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The role of early exercise in the management of muscle wasting following acute burn injury

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To my mum, whose unconditional love, despite leaving us far too early – two months into this doctoral journey – provided the inner strength and perseverance I needed.

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Summary

Burn injury is a complex form of trauma that, when severe enough, causes a sustained stress response that impacts all organ systems. Long-lasting derangements in muscle metabolism associated with the stress response lead to the loss of skeletal muscle mass and function. Postburn muscle wasting in turn is associated with considerable short-term and long-term morbidity. Despite its impact, postburn muscle wasting is often regarded as an inevitable burn-related symptom that is often left to develop unrestrained during the early phase of burn recovery – a phase during which it could theoretically be best countered by targeted interventions.

Resistance and aerobic training during burn centre stay, collectively referred to as 'early exercise training' in this dissertation, has been used successfully in other disease phenotypes to counteract muscle wasting. However, in burn care, many uncertainties persist over the role of early exercise training in the management of postburn muscle wasting. Reservations over its safety, feasibility, and efficacy in the adult burn population have hampered its integration into standard inpatient burn care. Thus, the overarching aim of this doctoral project was to better understand the role of early exercise training in the inpatient management of burn-induced muscle wasting.

The first part of this dissertation describes a survey of burn clinicians across European burn centres that was carried out to define the current practice of inpatient exercise prescription and the management of metabolic sequalae. The main findings of this survey revealed a low provision of early exercise training across different phases of inpatient recovery as well as considerable variation in the use of metabolic sequelae as targets of assessment and exercise. Clinician's low importance ratings of the prevention of metabolic sequelae combined with a limited knowledge of metabolic pathophysiology were identified as factors contributing to the observed non-uniformity in exercise prescription and metabolic management. The results of this survey reflect the lack of scientific evidence surrounding early exercise training, and the treatment of muscle wasting. Hence, more efficacy data is needed to support the inclusion of early exercise training in the standard management of muscle wasting in adults with burn injuries. Continued professional education and interdisciplinary exchange are among suggested strategies to address the observed gaps in the current practice. The ubiquitous lack of reported assessment of muscle wasting was another finding of the survey addressed by the second part of this dissertation.

In this second part, a study on the utility of ultrasound to measure quadriceps muscle size is presented. Acutely burned adults and a healthy control sample were tested by two raters to analyse its reliability and feasibility. The feasibility and reliability of the tested ultrasound protocol were influenced by several methodological factors. Recommendations are made accordingly by comparing the results between 1) the mean of three repeat measurement versus a single measurement, 2) different measurement locations, 3) the compression technique. With intraclass correlation coefficients confidence levels of around or above 0.9, reliability was judged to be good to excellent dependent on the chosen methodology. Quadriceps ultrasound was deemed feasible in most cases (90.5% - 97%). The second part of this dissertation therefore presents ultrasounds as a practical tool able to derive clinically reliable and feasible estimates of quadriceps muscle size in the acute burn setting – a phase during which most changes in muscle size occur. These findings aid clinicians in adopting ultrasound for the purpose of monitoring changes in muscle size as a measure of muscle wasting. The monitoring of muscle wasting during burn centre stay is thought to lead to an increased awareness of muscle wasting as well as a better evaluation of interventions targeting muscle wasting. To that end, minimal detectable changes of quadriceps ultrasound were acceptable, ranging between 6 – 15% of mean value depending on the chosen muscle size parameter and the used methodology. Measuring quadriceps muscle layer thickness without compression and averaging three measurements is the method that demonstrated the highest reliability and smallest minimal detectable changes. The ultrasound methodology and measured parameter can be chosen in line with different clinical scenarios, common to the acute burn setting.

The final part of this dissertation describes two intervention studies that compared early exercise training on top of usual care to usual care alone. The first study describes a multicentre quasi-randomized trial in adults with predominantly moderate burn injuries, recruited in two Belgian burn centres. The second study concerns a randomized controlled trial in adults with severe burn injury, recruited from a burn centre in China. The main findings of both of these studies support the beneficial effects of early exercise training on quadriceps muscle size and muscle strength during burn centre stay, while its effects on parameters of health-related quality of life remain to be established. Furthermore, both studies confirmed the safety and feasibility of early exercise training. As such these two studies add to the evidence base of early exercise training as part of the management of postburn muscle wasting.

Dutch Summary

Een brandwond is een complex trauma, welke gepaard gaat met een langdurige fysiologische stressrespons die vele orgaansystemen beïnvloed. Langdurige verstoringen van bijvoorbeeld het spiermetabolisme leidt tot o.a. tot verlies van skeletspiermassa en skeletspierfunctie. Skeletspiermassaverlies gaat gepaard met een grotere korte -en lange termijn comorbiditeit. Ondanks deze ernstige gevolgen voor patiënt wordt spiermassaverlies tijdens de vroege fase van herstel na brandwonden vaak als een onvermijdelijk brandwonden gerelateerd fenomeen beschouwd. Echter, tijdens deze vroege fase kan spiermassaverlies, althans theoretisch gezien, worden tegengegaan door gerichte interventies. Zo zijn weerstandstraining en aerobe training gedurende de ziekenhuisopname (in dit proefschrift 'vroegtijdige training' genoemd) bij andere ziektebeelden succesvol toegepast om spiermassaverlies tegen te gaan. In de brandwondenzorg is echter nog veel onduidelijkheid over de rol van vroegtijdige training in het voorkomen van spiermassaverlies. Zo bestaan er twijfels over de veiligheid, haalbaarheid en werkzaamheid van vroegtijdige trainingen in de volwassen brandwondenpopulatie en hebben deze twijfels de integratie van vroegtijdige training in de standaard brandwondenzorg belemmerd. Om meer inzicht te verwerven in de rol van vroegtijdige training bij patiënten met brandwonden en de impact daarvan op het spiermassaverlies zijn verschillende studies binnen dit proefschrift opgezet en uitgevoerd.

Het eerste deel van dit proefschrift betreft een enquête afgenomen bij clinici in Europese brandwondencentra waarmee we inzicht hebben verworven in het voorschrijven van fysieke revalidatie in de klinische zorg en het managen van de metabole gevolgen tijdens het herstel na brandwonden. Dit onderzoek toonde aan dat er een laag aanbod van vroegtijdige inspanningstraining in verschillende fasen van klinisch herstel werd aangeboden, evenals een aanzienlijke variatie in het gebruik van metabole gevolgen als doelen voor evaluatie en training. Vanwege een beperkte kennis van metabole pathofysiologie schatten clinici het belang van preventie van metabole gevolgen laag in. Beide factoren dragen bij aan het waargenomen niet-uniforme voorschrijven van fysieke oefeningen en metabool management. De resultaten van dit onderzoek weerspiegelen het gebrek aan wetenschappelijk kennis rondom vroegtijdige training en de behandeling van spiermassaverlies. Op basis van deze resultaten kunnen we concluderen dat er meer werkzaamheidsstudies nodig zijn om de implementatie van vroegtijdige training in de standaardbehandeling ter voorkoming van spierafbraak bij volwassenen met brandwonden te ondersteunen. Voorgesteld wordt om opleiding en interdisciplinaire samenwerking te verbeteren als strategieën om de waargenomen hiaten in de huidige praktijk aan te pakken.

Het gebrek aan gerapporteerde beoordeling van spiermassaverlies was een andere bevinding welke in het tweede deel van dit proefschrift is behandeld.

Het tweede deel van het proefschrift beschrijft de toepasbaarheid van ultrageluid om de spieromvang van de quadricepsspier te meten. Hiervoor werden volwassenen met acute brandwonden en een gezonde controlegroep door twee beoordeelaars onafhankelijk van elkaar gemeten om zo de betrouwbaarheid en haalbaarheid te bepalen. De haalbaarheid en betrouwbaarheid van de geteste echografieprotocollen werden beïnvloed door verschillende methodologische factoren en werden er praktische aanbevelingen opgesteld op basis van volgende vergelijkingen 1) het gemiddelde van drie herhaalde metingen ten opzichte van een enkele meting, 2) verschillende meetlocaties op de spier en 3) het gebruik van de compressietechniek. Intraclass correlatiecoëfficiënten toonden een goede tot uitstekende betrouwbaarheid aan. Echografie van de quadricepsspier werd in de meeste gevallen uitvoerbaar geacht (90,5% - 97%). Op basis van deze gegevens kunnen we echografie als een praktisch hulpmiddel zien waaruit klinisch betrouwbare en haalbare schattingen van de quadriceps spieromvang kunnen worden afgeleid in de acute brandwondensituatie. Deze bevindingen kunnen clinici helpen bij het juist gebruik van ultrageluid voor het monitoren van veranderingen in spieromvang als maat voor spiermassaverlies. De minimaal detecteerbare veranderingen van echografie van de quadriceps varieerde, afhankelijk van de gekozen spiergrootteparameter en de gebruikte methode, tussen 6 - 15% van de gemiddelde waarde. Het gemiddelde van drie metingen van de dikte van de spierlaag van de quadricepsspier zonder compressie is de methode met de laagste minimaal detecteerbare veranderingen en de hoogste betrouwbaarheid. Het accuraat monitoren van spiermassaverlies tijdens het verblijf in een brandwondencentrum zal leiden tot een groter bewustzijn van dit spiermassaverlies en tot een betere evaluatie van potentiële interventies die spiermassaverlies tegengaan.

Het laatste deel van dit proefschrift beschrijft twee interventiestudies die vroege oefentraining bovenop de standaardzorg vergeleken met standaardzorg alleen. De eerste studie beschrijft een multicentrische quasi-gerandomiseerde trial bij volwassenen met voornamelijk matige brandwonden, gerekruteerd in twee Belgische brandwondencentra. De tweede studie betreft een gerandomiseerde gecontroleerde trial bij volwassenen met ernstig brandwonden, gerekruteerd in een brandwondencentrum in China. Beide studies tonen gunstige effecten van vroegtijdige oefentraining aan op spieromvang van de quadricepsspier en spierkracht tijdens het verblijf in het brandwondencentrum. Bovendien bevestigden beide onderzoeken de veiligheid en haalbaarheid van vroegtijdige training. De gemeten effecten van de interventies op de kwaliteit van leven waren onduidelijk. Als zodanig dragen deze twee onderzoeken bij aan het bewijs dat vroegtijdige training als onderdeel van de behandeling van spiermassaverlies na matige tot ernstige verbranding zinvol is.

General introduction

1. Burn injury definition

A burn injury constitutes a traumatic insult to the skin or other tissue. Most burn injuries are caused by flames and hot liquids (scalds). Other causes include friction burns and exposure to hot solids, chemicals, electricity, or radiation.

2. Burden of burns

With over 8.9 million new cases of burn injury in 2019 and an estimated 180,000 deaths each year, burns are a leading cause of injury worldwide [1,2]. The global burden of burn injuries is estimated at over 7.4 million disability adjusted life years (DALY), of which 67% account for years of life lost, and 33% for years of life lost to disability [2]. While these are global estimates, burns disproportionally affect low- and middle-income countries, with over 95% of burn deaths occurring in these regions [3]. Similarly, the burden of burns is unequally distributed across the world, with burns leading to greater disability in low- and middle-income countries than in high-income countries [2,4,5]. These inequities in burn-related mortality and morbidity can also be seen on a subnational level. Irrespective of country, low socio-economic status is a major risk factor for sustaining a burn injury and worse long-term outcome [3]. Owing to progress in burn care, global mortality from burns has decreased dramatically over the past few decennia [6]. Consequently, the focus of burn care has progressively shifted towards improving outcomes for non-fatal burns. Of these outcomes, postburn muscle wasting forms the topic of this thesis, and will be introduced in the following section.

3. Pathophysiology of postburn muscle wasting

The systemic stress response to burn injury involves a complex cascade of events that disrupt whole-body metabolism and result in a catabolic state that ultimately leads to skeletal muscle wasting, defined as the quantitative and qualitative loss of muscle tissue. Following burn injury, skeletal muscle functions as a pool of readily available amino acids used as fuel for wound healing and the acute phase response [7,8]. Despite reaching its peak during the acute phase of burns, the catabolic state has shown to persist beyond wound closure for years after the burn injury [9,10]. While the cause and mechanisms underlying postburn muscle wasting are still poorly understand, several interlinked factors, as illustrated in Figure 1, are thought to contribute to its development and persistence over time.

Sustained elevations in energy expenditure - a hallmark of burn injury known as hypermetabolism, brought about by increased levels of circulating stress hormones and pro-inflammatory cytokines, is associated with proteolysis, lipolysis, and glycogenolysis. This in turn leads to hyperglycaemia, insulin resistance, and lipotoxicity, all of which exacerbate the hypermetabolic and catabolic response in a futile cycle. The hypermetabolic response is not unique to burn injuries, however, is unparalleled in its magnitude and persistence compared to other forms of trauma and disease [8]. Depending on burn severity, the resting energy expenditure can reach up to 180% of predicted values at its peak. While the resting energy expenditure decreases in magnitude over time, findings show that it stays elevated for years after the initial burn trauma [11]. Stress hyperglycaemia has been shown to worsen postburn muscle proteolysis in the presence of hyperinsulinemia [12] – an observation that is especially relevant given the high prevalence of insulin resistance in burn survivors in the acute phase but also long after wound closure [13–16]. The fact that muscle tissue is responsible for 70-80% of insulin-mediated glucose uptake, creates another vicious cycle of postburn muscle wasting and hyperglycaemia. Another factor contributing to muscle wasting is an excessive systemic inflammatory response seen particularly during the acute phase of burns [14,17,18]. Inflammation exerts a negative effect on muscle tissue by causing among others oxidative stress and mitochondrial dysfunction [19–21] and by interfering with muscle cell regeneration [22–24]. Besides these factors, an efflux of protein from muscle tissue towards the burn wounds can be observed, resulting in a whole-body redistribution of protein at the expense of muscle protein reserves [7,25].

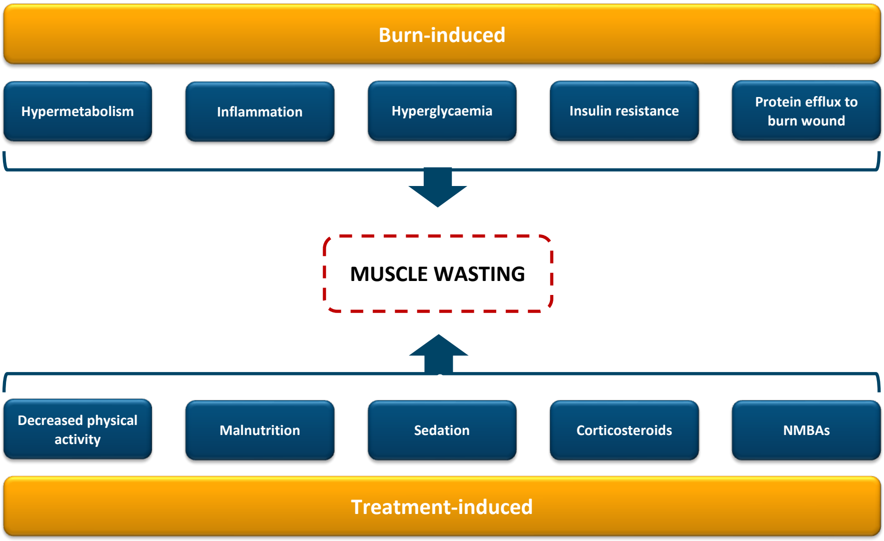

Figure 1. Theoretical overview of factors contributing to postburn muscle wasting

In addition to the above responses that are initiated by the burn injury, the clinical treatment of burn injury can further exacerbate skeletal muscle wasting. Bed rest and immobilisation related to pain and grafting surgery are major contributors to postburn muscle wasting. In the absence of disease, bed rest alone has shown to induce significant loss of muscle mass, primarily by inhibiting muscle protein synthesis [26,27]. Postburn muscle wasting affects all skeletal muscle; however, muscle disuse due to pain and immobilisation affects burned regions to a greater extent. Other iatrogenic factors with negative impact on skeletal muscle include the administration of sedatives, corticosteroids, neuromuscular blocking agents, and inadequate nutritional support [28–31], however, these are beyond the focus of this dissertation. Altogether, postburn muscle wasting occurs because of accelerated muscle protein degradation outpacing its synthetic rate, leading to a net negative protein balance that can be observed from the first few days of admission to long after wound healing and hospital discharge [32–36].

Many of the systemic responses following burn injury represent the host's adaptive survival response which prioritises thermoregulation, wound healing, and immune defences. It is an evolutionary response that functions to overcome transient stress. It is not a response that evolved to be sustained for long periods of time [37]. Nevertheless, medical progress in the past century has rendered formerly unsurvivable states survivable, thereby establishing a new pathophysiological state of prolonged acute stress. The present challenge in burn care is to know how deal with the many clinical sequelae that this new state brings with it. Skeletal muscle wasting is one of these sequelae that is accompanied by significant short and long-term morbidity [8].

4. Clinical sequelae of postburn muscle wasting

In the short term, associated effects of postburn muscle wasting include decreased wound healing, increased risk of infection, intensive care unit acquired weakness, and difficulty to wean from mechanical ventilation, with a loss of 40% of lean body mass reported to be lethal [31,38–40] (Fig. 2). These complications create a cascade of events that culminate in a delay in rehabilitation, a protracted hospital length of stay and consequently higher in-hospital expenses [8,41]. In addition to short-term outcomes, muscle wasting is likely implicated in the aetiology of the susceptibility of burn survivors to develop metabolic, cardiovascular, and musculoskeletal disorders years after the burn trauma [42–50]. Unsurprisingly, burn injury is associated with higher long-term mortality compared to the non-burned population [51]. Although causal links remain to be established, metabolic derangements that originate during the acute phase of burns are thought to be implicated [51,52]. Postburn muscle wasting therefore poses a significant health burden to burn survivors, underlining the importance of interventions that mitigate muscle wasting and promote its recovery. Exercise is one of these intervention strategies that will be introduced next.

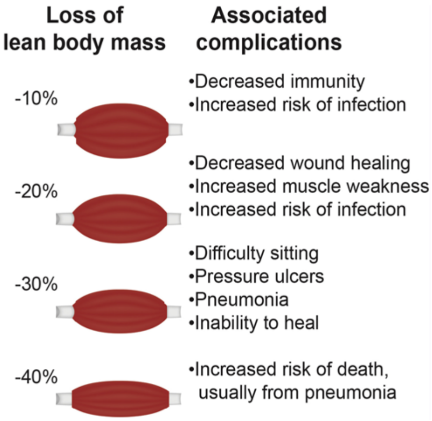

Figure 2. Short-term complications associated with muscle wasting Reproduced from Argilés et al. 2013 [38].

5. Exercise rehabilitation

Recovery from a burn injury is often a complex and protracted process that involves multidisciplinary expertise. Physical rehabilitation is paramount in maximising the recovery potential of burn survivors. Whereas there is a clear understanding that burn survivors might require life-long rehabilitation, at what point in time the physical rehabilitation should start is less clear [53,54]. Burn rehabilitation has traditionally been described as the phase of recovery starting after burn centre discharge [55]. The concept of physical rehabilitation commencing early after burn centre admission is a relatively recent concept. Physical rehabilitation components during this phase remain ill-defined and vary sharply between burn centres [56]. Whereas the physical rehabilitation components change over time according to changing needs, there is no clear consensus which component to focus on at what time of recovery.

Exercise training, defined as planned, structured, repetitive movement to improve or maintain physical fitness [57], is a component of burn rehabilitation, that has traditionally been reserved for after burn centre stay. During burn centre stay, physical rehabilitation efforts are traditionally directed at the patient’s range of motion, functional status, and scar quality [58], with guidelines emphasising positioning, splinting, and scar management [59,60]. While such physical rehabilitation targets are indispensable, they involve little physical activity. Postburn muscle wasting is then often left unchallenged during a phase when it develops and reaches its peak. Exercise training during burn centre stay, referred to in this dissertation as 'early exercise training', is of particular interest as it could act as an early deterrent to muscle wasting [36]. Resistance and aerobic training are established components in the treatment of muscle wasting in many other conditions [61]. However, in burns, the role of exercise training in the standard care of acute burn injuries remains to be defined, and many questions have hindered its adoption into clinical practice. Questions pertaining to its safety and feasibility in a population known for its high risk of infection, fragile skin grafts, and high pain experience, are among factors complicating the provision of exercise training during the acute phase of burns. Other questions concern its efficacy in ameliorating outcomes during the acute phase of burns. Most exercise intervention studies have taken place during later phases of recovery (i.e. after wound closure and, or after burn centre discharge), and have investigated outcomes other than muscle wasting [62–64]. Moreover, given that the majority of exercise studies have been carried out in paediatric burn patients, there is a paucity of efficacy data in adult patients [62,63].

For these reasons, the implementation of exercise training for adults with acute burn injury for the purpose of counteracting derangements such as postburn muscle wasting, has been slow. There has, nonetheless, been a recent trend towards early exercise in burn care – likely a spill-over from accumulating evidence in the wider intensive care population. In this population, early exercise approaches have shown benefits on important outcomes such as a shorter duration of mechanical ventilation and length of stay in ICU as well as the preservation of muscle mass [65–68]. Practice guidelines in burns have recently started to include exercise during the acute phase in their recommendations. However, little guidance is included vis-à-vis employed exercise type, timing, programme duration, and intensity, as well as therapeutic exercise targets [59,69–72].

6. Null Hypothesis

Early exercise training has no additional effect on postburn muscle wasting during burn centre stay in adults with moderate to severe burn injury.

7. Aims and outline

7.1. Aims

The primary aim of this doctoral project is to increase the understanding of the role of early exercise training in the clinical management of postburn muscle wasting in adults with acute burn injury. This overarching aim can be divided into the following three goals.

Goal 1 (Part 1, Chapter 1)

The first project goal was to provide an overview of the current practice of inpatient rehabilitation, focussed on the areas of exercise prescription, management of metabolic sequelae, and clinician's treatment priorities, rationale, and knowledge. To this end, a survey was distributed to burn clinicians working in European burn centres.

Goal 2 (Part 2, Chapter 2)

Flowing forth from the findings of the survey, the second goal was to develop and investigate a clinical tool to aid in monitoring muscle wasting. An ultrasound protocol was adapted for use in the acute burns population and investigated for its feasibility and reliability in measuring quadriceps muscle size.

Goal 3 (Part 3, Chapter 3 & 4)

The third goal was to test the effects of exercise training administered across the spectrum of adult burns during the acute phase of burns with regards to muscle size, muscle strength, and health-related quality of life. Two efficacy trials were conducted in moderate burns (chapter 3) and severe burns (chapter 4) comparing standard of care treatment to the additional provision of exercise training.

7.2. Outline

The current dissertation encompasses three parts, in line with the three goals.

The first part addresses the lack of clarity with respect to the current role of exercise training as a part of inpatient rehabilitation and as a strategy to manage postburn muscle wasting. Chapter 1 therefore describes a survey of burn centres across the European continent that was carried out to clarify the current state of 1) the administered components of inpatient exercise rehabilitation, 2) the management of metabolic sequelae including muscle wasting, and 3) treatment priorities, rationale, and knowledge of metabolic pathophysiology. The findings of the survey helped in defining the current standard-of-care. This chapter discusses the low prevalence of resistance and aerobic training across different phases of inpatient recovery, and its relation to the clinician's rehabilitation priorities, rationale, and knowledge. Variability between clinicians and burn centres is presented, and a potential neglect of metabolic sequelae (including muscle wasting) as targets of assessment and therapy is discussed. This chapter describes the identified gaps in the current state of inpatient rehabilitation in Europe, which is followed by recommendations to optimize inpatient rehabilitation.

The second part addresses the widespread lack of reported assessment of muscle wasting in burn care as a reflection of a wider neglect of metabolic sequelae in burn care. An adequate assessment of muscle wasting precedes any efforts to mitigate it. Consequently, a muscle ultrasound protocol was developed to provide a clinical tool for the monitoring of muscle wasting parameters. Chapter 3, therefore describes a feasibility and reliability study, in which ultrasound was used to quantify quadriceps muscle size in acutely burned adults as well as a healthy control sample. Factors that influenced the feasibility and reliability of the assessed protocol are discussed, and recommendations according to various clinical scenarios were synthesised.

The final part of the current dissertation is devoted to unravelling the effects of exercise training when added to the standard of care provided to adults with acute burn injury. Two intervention trials are presented. The first trial (chapter 3) concerns a multi-centre trial that recruited predominantly moderately burned adults from two Belgian burn centres. The efficacy of exercise training, consisting of resistance and aerobic training, in relation to ultrasound-derived quadriceps muscle size, muscle strength, and health-related quality of life is presented, and forms the main subject of this chapter. The second trial presented in chapter 4, involved a comparable randomized controlled trial that was carried out in China's largest burn centre. Similarly, outcomes of interest were quadriceps muscle size, muscle strength, and health-related quality of life. A major difference to the study presented in chapter 3, is that this trial was conducted in severely burned adults. Implications for clinical practice are discussed in both chapters.

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Part 1 Current-practice of inpatient exercise rehabilitation

Chapter 1. Status of adult inpatient burn rehabilitation in Europe: Are we neglecting metabolic outcomes?

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1.1 Abstract

Background: Hypermetabolism, muscle wasting and insulin resistance are challenging yet important rehabilitation targets in the management of burns. In the absence of concrete practice guidelines, however, it remains unclear how these metabolic targets are currently managed. This study aimed to describe the current practice of inpatient rehabilitation across Europe.

Methods: An electronic survey was distributed by the European Burn Association to burn centres throughout Europe, comprising generic and profession-specific questions directed at therapists, medical doctors and dieticians. Questions concerned exercise prescription, metabolic management and treatment priorities, motivation and knowledge of burn-induced metabolic sequelae. Odds ratios were computed to analyse associations between data derived from the responses of treatment priorities and knowledge of burn-induced metabolic sequelae.

Results: Fifty-nine clinicians with 12.3±9 years of professional experience in burns, representing 18 out of 91 burn centres (response rate, 19.8%) across eight European countries responded. Resistance and aerobic exercises were only provided by 42% and 38% of therapists to intubated patients, 87% and 65% once out-of-bed mobility was possible and 97% and 83% once patients were able to leave their hospital room, respectively. The assessment of resting energy expenditure by indirect calorimetry, muscle wasting and insulin resistance was carried out by only 40.7%, 15.3% and 7.4% respondents, respectively, with large variability in employed frequency and methods. Not all clinicians changed their care in cases of hypermetabolism (59.3%), muscle wasting (70.4%) or insulin resistance (44.4%), and large variations in management strategies were reported. Significant interdisciplinary variation was present in treatment goal importance ratings, motivation and knowledge of burn-induced metabolic sequelae. The prevention of metabolic sequelae was regarded as the least important treatment goal, while the restoration of functional status was rated as the most important. Knowledge of burn-induced metabolic sequelae was linked to higher importance ratings of metabolic sequelae as a therapy goal (odds ratio, 4.63; 95% CI, 1.50–14.25; p<0.01).

Conclusion: This survey reveals considerable non-uniformity around multiple aspects of inpatient rehabilitation across European burn care, including, most notably, a potential neglect of metabolic outcomes. The results contribute to the necessary groundwork to formulate practice guidelines for inpatient burn rehabilitation.

Keywords: Burn care, Burn rehabilitation, Exercise, Early mobilization, Hypermetabolism, Adults

1.2 Highlights

- Burn-induced metabolic derangements are challenging yet important rehabilitation targets in the successful management of burns. Early goal-directed rehabilitation has the potential to ameliorate metabolic derangements.
- European burn clinicians were surveyed to identify the current practice of inpatient rehabilitation across Europe.
- Resistance and aerobic exercises are not consistently provided in the early phase.
- Metabolic outcomes are under-used as therapeutic and assessment targets.
- Restoring functional status, not metabolic sequelae, is regarded as the most important therapeutic goal.
- Few burn clinicians demonstrated knowledge of post-burn metabolic pathophysiology.

1.3 Background

Continuing advances in post-burn care have progressively shifted the focus from mere survival towards long-term improvements in overall health and quality of life [1]. Among other significant challenges to these long-term outcomes are long-lasting derangements in glucose, lipid and protein metabolism. These burn-induced metabolic derangements are key drivers of the development of postburn hypermetabolism, a state of increased metabolic rate and one of the hallmarks of the stress response after burns [2]. The stress response entails two distinct phases of metabolic regulation. The first 24–48 hours of burn injury are known as the “ebb” phase, during which cardiac output, oxygen consumption, metabolism, and glucose tolerance are markedly reduced [3]. This is followed by the “flow” phase, which is characterized by gradual increases in cardiac output, oxygen consumption, metabolism, and catabolism [4, 5]. Together with prolonged periods of immobilization, these metabolic derangements contribute to persistent muscle wasting and insulin resistance, both of which hamper full recovery and may place the burn survivor at a higher risk of developing cardiovascular and metabolic comorbidities long after the initial burn trauma [2, 4–11]. Long-term comorbidities in turn pose substantial challenges to burn survivorship, impeding full return to work and reintegration into society [12, 13].

Significant research efforts over the past three decades have shed more light into the pathophysiological processes underlying the post-burn stress response and its detrimental effects on energy expenditure, skeletal muscle catabolism and glycaemic control [14]. This progressively increasing pathophysiological understanding has given rise to the development of interventions aimed at ameliorating associated metabolic outcomes.

However, many questions as to the optimal management of hypermetabolism, muscle wasting and insulin resistance remain unanswered.

Among interventions that have been proposed to alter the course of burn-induced metabolic sequelae is exercise-based rehabilitation [15–19]. Accumulating evidence for the restorative effects of exercise, in particular in the paediatric burn population, has led international practice guidelines to recommend exercise regimens to be routinely incorporated into the long-term rehabilitation of burn survivors posthospital discharge [20–22]. Favourable results of exercise, when commenced after hospital discharge, include an increase in lean mass, muscle strength, aerobic capacity and quality of life [20, 23, 24].

During the acute in-hospital phase, however, guidance concerning exercise is still in its infancy and there is little evidence regarding its effects [20–25]. The latest practice guidelines published by the International Society of Burn Injuries include the early institution of exercise as a part of the recommended metabolic management for the first time, but without concrete advice for exercise components [22]. It is during the acute phase that burn-induced metabolic sequelae are most prevalent and that exercise training might be most potent. In particular, aerobic and resistance exercise, as highly potent forms of metabolic stimuli [26, 27], could be key components in the early management of metabolic sequelae after burns. However, it remains unclear to what degree different types of exercise, as well as medical or nutritional interventions, are currently used in clinical practice for the purpose of optimizing metabolic outcomes.

Following overwhelming evidence in other critical illnesses [28], where early rehabilitative approaches have been long implemented (for their ability to resist metabolic sequelae [29–33], amongst other reasons), burn clinicians are increasingly adopting early rehabilitative approaches into their standard care [34–36]. Despite this clinical trend, prescribed exercise parameters, such as exercise type, intensity, timing and the physiological foundations upon which they are built, remain ill-defined in the absence of concrete exercise guidelines for adult burns. Recent findings from a large-scale study of exercise practice in both adult and paediatric burn patients confirm non-uniformity in the use of exercise and choice of exercise type in the acute phase of burns, both in the intensive care unit (ICU) and post-ICU prior to complete wound healing [36]. A key factor that might explain the nonuniformity in choice and use of early exercise is the clinician's perceived relative importance of different therapeutic goals. Perceived goal importance, in turn, is largely informed by the clinician's knowledge of burn pathophysiology and the perceived rationale of various types of exercise. However, to date, these factors have not yet been explored in burn clinicians in relation to clinical decision making in exercise rehabilitation.

Defining the role of metabolic outcomes in adult inpatient burn rehabilitation will serve to inform steps forward in developing practice guidelines aimed at creating more conformity. This study was therefore initiated to survey the European burn care community in order to provide insight into the current status of (1) inpatient exercise rehabilitation; (2) the management of hypermetabolism, muscle wasting and insulin resistance; and (3) treatment priorities, motivation and knowledge.

1.4 Methods

Upon approval by the Institutional Review Board of the Ziekenhuis Netwerk Antwerpen/OCMW, an electronic survey was distributed by the European Burn Association to burn centres across Europe, directed at burn clinicians, including physiotherapists and occupational therapists (from here on referred to as therapists), medical doctors and dieticians. Questions were designed and recorded using a transport layer-secure encrypted online platform (Qualtrics; LCC, USA).

The questions aimed to identify the following three components of current practice concerning the rehabilitation of adult patients with burns encompassing ≥20% total body surface area (TBSA): (1) inpatient exercise prescription, including exercise provision and components, inclusion/exclusion criteria, exercise parameters and the influence of metabolic sequelae; (2) metabolic management, including the evaluation and treatment of hypermetabolism, muscle wasting and insulin resistance; and (3) treatment priorities, motivation and knowledge, including therapeutic goal importance, exercise rationale and the clinician’s knowledge of burn-induced metabolic sequelae. The cut-off point of ≥20% TBSA was chosen as metabolic sequelae have been well documented in this adult patient population [37–40].

The survey (S1) comprised both generic and profession-specific questions in the form of multiple-choice and open questions. Generic questions concerned clinician and burn centre characteristics, as well as the clinician’s treatment priorities, motivation and knowledge (i.e. the third survey component as described above). Profession-specific questions for therapists primarily related to exercise prescription (first survey component), whereas medical doctors and dieticians answered questions largely concerned with the metabolic management (second survey component). Exercise provision and components across different phases of inpatient stay were determined through a “constant sum question” type (see Q21-23 in S1). According to this question type, therapists were asked to allocate a percentage of the total treatment time they spent per patient to prespecified treatment components, with the sum totaling 100%. The prevalence of provision of treatment components was determined through binary coding of the obtained responses into equal to (i.e. non-prevalent) or higher than (i.e. prevalent) 0% of allocated total treatment duration. Survey questions that investigated the management of hypermetabolism, muscle wasting and insulin resistance asked participants to report which, if any, outcome measures and intervention strategies they used, and at which frequency, for each respective outcome. Prespecified answer options and an open text field were used for questions regarding the type of outcome measures, whereas questions concerning the type of intervention strategies contained open text fields. To assess treatment priorities, all participants were asked to rate 5 pre-specified treatment goals over the acute phase of burns on a Likert scale of importance. The rated goals were:

1) range of motion (join mobility, skin mobility);
2) scar quality (aesthetics, pruritus, pain, prevention of hypertrophic scarring);
3) restoration of functional status (activities of daily living, ambulation ability, etc.);
4) prevention of deconditioning (muscle weakness, cardiovascular deconditioning, etc.); and
5) prevention of metabolic sequelae (insulin resistance, hyperglycaemia, fat and muscle catabolism, etc.).

Therapists were additionally asked to list (in descending priority) the reasons why they thought active exercise should be included in the acute phase of burns. Responses were grouped according to common therapeutic goals. To avoid suggestive cues, this question was asked prior to the aforementioned treatment goal importance ratings. Knowledge of burn-related metabolic pathophysiology was assessed by asking all survey participants to list short- and long-term metabolic effects occurring after burns. Entered responses were grouped according to common keywords (e.g. hypermetabolism or elevated metabolic rate or other deviations of the same term) and scored as present or absent knowledge in the following categories: ebb phase, flow phase, hypermetabolism, hyperglycaemia, insulin resistance and hypercatabolism. To ensure the validity of the responses, participants were asked not to consult additional resources as these questions assessed ad hoc (i.e. readily available) knowledge, as it is this knowledge that is mostly applicable to daily clinical practice).

The survey flow made use of a display logic method to skip or display questions based on those previously answered. Using this display logic, the number of questions posed to therapists ranged between 18 and 29, or 17 and 22 for medical doctors and dieticians. All but a small number of open questions required a response to progress. Survey structure and content were informed by a review of current evidence, including a comparable survey [41] and author expertise (UVD, DRS). Overall, it was estimated that survey completion would take participants 15–30 minutes.

To ensure that questions were correctly understood, the survey was first conducted in Belgian and Dutch burn centres with one of the authors (DRS) present during data collection. The survey was then distributed by the European Burn Association to all burn centres within the European Burn Association's email contact database (91 burn centres in 28 European countries). Burn centres had to be listed in the European Burn Association's email contact database to be eligible for survey distribution. This database comprises centres providing any form of services for inpatient burn care. Participants were eligible if they worked in burn centres at the time of survey participation; were therapists, medical doctors, dieticians or nurses involved in inpatient burn care; and treated adult burns. Participants that exclusively treated paediatric burns or only worked with outpatients were excluded from participation.

Email instructions were used to direct the survey to the respective burn clinicians within the institutions. As survey invitations were sent by the European Burn Association on the behalf of the authors of this study, it was impossible to verify how many email contacts were active, or to carry out a non-responder analysis.

Following its distribution in June 2018 and a reminder email 40 days later, the online survey remained active for 8 months. Partial responders received an automatic email reminder 1 week after an incomplete survey had been recorded, and unless completed within 30 days were otherwise excluded from analysis.

Complete responses were coded and exported to Microsoft Excel (Microsoft, USA) and, where appropriate, measures of distribution were calculated and presented as means and 95% CIs. Associations were analysed between the following variables: respondent's profession, importance ratings and knowledge of the flow phase of metabolic sequelae. Recoding of non-binary variables into binary data was carried out where low counts in some categories did not allow meaningful analysis. Accordingly, the importance ratings on the Likert scale were recoded into extremely important versus all other importance ratings. Odds ratios (ORs) were computed and associations were tested with the Fisher's exact test using SPSS Statistics Version 25 (IBM, USA). The significance level was set at $p = 0.05$.

	ROM	Resistance	Aerobic	Proprioception	Function	Respiratory
While intubated (%)[a]	95.8 (23)	41.7 (10)	37.5 (9)	25.0 (6)	50.0 (12)	83.3 (20)
OOB mobility allowed (%)[b]	96.8 (30)	87.1 (27)	64.5 (20)	41.9 (13)	90.3 (28)	45.2 (17)
Allowed to leave room (%)[c]	100.0 (30)	96.7 (29)	83.3 (25)	76.7 (23)	93.3 (28)	20.0 (6)

Table 1. Prevalence of treatment components per phase of inpatient stay. OOB, out of bed mobility; ROM, Range of motion exercises. [a]total number of responders n=24; [b]total number of responders n=31; [c]total number of responders n=30

1.5 Results

1.5.1 Characteristics

Overall, 64 burn clinicians responded to the survey, out of which 5 participants were excluded from analysis due to incomplete responses. All of the 5 excluded participants (3 medical doctors and 2 occupational therapists from the UK and The Netherlands) did not progress beyond 15% of the survey, which mostly equates with completing the demographics section. The remaining 59 clinicians (32 therapists (30 physiotherapists, 2 occupational therapists), 19 medical doctors and 8 dieticians), representing 18 out of 91 burn centres (19.8% response rate) across eight European countries (Belgium, Portugal, Slovakia, Spain, Sweden, Switzerland, The Netherlands and the United Kingdom) completed the survey and gave informed consent. The average years of professional experience in burns amongst participants was 12.3 ±9 (SD) years.

1.5.2 Exercise prescription

Exercise provision and components

All therapists stated that they used some form of active exercise (defined as any independent or assisted muscular activity involving skeletal muscle contractions) in their respective burn centre; however, only less than half of these categorically reported commencing resistance (41.7%) or aerobic exercise (37.5%) in intubated patients. The provision of resistance and aerobic exercise increased to 87.1% and 64.5% once out-of-bed mobility was possible, and to 96.7% and 83.3% once patients were able to leave their hospital room, respectively (Table 1).

The relative proportion of total treatment time that was allocated to resistance and aerobic exercise increased over the course of the hospital stay, however, this varied considerably between therapists (Table 2). The largest proportions of total treatment time across the different phases were for treatment aimed at preserving/restoring joint range of motion, with functional training making up the second-largest proportion once out-of-bed mobility was established.

Inclusion and exclusion criteria

Predefined inclusion/exclusion criteria for active exercise varied greatly among therapists and were only used by 40.6% of respondents (Figure 1). Of those 40.6%, the most common inclusion/exclusion criteria for active exercise were acute surgery (92.3%), host temperature (76.9%), cardiorespiratory stability (69.2%), breathing status (69.2%), level of cooperation (69.2%), neurological status (61.5%) and level of alertness (6.5%). Less frequently used criteria were %TBSA (30.8%), muscle strength (23.1%) and others (15.4%). Of those that reported not using any criteria, 35.7% stated that they carried out active exercise only if prescribed by a doctor.

Exercise parameters

The method used to determine exercise intensity varied considerably amongst respondents, with patient tolerance (68.8%), heart rate (12.5%), general exercise guidelines (12.5%) (without specifying employed methods) and V˙iO2 max (3.1%) being reported for aerobic exercise. Other methods (12.5%) used included the therapist's intuition, trial and error, haemodynamics and respiratory rate.

For resistive exercise, intensity was primarily based on patient tolerance (59.4%) and manual muscle testing (28.1%). The repetition maximum (12.5%), dynamometry (9.4%) and other methods (21.9%) were used less frequently by therapists, with other methods including the therapist's intuition and the functional status of the patient. Muscle groups targeted as part of the resistance exercise also varied, with the whole body, upper limbs, lower limbs, the core or the burned location being trained by 43.8%, 65.6%, 68.8%, 50% and 15.6% of therapists, respectively.

The majority of therapists (96.7%) stated that they did not work with an overall fixed-length exercise programme. Patient-dependent factors, such as goal achievement (31.3%), hospital discharge (37.5%) and burn unit discharge (6.3%), determined when exercise programmes were discontinued, or instead continued after hospital discharge in an outpatient setting (15.6%). The advice to follow an

	ROM	Resistance	Aerobic	Proprioception	Function	Respiratory
While intubated (%)[a]	48.8 (36.5-61)	6.5 (2.6-10.3)	4.8 (1.7-7.9)	2.7 (0-5.5)	8.8 (3.9-13.6)	26.9 (18.9-34.9)
OOB mobility allowed (%)[b]	33.1 (25.9-40.2)	16.5 (12.8-20.1)	11.5 (7.7-15.2)	4.4 (2.1-6.6)	26 (18.4-33.6)	7.4 (3.8-11)
Allowed to leave room (%)[c]	28.8 (23.2-34.4)	21.0 (17.4-24.6)	16.8 (13.2-20.4)	8.2 (5.7-10.6)	22.6 (17.7-27.5)	2.7 (0.1-5.2)

Table 2. Percentage of total treatment duration per treatment component per phase of inpatient stay. OOB, out of bed mobility; ROM, Range of motion exercises. Data presented as mean (95%CI). [a]total number of responders n=24; [b]total number of responders n=31; [c]total number of responders n=30

exercise programme after hospital discharge was given by most therapists either categorically (62.5%) or depending on the patient (34.4%).

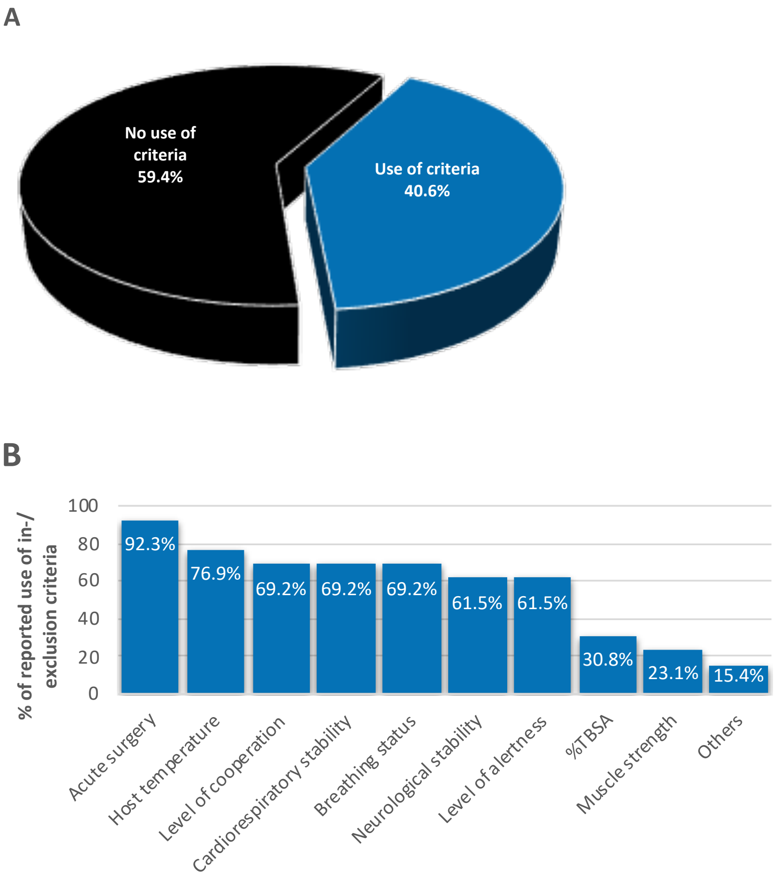

Figure 1. Predefined in-/exclusion criteria for active exercise. A: Reported use; B: Frequency of reported in-/exclusion criteria given by those that reported use. TBSA, total body surface area

Influence of metabolic sequelae

The post-burn development of hyperglycaemia, insulin resistance or a hypermetabolic state did not change the majority (87.5%) of therapists' exercise prescription. The main reasons given by therapists for this were: (1) a lack of understanding of the metabolic sequelae (50%); (2) it is not their responsibility (21.9%); and (3) a lack of understanding the effects of exercise on these parameters (15.6%).

1.5.3 Metabolic management

The use of outcome measures to assess energy expenditure, muscle wasting, insulin sensitivity and muscle force is summarized in Table 3. Table 4 gives an overview of the reported intervention strategies for the burn-induced development of hypermetabolism, muscle wasting and insulin resistance. For additional data presented per profession the reader is referred to Table S2 and Table S3 in the supplementary material.

Energy expenditure

The use of predictive formulas to estimate energy expenditure in burn patients was more common (88.9%) than the use of indirect calorimetry (40.7%). Of those that used indirect calorimetry, all did so via amechanical ventilator, with only one respondent reporting

Outcome	Methods	% (frequency)	Applied frequency	% (frequency)
Energy Expenditure *Respondents:* Medical doctors & dieticians (n=27)	Indirect calorimetry (IC)	40.7 (11)	Daily	3.7 (1)
	- Via mechanical ventilator	40.7 (11)	Weekly	25.9 (7)
	- Spontaneous breathing	3.7 (1)	Biweekly	0 (0)
	Criteria indicating use of IC:		Only when indicated	11.1 (3)
	- Mechanical ventilation	40.7 (11)		
	- %TBSA	14.8 (4)		
	- Unexplained weight loss	11.1 (3)		
	- Other metabolic issue	3.7 (1)		
	Prediction formulas	88.9 (24)	Daily	25.9 (7)
	- Toronto	37 (10)	Weekly	33.3 (9)
	- Fixed kcal/kg	18.5 (5)	Biweekly	7.4 (2)
	- Harris Benedict	14.8 (4)	Only when indicated	22.2 (6)
	- Curreri	14.8 (4)		
	- Others[a]	14.8 (4)		
Muscle wasting *Respondents:* Medical doctors & dieticians & therapists (n=59)	Not measured	84.7 (50)	Daily	0 (0)
	Body weight monitoring	11.9 (7)	Weekly	11.9 (7)
	Eye judgement of muscle volume	5.1 (3)	Biweekly	0 (0)
	Muscle force assessment	3.4 (2)	Only when indicated	3.4 (2)
	Muscle circumference	1.7 (1)		
	Nitrogen Balance	1.7 (1)		
	Bio impedance Analysis	1.7 (1)		
Insulin Sensitivity *Respondents:* Medical doctors & dieticians (n=27)	Not measured	92.6 (25)	Daily	0 (0)
	HOMA-IR	3.7 (1)	Weekly	3.7 (1)
	ISI	3.7 (1)	Biweekly	0 (0)
			Only when indicated	3.7 (1)
Muscle force *Respondents:* Therapists (n=32)	Not measured	40.6 (13)	Daily	3.1 (1)
	Manual muscle testing	46.9 (15)	Weekly	28.1 (9)
	Handheld dynamometry	31.3 (10)	Biweekly	9.4 (3)
	Indirectly through functional tests	25 (8)	Only when indicated	18.8 (6)
	Isokinetic Dynamometry	3.1 (1)		

Table 3. Outcome measures. HOMA-IR, homeostasis model assessment of insulin resistance; ISI, Insulin Sensitivity Index. [a]Including Henry's, Milner, Garland, Xi

methods during spontaneous breathing independent of a mechanical ventilator. Energy expenditure determination was mostly reported to be carried out on a weekly basis or only when indicated. The most common indication criteria for indirect calorimetry were mechanical ventilation, %TBSA and unexplained weight loss. The classical Toronto formula was most often used (37%) to estimate energy requirements. Less frequently mentioned formulas were fixed kcal/kg (18.5%), Harris–Benedict (14.8%) and Curreri (14.8%).

Therapeutic target	Intervention	% (frequency)
Hypermetabolism[a]	No strategy	40.7 (11)
Respondents:	Modify nutrition[b]	59.3 (16)
Medical doctors &	Betablockers	44.4 (12)
dieticians (n=27)	Early coverage / grafting	40.7 (11)
	Anabolic steroids	37 (10)
	Glycaemic control	29.6 (8)
	Early excision	25.9 (7)
	Adapt ambient temperature	22.2 (6)
	Exercise	11.1 (3)
	Infection control	11.1 (3)
	Others[c]	18.5 (5)
Muscle wasting	No strategy	29.6 (8)
Respondents:	Exercise	66.7 (18)
Medical doctors &	Modify nutrition	55.6 (15)
dieticians &	Anabolic steroids	14.8 (4)
therapists (n=59)	Betablockers	7.4 (2)
	Limit duration / depth of sedation	7.4 (2)
	Others[d]	11.1 (3)
Insulin Sensitivity	No strategy	55.6 (15)
Respondents:	Insulin infusion	48.1 (13)
Medical doctors &	Moderate glycaemic control	25.9 (7)
dieticians (n=27)	Tight glycaemic control	22.2 (6)
	Hypoglycaemic diet	7.4 (2)
	Avoid overfeeding	7.4 (2)
	Anabolic steroids	7.4 (2)
	Early excision	7.4 (2)
	Exercise	7.4 (2)
	Others[e]	18.5 (5)

Table 4. Metabolic interventions. [a]Defined as >10% predicted resting energy expenditure; [b]including increasing and decreasing caloric provision, supplementing nutrition content (protein, trace elements, vitamins) early enteral feeding; [c]including fenofibrates, growth hormones, early resuscitation, limiting sedation, anxiety reduction; [d]including fenofibrates, avoiding neuromuscular blockers, early excision, early coverage; [e]including Gliclazide, Metformin, betablockers, fenofibrates, early coverage

Employed strategies to manage the hypermetabolic response after burns varied widely, with 40.7% reporting no strategy whatsoever. The most common strategies were nutritional strategies (59.3%), betablockers (44.4%), early coverage and grafting (40.7%) and anabolic steroids (37%). Less frequently reported interventions included exercise (11.1%) and infection control (11.1%).

Muscle wasting

Few clinicians reported the assessment of muscle wasting (15.3%). Of the methods used, indirect methods, such as body-weight monitoring (11.9%), eye judgement of muscle volume (5.1%) or muscle force measurement (3.4%), were most commonly mentioned. Only one clinician reported the use of bioimpedance analysis, nitrogen balance or muscle circumference measurements. Muscle force, in contrast, was assessed more commonly, with 59.4% of therapists reporting its use. Manual muscle testing using the common Medical Research Council scale of 0–5 points was used most frequently (46.9%) together with handheld dynamometry (31.3%) and indirect measures through functional tests (25%). In contrast, isokinetic dynamometry was carried out less frequently (3.1%). Interventions to manage muscle wasting were reported by 70.4% of clinicians. These included exercise (66.7%) and nutritional adaptation (55.6%) as primary strategies, whereas the administration of anabolic steroids (14.8%) or betablockers (7.4%) were less frequently reported.

Insulin sensitivity

Measurement of insulin sensitivity in burn patients was not widespread, with only two medical doctors reporting its use. The insulin indices calculated were the homeostasis model assessment of insulin resistance (HOMA-IR) and the insulin sensitivity index (ISI). Insulin sensitivity was reported as a therapeutic target by 44.4% of respondents. A large variation in intervention strategies to manage the development of insulin resistance was noted. The main strategy of choice consisted of the infusion of insulin (48.1%), with glycaemic targets split between moderate or tight glycaemic control at 25.9% and 22.2%, respectively. Among the less-frequently-stated interventions were exercise, a hypoglycaemic diet, and the avoidance of overfeeding (each 7.4%).

1.5.4 Priorities, motivation, and knowledge

Treatment priorities

Responses showed interdisciplinary variations in the rating of importance (Figure 2). Most notable variations were seen in ratings of the restoration of functional status and the prevention of metabolic sequelae, with the former receiving the highest importance scores amongst medical doctors and therapists, yet the lowest importance scores by dieticians. Similarly, the latter group gave the highest importance to the prevention of metabolic sequelae, while medical doctors and therapists rated it as being of lowest importance

(Figure 2). Dieticians were nearly 18 times more likely than therapists to rate the prevention of metabolic sequelae as extremely important (OR, 17.89; 95%CI, 1.92–166.78; p<0.01) (Table S4).

Rationale for active exercise

A similar sequence of priorities was found when therapists were asked to list reasons (in descending priority) why they thought active exercise should be included in the acute phase of burns. The given reasons and their assigned priority varied considerably among therapists, with the restoration of functional status (78.1% of respondents) and preservation of joint range of motion (53.1%) being the most frequently mentioned. Psychological and motivational effects (34.4%), cardiovascular fitness (34.4%), muscle strength (31.1%) and the restoration of muscle mass (28.1%) were listed as reasons for active exercise less often. Besides the restoration of muscle mass, no mention was made of other potential metabolic effects of exercise, such as glycaemic control.

Knowledge of burn-induced metabolic effects

When asked to list the short- and long-term metabolic effects of major burns, few burn clinicians were able to correctly identify the ebb phase (11.9%) or any components of the flow phase (40.7%), including the potential development of hypermetabolism (27.1%), hyperglycaemia (18.6%), insulin resistance (8.5%) and hypercatabolism (37.3%). When divided into subgroups according to discipline, therapists demonstrated the least knowledge of metabolic sequelae, with none able to identify the ebb phase, and only 4 respondents (12.5%) correctly stating at least one component of the flow phase (Figure 3). Medical doctors were 12 times more likely than therapists to be able to identify at least one component of the flow phase (OR, 12.00; 95% CI, 2.95–48.78; p<0.01) (Table S4). While more medical doctors and dieticians correctly identified postburn metabolic sequelae, a significant number nonetheless were unable to do so, with the majority of respondents (12 medical doctors, 84.2%, 6 dieticians, 75%) not listing the potential development of insulin resistance as a metabolic sequela. Overall, being able to identify at least one component of the flow phase quadrupled the odds of assigning the highest importance rating to the prevention of metabolic sequelae (OR 4.63; 95%CI 1.50-14.25; p<0.01) (Table S4).

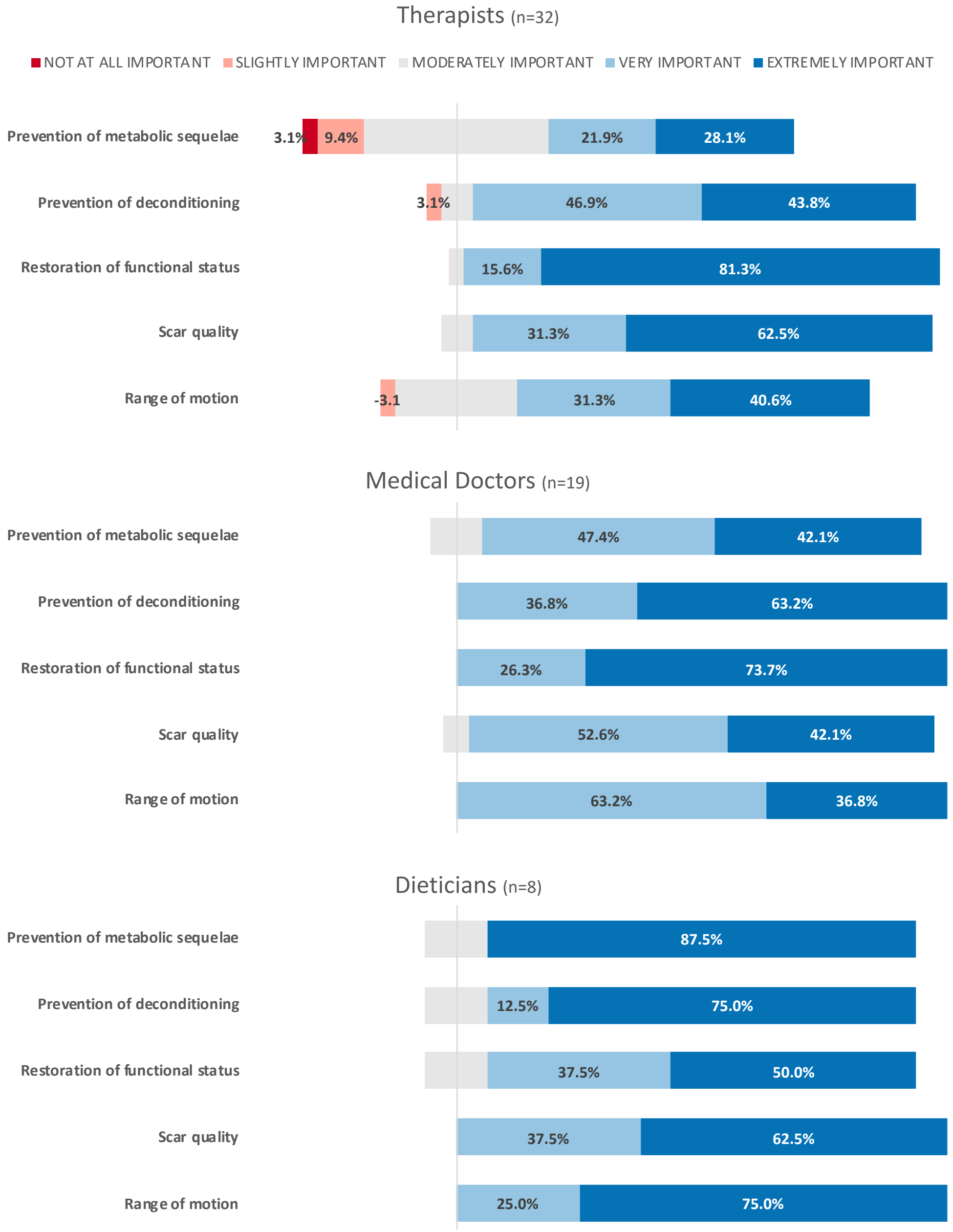

Figure 2. Importance ratings of treatment goals per profession.

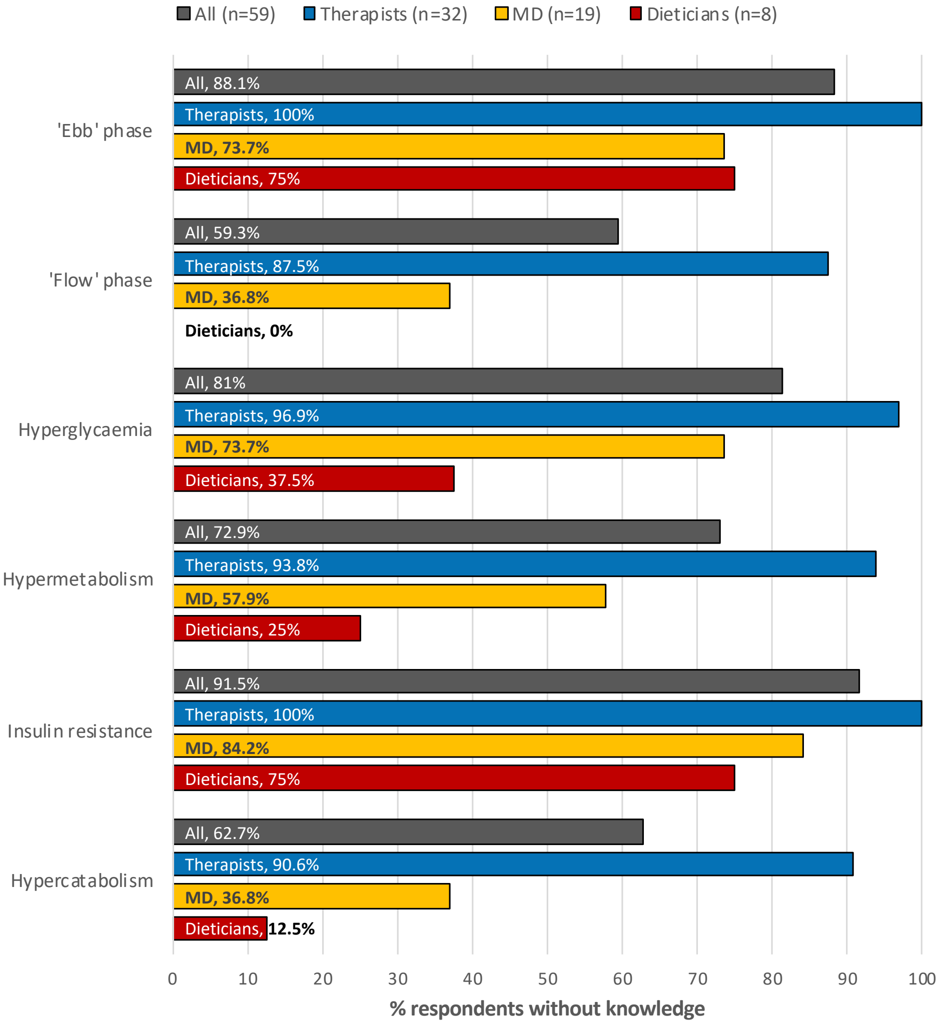

Figure 3. Percentage of respondents unable to correctly identify respective metabolic sequelae of burns. MD, medical doctors

1.6 Discussion

This study surveyed burn clinicians across European burn centres to examine current inpatient management of adults with moderate to severe burns with respect to metabolic outcomes, exercise prescription, treatment priorities and knowledge of burn-induced metabolic sequelae. The survey revealed considerable non-uniformity in multiple aspects of current rehabilitation practice. Our main findings indicate that resistance and aerobic exercise in particular are not invariably administered, and that burn-induced metabolic sequelae appear to be neglected as both assessment and therapeutic targets in the inpatient management of adults with moderate to severe burns across Europe.

1.6.1 Exercise prescription

Our data demonstrates that exercise is administered by all surveyed therapists at some stage of inpatient recovery. However, large variability was present between therapists in the timing of exercise initiation, the use of inclusion/exclusion criteria for exercise and exercise parameters. The majority of therapists stated that they did not categorically provide resistance or aerobic exercise to patients while intubated, and, for some, this remained in effect until patients were allowed to leave their hospital rooms. It is during the early phase of recovery that burn-induced metabolic derangements and prolonged inactivity are most prominent and combine to cause unwanted effects such as muscle wasting and glucose intolerance [2, 4, 5, 38]. Maximum exercise stimuli during this early phase, in particular through resistance and aerobic exercise, would seem most intuitive to lessen the negative sequelae of the metabolic imbalance [22, 42]. However, our data indicates that early exercise in European burn care does not categorically include resistive and aerobic components, both of which appear secondary to range-of-motion or functional exercise components.

Few other studies have surveyed inpatient rehabilitation in burns [34–36, 41, 43–46], of which two reports investigated the use of resistance and aerobic exercise in the acute phase of both adult and paediatric burns [35, 36]. Cambiaso-Daniels et al. reported that resistance and aerobic exercise was offered to all patients (mixed adult and paediatric burns) admitted to ICUs of six major American burn centres [35]. Our results differ from theirs in that not all our respondents stated using both resistance and aerobic exercises across all phases of inpatient stay. Instead, we were able to show a progression in resistance and aerobic exercise provision depending on the stage of recovery (Table 1). Such a progression is in agreement with the findings of another recent report by Flores et al., which provides an excellent overview of exercise use throughout the entire recovery continuum worldwide and reports the pooled results of both adult and paediatric burns [36]. Their reported results show an increased provision of resistance and aerobic exercise after ICU discharge, with the majority of respondents using resistive (79.3%) and aerobic (71%) exercise components in the later recovery stage after wound closing. Such an observed progression is likely a reflection of the limited capacity of these patients to engage in active exercise, which generally improves over time throughout their stay in the burn centre. Although patient participation is an important factor to consider [25] and active exercise might be relatively time-intensive, early exercise provision remains critical and should neither be delayed nor compromised on [25, 28].

Traditionally, inpatient burn rehabilitation has focused on the skin, return to function and joint mobility, with guidelines for both adult and paediatric burns primarily concerned with positioning, splinting and scar management [21, 47, 48]. Only recently have guidelines concerning adult and paediatric rehabilitation included advice regarding inpatient exercise [20, 22, 25, 49, 50], albeit largely without concrete recommendations as to specific exercise parameters, such as exercise components or starting criteria. The lack of reported use of resistance and aerobic exercise therefore likely mirrors the equivalent lack of international, national and/or institutional exercise guidelines for severely burned patients in the acute phase. A survey conducted among burn clinicians treating patients of all ages across the US, Canada, Australia and New Zealand indeed showed that not all have guidelines to follow for their inpatient treatment [44]. While our survey did not assess the use of guidelines, a similar situation across European burn centres might hamper consistent exercise provision.

The majority of respondents of our survey stated not using any inclusion/exclusion criteria for active exercise. In addition, the choice of criteria differed greatly between clinicians, which is in agreement with the findings of a previous report investigating both adult and paediatric rehabilitation practices [36]. These observations might explain why more active exercise is not currently carried out at an earlier time point throughout patient recovery. Using clearly defined criteria to determine when and in whom exercise can be safely carried out is paramount to encouraging early targeted exercise provision [49]. Recommendations for safety criteria for commencing exercise in critically ill adults have been published in the intensive care literature [51, 52]. Such recommendations are needed for the burn population and should include the formulation of clearly defined inclusion and exclusion criteria.

Another component of exercise prescription that still requires consensus recommendations is the methods to determine the intensity of aerobic and resistance exercise. Our data shows that methods varied considerably between clinicians, with the vast majority using subjective methods, such as patient tolerance, to determine the intensity. This observation is paralleled by two previous surveys of both adult and paediatric rehabilitation practices [35, 36] and highlights the discordance between research and clinical practice in the use of objective methods for the determination and progression of exercise intensity.

Evidence for the effects of early exercise approaches in adults, including resistive and aerobic components, has been firmly established in other critical illnesses, with favourable effects on a multitude of outcomes, such as muscle strength, duration of mechanical ventilation, ICU length of stay, hospital length of stay, and hospital mortality [28, 29, 53]. This is in stark contrast to the burn population, in which, to the best of our knowledge, only one trial has assessed the effect of early mobilization techniques in adult burn ICUs prospectively [54]; two retrospective trials have been reported [55, 56]. Positive outcomes reported include reductions in ICU length of stay, hospital length of stay improvements in joint range of motion and fewer complications and contractures [54–56]. Despite solid evidence from the intensive care literature and preliminary evidence in the burn population, our results indicate that the practice of early exercise is not consistently implemented in the current acute care of burn survivors in Europe.

1.6.2 Metabolic management

Burn patients undergo unparalleled surges in metabolic rate, protein catabolism and levels of insulin and fasting glucose. These metabolic changes have been shown to persist long after the initial trauma and produce impactful sequelae, such as loss of lean mass and insulin sensitivity, placing the burn survivor at an increased risk of long-term morbidity [7, 9, 11, 57].

Strategies to modulate the metabolic response and its sequelae during the acute phase of burns are thus invaluable to full recovery and rehabilitation [2]. The results of this study show large heterogeneity among surveyed burn clinicians in the use and choice of interventions used to manage the development of hypermetabolism, muscle wasting and insulin resistance (Table 4). A considerable number of respondents reported no specific strategy at all. Moreover, while exercise therapy was the main strategy of choice to counteract muscle wasting, very few opted for exercise as a strategy to manage insulin resistance or the hypermetabolic response.

Exercise-based interventions have been shown to mitigate muscle wasting and insulin resistance, as evidenced in healthy adults and patients with diabetes, as well as the critically ill [29, 32, 33, 58–60]. In burns, the potential of exercise to induce positive effects on energy expenditure, muscle mass and insulin sensitivity has also been investigated, albeit largely in the post-discharge phase and predominantly in paediatric patients [16, 18, 20, 23, 24, 61]. However, the use of exercise for these purposes in adults as part of inpatient care continues to be a largely unexplored, yet promising, area of future research [62]. Our data shows that metabolic outcomes are not consistently used as therapeutic exercise targets and that more guidance is needed to reach consensus about the role exercise can play in the metabolic management of burn patients.

The monitoring of metabolic outcomes provides invaluable information as to the effects of interventions and patient recovery. However, the results of this survey show that the assessment of energy expenditure, muscle wasting, muscle strength and insulin sensitivity was not widespread among respondents, and large variability was observed in employed methods of assessment (Table 3). Nutritional guidelines for major burns recommend the use of indirect calorimetry to match caloric provision with caloric requirements in all age groups [63]. However, energy expenditure was not measured by the majority of responding clinicians, but rather predicted via equations, paralleling the findings of a previous European survey in regard to the nutritional management of adult burn patients [19].

Similarly, the vast majority of respondents reported not measuring insulin sensitivity or muscle wasting, indicating that clinicians either lacked available tools of assessment or perceived the assessment of metabolic outcomes as less important. Dual X-ray absorptiometry, computed tomography and magnetic resonance imaging, histological analysis of muscle specimens, stable isotope infusions and the urea-to-creatinine ratio are excellent methods most commonly used in research to determine the degree of muscle wasting in critically ill adults and children [64–68]. The invasive or cost- and time-intensive nature of many of these methods, however, likely hinders their implementation into clinical practice. Other novel and promising methods that have been developed for the use in the ICU setting are bioelectrical impedance and musculoskeletal ultrasound [69–71]. Both are practical, non-invasive, bedside tools that have shown to be valid and related to a variety of clinical outcomes, such as mortality and morbidity in critically ill adults [72–80]. Their usefulness in assessing muscle parameters in burn patients has yet to be evaluated.

Likewise, the assessment of insulin sensitivity is clinically relevant, as persisting insulin resistance poses a significant challenge to the long-term health of survivors [7, 38, 81]. In the absence of hyperinsulinaemic euglycaemic clamp or oral glucose tolerance testing, valuable estimates of insulin resistance can be derived via simple indices, such as the homeostatic model assessment [82].

Consensus has yet to be established as to whether insulin sensitivity, as well as muscle wasting and energy expenditure, should be routinely measured as part of standard care, or whether certain criteria should indicate its use.

1.6.3 Priorities, motivation, and knowledge

Clinical decision making involves weighing competing priorities according to perceived importance of treatment goals. Successful burn rehabilitation also includes tailoring therapy to the individual needs of the patient [22]. While this may, at times, require therapy provision to focus more on one treatment goal, it should not lead to a systematic neglect of another.

Our results indicate that the therapist's primary efforts are directed at the preservation of range of motion and restoration of functional status, and not burn-induced metabolic sequelae, including hypermetabolism, hypercatabolism and insulin resistance. It is then not surprising that resistance and aerobic exercise were not invariably administered at the early stages by the respondents of this survey. The reason why burn therapists perceive burn-induced metabolic sequelae as less important remains unclear. It is striking, however, that this observation was paralleled by a substantial lack of understanding of metabolic sequelae among all clinicians. While there are no standards as to the "right" priorities and time allocation of treatment components, it seems concerning that a limited insight into metabolic sequelae after burns may have contributed to a lower assigned priority. Therapists in particular, as the primary provider of exercise [44], need to be able to engage in informed clinical decision making based on the perceived importance of treatment goals—a rather uninformed understanding of the metabolic sequelae and their impact on the burn survivor would certainly contribute to an inadequate management of them.

The ability to describe the physiological responses to increased activity, as well as the knowledge of indications and rationale for aerobic and resistance exercise are both described as core competencies in the burn rehabilitation therapist competency tool by the American Burn Rehabilitation Committee, concerning the treatment of all age groups [83]. In Europe, such knowledge core competencies are missing, and the results of this survey indicate that the adherence to such competencies would be challenging [25]. Qualitative research in the adult ICU setting has identified the expectations and knowledge (including rationale for rehabilitation, perceived benefits and experience) of clinicians as being a primary barrier to implementation of early exercise rehabilitation [84]. In a survey of Chinese burn centres for both adult and paediatric burns, Chen et al. likewise identified insufficient knowledge of burn clinicians as a primary factor impeding early rehabilitation practice in China [45]. Our findings indicate that such a knowledge barrier may indeed have played a role in the survey responses for two reasons. First, we found a significant positive association between the understanding of metabolic sequelae and their importance ratings. Secondly, exercise prescription remained unchanged in the face of post-burn metabolic sequelae due to a reported lack of understanding of metabolic sequelae and the effects of exercise on these parameters.

Therapists are classically trained in the musculoskeletal domain, whereas metabolic and internal disorders generally lie within the field of expertise of medical doctors and dieticians. Such a division, however, appears problematic as exercise therapy does play an important role in the management of burn-induced metabolic sequelae. Issues such as increased muscle catabolism and glucose intolerance present particularly promising therapeutic targets that ought not to be neglected during the acute phase of critical illness [15, 22, 33]. It needs to be emphasized that successful early exercise rehabilitation involves the entire multidisciplinary team [25, 84, 85]. The results of this survey show substantial interdisciplinary variations in both the understanding and importance of metabolic sequelae. To align treatment priorities across disciplines, a concomitant aligning of the understanding of metabolic sequelae becomes imperative.

This is the first study to survey burn clinicians with respect to inpatient rehabilitation exclusively for adult burns. Previous surveys have pooled responses for the rehabilitation of paediatric and adult patients, or had a different scope (post-grafting mobility, post-discharge rehabilitation [34–36, 41, 43–46]). According to our best knowledge, the present survey also forms the first of its kind to investigate burn rehabilitation with a focus on metabolic outcomes and the knowledge and priorities of clinicians. As such, it points to the necessity of education, or re-education, within the field of burn-induced metabolic sequelae for burn clinicians (therapists in particular) and draws out particular areas in need of attention for future practice guidelines.

1.6.4 Limitations

Several limitations can be identified in our study. One major shortcoming of this survey is its limited reach to only European countries, as well as burn clinicians not reached due to inactive or absent email addresses. This may have introduced potential nonresponse bias. Despite sending a reminder email, the response rate primarily relied on the initial recipient forwarding the email to the respective burn clinicians. As it is unclear how many overall eligible burn clinicians were active in European burn centres at the time of data collection, we were unable to determine the external validity of our sample. The results of this survey may therefore not adequately represent the entire European context, instead only providing a snapshot of selected countries and responding participants. The overall response rate may nonetheless be underestimated as it is uncertain how many of the email contacts were active at the point of distribution.

A second major shortcoming is that multiple surveys from the same burn profession at the same burn centres were allowed. While this slightly inflated the burn-centre-to-survey ratio, we opted for this strategy as we anticipated differing responses within the same discipline. Our primary interest was to investigate variability of current practice between burn clinicians, as opposed to between-centre variability.

Third, while we show that metabolic sequelae were neither widely understood nor commonly considered as therapeutic exercise targets by the majority of surveyed burn clinicians, this study was not designed to test a cause–effect relationship between the clinician's understanding and specific choices of treatment. Nonetheless, qualitative research into barriers of early exercise in the wider critically ill population points to the clinician's knowledge as a major barrier to implementation [84]. Whether this observation also holds true in the burn population remains to be confirmed.

Last, it is possible that differences in the responses given by burn clinicians might not fully represent true variability between respondents, but rather be attributed to differences in admission rate or burn centre size. We were unable to control for the number of admissions or size of the burn facilities, as the developers of the survey purposefully chose not to ask for this information. This decision was made in the hope of a higher response rate by minimizing the risk that respondents would abandon survey completion due to being unable to answer these early questions without consulting other administrative staff.

1.7 Conclusion

Burn-induced metabolic sequelae are important rehabilitation targets in the successful management of burns. Although early exercise rehabilitation has the potential to significantly alter the trajectory of metabolic sequelae of burn survivors, the results of this survey demonstrate that considerable nonuniformity exists around its provision across European burn care. This survey reveals a potential neglect of burn-induced metabolic sequelae as therapeutic and assessment targets, which might be grounded in a limited understanding of metabolic pathophysiology. Overall, our results reflect the paucity of scientific research into the effects of early exercise on metabolic outcomes in the adult burn population, and point to the need for well-designed trials to pave the way for more conformity in the acute care of burn survivors. Future direction and guidance should focus on: (1) further defining the role of metabolic outcomes as rehabilitation targets; (2) establishing core competencies for rehabilitation staff in Europe, including the rationale for resistance and aerobic exercise; and (3) further investigating barriers and enablers to implementing successful early rehabilitation of burn survivors.

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1.9 Availability of data and materials

All data generated or analysed during the current study is included in this manuscript.

1.10 Acknowledgements

We greatly appreciate the time that all our European colleagues have taken to respond to the survey.

1.11 Authors' contribution

All authors made substantial contributions to the article. DRS, UVD and EVB were involved in the conception, design, data analysis, interpretation, drafting and revising of the manuscript. DRS carried out the data acquisition under supervision of UVD and EVB.NG and JM were involved in the analysis and interpretation of data, drafting and revising of the manuscript on the basis of their critical expertise in the topic. All authors gave final approval of the version to be published.

1.12 Ethics approval and consent to participate

Ethical approval was granted by the Institutional Review Board of the Ziekenhuis Netwerk Antwerpen/OCMW (E.C.Approval No. 5018, 9 May 2018). All respondents of this survey provided informed consent prior to participation.

1.13 Consent for publication

Not applicable.

1.14 Conflict of interest

The authors have no competing interests to declare.

1.15 Supplementary material

See appendix at the end of this dissertation.

1.16 References

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Part 2 Assessment of muscle wasting

Chapter 2. Reliability and feasibility of skeletal muscle ultrasound in the acute burn setting

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2.1 Abstract

Objectives: Despite the impact of muscle wasting after burn, tools to quantify muscle wasting are lacking. This multi-centre study examined the utility of ultrasound to measure muscle size in acute burn patients comparing different methodologies.

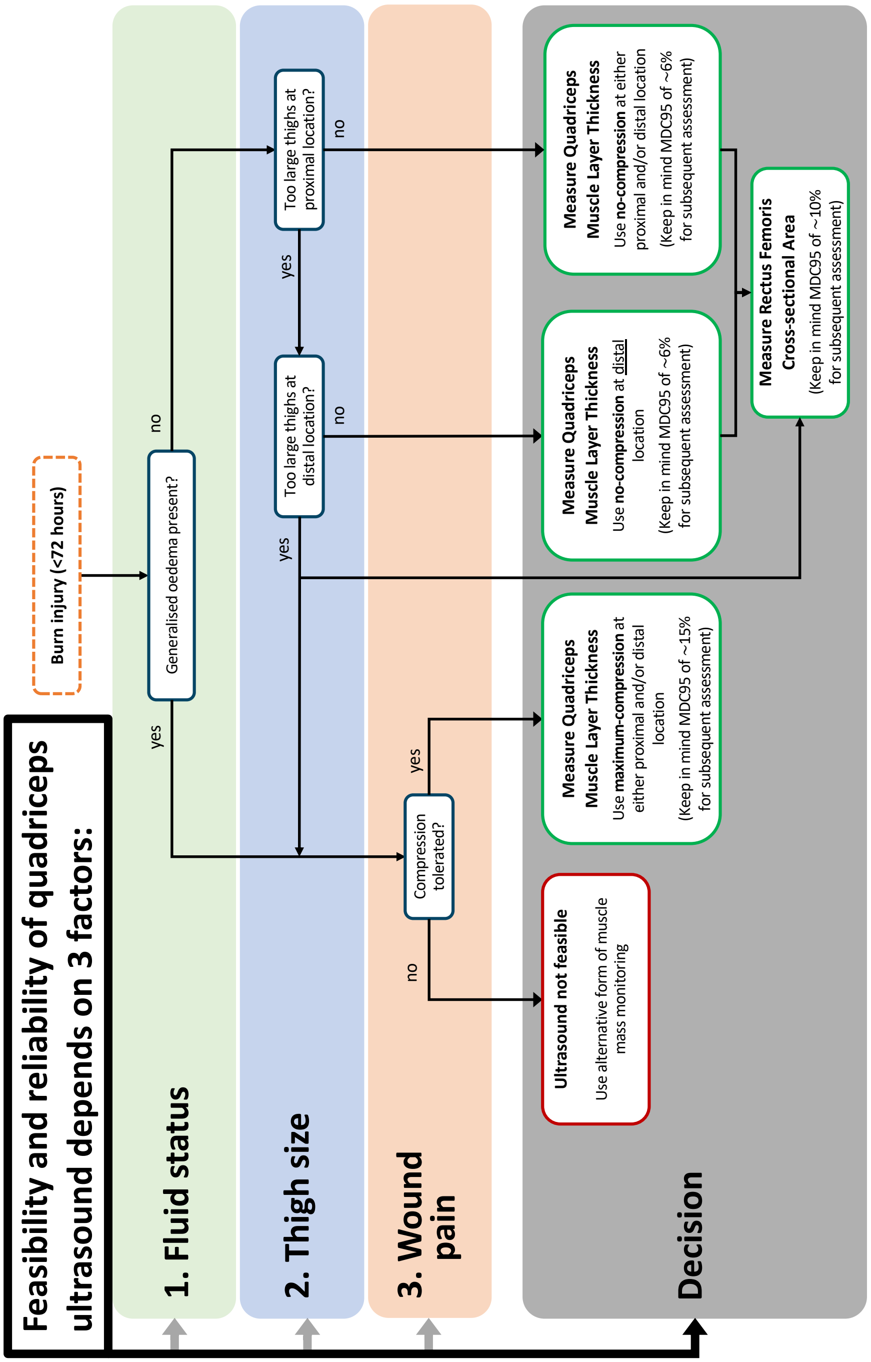
Methods: B-mode ultrasound was used by two raters to determine feasibility and inter-rater reliability in twenty burned adults following admission. Quadriceps muscle layer thickness (QMLT) and rectus femoris cross-sectional area (RF-CSA) were measured, comparing the use of i) a single versus average measurements, ii) a proximal versus distal location for QMLT, and iii) a maximum- versus no-compression technique for QMLT.

Results: Analysis of twenty burned adults (50 years [95%CI 42–57], 32%TBSA [95%CI 23–40]) yielded ICCs of > 0.97 for QMLT (for either location and compression technique) and > 0.95 for RF-CSA, using average measurements. Relative minimal detectable changes were smaller using no-compression than maximum-compression (6.5% vs. 15%). Using no-compression to measure QMLT was deemed feasible for both proximal and distal locations (94% and 96% of attempted measurements). In 9.5% of cases maximum-compression was not feasible. 95% of RF-CSA measurements were successfully completed.

Conclusion: Ultrasound provides feasible and reliable values of quadriceps muscle architecture that can be adapted to clinical scenarios commonly encountered in acute burn settings.

Keywords: Burns; Ultrasonography; Muscle wasting; Muscular Atrophy; Cachexia; Hypermetabolism

2.2 Graphical Abstract



2.3 Introduction

Ultrasound is widely used to measure changes in musculature in various disease populations, however, not in burn patients [1]. This is noteworthy since the persistent loss of muscle mass following burns is a well-documented metabolic phenomenon with tremendous potential to impact short and long-term health [2–7]. Burn injury is characterised by a sustained hypermetabolic response (i.e. elevated energy expenditure) which induces significant muscle wasting [8]. In the presence of burn trauma, muscle mass is thought to act as a gradually depleting functional reserve pool providing fuel for vital processes involved in the immune response and wound healing [8–10]. Prolonged periods of inactivity and the administration of corticosteroids, neuromuscular blockers, sedatives, and inadequate nutrition further exacerbate skeletal muscle wasting [11–14]. The resulting loss of muscle mass negatively impacts recovery by, among others, delaying wound healing, increasing infection rates, and prolonging time on mechanical ventilation [15–17]. These clinical complications create a chain reaction wherein rehabilitation is delayed and ICU and hospital length of stay is protracted, ultimately leading to higher in-hospital morbidity, mortality, and health care expenses [17,18]. Beyond these short-term outcomes, muscle wasting is also a likely key aetiological factor in the observed increased risk of burn survivors to develop long-term metabolic, cardiovascular, and musculoskeletal disorders [19–28].

Preserving muscle mass is recommended as a therapeutic goal in burn care [29,30]. However, muscle wasting is not generally measured in burn centres [1], likely due to the lack of practical and accurate tools capable of monitoring muscle mass at the bedside. In the absence of such tools, the assessment of muscle mass has commonly been substituted with the assessment of muscle function [1]. However, as muscle plays a pivotal role in the metabolic response to burns it should also be measured independently of its musculoskeletal function [31]. Moreover, the assessment of muscle function, by e.g. force measurements, is often not possible in the acute care setting where sedation and pain may limit patient cooperation.

Muscle ultrasound has been used in the wider critically-ill population as a practical and affordable surrogate measure of whole-body muscle mass at the bedside [32,33]. Its benefits comprise its low costs, the absence of radiation exposure, and its availability as a standard equipment in most burn intensive care units [34]. Particularly, when measured at the level of the quadriceps muscle, it has shown to provide reliable and valid information on the evolution of muscle architecture [35–44]. Whether this can be extrapolated to the burn-injured patient currently remains unknown. Open wounds, varying fluid status, and the limited time window during which dressings are removed are amongst factors that pose significant challenges to the use of ultrasound in this patient population. Its use is further complicated by the presence of multiple methodologies used to obtain ultrasound-derived parameters of the quadriceps muscle [45]. The location of the measurement, the amount of tissue compression, and whether to use an average or a single measurement remain unanswered questions.

Therefore, the present study was initiated to examine the reliability and feasibility of quadriceps muscle ultrasound measures in the acute burn setting. As such, it will lay the groundwork to determine if and how muscle ultrasound could help clinicians and researchers to better identify, treat and monitor burn patients with altered muscle mass.

2.4 Material and methods

This multi-centre cross-sectional reliability and feasibility study was approved by the institutional review board of the Ziekenhuis Netwerken Antwerpen (5018) and the Universitair Ziekenhuis Antwerpen on (B300201942189).

2.4.1 Study population

Twenty adults with burns were recruited between May 2020 and April 2021 upon admission to two Belgian burn centres (ZNA Stuivenberg & Military Hospital Queen Astrid), as part of a larger intervention trial investigating the effects of exercise during the acute phase of burns. Burn subjects were eligible if they met the eligibility criteria as listed in table 1. In addition, this study included twenty healthy adults control subjects to assess how much variability in reliability and feasibility originate from the ultrasound protocol itself versus the subjects in whom it is applied. The healthy subjects were recruited through convenience sampling and assessed in our metabolic research lab (M2RUN) at the University of Antwerp prior to assessing the burn cohort. Assuming a minimum ICC value of 0.75 for interobserver reliability, with alpha 0.05 and 80% power, we estimated a priori that we would need to enrol at least eighteen subjects. Hence, we enrolled twenty subjects to ensure sufficient power. All recruited subjects or their next-of-kin gave informed consent prior to ultrasound assessment.

Inclusion criteria	Exclusion criteria
Age ≥18 years	Electrical burns
%TBSA ≥10% (with the presence of at least deep second-degree burns)	Associated injury (e.g. lower limb fracture) (interfering with ability to exercise)
Burn centre admission ≤72 hours	Central neurological, peripheral neuromuscular disorders
	Psychological disorders interfering with cooperation
	Diabetes Mellitus type 1
	Pregnancy
	Palliative care

Table 1. Eligibility criteria. TBSA, Total body surface area

2.4.2 Measurement protocol

Two trained assessors (D.R.S. and D.D.) carried out measurements using B-mode ultrasound with a multifrequency linear transducer of either the SonoSite X-porte (FUJIFILM SonoSite, Brussels, Belgium) or the LOGIC V2 and VIVID S5 (GE Healthcare, Machelen, Belgium). Measurements were performed consecutively and in randomised order (random number sequencing generated using Microsoft Excel). Assessors were blinded from each other's measurements. Burn subjects were assessed within 72 hours of burn centre admission by the two assessors to provide feasibility and reliability data at baseline. To provide additional data for feasibility of ultrasound over the course of burn centre stay, one assessor (D.R.S.) carried out up to three follow-up measurements in burn subjects dependent on the burn centre length of stay.

A protocol for the assessment of quadriceps muscle size based on previous work [37,46–48] was adapted to acute burn patients with the help of experts in the field of musculoskeletal ultrasound imaging. Ultrasound-derived muscle parameters were quadriceps muscle layer thickness (QMLT) and rectus femoris cross-sectional area (RF-CSA) as shown in Figure 1.

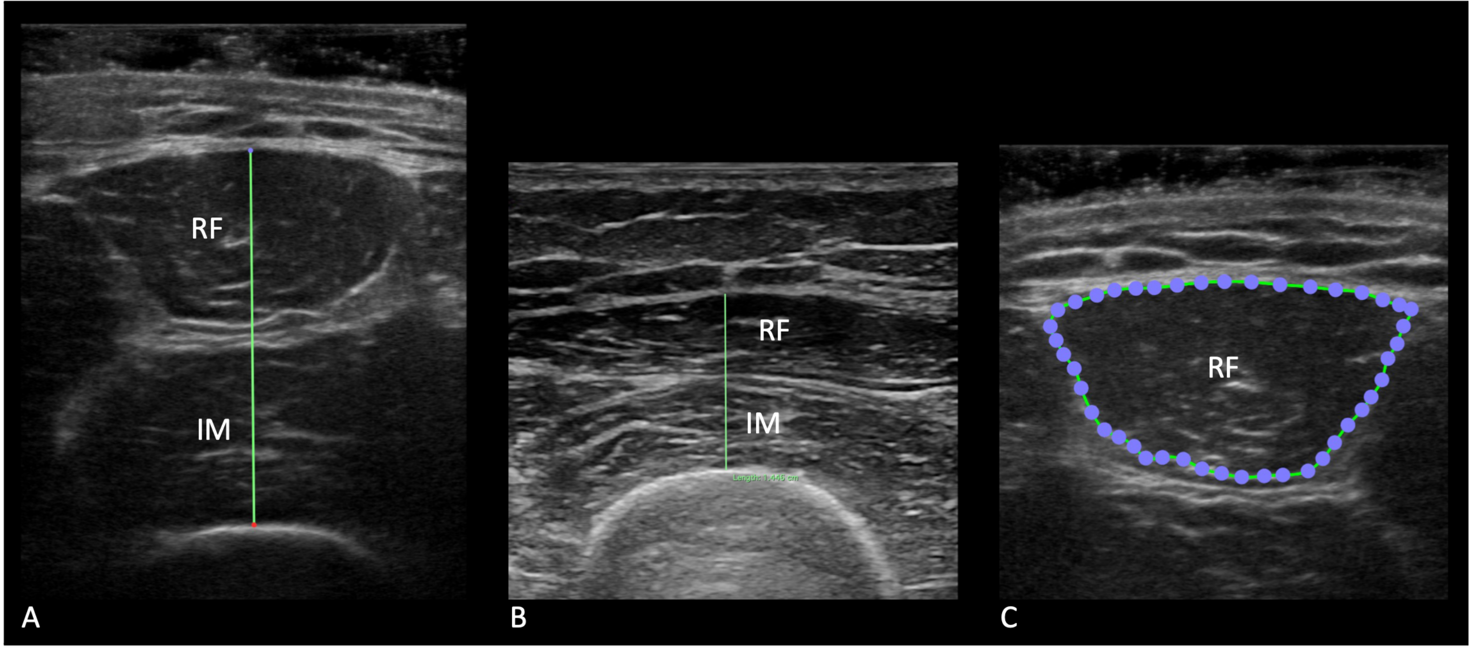


Figure 1. Ultrasound parameters. A quadriceps muscle layer thickness using no-compression (note the convex skin surface); B quadriceps muscle layer thickness using maximum-compression; C cross-sectional area of the rectus femoris muscle. RF, rectus femoris; IM, intermedius

of the rectus femoris muscle and the top of the femoral periosteum, comprising the combined thickness of the rectus femoris and intermedius muscle. QMLT was measured at two sites on the anterior aspect of the thigh – at the halfway (referred to as proximal from here on) and two-third (referred to as distal from here on) point of the distance on the midline between the anterior superior iliac spine and the superior patellar pole [46] (Figure 2). Image

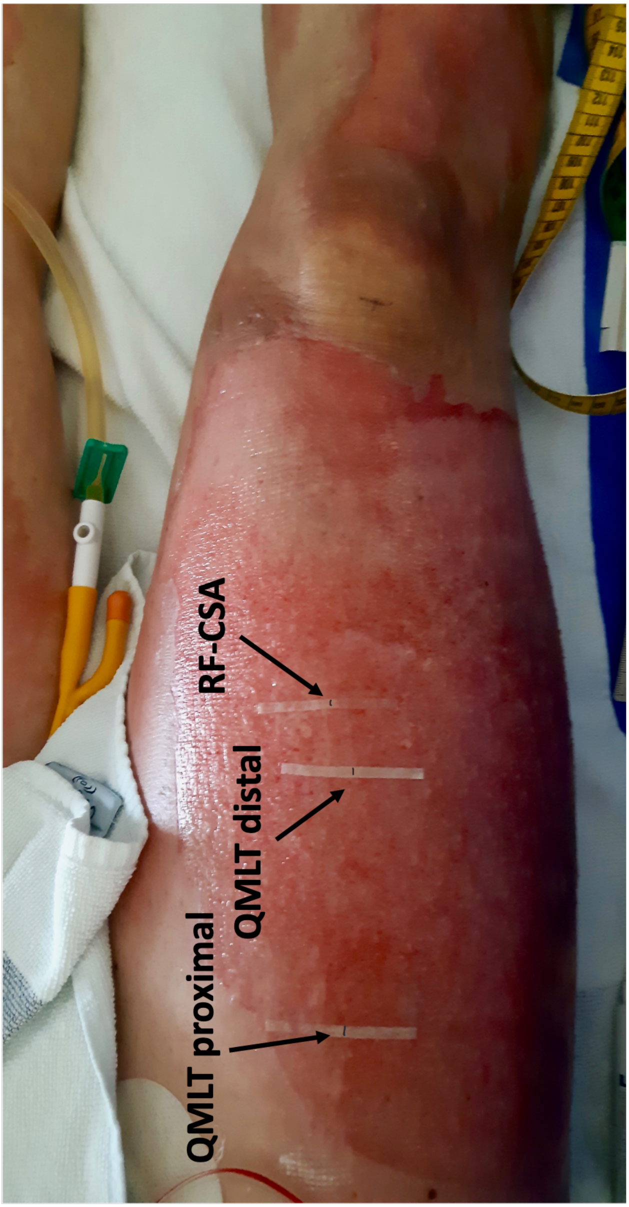


Figure 2. Location of measurements. Locations shown are quadriceps muscle layer thickness at the halfway (=QMLT proximal) and two thirds (QMLT distal) distance of the midline between the anterior superior iliac spine and the superior patellar pole. Cross-sectional area of the rectus femoris muscle (=RF-CSA) was measured at the most proximal point at which the muscle belly remained visible.

depth was as shallow as possible to visualise the femur, and if necessary, the transducer was tilted in the transversal plane to achieve central position of the femur (Figure 1). Two different compression techniques were used for determining QMLT – a maximum and no-compression technique. During maximum-compression the transducer was progressively compressed into the quadriceps muscle until additional pressure did not produce further of QMLT, as previously described [37]. This technique is thought to account for generalised intramuscular oedema which might interfere with measurement of true muscle size [32,37]. For the no-compression technique, the transducer and skin were separated by excess ultrasound transmission gel, avoiding distortion of muscle contour [46,49]. During this manoeuvre the transducer was gradually released until transmission was lost and no more structures were visible. Measurements with the no-compression technique preceded measurements with maximum-compression technique to account for a potential after-effect of compression.

RF-CSA was defined as the surface area within the rectus femoris muscle fascia. RF-CSA was measured at the most proximal point on the midline where the entire muscle contour of the rectus femoris muscle was still visible [47]. The transducer was moved away from the midline (laterally or medially) to ensure positioning directly above the middle of the muscle belly of the rectus femoris. RF-CSA was determined with no-compression only, using the same principles as described for the no-compression technique for determining QMLT (Figure 1).

All measurements were carried out with the subject in supine lying with straight knees and hips, and neutral rotation in the hips. If not tolerated by the patients, the head of the bed was elevated up to 30° prior to the measurements [50]. The transducer position remained perpendicular to the midline between the anterior superior iliac spine and the superior patellar pole at each measurement point. On open wound surfaces measurements were carried out using sterile ultrasound gel, sterile probe covers, sterile skin location markings (either by surgical marker or by sterile strips), and sterile measurement tape. In terms of ultrasound-specific parameters, the gain was always kept at zero and the applied depth was set as shallow as possible to visualise structures of interest while ensuring highest resolution. Both thighs were assessed, and each measurement was repeated three times.

2.4.3 Data analysis

Ultrasound data was stored as anonymised DICOM four to five seconds clips, and frames were selected and analysed using a DICOM reader software (Horos™ viewer v3.3.6, Horos Project) by a blinded assessor who was not present during the data collection. Frames were selected if no further change in muscle contour took place and image quality allowed delineation of structures of interest. For QMLT, a straight line was drawn from the top centre of the ultrasound image towards the middle of femoral shaft. Along this line, a second line was drawn from the inferior border of the superior muscle fascia of the rectus femoris towards the superior border of the femoral periosteum, to determine QMLT (Figure 1). For RF-CSA, a closed polygon tool was used to trace the inner lining of the rectus femoris muscle fascia (Figure 1). To determine whether it would be sufficient to use a single measurement as opposed to the average of three measurements, the first of three measurements was used as the single measurement and compared with the average of three measurements.

Differences in demographics between healthy and burn subjects were analysed using two-sample t-tests. Inter-rater reliability of QMLT and RF-CSA was analysed using two-way random effects model with absolute agreement for the calculation of intraclass correlation coefficients (ICC) estimates ICC (2,3) when the average of three measurements was used, or ICC (2,1) for single measurements [51]. Limits of agreement and systematic bias were assessed using Bland Altman plots and one-sample t-tests. Proportional bias was evaluated by means of linear regression. Minimum detectable changes at the 95% confidence interval (MDC95) were calculated with the formula [$MDC95 = SEM*1.96*\sqrt{2}$] [52]. The SEM was derived by $SEM = SD \times \sqrt{(1 - ICC)}$, where the SD represents the pooled standard deviation for the two raters [52]. Normality of data was determined with a one-sample Kolmogorov-Smirnov test. Where necessary, data was log-transformed to meet normality assumptions. However, when the difference between transformed and non-transformed ICCs was less than 1%, we chose to report the ICC and MDC95 on the original scale. ICC estimates and their 95% confidence interval were defined as ICC <0.5 indicative of poor reliability, moderate reliability if between ≥0.5 and <0.75, good reliability if between ≥0.75 and 0.9, and excellent reliability if greater than 0.9 [52]. Significance was set at $p < 0.05$. All statistical analysis was performed using SPSS Statistics Version 25 (IBM, USA).

Feasibility was determined by the number of attempted vs. realised measurements, with reasons for measurement failure noted. Finally, the duration of measurements was calculated from the first to the last recorded ultrasound clip for both assessors.

2.5 Results

2.5.1 Characteristics

Table 2 shows the characteristics of the recruited burn and healthy subjects. The burn group was comprised of fewer female subjects (n=4) than the healthy group (n=10). Besides this gender differences, groups were comparable, with non-significant differences in age (p=0.11) and body mass index (p=0.54). The total body surface area of burn subjects ranged from 10 to 70%, with nearly half of all measurements taking place on thighs with open wounds. A total of 1971 ultrasound clips from burn subjects (1122 at baseline + 849 at follow-up) and 1200 clips from healthy subjects were collected and analysed over the course of the study period. Sixteen out of twenty burn subjects provided data for follow-up measurements throughout burn centre stay, with four subjects unable to be followed-up for the following reasons: death n=2, repatriation n=1, psychosis n=1. Thirty follow-up measurements took place an average of 5.8 weeks after baseline assessment [95%CI 4.3 – 7.4].

	Burn subjects (n = 20)	Healthy subjects (n = 20)	t-test
Clinical trial site 1^{a} / trial site 2^{b}	9 / 11	/	
Females / Males	4 / 16	10/10	
Age (years)^{c}	50 [42.5 – 57.4]	42 [36.3 – 48.4]	*p*=0.11
BMI^{c}	27 [25 – 29]	28 [25 – 31]	*p*=0.54
TBSA (%)	32 [22.9 – 40.2]	/	
Days postburn	1.5 [1.1 – 2]	/	
Mechanically ventilated (n)	10	/	
Open wounds (%)	47.5 (19 thighs)	/	
Net fluid balance (ml)	+2410 [1058 – 3762]	/	

Table 2. Characteristics of tested subjects. Data displayed as mean [95%CI]. BMI, body mass index; TBSA, total body surface area. ^{a}Refers to the burn centre of ZNA Stuivenberg, Antwerp; ^{b}Refers to the burn centre of the Military Hospital Queen Astrid, Brussels; ^{c}Between groups differences tested by two-sample t-tests.

2.5.2 Feasibility

The complete measurement procedure in burn subjects of both thighs took an average of 22 min [CI95% 18 – 27] for rater D.R.S. and 20 min [CI95% 16 – 26] for rater D.D. for the baseline assessment, and 22 min for any follow-up measurements, with an overall ratio of approximately 2:1 for QMLT to RF-CSA measurement duration. Using no-compression to measure QMLT deemed feasible for both proximal and distal locations (92.5% and 97.5% of attempted measurements in burn subjects at baseline, 95% and 95% during follow-up measurements, and 95% and 95% in healthy subjects). The reason for measurement failure at baseline were very large thighs (>6 cm depth) due to obesity, high muscularity, oedema, or a combination of these factors, while during follow-up measurements non-penetrable donor site dressings rendered three out of sixty thighs inaccessible. In 10% of proximal and 12.5% distal of attempted measurements in burn subjects at baseline, maximum-compression was not tolerated on open wounds due to pain, whereas on intact skin this was tolerated in all cases. During follow-up measurements, maximum compression was not possible in 8.3% of cases due to pain on open wounds (3.3%) and non-penetrable donor sites (5%). All attempted RF-CSA measurements in healthy and burn subjects at baseline were successfully completed, while during follow-up measurements three thighs (5%) were not accessible due to non-penetrable donor sites. Of follow-up measurements, all failed attempts took place during the first follow-up measurement (n=16; mean 3.6 weeks after admission assessment, 95%CI 2.4 - 4.9 weeks). All further follow-up assessment at an average of 7 weeks (n = 11) and 14 weeks (n=3), or at discharge (n=16) were 100% feasible for any of the studied parameters. Beyond pain on some open wounds during maximum-compression, no other adverse events occurred.

2.5.3 Reliability

All reliability parameters are shown in table 3 (burn subjects) and table A.1 (healthy subjects). Measurements of QMLT yielded ICC values above 0.9 in all subjects. RF-CSA measurements achieved ICC values ranging from 0.76 to 0.99 in burn subjects and above 0.9 in healthy subjects. MDC95 values ranged between 5 and 18% of the mean score in burn subjects, and 2 and 16% in healthy subjects. Limits of agreement between raters were acceptable for all ultrasound-derived parameters in all subjects (Figure 3 and Figure A.1). RF-CSA showed somewhat larger limits of agreements than QMLT measurements. In burn subjects, mean differences between raters ranged from 0.01 to 0.1 cm depending on the administered methodology (table 4). In healthy subjects, mean differences between raters were very small, ranging between 0.01 and 0.03 cm (table A.2).

Number of measurements

Using only a single as opposed to the average of three measurements decreased the reliability of all ultrasounds-derived parameters in burn subjects and introduced more significant bias between raters in all subjects (table 4 to A.2). Averaging measurements decreased MDC95 values by approximately 0.1 cm for all QMLT parameters (equivalent to a decrease of 3 to 5% of the mean score depending on the type of compression), and 0.2 cm2 for RF-CSA (equivalent to 5% of the mean score) in burn subjects (table 3). In healthy subjects, MDC95 values were unchanged regardless of average or single measurements (table A.1).

QMLT compression technique

Using no-compression to measure QMLT generally yielded higher ICC and lower MDC95 values than the maximum-compression technique (table 3 and A.1) in all subjects. In burn subjects, MDC95 values for maximum-compression were on average equivalent to 15% of the mean score, as opposed to an average of 6% of the mean score when using the no-compression technique. Mean differences between raters, although mostly non-significant) were on average higher with maximum-compression than no-compression (0.7 cm vs. 0.2 cm).

QMLT location

Reliability parameters for QMLT were similar between the proximal and distal location and left and right side, irrespective of applied compression technique in both healthy and burn subjects.

2.6 Discussion

This study investigated the feasibility and reliability of B-mode ultrasound in measuring quadriceps muscle architecture in the acute burn setting with respect to different methodologies. Our main findings show that in the majority of cases quadriceps muscle ultrasound is reliable and feasible to carry out during hospitalisation, and that adapting the methodology to the individual burn patient can improve its feasibility and reliability. Based on these findings, we propose a three-step decision-making tree (Figure 4) to guide burn clinicians and researchers in deciding which ultrasound methodology is most appropriate based on different clinical scenarios.

The variability observed in our study can be explained by either subject- or operator-dependent factors. The inclusion of a healthy control group helped identify which of these factors are unique to the burn population. Subject-dependent factors in burn subjects might have been related to pain on compression of open wounds or the impact of oedema, decreasing the image quality and making delineation of structures of interests more difficult. Operator-dependent factors in burn subjects might have been related to the added stress and time pressure, which might have impacted measurement precision to a larger degree than in healthy subjects. However, as this study only produced minor differences in feasibility and reliability between the healthy and burn subjects, it seems more likely that other factors inherent to the methodology might better explain the observed variability. One such factor, associated with the QMLT protocol, is that measurements were administered on the midline between the superior anterior iliac spice and the superior pole of the patella to facility reproducibility, with operators not allowed to deviate from this midline. However, as there are large inter-individual differences in quadriceps morphology, these measuring points were not always perfectly positioned on top of the rectus femoris muscle, where its thickness is the largest. Small shifts in transducer position might therefore result in different thickness measurements, although this issue is inherent to all protocols using body landmarks [53].

This study sought to answer several methodological questions. First, we investigated whether it is necessary to repeat each measurement three times and calculate an average, or whether a single measurement would suffice. A single measurement is appealing as it would theoretically shorten the duration of the full measurement procedure. However, our data shows that, while reliability remained high for either method, the averaging of three measurements led to significant reductions in minimal detectable changes in all assessed muscle parameters in burn patients. This is in line with established protocols of quadriceps muscle ultrasound used in different patient populations [37,46–48].

		ICC [95%CI]		MDC95			
		Average[a]	Single[b]	Average[a]	%mean	Single[b]	%mean
RIGHT	QMLT (no compression, proximal location)	0.994 [0.986-0.998]	0.988 [0.97-0.995]	0.22 cm	5.4	0.31 cm	7.8
	QMLT (max. compression, proximal location)	0.98 [0.945-0.993]	0.957 [0.885-0.984]	0.29 cm	16.6	0.43 cm	24.2
	QMLT (no compression, distal location)	0.991 [0.976-0.996]	0.98 [0.95-0.992]	0.23 cm	7.6	0.34 cm	11.4
	QMLT (max. compression, distal location)	0.985 [0.961-0.995]	0.975 [0.934-0.991]	0.18 cm	14.2	0.25 cm	18.8
	RF-CSA	0.99 [0.974-0.996]	0.973 [0.934-0.989]	0.22 cm^2	7.3	0.35 cm^2	11.8
LEFT	QMLT (no compression, proximal location)	0.99 [0.973-0.996]	0.978 [0.945-0.992]	0.29 cm	7.5	0.42 cm	11
	QMLT (max. compression, proximal location)	0.971 [0.901-0.99]	0.953 [0.758-0.986]	0.31 cm	18.4	0.40 cm	23.2
	QMLT (no compression, distal location)	0.995 [0.988-0.998]	0.986 [0.965-0.994]	0.17 cm	5.6	0.28 cm	9.4
	QMLT (max. compression, distal location)	0.99 [0.974-0.996]	0.977 [0.843-0.994]	0.15 cm	10.7	0.22 cm	16
	$RF\text{-}CSA_{ln}$[c]	0.955 [0.888-0.982]	0.895 [0.756-0.957]	0.37 cm^2	12.7	0.57 cm^2	19.7

Table 3. Intraclass correlations coefficients and minimal detectable changes in burn subjects.

QMLT, quadriceps muscle layer thickness; RF-CSA, rectus femoris cross sectional area

[a]Refers to the average of three measurements; [b]Refers to the first of three measurements; [c]ICC values were backtransformed to derive MDC95 of RF-CSA of the left thigh.

		Systematic bias[a]				Proportional bias			
		Average[b]		Single[c]		Average[b]		Single[c]	
		Mean Δ	p-Value	Mean Δ	p-Value	β Co-eff	p-Value	β Co-eff	p-Value
RIGHT	QMLT (no compression, proximal location)	0.02 cm	0.665	0.03 cm	0.357	-0.031	0.118	0.019	0.614
	QMLT (max. compression, proximal location)	-0.08 cm	0.124	-0.08 cm	0.111	0.029	0.674	0.027	0.704
	QMLT (no compression, distal location)	0.02 cm	0.683	0.00 cm	0.958	0.084	0.066	0.075	0.125
	QMLT (max. compression, distal location)	-0.03 cm	0.309	-0.01 cm	0.645	0.001	0.987	0.025	0.671
	RF-CSA	-0.04 cm^2	0.287	-0.04 cm^2	0.286	0.058	0.221	0.115	0.027*
LEFT	QMLT (no compression, proximal location)	<0.01 cm	0.999	-0.02 cm	0.729	0.091	0.062	0.098	0.049*
	QMLT (max. compression, proximal location)	-0.11 cm	0.022*	-0.13 cm	0.003*	0.067	0.373	0.044	0.469
	QMLT (no compression, distal location)	-0.01 cm	0.726	-0.01 cm	0.803	-0.052	0.106	-0.072	0.063
	QMLT (max. compression, distal location)	-0.04 cm	0.131	-0.08 cm	0.001*	-0.019	0.685	-0.038	0.343
	$RF\text{-}CSA_{ln}$	-0.01 cm^2	0.598	-0.02 cm^2	0.459	0.036	0.725	0.009	0.935

Table 4. Systematic and proportional bias in burn subjects.

QMLT, quadriceps muscle layer thickness; RF-CSA, rectus femoris cross sectional area

[a]Systematic bias refers to the mean differences between raters, subtracting rater 1 - rater 2; [b]Refers to the average of three measurements; [c]Refers to the first of three measurements; *p value < 0.05

Secondly, we compared two different compression techniques for the measurement of

QMLT. While both techniques achieved comparable feasibility, the no-compression technique resulted in superior reliability with smaller minimal detectable changes relative to measured muscle thickness (6% vs. 15% of the mean thickness). The difficulty associated with standardising the amount of tissue compression provides a likely explanation for this observed difference that has been reported previously [37,38,54]. During compression, the

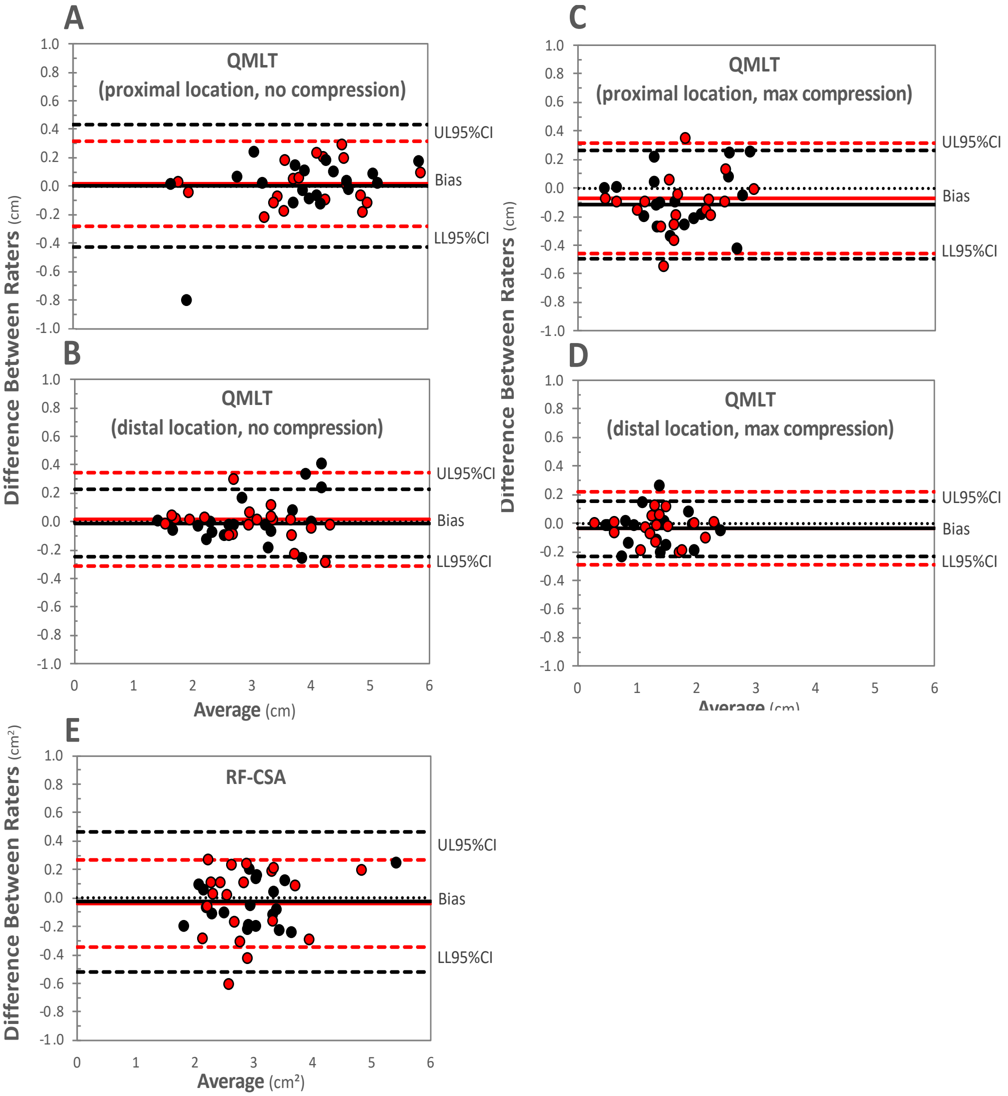


Figure 3. Bland-Altman plots for burn subjects.

A-D quadriceps muscle layer thickness, E rectus femoris cross-sectional area. Data presented is based on average of three measurements. Red lines and data points refer to the right thigh; black lines and data points refer to the left thigh. QMLT, quadriceps muscle layer thickness; RF-CSA, rectus femoris cross-sectional area.

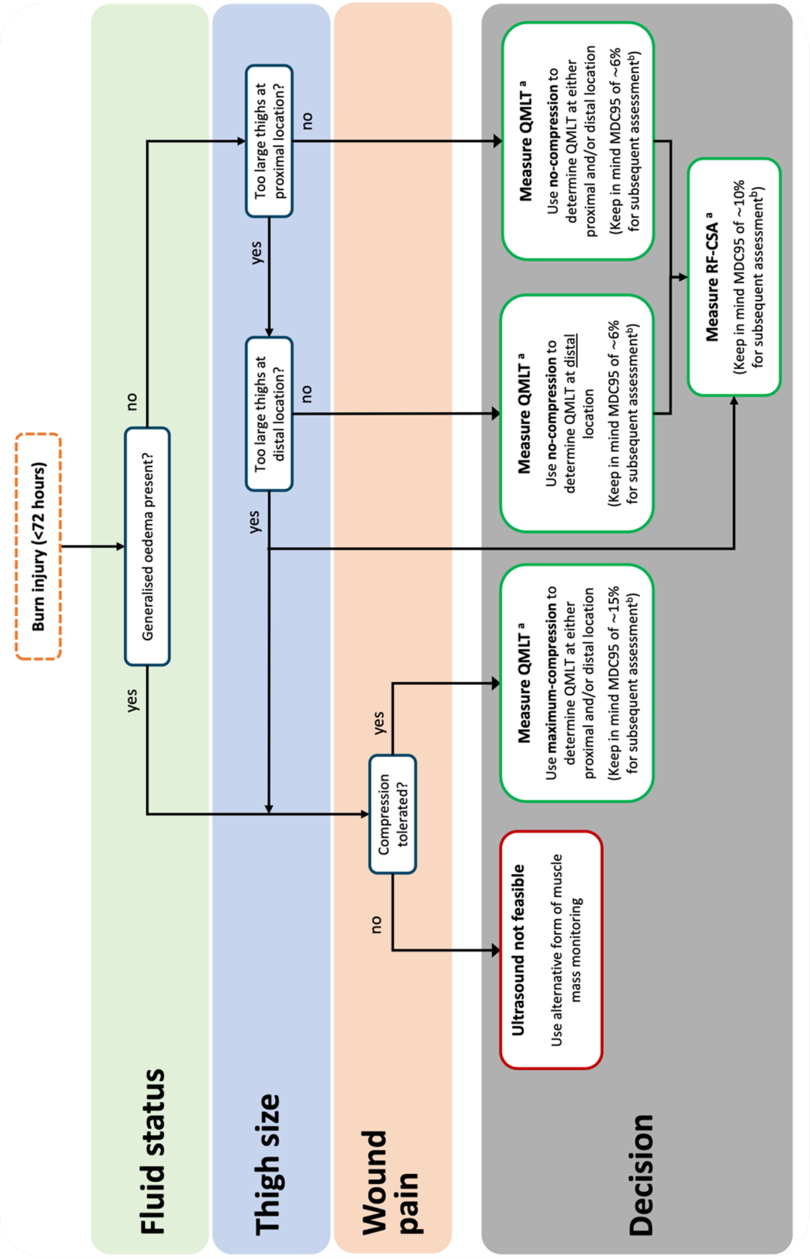


Figure 4. Decision-making tree to guide choice of methodology for quadriceps muscle ultrasound in the acute burn setting. QMLT, quadriceps muscle layer thickness; RF-CSA, rectus femoris cross-sectional area. [a]Always use the average of three measurements to increase reliability, and measure both right and left thighs to provide a more complete picture of whole-body muscle mass. [b]Note distance from superior pole of patella for any subsequent measurements.

position of the rectus femoris in relation to the femur may have been altered, introducing further variability. In the presence of oedema, the maximum-compression technique is nonetheless the more appropriate choice as it is thought to better reflect true muscle size [32,55]. Maximum-compression also offers a solution for exceptionally large thighs that exceed ultrasound penetration. Clinicians using maximum-compression must then bear in mind that changes below 15% are likely due to measurement error, which might potentially be further improved if the same rater repeated measurements in a given patient [37,56]. If that is not feasible, then the use of a curvilinear ultrasound transducer for very large thighs might provide another manner to circumvent the maximum-compression technique. Compared to linear arrays, curvilinear transducers have a deeper penetration at the expense of lower resolution. Despite this trade-off, QMLT and RF-CSA derived through curvilinear transducers have proven equal to those derived through linear transducers, albeit in a different patient population [57,58]. A second alternative in case of too large thighs would be to solely measure the thickness of the more superficial rectus femoris muscle, as done in other trials [37,43,59,60]. However, as the time course of muscle wasting has shown to affect the rectus femoris and intermedius muscle differently over time [59,61], we suggest not to exclude the latter. The fact that the minimal detectable changes during the no-compression manoeuvre in this study all ranged around the 0.2 cm mark regardless of measured thickness, further underlines the importance of using the entire quadriceps layer to be able to detect relative changes earlier. Hence, the alternative use of curvilinear transducers to enable the no-compression technique to determine QMLT in large thighs seems preferred. However, as we have not tested the use of curvilinear transducers in this study, this recommendation should be interpreted with caution.

Thirdly, this study compared two commonly reported locations to measure QMLT, the halfway (proximal) and two third (distal) point of the distance between the superior anterior iliac spine and the upper patellar pole. The reliability data of this study do not support one location over the other, confirming that both points can be reliably used to determine QMLT. In exceptional cases that thigh sizes are too large to allow ultrasound penetration via the no-compression technique, the distal location might prove slightly more feasible as the femur is generally located more superficially than at the proximal site. In all healthy and burn subjects included in this study, we were unable to measure QMLT in eight out of 140 measured thighs at the proximal site, and six out of 140 thighs at the distal site with the no-compression technique. As these are only minor differences in feasibility, one might be tempted to conclude that these two locations are interchangeable. Using multiple locations, including both left and right sides, however, has shown to provide a more complete surrogate measure of whole-body muscle mass [62,63]. Assessing both right and left thighs has additional advantages in the longitudinal assessment of burn subjects. Depending on the post-surgical protocols in place, the thigh, a common graft donor site, might be rendered inaccessible for a certain time due to wound dressings. In our sample, this occurred in three out of 60 measured thighs, and only affected one thigh at a time, leaving the other thigh to be used for the purpose of monitoring of muscle wasting. With respect to QMLT measurement location in burn patients, we therefore recommend the use of multiple locations, both proximal and distal on the right and left thigh.

One potential drawback of ultrasound in particularly major burns is that it needs to take place during wound dressing changes (nearly half of all measurements presented in this report). These dressing changes are one of the most difficult and stressful periods for both the burn team and the patient resulting among others from pain, prolonged wound exposure to air, and range of motion exercises. Consequently, adding muscle assessment to the to-do list during dressing changes is challenging, and has traditionally been postponed to a later timepoint once wound healing is completed. Based on the measured duration of the entire ultrasound procedure in this study, we estimate that it should take clinicians twenty minutes to complete the assessment, making this protocol feasible to take place during dressing changes. The importance of multi-disciplinary teamwork in these cases cannot be overstated. Patient education and coordination with nursing staff, intensivists and anaesthesiologists proved integral to the feasibility of the measurements.

Many previous studies have examined the reliability of QMLT and RF-CSA measurements in the critically-ill population, primarily using the no-compression technique, producing high inter-rater reliability coefficients (ICC >0.9) and small inter-rater differences (<0.1 cm) comparable to this study [35–37,40,53,64–67]. However, to the best of our knowledge, no study has to date examined ultrasound as a tool to measure muscle parameters in the burn population. This study is, therefore, the first to demonstrate that ultrasound can be reliably adapted to this population just as well as in the critically-ill population. Our results shows that ultrasound assessment of the quadriceps is feasible and reliable in acute burn patients and that the examined protocol can be used irrespective of wound status, fluid status, and body size.

2.6.1 Strengths and limitations

A primary strength of this investigation lies in its multi-centre nature, which allowed the recruitment of a heterogenous sample and the use of different ultrasound machines, thereby enhancing the external validity of our findings. Another strength can be found in the inclusion of a healthy control group, which aided in understanding to which degree subject- and operator-dependent factors caused the observed variability in feasibility and reliability.

In addition to the limitations already discussed, several limitations in this investigation can be identified. One such limitation was the fact that skin markings were not erased between raters, as most measurements had to take place during a very limited time window (during dressing changes) and we were unable to erase skin markings during the same session. While this choice might have overestimated reliability by eliminating potential variability associated with landmarking [53], it is the authors' experience from pilot testing that most of the observed procedural variability did not originate from landmarking, but rather from the ultrasound performance (applied tissue compression and tilt of the transducer) [54]. Nevertheless, in selected burn patients with intact thigh surface, the use of permanent skin markings, as is common in non-burned patient populations, might in fact be desirable for examining longitudinal changes [35].

Another shortcoming of this investigation is that the reliability analysis only focussed on measurements within 72 hours of admission, thereby limiting our ability to comment on the reliability of this ultrasound protocol at later stages of recovery. While this remains a subject of future research, to the best of our knowledge, no additional factors that could impact the reliability at later stages of recovery are present that did not exist during the admission assessment. Conversely, it is during the early days of a burn centre admission that muscle ultrasound assessment is most challenging and clinical priorities are elsewhere. Rather than delaying or entirely skipping the baseline assessment of muscle, we demonstrate that it is reliable during this crucial phase.

Lastly, as is the case with many clinical investigations, this study was based on the measurements of two raters. Including more raters was not feasible due to the short time-window in which measurements had to take place. While this could have limited our ability to extrapolate our findings to the wider population of raters in the clinical setting, other reports of intensive-care workers have previously demonstrated the reliability of quadriceps muscle ultrasound irrespective of the assessor's level of expertise [39,60,68]. For the same reason of time, we chose to test inter-rater as opposed intra-rater reliability, as this was more applicable to both participating trial sites, where the care of burn patients traditionally involves multiple clinicians of the same burn care team.

2.6.2 Future directions

This study lays a well-needed foundation for the many remaining clinical questions surrounding muscular ultrasound in the burn population. Future research should address the reliability of ultrasound at later stages of hospitalisation. Whether ultrasound-derived parameters of muscle size at baseline or over time, correlate with clinical outcomes, such as mortality, duration of mechanical ventilation, nutritional status, etc, forms another clinical question that may guide clinicians in deciding when and how regularly to use of ultrasound for muscular assessment. Finally, the two parameters of interest in this study (QMLT and

RF-CSA) were both quantitative in nature. But ultrasound can also measure the echogenicity, which, albeit less researched, may provide a better picture of the qualitative aspects of muscle [59].

2.7 Conclusion

Despite its importance as a metabolic reserve, muscle mass has traditionally not been part of the admission assessment in burn care. In this multi-centre study, we demonstrate that ultrasound measures of quadriceps muscle architecture are feasible and reliable and can be adapted to different clinical scenarios commonly encountered in the burn setting.

2.8 Declaration of interest

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2.9 Acknowledgements

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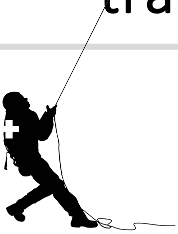
Part 3 Efficacy of early exercise training



Chapter 3. Effects of exercise training on muscle wasting, muscle strength and quality of life in adults with acute burn injury

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3.1 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-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.

Keywords: Burns; Rehabilitation; Exercise; Muscle wasting; Muscular atrophy; Cachexia

3.2 Highlights

- There is a lack of evidence regarding the safety and efficacy of early exercise training in burn care.
- Exercise training during the acute phase of burns increased muscle size and strength.
- The short-term effects on quality-of-life parameters remain to be established.
- Early exercise training is feasible and beneficial for adults with acute burns.

3.3 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.

3.4 Material and methods

3.4.1 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.

3.4.2 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.

3.4.3 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.

3.4.4 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.

Readiness criteria for exercise

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

Table 1. Readiness criteria to commence exercise intervention. All criteria had to be met to commence exercise. MAP, mean arterial pressure; FiO_2, inspired oxygen fraction; PaO_2/FiO_2, 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).

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.

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.

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].

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].

3.4.5 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.

3.4.6 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.

3.4.7 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).

3.5 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), 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

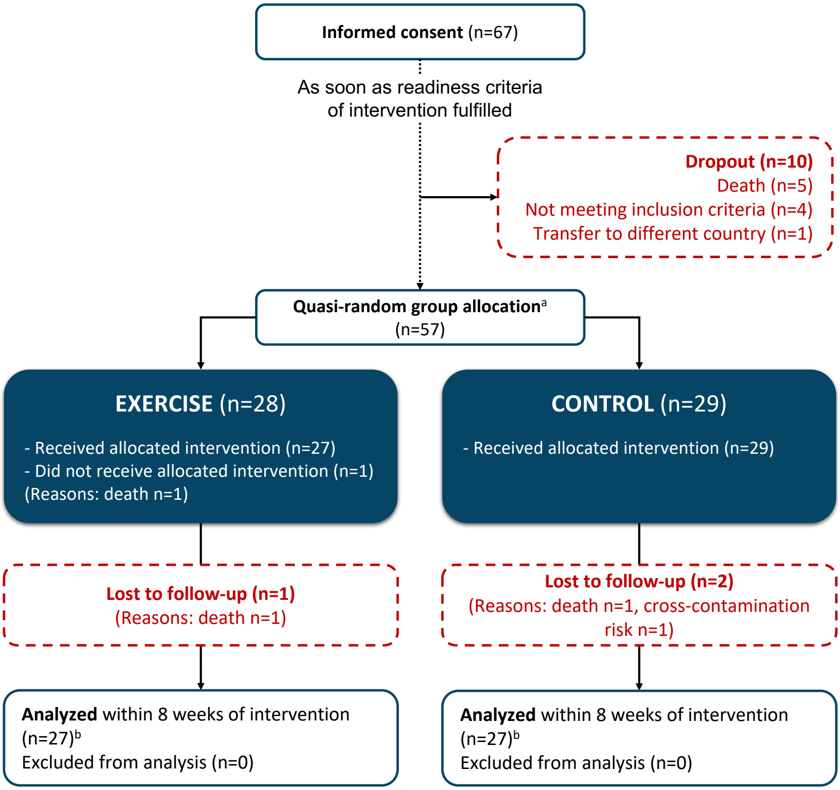

Figure 1. Study flow diagram.

[a] based on staff capacity to provide intervention due to COVID19. [b] refers to the primary outcome 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.

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.

	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, 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

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

3.5.1 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 cm2 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).

	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

Table 3. Baseline comparison of trial outcomes. 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

	Variable	β-coeff.	*p*-value	95%CI	
QMLT	Group[Exercise]	0.089	0.154	-0.034	0.212
	Week	-0.132	<.001	-0.157	-0.106
	Group[Exercise]*Week	0.055	0.005	0.017	0.093
	Loss between admission – baseline (cm)	-0.947	<.001	-1.032	-0.862
	Loss between admission – baseline*Week	0.096	<.001	0.074	0.117
	Admission value	0.907	<.001	0.849	0.964
RF-CSA	Group[Exercise]	0.072	0.258	-0.054	0.199
	Week	-0.138	<.001	-0.164	-0.112
	Group[Exercise]*Week	0.086	<.001	0.048	0.124
	Loss between admission – baseline (cm^2)	-0.942	<.001	-1.053	-0.830
	Loss between admission – baseline*Week	0.116	<.001	0.087	0.145
	Admission value	0.950	<.001	0.892	1.008

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

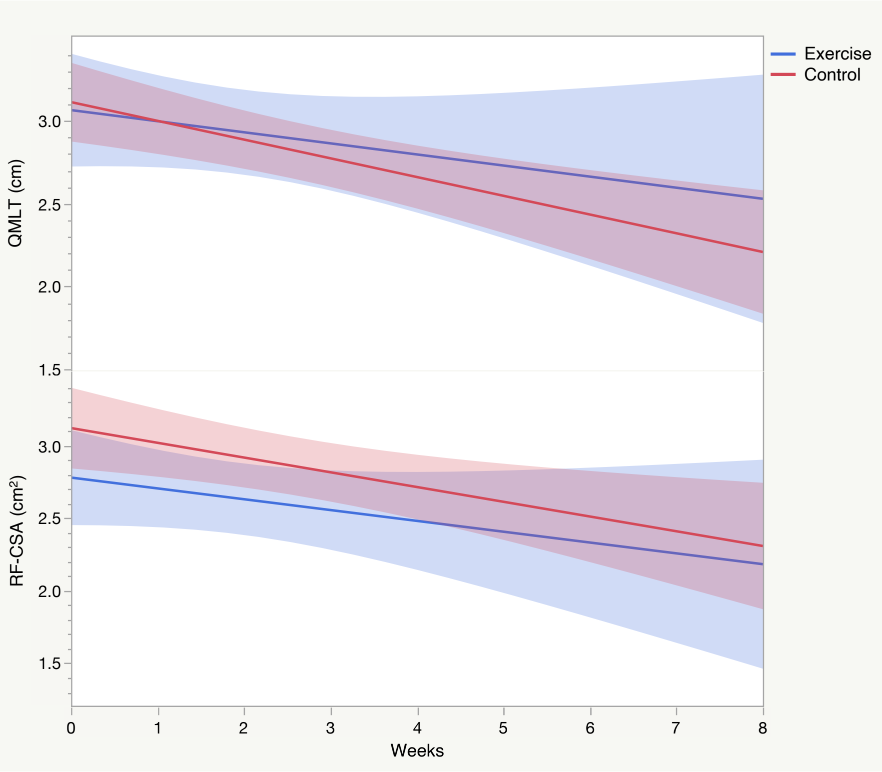

Figure 2. Change of ultrasound-derived muscle size parameters over time. Data displayed as unadjusted regression lines with confidence intervals (shaded area). Note that, while both groups decrease in muscle size parameters over time, the exercise group (blue line) decreases less. QMLT, quadriceps muscle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

3.5.2 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 baseline was associated with a greater force reduction over time.

	Variable	β-coeff.	*p*-value	95%CI	
Grip strength	Group[Exercise]	-0.408	0.786	-3.397	2.581
	Week	2.949	<.001	1.825	4.074
	Group[Exercise]*Week	1.472	0.005	0.466	2.477
	Baseline grip strength (N)	1.032	<.001	0.922	1.141
	Baseline grip strength*Week	-0.116	<.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	<.001	6.444	18.798
	Group[Exercise]*Week	8.999	0.004	2.964	15.033
	Baseline Hip Flexion strength (N)	0.921	<.001	0.789	1.052
	Baseline Hip Flexion strength*Week	-0.123	<.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	<.001	0.778	1.066
	Baseline Knee Extension strength*Week	-0.053	0.030	-0.100	-0.005

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

3.5.3 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.

3.5.4 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.

	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	<.001	0.684	0.940
BSHS-B Simple Abilities	Group[Exercise]	0.047	0.858	-0.475	0.570
	Week	0.294	<.001	0.192	0.396
	Group[Exercise]*Week	-0.020	0.810	-0.186	0.146
	Baseline value	0.700	<.001	0.532	0.868
EQ-5D-5L Health Utility Index	Group[Exercise]	0.047	0.409	-0.065	0.158
	Week	0.082	<.001	0.061	0.102
	Group[Exercise]*Week	0.004	0.827	-0.030	0.038
	Baseline value	0.882	<.001	0.730	1.034
	Baseline value*week	-0.129	<.001	-0.176	-0.082
EQ-5D-5L VAS	Group[Exercise]	1.378	0.706	-5.849	8.604
	Week	7.868	<.001	5.629	10.107
	Group[Exercise]*Week	1.190	0.288	-1.020	3.400
	Baseline value	0.907	<.001	0.769	1.046
	Baseline value*week	-0.128	<.001	-0.167	-0.089

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

3.6 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.

The observed benefit of exercise training regarding postburn 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], [67], [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, 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 as a result of the anabolic, anti-catabolic, anti-hyperglycemic, and anti-inflammatory effects of exercise [70], [71], [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.

3.6.1 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.

3.6.2 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.

3.6.3 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], [78], [79].

3.7 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.

3.8 Funding

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3.9 Conflict of interest

None.

3.10 References

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Chapter 4. Effects of early exercise training following severe burn injury: A randomized controlled trial

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Currently under review (third round) at *Burns & Trauma*.

4.1 Abstract

Background: Despite being a stable component of burn rehabilitation at later stages of recovery, exercise training is not commonly provided during the acute phase of burns. A lack of evidence surrounding its efficacy and safety in severely burned adults has hampered its implementation into acute burn care. The aim of this study was to study the capacity of exercise training to modulate parameters of postburn muscle wasting and quality of life during burn center stay.

Methods: Adults <65 years of age with burns ≥40% TBSA were randomly allocated to either receive early exercise (n=29) in addition to standard care or standard care alone (n=29). Early exercise involved resistance and aerobic training, which commenced as early as possible and lasted for a duration of six to twelve weeks, in line with burn center length of stay. Ultrasound-derived quadriceps muscle layer thickness (QMLT) and rectus femoris cross-sectional area, lower limb muscle force, EQ-5D-5L and BSHS-B were assessed six and twelve weeks after baseline. Mixed models were fitted to compare between-group changes over time.

Results: Fifty-eight adults (42 [95%CI 40-45] years; 40-94%TBSA range, 86% previously mechanically ventilated) participated in this study. Exercise commenced seven days [IQR 5-9] after burn center admission with an attendance rate of 93%. Allocation to the exercise group had a protective effect on the loss of muscle size from baseline to six weeks of follow-up (QMLT: β-coeff.: 0.05 cm, p=0.010; RF-CSA: β-coeff.: 0.05cm2, p=0.045), and resulted in an improved recovery from six to twelve weeks (QMLT: β-coeff.: 0.04 cm, p=0.01; RF-CSA: β-coeff.: 0.06cm2, p<0.001). Muscle force increased significantly more in the exercise group than the control group (β-coeff.: 3.102 N, p<0.001) between six and twelve weeks. Besides a significant effect for the BSHS-B domains 'affect' and 'interpersonal relationships' between six and twelve weeks, no benefits were observed in the other assessed quality-of-life measures. No serious adverse events were reported in the exercise group.

Conclusion: The results of this study support the use of early exercise training as a feasible and efficacious therapeutic strategy to manage burn-related changes in muscle size and strength in adults with acute severe burn injury.

Keywords: Burns; Exercise; Rehabilitation; Muscle wasting; Cachexia

4.2 Highlights

- Exercise training was administered to severely burned adults during the acute phase.
- Exercise on top of usual care resulted in an improved retention and recovery of muscle size and muscle strength.
- Early exercise training is a safe and efficacious strategy to manage muscle wasting in severely burned adults

4.3 Background

Postburn muscle wasting is rooted in an interlinkage of hypermetabolism, hyperglycemia, hypercatabolism, inflammation, and physical inactivity - all of which are most pronounced during the acute phase of burns [1–6]. There has been a growing awareness of postburn muscle wasting and its potential to increase the disease burden for burn patients from the first days of hospital admission to long after hospital discharge [2,7–11]. Associated short-term complications of muscle wasting include impaired wound healing, increased risk of infection, intensive care unit acquired weakness, and difficulty weaning off mechanical ventilation, ultimately leading to a protracted hospital length of stay and a delayed recovery. Beyond the short term, potential sequelae of muscle wasting include an increased risk of musculoskeletal, cardiovascular and metabolic morbidity years after the trauma, threatening the survivor's complete recovery and long-term quality of life [12–16]. Despite its impact, muscle wasting remains inadequately managed in most burn centers [17]. At the same time, there has been a growing trend towards starting exercise early on during burn center stay, echoed by practice guidelines recommendations [18–23]. It is during this early phase that exercise would be expected to have the largest preventative effect to counter the underlying processes of postburn muscle wasting [24]. In particular, resistance and aerobic forms of exercise, as anabolic, anti-hyperglycemic and anti-inflammatory stimuli, are used effectively in many other health and disease states to counteract muscle wasting and associated outcomes [25–28]. In the burn population, preliminary evidence of exercise-induced improvements in inflammation, glycemic control, and markers of muscle metabolism have been reported [29–33], and recently reviewed by Dombrecht et al. (2023) [24]. As part of the current practice of burn care, however, resistance and aerobic exercise are rehabilitation components that are often reserved for a time when they are perceived as safer and more comfortable for burn patients, and when there is less interference from open wounds, pain, and grafting surgery [17]. Recent evidence supporting the inclusion of resistance and, or aerobic exercise during the acute phase in adult burn patients is based on studies with predominantly non-severe burn injuries [29,34]. However, it is the severe burn population with the highest risk of muscle wasting in whom exercise training during burn center stay could be most beneficial, yet, also in whom its efficacy has not been studied as a counteracting strategy in adult patients. An adequate management of postburn muscle wasting in this population is needed, as postburn muscle wasting impacts the host's vital metabolic reserve that is integral to sustaining the immune response and overcoming critical illness during the acute phase of burns [8,35–37]. For this reason, a deeper understanding of the efficacy of exercise training commenced early during burn center stay in severely burned adults is needed to support its inclusion in inpatient rehabilitation. Therefore, the present study was initiated to test the effects of resistance and aerobic exercise administered during the acute phase on muscle wasting and health-related quality of life during burn center stay of severely burned adults.

4.4 Methods

4.4.1 Study design

This study was designed as a prospective participant-blinded single-center randomized controlled trial including two arms, with the control group following standard-of-care treatment and the experimental group additionally undergoing a protocolized exercise program as part their burn center stay. The study was registered at US National Institutes of Health (ClinicalTrials.gov) #NCT04372550 and approved by the Ethics Committee of the Wuhan Third Hospital on 10 May 2019 [#QT2019-002].

4.4.2 Participants

Study participants were recruited at the burn center of the Wuhan Third Hospital, Wuhan, China between December 2019 and November 2022 after being screened for eligibility upon admission. Adults were deemed eligible if they were between 18 and 64 years of age at the time of admission and presented with severe burn injuries equal to or above 40% total burn surface area (TBSA). Exclusion criteria for participation comprised electric burns, palliative care, pregnancy, lower limb fractures or amputations, or any premorbid neurological, cardiovascular, or psychological disorders expected to interfere with the intervention or outcome assessment. As soon as testing was available, all participants were tested for a SARS-COV2 infection prior to burn center admission and during burn center stay. While this was no formal exclusion criterium, burn patients with a SARS-COV2 infection were not admitted to the burn center to avoid cross-contamination. Written informed consent was obtained from all participants or their next-of-kin in line with the declaration of Helsinki.

4.4.3 Standard-of-care

Standard-of-care treatment was provided to all participants, and entailed standard intensive care, wound care, surgical care, nutritional care, positioning, and physical therapy. Physical therapy consisted of passive and active range of motion exercise, stretching, splinting, and compression garments. Under the standard-of-care, the scalp (if available) was used as a standard donor site for grafting, and strict post-grafting immobilization was applied for three to five days in case of split-thickness autografts. Standard feeding regimens on the intensive care unit were based on energy requirements as calculated with the Peng equation [38], with protein content set at 1.5 - 2.0 g/kg/d. Participants on the ward received food ordered from the hospital canteen or outside sources. The standard glycemic target for patients requiring exogenous insulin administration was set at 144-180 mg/dl. As the study took place throughout the COVID-19 pandemic, visits by family were prohibited throughout the entire hospital stay.

4.4.4 Early exercise training

In addition to the standard-of-care treatment, participants allocated to the exercise group underwent an inpatient six to twelve week-long exercise training program consisting of resistance and aerobic training commenced as early as possible during their burn center stay, collectively referred to as “early exercise training” in the remainder of this report. The exercise program took place at the bedside in the burn intensive care unit and burn ward or using designated exercise equipment in the rehabilitation unit of the burn center. Participants had to meet predefined readiness criteria before initiating the exercise program to ensure medical safety and feasibility of the exercise intervention. These readiness criteria were assessed prior to each exercise session and encompassed parameters of cardiorespiratory stability, body temperature, alertness, and cooperation in line with international safety recommendations of active exercise during critical illness [39]. The primary goal of the exercise program was to counteract muscle wasting. Hence, exercises that primarily targeted the lower limbs were prioritized, as collectively these include the largest amount of muscle mass in the body. Resistance training was provided at a frequency of three sessions per week at a volume of three exercises consisting of three sets of eight to twelve repetitions each. Exercises progressed from in-bed to out-of-bed exercises with free weights or strength appliances depending on individual mobility status (Figure 1). In-bed resistance exercises

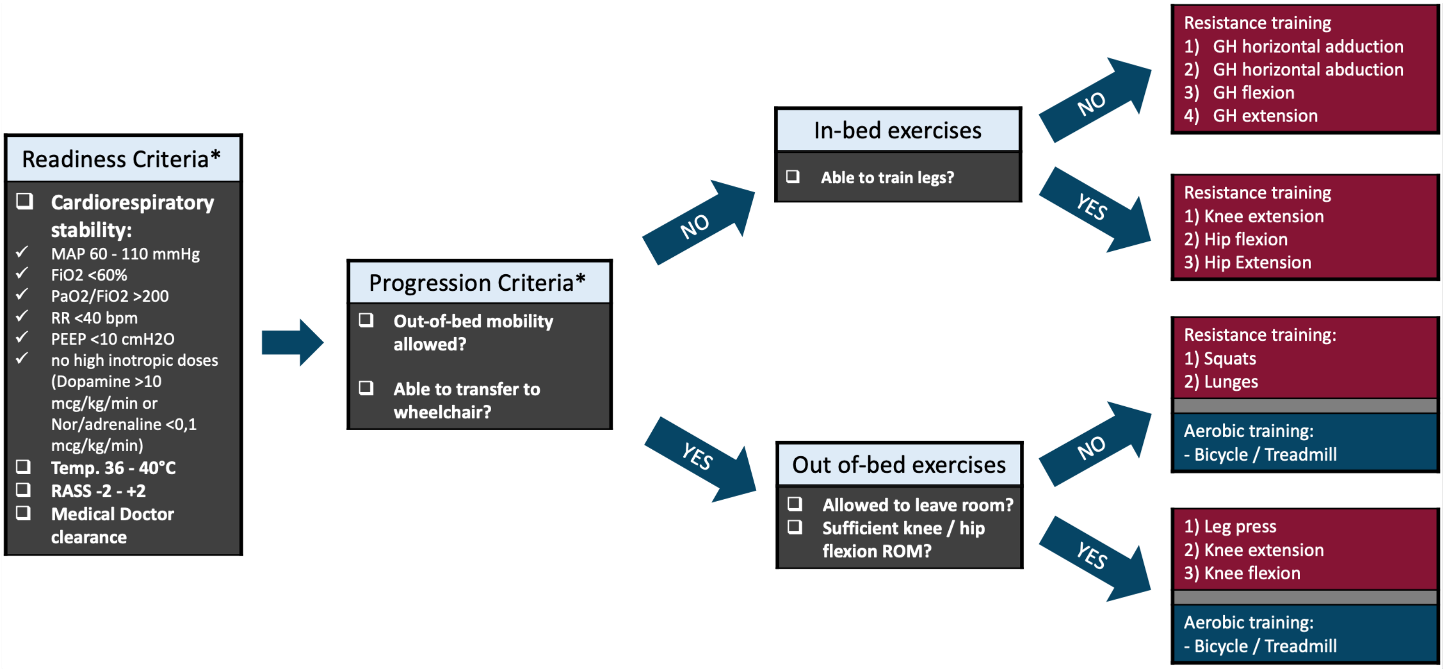

Figure 1. Decision-making tree to guide choice of exercise. MAP, Mean arterial pressure; FiO_2,inspired oxygen fraction; PaO_2/FiO_2, arterial oxygenation relative to inspired oxygen; RR, respiratory rate; bpm, breaths/min; PEEP, positive end expiratory pressure; RASS, Richmond Agitation Sedation Scale; ROM, range of motion; GH, glenohumeral. *Criteria to be checked prior to each training session

were provided at a target intensity of 60% of the peak force as produced during a maximal voluntary contraction using a hand-held dynamometer (for methods see section ‘muscle force’) [Lafayette, Indiana, USA], while intensity of out-of-bed exercises was determined using 8-repetition maximum testing [40]. Aerobic training was carried out twice weekly on a bicycle ergometer or a treadmill, with sessions entailing 24 minutes of interval training consisting of alternating 3-minute bouts of 50% or 70% of peak wattage or metabolic equivalents [41], as assessed by a maximal ramp test. The steep ramp test provided peak wattage values for cycling, as described by De Backer et al. (2007) [42], while the Naughton protocol or the Modified Bruce protocol was used on the treadmill for patients with or without walking impairment, respectively. The exercise program was built and progressed based on general principles of strength and cardiorespiratory conditioning [43,44], with the relative exercise intensity maintained by weekly repetition of the respective maximal tests. All exercises were administered by physiotherapy staff trained in the management of burns, and trained in the study protocol by the first author (DRS).

4.4.5 Outcomes

Assessment of muscle size, muscle force and quality of life was conducted throughout hospital stay at baseline, six weeks after baseline, and if participants had not been discharged yet, additionally at twelve weeks. On the day before follow-up assessment, the intensity of the experimental exercise program was reduced to prevent interference with the outcome assessment. The assessment was carried out by a team of three assessors, who were trained prior to the study to ensure uniformity. Results of previous assessments were not checked during follow-up assessment to prevent detection bias.

Muscle size

B-mode ultrasound was used to determine quadriceps muscle layer thickness (QMLT) and rectus femoris cross-sectional area (RF-CSA), with QMLT as the primary outcome. QMLT comprises the combined thickness of the rectus femoris and intermedius muscle, measured between the superior fascial layer of the rectus femoris and the femoral periosteum [45] (Figure 2). Quadriceps ultrasound provides a valid and reliable measure to track muscle wasting and has been studied in various populations [46–51], including acute burn injuries [52]. To derive the QMLT, a multifrequency linear probe was aligned perpendicular to the longitudinal axis of the anterior thigh at the halfway and two-thirds point between the anterior superior iliac spine and the superior patellar pole [47] (Figure 3). RF-CSA was measured on the anterior thigh at the most proximal site where the rectus femoris muscle belly remained visible on the ultrasound screen. The ultrasound procedure was sterile in case the wound surface over measurement points was not intact. Averages of triplicate bilateral measurements were calculated for both QMLT and RF-CSA, as this has shown to reduce test-retest variability [52] and better reflect whole-body muscle mass [49,53]. Further details of the employed methods of quadriceps ultrasound have been described elsewhere [52]. Ultrasound data was exported and analyzed using a DICOM reader software (Horos™ viewer v3.3.6, Horos Project).

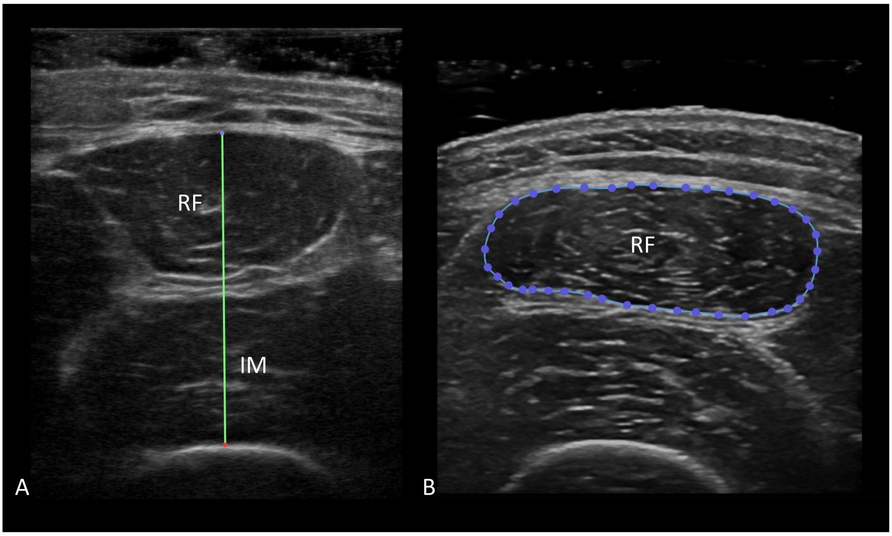

Figure 2. Example of ultrasound image analysis. A: Quadriceps muscle layer thickness. B: Cross-sectional area of the rectus femoris muscle. RF, rectus femoris; IM, intermedius. Adapted from "Reliability and feasibility of skeletal muscle ultrasound in the acute burn setting." by Schieffelers DR et al, 2023, Burns, 49:68–79. Copyright 2023 Elsevier

Muscle force

Handheld dynamometry [Lafayette, Indiana, USA] was used to measure changes in lower limb muscle force. Maximal voluntary contraction force of the lower limb was measured in supine lying with the dynamometer placed on the anterior surface of the distal tibial, just above the talocrural joint [Figure 4]. Participants then carried out an isometric combined hip flexion and knee extension moment with both hip and knees extended to zero degrees. This muscle force measure is not a direct measure of quadriceps muscle force alone, but a compound measure hip flexor and knee extensor muscles. A fixation band, fixed around the bed frame, provided the necessary counter-resistance to ensure isometric contraction during the test [54]. This test position was chosen to make muscle force assessment possible for bed-bound participants whose joint range of motion is too limited to reach traditional positions of muscle force assessment (e.g. 90° hip flexion and 90° knee flexion) due to bandages, pain, and grafts interfering with joint movement in the context of acute burn wounds. As part of trial preparation this testing protocol displayed good reliability (intra-rater ICC = 0.885, inter-rater ICC = 0.826; unpublished data in healthy adults). This data is in line with previously published

Figure 3. Ultrasound technique of quadriceps muscle size. A: Measurement locations. B: Sterile method over open wounds. QMLT, quadriceps muscle layer thickness measured at the halfway point (=proximal) and two-thirds (=distal) between the anterior superior iliac spine and the superior pole of the patella; RF-CSA, rectus femoris cross-sectional area as measured at the most proximal point where the rectus femoris muscle belly remained visible. Adapted from "Reliability and feasibility of skeletal muscle ultrasound in the acute burn setting." by Schieffelers DR et al, 2023, Burns, 49:68–79. Copyright 2023 Elsevier

reliability data of handheld dynamometry in burn patients [55]. The test maneuver was repeated three times with the highest value used for analysis. If the highest achieved force value was not within ten percent of the second highest value, additional test maneuvers were carried out. Measurements where pain interfered with test validity were considered invalid if participants' pain score on a 0-10 numeric rating scale equaled six or higher.

Figure 4. Muscle force assessment by hand-held dynamometry. A fixation band bound around the hospital bed provides counter-resistance while the assessor ensures correct positioning of the hand-held dynamometer. Consent for publication of image was obtained from the pictured patient.

Quality of life

To capture the full impact of a burn injury on health-related quality of life, both generic and disease-specific data was collected using the Chinese language versions of the Burn Specific Health Scale Brief (BSHS-B) and the Eurocol Quality of Life-5 Dimensions (EQ-5D-5L) [56–58]. As the BSHS-B was primarily developed for the post-acute phase, not all the items were applicable during burn center stay and a total score could not be calculated. Instead, we report the subdomains 'simple abilities', 'affect', and 'Interpersonal relationships'

[57]. Items are scored on a five-point scale with lower scores indicating worse impact on quality of life [59]. The EQ-5D-5L entails rating the overall health state on a visual analogue scale of 0-100 (0 = worst possible health, 100 = best imaginable health) as well as scoring five dimensions (self-care, mobility, daily activities, pain/discomfort, and anxiety/depression) on a five-point scale, roughly corresponding to no, slight, moderate, severe, and extreme problems in ascending order. From each possible scoring combination in these five dimensions, the EQ-5D-5L utility index was derived based on a value set for Chinese urban residents [60]. This index ranges from -1 to 1, where 1 describes 'full health' and -1 refers to the worst possible health status. Both the BSHS-B and EQ-5D-5L are validated questionnaires widely used in the burn population [61,62].

4.4.6 Data collection

Data was collected by three assessors, with the goal of the same assessor performing follow-up assessments in the same participants. While therapists and assessors were not blinded to group assignment, they were blinded to results of the muscle size assessment. This was achieved by pseudonymization of the exported ultrasound images, which were analyzed by a party without clinical involvement (DRS).

4.4.7 Sample size

A target sample size of 58 participants was calculated using G*Power 3.1.9.2 based on a similar study by our group in Belgian burn centers [34]. To detect a group difference of 0.055 cm of QMLT with 80% power (alpha = 0.05, SD = 0.073, ES = 0.752), and taking an estimated dropout of 33% into account, 44 participants were required per study arm (n=29 after dropout).

4.4.8 Randomization

Following the baseline assessment, participants were randomly allocated to either receive standard-of-care (control group) or standard-of-care and exercise training (exercise group). Participants were blinded to group allocation. Randomization sequence was generated using computerized minimization software (MinimPy) [63] with %TBSA and age as stratified factors and marginal balance as a distance measure to ensure group balance. To prevent selection bias, input of new participants into the minimization matrix was completed by a party (DRS) blinded to participant characteristics other than %TBSA and age needed for stratification.

4.4.9 Data analysis

Group comparisons of characteristics and baseline values of the study outcomes were performed using either independent t-tests, Mann Whitney U test, or Fisher's Exact test, as appropriate given the data type and normality. The effects of the experimental intervention on all dependent variables were tested using linear mixed models. Normality of the residuals was examined by histogram and homoscedasticity was checked by plotting the residuals vs. the predicted values. To account for individual participants' change over time, the models employed subject ID as a random effect. Group type, weeks from baseline and their interaction effect (signifying the added effects of the experimental intervention) were used as fixed effects. The regression models furthermore controlled for a number of covariates, including %TBSA, age, gender, presence of inhalation trauma, postburn days until baseline, length of stay in the intensive care unit, duration of mechanical ventilation, and baseline values of study outcomes. These covariates were added by stepwise forward modeling to avoid multicollinearity as long as the two following conditions were met: 1) statistical significance of the respective covariate at $p<0.05$ and 2) substantial model fit improvement as evaluated by a decrease of ≥10 points in the corrected Akaike information criterion (AICc) [64]. Separate models were fitted for baseline to six weeks and from six to twelve weeks, as the assumption of linearity was violated for a combined model from baseline to 12 weeks for all outcomes. This study made use of an intention-to-treat analysis for missing data. For the analysis of the muscle force values, models could only be fitted for the period between six to twelve weeks, as pain during the baseline assessment interfered with the validity of the muscle force assessment. Statistical significance was set at $p<0.05$, and analysis was performed using JMP® Pro 17.0.0 (SAS Institute Inc., Marlow, UK).

4.5 Results

4.5.1 Participant flow

Participant flow throughout the study period is shown in Figure 5. Overall, formal informed consent was obtained from a total of 71 eligible participants upon admission to the burn center. Of these, thirteen participants dropped out prior to the baseline assessment and random group allocation (early discharge due to financial reasons n=9, withdrawn consent n=2, death n=1, amputation n=1). The remaining 58 participants underwent random group allocation to the exercise (n=29) or control group (n=29) following the baseline assessment. Data from these 58 participants formed the basis for all reported baseline and outcome analysis. Eleven participants (exercise n=7, control n=4) dropped out between the baseline assessment and the six-week assessment (financial reasons n=7, COVID19-related measures n=2, pain due to previous bilateral hip prosthesis n=1, withdrawn consent n=1),

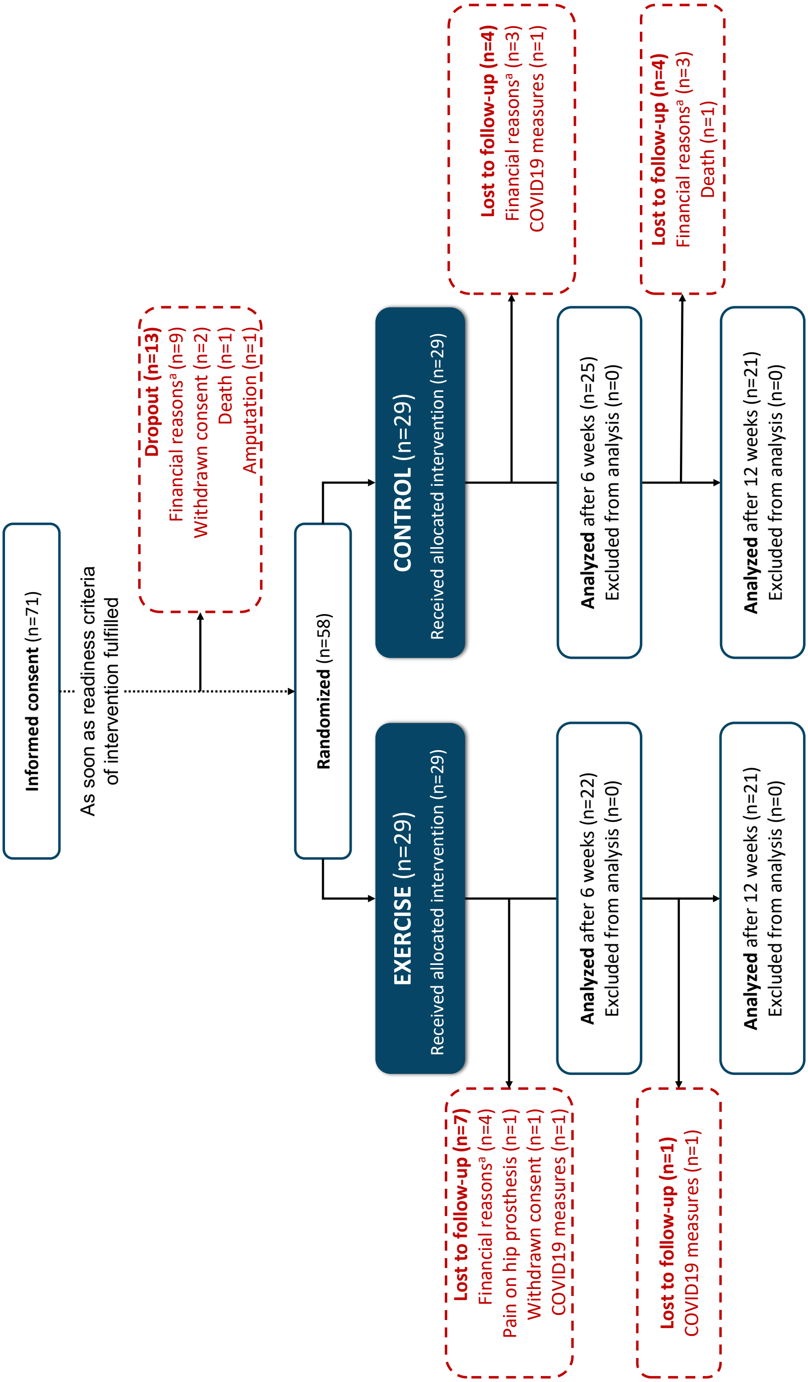

Figure 5. Study flow diagram. ^{a}High out-of-pocket expenses associated with burn center stay resulting in early discharge.

and a further five participants (exercise n=1, control n=4) dropped out between the six and twelve weeks assessment point (financial reasons n=3, COVID19-related measures n=1, death n=1). The dropout of participants related to the COVID19 pandemic were the result of a shortage of rehabilitation staff due to state-enforced quarantine measures, rendering it impossible to continue study treatments.

4.5.2 Characteristics

Clinical characteristics of the sample are presented in Table 1. Recruited patients were on average 42 [95%CI 40-45] years old, had burns ranging from 40 to 94 %TBSA [median 54%, IQR 48-70%] of which almost all [median 95%, IQR 87-100%] were full thickness burns and had burns on their lower limbs (98%). No participants tested positive on daily nuclear acid testing for a SARS-COV2 infection during the study period. The majority of participants (86%) were mechanically ventilated following admission and 38% experienced septic episodes. All subjects underwent multiple grafting surgeries during the study period. Besides the number of postburn days until baseline, clinical characteristics were comparable between groups.

	Exercise (n=29)	Control (n=29)	*p*-value
Gender	7 Females / 22 Males	8 Females / 21 Males	0.764
Age, mean [95%CI]	43 [40;46] years	42 [38;46] years	0.581
TBSA, median [IQR] (range)	60% [45;67.5] (40-94)	50% [48;70] (40-80)	0.645
Full thickness, mean [95%CI]	54% [47;61]	51% [46;57]	0.501
Lower Limb burns	n = 28 (97%)	n = 29 (100%)	0.313
Burn type			0.111
- Flame	n = 16 (55%)	n = 23 ((79%)	
- Chemical	n = 6 (21%)	n = 5 (17%)	
- Scald	n = 5 (17%)	n = 1 (3%)	
- Contact	n = 2 (7%)	n = 0 (0%)	
Inhalation trauma	n = 7 (24%)	n = 6 (21%)	0.753
Duration mechanical ventilation, median [IQR]	4.5 [3;9.5] days	6 [4;9] days	0.618
Number of surgeries, median [IQR]	4 [3;5]	4 [2.5;5]	0.269
Number of infections, median [IQR]	2 [1.25;4]	2 [1-3]	0.329
Revised BEAUX score, mean [95%CI]	107 [97;117]	102 [95;109]	0.406
Length of stay burn ICU, median [IQR]	7 days [0;18]	10 days [0;12.8]	0.969
Length of stay burn center, median [IQR]	92 days [61;110]	91 days [84;107]	0.546
Postburn days until baseline, median [IQR]	7 [5;9] days	9 [6;12] days	0.045

Table 1. Clinical characteristics. 95%CI, 95% confidence interval; IQR, interquartile range; TBSA, total burn surface area; LOS burn ICU, length of stay in the burn intensive care unit; Postburn days until baseline refers to the point in time when participants met readiness criteria to start the assigned study intervention.

As such, the exercise group met the readiness criteria to start the experimental intervention two days earlier than the control group (7 versus 9 days median, p=0.045). With respect to baseline comparisons of outcomes, the exercise group presented with significantly larger baseline QMLT (p=0.009). Groups were well-matched in all other outcomes at baseline (see Table 1; and Table S1 in the supplementary material).

4.5.3 Feasibility and safety

On average, participants in the exercise group followed 3.2 exercises sessions [95%CI 2.9-3.5] per week, with an attendance rate of 93% [95%CI 91-96]. Grafting surgery and associated postsurgical bedrest were the main reason for not completing the exercise protocol, accounting for an average total of three sessions [95%CI 1.8-4.2] lost per participant. None of the exercise sessions were ceased prematurely due to pain. Similarly, participants did not require additional analgesia following exercise sessions. Few adverse events of the experimental intervention were observed. Four participants experienced postural hypotension during two to three sessions when transitioning from in-bed to out-of-bed exercises. Furthermore, participants in the exercise group developed blisters after wound closure more frequently than participants in the control group. Of all observed blisters, approximately 70% occurred in the exercise group, and 30% in the control group, and were more commonly located over joint surfaces where friction and pulling forces might have been causative factors. Blisters were all transient, mostly resolved spontaneously and did not interfere with exercise training.

4.5.4 Muscle size

Muscle size decreased from baseline to six weeks in both groups, with a more pronounced decrease in the control group (Figure 6). There was a significant interaction effect for exercise over time, with a mean retention of 0.306 cm of QMLT and 0.294 cm2 of RF-CSA from baseline to six weeks attributed to the administration of early exercise (Table 2). From six to twelve weeks of follow up, the exercise group showed a faster recovery of QMLT (0.246 cm, p=0.010) and RF-CSA (0.342 cm2, p<0.001).

		Variable	β-coeff.	*p*-value	95%CI	
QMLT	0-6 weeks	Group[Exercise]	0.056	0.461	-0.094	0.206
		Week	-0.117	<.001	-0.143	-0.092
		Group[Exercise]*Week (cm)	0.051	0.010	0.013	0.088
		Baseline QMLT (0 weeks) (cm)	0.889	<.001	0.804	0.975
	6-12 weeks	Group[Exercise]	-0.193	0.176	-0.476	0.090
		Week	0.017	0.118	-0.004	0.038
		Group[Exercise]*Week (cm)	0.041	0.010	0.010	0.071
		Baseline QMLT (6 weeks) (cm)	0.939	<.001	0.864	1.014
RF-CSA	0-6 weeks	Group[Exercise]	0.029	0.753	-0.155	0.213
		Week	-0.080	<.001	-0.112	-0.048
		Group[Exercise]*Week (cm^2)	0.049	0.045	0.001	0.098
		Baseline RF-CSA (0 weeks) (cm^2)	0.898	<.001	0.823	0.973
	6-12 weeks	Group[Exercise]	-0.336	0.021	-0.619	-0.054
		Week	0.004	0.718	-0.017	0.025
		Group[Exercise]*Week (cm^2)	0.057	<.001	0.026	0.088
		Baseline RF-CSA (6 weeks) (cm^2)	0.996	<.001	0.933	1.059

Table 2. Regression models for ultrasound-derived muscle size parameters, adjusted for baseline values. 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.

4.5.5 Muscle force

Lower limb muscle force increased in both groups between six and twelve weeks of follow-up, with a significantly larger increase observed in the exercise group (interaction effect p<0.001) (Table 3). The impact of exercise over this period increased the muscle force by 19 newtons, equivalent to 19.5% of group mean force values.

		Variable	β-coeff.	*p*-value	95%CI	
Lower limb muscle force	0-6 weeks	Group[Exercise]	-18.631	0.007	-31.971	-5.290
		Week	2.193	<.001	1.168	3.219
		Group[Exercise]*Week (N)	3.102	<.001	1.604	4.601
		Baseline value (6 weeks) (N)	1.002	<.001	0.942	1.063

Table 3. Regression models for leg muscle force, adjusted for %TBSA. 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; TBSA, total burn surface area

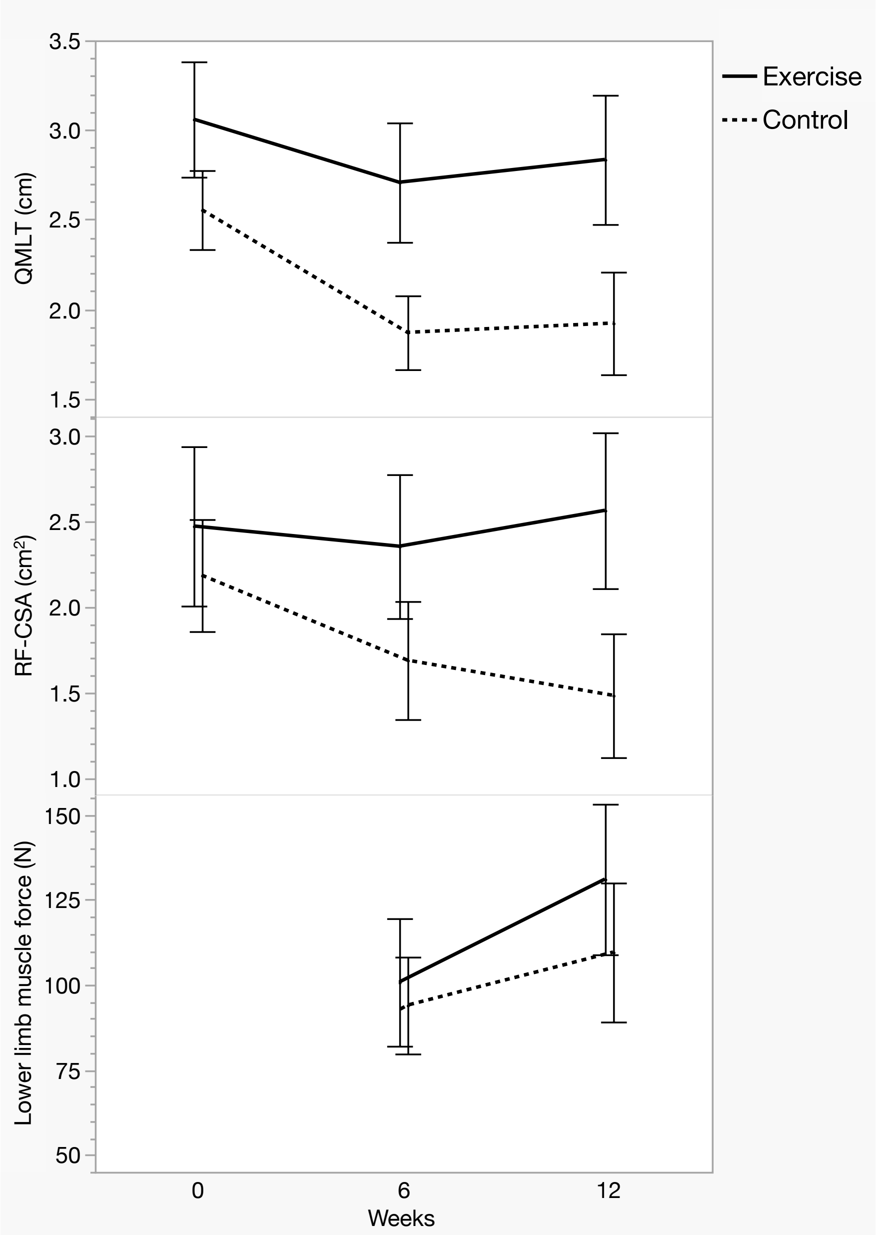

Figure 6. Group means for ultrasound-derived muscle size parameters and lower limb muscle force. Data presented as unadjusted means and error bars that depict 95% confidence intervals. Baseline values for lower limb muscle force are not shown as pain rendered the muscle assessment invalid at this time point.

4.5.6 Health-related quality of life

Baseline scores of all quality-of-life outcomes showed substantial impact of the burn injury on disease specific and generic quality of life, with highly negative scores on the EQ-5D-5L health utility index, indicating health states perceived to be worse than death at baseline (supplementary material Table S1). Both groups displayed comparable recovery trajectories over time in EQ-5D-5L parameters, with non-significant between-group differences (supplementary material Table S2). With respect to the assessed BSHS-B subdomains, time trajectories of recovery were comparable between baseline and six weeks of follow up, however, from six to twelve weeks the control group did not exhibit the continued improvement the exercise group did (Figure 7), with a significant interaction effect favoring the exercise group for the BSHS-B domains 'affect' (p=0.022) and 'interpersonal relationships' (p=0.040).

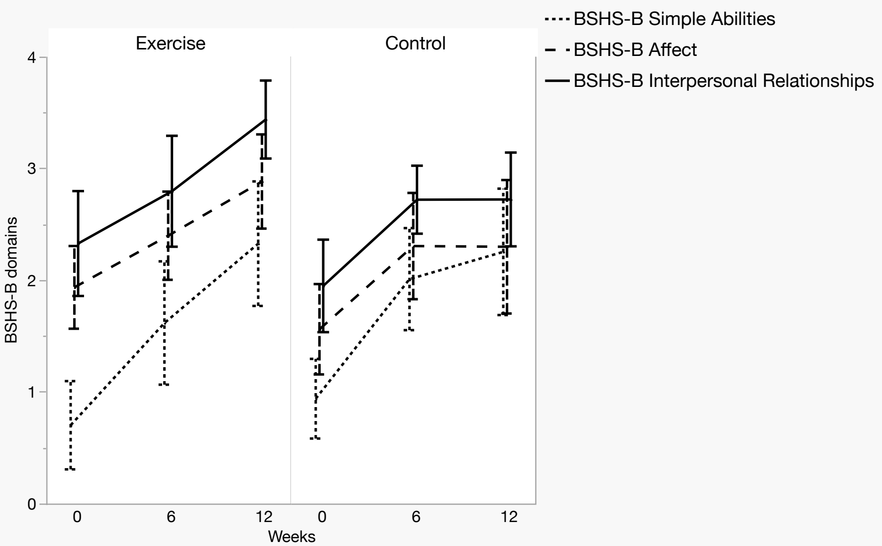

Figure 7. Group means for BSHS-B subdomains. Data presented as unadjusted means and error bars that depict 95% confidence intervals.

4.6 Discussion

The main findings of this study indicate that early exercise training was associated with a protective effect on muscle size and force reduction during the first six weeks of exercise, and an improved recovery of muscle size and force in the second six-week training period. No evidence of benefit for any of the assessed quality-of-life parameters could be found in the first six-week training period, whereas in the second six-week training period, early exercise training was associated with an improved recovery in the BSHS-B subdomains 'affect' and 'interpersonal relationships'.

The administered training protocol succeeded in allowing participants to commence exercise at a crucial point in time (i.e. approximately one week after burn center admission). As such, our data shows that the negative impact of severe burn injury on muscle metabolism can be countered early on, as observed by a reduced loss of muscle size in the first six weeks of exercise. This is highly relevant as alterations in muscle metabolism are thought to be most prevalent in the first few weeks postburn when the hypermetabolic response reaches its peak [2,37,65]. Notably, while significant, our results may underestimate the true effect size of exercise training on muscle size in the first six weeks of exercise training. This is likely, because the exercise group presented with a significantly larger baseline muscle size than the control group. Larger baseline muscle size is associated with a greater loss of muscle over time [45]; an observation we have previously also shown in burn patients [34]. Such an inverse relationship is likely the result of a more-to-give, more-to-lose paradigm, with larger muscles functioning as larger protein reserves that are more easily sacrificed as fuel for wound healing and increased energy demands. In contrast, patients with smaller muscle protein reserves reach a depleted status earlier, and have consequently less to spare. In that regard, maximizing the maintenance of muscle mass should be a therapy goal that is both desirable and acceptable during the acute phase of burns.

Few studies have evaluated the effects of early exercise training on muscle wasting and muscle force. While our results corroborate findings of improved muscle mass and strength following exercise in animal burn models and pediatric burns during the acute phase of burns, and adult burns during later phases [66–69], they stand in contrast with findings from a similar study of adult burns by Gittings et al. (2021), who found no significant effects for fat-free mass or muscle force following four weeks of resistance training [29]. A plausible explanation for the contrast in findings is the difference in burn severity between recruited samples. Gittings et al. (2021) included non-severe burns between 5-40% TBSA (with the majority of patients at the lower end of burn severity) with a short burn center stay (median 12-13 days) [29]. Participants in the present study had severe burns ranging between 40-94% TBSA and spent a longer time in the burn center (median length of stay 91-92 days). Patients with minor burns might be overall less responsive to exercise as they likely undergo less muscle wasting and weakness than their severely burned peers. In addition, four weeks of exercise might not be long enough to elicit detectable changes in parameters of muscle mass and force. Indeed, a longer duration of early exercise training (up to eight weeks) has been shown to exert a significantly higher retention of muscle size and force in adults with predominantly non-severe burns [34]. Despite the short exercise duration in the trial by

Gittings et al. (2021), their exercise program had a positive impact on systemic inflammation [29]. This is noteworthy and highly desirable as inflammation is a significant contributor to postburn muscle wasting [70–72].

In regard to health-related quality of life, this study found no evidence of a significant influence of exercise training except for a significant improvement in the BSHS-B subdomains ‘affect’ and ‘interpersonal relationships’ between six and twelve weeks of follow up. While the low statistical power limits conclusions, it seems plausible that any benefits of exercise would be more detectable at later stages of recovery – stages when the true impact of the burn injury will have had more time to transpire [62]. The finding that exercise training improved the BSHB-B subdomain ‘affect’ and ‘interpersonal relationships’ more than standard of care alone might be traced back to the fact that participation in the exercise protocol provided an opportunity to engage with other burn patients in the exercise room and overcome previous physical boundaries. Exercise training has previously been shown to have a positive impact on mental health [73]. This is particularly relevant given that family visits were entirely prohibited in line with COVID19-related measures. The observed lack of effects in the other assessed quality-of-life parameters is in line with previous reports of early exercise in adults [34,74] and children [75]. Besides being underpowered to detect effects, another methodological aspect that could explain the lack of efficacy in the quality-of-life domain, is that our exercise training protocol was designed to achieve maximum metabolic modulation. This focus differs from more traditional burn rehabilitation protocols that have a primary focus on functional exercises [17]. Such exercises might be more applicable to patients’ quality of life. However, as postburn muscle wasting is commonly neglected as a metabolic sequela [17], we consider the lack of functional stimuli in our protocol an acceptable compromise. Lastly, as the administered training protocol in our study was challenging to many participants on multiple levels relating to their perceived health state (pain, anxiety, perceived safety, etc.), it is reassuring that we did not find any evidence of harm for the self-reported quality of life.

4.6.1 Clinical relevance

This study identified several benefits of early exercise training that have significant implications for clinical practice. Given that postburn muscle wasting remains a challenge in burn care, the preservation and recovery of muscle mass and muscle function are highly desirable therapeutic targets, particularly following severe burn injuries. This is the first study to show beneficial adaptations in muscle size and force resulting from early exercise training in adults with severe burns. Incorporating exercise training as an adjunct to standard care during burn center stay resulted in an average weekly retention of 0.05 cm in QMLT and 0.05

cm2 in RF-CSA in the first six weeks. Over six weeks this equated to 11 and 13% additional retention of baseline value, respectively, amounting to 26% after twelve weeks, compared to standard care alone. Considering that a loss of 10% postburn muscle mass has been linked to complications such as impaired wound healing, insulin resistance and an increased risk of infections [76,77], such an improvement should be considered clinically significant. Over the duration of burn center stay such a cumulative effect might lead to a faster recovery, shorter length of stay and reduced health care expenses. However, as the length of stay in our study was highly confounded by the ability of participants to afford out-of-pocket expenses associated with specialized burn care in China (leading to early discharge) [78], such secondary outcomes remain to be tested. To prevent high out-of-pocket expenses, many burn patients in China (as is the case in many other regions [79]) choose to forego rehabilitation, seen as an optional luxury of burn care. Consequently, burn patients often develop preventable long-term disability which impedes return to work and reinforces cycles of socioeconomic disparities. By establishing evidence in support of the efficacy of burn rehabilitation, it is hoped that the results of this study will increase its perceived value and encourage adoption into clinical practice [80].

Widespread inconsistencies in the use of exercise training during burn center stay have hindered its implementation [78,81,82]. The fact that burn patients and clinicians often perceive exercise training during the acute phase of burns as highly challenging is certainly a contributing factor [83]. The present study supports the overall safety and feasibility of exercise training commenced shortly after burn center admission. The higher incidence of postburn blistering in the exercise group was not interpreted as a serious complication, given that blistering is a common transient occurrence during burn recovery that mostly resolves spontaneously [84]. However, blistering might indirectly exert a potential negative impact on scar formation by interfering with the use of compression garments and causing prolonged healing. While it did not affect the use compression garments in our study, further study of the effect of exercise-induced blisters on scar quality is needed to establish this as a complication.

This study also underlines the importance of a concerted effort of the multi-disciplinary team to achieve early exercise participation. In many high-income regions, patients with severe burn injuries are often sedated and mechanically ventilated for prolonged periods of time [85] - a practice that interferes with exercise participation [83]. It is of interest that the duration of mechanical ventilation in our sample, on average four to six days, was far lower than has been reported in other regions [85], pointing to the potential of early extubation to facilitate early exercise [86,87].

4.7 Conclusion

The evidence provided by this study supports the inclusion of exercise training into the acute management of adults with severe burn injury. Early exercise training is a safe and efficacious strategy that appears to promote the retention and recovery of postburn muscle size and muscle strength.

4.8 Strengths and limitations

There is currently little evidence surrounding exercise training during burn center stay in severely burned adults. A major reason for this certainly relates to the fact that severe burns are less common in regions where most of the research funding exists and where rehabilitation is most established. In light of this, a main strength of this study is that it recruited participants from the largest burn center in China, where, similar to other low-/middle income countries, severe burn injuries are more common and rehabilitation is still considered a young profession [78,80]. With over 5000 admissions annually, the department of burns in Wuhan serves a population of almost 60 million as the only burn center in the province of Hubei [88]. The present study currently forms the first and largest clinical trial to date incorporating resistance and aerobic training in severely burned adults commenced during the acute phase of burns. Another strength of this study pertains to the use of ultrasound to quantify muscle size – a tool with good clinical applicability to monitor postburn muscle wasting at all stages of burn recovery [52], which is particularly relevant given that muscle wasting is not commonly measured in burn care and intervention trials [17,89].

Several limitations need to be considered when interpreting the findings of this study. Firstly, it is important to note that the comparator group in our study followed a relatively passive standard-of-care treatment that did not include ambulation, and aerobic or resistance training, as is common in the majority world. While this affects the applicability of our findings to settings with a more active standard-of-care, it supports keeping resistance and aerobic training as part of the standard-of-care, if already provided, or adding it if not yet included. A second limitation relates to potential performance and detection bias in our study, as is common in non-pharmacological trials [90]. Although it is our view that blinding of participants was successfully achieved, we cannot rule out that participants became aware of which group they were allocated to as no placebo intervention was provided to participants in the control group. However, none of the participants indicated knowledge of group belonging throughout the study duration. Likewise, we were unable to blind assessors, as the staff that carried out the outcome assessment also administered the intervention.

However, the potential of detection bias was minimized by 1) blinding assessors to the results of all previous outcome assessment, and 2) conducting the ultrasound image measurement of quadriceps muscle size, as the primary outcome in this study, by a party without clinical involvement (DRS). Lastly, it needs to be noted that the random allocation process failed to achieve group balance in the QMLT value at baseline, burn type, ICU length of stay. Although the latter two were not significantly different between groups and the former was controlled for in the statistical analysis, the impact of these variables needs to be considered

4.9 Future directions

The positive impact of early exercise training on muscle outcomes, as shown in this study, leads to further questions about the underlying mechanisms. Understanding exercise-induced changes in systemic inflammation, hyperglycemia, insulin sensitivity, as well as anabolic and anti-catabolic actions will aid in optimizing exercise training delivery to better target postburn muscle wasting and related metabolic morbidity. Another area of particular interest for low-/middle income regions where financial access to exercise rehabilitation presents a major barrier, is its cost-effectiveness. Hospital length of stay, days until wound closure, and time till return to work relative to measures of disease burden are associated measures relevant to burn survivors and their families [91]. Future study designs should incorporate different experimental groups comparing different exercise programs, starting points (early vs. late), and include long-term follow-up beyond discharge where possible. Lastly, the elderly burn population is a challenging age group with prolonged convalescence and metabolic morbidity [92,93], that while excluded in this study to reduce sample heterogeneity, presents a particular group that may benefit from the early institution of exercise training.

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4.12 Availability of data

All data collected for this study can be obtained by correspondence with the corresponding authors.

4.13 Competing interests

None.

4.14 Authors' contributions

All authors have made substantial contributions to the study. DRS trained clinical staff in the study intervention and assessment, supervised all study proceedings, carried out data analysis, and drafted the manuscript. TFR, HD, ZY administered all treatments, and carried out data acquisition. WGX was involved in clinical trial supervision. EVB, UVD, and JW contributed to the conception and design of the study. All authors contributed to the revision of the manuscript and approved the final manuscript.

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General discussion

1. Overview of aims

This doctoral project was initiated to increase our understanding of the role of early exercise training in the management of postburn muscle wasting in adults with burn injury. To test the hypothesis that early exercise training has an additional effect on postburn muscle wasting during burn centre stay in adults with moderate to severe burn injury, three subgoals were identified, forming the three parts of this thesis.

Goal 1

The first goal was to provide an overview of the current-practice of inpatient rehabilitation, focussed on the areas of exercise prescription, management of metabolic sequelae, and clinician's treatment priorities, rationale, and knowledge of metabolic sequelae. European burn clinicians were surveyed to identify the current practice of adult inpatient rehabilitation across Europe.

Goal 2

The second goal was to develop and study a clinical tool to aid in the assessment of postburn muscle wasting. To this end, a feasibility and reliability study of quadriceps ultrasound measurements was carried out in adults with burn injury during the acute phase.

Goal 3

The third goal was to investigate the efficacy of exercise training administered across the spectrum of adult burns during the acute phase in multiple burn centres with respect to muscle size, muscle strength, and health-related quality of life. Two prospective intervention trials were performed across different burn centres in with moderate or severe burns comparing the standard-of-care treatment to standard of care plus exercise training.

2. Synthesis of main results

Part 1: Current practice of inpatient exercise rehabilitation

The survey, as published in *Burns & Trauma* [1], identified numerous shortcomings and inconsistencies in multiple aspects of current rehabilitation practice. In terms of exercise training, resistance and aerobic training were not consistently provided throughout burn centre stay. This was particularly pronounced during the early phases of burn centre stay (before out-of-room mobility was possible), during which rehabilitation efforts predominantly involved range of motion and functional exercises. Few burn therapists made use of predefined in-/exclusion criteria for active exercise. The restoration functional status was rated as the most important rehabilitation goal, whereas the treatment of burn-induced metabolic sequelae, including muscle wasting, was overall rated as the least important. Large interdisciplinary differences were present in readily-available knowledge of burn-induced metabolic sequelae, with burn therapists demonstrating the least knowledge compared to medical doctors and dieticians. Interestingly, knowledge of metabolic sequelae was significantly associated with higher importance ratings of the prevention of metabolic sequelae. With respect to the management of metabolic sequelae, including muscle wasting, hypermetabolism, and insulin resistance, the survey found considerable variation and an overall lack of the assessment and intervention strategies. The majority of clinicians (85%) reported not to measure muscle wasting, and almost 30% of clinicians did not make use of any intervention strategies that targeted muscle wasting.

Overall, the main findings of the survey reveal considerable non-uniformity in inpatient rehabilitation practices concerning the use of exercise training and the management of metabolic sequelae. A limited understanding of metabolic pathophysiology and a low importance rating of maintaining metabolic health, particularly in burn therapists, was identified as a factor that might explain the low provision of early exercise training as well as the infrequent use of metabolic sequelae as assessment and therapy targets. To address the reported lack of assessment of muscle wasting, part 2 ‘assessment of muscle wasting’ was initiated.

Part 2: Assessment of muscle wasting

In chapter 2, a feasibility and reliability study of quadriceps muscle size measurements by B-mode ultrasound, published in *Burns* [2], is presented. The main findings indicate that ultrasound is a reliable and feasible tool that can be used in the acute burn setting to monitor changes in quadriceps muscle size. The comparison of burn with healthy control subjects indicated that the source of observed measurement variability is likely not population-dependent but is to be found in methodological aspects of the measurement protocol itself.

Accordingly, several methodological aspects of the employed protocol were evaluated. First, for all measured parameters (quadriceps muscle layer thickness, QMLT and rectus femoris cross-sectional area, RF-CSA), averaging the combined result of three measurements yielded higher reliability values than using a single measurement alone. Secondly, carrying out the QMLT measurement with no compression resulted in better reliability than using the maximum compression technique. Likewise, minimal detectable changes relative to mean score were smaller using no compression than maximum compression. Thirdly, no difference in reliability was observed when comparing two measurement locations for QMLT (halfway vs. two-thirds of the distance between the anterior superior iliac spine and the superior patellar pole). Using the average of three measurements, the 95%CI of intraclass correlation coefficients were all above 0.9 for QMLT and above 0.89 for RF-CSA, indicating good to excellent reliability between raters.

The feasibility analysis showed that the no compression technique to determine QMLT was deemed feasible in 95% of attempted measurements, with the feasibility limited by donor site dressings or exceptionally large thigh sizes, interfering with ultrasound penetration. QMLT measured by maximum compression was feasible in 90.5% of cases, with pain on open wounds as the reason for failed measurement attempts. 97% of all attempted RF-CSA measurements were successfully completed, with non-penetrable donor site dressings accounting for all failed attempts. Feasibility of measurements generally improved over the course of burn centre stay, with all failed sessions occurring at admission and during the first follow-up measurement at a mean of 3.6 weeks following admission.

Based on these findings, a three-step decision-making tree was developed in line with clinical scenarios to guide burn clinicians and researchers in the choice of ultrasound parameters. Overall, this study demonstrated that ultrasound provides reliable and feasible values of quadriceps muscle size, and that the choice of employed ultrasound methodology can be adapted according to various clinical scenarios commonly encountered in acutely burned patients.

Part 3: Effects of early exercise training

In part 3, two prospective trials of early exercise training in adults with mostly moderate burn injury, published in *Burns* [3] (chapter 3) and severe burn injury (chapter 4), are presented.

Early exercise training, added to the standard-of-care treatment administered to adults with predominantly moderate burn injuries during burn centre stay, induced significant improvements in ultrasound-derived quadriceps size, grip strength, hip flexion, and knee extension compared to standard of care alone. Besides self-reported hand function, no benefits were found for early exercise training in health-related quality of life, as assessed by the Burn Specific Health Scale-Brief and EQ-5D-5L questionnaires during the trial period.

The administered exercise training protocol proved feasible in the majority of cases, with 80% of all planned exercise sessions commenced but not fully completed, and 64% of sessions fully completed according to protocol. Main factors that interfered with successful completion of exercise session included surgery or postsurgical immobilisation (15% of failed sessions), pain (11%), and a lack of patient cooperation (3%). This multicentre trial thus showed that the tested exercise training protocol is a safe and feasible therapeutic strategy to counteract acute changes in muscle size and muscle strength of adults during burn centre stay.

The randomised controlled trial in severely burned adults, as reported in chapter 4, found several effects in support of early exercise training as an addition to the standard-of-care treatment. In the first six weeks of follow-up, early exercise training led to significant retentions of ultrasound-derived parameters of quadriceps muscle size compared to standard-of-care alone. Between six and twelve weeks of follow-up, significantly greater increases were observed in the early exercise training group in muscle size parameters and lower limb muscle strength, compared to control group. In terms of health-related quality-of-life, the assessed BSHS-B domains increased from baseline to six weeks in both groups, and continued to increase more in the following six weeks in the early exercise training group, with significant effects in the BSHS-B domains 'affect' and 'interpersonal relationships'. There were no significant between group differences in EQ-5D-5L parameters.

Early exercise training was found to be safe and feasible, with an attendance rate of 93% and no serious adverse events reported. The findings of this randomised controlled trial confirm that early exercise training can increase the retention and recovery of muscle size and strength in severely burned adults, and does not harm the health-related quality of life of burn survivors.

Overall, the results of the two intervention trials reported in part 3 provide evidence of the preventative and restorative effects early exercise training on burn-induced changes in muscle size and strength.

3. Critical Review

The different studies reported in the three parts of this dissertation addressed the overall aim to elucidate the role of early exercise training in the management of postburn muscle wasting. The assessment and treatment of postburn muscle wasting was identified as a key gap in the current clinical practice (i.e. survey, chapter 1)– a gap addressed by the subsequent studies on quadriceps ultrasound (i.e. assessment, chapter 2) and early exercise training (i.e. treatment, chapter 3 & chapter 4).

Underlying the clinical decision-making whether to offer exercise training during burn centre stay is a cost-benefit analysis, wherein one may outweigh the other. The costs of early exercise training are primarily short-term in nature. They involve the fact that engaging in intense resistance and aerobic exercise while recovering from acute burn wounds is often counter-intuitive to many patients and might come with a sense of discomfort due to factors such as pain, sweating, and fatigue. This sense of discomfort, while temporary, might compromise the clinician-patient relationship resulting in a lower patient satisfaction. Safety concerns associated with early exercise training further adds to the clinician's calculation of perceived costs. This is reasonable, as a recent systematic review of exercise after burn injury identified a lack of safety data of exercise, even when commenced after burn centre stay [4]. The mutually beneficial 'easy way out' for clinicians and patients is then to avoid or postpone exercise training to later stages when exercise is perceived as less difficult with no apparent threat to patient safety.

The findings of the intervention trials (chapter 3 and 4) contribute to our understanding of the overall safety and feasibility of exercise training during the acute phase of burns across the spectrum of burn severity. In the Belgian sample, the provided exercise training had a session feasibility of 80%, whereas in the Chinese sample, these reached 93%. An explanation for the difference in feasibility is not easy to provide, but we hypothesize that the scalp as a standard donor site location in the Chinese sample (as opposed to the thigh in the Belgian sample) as well as an increased patient cooperation rooted in a more authoritative Chinese culture led to a higher feasibility. The minor adverse events such as nausea and blistering that were associated with participation in the administered exercise programmes do not form substantial reasons to delay exercise initiation. The largely modifiable nature of many of the observed reasons that interfered with exercise speaks to the potential to further improve its feasibility. As the main interfering reasons observed in the both trials, grafting surgery (primarily split-thickness procedures) is generally followed by a strict period of immobilization. While it has shown to be safe to considerably shorten this period in some cases [5], exercise can also be tailored to the individual needs of the patient, with training non-grafted body parts and isometric exercise as options that allow exercise continuity. Pain, often associated with open wounds, was another commonly encountered barrier to exercise that was best managed when prophylactic analgesia was provided ahead of exercise sessions, and the timing of exercise was coordinated with daily painful procedures after being discussed at daily patient rounds. This underscores the importance of optimal pain management and a concerted effort by the multidisciplinary team. Similarly, educating patients on the importance of early exercise might effectively counteract uncooperative patient attitudes including fear of movement.

In addition to high perceived costs of early exercise training, its benefits on metabolic outcomes, such as muscle wasting are poorly understood. The survey revealed a lack of understanding how exercise training can impact metabolic outcomes. This finding mimics the lack of efficacy data that exists for exercise training during burn centre stay.

In 2016, the American burn association has published the first practice guidelines on exercise prescription for resistance and aerobic training based on a narrative review of the literature [6]. The authors concluded that there is ‘strong evidence’ to support the use of exercise training in adult burn patients for improving outcomes including in physical function, gait measures, muscle strength, lean body mass, quality of life, and aerobic fitness. The strength of these recommendations, however, are not in line with conclusions by two systematic reviews on postburn exercise training that have since been published [4,7]. Flores et al. (2018) carried out a systematic review of randomized and non-randomized controlled trials on resistance and aerobic exercise, and found only four studies in adult burn patients, concluding that there is only low to moderate evidence for exercise training [4]. Gittings et al. (2018) found two trials in adults in their systematic review of resistance exercise after burn injury, and reached similar conclusion of low to very low evidence supporting the use of resistance training after burns [7]. The low level of evidence for the efficacy of exercise is further compounded by the fact that none of the included studies in adults in the two systematic reviews or the practice guidelines took place during the acute phase of burns. All included studies reported commencing exercise after burn centre discharge, or exceptionally after wound closure - leading the practice guidelines by the American burn association to recommend exercise programmes to be started at any time point following burn centre discharge [6]. The observed lack of clinicians’ consistent adoption of resistance or aerobic training during burn centre stay, as described in chapter 1, is then not a surprising finding. In addition, meta-analyses in both systematic reviews found no significant effects with respect to knee extensor strength in adults, while none of the included studies in adults investigated changes in muscle mass. The survey findings therefore overall reflect the paucity of scientific research into the effects of early exercise training on metabolic outcomes in the adult burn population at the time of survey completion (i.e. 2018 – 2019).

Together with low importance ratings and low understanding of metabolic sequelae, as reported in the survey in chapter 1, the lack of efficacy data of early exercise training in adult burns, results in a cost-benefit analysis wherein the perceived costs outweigh the benefits. Figure 1 depicts this paradigm.

By presenting evidence in support of early exercise training on muscle wasting across the spectrum of burn severity in adults with burn injury, the intervention studies as presented in chapter 3 and 4 address the lack of understanding of the effects of exercise in burn clinicians as identified by the survey in chapter. The findings of the intervention studies indicate that early exercise training can improve the retention and restoration of muscle size and muscle strength over time. An increased understanding of the efficacy of early exercise training helps shifting the cost-benefits balance towards providing early exercise training.

Similarly, understanding the true cost of not providing early exercise training seems conditional to understanding its potential benefits. However, as reported in chapter 1, there appears to be a low awareness of muscle wasting as a costly metabolic sequela that is most prevalent during the acute phase of burns. A key source of this low awareness among clinicians might be the lack of monitoring of parameters of postburn muscle wasting. Not measuring the extent of muscle wasting creates a vicious cycle wherein clinicians are left ignorant to its occurrence and timely therapy is not initiated.

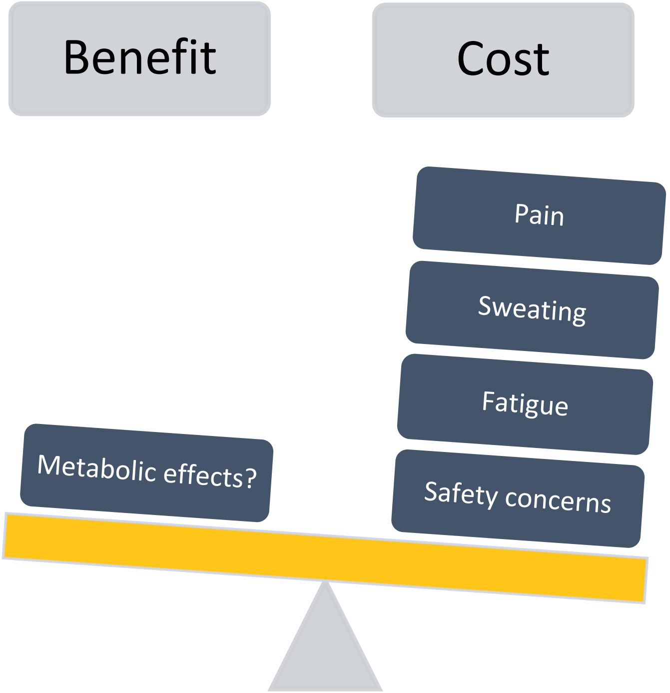

Figure 1. Theoretical factors included in the clinician's cost-benefit analysis of early exercise training. This figure illustrates how the perceived costs of early exercise training and an incomplete understanding of its beneficial effects on metabolic outcomes such as muscle wasting negatively impact the clinician's choice for or against early exercise training.

Interestingly, there appears to be a gap between the use of body composition assessment in research and use in clinical practice. In the two previously mentioned systematic reviews that evaluated the use of postburn exercise training in children and adults, the assessment of muscle wasting was performed by 37% (7 out of 19) and 64% (7 out of 11) of included studies, respectively [4,7]. The results of our survey, however, showed that few burn clinicians (15%) measure muscle wasting. Such dissonance between research and clinical practice might be rooted in several factors.

First, there seems to be a low appreciation of muscle wasting as an outcome important enough to be measured in clinical practice. The survey findings confirm this to be the case by showing that there is a low understanding and perceived importance of postburn metabolic outcomes, that include muscle wasting.

Secondly, the limited clinical availability and feasibility of the assessment tools used in research render their use in clinical practice unfeasible. Dual energy X-ray absorptiometry is the most common tool used in burns research for the determination of lean body mass [4,7]. While described as the gold standard in burns [8], it lacks applicability at the bedside and may compromise infection control standards. Bioimpedance spectroscopy, another method previously used in burns research [9], is a simple bedside tool for body composition monitoring, but as a relatively new tool in burns, is often not available in burn centres. Moreover, its interpretability is complicated by the use of raw parameters, necessary to avoid using non-valid predefined formulas that are based on healthy populations. Lastly, its use to assess longitudinal changes in the presence of weight loss is controversial and has limited accuracy [10,11].

Another factor relates to the timing of body composition measures used in research. As discussed earlier, studies of exercise in burns have predominantly taken place in the post-acute phase of recovery [4,7], thereby emulating the lack of focus of muscle wasting during the acute phase of burns. Clinical practice might then mimic research practice by focussing on the restoration of muscle mass at later stages of recovery, rather than its preservation at earlier time points. This presents a missed opportunity to minimise postburn muscle wasting during a time when it develops and reaches its peak [12–14].

To the best of our knowledge, the two intervention trials in this doctoral project are the first reports in the adult burns literature that used changes in muscle size as a primary endpoints of early exercise training. Such choice of outcome underscores the importance of monitoring changes in musculature during burn centre stay.

Ultrasonography in burn care is traditionally carried out by medical doctors, who make up the only discipline to use of this technique, most often for catheter placement, cardiac monitoring, and peripheral pulsometry. At the same time, muscles are conventionally seen as the responsibility of burn therapists. Such a division of responsibilities might have created a clinical situation wherein the assessment of muscle wasting by ultrasound has "fallen through the cracks" of multidisciplinary practice. This emphasizes the potential of multidisciplinary team to work together and create an environment of shared expertise that facilitate the assessment of muscle wasting.

Additionally, ultrasound is often perceived as a training-intensive tool reserved for experts. However, previous studies investigating the reliability of quadriceps measurements in newly trained staff have achieved good results, showing that quadriceps ultrasound is in fact a low-threshold technique that does not require extensive training [15–17]. However, the fact that there is a plethora of different measurement protocols and no consensus for which method is the best [18], has been a likely hindrance to its use in practice. Moreover, in the acute burn setting, open wounds, pain, wound dressings, and varying fluid statuses are other disease-specific barriers that likely impact the clinician's sense of perceived clinical feasibility.

The findings of the study of quadriceps muscle size measurements by ultrasound, as presented in chapter 2, aids the clinical adoption of ultrasound by addressing methodological questions relevant to the acute burn setting. The results of this study indicate that ultrasound is a feasible and reliable tool widely available in burn centres that can be used to measure muscle size during the acute phase of burns – a time during which most changes in muscle mass occur [12–14].

In conclusion, the findings accumulated by all the studies included in this doctoral dissertation, combine to advocate that the clinical benefits of targeting postburn muscle wasting by early exercise training outweigh its costs. We showed this by demonstrating that muscle wasting is an important outcome that can be captured by ultrasound, and by establishing the safety, feasibility, and efficacy of early exercise with respect to changes in muscle size and strength.

4. Methodological considerations

Strengths

A major strength of this dissertation lies in the aggregation of the different studies that build on each other. By surveying burn clinicians as to their standard of care, we were able to determine the generalisability of the findings of the two intervention studies. Studying the utility of ultrasound helped us understand and choose the specific methodology that was then used in the two intervention studies (chapter 3 and 4) to adequately measure changes in muscle size as primary endpoints.

The fact that multiple burn professions were surveyed was a methodological strength that allowed for an analysis of interdisciplinary differences. Including questions concerning the knowledge, motivation, and priority ratings enabled us to draw links between these and exercise prescription or the management of metabolic outcomes. These links had not been studied previously.

A major strength of the study on the utility of ultrasound in the acute burn setting (chapter 2) pertains to the inclusion of a healthy control group, allowing us to distinguish between operator-dependent and patient-dependent factors that impacted its reliability and feasibility. Although commonly used in the other populations, ultrasound has not been used for the assessment of muscle wasting in patients with burn injury. Thus, this study is the first and to date only study in the burns literature to do so.

The multicentre nature of both the ultrasound study (chapter 2) and the intervention study of exercise in Belgium (chapter 3) increased the external validity of the findings and allowed for a larger sample to be recruited. The inclusion of the randomized controlled trial in China (chapter 4) extended the reach of this doctoral project to more severely burned adults as well as other low-/middle income regions with similar standard of care treatment. With a true randomisation design and allocation concealment as opposed to the non-concealed quasi-randomised design of the intervention study in Belgium, the study in China was able to increase the evidence level for early exercise training and simultaneously provide a level of quality control to the Belgian study. To date, the intervention study in China forms the largest randomised controlled trial of early exercise training in severely burned adults – a population that is infrequently studied as most severe burn injuries occur in low-/middle-income regions where little research funding is available. The fact that the analysis of quadriceps muscle size as the primary endpoints in both intervention studies was carried out blinded minimizes the risk of detection bias in these studies.

Limitations

Although the survey pinpointed major gaps in the current-practice of inpatient burn rehabilitation, the results of the survey need to be interpreted with some caution, as survey participation was voluntary and we were unable to estimate the impact of non-responders. While non-response bias therefore needs to be considered, empirical evidence indicates that responders tend to be more eager, educated, and willing to improve [19,20]. Following this line of thought, the actual state of inpatient rehabilitation, including the rate of exercise provision and the knowledge and importance of muscle wasting may then be even worse in reality. Unequal representation of burn professions needs to be kept in mind when considering the inter-disciplinary comparisons.

Beyond the limitations already mentioned in the respective chapter of the study on the utility of ultrasound to measure muscle size, it needs to be understood that minimal detectable changes were not calculated based on temporal changes. Instead, its calculation was based on intra correlation coefficients and standard error of two raters, thereby providing an estimation of internal responsiveness [21]. As the use of a reference test such as magnetic resonance imaging or computed tomography was not feasible in the study, we were unable to determine the external responsiveness of ultrasound to accurately measure change of muscle size over time.

As mentioned in the limitation section in chapter 3, a methodological weakness of this study involved the method of group allocation (based on staff capacity in line with COVID-19 related measures). However, the fact that intervention study in China (chapter 4) made use of a randomized group allocation and found similar findings as the intervention study in Belgium strengthens the likeliness of the findings of both studies as well as the conclusions of this dissertation. Nevertheless, the fact that the two intervention studies were carried out in different regions and populations characteristics need to be considered when judging comparability and generalisability.

In addition to the limitations discussed in the respective sections of chapter 3 and 4, this doctoral project was unable to adequately analyse the effects of early exercise training on burn centre length of stay as well as quality of life. This was likely due to insufficient statistical power, the lack of long-term follow-up, and early discharge due to financial affordability as a confounding factor that was observed in the study in chapter 4. The latter observation limits the external validity of the study findings in chapter 4, as patients of lower socio-economic status were likely underrepresented.

5. Clinical implications

This doctoral project attempted to better understand the role of early exercise training in the management of postburn muscle wasting. The findings of this dissertation carry several important lessons that are applicable to the inpatient rehabilitation of individuals with burn injuries.

1. The findings of our survey show that metabolic outcomes are not consistently used as targets of exercise and assessment. Instead of metabolic outcomes, there was a focus on functional return. Clinically, therapists are taught to treat muscle primarily as a musculoskeletal organ, whereby exercise then has a large focus on musculoskeletal function. Treating muscles as a metabolic organ, requires seeing burn injury as an internal disorder with systemic consequences. The findings of our survey indicate that a higher understanding of postburn metabolic sequelae is associated with a higher importance rating of treating them. Thus, the first lesson of this dissertation is the need for a better understanding of burn-induced metabolic outcomes among clinicians. (Re-)education of burn clinicians would contribute to shifting clinical priorities towards a better management of metabolic outcomes. The fact that large interdisciplinary variation was present in the knowledge and importance ratings of burn-induced metabolic sequelae moreover points to the potential of interdisciplinary exchange as second strategy in addition to (re-)education to increase the understanding and perceived importance of metabolic outcomes. To this end, a burn centre culture that prevents the formation of 'islands of expertise' and facilitates intersectional burn care would certainly be helpful aspects to promote a greater appreciation of metabolic outcomes in burn care. A better understanding and higher importance ratings of metabolic outcomes would also be expected to motivate burn clinicians to include the monitoring of postburn muscle wasting in their clinical repertoire.

2. This brings us to the second lesson of this dissertation: There is a clinical need for a practical tool to monitor postburn muscle wasting during burn centre stay. By presenting quadriceps ultrasound as a feasible and reliable method to quantify parameters of muscle wasting during the acute phase of burns, this dissertation enables burn clinicians to monitor changes in muscle size and evaluate the effect of targeted interventions such as early exercise training. The choice of ultrasound parameter, measurement location, and compression technique can be adapted according to different clinical scenarios commonly encountered in the acute burn setting. With minimal detectable changes of on average 6% of mean quadriceps muscle layer thickness, the no-compression technique should be the measurement of choice. When this technique is not possible and the maximum-compression technique is used, it needs to be taken into account that any measured change below 15% might not be a real change. Clinicians may additionally decide to measure rectus femoris cross-sectional area, which on average yielded minimal detectable changes of 10% of baseline values. Clinically, the measurement of this parameter is more time consuming, however, has shown to better correlate with myofiber cross-sectional area

than thickness measurements in a study of critically-ill patients [22]. Recent evidence shows that adults with burn injury lost 23% of quadriceps muscle layer thickness within the first seven days of burn centre admission [14]. Given this extent of change, all analysed measurement methods should be able to detect real change in muscle size during this time frame.

3. The third lesson of this dissertation with major clinical implication is the finding that early exercise training is able to retain and improve the recovery of muscle wasting during burn centre stay across a wide spectrum of burn severity. The presented efficacy of early exercise training in aiding the prevention and restoration of muscle wasting presents a clinical opportunity that might be unique to the acute phase of burns. It is during this phase that most of the metabolic derangements develop, and that exercise could reap maximal benefits. To minimise postburn muscle wasting during burn centre stay is especially relevant in light of the fact that exercise training after hospital discharge is not commonly offered to burn survivors, as reported in our survey. The findings of this dissertation concerning the safety and feasibility show that early exercise training is a clinically realistic intervention strategy with low health risks for adults with moderate to severe burn injuries.

   In the absence of an agreed cut off for what constitute clinically meaningful change, it is difficult to judge whether the improvements in quadriceps muscle size, as observed in the two intervention studies, are also clinically relevant. According to empirical evidence, a lean mass loss of 10% is considered sufficient to elicit complications [23–25]. With a degree of improvement ranging between 11% to 26% depending on muscle size parameter, the observed effects of two intervention studies of early exercise training seem clinically meaningful. A generic cut off at 10%, however, negates the findings of both intervention studies that a larger muscle size at baseline (or greater retention until baseline), led to a greater loss over time, and vice versa. Patients with larger baseline muscle size have a larger functional reserve that can be spared. Conversely, those that start off with smaller muscle size, have less to spare. It would thus be facile to equate a greater amount of muscle wasting with a worse health impact. Therefore, taken together, both the admission muscle size and the extent of subsequent muscle wasting provide a better picture of individual health status.

6. Future directions

Several directions for future research flow forth from the presented findings in this dissertation. These will be described in the following section.

The survey findings, as reported in chapter 1, point to the potential of (re-)education for burn clinicians in increasing clinicians' appreciation of muscle wasting as an important target of assessment and therapy in burn care. Establishing competence standards for burn rehabilitation staff that include knowledge of metabolic postburn pathophysiology and the physiological rationale behind the early provision of resistance and aerobic exercise could be instrumental in addressing these findings. Similarly, the findings of the survey and exercise trials emphasise the importance of multidisciplinary teamwork in facilitating early exercise training. Whether competence standards and other educational interventions of the entire burn team lead to greater adoption of early exercise training for the purpose of targeting postburn muscle wasting, should be subject to prospective research.

For muscle wasting to be at the forefront of burn clinicians' priorities, more information on its actual impact on patient relevant outcomes is needed. In the critically ill population, ultrasound-derived quadriceps muscle thickness has been associated with a variety of critical outcomes, including hospital length of stay and death, with the extent of change over the first 7 days able to predict ICU and hospital mortality [26]. In the burn population, the evidence for such inferences is low, with only one recent study to date describing serial measurements of quadriceps muscle thickness by ultrasound [14]. This study revealed a median loss of 23% in the first 7 days of burn centre stay, but data beyond the first week of burn centre stay was not analysed [14]. Understanding the specific time course of muscle wasting will increase our understanding when targeted treatment might be most effective and should be prioritised. More long-term data is needed to understand the how muscle wasting impacts relevant outcomes such as metabolic and cardiovascular morbidity, and whether targeting it will improve long-term prognosis. This is particularly relevant as a limited number of quality-of-life parameters in the exercise trial in severe burns (chapter 4) showed significant improvements not in the first, but in the second six-week training period.

Identifying subgroups who would most need and benefit from early exercise is relevant for resource-constricted contexts such as China where high workloads do not allow equal treatment allocation. For this, patient and disease characteristics that can predict the extent of postburn muscle wasting as well as what constitutes low muscle size at admission need to be identified.

Exercise training during burn centre stay might also play an important role beyond short-term achievements. This is relevant as burn survivors have shown reduced physical activity levels [27,28], below the recommendations for healthy adults [29], long after burn centre stay. In turn, low physical activity levels and sedentary behaviour have been associated with a higher risk of cardiovascular and metabolic morbidity and mortality [30–33]. Whether a retention of muscle mass and muscle strength is protective against the increased postburn risk of long-term morbidity by enabling individuals to return to healthier levels of physical activity [34] is a hypothesis that remains to be tested.

With respect to the presented benefits of early exercise training, little is known of the underlying mechanisms by which early exercise training was able to positively impact muscle outcomes. A deeper understanding of exercise-induced changes in markers of inflammation, hyperglycaemia, insulin sensitivity, muscle anabolism and catabolism is instrumental to better target postburn muscle wasting and related metabolic morbidity. Fundamental studies in rats are underway in our laboratory to unravel the molecular pathways of severe burns and exercise training. The experimental trials reported in this dissertation were unable to draw up conclusive evidence concerning the effects of early exercise training on length of burn centre stay and parameters of quality of life. Future trials of early exercise training should hence focus on these highly relevant outcomes, too.

Lastly, although the present doctoral project includes two intervention studies of early exercise, the similarities in exercise protocols between the studies limited comparisons between protocols. To improve the efficacy of exercise, future study designs should incorporate different exercise protocols with respect to exercise timing (early vs. late start during inpatient stay), training intensity, progression models, and weekly frequency.

7. Final Conclusions

The findings accumulated by all the studies included in this doctoral dissertation, combine to advocate that the clinical benefits of targeting postburn muscle wasting by early exercise training outweigh its costs. We show this by demonstrating that muscle wasting is an important outcome that can be captured by ultrasound, and by establishing the safety, feasibility, and efficacy of early exercise with respect to changes in muscle size and strength. As a result, we reject the null hypothesis that early exercise training has no additional effects in adult patients with burn injury on postburn muscle wasting above standard-of-care rehabilitation.

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Appendix: Supplementary material

Chapter 1 - Supplementary Material

S1. Copy of Survey

* denotes forced-response question

QUESTIONS FOR ALL PROFESSIONS:

Q1. Affiliated burn centre:* *Please enter text here*

Q2. What is your profession?*

- ☐ Physiotherapist
- ☐ Occupational therapist
- ☐ Dietician
- ☐ MD
- ☐ Nurse

Q3. How many years of professional experience do you have in burns?*

Years: *Please enter text here*

Q4. Do you work in inpatient burn care (i.e. stationary patients)?*

- ☐ Yes
- ☐ No

9.

Q5. What age group of burn patients do you treat?*

- ☐ adult (≥18 years)
- ☐ children (<18 years)
- ☐ all ages

Q6. Currently, very little is known about the (patho-)physiological short- and long-term metabolic effects of severe burns (≥20%TBSA) in adult patients. Do you know anything about these effects?*

- ☐ No idea
- ☐ Yes (you will be asked to specify in the next question)

Q7. Please list as many (patho-)physiological short- and long-term metabolic effects of severe burns (≥20%TBSA) in adult patients as you can think of below:

Please answer this question without consulting other knowledge resources. The aim of this question is to get a realistic picture of the readily available knowledge (that which you can recall without any additional resources) which informs daily clinical decision-making

Short-term (<24-72 hours postburn):

(1) *Please enter text here*

(2) *Please enter text here*

(3) *Please enter text here*

(4) *Please enter text here*

(5) *Please enter text here*

(6) *Please enter text here*

(7) *Please enter text here*

(8) *Please enter text here*

(9) *Please enter text here*

(10) *Please enter text here*

Long-term (>24-72 hours postburn):

(1) *Please enter text here*

(2) *Please enter text here*

(3) *Please enter text here*

(4) *Please enter text here*

(5) *Please enter text here*

(6) *Please enter text here*

(7) *Please enter text here*

(8) *Please enter text here*

(9) *Please enter text here*

(10) *Please enter text here*

All following questions concern the acute phase (i.e. in-hospital stay) of severely burned adults (≥20%TBSA)

Q8. How important are the following treatment goals for severely burned adult patients (≥20%TBSA) over the entire hospital stay in your opinion?*
(on a scale from "not at all important" to "extremely important")

	Not at all important	Slightly important	Moderately important	Very important	Extremely important
Range of motion (joint mobility, skin mobility)	☐	☐	☐	☐	☐
Scar quality (aesthetics, pruritus, pain, prevention of hypertrophic scarring, etc.)	☐	☐	☐	☐	☐
Restoration of functional status (ADL's, ambulation ability, etc.)	☐	☐	☐	☐	☐
Prevention of deconditioning (muscle weakness, cardiovascular deconditioning, etc.)	☐	☐	☐	☐	☐
Prevention of metabolic sequelae (insulin resistance, hypermetabolism, hyperglycaemia, fat and muscle catabolism, etc.)	☐	☐	☐	☐	☐

Q9. Do you measure loss of muscle mass (i.e. muscle wasting) in adult burn patients (≥20%TBSA) in the acute phase (in-hospital stay)?*

☐ Yes
☐ No

Q10. How do you measure loss of muscle mass (i.e. muscle wasting) in adult burn patients (≥20%TBSA) in the acute phase (in-hospital stay)?* *(Multiple answers possible)*

☐ DXA scan
☐ MRI scan
☐ CT scan
☐ Musculoskeletal ultrasound
☐ Bioimpedance
☐ Nitrogen balance
☐ Indirectly through muscle strength
☐ Muscle circumference measures
☐ Eye judgement of muscle volume
☐ Other (please specify): *Please enter text here*

Q11. How regularly do you measure loss of muscle mass (i.e. muscle wasting) in adult burn patients (≥20%TBSA) in the acute phase (in-hospital stay)?*
Daily

☐ Weekly
☐ Biweekly
☐ Only when indicated (please specify): *Please enter text here*

ADDITIONAL QUESTIONS FOR THERAPISTS:

Q12. Do you include <u>active</u> exercise as part of the adult burn rehabilitation (≥20%TBSA) in the acute phase (in-hospital stay)?*

(Active exercise = independent or assisted movements / contractions of the patients' muscles)

- ☐ Yes
- ☐ No
- ☐ Sometimes

Q13. How do you determine whether active exercise training is indicated for adult burns (≥20%TBSA) in the acute phase (in-hospital stay)?* *(Active exercise = independent or assisted movements / contractions of the patients' muscles)*
(Multiple answers possible)

- ☐ I use predefined in-/exclusion criteria
- ☐ I do NOT use in-/exclusion criteria
- ☐ By doctors' prescription only

Q14. Which in-/exclusion criteria do you use to decide when active exercise training in the acute phase (in-hospital stay) is indicated for adult burns (≥20%TBSA)?* *(Active exercise = independent or assisted movements / contractions of the patients' muscles)*

- ☐ %TBSA
- ☐ Neurological stability
- ☐ Cardiorespiratory stability
- ☐ Breathing status
- ☐ Acute surgery
- ☐ Temperature
- ☐ Level of cooperation
- ☐ Level of alertness
- ☐ Muscle strength
- ☐ Other (please specify): *Please enter text here*

Q15. Do you use aerobic training as part of your exercise training in the acute phase (in-hospital stay) for adult burns (≥20%TBSA)?*

- ☐ Yes
- ☐ No
- ☐ Sometimes

Q16. How do you determine the intensity of the aforementioned aerobic training?*
(Multiple answers possible)

- ☐ Heart Rate
- ☐ VO2 max
- ☐ General exercise guidelines (please specify): *Please enter text here*
- ☐ Patient Tolerance
- ☐ Other (please specify): *Please enter text here*

Q17. Do you use strength training as part of your exercise training in the acute phase (in-hospital stay) for adult burns (≥20%TBSA)?*

- ☐ Yes
- ☐ No
- ☐ Sometimes

Q18. How do you determine the intensity of the aforementioned strength training?*
(Multiple answers possible)

- ☐ Manual muscle testing
- ☐ Dynamometry
- ☐ RM's (repetition maximum)
- ☐ Patient tolerance
- ☐ Other (please specify): *Please enter text here*

Q19. Which muscle groups do you generally train during the aforementioned strength training in the acute phase (in-hospital stay) for adult burns (≥20%TBSA)?*
(Multiple answers possible)

- ☐ Whole body
- ☐ Lower limbs
- ☐ Upper limbs
- ☐ Core
- ☐ Other (please specify): *Please enter text here*

Q20. What therapy components do you generally train when adult burn patients (≥20%TBSA) are <u>intubated</u>, and how much % of total treatment duration does each represent approximately?*
Write 0% when you do not train a particular component, total must amount to 100%
If you do not treat the intubated at all, please write: "not applicable" in the "other" box and assign 100% to it.

Range of Motion	0%
Aerobic	0%
Strength	0%
Proprioception	0%
Function	0%
Respiratory	0%
Other (please specify): *Please enter text here*	0%
Total	100%

Q21. What therapy components do you generally train when adult burn patients (≥20%TBSA) are <u>NOT able to leave their room</u>, and how much % of total treatment duration does each represent approximately?*
Write 0% when you do not train a particular component, total must amount to 100%
If you do not treat these patients at all, please write: "not applicable" in the "other" box and assign 100% to it.

Range of Motion	0%
Aerobic	0%
Strength	0%
Proprioception	0%
Function	0%
Respiratory	0%
Other (please specify): *Please enter text here*	0%
Total	100%

Q22. What therapy components do you generally train when adult burn patients (≥20%TBSA) are <u>able to leave their room</u>, and how much % of total treatment duration does each represent approximately?*
Write 0% when you do not train a particular component, total must amount to 100%
If you do not treat these patients at all, please write: "not applicable" in the "other" box and assign 100% to it.

Range of Motion	0%
Aerobic	0%
Strength	0%
Proprioception	0%
Function	0%
Respiratory	0%
Other (please specify): *Please enter text here*	0%
Total	100%

Q23. Do you measure muscle strength in adult burn patients (≥20%TBSA) in the acute phase (in-hospital stay)?*

- ☐ Yes
- ☐ No

Q24. How do you measure muscle strength in adult burn patients (≥20%TBSA) in the acute phase (in-hospital stay)?*

(Multiple answers possible)

- ☐ Manual Muscle Testing (Medical Research Council)
- ☐ Hand-held dynamometry
- ☐ Isokinetic dynamometry (e.g. Biodex)
- ☐ Indirectly through functional tests
- ☐ Other (please specify): *Please enter text here*

Q25. How regularly do you measure muscle strength in adult burn patients (≥20%TBSA) in the acute phase (in-hospital stay)?*

- ☐ Daily
- ☐ Weekly
- ☐ Biweekly
- ☐ Only when indicated (please specify): *Please enter text here*

Q26. How long does the overall exercise programme for adult burn patients (≥20%TBSA) generally last?*

- ☐ For ___ weeks (please specify)
- ☐ until discharge from intensive care
- ☐ until discharge from burn unit
- ☐ until discharge from hospital
- ☐ until after discharge from hospital
- ☐ until goals are achieved
- ☐ Other (please specify): *Please enter text here*

Q27. Do you advise adult burn patients (≥20%TBSA) to follow an exercise programme after hospital discharge?*

- ☐ Yes
- ☐ No
- ☐ Depends on the patient

Q28. Why, according to you, should exercise training be included in the acute phase of severe burns (≥20%TBSA)?

List as many reasons as you can think of according to priority. (1 = highest priority)
If you cannot think of any, leave the fields empty.

(1) *Please enter text here*

(2) *Please enter text here*

(3) *Please enter text here*

(4) *Please enter text here*

(5) *Please enter text here*

(6) *Please enter text here*

(7) *Please enter text here*

(8) *Please enter text here*

(9) *Please enter text here*

(10) *Please enter text here*

Q29. Does the development of insulin resistance, hyperglycaemia, hypermetabolism (i.e. >10% increased metabolic rate above predicted) in severely burned adults (>20%TBSA) change your exercise prescription in the acute phase (in-hospital stay)?*
(Multiple answers possible)

☐ Yes
☐ No, this is the responsibility of doctors, dietists, intensivist
☐ No, I don't know enough about metabolic sequelae after burns
☐ No, I wouldn't know how to change the exercise prescription accordingly
☐ Other (please specify): *Please enter text here*

ADDITIONAL QUESTIONS FOR MEDICAL DOCTORS / DIETICIANS:

Q30. How do you determine energy expenditure / caloric requirements for adult burn inpatients (>20%TBSA)?*
(Multiple answers possible)

☐ Prediction formulas (please specify): *Please enter text here*
☐ Indirect calorimetry
☐ Other (please specify): *Please enter text here*

Q31. How regularly do you use <u>prediction formulas</u> to determine energy expenditure / caloric requirements in adult burn inpatients (>20%TBSA)?*

☐ Daily
☐ Weekly
☐ Biweekly
☐ Only when indicated (please specify): *Please enter text here*

Q32. How regularly do you use <u>indirect calorimetry</u> to determine energy expenditure / caloric requirements in adult burn inpatients (>20%TBSA)?*

☐ Daily
☐ Weekly
☐ Biweekly
☐ Only when indicated (please specify): *Please enter text here*

Q33. How regularly do you use "<u>value entered in text field Q31</u>" to determine energy expenditure / caloric requirements in adult burn inpatients (>20%TBSA)?*

☐ Daily
☐ Weekly
☐ Biweekly
☐ Only when indicated (please specify): *Please enter text here*

Q34. Describe the methods you use for indirect calorimetry in adult burn inpatients (>20%TBSA).*
(e.g. fasted state, face mask, ventilated hood method, through mechanical ventilation, duration of measurement, time point of the day, etc)
Please enter text here

Q35. Which intervention strategies do you use at your burn centre to manage the development of a hypermetabolic state (i.e. >10% of predicted resting energy expenditure) in adult burn patients (>20%TBSA) in the acute phase of burns (in-hospital stay)?
(If you do not use any, leave the fields empty)

(1) *Please enter text here*
(2) *Please enter text here*
(3) *Please enter text here*
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(5) *Please enter text here*
(6) *Please enter text here*
(7) *Please enter text here*
(8) *Please enter text here*
(9) *Please enter text here*
(10) *Please enter text here*

Q36. Do you measure insulin sensitivity in adult burn patients (≥20%TBSA) in the acute phase (in-hospital stay)?*

☐ Yes
☐ No

Q37. How do you determine insulin sensitivity in adult burn patients (≥20%TBSA) in the acute phase (in-hospital stay)?*
(Multiple answers possible)

☐ Euglycemic Clamp
☐ OGTT (Oral Glucose Tolerance Test)
☐ HOMA (homeostatic model assessment)
☐ HOMA2 (improved model of HOMA)
☐ QUICKI (quantitative insulin-sensitivity check index)
☐ ISI (insulin sensitivity index)
☐ IGI (insulinogenic index)
☐ Other (please specify): *Please enter text here*

Q38. How regularly do you measure insulin sensitivity in adult burn patients (≥20%TBSA) in the acute phase (in-hospital stay)?*

☐ Daily
☐ Weekly
☐ Biweekly
☐ Only when indicated (please specify): *Please enter text here*

Q39. Which intervention strategies do you use at your burn centre to manage the development of insulin resistance in adult burn patients (>20%TBSA) in the acute phase of burns (in-hospital stay)?
(If you do not use any, leave the fields empty)

(1) *Please enter text here*
(2) *Please enter text here*
(3) *Please enter text here*
(4) *Please enter text here*
(5) *Please enter text here*
(6) *Please enter text here*
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(9) Please enter text here
(10) Please enter text here

Q40. Which intervention strategies do you use at your burn centre to manage the loss of muscle mass (i.e. muscle wasting) in adult burn patients (>20%TBSA) in the acute phase of burns (in-hospital stay)?
(If you do not use any, leave the fields empty)

(1) Please enter text here
(2) Please enter text here
(3) Please enter text here
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Table S2 **Outcome measures**. Data presented per profession.

Methods	% (frequency)				Applied frequency	% (frequency)			
ENERGY EXPENDITURE – Responders: Medical doctors & dieticians (n=27)									
	MD	Dietician	Therapists	TOTAL		MD	Dietician	Therapists	TOTAL
Indirect calorimetry (IC)	25.9% (7)	14.8% (4)	/	40.7% (11)	Daily	3.7% (1)	0% (0)	/	3.7% (1)
- Via mechanical ventilator	25.9 % (7)	14.8% (4)	/	40.7% (11)	Weekly	14.8% (4)	11.1% (3)	/	25.9% (7)
- Spontaneous breathing	3.7% (1)	0% (0)	/	3.7% (1)	Biweekly	0% (0)	0% (0)	/	0% (0)
Criteria indicating use of IC:					Only when indicated	7.4% (2)	3.7% (1)	/	11.1% (3)
- Mechanical ventilation	25.9% (7)	14.8% (4)	/	40.7% (11)					
- %TBSA	14.8% (4)	0% (0)	/	14.8% (4)					
- Unexplained weight loss	7.4% (2)	3.7% (1)	/	11.1% (3)					
- Other metabolic issue	0% (0)	3.7% (1)	/	3.7% (1)					
Prediction formulas	63% (17)	25.9 % (7)	/	88.9% (24)	Daily	14.8% (4)	11.1% (3)	/	25.9% (7)
- Toronto	22.2% (6)	14.8% (4)	/	37% (10)	Weekly	29.6% (8)	3.7% (1)	/	33.3% (9)
- Fixed kcal/kg	7.4% (2)	11.1% (3)	/	18.5% (5)	Biweekly	7.4% (2)	0% (0)	/	7.4% (2)
- Harris Benedict	3.7% (1)	11.1% (3)	/	14.8% (4)	Only when indicated	11.1% (3)	11.1% (3)	/	22.2% (6)
- Curreri	7.4% (2)	7.4% (2)	/	14.8% (4)					
- Others[a]	7.4% (2)	7.4% (2)	/	14.8% (4)					
MUSCLE WASTING – Respondents: Medical doctors & dieticians & therapists (n=59)									
	MD	Dietician	Therapists	TOTAL		MD	Dietician	Therapists	TOTAL
Not measured	22% (13)	10.2% (6)	52.5% (31)	84.7% (50)	Daily	0% (0)	0% (0)	0% (0)	0% (0)
Body weight monitoring	14.8% (4)	3.4% (2)	1.7% (1)	11.9% (7)	Weekly	10.2% (6)	1.7% (1)	0% (0)	11.9% (7)
Eye judgement of muscle	1.7% (1)	1.7% (1)	1.7% (1)	5.1% (3)	Biweekly	0% (0)	0% (0)	0% (0)	0% (0)
volume	1.7% (1)	1.7% (1)	0% (0)	3.4% (2)	Only when indicated	0% (0)	1.7% (1)	1.7% (1)	3.4% (2)
Muscle force assessment	0% (0)	1.7% (1)	0% (0)	1.7% (1)					
Muscle circumference	1.7% (1)	0% (0)	0% (0)	1.7% (1)					
Nitrogen balance	1.7% (1)	0% (0)	0% (0)	1.7% (1)					
Bio impedance analysis	1.7% (1)	0% (0)	0% (0)	1.7% (1)					

MD, medical doctors; [a]including Henry's, Milner, Garland, Xi

Table S2 Outcome measures (continued)

Methods	% (frequency)				Applied frequency	% (frequency)			
INSULIN SENSITIVITY – Respondents: Medical doctors & dieticians (n=27)									
	MD	Dietician	Therapists	TOTAL		MD	Dietician	Therapists	TOTAL
Not measured	63% (17)	29.6% (8)	/	92.6% (25)	Daily	0% (0)	0% (0)	/	0% (0)
HOMA-IR	3.7% (1)	0% (0)	/	3.7% (1)	Weekly	3.7% (1)	0% (0)	/	3.7% (1)
ISI	3.7% (1)	0% (0)	/	3.7% (1)	Biweekly	0% (0)	0% (0)	/	0% (0)
					Only when indicated	3.7% (1)	0% (0)	/	3.7% (1)
MUSCLE FORCE – Respondents: Therapists (n=32)									
	MD	Dietician	Therapists	TOTAL		MD	Dietician	Therapists	TOTAL
Not measured	/	/	40.6% (13)	40.6% (13)	Daily	/	/	3.1% (1)	3.1% (1)
Manual muscle testing	/	/	46.9% (15)	46.9% (15)	Weekly	/	/	28.1% (9)	28.1% (9)
Handheld dynamometry	/	/	31.3% (10)	31.3% (10)	Biweekly	/	/	9.4% (3)	9.4% (3)
Indirectly through functional tests	/	/	25% (8)	25% (8)	Only when indicated	/	/	18.8% (6)	18.8% (6)
Isokinetic Dynamometry	/	/	3.1% (1)	3.1% (1)					

MD, medical doctors; HOMA-IR, homeostasis model assessment of insulin resistance; ISI, Insulin Sensitivity Index

Table S3. ***Metabolic interventions.*** Data presented per profession.

Therapeutic target	Intervention	% (frequency)		
		MD	Dietician	TOTAL
Hypermetabolism[a] Respondents: Medical doctors & dieticians (n=27)	No strategy	25.9% (7)	14.8% (4)	40.7% (11)
	Modify nutrition[b]	37% (10)	22.2% (6)	59.3% (16)
	Betablockers	40.7% (11)	3.7% (1)	44.4% (12)
	Early coverage / grafting	37% (10)	3.7% (1)	40.7% (11)
	Anabolic steroids	33.3% (9)	3.7% (1)	37% (10)
	Glycaemic control	25.9% (7)	3.7% (1)	29.6% (8)
	Early excision	22.2% (6)	3.7% (1)	25.9% (7)
	Adapt ambient temperature	18.5% (5)	3.7% (1)	22.2% (6)
	Exercise	11.1% (3)	0% (0)	11.1% (3)
	Infection control	11.1% (3)	0% (0)	11.1% (3)
	Others[c]	18.5% (5)	0% (0)	18.5% (5)
Muscle Wasting Respondents: Medical doctors & dieticians (n=27)	No strategy	22.2% (6)	7.4% (2)	29.6% (8)
	Exercise	44.4% (12)	22.2% (6)	66.7% (18)
	Modify nutrition	33.3% (9)	22.2% (6)	55.6% (15)
	Anabolic steroids	11.1% (3)	3.7% (1)	14.8% (4)
	Betablockers	7.4% (2)	0% (0)	7.4% (2)
	Limit duration / depth of sedation	7.4% (2)	0% (0)	7.4% (2)
	Others[d]	11.1% (3)	0% (0)	11.1% (3)
Insulin Sensitivity Respondents: Medical doctors & dieticians (n=27)	No strategy	33.3% (9)	22.2% (6)	55.6% (15)
	Insulin infusion	25.9% (7)	22.2% (6)	48.1% (13)
	Moderate glycaemic control	11.1% (3)	14.8% (4)	25.9% (7)
	Tight glycaemic control	14.8% (4)	7.4% (2)	22.2% (6)
	Hypoglycaemic diet	0% (0)	7.4% (2)	7.4% (2)
	Avoid overfeeding	3.7% (1)	3.7% (1)	7.4% (2)
	Anabolic steroids	3.7% (1)	3.7% (1)	7.4% (2)
	Early excision	0% (0)	7.4% (2)	7.4% (2)
	Exercise	0% (0)	7.4% (2)	7.4% (2)
	Others[e]	18.5% (5)	0% (0)	18.5% (5)

MD, medical doctors

[a] Defined as >10% predicted resting energy expenditure, [b] including increasing and decreasing caloric provision, supplementing nutrition content (protein, trace elements, vitamins) early enteral feeding, [c] including fenofibrates, growth hormones, early resuscitation, limiting sedation, anxiety reduction, [d] including fenofibrates, avoiding neuromuscular blockers, early excision, early coverage, [e] including Gliclazide, Metformin, betablockers, fenofibrates, early coverage

Table S4. ***Odds ratios.*** Data presented as odds ratio (95%CI).

	MD vs. therapists	Dieticians vs. therapists	Dieticians vs. MD	Knowledge of 'flow' phase[a]
Knowledge of the 'flow' phase[a]	12.00 (2.95-48.78) p<0.01	/ [b]	/ [b]	/
Importance ratings of prevention of metabolic sequelae[c]	1.85 (0.56-6.13) p=0.37	17.89 (1.92-166.78) p<0.01	9.63 (0.98-94.54) p=0.43	4.63 (1.50-14.25) p<0.01
Importance ratings of prevention of deconditioning sequelae[c]	2.20 (0.69-7.07) p=0.25	3.86 (0.67-22.11) p=0.24	1.75 (0.28-11.15) p=0.68	2.25 (0.76-6.65) p=0.18
Importance ratings of range of motion sequelae[c]	0.85 (0.27-2.27) p=1.00	4.39 (0.76-25.20) p=0.12	5.14 (0.81-32.77) p=0.10	1.91 (0.66-5.51) p=0.29
Importance ratings of scar quality[c]	0.44 (0.14-1.39) p=0.24	1.00 (0.20-4.96) p=1.00	2.29 (0.42-12.50) p=0.42	0.70 (0.24-2.00) p=0.60
Importance ratings of restoration of functional status[c]	0.65 (0.17-2.50) p=0.73	0.23 (0.05-1.20) p=0.09	0.36 (0.06-2.00) p=0.38	0.63 (0.19-2.11) p=0.54

MD, medical doctors

[a] comparing present vs. absent ability to identify at least one component of the 'flow' phase in all respondents; [b] no odds ratio could be computed as no dietician with absent knowledge was observed; [c] comparing extremely important vs. all other importance ratings of respective therapy goals.

Chapter 2 – Supplementary material

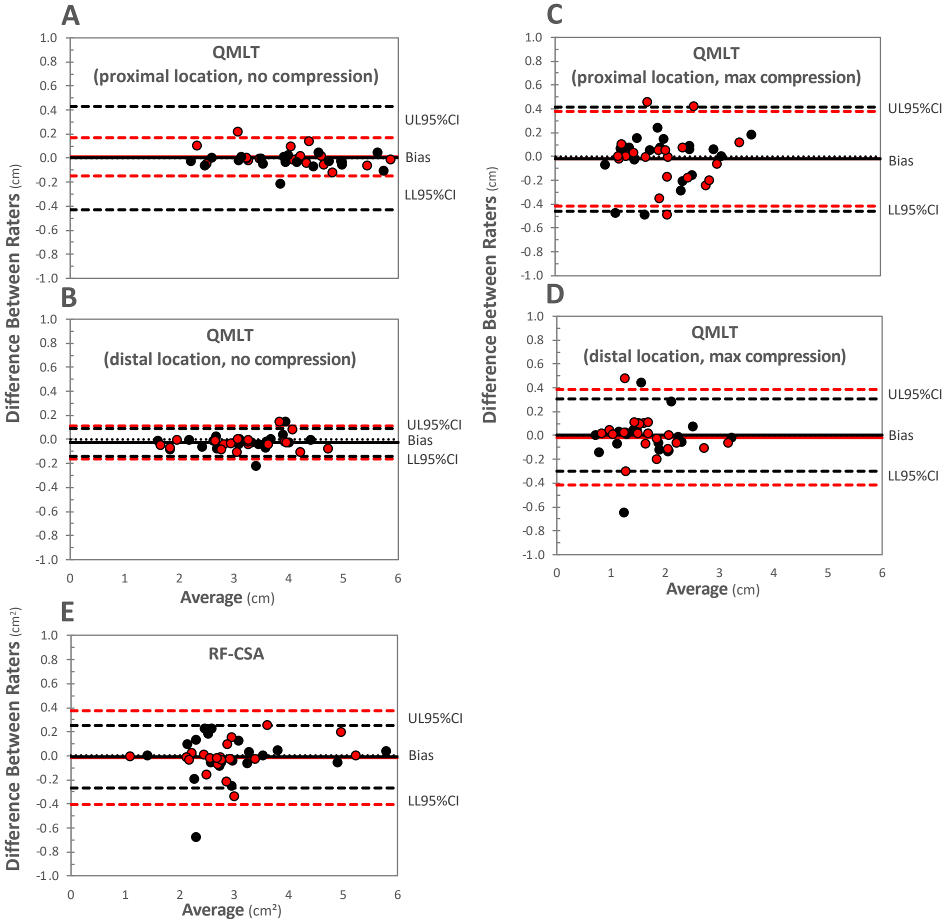

Figure A.1. Bland-Altman plots for healthy subjects. A-D quadriceps muscle layer thickness, E rectus femoris cross-sectional area. Data presented is based on average of three measurements. Red lines and data points refer to the right thigh; black lines and data points refer to the left thigh. QMLT, quadriceps muscle layer thickness; RF-CSA, rectus femoris cross-sectional area.

		ICC [95%CI]		MDC95			
		Average^a	Single^b	Average^a	%mean	Single^b	%mean
RIGHT	QMLT (no compression, proximal location)	0.998 [0.996-0.999]	0.994 [0.985-0.998]	0.12 cm	2.9	0.2 cm	5
	QMLT (max. compression, proximal location)	0.981 [0.951-0.992]	0.975 [0.937-0.99]	0.28 cm	13.9	0.32 cm	15.8
	QMLT (no compression, distal location)	0.998 [0.994-0.999]	0.998 [0.994-0.999]	0.1 cm	3.1	0.1 cm	3.1
	QMLT (max. compression, distal location)	0.974 [0.935-0.99]	0.974 [0.933-0.99]	0.28 cm	16.7	0.28 cm	16.3
	RF-CSA	0.99 [0.975-0.996]	0.995 [0.986-0.998]	0.27 cm^2	9.2	0.19 cm^2	6.4
LEFT	QMLT (no compression, proximal location)	0.999 [0.997-1]	0.999 [0.995-1]	0.09 cm	2.2	0.09 cm	2.2
	QMLT (max. compression, proximal location)	0.971 [0.927-0.988]	0.974 [0.934-0.99]	0.31 cm	15	0.29 cm	14
	QMLT (no compression, distal location)	0.999 [0.996-0.999]	0.999 [0.997-1]	0.07 cm	2.3	0.07 cm	2.3
	QMLT (max. compression, distal location)	0.983 [0.956-0.993]	0.98 [0.95-0.992]	0.21 cm	12.5	0.23 cm	13.3
	RF-CSA	0.995 [0.987-0.998]	0.99 [0.975 0.996]	0.18 cm^2	6.2	0.25 cm^2	8.8

Table A.1. Intraclass correlations coefficients and minimal detectable changes in healthy subjects.

QMLT, quadriceps muscle layer thickness; RF-CSA, rectus femoris cross sectional area. ^{a}Refers to the average of three measurements. ^{b}Refers to the first of three measurements

		Systematic bias^a				Proportional bias			
		Average^b		Single^c		Average^b		Single^c	
		Mean Δ	p-Value	Mean Δ	p-Value	β Co-eff	p-Value	β Co-eff	p-Value
RIGHT	QMLT (no compression, proximal location)	0.01 cm	0.586	0.04 cm	0.233	-0.031	0.118	-0.085	0.011*
	QMLT (max. compression, proximal location)	-0.02 cm	0.659	-0.02 cm	0.761	0.061	0.366	0.036	0.639
	QMLT (no compression, distal location)	-0.03 cm	0.134	-0.02 cm	0.289	0.02	0.377	0.009	0.687
	QMLT (max. compression, distal location)	-0.02 cm	0.742	-0.01 cm	0.779	0.042	0.59	0.049	0.533
	RF-CSA	-0.01 cm^2	0.761	0.04 cm^2	0.216	0.014	0.78	-0.006	0.873
LEFT	QMLT (no compression, proximal location)	-0.03 cm	0.033*	-0.04 cm	0.02*	-0.001	0.931	-0.002	0.917
	QMLT (max. compression, proximal location)	-0.02 cm	0.689	0.01 cm	0.908	-0.037	0.652	-0.005	0.953
	QMLT (no compression, distal location)	-0.02 cm	0.088	-0.01 cm	0.362	0.011	0.523	0.017	0.315
	QMLT (max. compression, distal location)	0.01 cm	0.886	-0.03 cm	0.394	-0.084	0.183	-0.144	0.024*
	RF-CSA_{ln}	-0.01 cm^2	0.807	0.02 cm^2	0.567	0.043	0.201	0.025	0.603

Table A.2. Systematic and proportional bias in healthy subjects.

QMLT, quadriceps muscle layer thickness; RF-CSA, rectus femoris cross sectional area

^{a}Systematic bias refers to the mean differences between raters, subtracting rater 1 - rater 2. ^{b}Refers to the average of three measurements. ^{c}Refers to the first of three measurements. *p value < 0.05

Chapter 4 – Supplementary material

	Weeks	Exercise (n=29)	Control (n=29)
QMLT (cm)	0	3.060 [2.738;3.382]	2.554 [2.334;2.775]
	6	2.708 [2.374;3.041]	1.869 [1.663;2.075]
	12	2.835 [2.474;3.195]	1.921 [1.635;2.208]
RF-CSA (cm^2)	0	2.471 [2.006;2.936]	2.184 [1.858;2.511]
	6	2.353 [1.934;2.773]	1.689 [1.345;2.033]
	12	2.562 [2.108;3.017]	1.484 [1.123;1.845]
Lower limb muscle force (N)	0	N.A.	N.A.
	6	100.79 [82.04;119.54]	94.00 [79.76;108.23]
	12	131.04 [108.92;153.17]	109.58 [89.15;130.02]
EQ-5D-5L health utility index	0	-0.286 [-0.341;-0.232]	-0.317 [-0.362;-0.271]
	6	-0.076 [-0.234;0.083]	0.037 [-0.149;0.224]
	12	0.273 [0.113;0.434]	0.292 [0.096;0.487]
EQ-5D-5L VAS	0	27.29 [20.27;34.32]	27.18 [19.69;34.67]
	6	39.80 [31.04;48.55]	41.04 [30.54;51.55]
	12	54.56 [42.36;66.76]	54.36 [43.96;64.76]
BSHS-B simple abilities	0	0.701 [0.306;1.096]	0.939 [0.582;1.295]
	6	1.616 [1.064;2.168]	2.009 [1.552;2.466]
	12	2.326 [1.769;2.884]	2.253 [1.687;2.819]
BSHS-B affect	0	1.935 [1.565;2.306]	1.560 [1.156;1.965]
	6	2.398 [2.003;2.792]	2.305 [1.829;2.781]
	12	2.883 [2.461;3.304]	2.299 [1.701;2.896]
BSHS-B interpersonal relationships	0	2.328 [1.858;2.797]	1.948 [1.534;2.362]
	6	2.795 [2.299;3.292]	2.720 [2.416;3.024]
	12	3.438 [3.088;3.787]	2.722 [2.302;3.142]

Table S1. Group means per outcome and time points. Data presented as unadjusted means with 95% confidence intervals. QMLT, quadriceps muscle layer thickness; RF-CSA, rectus femoris cross-sectional area; EQ-5D-5L, Eurocol Quality of Life-5 Dimensions; BSHS-B, Burn Specific Health Scale Brief; VAS, Visual Analogue Scale

		Variable	β-coeff.	*p*-value	95%CI	
EQ-5D-5L Health Utility Index	0-6 weeks	Group[Exercise]	-0.004	0.957	-0.136	0.128
		Week	0.062	<.001	0.039	0.085
		Group[Exercise]*Week	-0.025	0.133	-0.058	0.008
		Baseline value (0 weeks)	1.120	<.001	0.736	1.504
	6-12 weeks	Group[Exercise]	-0.118	0.432	-0.415	0.180
		Week	0.050	<0.001	0.028	0.073
		Group[Exercise]*Week	0.017	0.313	-0.016	0.050
		Baseline value (6 weeks)	0.853	<0.001	0.728	0.978
EQ-5D-5L VAS	0-6 weeks	Group[Exercise]	0.458	0.885	-5.822	6.738
		Week	2.837	<.001	1.720	3.954
		Group[Exercise]*Week	-0.277	0.728	-1.865	1.311
		Baseline value (0 weeks)	0.933	<.001	0.800	1.066
	6-12 weeks	Group[Exercise]	-0.982	0.908	-17.944	15.980
		Week	2.424	<0.001	1.125	3.722
		Group[Exercise]*Week	0.141	0.881	-1.744	2.027
		Baseline value (6 weeks)	0.893	<0.001	0.759	1.026
BSHS-B Simple Abilities	0-6 weeks	Group[Exercise]	-0.136	0.599	-0.647	0.376
		Week	0.185	<.001	0.134	0.235
		Group[Exercise]*Week	-0.025	0.498	-0.098	0.049
		R-BEAUX Score	-0.021	<.001	-0.032	-0.010
	6-12 weeks	Group[Exercise]	-0.569	0.211	-1.469	0.332
		Week	0.070	0.046	0.001	0.139
		Group[Exercise]*Week	0.085	0.097	-0.016	0.185
		Baseline value (6 weeks)	0.843	<0.001	0.715	0.971
BSHS-B Affect	0-6 weeks	Group[Exercise]	0.113	0.467	-0.195	0.421
		Week	0.142	<.001	0.088	0.196
		Group[Exercise]*Week	-0.078	0.053	-0.156	0.001
		Baseline value (0 weeks)	0.808	<.001	0.708	0.909
		Duration on mechanical ventilation	-0.026	0.007	-0.045	-0.007
	6-12 weeks	Group[Exercise]	-0.480	0.124	-1.096	0.137
		Week	0.021	0.368	-0.026	0.068
		Group[Exercise]*Week	0.081	0.022	0.012	0.150
		Baseline value (6 weeks)	0.926	<0.001	0.824	1.027
BSHS-B Interpersonal Relationships	0-6 weeks	Group[Exercise]	0.379	0.182	-0.181	0.940
		Week	0.134	<.001	0.059	0.208
		Group[Exercise]*Week	-0.057	0.295	-0.164	0.051
	6-12 weeks	Group[Exercise]	-0.560	0.179	-1.484	0.284
		Week	0.016	0.641	-0.052	0.084
		Group[Exercise]*Week	0.104	0.040	0.005	0.203
		Baseline value (6 weeks)	0.661	<0.001	0.535	0.786

Table S2. Regression models for quality-of-life measures, adjusted for covariates. 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. EQ-5D-5L, Eurocol Quality of Life-5 Dimensions; BSHS-B, Burn Specific Health Scale Brief; VAS, Visual Analogue Scale

Curriculum Vitae

Curriculum Vitae

Education

Doctoral studies in Medical Sciences, Department of Rehabilitation Sciences and Physiotherapy, 2017 – 2023, University of Antwerp, Belgium

Master of Sciences, Rehabilitation Sciences and Physiotherapy, 2015 – 2017, KU Leuven, Belgium (Magna Cum Laude)

Bachelor of Health, Physiotherapy, 2009 – 2012, European School of Physiotherapy, Amsterdam, The Netherlands (Magna Cum Laude)

Prior clinical experience

Aug/2017 – Oct/2017	ICU department, UZ Leuven, Gasthuisberg, BELGIUM
Experience:	- Medical ICU, cardiac ICU, burn ICU, neurological ICU
Jul/2016 – Aug/2016	Bless China International (NGO), Kunming, CHINA
Experience	- Volunteer: community-based rehabilitation for amputees, leprosy, burns, HIV - Training of local rehabilitation staff
Feb/2012 – Feb/2015	Fysio- en Manuele Therapie Van Breestraat, Amsterdam, The Netherlands
Experience:	- shoulder-/ knee specialisation - management / marketing - supervision interns - team physiotherapy at AMVJ Football Men / HIC Hockey Ladies
Season 2014	Hockey India League 2014, Delhi Waveriders, India
Experience:	- team physiotherapist - on / off field care
Mar/2013 – Aug/2014	Amsterdams Solidariteits Komitee Vluchtelingen, The Netherlands
Experience::	- Volunteer: "Medisch Opvangproject Ongedocumenteerden" - Physiotherapy for undocumented migrants
Aug/2011 – Mar/2012	Corver Fysio- en Manuele Therapie, Amsterdam, NL
Experience:	- Guideline development: COPD rehabilitation, anterior shoulder pain syndrome, a-spec. low back pain - Ergonomic physiotherapy

Journal publication as first author

Schieffelers DR, Dombrecht D, Lafaire C, De Cuyper L, Rose T, Vandewal M, Meirte J, Gebruers N, van Breda E, Van Daele U. Effects of exercise training on muscle wasting, muscle strength and quality of life in adults with acute burn injury. Burns 2023. https://doi.org/10.1016/j.burns.2023.04.003.

Schieffelers DR, Dombrecht D, Lafaire C, De Cuyper L, Rose T, Vandewal M, Meirte J, Gebruers N, van Breda E, Van Daele U. Reliability and feasibility of skeletal muscle ultrasound in the acute burn setting. Burns 2022. https://doi.org/10.1016/j.burns.2022.03.003.

Schieffelers DR, van Breda E, Gebruers N, Meirte J, Van Daele U. Status of adult inpatient burn rehabilitation in Europe: Are we neglecting metabolic outcomes? Burns & Trauma 2021;9:tkaa039. https://doi.org/10.1093/burnst/tkaa039.

Journal publication as co-author

Dombrecht D, Van Daele U, Van Asbroeck B, Schieffelers DR, Guns P, Gebruers N, Meirte J, van Breda E. Molecular mechanisms of post-burn muscle wasting and the therapeutic potential of physical exercise. J Cachexia Sarcopenia Muscle 2023:jcsm.13188. https://doi.org/10.1002/jcsm.13188.

Dombrecht D, Van Daele U, Van Asbroeck B, Schieffelers DR, Guns P-J, van Breda E. Skeletal muscle wasting after burn is regulated by a decrease in anabolic signaling in the early flow phase. Burns 2023;49:1574–84. https://doi.org/10.1016/j.burns.2023.08.011.

Conference proceedings as first author

Schieffelers DR, Dombrecht D, van Breda E, Van Daele U. O2.1.5 The Role of Exercise in Wound Healing: Results of a Feasibility Study of Exercise Training. EJBC 2023;4:330–491. https://doi.org/10.3390/ebj4030030.

Schieffelers DR, van Breda E, Lafaire C, De Cuyper L, Rose T, Gebruers N, Meirte J, Dombrecht D, Van Daele U. O.100 Correlation between muscle wasting and muscle weakness in adult burns throughout burn centre stay. EJBC 2022;3:621–2. https://doi.org/10.3390/ebj3040046.

Schieffelers DR, Dombrecht D, van Breda E, Lafaire C, De Cuyper L, Rose T, Gebruers N, Meirte J. O.096 Efficacy of exercise rehabilitation during the acute phase of burns: A multicenter trial. EJBC 2022;3:618. https://doi.org/10.3390/ebj3040046.

Schieffelers DR, van Breda E, Gebruers N, Meirte J, Van Daele U. O32.07 Early Exercise Rehabilitation during the Acute Phase of Severe Burns: A European Survey of Current Practice. EJBC 2019;1:112. https://doi.org/10.3390/ejbc1010002.

Oral presentations

Schieffelers DR, Dombrecht D, van Breda E, Van Daele U. O2.1.5 The Role of Exercise in Wound Healing: Results of a Feasibility Study of Exercise Training. 20th Congress of the European Burn Association; Nantes, France. 2023.

Schieffelers DR, Dombrecht D, van Breda E, Lafaire C, De Cuyper L, Rose T, Gebruers N, Meirte J. O.096 Efficacy of exercise rehabilitation during the acute phase of burns: A multicenter trial. 19th Congress of the European Burn Association; Turin, Italy. 2022.

Schieffelers DR, van Breda E, Lafaire C, De Cuyper L, Rose T, Gebruers N, Meirte J, Dombrecht D, Van Daele U. Correlation between muscle wasting and muscle weakness in adult burns throughout burn centre stay. 19th Congress of the European Burn Association; Turin, Italy. 2022.

Schieffelers DR, Xie W, Wu J, Ru T, Ye Z, van Breda E, Van Daele, U. The impact of high-intensity exercise on postburn muscle function: Preliminary data from a randomized controlled trial. 21st Congress International Society for burn injuries; Guadalajara, Mexico. 2022.

Schieffelers DR, Dombrecht D, van Breda E, Lafaire C, De Cuyper L, Rose T, Meirte J, Gebruers N, Van Daele U.. Feasibility of high-intensity exercise throughout burn center stay. 21st Congress International Society for burn injuries; Guadalajara, Mexico. 2022.

Schieffelers DR, Dombrecht D, van Breda E, Lafaire C, De Cuyper L, Rose T, Meirte J, Gebruers N, Van Daele U.. Postburn muscle wasting throughout burn center stay. 21st Congress International Society for burn injuries; Guadalajara, Mexico. 2022.

Schieffelers DR. Financiële problemen van brandwondenpatiënten in China. USAB visit to FGGW. Antwerp, Belgium. 2022.

Schieffelers DR, Dombrecht D, van Breda E, Lafaire C, De Cuyper L, Rose T, Meirte J, Gebruers N, Van Daele U. Ultrasound measurement of muscle size in burns: How reliable and feasible is it? 20th Congress International Society for burn injuries; Birmingham. UK. 2021.

Schieffelers DR, van Breda E, Gebruers N, Meirte J, Van Daele U. Status of adult inpatient burn rehabilitation in Europe: Are we neglecting metabolic outcomes? 20th Congress International Society for burn injuries; Birmingham. UK. 2021.

Schieffelers DR, van Breda E, Gebruers N, Meirte J, Van Daele U. Early Exercise Rehabilitation during the Acute Phase of Severe Burns. 18th Congress of the European Burn Association; Helsinki, Finland. 2019.

Invited Speaker

Schieffelers DR. “The importance of exercise during the acute phase of burns – from evidence to clinical application.” Annual congress of the Mexican Burn Society (CENIQ-INR), Mexico City, Mexico. 2023.

Schieffelers DR. “Rehabilitation of the acute burn patient”. Burn Symposium of the Mediterranean Burn Council, Lausanne, Switzerland. 2023.

Schieffelers DR. “The role of exercise in counteracting metabolic outcomes.” National symposium of Association of Dutch Burn Centers; Wijk-aan-Zee, The Netherlands. 2023.

Schieffelers DR. “Pathophysiological mechanisms and exercise rehabilitation counter measures of hypermetabolism and muscle wasting in severe burns. A protocol of a randomized controlled trial.” Shenzhen Burn Symposium; Shenzhen, China. 2018

Website publications

MOVANT research blogpost: “Wuhan, lessons from burn rehabilitation in China” (2021)

Prices / awards

Best OT/PT presentation (2023). Awarded for the oral presentation “*The role of exercise in wound healing: results of a feasibility study in exercise training”* at the 20th congress of the European Burns Association in Nantes, France.

André Zagamé Rehabilitation Specialist Prize (2022). Awarded “in recognition of significant contributions to the rehabilitation of patients with burn injuries” by the International Society for Burn Injuries at the 21st congress in Guadalajara, Mexico.

ActUA prize (2019): Awarded by the University of Antwerp to outstanding students with a high level of commitment to social justice to support their personal development.

Research stays

Institute of Burns, Wuhan Third Hospital & Tongren Hospital of Wuhan University School of Medicine, Wuhan, China. (Oct - Dec 2019). Subject: Trial setup, including protocol adaptation to local context, identifying standard-of-care, training research staff, carrying out pilots, coordinating start of recruitment.

University of Applied Sciences of Southern Switzerland, Landquart, Switzerland. (Aug 2019). Subject: Protocol development of B-mode ultrasound measurements quadriceps muscle thickness and cross-sectional area.

Teaching Activities

Lecturer: Interuniversity course ‘Capita Selecta’ of the major ‘Rehabilitation of internal disorders’ (2018 – 2023)
Lecturer: Course: ‘Introduction to global development and health care’ (IGOG). Global Health Institute (2019 – 2023)
Supervision: Course ‘Integrated case’ (2019-2022)
Supervision of Master theses (2018-2022)
Supervision of Bachelor theses (2018-2022)

Academic courses / workshops / seminars

The role of scientists in social debate, Let’s talk Science (2021)
Digital storytelling & video marketing, Let’s talk Science (2021)
Analysis of categorical data with logistic regression, StatUA (2021)
Data Visualization, FLAMES (2021)

Academic courses / workshops / seminars (continued)

The muscle: why and how should we target this crucial organ in the rehabilitation of patients with chronic internal diseases, FIRRI (2021)

Regression with ordinal variables, StatUA (2020)
Research Data Management and Data Management Plan, Antwerp Doctoral School (2020)
Annual Meeting: "Data confidentiality in research and society", FLAMES (2020)
Developing a publication strategy in the physical sciences and life sciences, Antwerp Doctoral School (2020)
Introduction to JMP Pro software, StatUA (2020)
Unequal Roads to Healthcare, European Medical Students' Association Antwerpen (2020)
Analysis of Grouped and Longitudinal data using Linear Mixed Models, StatUA (2019)
Multiple regression and ANOVA, StatUA (2019)
Project management, Antwerp Doctoral School (2019)
Personal Effectiveness, Antwerp Doctoral School (2019)
Achieving your goals and performing more successfully, Antwerp Doctoral School (2019)
Migration and health, Institute of Tropical Medicine (2019)
Science communication, The Floor is Yours (2018)
Cochrane Systematic Review, University of Ghent(2018)
Methods in Data Collection, StatUA (2018)
Scar Academy, Oscare & University of Antwerp (2017)
Physiotherapy in low income countries, KU Leuven (2016)
Annual symposium respiratory physiotherapy, BVP (2016)
Core Stability, KU Leuven (2016)
Shoulder & elbow instability, EUSSER conference (2014)
Masterclass Schouderklachten: State of the art, NPI (2014)
Schouderpijnsyndroom, NPI (2014)
Schouderklachten binnen de Zorgketen Orthopedie-Fysiotherapie, NPI (2014)
Claudicatio Intermittens National Symposium, ClaudicatioNet (2013)
Knie-Festival, OLVG hospital (2012)
Sports Physiotherapy, KNGF (2011)