The Analgesic Effect of Resistance Training after Breast Cancer (ANTRAC): A Randomized Controlled Trial

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[1]Sport Sciences–Performance and Technology, Department of Health Science and Technology, Aalborg University, Aalborg, DENMARK; [2]Department of Physical Therapy, Faculty of Health Sciences, Sport and Health Institute Research, University of Granada, Granada, SPAIN; and [3]Biohealth Institute Research Granada, Granada, SPAIN

ABSTRACT

RASMUSSEN, G. H. F., M. KRISTIANSEN, M. ARROYO-MORALES, M. VOIGT, and P. MADELEINE. The Analgesic Effect of Resistance Training after Breast Cancer (ANTRAC): A Randomized Controlled Trial. *Med. Sci. Sports Exerc.*, Vol. 55, No. 2, pp. 167–176, 2023. **Objective:** The objective of this blinded parallel-arm randomized controlled trial was to investigate the effect of resistance training (RT) on pain, maximal strength, and shoulder function in breast cancer survivors (BCS) with persistent pain after treatment. **Methods:** Twenty BCS with self-reported pain ≥1.5 yr after treatment were randomized to an experimental group (EXP, $n = 10$), who performed a supervised progressive total body heavy RT program 2 times per week for 12 wk, or a control group (CON, $n = 10$), who was instructed to continue their everyday life. Perceived pain intensity, pressure pain threshold (PPT) levels, one-repetition maximum (1RM), and active range of motion were collected pre- and postintervention and at 3 months follow-up. **Results:** There was a significant 11% decrease in peak pain intensity ($P < 0.05$) for both groups, a significant 48% increase in 1RM ($P < 0.05$), and a significant 35% increase in PPT levels ($P < 0.001$) for EXP, but not for CON. For EXP, maximal strength at follow-up was still significantly greater than at preintervention ($P < 0.05$), whereas PPT levels had reverted to baseline levels. There was no change in active range of motion ($P < 0.05$) and no change in arm circumference ($P < 0.05$). **Conclusions:** RT had a significant effect on 1RM and PPT of BCS with persistent pain after treatment, demonstrating both a functional and analgesic effect of progressive RT in this population. Strength was largely maintained after detraining, whereas PPT levels were not, indicating that the process of RT rather than the gain in strength may be associated with analgesia. **Key Words:** HYPOALGESIA, PAIN SENSITIVITY, BREAST CANCER SURVIVORS, STRENGTH TRAINING, SHOULDER FUNCTION, PRECISION EXERCISE MEDICINE

Persistent pain after breast cancer treatment is a considerable problem, with more than one third of breast cancer survivors (BCS) reporting pain up to 7 yr after the initial treatment (1). The pain is commonly reported in and around the surgical area at both the ventral and dorsal side, possibly because of damage to the peripheral nerves from the surgical incisions and/or adjuvant therapy (2), causing considerable physical and psychological distress to the patients (3). Pain after breast cancer treatment is also associated with mechanical hyperalgesia (i.e., mechanical pain hypersensitivity) (2) and is a primary cause of upper limb impairments (4). These impairments are reflected in loss of shoulder strength and shoulder range of motion (ROM) (5), which thereby limits performance in activities of daily living (6). Collectively, these issues have a profound negative effect on quality of life and long-term survival in BCS (7,8), and hence, there is a need for novel and effective strategies to reduce pain and improve physical function after treatment for breast cancer.

Progressive resistance training (RT) has previously been shown to improve muscular strength, physical function, and quality of life in BCS (9,10), and research suggests that progressive RT may effectively improve ROM (11). However, as highlighted by Campbell et al. (12), few exercise trials on cancer survivors have included pain as a primary outcome, and little is known about the effects of exposure to progressive RT on BCS experiencing persistent pain. At the time of this writing (August 2022), only two randomized controlled trials (RCT) have specifically tested the effect of progressive RT on persistent pain postoperatively (13,14) with modest effects on pain. Specifically, Cormie et al. (13) reported no significant pain-relieving effect after supervised RT intervention. By contrast, the results of Ammitzbøl et al. (14) did indicate a favorable effect of a semisupervised RT

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intervention on perceived pain, although most differences were not statistically significant.

Consequently, our current knowledge of the potential pain-relieving benefits of progressive RT in BCS experiencing persistent pain is still lacking. Furthermore, a growing body of evidence demonstrates a substantial inter individual variability in the response to a standard dose of exercise, highlighting the importance of individualized exercise prescription (i.e., precision exercise medicine) (15). Although previous interventions did standardize load progression to accommodate individual rates of adaptation, no other means of individualization (i.e., within or between session training adjustments) were used to adjust and personalize the RT stimuli more appropriately. Therefore, the purpose of the present RCT, named Analgesic Effect of Resistance Training after Breast Cancer (ANTRAC), was to investigate the effects of progressive individualized RT on measures of pain and shoulder function in BCS experiencing persistent pain. We investigated the clinically meaningful effect of progressive RT on perceived pain intensity (PI), mechanical pain sensitivity, active ROM, and muscular strength delineating an analgesic effect.

METHODS

Participants

Participants were recruited by means of a recruitment letter forwarded to BCS appearing in the national database managed by the Danish Breast Cancer Corporate Group through the official Danish e-mail service named e-Boks. Participants were recruited sequentially and prescreened for participation with the Physical Activity Readiness Questionnaire. Assuming an alpha level of 0.05, a beta level of 0.20, and a moderate effect size of 0.25, the minimum required sample size to detect a significant difference in pressure pain threshold (PPT) levels was determined to be 28. To account for a potential dropout of 20%, 34 participants were invited to participate in the study. See Rasmussen and colleagues (16,17) for inclusion and exclusion criteria.

By means of a computer-generated list stratified by age, peak pain, and maximum upper body strength, defined as one-repetition maximum (1RM) in bench press, participants were randomly assigned to an experimental group (EXP) or a control group (CON). The random allocation sequence was generated by a third-party researcher not involved in recruitment, data collection, or statistical analysis. Assessors and researchers were blinded to the group allocation. Because of the nature of the intervention, participants could not be blinded but were strongly inculcated not to disclose their allocation status at the follow-up assessments. Baseline characteristics of EXP (n = 10) and CON (n = 10) are shown in Table 1.

TABLE 1. Sociodemographic, surgical, and medical profile of the clinical population.

Characteristic	EXP	CON
Age, mean (95% CI), yr	58.9 (52.1–65.7)	60.5 (56.3–64.7)
Height, mean (95% CI), cm	165.8 (160.6–171.1)	168.4 (164.9–171.8)
Living arrangement, *n* (%)		
Living with a partner	8 (80)	8 (80)
Education, *n* (%)		
Short	0 (0)	2 (20)
Medium	9 (90)	7 (30)
Long	1 (10)	1 (10)
Employment, *n* (%)		
Full time	4 (40)	3 (30)
Part time	3 (30)	5 (50)
Retired	3 (30)	2 (20)
Time since treatment, mean (95% CI), months	80.1 (55.6–104.6)	64.9 (44.1–85.7)
Pain duration, mean (95% CI), months	74.3 (49.6–99.0)	64.3 (42.9–85.7)
Pain since treatment, *n* (%)	8 (80)	9 (90)
Body mass index, mean (95% CI), $kg \cdot m^{-2}$	25.6 (22.1–29.1)	26.7 (23.3–30.1)
Body mass index, *n* (%)		
≤25 $kg \cdot m^{-2}$	6 (60)	5 (50)
>25–≤30 $kg \cdot m^{-2}$	3 (30)	3 (30)
>30 $kg \cdot m^{-2}$	1 (10)	2 (20)
Menopausal status, *n* (%)		
Post	10 (100)	9 (90)
Smoking, *n* (%)		
Former smoker	5 (50)	6 (60)
Never smoker	5 (50)	4 (40)
Alcohol consumption		
No. units per week, mean (95% CI)	5.6 (2.5–8.7)	4.3 (0.8–7.8)
Histological stage of malignancy, *n* (%)		
I	3 (30)	4 (40)
II	3 (30)	4 (40)
III	4 (40)	2 (20)
Tumor diameter, mean (95% CI), mm	21.2 (6.5–35.9)	20.1 (12.6–27.6)
Surgical protocol, *n* (%)		
Breast conserving surgery	7 (70)	8 (80)
Mastectomy	3 (30)	2 (20)
Lymph node protocol, *n* (%)		
Sentinel lymph node biopsy	7 (70)	7 (70)
Axillary dissection	2 (20)	0 (0)
Both	1 (10)	3 (30)
No. of lymph nodes dissected, mean (95% CI)	4.9 (1.6–8.2)	5.5 (1.7–9.3)
Dominant limb affected, *n* (%)	5 (50)	4 (40)
Adjuvant treatment, *n* (%)		
Chemotherapy only	0 (0)	0 (0)
Radiotherapy only	3 (30)	2 (20)
Both	7 (70)	8 (80)
Endocrine therapy, *n* (%)		
Yes	6 (60)	8 (80)
No	3 (30)	0 (0)
Ceased	1 (10)	2 (20)
Receptor status, *n* (%)		
Estrogen positive	7 (70)	10 (10)
HER2 positive	3 (30)	1 (10)

HER2, human epidermal growth factor receptor 2.

Study Design

The ANTRAC study was a single-blinded parallel-arm RCT to investigate the effects of RT on pain and function. The study complies with the CONSORT guidelines for RCT reporting and incorporates the TIDieR and CONSERVE extensions for intervention description and trial modifications, respectively (see Supplemental Digital Content 1, CONSORT checklist, http://links.lww.com/MSS/C708; Supplemental Digital Content 2, CONSERVE checklist, http://links.lww.com/MSS/C709; and Supplemental Digital Content 3, TIDieR checklist, http://links.lww.com/MSS/C710). Participants randomized to EXP completed a 12-wk supervised progressive RT program, with two supervised sessions per week. Participants randomized to CON were advised not to change habitual activity levels but received no specific instructions regarding physical activity or access to equipment during the intervention period. Both groups continued to receive their medical care as per usual throughout the study period and were instructed to avoid

consumption of alcohol, caffeine, nicotine, or analgesics in the last 24 h before the experimental sessions.

All outcome measures were collected at a familiarization, PRE, POST, and FOLLOW-UP session. Familiarization and PRE sessions were respectively conducted 2 and 1 wk before the intervention, whereas POST and FOLLOW-UP were conducted 1 and 12 wk after (Fig. 1). All testing and exercise training took place at the Sport Sciences–Performance and Technology laboratories (Aalborg University), between August 2020 and March 2021 in agreement with the national COVID-19 restrictions at the time, using calibrated weight discs and barbells (Rogue Fitness, Columbus, OH), competition combo racks (ER Equipment, Albertslund, Denmark), a prone row bench (Thor Fitness, Finnerödja, Sweden), and a vertical pulldown (FASSI, Remanzacco, Italy). The study protocol was approved by the local Ethics Committee (N-20180090), registered at ClinicalTrials.gov (NCT04509284), and conducted according to the Declaration of Helsinki. After a detailed written and verbal explanation of the experimental benefits and risks, the participants gave their written informed consent before participating in the study.

Intervention

The ANTRAC program was separated into three distinct phases: 1) 2–4 sets of 10–12 repetitions, 2) 2–4 sets of 6–8 repetitions, and 3) 2–4 sets of 2–4 repetitions (Fig. 2A). Each phase lasted 4 wk, creating a progressive decrease in number of repetitions to accommodate load progression. Load and number of sets were individually adjusted within and between sessions. A 3- to 5-min rest period was provided between sets across all phases. Initial loads were set to 60% of 1RM, and all further sets were adjusted according to individual performance to provide precision exercise medicine (15). For within sessions, load was increased by 1–10 kg when an individual was able to complete the maximum number of repetitions prescribed and decreased by 1–10 kg when an individual failed to complete the minimum number of prescribed repetitions. For between sessions, load was increased by 1–10 kg when an individual was able to complete the maximum number of prescribed repetitions in the final set of the previous session and otherwise maintained. Total number of sets was adjusted in accordance with the perceived readiness of an individual. Individuals with low level of perceived readiness (i.e., low mental readiness to exertion [MRE] or physical readiness to exertion [PRE], see outcome measures section, score ≤5) were only required to complete the minimum number of prescribed sets, whereas individuals with high level of readiness (i.e., MRE or PRE score ≥6) were encouraged to complete the maximum number of prescribed sets. In agreement with Smith et al. (18), movement-evoked pain (MEP) was not discouraged, and adjustments were made only in case the participants perceived it as too severe to continue as planned.

Each session began with a general warm-up, consisting of 5 min of aerobic activity and stretching for the primary muscles

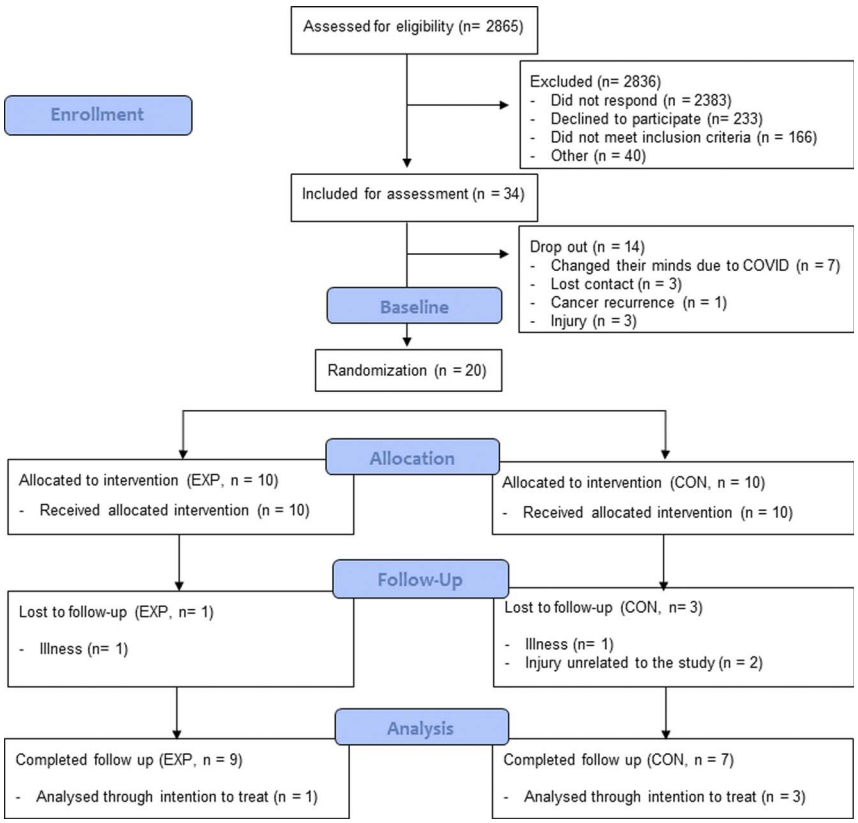

FIGURE 1—Enrolment, randomization, and dropout of participants allocated to the experimental group (EXP) or control group (CON). Injury or illness was defined as a change in physical status, unrelated to the intervention that altered the outcome of the Physical Activity Readiness Questionnaire.

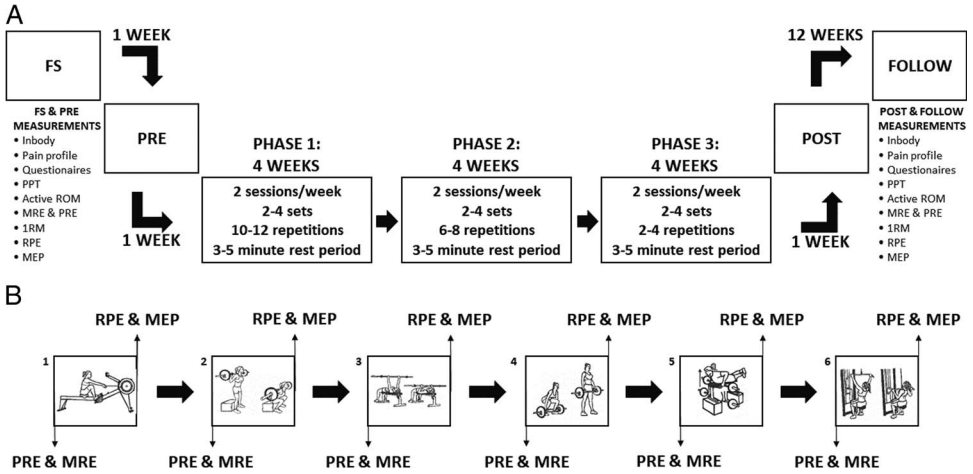

FIGURE 2—The ANTRAC trial design (A) consisting of 3-month training divided into 4-wk phases preceded by a familiarization (FS) and a preintervention test (PRE) and followed by a postintervention test (POST) and a 3-month follow-up test (FOLLOW-UP). Body composition, pain profile, questionnaire, PPT, active ROM, MRE, PRE, 1RM, RPE, and MEP were collected at FS, PRE, POST and FU, respectively. Each training session (B) began with a general warm-up (1) followed by exercise one through five (1–5) in that order. PRE and MRE were collected before the general warm-up and exercises 1–5, respectively, whereas RPE and MEP were collected immediately after.

involved in the RT exercises. This was followed by five exercises performed according to the ANTRAC program in systematic order (Fig. 2B). The training was delivered in a small-group format with two to four participants exercising concurrently under supervision from a certified strength and conditioning specialist educated in the current guidelines for exercise medicine in cancer management (19). To monitor fidelity and adherence, each session began with assessment of attendance and potential changes in group constellation.

Outcomes Measures

Primary outcomes: changes in PPT and PI. PPT is a reliable measure of mechanical pain sensitivity in BCS (16). PPT levels were measured unilaterally across 17 points of the dorsal and ventral regions on the affected shoulder and at a single point on the ipsilateral tibialis anterior muscle. All PPT measurements were collected twice in systematic order using a handheld pressure algometer (Somedic AB, Farsta, Sweden) and a third time if the coefficient of variance was ≥20% (16). The PPT maps were constructed from the mean PPT levels of each point by applying inverse distance weighted interpolation to the inter point distance, thereby enabling a visualization of changes in spatial distribution of mechanical sensitivity (20). For greater detail, see Rasmussen et al. (16,17).

PI and pain frequency during everyday living of the past 3 months was rated for the chest, shoulder, axilla, arm, and side of body. PI was rated on an 11-point numeric rating scale (NRS), where 0 corresponded to "no pain" and 10 to "worst pain imaginable" (21). Pain frequency was rated as every day or almost every day, 1–3 times per week or more rarely (22).

MEP intensity was rated immediately following every set of each exercise on the same 11-point NRS.

Secondary outcomes: maximal strength, shoulder ROM, and body composition. In agreement with the recommendations of the American College of Sports Medicine (23), participants performed a general warm-up, followed by a warm-up set of 8–10 repetitions and 3–5 repetitions with approximately 50% and 70% of 1RM. Participants then performed a maximum of five single repetitions with an initial load of approximately 90% of 1RM and increments of 1–20 kg until a true 1RM was achieved. Incremental rest periods were provided between sets with 1–4 min between warm-ups and 3–5 min between 1RM attempts to prevent excessive fatigue.

Active ROM was measured with a universal goniometer for six movement directions: 1) supine shoulder flexion, 2) supine horizontal shoulder flexion, 3) horizontal shoulder extension, 4) seated upright shoulder abduction, 5) supine internal shoulder rotation, and 6) supine external shoulder rotation. Goniometric measurements of active ROM are reliable in BCS and were conducted in agreement with Rasmussen et al. (16).

Body mass index ($kg \cdot m^{-2}$) was calculated from height and body mass measured at baseline. Body fat mass, skeletal muscle mass (SMM), and body fat percentage of each participant were computed using direct segmental multifrequency bioelectrical impedance analysis (InBody 370, Biospace, Seoul, Korea), which is considered valid and reliable for body composition measures (24). In agreement with the manufacturer guidelines, measurements were collected with similar baseline conditions (i.e., time of day, ≥2 h since last meal, visit to the bathroom before testing, etc.). Failure to keep conditions such as bowel and bladder content similar between measurements can influence the results as residue and/or wastes in the body are interpreted as fat mass by the analysis.

Other outcomes: psychometrics. MRE and PRE were rated before each exercise in every laboratory session on an 11-point NRS, where 0 corresponded to "no readiness to exertion" and 10 corresponded to "maximum readiness to exertion" (25). MRE and PRE were obtained before each exercise to account for the potential influence of readiness on 1RM performance.

RPE was rated immediately following every set of each exercise every laboratory session on a RT-specific 10-point NRS based on repetitions in reserve (RIR), where RPE 10 = 0 − RIR, RPE 9 = 1 − RIR, and so forth. This scale has been validated as a subjective measure of intensity in both novice and experienced power lifters (26).

Compliance and Adverse Events

Compliance to the intervention was measured as the percentage of supervised RT sessions effectively achieved by the participants (27). Adverse events caused by RT throughout the intervention period were reported by the participants and registered by the trainers, and arm circumference was measured pre- and postintervention to monitor any development of lymphedema on the affected arm.

Statistics

Sociodemographic and clinical characteristics of all participants are presented as frequencies or proportions and group means with 95% confidence intervals (CI). A linear mixed model (LMM) incorporating three fixed effect factors was applied to investigate the effect of RT on PPT levels using an intention-to-treat analysis to account for missing data and/or dropouts. PPT was used as the dependent factor with location (dorsal, ventral, and reference) and time (PRE, POST, and FOLLOW-UP) as within-subject factors and group (EXP/CON) as the between-subject factor. Identical procedures were applied to the remaining outcomes. If no significant interaction effects were found, main effects were reported. *Post hoc* analyses were performed as univariate analyses with Bonferroni correction for multiple comparisons. All statistical procedures were conducted in IBM SPSS Statistics (26.0 version; IBM Corp., Armonk, NY). A P value <0.05 was considered statistically significant. Differences are expressed as mean (95% CI). Effect size estimates are reported as Cohen's d and interpreted according to Cohen (28) in which ≥0.20–<0.50 = small, ≥0.50–<0.80 = moderate, and ≥0.80 = large.

RESULTS

This study was affected by the COVID-19 pandemic making recruitment particularly difficult and causing higher dropout rate than originally anticipated. Therefore, we were not able to recruit as many participants as planned. Moreover, the nationwide restrictions created significant practical challenges for the execution of the study as the training intervention had to be relocated and additional measures were taken to ensure the safety of each participant. Accordingly, training was organized in smaller groups than originally planned, and additional trainers were hired to account for the greater number of training groups. These modifications were approved by the Danish Cancer Society, the head of department and the project leader, and implemented throughout the intervention period from September to November 2020.

Compliance and adverse events. The mean (95% CI) number of scheduled sessions completed by the participants was 89 (83%–95%). There was no change in interarm difference in circumference ($F_{2,\ 25.063} = 0.267$, $P = 0.768$, $d = 0.04$), and no other adverse events were reported from the intervention.

Primary outcomes. Mean PPT levels for EXP ($n = 10$) and CON ($n = 10$) are shown in Table 2. The LMM revealed a significant interaction between group and time ($F_{2,62.476} = 9.253$, $P < 0.001$, $d = 0.47$), and univariate analyses demonstrated that there was a significant effect of time but only for EXP ($F_{2,\ 58.929} = 16.748$, $P < 0.001$, $d = 0.78$). Specifically, PPT levels for EXP were significantly higher at POST compared with both PRE and FOLLOW-UP, but not at FOLLOW-UP compared with PRE (see Table 2 for pairwise comparisons). This is further illustrated by the alterations in spatial distribution of mechanical pain sensitivity between groups shown in Figures 3 and 4.

Mean (95% CI) pain levels on the affected side for EXP ($n = 10$) were 7.7 (6.5–8.9), 6.7 (5.1–8.3), and 5.6 (4.3–6.9) at PRE, POST, and FOLLOW-UP, respectively. For CON ($n = 10$), the corresponding values were 8.1 (6.9–9.3), 7.1 (5.4–8.9), and 7.4 (5.9–8.9). The LMM revealed an overall main effect of time ($F_{2,\ 27.817} = 3.697$, $P = 0.038$, $d = 0.53$), demonstrating a significant decrease in PI over time for both groups. Although there was no statistically significant difference, 50% of the participants in EXP experienced a reduction of ≥2 points from PRE to POST.

Secondary outcomes. One-repetition maximums for EXP ($n = 10$) and CON ($n = 10$) are shown in Figure 5. The LMM revealed a significant three-way interaction between group, time, and exercise on 1RM ($F_{8,68.615} = 4.798$, $P < 0.001$, $d = 0.77$). Specifically, 1RM was significantly higher across all exercises at POST and FOLLOW-UP compared with PRE for EXP, but not for CON. Further, 1RM was significantly higher for EXP at POST and FOLLOW-UP when compared with CON for box squat, bench press, and lat pulldown. Similarly, there was a significant two-way interaction between time and exercise ($F_{8,74.912} = 2{,}287$, $P = 0.030$, $d = 0.40$), group and time ($F_{2,59.449} = 6{,}349$, $P = 0.003$, $d = 0.36$), and group and exercise ($F_{4,82.685} = 3{,}421$, $P = 0.012$, $d = 0.29$) (for pairwise

TABLE 2. Mean PPT levels of the ventral and dorsal regions of the affected shoulder, and at a distant reference point, collected at PRE, POST, and FOLLOW (3-month follow-up) for experimental (EXP) and control (CON) group.

	EXP			CON		
PPT (kPa)	PRE mean (95% CI)	POST mean (95% CI)	FOLLOW mean (95% CI)	PRE mean (95% CI)	POST mean (95% CI)	FOLLOW mean (95% CI)
Reference	226.5 (121.8–331.2)	317.4 (214.1–420.7)*	242.5 (154.7–330.3)**	302.5 (197.8–407.2)	293.0 (183.6–402.3)	307.0 (211.9–402.2)
Mean dorsal	207.4 (143.2–271.7)	257.9 (188.8–327.1)*	208.9 (147.8–270.0)**	261.4 (197.1–325.6)	247.7 (175.3–320.0)	250.2 (186.9–313.6)
Mean ventral	142.6 (105.1–180.1)	174.1 (132.0–216.3)*	149.2 (106.9–191.5)**	170.7 (133.2–208.2)	165.8 (121.7–209.9)	168.8 (124.9–212.6)

*Significant difference from PRE ($P < 0.05$).
**Significant difference from POST ($P < 0.05$).

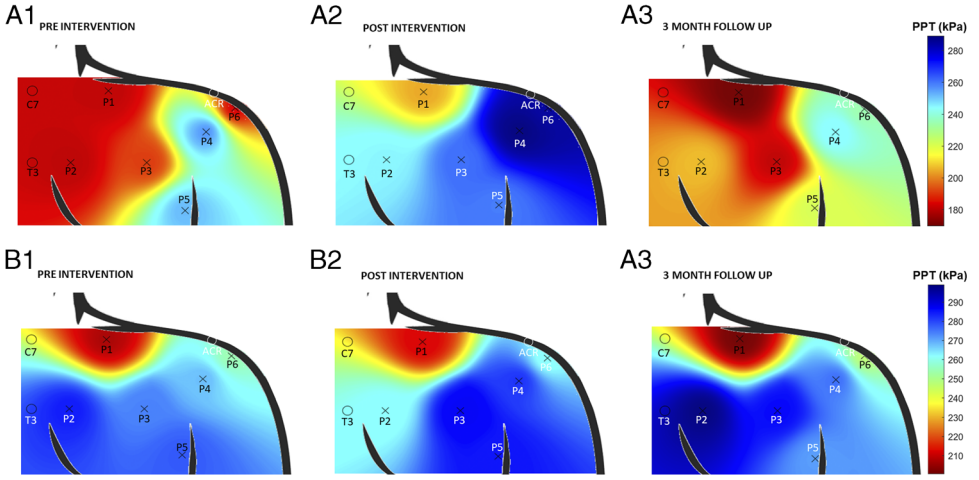

FIGURE 3—Topographical maps of the PPT located on the dorsal region of the affected shoulder in EXP (A1–3) and CON (B1–3) collected PRE (A1 + B1) and POST (A2 + B2) a 12-wk supervised RT intervention and at a 3-month FOLLOW-UP (A3 + B3).

comparisons, see Supplemental Tables A1–A4, Supplemental Digital Content 4, http://links.lww.com/MSS/C711).

Active shoulder ROM for EXP (n = 10) and CON (n = 10) are shown in Fig. 6. The LMM revealed a significant two-way interaction between group and movement ($F_{5,102.765}$ = 2.364, P = 0.045, d = 0.21). *Post hoc* analyses demonstrated that active ROM differed between movement directions for both groups (see Supplemental Table B1, Supplemental Digital Content 5, Pairwise comparisons for the simple effect of Movement at each level of Group, http://links.lww.com/MSS/C712).

For EXP (n = 10) and CON (n = 10), the LLM only revealed a main effect of time on SMM ($F_{2,\ 31.065}$ = 3.487, P = 0.043, d = 0.37), demonstrating that SMM increased from PRE to POST and decreased from POST to FOLLOW-UP (for specific values, see Supplemental Table C1, Supplemental Digital Content 6, Bioelectrical impedance analysis, http://links.lww.com/MSS/C713).

DISCUSSION

At the time of this writing, the ANTRAC trial is the first study specifically designed to investigate the effect of progressive RT on persistent pain in BCS. The RT intervention was effective and well tolerated with no adverse events, as evidenced by the significant increase in 1RM for EXP in all exercises, high levels of participant compliance, and absence of arm lymphedema. We found that RT significantly increased the PPT levels in EXP, whereas a decrease in peak PI was seen for both groups. Importantly, the gains in maximal strength occurred only in EXP and were largely maintained at follow-up, whereas PPT levels had mostly returned to baseline, suggesting that the analgesic effect seen in mechanical pain sensitivity after RT may not be dependent on gains in maximal strength.

Similar to previous studies in other pain populations (29), the ANTRAC trial had a substantial effect on mechanical pain sensitivity. This is evidenced by the statistically and clinically

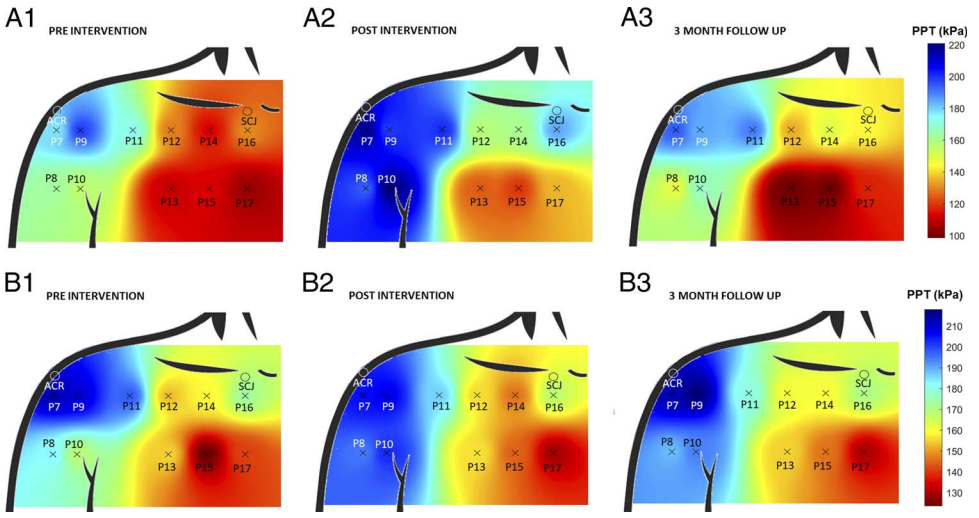

FIGURE 4—Topographical maps of the PPT located on the ventral region of the affected shoulder in EXP (A1–3), and CON (B1–3) collected PRE (A1 + B1) and POST (A2 + B2) a 12-wk supervised RT intervention and at a 3-month FOLLOW-UP (A3 + B3).

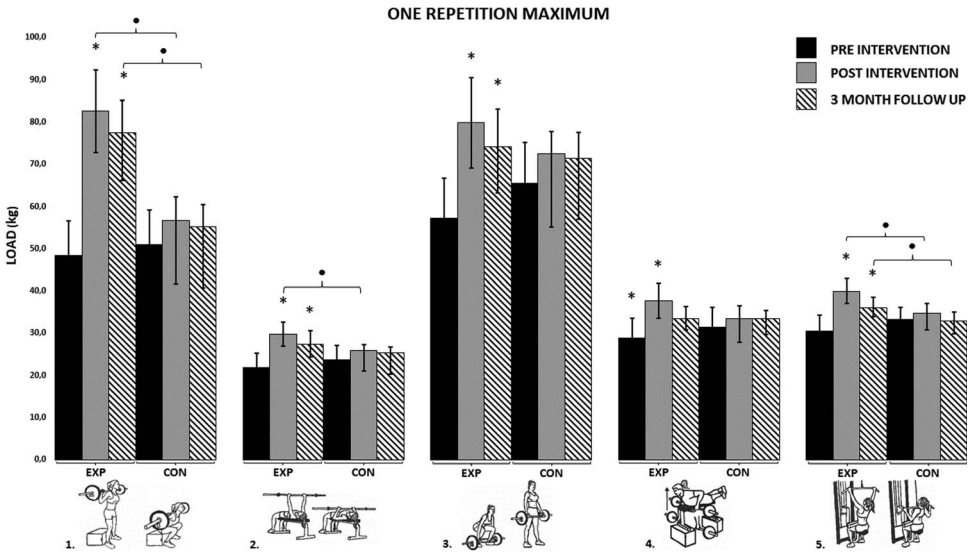

FIGURE 5—One-repetition maximum in kilograms for each of the five strength exercises: 1) box squat, 2) bench press, 3) trap bar deadlift, 4) bench pull, and 5) lat pulldown. Assessments were performed PRE and POST a 12-wk supervised RT program and at a 3-month FOLLOW-UP. Results for each time point are further expressed as mean (95% CI). EXP, experimental group; CON, control group. *Significantly different from PRE ($P < 0.05$). •Significant difference between groups ($P < 0.05$).

significant increase in mean PPT levels (i.e., $d = 0.78$) and further illustrated by the spatial alterations in mechanical pain sensitivity distribution. Importantly, these increases were well in excess of the minimum detectable change previously reported for this population (16). The mechanisms underlying this effect are not entirely clear but may include a combination of short- and long-term physiological responses to exercise. In the short term, the general consensus is that upregulation and release of endogenous opioids, endocannabinoids, and anti-inflammatory cytokines are the source of a transient reduction to noxious stimuli following a bout of exercise (30). In the long-term, however, it becomes more speculative. Possible mechanisms include neuroplastic changes promoted by exercise, which have been theorized to alter pain processing (29). The PPT levels recorded at baseline were similar to those previously reported as indicative of a central sensitization mechanism (17), indicative of plasticity in the central nervous system (31). The systematic increase in PPT levels after RT may therefore reflect reduction in central sensitization and, thus, neuroplastic changes to the pain pathways. Assuming this is the case, the clinically significant increase in PPT levels indicates that RT is particularly useful for managing central sensitization pain, which could have important implications for clinical practice.

The active ROM observed in the present study was in agreement with previous studies (16,17) and reflected similar

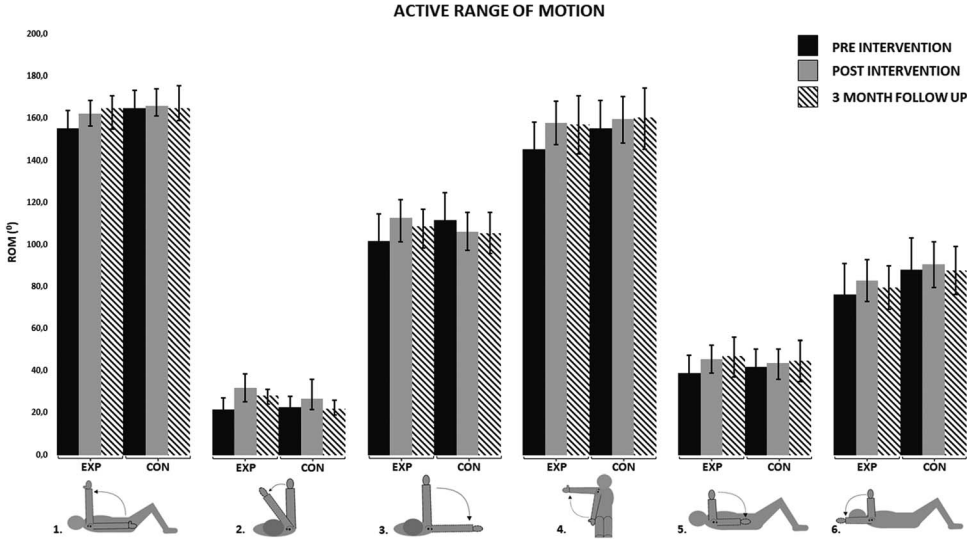

FIGURE 6—Active ROM for each of the six different movement patterns: 1) flexion, 2) horizontal flexion, 3) horizontal extension, 4) abduction, 5) internal rotation, and 6) external rotation. Assessments were performed PRE and POST a 12-wk supervised RT program and at a 3-month FOLLOW-UP. Results for each time point are further expressed as mean (95% CI). EXP, experimental group; CON, control group.

movement specific shoulder dysfunction (17). However, there were no significant amelioration in active ROM after RT, indicating no improvement in shoulder joint mobility. This is in line with Cormie et al. (13), who found little change in shoulder ROM after RT despite a significant increase in strength. A recent study by Özden et al. (32) reported an association between pain and shoulder ROM, suggesting a pain-related inhibition in ROM. Hence, it could be speculated that pain could have influenced the assessments of active ROM in the present study, indicating that measured ROM may only reflect pain-free ROM. Moreover, RT has been suggested to improve ROM by augmenting fascicle length (11) through a combination of mechanical tension and sarcomere lengthening (33). However, the five strength exercises (i.e., box squat, bench press, trap bar deadlift, bench pull, and lat pulldown) may not have induced sufficient movement toward the end of ROM for the shoulder girdle to result in an increase of fascicle length.

Peak PI decreased significantly over time for both groups with no significant difference between groups, which is partly in agreement with Cormie et al. (13) and Ammitzbøl et al. (14). Collectively, this may indicate a limited effect of RT on perceived PI of BCS as any potential benefits could not be differentiated from the reference condition, nor between sessions. In our case, this may be partially explained by pain variability as PI is known to fluctuate over time (34). Moreover, baseline pain severity has been demonstrated as an important predictor of pain variability (34), and hence, the severe baseline intensity in this study (i.e., >7 on a 0–10 scale) (35) may have influenced the observed variability in PI. However, like Ammitzbøl et al. (14), the results appear to favor the intervention despite the absence of a statistically significant difference, as half of the participants in EXP reported a decrease of 2 points or more on the NRS, which can be considered clinically important (36). Hence, it could be speculated that the sample size originally planned for this study might have yielded the necessary power to detect a difference in PI. A sample size estimated with a two tailed dependent sample *t*-test, an α of 0.05, a β of 0.20, and the mean and SD values for PI assessed at PRE and POST for EXP yielded a total of 26 participants. Thus, the original sample size estimate of 28 would likely have provided the required statistical power.

Maximal strength increased after the ANTRAC trial as evidenced by the significant increase in 1RM for all exercises. This is in agreement with the majority of previous studies in a recent review (9), and the moderate effect size (i.e., $d = 0.77$) demonstrates a robust increase in muscular strength. Moreover, and similar to previous reports in BCS (37), 1RM recorded after 3 months remained mostly unchanged for EXP. This is particularly interesting considering that the increase in PPT levels had completely reverted during the same period, indicating that the neural adaptations related to strength may be unrelated to those modulating pressure pain sensitivity. Indeed, current evidence suggests that neural adaptations related to RT may include increased cortical and corticospinal excitability (38), whereas the opposite appears to be true for neurological adaptations related to analgesia (39). Hence, it could be speculated that the regular exposure to RT, rather than the gains in strength, provided the pain-relieving benefits. However, although more research is warranted to elucidate the pain-relieving benefits of RT in BCS with persistent pain. The results of the ANTRAC trial showed that RT is a safe and well-tolerated training modality for improving muscular strength this population.

Limitations

The ANTRACT trial has some limitations. Foremost, COVID-19 affected our study resulting in substantially larger dropout rate and statistical power issues. However, when considering the intention-to-treat analysis, the observed range of effect sizes (0.29–0.78), the pre- to postincrease in PPT greater than the previously reported minimum detectable change, and the pre- to postdecrease of ≥2 NRS points in peak PI for 50% of EXP, we assume that a larger sample most likely would simply confirm the results of this trial. Second, we only included active ROM as a measure of shoulder function, and although this is arguably an important clinical outcome, many functional tasks require less than maximal active ROM (40). Hence, the inclusion of assessments, such as the Simple Shoulder Test, might have revealed improvements in shoulder function during activities of daily living. Last, the ANTRAC trial may suffer from a certain level of recruitment bias, which could have influenced the results. Specifically, most of the participants were used and still found the time and energy to participate in the study, which indicate a certain level of resourcefulness that may not be representative for the majority of BCS with persistent pain. Further, all participants expected a positive effect of the ANTRAC trial before randomization, which can introduce a motivational bias. In addition, proximity to breast cancer treatment was approximately 80 months for participants in EXP. Thus, the results may not be applicable to BCS in earlier stages of recovery.

CONCLUSIONS

In conclusion, the ANTRAC trial revealed statistically and clinically significant increases in PPT levels before and after a progressive individualized RT program. The intervention yielded a significant increase in maximal strength, which was largely maintained after a 3-month period of detraining, without adverse effects. This demonstrates a normal training response in BCS with persistent pain and further support the safety of RT as a training modality for this population. Collectively, the results of the ANTRAC trial suggest that progressive RT can reduce mechanical pain sensitivity but has a limited effect on perceived pain. Moreover, the discrepancy between maintenance of strength and PPT levels suggests that neural adaptations responsible for the increase in strength are not associated with modulation in pressure pain sensitivity.

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falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

The authors declare that no competing interests exist.

Trial Registration: ClinicalTrials.gov (NCT04509284).

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REFERENCES

1. Mejdahl MK, Andersen KG, Gärtner R, Kroman N, Kehlet H. Persistent pain and sensory disturbances after treatment for breast cancer: six year nationwide follow-up study. *BMJ*. 2013;346:f1865.
2. Caro-Morán E, Fernández-Lao C, Díaz-Rodríguez L, Cantarero-Villanueva I, Madeleine P, Arroyo-Morales M. Pressure pain sensitivity maps of the neck-shoulder region in breast cancer survivors. *Pain Med*. 2016;17(10):1942–52.
3. Jung BF, Ahrendt GM, Oaklander AL, Dworkin RH. Neuropathic pain following breast cancer surgery: proposed classification and research update. *Pain*. 2003;104(1–2):1–13.
4. Andersen KG, Christensen KB, Kehlet H, Bidstup PE. The effect of pain on physical functioning after breast cancer treatment development and validation of an assessment tool. *Clin J Pain*. 2015;31(9):794–802.
5. Levy EW, Pfalzer LA, Danoff J, et al. Predictors of functional shoulder recovery at 1 and 12 months after breast cancer surgery. *Breast Cancer Res Treat*. 2012;134(1):315–24.
6. Harrison SA, Hayes SC, Newman B. Age-related differences in exercise and quality of life among breast cancer survivors. *Med Sci Sports Exerc*. 2010;42(1):67–74.
7. Syrjala KL, Jensen MP, Mendoza ME, Yi JC, Fisher HM, Keefe FJ. Psychological and behavioral approaches to cancer pain management. *J Clin Oncol*. 2014;32(16):1703–11.
8. Wang X, Wang N, Zhong L, et al. Prognostic value of depression and anxiety on breast cancer recurrence and mortality: a systematic review and meta-analysis of 282,203 patients. *Mol Psychiatry*. 2020; 25(12):3186–97.
9. Dos Santos WDN, Gentil P, de Moraes RF, et al. Chronic effects of resistance training in breast cancer survivors. *Biomed Res Int*. 2017; 2017:8367803.
10. Montaño-Rojas LS, Romero-Pérez EM, Medina-Pérez C, Reguera-García M, de Paz JA. Resistance training in breast cancer survivors: a systematic review of exercise programs. *Int J Environ Res Public Health*. 2020;17(18):6511.
11. Afonso J, Moscão J, Rocha T, et al. Strength training versus stretching for improving range of motion: a systematic review and meta-analysis. *Healthcare (Basel)*. 2021;9(4):427.
12. Campbell KL, Winters-Stone KM, Wiskemann J, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. *Med Sci Sports Exerc*. 2019; 51(11):2375–90.
13. Cormie P, Pumpa K, Galvão DA, et al. Is it safe and efficacious for women with lymphedema secondary to breast cancer to lift heavy weights during exercise: a randomised controlled trial. *J Cancer Surviv*. 2013;7(3):413–24.
14. Ammitzbøll G, Andersen KG, Bidstrup PE, et al. Effect of progressive resistance training on persistent pain after axillary dissection in breast cancer: a randomized controlled trial. *Breast Cancer Res Treat*. 2020;179(1):173–83.
15. Ross R, Goodpaster BH, Koch LG, et al. Precision exercise medicine: understanding exercise response variability. *Br J Sports Med*. 2019; 53(18):1141–53.
16. Rasmussen GHF, Kristiansen M, Arroyo-Morales M, Voigt M, Madeleine P. Absolute and relative reliability of pain sensitivity and functional outcomes of the affected shoulder among women with pain after breast cancer treatment. *PLoS One*. 2020;15(6):e0234118.
17. Rasmussen GHF, Madeleine P, Arroyo-Morales M, Voigt M, Kristiansen M. Pain sensitivity and shoulder function among breast cancer survivors compared to matched controls: a case-control study. *J Cancer Surviv*. 2021. doi: 10.1007/s11764-021-00995-y.
18. Smith BE, Hendrick P, Smith TO, et al. Should exercises be painful in the management of chronic musculoskeletal pain? A systematic review and meta-analysis. *Br J Sports Med*. 2017;51(23):1679–87.
19. Hayes SC, Newton RU, Spence RR, Galvão DA. The exercise and sports science Australia position statement: exercise medicine in cancer management. *J Sci Med Sport*. 2019;22(11):1175–99.
20. Fernández-Carnero J, Binderup AT, Ge HY, Fernández-De-Las-Peñas C, Arendt-Nielsen L, Madeleine P. Pressure pain sensitivity mapping in experimentally induced lateral epicondylalgia. *Med Sci Sports Exerc*. 2010;42(5):922–7.
21. Jensen MP, Turner JA, Romano JM, Fisher LD. Comparative reliability and valididty of chronic pain intensity measures. *Pain*. 1999; 83(2):157–62.
22. Gärtner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. *JAMA*. 2009;302(18):1985–92.
23. Pescatello LS, Arena R, Riebe D, Thompson PD. Guidelines for exercise testing, Muscular strength. In: Pescatello LS, Arena R, Riebe D, Thompson PD, editors. *ACSM's Guidelines for Exercise Testing and Prescription*. 9th ed. Philadelphia: Wolters Kluwer | Lippincott Williams & Wilkins; 2014. pp. 96–9.
24. Miller RM, Chambers TL, Burns SP. Validating inbody® 570 multi-frequency bioelectrical impedance analyzer versus DXA for body fat percentage analysis. *J Exerc Physiol Online*. 2016;19(5):71–8.
25. Duncan MJ, Smith M, Cook K, James RS. The acute effects of a caffeine-containing energy drink on modde, state, readiness to invest effort, and resistance exercise to failure. *J Strength Cond Res*. 2012; 26(110):2858–65.
26. Zourdos MC, Klemp A, Dolan C, et al. Novel resistance training-specific rating of perceived exertion scale measuring repetitions in reserve. *J Strength Cond Res*. 2016;30(1):267–75.
27. Andersen LL, Zebis MK. Process evaluation of workplace interventions with physical exercise to reduce musculoskeletal disorders. *Int J Rheumatol*. 2014;2014:761363.
28. Cohen J. *Statistical Power Analysis for The Behavioral Sciences*. 2nd ed. Hillsdale (NJ): Lawrence Erlbaum Associates; 1988. p. 567.
29. Belavy DL, Van Oosterwijck J, Clarkson M, et al. Pain sensitivity is reduced by exercise training: evidence from a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2021;120:100–8.
30. Rice D, Nijs J, Kosek E, et al. Exercise-induced hypoalgesia in pain-free and chronic pain populations: state of the art and future directions. *J Pain*. 2019;20(11):1249–66.
31. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain*. 1993;52(3):259–85.
32. Özden F, Tuğay N, Karaman ÖN, Kilinç CY, Tuğay BU. The relationship of fear of movement with pain, range of motion and function in patients with shoulder pathologies. *Bull Fac Phys Ther*. 2021;26(1):4–8.
33. McMahon GE, Morse CI, Burden A, Winwood K, Onambélé GL. Impact of range of motion during ecologically valid resistance training protocols on muscle size, subcutaneous fat, and strength. *J Strength Cond Res*. 2014;28(1):245–55.
34. Zakoscielna KM, Parmelee PA. Pain variability and its predictors in older adults: depression, cognition, functional status, health, and pain. *J Aging Health*. 2013;25(8):1329–39.

35. McCaffery M, Beebe A. Pain: clinical manual for nursing practice. The numeric pain rating scale. *Pain*. 1989.
36. Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94(2): 149–58.
37. Herrero F, San Juan AF, Fleck SJ, Foster C, Lucia A. Effects of detraining on the functional capacity of previously trained breast cancer survivors. *Int J Sports Med*. 2007;28(3):257–64.
38. Folland JP, Williams AG. The adaptations to strength training: morphological and neurological contributions to increased strength. *Sports Med*. 2007;37(2):145–68.
39. Lima LV, Abner TSS, Sluka KA. Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena. *J Physiol*. 2017;595(13):4141–50.
40. Namdari S, Yagnik G, Ebaugh DD, et al. Defining functional shoulder range of motion for activities of daily living. *J Shoulder Elbow Surg*. 2012;21(9):1177–83.