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ABSTRACT

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 years after treatment were randomized to an experimental group (EXP, n = 10), who performed a supervised progressive total body heavy RT program 2x/week for 12 weeks, or a control group (CON, n = 10) who was instructed to continue their everyday life. Perceived pain intensity (PI), pressure pain thresholds (PPT), one-repetition maximum (1RM) and active range of motion (ROM) were collected pre and post intervention and at three months follow up. **Results:** There was a significant 11% decrease in peak PI ($P < 0.05$) for both groups, a significant 48% increase in 1RM ($P < 0.05$) and a significant 35% increase in PPTs ($P < 0.001$) for EXP, but not for CON. For EXP, maximal strength at follow up was still significantly greater than at pre ($P < 0.05$), whereas PPTs had reverted to baseline levels. There was no change in active ROM ($P < 0.05$), and no change in arm circumference ($P < 0.05$). **Conclusions:** RT had a significant effect on 1RM and PPTs 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

INTRODUCTION

Persistent pain after breast cancer treatment is a considerable problem, with more than one third of breast cancer survivors (BCS) reporting pain up to seven years 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 impact 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. 2019 (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 suffering from persistent pain. At the time of this writing (August 2022), only two randomized controlled trials (RCTs) 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 following supervised RT intervention. In contrast, the results of Ammitzbøl et al.

(14) did indicate a favourable effect of a semi-supervised RT 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 suffering from 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 employed to adjust and personalize the RT stimuli more appropriately. Therefore, the purpose of the present randomized clinical trial (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 suffering from persistent pain. We investigated the clinically meaningful effect of progressive RT on perceived pain intensity, 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 email service named e-boks. Participants were recruited sequentially and pre-screened for participation with the Physical Activity Readiness Questionnaire (PAR-Q).

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 PPTs was determined to be 28. To account for a potential, drop out of 20%, 34 participants were invited to participate in the study. See Rasmussen & Colleagues for inclusion and exclusion criteria (16,17).

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 neither recruitment, data collection nor statistical analysis. Assessors and researchers were blinded to the group allocation. Due to 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.

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-week 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 hours prior to the experimental sessions.

All outcome measures were collected at a familiarization, PRE, POST and FOLLOW UP session. Familiarization and PRE sessions were respectively conducted two and one week prior to the intervention, whereas POST and FOLLOW UP were conducted one and 12 weeks after (Figure 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, Ohio, USA), 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. Following a detailed written and verbal explanation of the experimental benefits and risks, the participants gave their written informed consent prior to 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 (Figure 2, A). Each phase lasted four weeks, 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 3-5min 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 or physical readiness to exertion (MRE or 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 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 five minutes of aerobic activity and stretching for the primary muscles involved in the RT exercises. This was followed by five exercises performed according to the ANTRAC program in systematic order (Figure 2, B). The training was delivered in a small-group format with 2-4 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 pressure pain thresholds and pain intensity

Pressure pain threshold (PPT) is a reliable measure of mechanical pain sensitivity in BCS (16). PPTs 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 values 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).

Pain intensity (PI) and frequency (PF) during everyday living of the past three 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, 1-3x/week or more rarely (22).

Movement evoked pain (MEP) intensity was rated immediately following every set of each exercise on the same 11-point numeric rating scale.

Secondary outcomes: Maximal strength, shoulder range of motion 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 1-20kg until a true 1RM was achieved. Incremental rest periods were provided between sets with 1-4 minutes between warmups and 3-5 minutes 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/m^2) was calculated from height and body mass measured at baseline. The body fat mass (BFM), skeletal muscle mass (SMM) and body fat percentage (BF%) of each participant was computed using direct segmental multi-frequency 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 hours since last meal, visit to the bathroom prior to 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

Mental and physical readiness to exertion (MRE & PRE) were rated prior to each exercise in every laboratory session on an 11-point numeric rating scale, where 0 corresponded to "no readiness to exertion" and 10 corresponded to "maximum readiness to exertion" (25). MRE and PRE were obtained prior to each exercise to account for the potential influence of readiness on one repetition maximum performance.

Rating of perceived exertion (RPE) was rated immediately following every set of each exercise every laboratory session on a RT-specific 10-point numeric rating scale 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 resistance training 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 post intervention 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 (CI) intervals. A linear mixed model (LMM) incorporating three fixed effect factors was applied to investigate the effect of resistance training on PPTs using an intention to treat (ITT) analysis to account for missing data and/or dropouts. PPT was used as the dependent factor with location (dorsal, ventral & reference) and time (PRE, POST & FOLLOW UP) as within subject factors, and group (EXP/CON) as the between a 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, USA). A P-value < 0.05 was considered statistically significant. Differences are expressed as mean (CI 95%). Effect size estimates are reported as Cohens *d*, and interpreted according to Cohen (28) in which $\geq 0.20 - < 0.50$ = small, $\geq 0.50 - < 0.80$ = moderate, and ≥ 0.80 = large.

RESULTS

This study was impacted 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

Mean (Confidence Interval (CI) 95%) 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 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, PPTs for EXP were significantly higher at POST compared to both PRE and FOLLOW UP, but not at FOLLOW UP

compared to 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 (CI95%) pain 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 3-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 to PRE for EXP, but not for CON. Further, 1RM was significantly higher for EXP at POST and FOLLOW UP when compared to CON for boxsquat, bench press and lat pulldown. Similarly, there was a significant 2-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 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 figure 6. The LMM revealed a significant 2-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 PPTs in EXP while a decrease in peak pain intensity was seen for both groups. Importantly, the gains in maximal strength occurred only in EXP and were largely maintained at follow up, whereas PPTs had mostly returned to baseline, suggesting that the analgesic effect seen in mechanical pain sensitivity following 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 significant increase in mean PPTs (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 (MDC) 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 PPTs 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 PPTs following 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 PPTs 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 movement specific shoulder dysfunction (17). However, there were no significant amelioration in active ROM following RT, indicating no improvement in shoulder joint mobility. This is in line with Cormie et al. (13), who found little change in shoulder ROM following 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 towards the end of range of motion 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. & Ammitzbøl et al. (13,14). 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. the results appear to favour the intervention despite the absence of a statistically significant difference, as half of the participants in EXP reported a decrease of 2 point 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 means and standard deviations 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 following 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) demonstrate a robust increase in muscular strength. Moreover, and similar to previous reports in BCS (37), 1RMs recorded after three months remained mostly unchanged for EXP. This is particularly interesting considering that the increase in PPTs 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. First and foremost, COVID-19 impacted our study resulting in substantially larger dropout rate and statistical power issues. However, when considering the ITT analysis, the observed range of effect sizes (0.29-0.78), the pre to post increase in PPT greater than the previously reported MDC and the pre to post

decrease 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 while 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 employed 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 prior to 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 PPTs from pre- to post a progressive individualized resistance training program. The intervention yielded a significant increase in maximal strength which was largely maintained following a three-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 PPTs suggest that neural

adaptations responsible for the increase in strength, are not associated with modulation in pressure pain sensitivity.

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Disclosures

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

Conflict of Interest Statement

The authors have declared that no competing interests exist.

Trial Registration

ClinicalTrials.gov (NCT04509284).

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Author Contributions

All authors contributed significantly to the preparation of this manuscript. GHFR wrote the initial draft and completed data analysis. All authors participated in the design of the study. PM, MK and MV assisted with data analysis. All authors contributed to improve the manuscript by providing input and guidance over numerous manuscript drafts. All authors approved this final draft of this manuscript.

Experimental Location

Strength Laboratory, Room A2-102, 104 and 106, Department of Health Science and Technology, Aalborg University, 9220 Aalborg, Denmark.

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FIGURE LEGENDS

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 three-month training divided into four-week phases preceded by a familiarization (FS) and a pre intervention test (PRE) and followed by a post intervention test (POST and a 3 month follow up test (FOLLOW UP). Body composition, pain profile, questionnaire, pressure pain thresholds (PPT), active range of motion (Active ROM), mental and physical readiness to exertion (MRE & PRE), one-repetition maximum (1RM), rating of perceived exertion (RPE) and movement-evoked pain (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 prior to the general warm up and exercise 1-5, respectively, while RPE and MEP were collected immediately after.

Figure 3: Topographical maps of the pressure pain threshold 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-week supervised resistance training intervention and at a 3 month FOLLOW UP (A3+B3).

Figure 4: Topographical maps of the pressure pain threshold 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-week supervised resistance training intervention and at a 3 month FOLLOW UP (A3+B3).

Figure 5: One repetition maximum in kg 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-week supervised resistance training program, and at a 3 month FOLLOW UP. Results for each time point are further expressed as Mean (CI95%). Abbreviations; Experimental group: EXP, Control group: CON, 95% confidence interval: CI95%. *Significantly different from PRE ($p < 0.05$), •Significant difference between groups ($p < 0.05$).

Figure 6: Active range of motion for each of the six different movement patterns: 1. Flexion, 2. Horizontal flexion, 3. Horizontal extension, 4. Abduction, 5. Internal rotation, 6. External rotation. Assessments were performed PRE and POST a 12-week supervised resistance training program, and at a 3 month FOLLOW UP. Results for each time point are further expressed as Mean (CI95%). Abbreviations; Experimental group: EXP, Control group: CON, 95% confidence interval: CI95%.

SUPPLEMENTAL DIGITAL CONTENT

SDC 1: Appendix1.docx: CONSORT checklist

SDC 2: Appendix2.docx: CONSERVE checklist

SDC 3: Appendix3.docx: TIDieR checklist

SDC 4: Appendix4.docx:

Table A1: Pairwise comparisons for the simple effect of Exercise at each level of Time.

Table A2: Pairwise comparisons for the simple effect of Time at each level of Exercise

Table A3: Pairwise comparisons for the simple effect of Time at each level of Group & The effect of Group at each level of Time

Table A4: Effect of Exercise at each level of Group & The effect of group at each level of Exercise

SDC 5: Appendix5.docx

Table B1: Pairwise comparisons for the simple effect of Movement at each level of Group

SDC 6: Appendix6.docx

Table C1: Bioelectrical impedance analysis

Figure 1

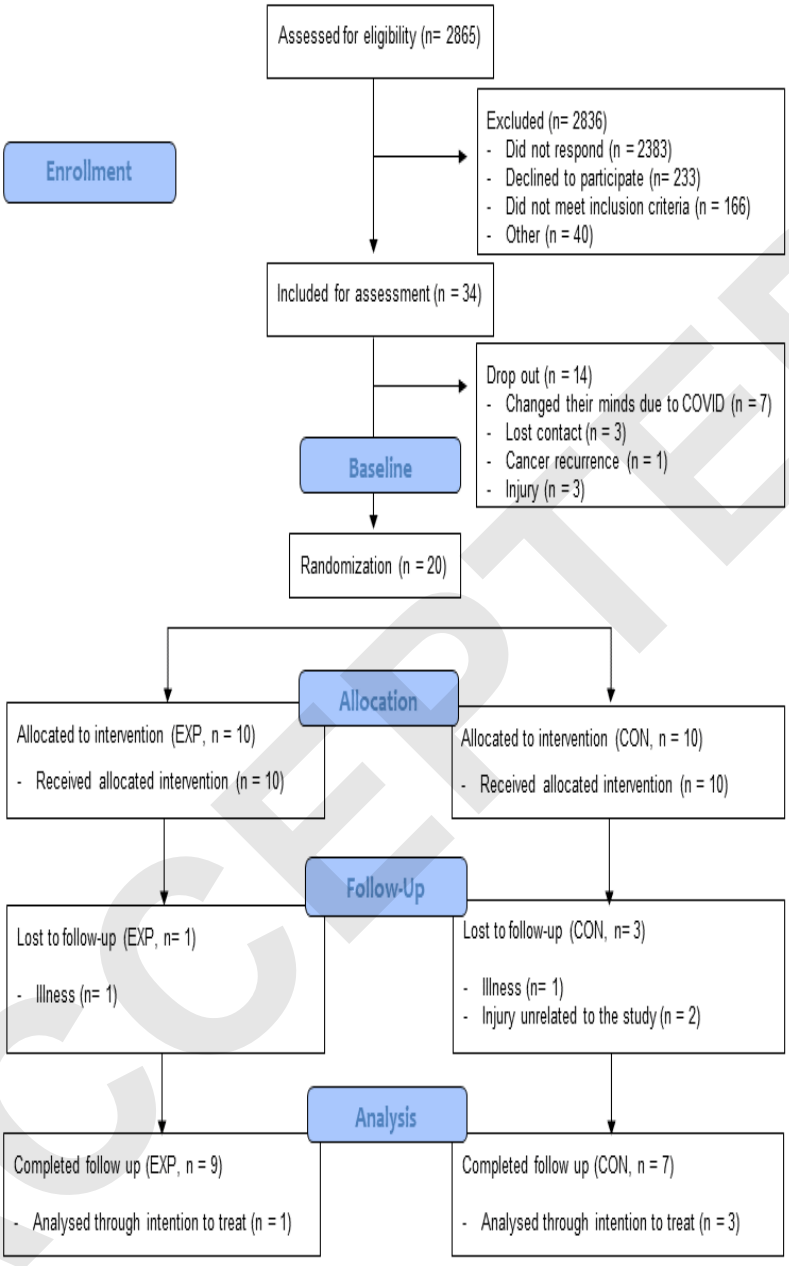

Figure 2

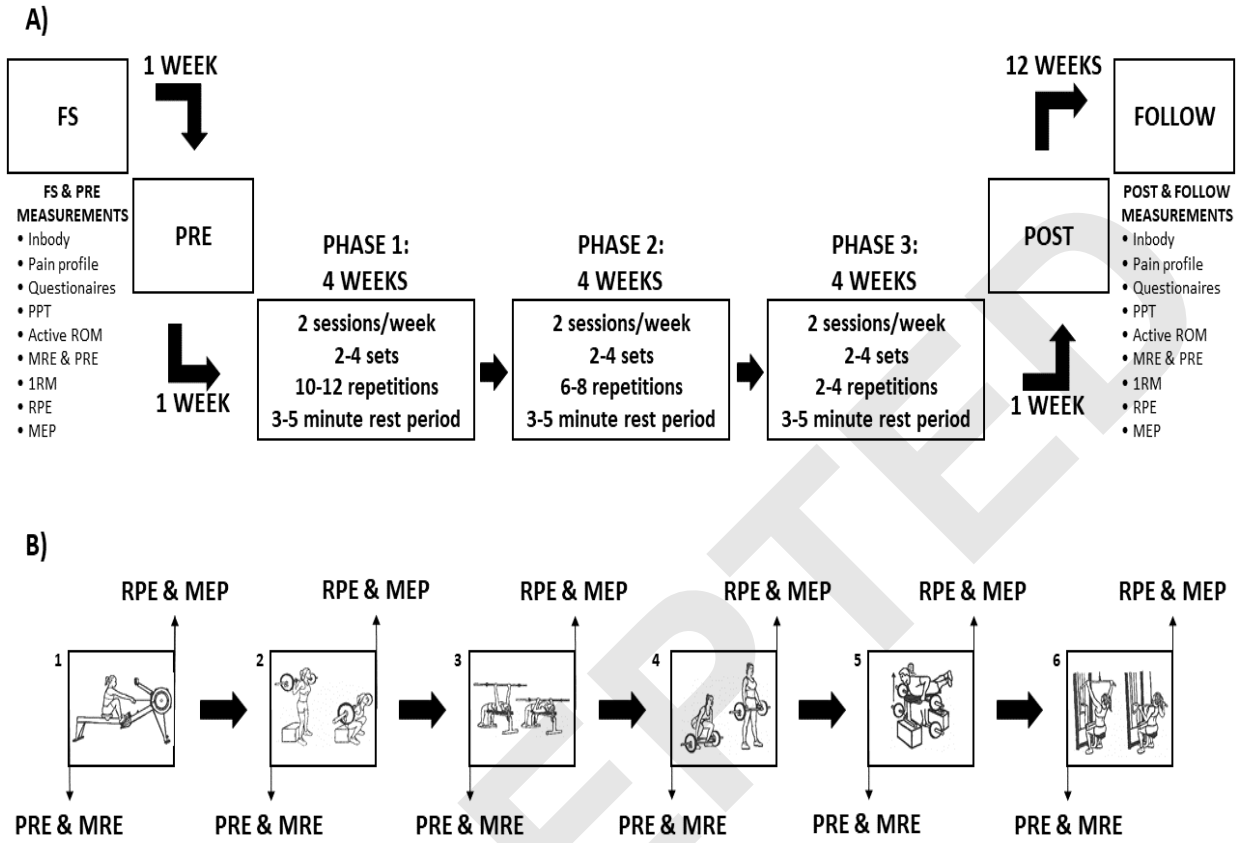

Figure 3

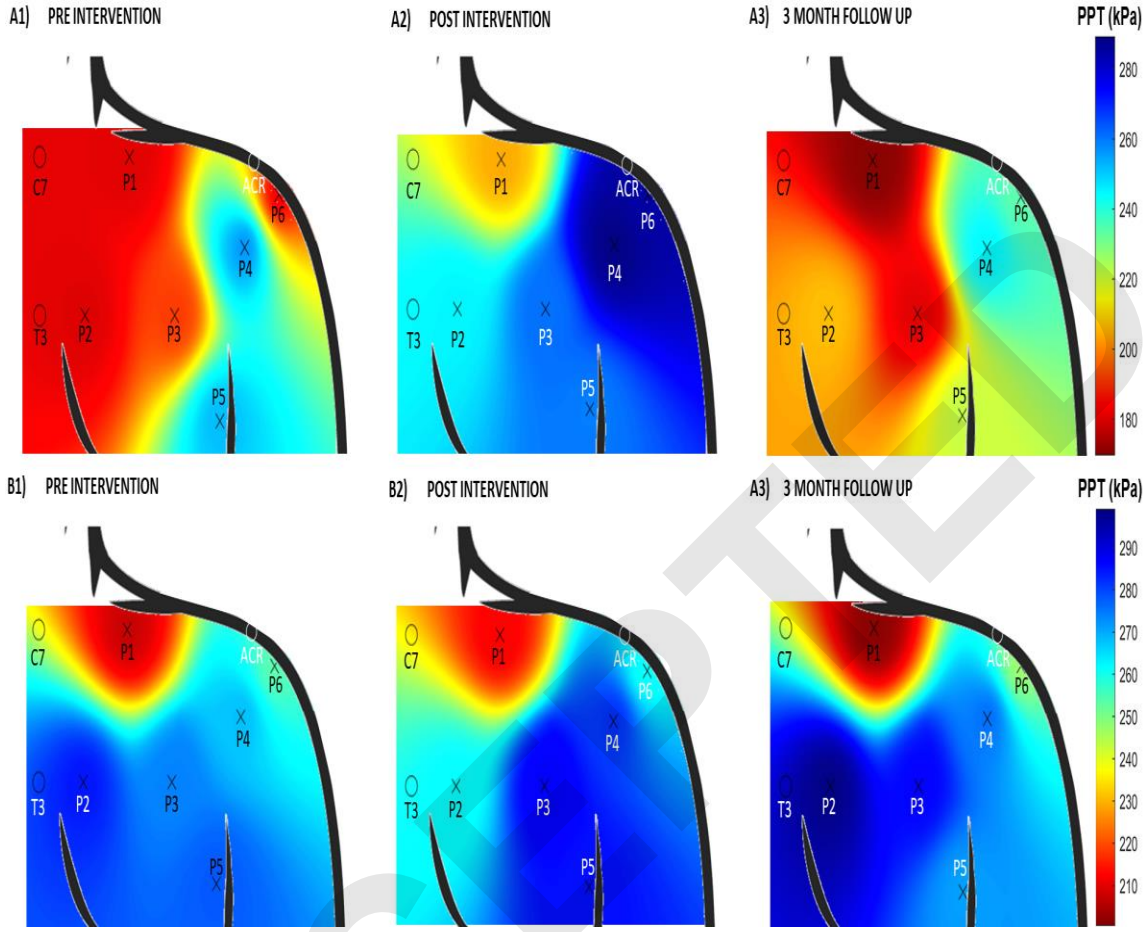

Figure 4

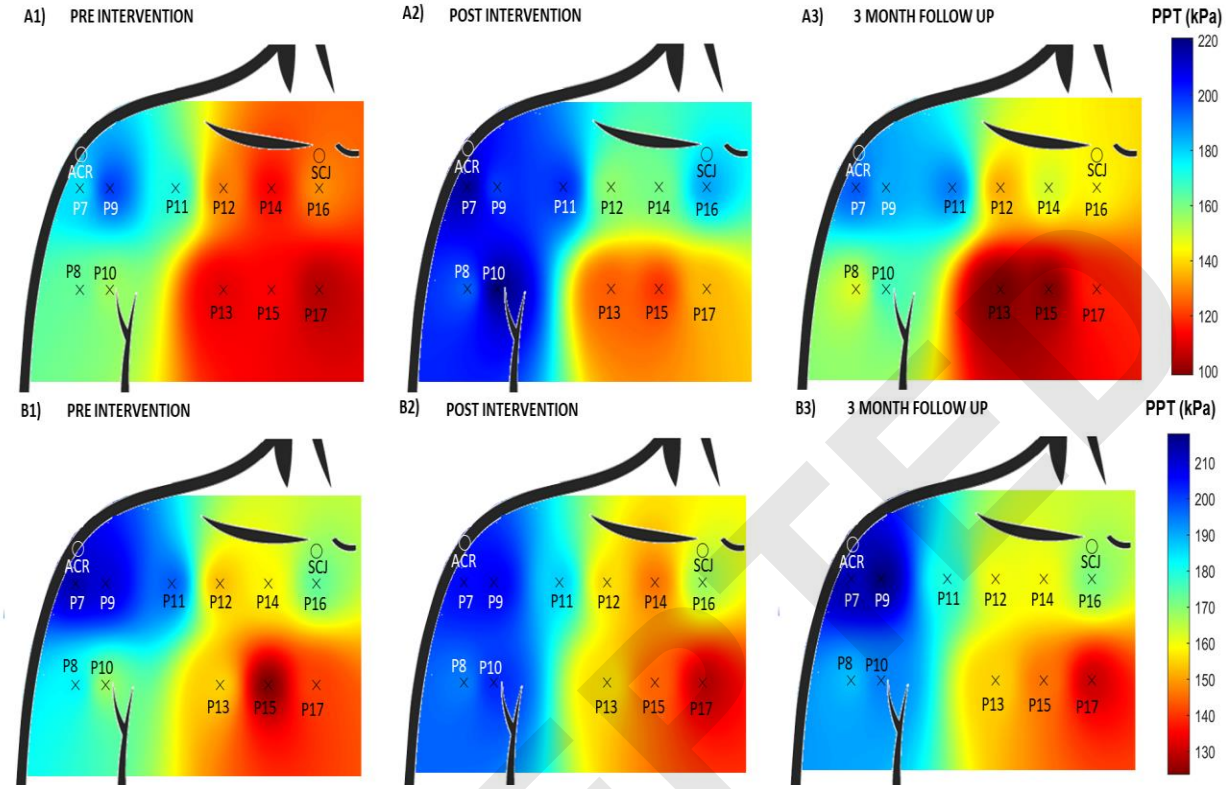

Figure 5

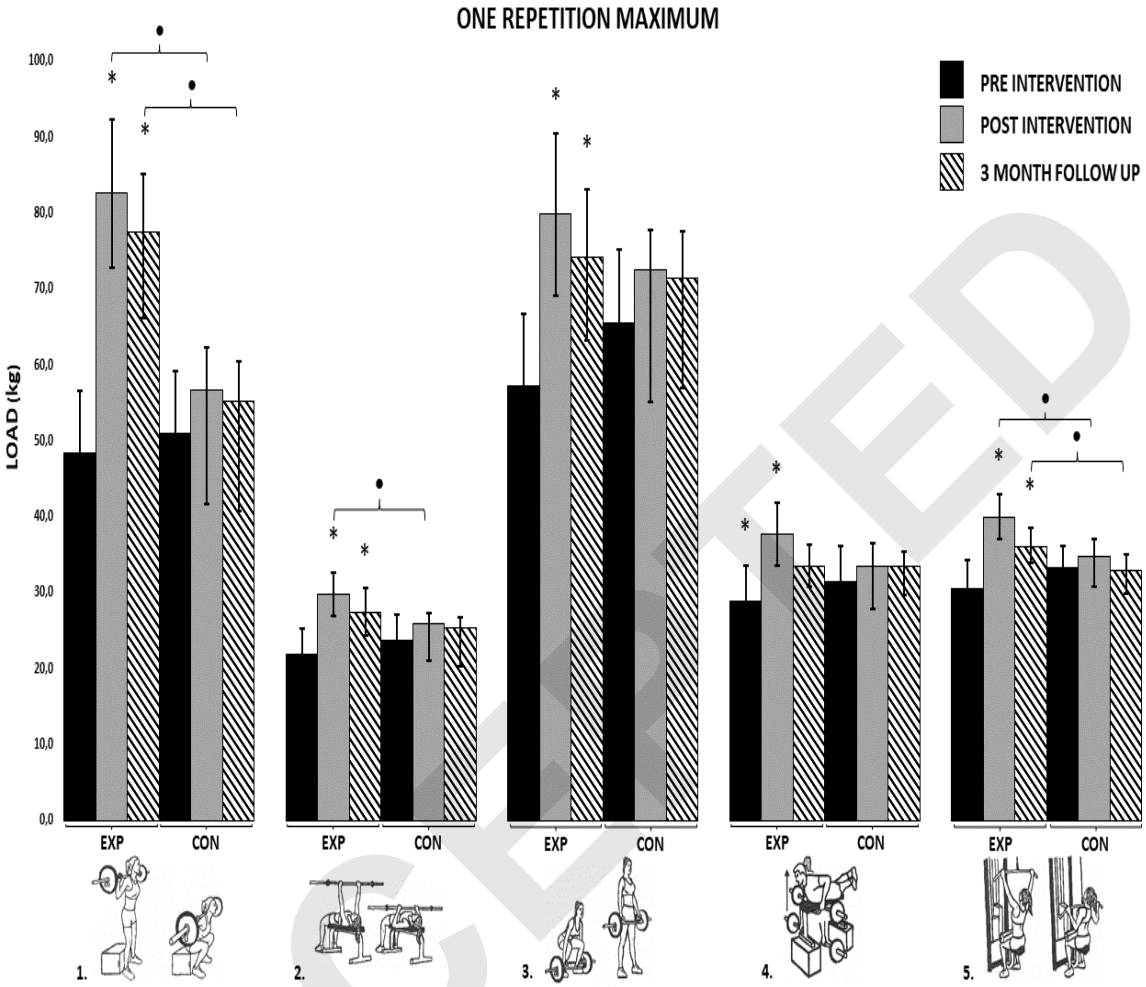

Figure 6

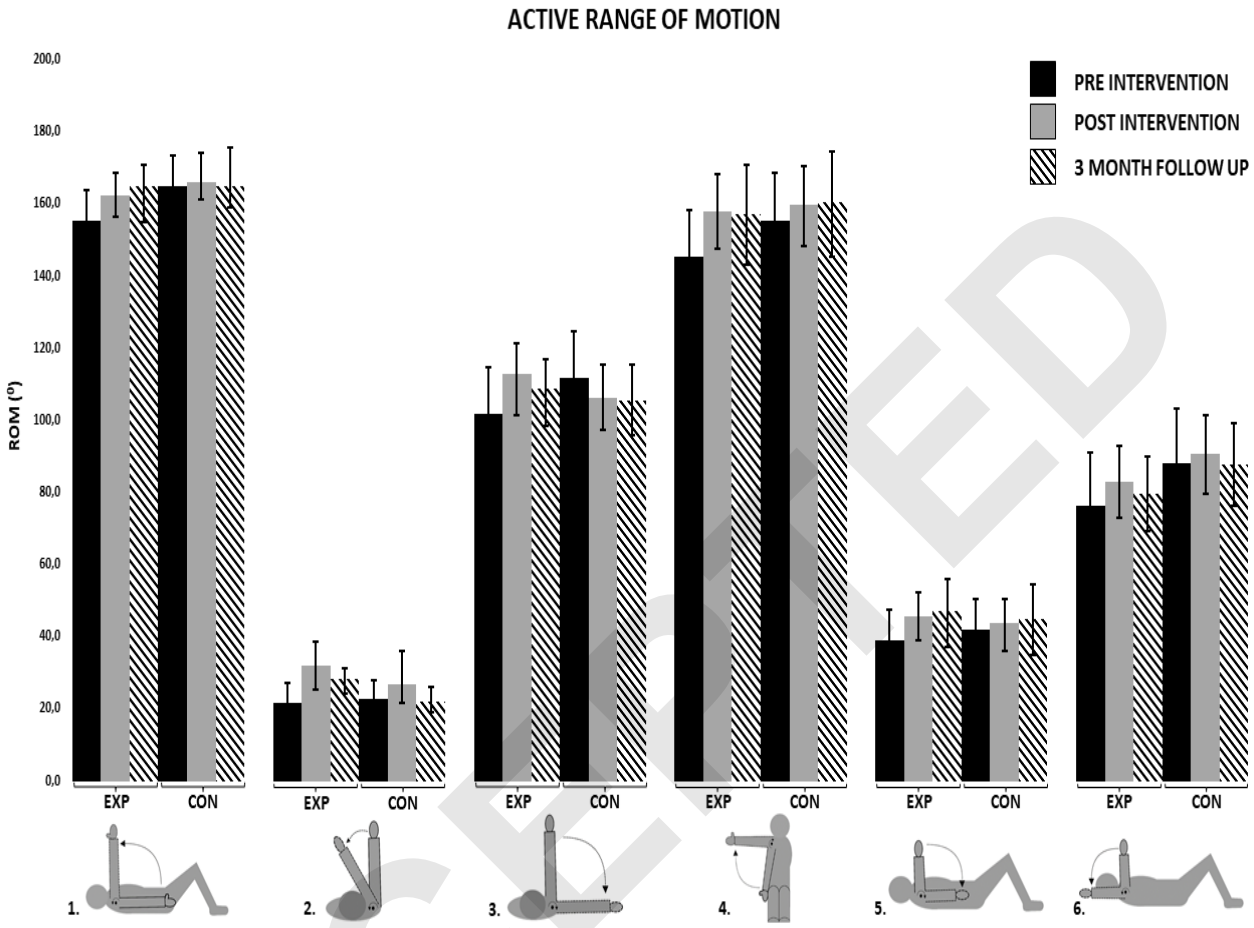

Table 1: Sociodemographic, surgical, and medical profile of the clinical population

CHARACTERISTIC:	**EXP**	**CON**
Age, mean (CI: 95%), y	58.9 (52.1;65.7)	60.5 (56.3;64.7)
Height, mean (CI: 95%), cm	165.8 (160.6;171.1)	168.4 (164.9;171.8)
Living arrangement, No. (%)		
Living with a partner	8 (80)	8 (80)
Education, No. (%)		
Short	0 (0)	2 (20)
Medium	9 (90)	7 (30)
Long	1 (10)	1 (10)
Employment, No. (%)		
Full time	4 (40)	3 (30)
Part time	3 (30)	5 (50)
Retired	3 (30)	2 (20)
Time since treatment, mean (CI: 95%), months	80.1 (55.6;104.6)	64.9 (44.1;85.7)
Pain duration, mean (CI: 95%), months	74.3 (49.6;99.0)	64.3 (42.9;85.7)
Pain since treatment No. (%)	8 (80)	9 (90)
Body mass index, mean (CI: 95%), kg/m^2	25.6 (22.1;29.1)	26.7 (23.3;30.1)
Body mass index, No. (%)		
≤ 25 kg/m^2	6 (60)	5 (50)
>25 - ≤30 kg/m^2	3 (30)	3 (30)
>30 kg/m^2	1 (10)	2 (20)
Menopausal status, No. (%)		
Post	10 (100)	9 (90)
Smoking, No. (%)		
Former smoker	5 (50)	6 (60)
Never smoker	5 (50)	4 (40)
Alcohol consumption		
No. units per week, mean (CI: 95%)	5.6 (2.5;8.7)	4.3 (0.8;7.8)
Histologic stage of malignancy, No. (%)		
I	3 (30)	4 (40)
II	3 (30)	4 (40)
III	4 (40)	2 (20)
Tumor diameter, mean (CI: 95%), mm	21,2 (6,5;35,9)	20,1 (12,6;27,6)
Surgical protocol, No. (%)		
Breast conserving surgery	7 (70)	8 (80)
Mastectomy	3 (30)	2 (20)

Lymph node protocol No. (%)		
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 (CI: 95%)	4.9 (1.6;8.2)	5.5 (1.7;9.3)
Dominant limb affected, No. (%)	5 (50)	4 (40)
Adjuvant treatment, No. (%)		
Chemotherapy only	0 (0)	0 (0)
Radiotherapy only	3 (30)	2 (20)
Both	7 (70)	8 (80)
Endocrine therapy, No. (%)		
Yes	6 (60)	8 (80)
No	3 (30)	0 (0)
Ceased	1 (10)	2 (20)
Receptor status, No. (%)		
Estrogen positive	7 (70)	10 (10)
HER2 positive	3 (30)	1 (10)

Abbreviations: 95% Confidence interval: CI: 95%, No: number, human epidermal growth factor receptor 2: HER2, Numeric rating scale: NRS.

Table 2: Mean pressure pain thresholds (PPT) of the ventral and dorsal regions of the affected shoulder, and at a distant reference point, collected at PRE, POST and FOLLOW (three-month follow up) for experimental (EXP) and control (CON) group.

PPT (kPa)	EXP			CON		
	PRE mean (CI:95%)	***POST mean (CI:95%)***	***FOLLOW mean (CI:95%)***	***PRE mean (CI:95%)***	***POST mean (CI:95%)***	***FOLLOW mean (CI:95%)***
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)

Abbreviations: 95% Confidence interval: CI: 95%. *****Significant difference from PRE ($P<0.05$). †Significant difference from POST ($P<0.05$).

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	P1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	P2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	P3-4
	2b	Specific objectives or hypotheses	P4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	P5-6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	P9-10
Participants	4a	Eligibility criteria for participants	P4-5
	4b	Settings and locations where the data were collected	P5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	P5 + P6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	P7-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	P4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	P4-5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	P4-5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	P4-5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	P4-5

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	P4-5
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	P9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	P9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	P5-6
	13b	For each group, losses and exclusions after randomisation, together with reasons	P5-6
Recruitment	14a	Dates defining the periods of recruitment and follow-up	P5-6
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	P4-5
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	P9-P12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	P9-12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	P10
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	P14-15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	P17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	P17
Other information			
Registration	23	Registration number and name of trial registry	P5
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	P15-16

Appendix 1: CONSORT checklist

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

CONSERVE Checklists

Use CONSERVE-CONSORT for completed trial reports and CONSERVE-SPIRIT for trial protocols.

CONSERVE-CONSORT Extension: 25-04-2022					
Item	**Item Title**	**Description**			**Page No.**
I.	Extenuating Circumstances	Describe the circumstances and how they constitute extenuating circumstances.			9-10
II.	Important Modifications	a. Describe how the modifications are important modifications.			9-10
		b. Describe the impacts and mitigating strategies, including their rationale and implications for the trial.			9-10
		c. Provide a modification timeline.			10
III.	Responsible Parties	State who planned, reviewed and approved the modifications.			10
IV.	Interim data	If modifications were informed by trial data, describe how the interim data were used, including whether they were examined by study group, and whether the individuals reviewing the data were blinded to the treatment allocation.			n/a
CONSORT Number and Item		For each row, if important modifications occurred check “direct impact” and/or “mitigating strategy” and describe the changes in the trial manuscript or supplement. Check “no change” for items that are unaffected in the extenuating circumstance.			**Page No.**
		No Change	**Impact***	**Mitigating Strategy****	
1	Title and abstract	x			
2	Introduction	x			
3	Methods: Trial Design	x			
4	Methods: Participants	x			
5	Methods: Interventions	x			
6	Methods: Outcomes	x			
7	Methods: Sample Size	x			

8-10	Methods: Randomisation	x			
11	Methods: Blinding	x			
12	Methods: Statistical methods		x	Linear mixed model with maximum likelihood estimation for missing data replaced 3-way Mixed model ANOVA	9
13	Results: Participant flow		x	Intention to treat analysis	9
14	Results: Recruitment		x		
15	Results: Baseline data	x			
16	Results: Numbers analysed	x			
	Results: Outcomes and estimation	x			
18	Results: Ancillary analyses	x			
19	Results: Harms	x			
20	Discussion: Limitations		x	Sample size	14-15
21	Discussion: Generalisability	x			
	Other information: Registration	x			
24	Other information: Protocol	x			
25	Other information: Funding	x			

*Aspects of the trial that are directly affected or changed by the extenuating circumstance and are not under the control of investigators, sponsor or funder.
**Aspects of the trial that are modified by the study investigators, sponsor or funder to respond to the extenuating circumstance or manage the direct impacts on the trial.

Table 1: ANTRAC trial description in accordance with the TIDiER guidelines

NR.	ITEM	DESCRIPTION
1	NAME	The intervention was named the Analgesic effect of resistance TRAining After breast Cancer (ANTRAC) trial.
2	WHY	The ANTRAC trial will provide new and important information on the potential pain-relieving benefits of resistance training for women with persistent pain after breast cancer treatment.
3	WHAT	The training was performed calibrated weight plates (ranging 0,5-25kg) and barbells (10 and 20kg), competition squat/bench press combination racks, a specialized bench for bench pull and standard lat-pulldown tower. Other equipment included a Concept II rowing ergometer and a standard timer for rest periods.
4	PROCEDURES	Each session began with an assessment of attendance, arm circumference, and perceived mental and physical readiness to exertion. This was followed by a general warm up consisting of five minutes of moderate aerobic exercise and five minutes of general stretching for the upper and lower limbs. Participants then performed five resistance training exercises in systematic order within the framework of the ANTRAC trial (i.e., 2-4 sets of 10-12 repetitions for four weeks, 2-4 sets of 6-8 repetitions for four weeks, and 2-4 sets of 2-4 repetitions for four weeks). A 3–5-minute rest periods was provided between sets. Preliminary load was 60% of 1RM and adjustments were made to load, number of reps and number of sets of each exercise according to the individual progress, readiness, and pain of each participant.
5	PROVIDERS	The ANTRAC trial was delivered by certified strength and conditioning specialist (CSCS) educated in the current exercise guidelines for cancer survivors and modern pain theory.
6	HOW	The ANTRAC trial was delivered face to face twice per week in a small group setting with 2-4 participants per CSCS.
7	WHERE	The ANTRAC trial was performed in the laboratory buildings located at Fredrik Bajers Vej 7 A, 9220, Aalborg, Denmark. To accommodate participant schedules and attendees of the laboratories, training was performed either in the morning (i.e., 06:00-08:00) or the evening (18:00-20:00).

Abbreviations: 1RM: One repetition maximum.

Table A1: Pairwise comparisons for the simple effect of Exercise at each level of Time.

PRE	Box squat	Bench press	Deadlift	Bench pull	Lat pulldown
Boxsquat	0	↑ P < 0.001	↓ P = 0.024	↑ P < 0.001	↑ P < 0.001
Bench press		0	↓ P < 0.001	↓ P = 0.001	↓ P < 0.001
Trapbar deadlift			0	↑ P < 0.001	↑ P < 0.001
Bench pull				0	-
Lat pulldown					0
POST	**Box squat**	**Bench press**	**Deadlift**	**Bench pull**	**Lat pulldown**
Boxsquat	0	↑ P < 0.001	-	↑ P < 0.001	↑ P < 0.001
Bench press		0	↓ P < 0.001	↓ P < 0.001	↓ P < 0.001
Trapbar deadlift			0	↑ P < 0.001	↑ P < 0.001
Bench pull				0	-
Lat pulldown					0
FOLLOW UP	**Box squat**	**Bench press**	**Deadlift**	**Bench pull**	**Lat pulldown**
Boxsquat	0	↑ P < 0.001	-	↑ P < 0.001	↑ P < 0.001
Bench press		0	↓ P < 0.001	↓ P < 0.001	↓ P < 0.001
Trapbar deadlift			0	↑ P < 0.001	↑ P < 0.001
Bench pull				0	-
Lat pulldown					0

Abbreviations: PRE: Pre intervention, POST: Post intervention, FOLLOW UP: Follow up 3 months after the intervention, ↑: 1RM significantly higher, ↓: 1RM significantly lower.

Table A2: Pairwise comparisons for the simple effect of Time at each level of Exercise.

BOXSQUAT	PRE	POST	FOLLOW UP
Pre	0	↓ P < 0.001	↓ P < 0.001
Post		0	-
Follow up			0
BENCH PRESS	**PRE**	**POST**	**FOLLOW UP**
Pre	0	↓ P < 0.001	↓ P = 0.021
Post		0	-
Follow up			0
TRAPBAR DEADLIFT	**PRE**	**POST**	**FOLLOW UP**
Pre	0	↓ P < 0.001	↓ P = 0.001
Post		0	-
Follow up			0
BENCH PULL	**PRE**	**POST**	**FOLLOW UP**
Pre	0	↓ P < 0.001	-
Post		0	-
Follow up			0
LAT PULLDOWN	**PRE**	**POST**	**FOLLOW UP**
Pre	0	↓ P < 0.001	↓ P = 0.022
Post		0	↑ P = 0.001
Follow up			0

Abbreviations: PRE: Pre intervention, POST: Post intervention, FOLLOW UP: Follow up 3 months after the intervention, ↑: 1RM significantly higher, ↓: 1RM significantly lower.

Table A3: Pairwise comparisons for the simple effect of Time at each level of Group & The effect of Group at each level of Time.

EXP	**PRE**	**POST**	**FOLLOW UP**
Pre	0	↓ P < 0.001	↓ P < 0.001
Post		0	↑ P < 0.001
Follow up			0
CON	**PRE**	**POST**	**FOLLOW UP**
Pre	0	-	-
Post		0	-
Follow up			0
EXP vs. CON	**PRE**	**POST**	**FOLLOW UP**
Group difference	-3,5 (-9,4:2,4)	12,2 (6:18,5)*	7,9 (2,3:13,6)**

Abbreviations: PRE: Pre intervention, POST: Post intervention, FOLLOW UP: Follow up 3 months after the intervention, ↑: 1RM significantly higher, ↓: 1RM significantly lower, *: Significant difference between groups (P < 0.01).

Table A4: Effect of Exercise at each level of Group & The effect of group at each level of Exercise.

EXP	**Box squat**	**Bench press**	**Deadlift**	**Bench pull**	**Lat pulldown**
Boxsquat	0	↑ P < 0.001	-	↑ P < 0.001	↑ P < 0.001
Bench press		0	↓ P < 0.001	↓ P = 0.002	↓ P < 0.001
Trapbar deadlift			0	↑ P < 0.001	↑ P < 0.001
Bench pull				0	-
Lat pulldown					0
CON	**Box squat**	**Bench press**	**Deadlift**	**Bench pull**	**Lat pulldown**
Boxsquat	0	↑ P < 0.001	↓ P = 0.034	↑ P < 0.001	↑ P 0 0.001
Bench press		**0**	↓ P < 0.001	↓ P < 0.001	↓ P < 0.001
Trapbar deadlift			0	↑ P < 0.001	↑ P < 0.001
Bench pull				0	-
Lat pulldown					0
EXP vs. CON	**Box squat**	**Bench press**	**Deadlift**	**Bench pull**	**Lat pulldown**
Group difference	17,7 (5,7:29,6)*	2,6 (-1,5:6,7)	3,7 (-9,4:16,7)	1,3 (-3,7:6,3)	2,6 (-1,2:6,5)

Abbreviations: PRE: Pre intervention, POST: Post intervention, FOLLOW UP: Follow up 3 months after the intervention, ↑: 1RM significantly higher, ↓: 1RM significantly lower, *: Significant difference between groups (P < 0.01).

Table B1: Pairwise comparisons for the simple effect of Movement at each level of Group.

EXP	Flexion	Hor.Flexion	Hor.Extension	Abduction	Int. Rotation	Ext.Rotation
Flexion	0	↑ P < 0.001	↑ P < 0.001	-	↑ P < 0.001	↑ P < 0.001
Hor.Flexion		0	↓ P < 0.001	↓ P < 0.001	↓ P < 0.001	↓ P < 0.001
Hor.Extension			0	↑ P < 0.001	↓ P < 0.001	↓ P < 0.001
Abduction				0	↑ P < 0.001	↑ P < 0.001
Int. Rotation					0	↓ P < 0.001
Ext.Rotation						0
CON	Flexion	Hor.Flexion	Hor.Extension	Abduction	Int. Rotation	Ext.Rotation
Flexion	0	↑ P < 0.001	↑ P < 0.001	-	↑ P < 0.001	↑ P < 0.001
Hor.Flexion		0	↓ P < 0.001	↓ P < 0.001	↓ P < 0.001	↓ P < 0.001
Hor.Extension			0	↑ P < 0.001	↓ P < 0.001	↓ P < 0.001
Abduction				0	↑ P < 0.001	↑ P < 0.001
Int. Rotation					0	↓ P < 0.001
Ext.Rotation						0

Abbreviations: EXP: Experimental group, CON: Control group, ↑: ROM significantly higher, ↓: ROM significantly lower.

Table C1: Bio electrical impedance analysis

Body composition estimates	EXP (n =10)			CON (n =10)		
	Pre, mean (CI:95%)	***Post, mean (CI:95%)***	***Follow up, mean (CI:95%)***	***Pre, mean (CI:95%)***	***Post, mean (CI:95%)***	***Follow up, mean (CI:95%)***
BW(kg)	70,6 (63,9:77,4)	70,9 (64,3:77,5)	71,5 (64,8:78,2)	74,8 (68,1:81,5)	76 (69,4:82,6)	75,7 (69:82,4)
SMM(kg)	24,8 (22,9:26,7)	25,3 (23,4:27,1)	25,1 (23,1:27)	25,2 (23,3:27,1)	25,6 (23,7:27,4)	25,3 (23,4:27,3)
BFM(kg)	24,9 (18:31,8)	24,6 (17,5:31,7)	25,4 (18,6:32,2)	28,4 (21,4:35,3)	28,9 (21,8:36,1)	29,1 (22,2:35,9)
BF%	33,9 (29:38,8)	33,3 (28,2:38,3)	34,3 (29,7:39)	36,4 (31,5:41,3)	36,6 (31,5:41,7)	37 (32,3:41,6)

Abbreviations: EXP: Experimental group, CON: Control group, BW: Bodyweight, SMM: Skeletal muscle mass, BFM: Bodyfat mass, BF%: Bodyfat percentage.