrition [body mass index (BMI) <20], the practice of physical activity, treatment with high-dose corticoids (prednisone >50 mg/day or equivalent dose of related agents), chronic diseases exacerbated by exercise (coronary artery disease, chronic obstructive pulmonary disease, osteoarthritis), hemoglobin concentration <8 g/dl, chronic infection, platelet count <20/nl, obesity (BMI >30), neurologic or muscular impairment, skeletal metastases resulting in bone instability, or progressive disease with indication of new or additional therapy.

The study started with a total of 39 patients. These patients were recruited from a larger population of 730 patients who were being followed in the Oncology Department of the hospital. Recruited subjects were randomly assigned to two homogenous groups: one training (experimental) group (n=20) and one control group (n=19). At the end of the experimental period, seven participants from the control group were excluded because they could not perform the retest due to a change in their homes and/or hospitals (Figure 1). Only patients in the training group participated in the rehabilitation program. The patients in the control group continued to receive adjuvant chemotherapy throughout the 6-week study period. However, they did not take part in any physical exercise or rehabilitation program. The characteristics of patients in both groups are presented in Table I. The study has received ethics approval from the Institutional Review Board of the medical center (Approval number: ISA/2016/01bis). The clinical trial was registered with the Pan African Clinical Trials Registry (Trial ID: PACTR202007730554581). Written informed consent was obtained from all participants, and confidentiality was maintained throughout the study.

Protocol

After recruitment, the same pre-test and post-test trial of muscular performance was carried out. This test consisted of an isometric exercise to measure the Maximal Voluntary isometric Contraction (MViC) and endurance time (ET) of the quadriceps muscle. Electric muscle activity changes during a maintained constant exercise at 50% of MViC were assessed using surface electromyography (EMG). Experiments took place in the mornings at the Medical Oncology Department at the Salah Azaiez Hospital. The order of passage

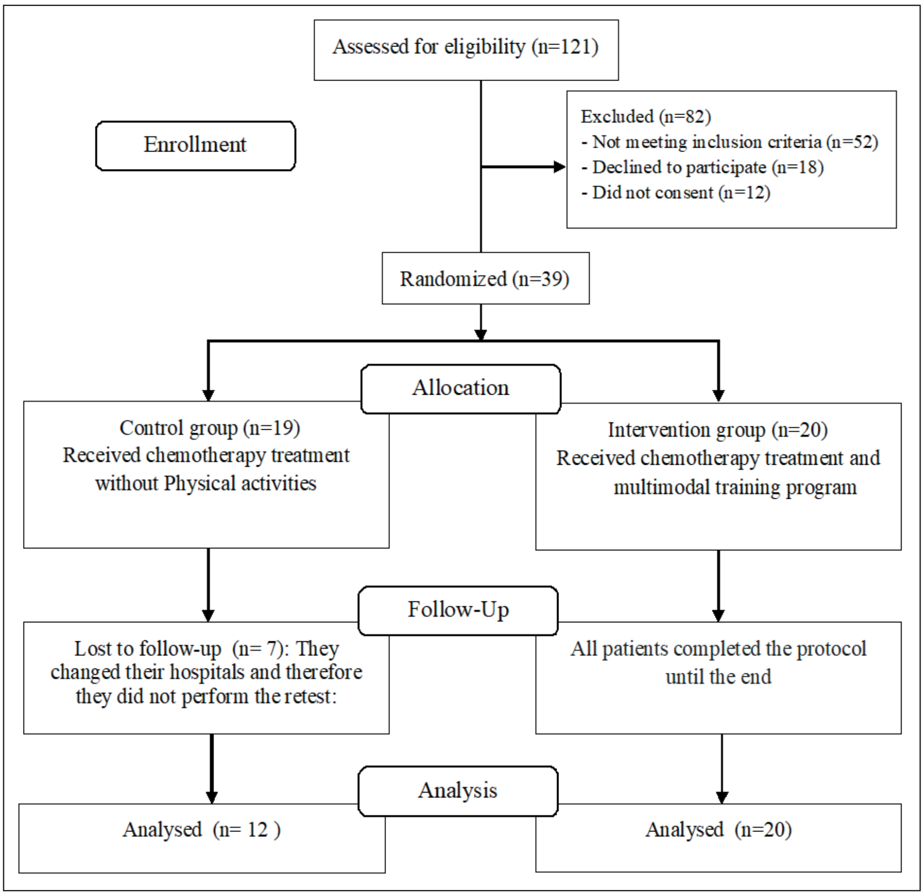

Figure 1. Flow diagram of randomization procedure.

in the test was counterbalanced, and the passages were spaced at least 24 hours and, at most, 3 days apart. Atmospheric conditions in terms of temperature and humidity were not different in the pre-test and the post-test (temperature ranges: 20-23°C; humidity: 60±2%). We suggested that patients perform the walking exercise during the day and the day after the chemotherapy session. Patients were asked to take their last meal at least two hours before the test, abstain from caffeine, and exercise 24 hours before all tests.

Quadriceps Muscle Strength

Quadriceps muscle strength was assessed using a universal dynamometer (Dynamomètre PCE-FG K, Soultz-sous-Forêts, France). Patients were seated comfortably with the back supported in a sturdy chair with hips and knees at 90°. A strap was positioned above 2 cm lateral malleolus of the ankle of the dominant leg; the other end of the strap was attached to a strain gauge dynamometer.

During contractions, the direction of force generation was perpendicular to the axis of the leg. Patients had to push as hard as possible for three seconds. After a familiarization test period, the patients began three attempts, interspersed with a 2-minute passive recovery. Verbal encouragements were always given to the subjects to develop maximal force (kg) during the test. To determine MViC, the average of the values of the three MViC obtained during the three maximum extensions was calculated.

After the three maximum extensions, a 5-minute recovery period was proposed for patients before starting the maintained constant exercise at 50% of MViC. To assess endurance time (s), patients maintained an exercise at 50% of MViC as long as possible. Endurance time corresponded to the maintained time during this exercise test. MViC and ET were assessed using an electronic card associated with a software on a computer. A strength sensor was connected to the measuring card. The kinetics of the developed force and the holding time were displayed on the computer screen and visible to the patients.

Electromyography Signal Detection and Processing

During Endurance Time, EMG activity was recorded from the Vastus Lateralis (VL). Bipolar surface electrodes (WS EMG Electrodes, active electrode diameter: 8 mm, inter-electrode distance: 20 mm, with a high-tack and highly conductive gel; Ambu® White Sensor, Ambu, Ballerup, Denmark) were employed and placed according to a previously published methodology[25].

Table I. Characteristics of patients in both groups

	Training group	Control group
N	20	12
Gender	Female	Female
Age (years)	49.71±5.41	48.93±4.76
Q_{25}	45.25	44.25
Q_{50} (Med)	47.5	49.5
Q_{75}	55.75	53
Weight (kg)	73.1±6.63	70.25±5.03
Q_{25}	67.25	65.5
Q_{50} (Med)	71.5	71
Q_{75}	80.75	73.5
Height (cm)	160.47±4.75	159.87±3.25
Q_{25}	155.25	157
Q_{50} (Med)	162.5	159.5
Q_{75}	164	163
BMI (kg/m^2)	28.42±2.55	27.55±2.62
Q_{25}	26.45	24.83
Q_{50} (Med)	28.32	27.79
Q_{75}	30.02	29.26
Type of Tumor	Breast cancer	Breast cancer
Side of the operated breast		
Right	11 (55%)	7 (58.33%)
Left	9 (45%)	5 (41.67%)
Treatment	Adjuvant Chemotherapy	Adjuvant Chemotherapy

Data are expressed as mean± standard deviation and Quartiles 25,50,75.

Electrodes were located on (1/4) distance proximal to the lateral tibial condyle on a line connecting this and the anterior-superior-iliac-spine.

Before electrode application, the skin was cleaned and abraded with an alcohol-ether-acetone mixture to reduce the inter-electrode impedance below 2 kΩ. The signal of Vastus Lateralis was stored on the computer after isolated differential amplification (bandwidth = 1 Hz-1 kHz, gain = 1,000, Gould 6600 amplifier; Gould Electronics, Eichstetten, Germany). EMG signal was analyzed online using acquisition and spectral analysis software (Ad Instruments, LabChart V7.3.1, USA). The EMG signal was sampled at 1,024 Hz. Each spectrum was calculated from 0.5 s time windows and was defined by 256 points, on a 0-512-frequency band. The root mean square (RMS) and median power frequency (MPF) were calculated in real time by the computer. RMS and MPF were averaged for each muscle and normalized[25].

Training Program

The training program was conducted during a period of six weeks and included strength resistance and aerobic exercise training.

The resistance-training program consisted of knee extensor muscles isometric exercises (10*10 contractions of 3 seconds in the first week, 15*15 contractions of 4 seconds for 2 weeks, and 20*20 contractions of 5 seconds in the last 3 weeks, 5 days/week). This program was coupled with the home-based walking program.

Electrical muscle stimulation (EMS) was applied to knee extensor muscles. We used Compex-P devices (Compex, Singapore) producing biphasic symmetric impulses with a 50 Hz frequency, a pulse width of 0.35 ms (stimulus regime: 8 s on/24 s off; session time 30 min/day in the first 2 weeks, increased to 40 min/day in the last 4 weeks, 2 days/week). A pre-established electrostimulation protocol in Compex system was used. Stimulation intensity was individually adjusted for each limb in order to obtain tetanic contraction or maximum tolerated intensity. The device provided 4 output channels with the possibility to adjust intensity. It was effected via self-adhering surface electrodes (2”×2” and 2”×4”, Compex, Medi-Konzept GmbH). To stimulate the quadriceps muscle, the electrodes were placed bilaterally, medially, and laterally, 3 cm proximal to the upper border of the patella and 5 cm distal to the inguinal fold[26].

The aerobic training included a home-based walking and supervised intermittent cycling program. The cycling training program consisted of exercises on a cycle ergometer (Finnlo Exum 3157, Neu-Ulm, Germany) twice a week. The subjects in the training group wore a Polar heart rate monitor (Polar Electro, Port Washington, NY, USA) during each cycling and walking exercise-training session to monitor their heart rates.

The theoretical maximal Heart Rate TMHR was calculated using the following formula by Gulati et al[27]: (206 – [0.88×age]). A passive recovery was suggested in all cycling training sessions.

The cycling exercise started with 5 minutes of warming-up at an intensity of 50% of the HR max. During the 1st week, patients carried out two cycling training sessions of 2×10 minutes at an intensity of 55% of TMHR. During the 2nd week, the exercise intensity was increased by 60% of TMHR with a 2×12-min training session. During the 3rd week, the exercise intensity was 65% of TMHR for an exercise duration of 2×15 minutes. In the last 3 weeks, the patients performed six cycling training sessions of 2×20 minutes at 70% of TMHR for the 4th week, 75% of TMHR for the 5th week, and 80% of TMHR for the last training week.

The home-based walking program consisted of walking continuously for 20 minutes for 5 days per week during the first two training weeks, 25 minutes during the 3rd and the 4th weeks, and 30 minutes during the last two weeks. The exercise intensity was between 50-60% of TMHR. We read and calculated patients’ mean exercise heart rates weekly from their heart rate monitor to control and adjust the training load. Furthermore, an increase in walking intensity by 5% compared to the average exercise heart rate calculated each week was applied every two weeks. The Borg scale was used to evaluate the perceived rate of exertion (PRE) systematically during all training sessions.

Statistical Analysis

Shapiro-Wilk and Levin’s tests were used, respectively, to verify the normality and homogeneity of variances. All variables showed a normal distribution at every time point. Means and standard deviations of dependent variables were calculated across participants. A two-way analysis of variance with repeated measures (groups *vs.* pre-post training) was conducted to compare changes in ET, MViC, RMS, and MPF in training and control groups. A Bonferroni post-hoc test was applied whenever the difference was significant. Effect sizes (η^2) were determined from ANOVA output by converting partial eta squared to Cohen’s *d* values. Moreover, within-group ESs were computed using the equation: ES= (mean post-mean pre)/pooled SD, and were considered trivial (<0.2), small (0.2-0.6), moderate (0.6-1.2), large (1.2-2.0) and very large (2.0-4.0). Data were analyzed using Sigma Stat 3.1 (Systat Software Inc, San Jose, California, USA). The accepted level of significance was set at $p< 0.05$.

Results

The results of the Shapiro-Wilk and Levin tests were not significant ($p>0.05$), proving a normal distribution with homogeneous variance for all dependent variables measured in this study. Anthropometric and characteristics data of experimental and control groups are presented in Table I. The training and control groups showed no differences in mean data for age, body mass, height, BMI, or type of tumor. We have reported no dropouts in the training group. The adherence was 100%. However, seven patients in the control group were eliminated because they did not perform the retest. The adherence in this group was 63%.

Myoelectric Activity

Changes in Root Mean Square (RMS)

The Root Mean Square of the training group decreased significantly after six weeks of training period (0.39±0.18 mV *vs.* 0.20±0.09 mV, respectively, in test and retest; p=0.007, ES=1.34). However, no significant differences were observed in the controls (0.28±0.17 mV *vs.* 0.35±0.09 mV, respectively, in test and retest) (Figure 2).

Changes in Mean Power Frequency (MPF)

No significant differences were observed in Mean Power Frequency in controls (123.2±51.31 Hz *vs.* 106.99±55.92 Hz, respectively in test and retest). However, a significant increase was observed in MPF (104.33±48.33 Hz *vs.* 159.12±48.26 Hz, respectively, in test and retest; p=0.002, ES=1.14) of the training group (Figure 3).

Muscle Performance

Changes in Maximal Voluntary Isometric Contraction (MViC)

The Maximal Voluntary Isometric Contraction in the training group increased significantly following six weeks of training period (14.79±2.58 Kg *vs.* 17.06±2.61 kg, respectively, in test and retest; p=0.001, ES=0.87). However, the differences were not significant in patients of the control group (15.12±1.19 Kg *vs.* 14.39±1.38 kg, respectively, in test and retest) (Table II).

Changes in Endurance Time (ET)

The Endurance Time in the training group increased significantly following the training period (50±24.58 s *vs.* 69.25±29.75 s, respectively, in test and retest; p=0.005, ES=0.71). However, differences were not significant in patients of control group (51±14.06 s *vs.* 48.17±9.45 s, respectively, in test and retest) (Table II).

Perceptual exertion responses (PRE)

For the perceived rating of exertion parameter, results showed no statistical difference in the control group (6.17±0.94 *vs.* 6.42±0.90, respectively, in test and retest). However, a significant increase was observed in patients of the training group (6.35±0.93 *vs.* 5.7±0.12, respectively, in test and retest; p=0.03, ES=0.98).

Discussion

The aim of this study was to investigate the effects of combined strength resistance and supervised aerobic training programs on myoelectric activity of Vastus Lateralis and muscular performance during isometric tests in patients with breast cancer undergoing adjuvant chemotherapy.

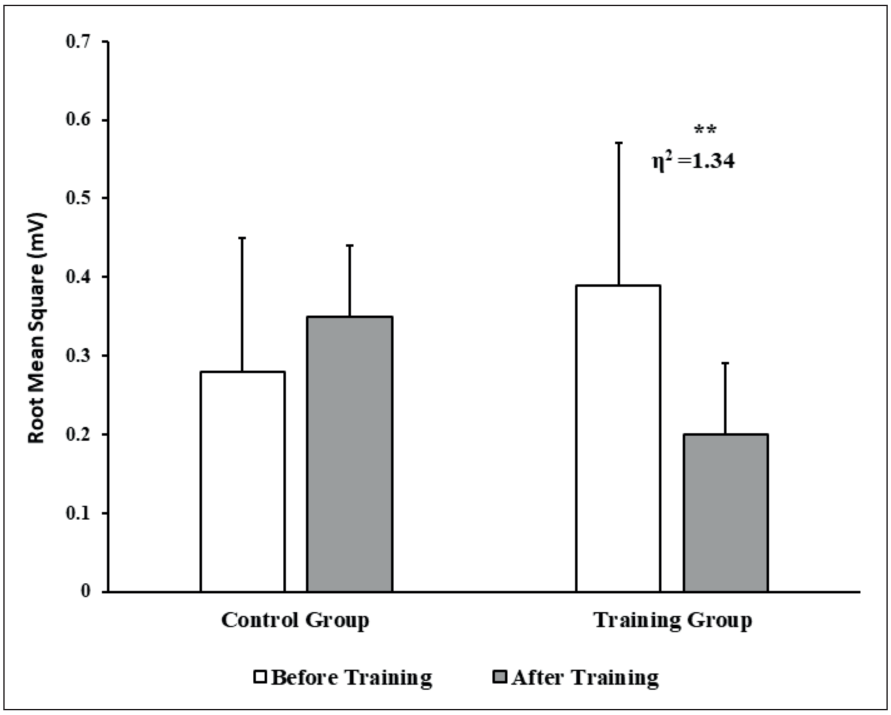

Figure 2. Changes in Root Mean Square (RMS). **: p<0.01.

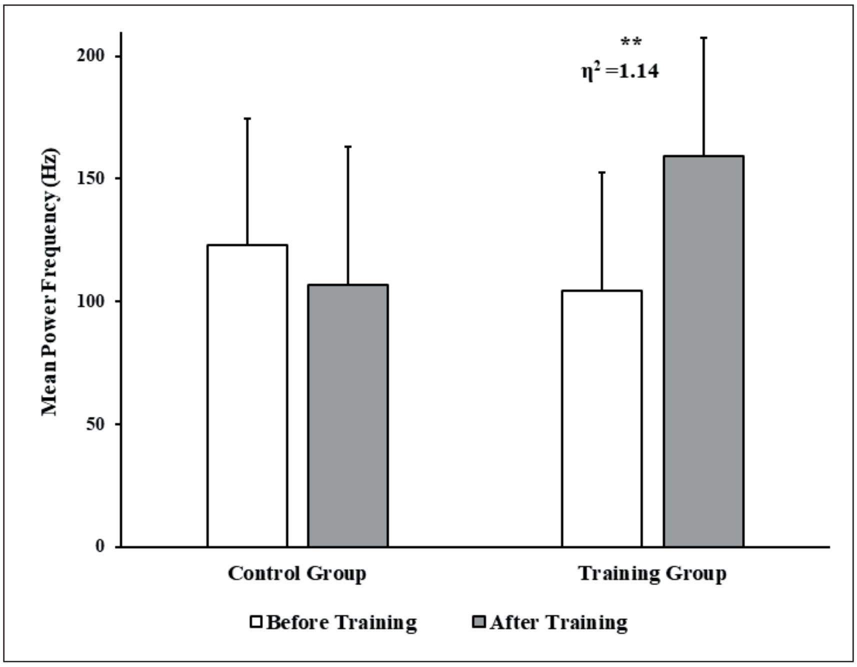

Figure 3. Changes in Mean Power Frequency (MPF). **: $p<0.01$.

Table II. Changes in Maximal Voluntary Isometric Contraction (MViC), Endurance Time (ET) and Perceptual exertion responses (PRE) before and after training program in experimental and control groups.

	Experimental Group (Mean±SD)			Control Group (Mean±SD)			Variance analysis/effects					
							Group		Time		Group x Time	
Parameter	Pre	Post	ES	Pre	Post	ES	p	η^2	p	η^2	p	η^2
MVIC (kg)	14.79±2.58	££17.06±2.61**	0.87	15.12±1.19	14.39± 1.38	0.56	.01	.10	.05	.06	.002	.14
ET(s)	50±24.58	££69.25±29.75**	0.71	51±14.06	48.17± 9.45	0.24	.000	.23	.000	.20	.000	.25
RPE	£6.35±0.93*	5.7±0.12	0.98	6.17±0.94	6.42± 0.90	0.25	.27	.02	.41	.01	.06	.05

ES: Effect size; η^2: Partial eta squared for ANOVA; **: $p<0.01$ between test-retest in experimental group; *: $p<0.05$ between test-retest in experimental group; ££: $p<0.01$ between experimental and control groups in retest; £: $p<0.05$ between experimental and control groups in retest.

Our findings highlight that six weeks of combined strength and aerobic training program improves muscular performance and myoelectric activity in women with breast cancer. Indeed, compared to controls, an increase in MViC and ET during the isometric test accompanied by a decrease in the RMS and an increase in MPF have been obtained in the training group following a training program.

In the present study, both resistance and aerobic training programs were designed to introduce progressive increments in intensity and volume, allowing progressive adaptation and avoiding the risk of overtraining[28]. Moreover, a systematic increase in exercise intensity and volume is necessary for progressive physical fitness improvement[29]. Furthermore, no study has proposed isometric resistance exercises for cancer patients. Usually, the dynamic form using the estimated one repetition maximum of patients was suggested[4,23,30].

Surface electromyography (EMG) is a relevant objective method and non-invasive assessment of muscle activity. EMG is a technique used to record and evaluate the electrical activity produced by skeletal muscles. It is able to measure the activity and fatigue of a specific muscle and has thus been suggested[31] for the diagnosis of muscular diseases. In fact, generally, muscle fatigue has been checked with RMS and MPF, those presented as indicators of fatigue and believed to be evidenced by increases in RMS and decreases in MPF[32]. In our study, EMG RMS and EMG MPF were investigated. EMG RMS is a global measure of Motor Unit (MU) recruitment and firing rates, while EMG MPF reflects the average muscle fiber conduction velocity[33].

In the present study, we observed a significant decrease of RMS (p=0.007) and an increase of MPF (p=0.002) in the training group following six weeks of combined aerobic and strength training program. This finding showed that Motor Units were recruited in a slower threshold, and they caused less fatigue than in the pre-test, which is why we have observed an increase in endurance time following the training program.

In addition, De Luca and Hostage[34] suggested that if the high-threshold motor units (MU) discharged at relatively higher rates, high-threshold MUs would fatigue more quickly, and force would not be maintained. An increase in RMS is the result of the synchronization of active MUs and the recruitment of new Mus, while the decrease in MPF has been primarily attributed to a reduction in muscle fiber conduction velocity[35].

In fact, the conduction velocity of the motor unit during submaximal isometric contractions depends on the Na^+ and K^+ pump capacity[36], and both resistance and endurance training upregulate the Na^+ and K^+ pump capacity in the skeletal muscle[37]. Furthermore, Majerczak et al[38] showed that five weeks of endurance training provoke a down regulation of the calcium cycling due to a reduction of the Ca^{2+}-ATPase activity. These adaptations might contribute to a lengthening of the twitch duration, which would result in a similar twitch fusion at lower discharge rates[28].

Previous studies[39,40] showed that electrical muscle stimulation of the large lower limb muscles, improves muscular strength and overall exercise capacity. In addition, EMS has become clinically established as a method allowing the improvement of muscle strength[41], prevention of muscle mass loss and endurance capacity of patients unable to perform active exercise[42,43].

Our results are in agreement with the findings of several studies[39-42]; we observed a significant increase in the MViC in the training group following six weeks of training program. Furthermore, a significant increase has been observed in the Endurance Time of the training group following six weeks of training program.

We can explain this increase in response to a resistance training program results by the combination of muscular and neural adaptations[44,45]. Moreover, aerobic exercise provokes an increase in the muscle myoglobin content, volume, and size of mitochondria[46]. Thus, skeletal muscle strength and endurance can be increased[47]. The decrease in effort perception (PRE) in patients of our training group seems to be related to such adaptations.

In this connection, Hiraoui et al[48] have shown positive effects of combined intermittent aerobic and muscle strength training programs on cardio-respiratory responses in women with breast cancer during adjuvant chemotherapy treatment. The authors pointed out that the use of this modality of training program improves aerobic fitness level and reduces the perception of fatigue in patents with breast cancer. In addition, the same research team recently confirmed in another study[49] that multimodal aerobic and strength exercises programs improve muscular strength and enhances muscle oxygen utilization in patients with breast cancer during the adjuvant chemotherapy period.

Limitations

The present study has obvious limitations. The sample size is relatively small, and the inter-individual variability of the dependent variables measured within the two groups was relatively high due to the differences related to the age and level of physical ability of the patients recruited in this study.

Conclusions

It is concluded that combined muscle strength and supervised aerobic training programs improves muscle performance and myoelectric activity in women with breast cancer undergoing adjuvant chemotherapy. This improvement was displayed by an increase of MViC and Endurance Time that was accompanied with a decrease in the RMS and an increase in MPF of Vastus Lateralis.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Ethics Approval

The article has received ethics approval from the Institutional Review Board of the Salah Azaiez Oncologic Hospital, Tunisia (Approval No. ISA/2016/01bis). The study was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration.

Trial Registration

Pan African Clinical Trials Registry (Trial ID: PACTR202007730554581).

Informed Consent

Written informed consent was obtained from patients and signed prior to enrolment in the study.

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Authors' Contributions

SA and AM were responsible for the primary conception and design of the article with input from co-authors. MH, FB, and KJ provided data collection. MH, PLD, and NG prepared initial drafts of the article. Additions, modifications, and critical revisions for the relevant intellectual content of the report were performed by MH, NG, BH, MB, and MK, including final approval of the version to be published. All the authors have read and agreed to the final manuscript.

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Data Availability

The datasets of the current study are available from the corresponding author on reasonable request.

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