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# Effects of exercise training on muscle wasting, muscle strength and quality of life in adults with acute burn injury☆

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ABSTRACT

*Objectives:* Exercise training during the acute phase of burns is difficult to implement but offers potential benefits. This multicenter trial explored the effects of an exercise program on muscular changes and quality of life during burn center stay.

*Methods:* Fifty-seven adults with burns ranging between 10% and 70% TBSA were allocated to receive either standard of care (n = 29), or additionally exercise (n = 28), consisting of resistance and aerobic training, commenced as early as possible according to safety criteria. Muscle wasting (primary outcome), quantified by ultrasound-derived quadriceps muscle layer thickness (QMLT) and rectus femoris cross-sectional area (RF-CSA), muscle strength and quality of life (Burn Specific Health Scale-Brief (BSHS-B) and EQ-5D-5L) were assessed at baseline, four and eight weeks later, or hospital discharge. Mixed models were used to analyze between-group changes over time with covariates of interest added in stepwise forward modeling.

*Results:* The addition of exercise training to standard of care induced significant improvements in QMLT, RF-CSA, muscle strength and the BSHS-B subscale hand function (ß-

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coefficient. 0.055 cm/week of QMLT, p = 0.005). No added benefit was observed for other quality-of-life measures.

*Conclusions:* Exercise training, administered during the acute phase of burns, reduced muscle wasting, and improved muscle strength throughout burn center stay.



## 1. Introduction

Exercise training has shown to be an effective component in the rehabilitation of several pathologies for improving outcomes such as functional disability and physical performance but also specifically for counteracting muscle wasting [1–3]. In burn care, exercise is among interventions that play an important role in maximizing the rehabilitation potential of burn survivors [4]. However, exercise has not traditionally been part of burn rehabilitation throughout burn center stay [5,6]. It is during this early phase that extensive metabolic adaptations develop, and that exercise might be most potent as a counteracting strategy. If left untreated, the metabolic adaptations become maladaptive, impacting multiple organ systems, which, in the long term, can leave burn survivors with considerable morbidity [7–16]. In particular, the loss of muscle tissue (muscle wasting) is a commonly observed phenomenon of the postburn catabolic state that is sensitive to prolonged periods of inactivity [17–20]. Muscle wasting has been associated with muscle weakness, delayed wound healing, increased infection rates, and mortality [21,22]. When administered during the acute phase of burns, exercise could be most effective in reducing postburn muscle wasting and associated morbidity [4]. Particularly forms of resistance and aerobic exercise have shown to be capable of modulating metabolic sequalae in other disease populations [3,8,23]. In burns, however, despite existing guidelines advocating the use of exercise during the acute phase of burns [24–29] a lack of evidence surrounding its efficacy and feasibility has hampered its integration into standard inpatient care [29]. Most exercise trials to date have been carried out in the pediatric burn population or have commenced exercise at later stages of recovery, i.e. after wound closure or after burn center discharge [30,31]. Pain, exertion, grafting surgery, and hemodynamic instability are among many factors that might further complicate the administration of exercise during burn center stay [32]. As opposed to resistance and aerobic exercise at higher intensities, therapy efforts during the acute phase of burns have hence primarily consisted of passive forms of exercise (positioning, passive movement, etc.) and active exercise at low intensities (functional training) [5]. Consequently, postburn muscle wasting has commonly been viewed as an inevitable burn-related symptom, and not as a therapeutic target. A deeper understanding of the efficacy of exercise training during the acute phase of burns will aid in strengthening its role in inpatient burn rehabilitation. Therefore, the aim of this trial was to investigate the effects of exercise training program during the acute phase of burns on muscle size, muscle strength and quality of life.

## 2. Material & methods

### 2.1. Trial design

Ethical approval for the trial was obtained by the institutional review board of the Ziekenhuis Netwerken Antwerpen (5018). The trial was registered at the US National Institutes of Health (ClinicalTrials.gov) #NCT04511104.

This study was set up as a quasi-randomized multicenter trial. Group allocation was dependent on the physiotherapy staff's capacity to administer the trial intervention in line with COVID-19-related restrictions throughout the trial period in the following manner: Each week D.R.S. and study staff of each trial site determined the maximum number of participants that could be allocated to the exercise group, as allocation to this group involved an additional workload for physiotherapy staff, whose capacity was severely limited due to circumstances relating to the COVID-19 pandemic (e.g. staff shortage due to COVID-19 infections, more patient referrals from other Belgian burn centres that had closed to free beds for COVID-19 patients, etc.). Accordingly, participants were allocated to the control group when staff capacity was saturated, or after the desired sample size was reached in the intervention group. For example, if the weekly capacity to provide exercise training was determined to be four participants at the beginning, and three participants were already active in the exercise group at the time, then the following recruited participant was allocated to the exercise training group, and any further patients would be allocated to the control group. This method of group allocation was therefore independent of patient presentation while making the trial feasible for the participating burn centers during the COVID-19 pandemic.

### 2.2. Participants

We assessed the eligibility of all adults admitted to two Belgian burn centers, the ZNA Stuivenberg, Antwerp and the Military Hospital Queen Astrid, Neder-Over-Heembeek, between May 2020 and March 2022. Subjects were eligible for participation if they had burns encompassing ≥ 10% total body surface area (TBSA) with the presence of deep partial thickness or full thickness burns. The burn depth was estimated at admission and confirmed by laser doppler imaging within 72 h. Subjects were excluded if they were under palliative care, had electric burns, presented with lower limb fractures or amputations, were pregnant, or had any premorbid neurological, cardiovascular, or psychological disorders that would have interfered with safety and feasibility of the trial outcome assessment or exercise participation. As per hospital protocol, all participants were tested for a SARS-

COV-2 infection upon admission to the burn center, whereas a positive test result did not form a reason for exclusion. All participants or their next-of-kin provided written informed consent.

### 2.3. Study intervention

All participants received the standard of care treatment for burns, consisting of intensive care, wound care, surgery, standard physiotherapy, and if indicated occupational therapy and psychological support. Standard physiotherapy consisted of passive and active range of motion exercises, functional training, positioning, stretching, and splinting. Both trial sites had similar standard care protocols in place including feeding regimens, glycemic targets, respiratory care, and post-surgical immobilization. In addition to the standard of care, the intervention group performed an exercise program during their stay at the burn center up to eight weeks or until discharge, whichever point in time occurred first. This exercise program was commenced as early as possible, according to predefined readiness criteria (see Table 1) in line with international safety recommendation of early mobilization of critically ill patients [33]. These readiness criteria were checked prior to each exercise session to ensure patient safety. The exercise program entailed approximately 30 min-long sessions daily, alternating between resistance and aerobic exercises. Resistance exercise was administered three times per week, while aerobic exercise was provided two times per week. A decision tree was provided to guide the therapists in the choice of exercise based on individual patient status (i.e. out-of-bed mobility, out-of-room mobility, muscle strength and joint range of motion, and patient preference). Accordingly, patients either received in-bed or out-of-bed exercises on machines or with free weights. The administered exercise program had as its primary goal to minimize muscle wasting. Therefore, exercises that targeted large muscle groups (thigh and gluteal muscles) were prioritized. Resistance training consisted of three exercises, each with three sets of eight to twelve repetitions, in line with training prescriptions by the American College of Sport Medicine [34,35]. Baseline intensity of resistance exercises was set at 60% of the peak force produced during hand-held dynamometry or a three-repetition maximum test. The intensity was then readjusted weekly based on a new peak force assessment, and the number of repetitions was progressed from eight to ten to twelve repetitions over the three weekly exercise sessions. Aerobic exercise was administered on a bicycle ergometer or a treadmill, with a total duration of 24 min, consisting of alternating three-minute intervals of 50% and 70% of peak watts reached during a weekly ramp test, using the steep ramp test [36]. The exercise program was provided by physiotherapists at the respective burn centers, who were trained prior to study commencement to ensure uniformity in the delivered intervention.

**Table 1 – Readiness criteria to commence exercise intervention.**

| Readiness criteria for exercise |
|---|
| 1. Cardiorespiratory stability: |
| 1. MAP 60–110 mmHg |
| 2. FiO2 < 60% |
| 3. PaO2/FiO2 > 200 |
| 4. RR < 40 bpm |
| 5. PEEP < 10 cmH2O |
| 6. no high inotropic doses (Dopamine > 10 mcg/kg/min or Nor/adrenaline < 0,1 mcg/kg/min) |
| 1. Temp. 36 – 38.5C |
| 2. RASS −2 - +2 |
| 3. Medical Doctor clearance |
| 4. MRC lower limbs ≥3 |

All criteria had to be met to commence exercise. MAP, mean arterial pressure; FiO2, inspired oxygen fraction; PaO2/FiO2, arterial oxygenation relative to inspired oxygen; RR, respiratory rate; bpm, breaths/min; PEEP, positive end expiratory pressure; RASS, Richmond Agitation Sedation Scale; MRC, Medical Research Council muscle force score (score = 3 refers to the ability to lift limbs against gravity).

### 2.4. Outcomes

Repeated assessment of muscle size, muscle force, and quality of life was completed throughout hospitalization. Participants were assessed at baseline, four and eight weeks later, or at hospital discharge if discharged prior to four or eight weeks. The timing of the baseline assessment differed per participant according to whether the aforementioned readiness criteria were met. To prevent detection bias, assessors refrained from checking baseline results during follow-up assessment.

#### 2.4.1. Muscle size

To investigate the effect of exercise training on muscle wasting, quadriceps muscle layer thickness (QMLT) and rectus femoris cross-sectional area (RF-CSA) were measured by muscular ultrasound, with QMLT as the primary endpoint. Our group and others have reported that ultrasound has shown to be a valid and reliable tool to quantify parameters of muscle size at the bedside in the critically-ill [37–42], and in the acute burns population – even in the presence of open wounds and edema [43]. QMLT is defined as the distance between the superior fascia of the rectus femoris muscle and the periosteum of the femoral shaft, making up the combined thickness of the rectus femoris and intermedius muscle [44]. The methods used to determine QMLT and RF-CSA were developed together with a radiologist and experts in the field of muscle ultrasound, and have previously been described in detail [43]. In short, two trained physiotherapists carried out B-mode ultrasound measurements with a multifrequency linear transducer of either the SonoSite X-porte (FUJIFILM SonoSite, Brussels, Belgium) or the VIVID S5 (GE Healthcare, Machelen, Belgium). QMLT was measured at four points on the both anterior thighs at the halfway and two-thirds point of the distance between the anterior superior iliac spine and the superior patellar pole [38]. All four points were averaged across both thighs to derive a four-point score, which is considered to be an adequate surrogate measure of whole-body muscle mass [40,45]. The measurement point of RF-CSA was determined based on the distance where the entire width of the rectus femoris muscle belly was still visible on

the ultrasound screen [46]. All ultrasound measurements were repeated three times and averaged to reduce variability [43]. In addition to the other assessment time points, QMLT and RF-CSA were also measured at admission to control for varying muscle size at admission as well as the amount of change in muscle size until the baseline assessment. All parties were blind to QMLT and RF-CSA values throughout the study period, as ultrasound-derived parameters were only analyzed after study completion.

#### 2.4.2. *Muscle force*

Measures of lower limb muscle strength and hand grip strength were used to determine change in muscle force. Lower limb muscle strength was determined by hand-held dynamometry (microFET®2, Hoggan Scientific, LLC, Salt Lake City, U.S.A.) with three trials of maximal voluntary isometric contraction used to derive peak force. Additional trials were performed if peak force was not within 10% of the second highest force measurement. Traditional muscle testing positions were adapted to bed-bound positions in supine lying with a fixation belt bound around the bed frame providing counter-resistance. Knee extension force was assessed in 90° degrees hip and knee flexion, and hip flexion in 0° degrees of elevation, with the dynamometer positioned on the distal anterior surface of the tibia above the ankle. Both right and left sides were assessed and averaged. We tested the clinimetric properties of this strength testing protocol in healthy participants (unpublished data), demonstrating good to excellent intra-/ inter-rater reliability intraclass correlation coefficients [knee extension intra-rater ICC = 0.928, inter-rater ICC = 0.860; hip flexion intra-rater ICC = 0.885, inter-rater ICC = 0.826]. Hand grip strength was evaluated using the interchangeable JAMAR or Baseline® dynamometer [47] as per protocol of the American Society of Hand Therapist with the best of three measurements taken [48]. All force measurements were deemed valid if pain ratings for each test were below six on a numeric rating scale of 0–10.

#### 2.4.3. *Quality of life*

Self-reported quality of life was assessed by the Dutch or French versions of the Burn Specific Health Scale Brief (BSHS-B) and the European Quality of Life-5 Dimensions (EQ-5D-5L) [49–53]. As not all of the subdomains of the BSHS-B questionnaire are applicable to participants throughout their hospital stay, we did not calculate a total sore of all items, but chose to evaluate two subdomains concerning participants' physical functioning: 1) simple abilities and 2) hand function. BSHS-B items are scored on a 5-point scale ranging from 0 (=all the time/great difficulty) to 4 (=never/no difficulty). Mean scores are calculated for each subscale and high scores indicate a good perceived health status [54]. The EQ-5D-5L questionnaire encompasses five dimensions (Self-care, Mobility, Daily Activities, Pain, Anxiety/Depression) and a visual analogue scale of 0–100, rating the overall health state from immediate death (=0) to full health (=100). A value set for the Belgian population [55] was used to derive the EQ-5D-5L health utility index - an index between −1 and 1, where zero signifies 'dead', one refers to 'full health', and negative values are perceived as health states worse than death. Both the BSHS-B and the EQ-5D-5L questionnaires are validated, and have been extensively used in the burn population [56,57]. Expert consensus exists on using both generic and disease-specific quality of life questionnaires to capture the full impact of a health condition [58,59].

#### 2.4.4. *Compliance*

Parameters of each exercise session were recorded including reasons for incomplete or failed sessions. Compliance was assessed as the ratio of failed (or incomplete) to attempted sessions. Participants were, additionally, asked to rate the intensity of each exercise on a scale of perceived exertion, an ordinal scale of 0–10, where zero stands for the least effort and ten for the maximum exertion [60].

### 2.5. *Data collection*

Data was collected and processed by D.R.S. as the main assessor, and D.D. as a backup assessor. To minimize error margins arising from the assessment of different raters, the same assessor carried out all follow-up assessment of the same participants as much as possible. Ultrasound clips were exported, de-identified and stored on a secured external hard drive.

### 2.6. *Sample size*

Sample size was determined using G*Power 3.1.9.2 based on observed change quadriceps peak force in a comparable trial of early exercise in critically-ill patients during the acute phase of hospital stay [61]. Accordingly, estimating a dropout rate of 33%, 45 patients per group (resulting in 30 patients per group) were required to achieve 80% power (alpha = 0.05, SD=0.685, ES=0.50). The choice of muscle force as a basis for the sample size calculation was made in the absence of available effect size for the primary outcome (QMLT). This trial was completed prior to achieving the desired sample size due to a delayed start of recruitment and lower than anticipated recruitment rate related to the COVID-19 pandemic.

### 2.7. *Data analysis*

Descriptive statistics of group characteristics and baseline values of dependent variables are presented as mean (95%CI) or median (IQR) for continuous variables, or as frequencies (proportions) for categorical variables. Group comparisons at baseline were carried out using independent t-test, Mann Whitney U test, or Fisher's Exact tests, depending on data type and normality. Mixed models were fitted to evaluate the effects of the exercise intervention on trial outcomes once model assumptions were met. The models included subject ID as random effects and group allocation, weeks from baseline and their interaction as fixed effects. Covariates of interest, including trial site, %TBSA, the presence of lower limb burns, the number of days until baseline, and baseline values of dependent variables or their change of between admission and baseline were added to the models in a stepwise forward manner, if they were statistically significant ($p < 0.05$) and if model fit improved considerably, as assessed by a reduction of at least 10 points of the corrected

Akaike information criterion (AICc) [62]. Missing data, due to dropouts or inability to measure specific endpoints, was dealt with by intention-to-treat analysis. Statistical significance was defined as alpha ≤ 0.05. All statistical analysis was completed using JMP® Pro 15.2.1 (SAS Institute Inc., Marlow, UK).

## 3. Results

Throughout the study period (May 2020 - March 2022), 67 eligible participants gave initial informed consent upon admission to the burn center and were examined for readiness of the trial intervention. Ten participants were excluded prior to the baseline assessment for various reasons (death n = 5, history of cardiovascular accident with neuromotor impairment n = 2, transfer n = 1, lower limb fracture n = 1, psychosis n = 1). The remaining 57 participants were allocated to the exercise (n = 28) or control group (n = 29) and underwent the baseline assessment once they met the readiness criteria of the trial intervention. All reported data is based on these 57 participants (Fig. 1). With respect to the primary outcome (ultrasound-derived QMLT), three participants had missing follow-up values for the following reasons: Two participants (exercise group n = 1, control group n = 1) passed away between the baseline and follow-up assessment after deteriorating health states without having undergone a single exercise session. In another participant (control group) it was deemed unsafe to measure muscle size, due to a high risk of cross-contamination of multi-resistant bacterial infections.

Participants' clinical characteristics and baseline values of all trial outcomes were comparable between groups (see Table 2 and Table 3). The median length of stay in the burn center for the participants in the exercise group was shorter compared to the control group (28 days [IQR 21–49] vs. 42 days [IQR 27–73]), showing a trend towards significance ($p = 0.077$). This also resulted in a shorter duration of follow-up in the exercise group (median 22 days [IQR 15–31]) compared to the control group (median 28 days [IQR 21–55]) ($p = 0.065$). Seventeen participants in the exercise group and 20 participants in the control group met the readiness criteria of the trial intervention immediately at admission, while the remaining participants met the readiness criteria at a median of 18 days [IQR 9–29] of admission.

### 3.1. *Muscle size*

The addition of exercise, as shown in the mixed model output in Table 4 and Fig. 2, resulted in a mean additional retention of 0.06 cm of QMLT ($p = 0.003$) and 0.09 $cm^2$ of RF-CSA ($p < 0.001$) of weekly change, when compared to the control group (see Table 4). In both groups, participants, who lost the least amount of muscle size between admission and baseline, also lost the most over time from baseline onwards. This inverse relationship was also observed vice versa, with participants who experienced greater muscle size loss prior to the baseline assessment, gaining more over time after baseline. For every cm of QMLT lost between admission and baseline, participants gained on average 0.1 cm per week of follow-up ($p < 0.001$).

### 3.2. *Muscle force*

Table 5 shows the regression output for the impact of exercise training on the change of muscle strength over time. Allocation to the exercise group led to a significantly greater retention of muscle strength over time for all measures. Across all assessed strength measures, there was an inverse relationship between the amount of force at baseline and change over time thereafter, in the sense that greater force at

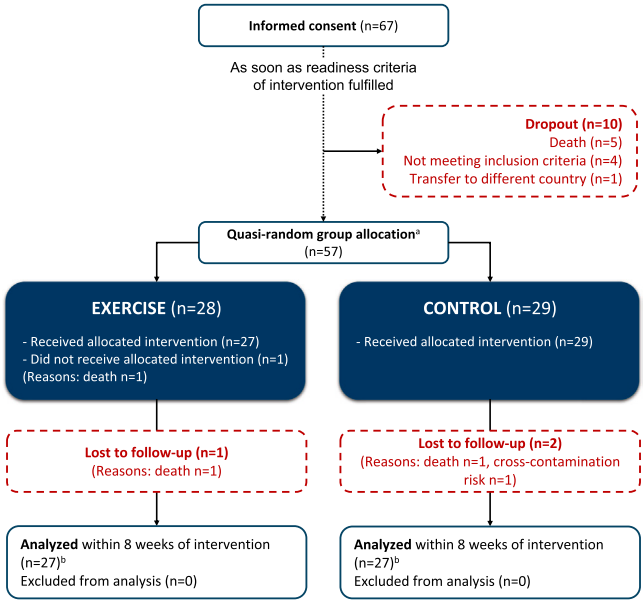


**Fig. 1 – Study flow diagram.**
**[a]based on staff capacity to provide intervention due to COVID19. [b]refers to the primary outcome.**

**Table 2 – Demographics and clinical characteristics of the sample.**

| | Exercise (n = 28) | Control (n = 29) | *p*-value |
|---|---|---|---|
| **Trial site 1/ Trial site 2** | 13 / 15 | 8 / 21 | 0.175 |
| **Gender** | 5 Females / 22 Males | 11 Females / 18 Males | 0.141 |
| **Age**, mean [95%CI] | 48 years[43–55] | 52 years[47–58] | 0.406 |
| **TBSA burned**, median [IQR] (range) | 17%[12–32], (10–60) | 18%[14–21], (10–70) | 0.955 |
| **Full thickness**, median [IQR] | 6%[3–19] | 8%[4–18] | 0.522 |
| **Lower Limb burns** | n = 22 (81%) | n = 15 (52%) | 0.052 |
| **Bilateral lower limbs** | n = 18 (64%) | n = 13 (45%) | 0.186 |
| **Inhalation trauma** | n = 4 (14%) | n = 3 (10%) | 0.705 |
| **Previously mechanically ventilated** | n = 12 (43%) | n = 10 (34%) | 0.592 |
| **Number of surgeries**, median [IQR] | 1 [0–2] | 1 [0–3] | 0.166 |
| **Previously septic** | n = 10 (36%) | n = 9 (31%) | 0.931 |
| **Revised BEAUX score**, mean [95%CI] | 75[66–84] | 76[69–84] | 0.831 |
| **COVID-19 infection at admission** | n = 1 (4%) | n = 1 (3%) | 0.491 |
| **LOS burn ICU**, median [IQR] | 4 days [0–20] | 4 days [0–29] | 0.550 |
| **Days till start of intervention**, median [IQR] | 0 days [0–15] | 0 days [0–26] | 0.822 |
| **Duration of follow-up (weeks),** median [IQR] | 22 days[15–31] | 28 days[21–55] | 0.065 |

Trial site 1 signifies the burn unit of the ZNA Stuivenberg and trial site 2 signifies the Military Hospital Queen Astrid; 95%CI, 95% confidence interval; IQR, interquartile range; TBSA, total burn surface area; The revised BEAUX score is a prognostic score of burn severity comprising %TBSA, age, and inhalation trauma; LOS burn ICU, length of stay in the burn intensive care unit.

baseline was associated with a greater force reduction over time.

### 3.3. *Quality of life*

Final regression models of the BSHS-B subscales and EQ-5D-5L measures are shown in Table 6. Both groups increased their self-reported quality of life over time, with a larger increase over time in the BSHS-B subscale 'hand function' in the exercise group compared to the control group, albeit only marginally significant (ß = 0.13, p = 0.049). There were no significant differences observed over time between the groups for any of the other quality-of-life measures, i.e. the BSHS-B subscale 'simple abilities', or the EQ-5D-5L health utility index and visual analogue scale.

### 3.4. *Compliance and adverse events*

Participants in the exercise group completed exercise training at a mean frequency of 3.8 [95%CI 3.3–4.2] sessions per week, completing on average 12.2 [95%CI 9.4–15.1] sessions over the course of the study, consisting of 9.1 [95%CI 6.8–11.5] sessions of resistance training and 3.1 [95%CI 2.1–4.2] sessions of aerobic training. Participants performed exercises at a mean intensity of 7.9 [95%CI 7.5–8.3] rating of perceived exertion. Of the attempted 412 exercise sessions, 330 were successfully commenced (80%), and 264 (64%) were completed according to protocol. Non-compliance was unevenly distributed amongst participants, with four participants accounting for 41% of all failed sessions. Main causes for incomplete or failed sessions were surgery or postsurgical immobilization (60 sessions, 16 subjects), pain (44 sessions, 15 subjects), and uncooperative patient (13 sessions in 7 subjects). Besides one episode of vomiting no adverse events occurred during the exercise session.

## 4. Discussion

This trial investigated the efficacy of an exercise program during the acute phase of burns with respect to muscle size, muscle strength and quality of life. Our main findings indicate that exercise training is able to improve muscle size and muscle strength. Beyond the BSHS-B subscale 'hand function', this study found no evidence of an added benefit for other assessed measures of quality of life in the short-term.

**Table 3 – Baseline comparison of trial outcomes.**

| | Exercise (n = 28) | Control (n = 29) | *p*-value |
|---|---|---|---|
| **QMLT** (cm), mean [95%CI] | 2.97 [2.56–3.39] | 3.13 [2.82–3.44] | 0.534 |
| **RF-CSA** ($cm^2$), mean [95%CI] | 2.64 [2.26–3.02] | 3.14 [2.78–3.49] | 0.056 |
| **Handgrip force** (N), mean [95%CI] | 35.37 [28.33–42.42] | 26.43 [20.34–32.52] | 0.060 |
| **Hip flexion force** (N), mean [95%CI] | 172.96 [134.18–211.74] | 146.88 [116.55–177.21] | 0.456 |
| **Knee extension force** (N), mean [95%CI] | 248.38 [197.1–299.66] | 189.57 [153.73–225.4] | 0.057 |
| **EQ-5D-5L health index**, mean [95%CI] | 0.27 [0.12–0.42] | 0.23 [0.1–0.37] | 0.720 |
| **EQ-5D-5L VAS**, mean [95%CI] | 45.26 [34.96–55.56] | 49.79 [39.77–59.81] | 0.520 |
| **BSHS-B simple abilities**, mean [95%CI] | 1.18 [0.6–1.76] | 0.96 [0.5–1.42] | 0.933 |
| **BSHS-B hand function**, mean [95%CI] | 1.95 [1.35–2.55] | 2.11 [1.62–2.59] | 0.672 |

QMLT, quadriceps muscle layer thickness; RF-CSA, rectus femoris cross-sectional area; VAS, visual analogue scale; BSHS-B, burn specific health scale brief. 95%CI, 95% confidence interval.

**Table 4 – Mixed models for ultrasound-derived muscle size parameters, adjusted for covariates.**

| | Variable | ß-coeff. | *p*-value | 95%CI | |
|---|---|---|---|---|---|
| QMLT | Group[Exercise] | 0.089 | 0.154 | -0.034 | 0.212 |
| | Week | -0.132 | < 0.001 | -0.157 | -0.106 |
| | Group[Exercise]*Week | 0.055 | 0.005 | 0.017 | 0.093 |
| | Loss between admission – baseline (cm) | -0.947 | < 0.001 | -1.032 | -0.862 |
| | Loss between admission – baseline*Week | 0.096 | < 0.001 | 0.074 | 0.117 |
| | Admission value (cm) | 0.907 | < 0.001 | 0.849 | 0.964 |
| RF-CSA | Group[Exercise] | 0.072 | 0.258 | -0.054 | 0.199 |
| | Week | -0.138 | < 0.001 | -0.164 | -0.112 |
| | Group[Exercise]*Week | 0.086 | < 0.001 | 0.048 | 0.124 |
| | Loss between admission – baseline ($cm^2$) | -0.942 | < 0.001 | -1.053 | -0.830 |
| | Loss between admission – baseline*Week | 0.116 | < 0.001 | 0.087 | 0.145 |
| | Admission value ($cm^2$) | 0.950 | < 0.001 | 0.892 | 1.008 |

The significant ß-coefficient for interaction term "Group[Exercise]*Week" signifies the added impact of the exercise intervention to standard care, expressed as absolute change per week of follow-up. QMLT, quadriceps muscle layer thickness; RF-CSA, rectus femoris cross-sectional area.

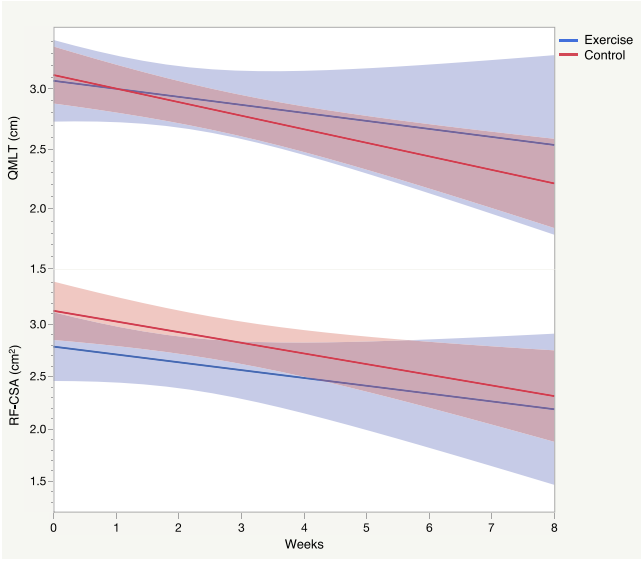


**Fig. 2 – Change of ultrasound-derived muscle size parameters over time.**
**Data displayed as unadjusted regression lines with confidence intervals (shaded area). Note that, while both groups decrease in muscle size parameters over time, the exercise group (blue line) decreases less. QMLT, quadriceps muscle layer thickness; RF-CSA, rectus femoris cross-sectional area.**

The observed benefit of exercise training regarding post-burn muscle wasting is a plausible effect that has previously only been demonstrated in rodent burn models and pediatric burns [30,31,63], but not adult burns. One previous trial of resistance exercise in adult burn patients by Gittings et al. (2021) found no significant effect for fat free mass using bioimpedance spectroscopy [64]. While their trial showed large similarities to our trial protocol, the opposing findings might be explained by differences in 1) the intervention (no aerobic training stimuli, commenced within 72 h of burn injury, exercise continued after discharge), 2) the studied sample (less severe burns, and fewer total participants), 3) the timing of assessment (two weeks after treatment cessation), and 4) the assessment method. In burns, direct comparisons between ultrasound and bioimpedance remains unchartered territory, but in the critically-ill, ultrasound has been used more frequently than bioimpedance [65], has been shown to be more sensitive to track muscle loss over time [66], and appears to better correlate with reference tests of muscle mass such as computed tomography and dual-energy X-ray absorptiometry [38,42,66–68]. A main difference between ultrasound and bioimpedance spectroscopy is that the latter measures whole-body parameters as opposed to local muscle size, as is the case for ultrasound. While quadriceps muscle thickness is highly correlated to whole-body muscle mass, it is possible that the observed changes in the quadriceps muscles do not reflect equivalent changes in whole-body muscle mass, as the exercise training program primarily involved the lower limbs. Furthermore, Gittings et al. (2021) acknowledge that their trial may have been underpowered to detect a difference between the experimental group and a relatively active comparator group [64].

Similarly, our observed improvements in muscle strength are not in line with the findings by Gittings et al. (2021), who found no significant differences in either knee extensor or hand grip strength [64]. Besides the aforementioned methodological differences, another main fact that might have contributed to this difference in findings is that they excluded patients with hand burns. In our trial, patients with hand burns had likely lost more hand grip strength between admission and baseline, and therefore may have been more responsive to exercise, especially exercises that involve holding free weights. Our observed improvements in lower limb strength corroborate previous findings by Paratz et al. (2012), who provided exercise at later stages of recovery (mostly after discharge) and among others found benefits in quadriceps strength, but not hand grip strength [69]. As the authors hypothesized, the lack of observed efficacy of exercise in improving hand grip strength in their trial is likely a result of a group imbalance in septic episodes and hand burns (significantly more in the exercise group) [69].

In the quality-of-life domain, our data revealed a marginally significant increase in the BSHS-B subscales 'hand function' favoring the exercise group. While caution is advised in interpreting such a marginally significant effect as definitive,

**Table 5 – Mixed models for muscle strength measures, adjusted for covariates.**

| | Variable | β-coeff. | p-value | 95%CI | |
|---|---|---|---|---|---|
| **Grip strength** | Group[Exercise] | -0.408 | 0.786 | -3.397 | 2.581 |
| | Week | 2.949 | < 0.001 | 1.825 | 4.074 |
| | Group[Exercise]*Week | 1.472 | 0.005 | 0.466 | 2.477 |
| | Baseline grip strength (N) | 1.032 | < 0.001 | 0.922 | 1.141 |
| | Baseline grip strength*Week | -0.116 | < 0.001 | -0.156 | -0.076 |
| | Duration of mechanical ventilation (days) | 0.304 | 0.021 | 0.048 | 0.560 |
| **Hip flexion** | Group[Exercise] | 13.361 | 0.193 | -6.900 | 33.623 |
| | Week | 12.621 | < 0.001 | 6.444 | 18.798 |
| | Group[Exercise]*Week | 8.999 | 0.004 | 2.964 | 15.033 |
| | Baseline Hip Flexion strength (N) | 0.921 | < 0.001 | 0.789 | 1.052 |
| | Baseline Hip Flexion strength*Week | -0.123 | < 0.001 | -0.166 | -0.079 |
| **Knee Extension** | Group[Exercise] | -7.922 | 0.560 | -34.922 | 19.078 |
| | Week | 2.699 | 0.517 | -5.577 | 10.974 |
| | Group[Exercise]*Week | 11.856 | 0.042 | 0.475 | 23.236 |
| | Baseline Knee Extension strength (N) | 0.922 | < 0.001 | 0.778 | 1.066 |
| | Baseline Knee Extension strength*Week | -0.053 | 0.030 | -0.100 | -0.005 |

The significant ß-coefficient of interaction term "Group[Exercise]*Week" signifies the added impact of the exercise intervention, expressed as absolute change per week of follow-up. N, Newtons.

it would theoretically be in agreement with a previous report that showed a significant improvement in the combined score of the BSHS-B subscales 'hand function' and 'simple abilities', but not other BSHS-B domains [64]. The present trial complements these findings by specifying in which of the two subscales this improvement may have taken place. In theory, however, clinical improvements in muscle strength would be expected to eventually translate into the entire functional domain. It remains unclear, then, why our trial was unable to do so in regards to the BSHS-B subscale 'simple abilities'. Beside the fact that our trial was not sufficiently powered to detect between group differences in quality-of-life outcomes, this may be explained by the fact that our exercise intervention was designed to target muscle as a metabolic tissue. Accordingly, exercises focused primarily on the prevention of muscle wasting. This focus comes at a trade-off of more functional exercises, that challenge concepts of coordination, balance, and proprioception. However, we consider this an adequate trade-off, as functional training is traditionally already part of the standard of care in many burn centers [5]. Another factor that might explain the absence of a measurable effect in the BSHS-B subscale 'simple abilities' as well as the EQ-5D-5L measures is that the follow-up duration of the present trial (limited to hospital stay) might be too short to observe effects [57]. However, further long-term follow-up of the present trial has been planned and will establish the impact of exercise training on the quality of life of trial participants beyond discharge.

This trial also found a shorter length of burn center stay in the exercise group (28 vs. 42 days), albeit not reaching significance ($p = 0.077$). The potential mechanisms behind a faster recovery may pertain to a shorter wound healing time

**Table 6 – Mixed models for quality-of-life measures, adjusted for covariates.**

| | Variable | β-coeff. | p-value | 95%CI | |
|---|---|---|---|---|---|
| **BSHS-B hand function** | Group[Exercise] | 0.014 | 0.947 | -0.399 | 0.427 |
| | Week | 0.108 | 0.007 | 0.030 | 0.186 |
| | Group[Exercise]*Week | 0.130 | 0.046 | 0.003 | 0.258 |
| | Baseline value | 0.812 | < 0.001 | 0.684 | 0.940 |
| **BSHS-B Simple Abilities** | Group[Exercise] | 0.047 | 0.858 | -0.475 | 0.570 |
| | Week | 0.294 | < 0.001 | 0.192 | 0.396 |
| | Group[Exercise]*Week | -0.020 | 0.810 | -0.186 | 0.146 |
| | Baseline value | 0.700 | < 0.001 | 0.532 | 0.868 |
| **EQ-5D-5L Health Utility Index** | Group[Exercise] | 0.047 | 0.409 | -0.065 | 0.158 |
| | Week | 0.082 | < 0.001 | 0.061 | 0.102 |
| | Group[Exercise]*Week | 0.004 | 0.827 | -0.030 | 0.038 |
| | Baseline value | 0.882 | < 0.001 | 0.730 | 1.034 |
| | Baseline value*week | -0.129 | < 0.001 | -0.176 | -0.082 |
| **EQ-5D-5L** | Group[Exercise] | 1.378 | 0.706 | -5.849 | 8.604 |
| **VAS** | Week | 7.868 | < 0.001 | 5.629 | 10.107 |
| | Group[Exercise]*Week | 1.190 | 0.288 | -1.020 | 3.400 |
| | Baseline value | 0.907 | < 0.001 | 0.769 | 1.046 |
| | Baseline value*week | -0.128 | < 0.001 | -0.167 | -0.089 |

The significant ß-coefficient of interaction term "Group[Exercise]*Week" signifies the added impact of the exercise intervention, expressed as absolute change per week of follow-up. VAS, Visual Analogue Scale.

as a result of the anabolic, anti-catabolic, anti-hyperglycemic, and anti-inflammatory effects of exercise [70–72]. Previously, one case-control study of adult burn patients by Deng et al. (2016) showed a significantly shorter hospital length of stay (101 vs. 184 days) as a result of early mobilization compared to standard care [73]. Among factors that might explain the larger effect size is that, unlike our trial, their standard care did not include any active exercise stimuli, accounting for a larger difference between experimental intervention and its comparator. Secondly, their early mobilization protocol took place during the burn intensive care unit stay, and may have produced a larger preventive effect that the exercise training in our trial, which mostly took place after intensive care unit stay, could not achieve.

### 4.1. *Clinical implications*

A greater retention of muscle size and strength induced by exercise training is highly relevant for clinical practice. The addition of exercise training to the standard care rehabilitation regimen led to an additional average weekly retention of 0.06 cm [95%CI 0.02–0.09] of QMLT and 0.09 $cm^2$ [95%CI 0.05–0.12] of RF-CSA. Over 8 weeks this would equate to an additional 15% [95%CI 5–25%] QMLT or 26% [95%CI 15–38%] of RF-CSA (as a proportion of baseline) compared to the control group. As a degree of 10% of postburn muscle wasting has previously been associated with complications, including a higher risk of infections, decreased wound healing, or the development of insulin resistance [21], such a degree of improvement should be regarded as clinically meaningful. However, as the present trial was not designed to test the effect on these secondary implications, such inferences remain to be established. Similarly, all tested muscle strength parameters improved on average 4–5% per week more in the exercise group than the control group. Over the course of burn center stay this becomes substantial, potentially leading to a faster restoration of functional status and independence [74].

Clinically, active forms of exercise are perceived as extremely challenging for both clinicians and patients. In European burn centers, as is the case for the participating trial sites, resistance and aerobic forms of exercise are either avoided or carried out at low intensities which lack palpable impact [5]. Our data demonstrates that resistance and aerobic exercise training is both safe and feasible during burn center stay. Furthermore, the largely modifiable nature of the encountered causes for failed or incomplete exercise sessions in the present trial underlines the importance of the multidisciplinary team in creating an environment that facilitates exercise training. Delivering optimal pain management, patient education, and coordinating the timing of exercise with other procedures are among key strategies vital to achieving high exercise compliance. Exercise training therefore presents a clinically realistic strategy that need not be avoided to maximize the recovery potential of burn patients.

### 4.2. *Strengths and limitations*

A clear strength of this trial is its multicenter nature and wide eligibility criteria, supporting the external validity of our findings. The facts that this trial included a wide range of burn severity, provided the intervention of varying durations and at differing times after admission, and included both sexes and adults of all ages, suggest that exercise training can be applied to the wider clinical context of inpatient burn care. Another strength relates to the use of ultrasound – a novel method that allowed us to derive objective measures of muscle size at all points of burn center stay independent of patient cooperation and wound status. This trial shows that ultrasound can be used to measure postburn muscle wasting as a target in intervention trials.

A few limitations need to be kept in mind when interpreting the present study. One such limitation is the fact that, due to the COVID-19 pandemic, the randomization method had to be adapted from a purely random allocation to a randomization based on staff capacity. Steps were taken to eliminate selection bias by predetermining the staff's weekly capacity to deliver the trial intervention irrespective of patient presentation. Furthermore, the fact that the groups were comparable at baseline indicates limited impact of selection bias. The applied group allocation method also resulted in an imbalance in group allocation between the two trial sites, limiting single-center conclusions. The inclusion of trial site as a covariate in the regression analyses, however, did not significantly explain any of the observed model variance, and thus did not impact any of our conclusions.

Other limitations relate to the fact that we were unable to blind the patients, therapists, and assessors to group allocation. This is a limitation frequently seen in rehabilitation research, as a placebo treatment is often difficult to implement [75,76]. While the influence of performance and detection bias need to be considered in our trial, it also needs to be emphasized that the analysis of the ultrasound-derived data, as the primary endpoint of this trial, was carried out blinded.

### 4.3. *Future directions*

While the present exercise trial forms one of the first to include severe adult burn patients (up to 70% TBSA), the distribution of TBSA in our sample was heavily skewed towards the lower end (Median 17%, IQR 13 – 28% TBSA). Yet, it is the more severe burn population with associated prolonged convalescence, who are most at risk of developing extensive metabolic sequelae, but also who may most benefit from exercise training. Future trials should establish the potential of exercise training to improve outcomes in this important subgroup. Identifying subgroups within the burn population that require more intensive exercise rehabilitation would be especially beneficial for regions of high patient-to-therapist ratios, where clinicians need to prioritize patients with high morbidity risk. While statistical power remains a challenge in burn research, patients with sepsis or those on prolonged mechanical ventilation present particular groups at risk of muscle wasting [77–79].

## 5. Conclusion

The present study is the first multicenter trial to date to examine the effects of exercise training in the inpatient adult

burn population. As such, it supports the role of exercise training as a feasible and efficacious component of acute burn rehabilitation to manage burn-related changes in muscle size and function.

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## Conflict of interest

None.

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