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Outcomes of Resistance Exercise Training in Adults with Acute Burn Injury.

Paul Michael Gittings

BSc (Physiotherapy) (Honours 1st Class)

Submitted in fulfilment of the requirements for the degree of **Doctor of Philosophy**

School of Physiotherapy
Fremantle Campus

April 2020

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Declaration of Authorship

I declare that this thesis contains no material previously published by another person, except where due acknowledgement has been made.

This thesis is the candidate's own work and contains as its main content work which has not previously been accepted for the award of any other degree or diploma at any institution.

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007, updated 2018). The proposed research study received human research ethics approval from the University of Notre Dame Australia Human Research Ethics Committee (EC00418), Approval number #014138F.

Paul Michael Gittings

Date: April 2020

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Abstract

Decreased quality-of-life and impairments in physical function, muscle strength and muscle volume are known complications of a burn injury. As such, rehabilitation is an important aspect of the burn care journey. Rehabilitation of burn injury is currently hampered by a lack of tools to reliably measure muscle strength and lower limb function, as well as an incomplete understanding of the effect of resistance training after a burn injury. Specifically, there is currently no data on the safety or efficacy of resistance training immediately after a burn injury.

The series of studies presented in this thesis aimed to: 1) systematically review the current literature and evaluate the usefulness of resistance training during recovery from burn injury, 2) determine the ability of the Lower Limb Functional Index-10 to assess lower limb function after a burn injury, 3) determine the reliability and validity of hand held dynamometry to measure strength in people with an acute burn injury, and 4) evaluate the effect of an individually prescribed resistance training programme on quality-of-life, physical function, muscle strength, muscle volume and biochemical markers of inflammation in people with an acute burn injury.

The novel findings from this thesis include: 1) estimates of effectiveness of resistance training in burn injury are based on low quality data and no data is available on acute injury rehabilitation 2) lower limb function can be reliably assessed using the Lower Limb Functional Index-10 after a lower limb burn injury, 3) hand held dynamometry is a reliable and valid assessment of muscle strength in burn injuries up to 40% total burn surface area, 4) resistance training commenced within 72-hours of burn injury improves quality-of-life, upper limb function and blood markers of inflammation compared to sham resistance training, and, 5) resistance training for acute burn injuries appears to be a safe and feasible practice.

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List of Publications Contributing to this Thesis

The Lower Limb Functional Index - A reliable and valid functional outcome assessment in burns

Gittings, P. M., Heberlien, N., Devenish, N., Parker, M., Phillips, M., Wood, F. M., & Edgar, D. W. (2016). The Lower Limb Functional Index - A reliable and valid functional outcome assessment in burns. *Burns, 42*(6), 1233-1240. doi: 0.1016/j.burns.2016.03.028

Grip and Muscle Strength Dynamometry Are Reliable and Valid in Patients With Unhealed Minor Burn Wounds

Gittings, P., Salet, M., Burrows, S., Ruettermann, M., Wood, F. M., & Edgar, D. (2016). Grip and Muscle Strength Dynamometry Are Reliable and Valid in Patients With Unhealed Minor Burn Wounds. *J Burn Care Res, 37*(6), 388-396. doi: 0.1097/BCR.0000000000000414

Resistance training for rehabilitation after burn injury: A systematic literature review & meta-analysis

Gittings, P. M., Grisbrook, T. L., Edgar, D. W., Wood, F. M., Wand, B. M., & O'Connell, N. E. (2017). Resistance training for rehabilitation after burn injury: A systematic literature review & meta-analysis. *Burns*. doi:1016/j.burns.2017.08.009

Grip and Muscle Strength Dynamometry in Acute Burn Injury: Evaluation of an Updated Assessment Protocol

Gittings, P. M., Hince, D. A., Wand, B. M., Wood, F. M., & Edgar, D. W. (2018). Grip and Muscle Strength Dynamometry in Acute Burn Injury: Evaluation of an Updated Assessment Protocol. *J Burn Care Res*. doi: 10.1093/jbcr/iry010

The efficacy of resistance training in addition to usual care for adults with acute burn injury: A randomised controlled trial. [1]

Gittings, P.M., Wand, B.M., Hince, D.A., Grisbrook, T.L., Wood, F.M., & Edgar, D.W.

[1] Accepted for publication to *Burns* and awaiting publication at time of writing

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List of Abbreviations

BIS: Bioimpedance spectroscopy

BSHS-B: Burn Specific Health Scale Brief survey

CG: Control group

CRP: C-reactive protein

GSD: Grip strength dynamometry

HHD: Hand held dynamometry

ICC: Intra-class correlation coefficient

LEFS: Lower Extremity Functional Scale

LLFI: Lower Limb Functional Index

LLFI-10: Lower Limb Functional Index-10 survey

MDD: Minimal detectable difference

MSD: Muscle strength dynamometry

MVIC: Maximum voluntary isometric contraction

QoL: Quality of life

Quick-DASH: Quick Disability of Arm, Shoulder and Hand survey

R: Resistance to flow of current in bioimpedance spectroscopy

RBP: Retinol binding protein

Ri: Resistance of intra-cellular water component (Rinf – Ro)

Rinf: Resistance at infinite frequency (intra- and extra-cellular water volume)

Ro: Resistance at zero frequency (intra-cellular water volume)

ROM: Range of motion

RT: Resistance training

RT: Resistance training

RTG: Resistance training group

SF-36: Short-Form 36

SSG: Split skin graft

TBSA: Total Burn Surface Area

TUG: Timed Up and Go

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Chapter 1 Introduction

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1.1 Significance of a Burn Injury

Burn injuries are devastating to the survivor and result in significant impairments in bodily structure and function, which have long term implications for health related quality of life. The potential life-long impact of a burn injury is epitomised by research which reports ongoing disability on average 17 years after burn injury (range 3-53 years) (Holavanahalli, Helm, & Kowalske, 2016). In addition, a qualitative synthesis of research data concluded that nearly 28% of survivors were unable to return to work after a burn injury (Mason et al., 2012). Mortality due to a burn injury is below 1% in developed countries such as Australia, New Zealand and the United States of America (Crowe et al., 2019; Duke et al., 2011; McInnes et al., 2019), reflecting improving burn care protocols. As such, 99% of patients will survive a burn injury, with the probability of life-long consequences. These patients will require significant resources and expertise to facilitate ongoing rehabilitation to address the impairments in body function and associated activity limitations caused by the burn injury.

1.1.1 Physiological Effects of a Burn Injury

Burn injuries induce a widespread inflammatory and metabolic response in the body. Severe burns, defined as damage to 30% or more of the skin (Jeschke et al., 2011) have been well researched and the physiological response is well defined. A burn of this magnitude instigates a systemic response, characterised by a prolonged hypermetabolic state up to three years after the initial burn injury (Hart, Wolf, Mlcak, et al., 2000; Jeschke et al., 2011). However, severe burn injuries are the least commonly treated with over 90% of hospitalised burn injuries meeting the classification of a non-severe injury (Duke et al., 2011).

There is less available research regarding the physiological response to non-severe burn injuries. Non-severe injuries are more prevalent than severe injuries, making this an important area of ongoing investigation. In response to non-severe burn injury, rodent models have demonstrated changes in peripheral cutaneous innervation (Anderson et al., 2010), loss of bone volume (O'Halloran, Kular, Xu, Wood, & Fear, 2015) and reduced force-generating capacity of muscle fibres (Bakker, O'Neill,

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Pinniger, Wood, & Fear, 2012). Cardiovascular structural and functional changes have been reported in both rodents and humans after non-severe burn injury (O'Halloran et al., 2016). Large population based studies have demonstrated that burn injury, regardless of total burn surface area (TBSA), have chronic sequelae. Patients with a history of a burn injury have increased hospitalisation rates and length of stay for many health disorders, including; musculoskeletal conditions (Duke et al., 2015; Randall et al., 2015), orthopaedic fractures (Duke, Randall, Fear, Boyd, & Wood, 2017) neurological conditions (Vetrichevvel et al., 2016), cardiovascular disease (Duke, Randall, Fear, O'Halloran, et al., 2017), gastrointestinal disease (Stevenson et al., 2017) and diabetes mellitus (Duke et al., 2016). Additionally, oncological diagnoses were found to be higher in females who had experienced a burn injury (Duke et al., 2014). The results from these studies suggest that non-severe burn injuries have a significant systemic impact which highlights the need for effective acute-phase management and treatment of burn injuries.

1.1.2 Physical and Functional Impact of a Burn Injury

Survivors of a burn injury are challenged with considerable impairment in bodily function and associated activity limitations. Scar and joint contracture with associated loss of range of movement has an incidence between 23 – 54% at hospital discharge after a burn injury (Goverman et al., 2017a, 2017b; Oosterwijk et al., 2017) and loss of range of movement is a primary barrier to return to work after a burn (Carrougher, Brych, Pham, Mandell, & Gibran, 2017). Decreased muscle strength (Alloju, Herndon, McEntire, & Suman, 2008; Bjornhagen, Schuldt Ekholm, Larsen, & Ekholm, 2018; Cambiaso-Daniel et al., 2018; Ebid, El-Shamy, & Draz, 2014; Ebid, Omar, & Abd El Baky, 2012; Omar, Abd El Baky, & Ebid, 2017; St-Pierre, Choiniere, Forget, & Garrel, 1998) and an accelerated loss of muscle mass (Hart, Wolf, Chinkes, et al., 2000; Hart, Wolf, Mlcak, et al., 2000; Porter, Hurren, Herndon, & Borsheim, 2013) are observed consequences of the physiological response to a burn injury. Furthermore, the frequency with which patients continue to participate in physical activity and exercise after a burn injury is reduced, potentially further contributing to impaired physical conditioning (Baldwin & Li, 2013).

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Physical impairments may also manifest as activity limitations or reduced quality of life (QoL). In burn injuries of varying severity, physical function is reported by patients to be below baseline level for a number of years (Holavanahalli et al., 2016; Klein et al., 2011; Palmu, Partonen, Suominen, Vuola, & Isometsa, 2016; Renneberg et al., 2014; Shakespeare, 1998; Wasiak, Paul, et al., 2014). Previous literature demonstrated that burn injury negatively impacts the short and long-term health related QoL of a patient, particularly when compared to non-burned individuals (Moi, Haugsmyr, & Heisterkamp, 2016; Palmu et al., 2016; Spronk et al., 2019; Wasiak, Lee, et al., 2014; Wasiak, Paul, et al., 2014). A systematic literature review by Spronk et al (2018) concluded that this finding was consistent across the most commonly utilised QoL assessments. Two studies undertaken by one research group compared the physical function and QoL of a burn injured patient group to that of a matched, non-burned control group prior to the implementation of an exercise program (Grisbrook et al., 2013; Grisbrook et al., 2012). The time from burn injury reported in these studies ranged from two to 14 years. Utilising self-report surveys, greater upper limb disability (Grisbrook et al., 2013) and reduced health related QoL were reported by the burn injured group (Grisbrook et al., 2012). Holavanahalli et al. (2016) demonstrated that a cohort of 98 patients with a severe burn injury (on average 17 years previous) still reported problems related to joint pain, joint stiffness, difficulty walking, difficulty running and weakness. However, not all problems are associated with severe burn injuries only.

Non-severe burns have been documented to impair physical function and QoL (Shakespeare, 1998; Spronk et al., 2019). In a group of patients with an average TBSA of 4%, problems with activities of daily living (ADLs) were reported 15 weeks after injury (Shakespeare, 1998). Spronk et al (2019) reported that at five to seven years after a burn injury, 5.9% of their non-severe burn injury cohort were self-assessed as having ongoing “extreme or severe problems”. These studies highlight the chronicity of impairments obtained secondary to a burn injury, regardless of the severity of burn, and again emphasises the need for optimising all facets of acute-phase management in effort to minimise or avoid the occurrence of ongoing disability.

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1.1.3 Impact on Skeletal Muscle after Burn Injury

A feature of burn injury is substantial and ongoing loss in muscle strength and mass. Muscle provides the force generation to allow locomotion and movement of the skeleton. It is also a major intrinsic patient factor which can be utilised to overcome the contraction of a scar formed after a burn injury. Therefore, it would be realistic to consider the loss of muscle strength as a primary impairment leading to reduced functional ability in survivors of a burn injury.

1.1.3.1 Impairment of Skeletal Muscle Mass

In response to a burn injury an up-regulation of total protein turnover occurs, particularly protein breakdown to facilitate a redistribution of amino acids around the body and to provide an alternate fuel source for the hypermetabolic response. This results in nett protein breakdown and contributes directly to skeletal muscle atrophy (Borsheim et al., 2010; Chao et al., 2015; Hart, Wolf, Mlcak, et al., 2000; Merritt, Cross, & Bamman, 2012). Merritt et al. (2012) found elevated levels of molecules signalling the breakdown of protein in burn injured patients compared to non-burned controls. Chao et al. (2015) found in severely burn injured children an increase in the rate of protein breakdown of four to six times higher, and protein synthesis of two to three times higher than that of healthy adult males. This study did not elaborate whether this difference was driven by age or specifically the burn injury. Borsheim et al. (2010) also reported significantly higher rates of protein turnover in burned children at hospital discharge compared to non-burned children.

Changes in muscle and protein kinetics are thought to be associated with increasing burn size and can continue to persist for up to one year after complete healing of the burn (Chao et al., 2015; Hart, Wolf, Chinkes, et al., 2000; Hart, Wolf, Mlcak, et al., 2000; Porter et al., 2013). Net negative protein balance has been observed in paediatric populations up to 12 months after major burn injury (Chao et al., 2015; Hart, Wolf, Mlcak, et al., 2000). To date, muscle mass changes have been studied almost solely in severe burn injuries. As a result, we do not have a complete understanding of how this response is shaped in non-severe burn injuries. As non-severe injuries form the

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majority of burn injuries managed on a daily basis, it is important to understand the magnitude of effect these injuries will have on the skeletal muscle turnover.

Bed rest is another factor responsible for muscle atrophy in the burn injured population. When an individual is put to bed for a period of time, off-loading of the musculoskeletal system and muscle wasting occurs. The traditional management of an acute burn injury has been surgical intervention to repair the wound. This is generally followed by a period of bed rest and inactivity whilst wounds heal. Unpublished data from a group of 19 acute burn injured patients with an average TBSA of 6%, who wore activity monitors for at least an 18 hour time period before and after surgery, demonstrated that 73% of their monitored time period was spent lying down, with only 2% of their monitored time involving ambulation (Chan, Gittings, Wood, Edgar; Unpublished data). Physical activity was particularly decreased in those with lower limb injuries, suggesting a direct impact on their ability to get out of bed and mobilise independently.

Whilst bed rest induces many deleterious effects on the body, exercise and nutrition are viewed as effective mitigation strategies. Trappe et al. (2004) studied the effect of 90 days bed rest in healthy, young males and demonstrated significant reductions in whole muscle size (17%), maximal voluntary contraction (43%), peak force (41%) and peak power (47%) after the bed rest period. One study group performed resisted exercise during bed rest and it was demonstrated to be effective in minimising the negative effects of bed rest. In a separate study, an experimental group of healthy, young volunteers undertook 28 days of bed rest testing the effect of nutritional supplementation during bed rest. Significant reductions in leg lean mass (-0.4 ± 0.1kg) and leg muscle strength (-17.8 ± 4.4kg) were demonstrated in the bed rest only group and were shown to be more pronounced than the group who received nutritional supplementation during this time (Paddon-Jones et al., 2004).

Particularly susceptible to the effects of bed rest are the older adult population. Significant losses in whole body lean mass (3.2%), lower limb lean mass (6.3%), leg muscle strength (15.6%) and a decrease in the rate of muscle protein synthesis of 30% have been reported after 10 days of bed rest in older adults (Kortebein, Ferrando, Lombeida, Wolfe, & Evans, 2007). Another study revealed that just five days of bed

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rest in older adults was enough to demonstrate significant reductions in lower limb lean muscle mass and strength (Tanner et al., 2015). Whilst a high intensity resistance training programme did return muscle size and function to pre-study levels in this elderly group, eight weeks of training was required to undo the effects of five days of bed rest. The described rates of deterioration and prolonged recovery emphasise that preventing the effects of bed rest is an important management strategy.

The above data are from healthy participants, and it is likely that such effects are exacerbated in clinical populations. This idea has been tested experimentally, where a stress response similar to that experienced in illness and trauma was elicited by the administration of cortisol to healthy participants undergoing bed rest. An amplified response to bed rest was noted with significant decreases in leg muscle strength, a three-fold greater loss of leg muscle mass, as well as significantly increased levels of skeletal muscle catabolism when compared to bed rest alone (Ferrando, Stuart, Sheffield-Moore, & Wolfe, 1999; Paddon-Jones et al., 2006). Based on these findings, it is reasonable to hypothesise that extended bed rest during hospital admission plus surgical intervention will exacerbate the catabolism elicited by the initial burn injury, further compromising skeletal muscle mass and function.

1.1.3.2 Impairment of Skeletal Muscle Strength

Any loss of muscle mass is expected to manifest clinically as a reduction in the force producing capability of that muscle. This is due to the relationship between muscle hypertrophy and the increase in numbers of force-generating fibres within the muscle in series (Frontera & Ochala, 2015). Unfortunately, a persistent loss in skeletal muscle strength has been an expected and documented outcome of a burn injury for the past two decades. St-Pierre et al. (1998) completed a one-off assessment of muscle strength in a group of 30 patients 15 – 92 months post burn injury (mean 37.7 months) with a TBSA range of 15 – 75%. Patients with a severe burn (>30% TBSA) were assessed to have persistent and significantly decreased knee extensor torque, power and work when compared with an uninjured control group. This difference was statistically significant at a faster velocity of muscle action. The authors suggest that the prominence of muscle weakness at fast velocities was possibly due to preferential atrophy of fast twitch muscle fibres. The clinical importance of this finding about fibre

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type was not explored. However, there may be an implication for exercise prescription as fast twitch fibre size and number are increased with high velocity and high intensity exercise (McKinnon et al, Wang et al, Wilson et al & Fry 2004).

More recently, studies have continued to compare the muscle strength of a burned patient cohort to matched non-burned control groups to describe the change of muscle strength experienced by patients at different times in the burn recovery continuum. Ebid et al. (2012) assessed adult patients with a TBSA greater than 35% six months after injury. Peak torque was significantly decreased for both knee flexion and extension in the burn injured group. Similarly, Omar et al. (2017) demonstrated reductions in knee flexion and extension strength 16-24 weeks after severe burn injury relative to matched, unburned controls. Bjornhagen et al. (2018) compared muscle strength of 25 burn injured patients (median TBSA of 27%) to reference values for strength from healthy subjects in the literature. It was determined that there was ongoing weakness and large variation in the strength of knee extensors and shoulder flexors in this group who were on average 17 months after burn injury. However, there was no statistical analysis which investigated how TBSA and other burn injury factors were related to changes in muscle strength after burn injury.

These patterns of muscle strength loss after burn injury are also demonstrated in children (Alloju et al., 2008; Cambiaso-Daniel et al., 2018; Ebid et al., 2014). Alloju et al. (2008) assessed children 6 months after a severe burn injury, with an average TBSA of 57%, in comparison to a non-injured group. It was found that peak normalised quadriceps torque was 68% lower in the burn injured group. Ebid et al. (2014) found a similar pattern of outcome for knee extension torque assessed as close as possible to 42 days post burn injury. Cambiaso-Daniel et al. (2018) retrospectively evaluated children between three and four years after burn injury. Muscle strength, assessed by peak torque of knee extensors on the dominant leg, was noted to remain significantly reduced compared to non-burned age and sex matched controls ($p<0.001$). Interestingly, this result was found despite the burn injured group having engaged in 6-12 weeks of exercise training upon discharge from their acute hospital admission.

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Not all data demonstrate a reduction in muscle strength. In the study by St-Pierre et al. (1998), the sample of 14 patients with a non-severe burn injury were not observed to be different in knee flexor and elbow flexor torques from the matched, non-burned control participants at any movement speed. The authors of the study acknowledge that longer periods of bed rest and hospitalisation in larger burns may attribute to the difference in the pattern of muscle strength recovery described for different injury severities. Grisbrook et al. (2013) studied adult participants and reported no difference in muscle strength between nine burn injured (range 22 – 75% TBSA) and nine matched non-burned control participants, but this was at an average of 6.56 (range 2-14) years after their initial burn injury. It is possible that the time from burn injury is a factor in these results, so too may be the small sample sizes of the aforementioned studies. The results described here, when taken in isolation may suggest that there is a different recovery trajectory for TBSA and age, though further assessment of muscle strength changes in relation to these variables would be required.

Reduced muscle strength after burn injury is well documented. It is likely to negatively impact a patient's ability to return to what they consider to be a normal active and productive lifestyle. Esselman et al. (2007) identified physical function, which can be directly related to muscle strength as previously described, as the primary implication of return to work after a burn injury. Therefore, exploring modes of treatment and rehabilitation which are successful in the mitigation of this muscle strength complication is vital in order to optimise a patient's rehabilitation experience and their ongoing quality of life after a burn injury.

1.1.3.3 Mitigating the Impact of Burn Injury on Muscle

Burns research has been attentive to methods of limiting the hyper-metabolic response and subsequent muscle catabolism. Efforts have included environmental manipulation such as warming the environment and operating theatre which was effective in reducing metabolic rate in severe burns (Wilmore, Mason, Johnson, & Pruitt, 1975). Beta-blockade has been shown to reduce skeletal muscle catabolism (Herndon, Hart, Wolf, Chinkes, & Wolfe, 2001), as did the administration of testosterone in severe burn injury which reduced the rate of protein breakdown (Ferrando, Sheffield-Moore, Wolf, Herndon, & Wolfe, 2001). Oxandrolone, an anabolic steroid, administered alone

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or combined with supervised exercise after discharge from hospital has been recognized as beneficial in improving muscle strength and lean mass when compared to placebo and no exercise in a randomised controlled trial in severely burned children (Przkora, Herndon, & Suman, 2007). However, this study had high risk of bias related to allocation procedures and blinding. In a study by Hart et al. (2003) protein kinetic analyses were undertaken to determine whole body nett protein synthesis and breakdown. Early feeding and surgical intervention significantly reduced protein catabolism. Nutritional support is further advocated by Herndon and Tompkins (2004) in a review of the literature. No studies to date have investigated the effects of physical exercise and RT in isolation on stimulating muscle synthesis to improve muscle mass and muscle strength, in particular during the acute stages of burn injury. This remains an important area of research as exercise and RT are relatively inexpensive rehabilitation options which are widely applicable.

1.1.4 Muscle Mass, Muscle Strength & Function

Skeletal muscle creates torque around a joint, producing movement. It is widely accepted that a larger muscle will produce greater torque. Clinical studies comparing the relationship of muscle size and cross sectional area with muscle strength confirm this relationship (Bamman, Newcomer, Larson-Meyer, Weinsier, & Hunter, 2000; Castro, McCann, Shaffrath, & Adams, 1995; Fukunaga et al., 2001; Newman et al., 2003). In both males (Bamman et al., 2000) and females (Fukunaga et al., 2001), all measures of muscle size, that is, both muscle volume and muscle cross sectional area, were significantly associated with maximum voluntary contraction strength in upper and lower limbs.

Another assumption of muscle strength is a direct relationship with physical ability and function, which has been demonstrated in the literature in various populations. In older adults, the ability to generate force in the lower limb during functional tasks, as well as the self-rating of health related quality of life were significantly correlated with increased skeletal muscle strength measures (Samuel, Rowe, Hood, & Nicol, 2012). In a large study of adults over 55 years of age, regression analysis concluded that leg muscle strength was an independent predictor of physical function in males and females (Bouchard, Heroux, & Janssen, 2011). This apparent relationship between

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muscle strength and function has also been examined in subjects with a clinical condition. In a group of patients with Systemic Lupus Erythematosus, Andrews et al. (2015) concluded that reduced lower limb strength was a predictor for future decline in physical function. Hall et al. (2017) studied a group of adults with knee osteoarthritis and provided preliminary evidence that knee extensor strength was a determining factor for self-reported physical function, adjusting for all baseline characteristics and covariables. In individuals with hip osteoarthritis, Judd, Thomas, Dayton, and Stevens-Lapsley (2014) reported that lower limb muscle strength was up to 38% less in the osteoarthritis group and multiple functional assessments were completed at a significantly slower speed compared to healthy adults. Perhaps unsurprisingly, they were also found to be less physically active. These relationships of strength and physical function are reported in the upper limb.

The results from these studies imply that muscle strength and physical function are intimately linked. Rehabilitation aimed at improving muscle strength should assist with returning patients to an improved functional capacity and would be likely to improve the extent of recovery and QoL.

1.2 Burn Patient Outcome Assessment

1.2.1 Assessment of Quality of Life & Function

Quality of life surveys, such as the Burn Specific Health Scale-Brief (BSHS-B) and Short-Form-36 (SF-36) are among the most commonly used in the burn literature (Spronk et al., 2018). They have been shown to possess construct, criterion and convergent validity for use in burn injured populations (Edgar, Dawson, Hankey, Phillips, & Wood, 2010; Willebrand & Kildal, 2011). Additionally, the use of such patient reported outcome assessments offer a chance to understand patient centred progress and concerns during their recovery. This allows clinicians to provide targeted treatments to the patient, specific to their needs, in order to prevent ongoing and possibly lifelong problems. However, these QoL survey tools often lack the level of detail in assessment of bodily function and activity limitation that specific functional surveys provide.

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Due to the absence of validated burn specific activity limitation assessment tools, the validation of existing patient reported outcome measurements to use in the burn injured population is an important pursuit. The Disability of Arm, Shoulder and Hand (DASH) and the Quick Disability of the Shoulder, Arm and Hand (Quick-DASH) surveys are clinically applicable in patients with an upper limb burn injury (Wu, Edgar, & Wood, 2007). For patients with a lower limb burn injury, a previous interventional study has utilised the patient reported Lower Extremity Functional Scale (LEFS) to assess lower limb function during recovery (Paratz, Stockton, Plaza, Muller, & Boots, 2012). Despite the use of this tool in research, there are no patient reported outcome measurement tools which are specifically designed for burn injured populations, or, which have been validated to be used in patients with lower limb burn injuries (Falder et al., 2009). The Lower Limb Functional Index-10, which is a shortened form of the Lower Limb Functional Index (Gabel, Melloh, Burkett, & Michener, 2012), is a self-report assessment of function specific to the lower limb. It is reported to have improved psychometric properties and readability compared to other lower limb assessment tools, including the LEFS (Gabel et al., 2012). Ryland, Grisbrook, Wood, Phillips, and Edgar (2016) have demonstrated test-retest reliability of the LLFI-10 in burns. Further assessment of the clinical applicability of the LLFI-10 in a burn injured population would confirm the appropriateness of this self-reported functional assessment tool as an outcome measurement for patients with a lower limb burn.

1.2.2 Assessment of Muscle Strength

The assessment of muscle strength is an important part of a clinical physical assessment. This is of particular interest when the subject has a condition known to impact muscle dynamics, or, when prescribing an intervention which is aimed at improving the strength of the subject. In a burn injured population, extraneous factors such as pain, wound healing and the ongoing process of muscle atrophy may complicate assessment. Therefore, a safe and validated assessment tool is required to accurately and regularly assess capacity, as well as monitor the change in muscle strength after a burn injury. Isokinetic dynamometry and repetition maximum testing are two processes that have been used previously in the burn population.

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Isokinetic dynamometry is a process of dynamically testing muscular force generation. It is performed on a machine which provides a force equal to that being exerted by the participant's muscle, at a pre-determined and constant velocity. The advantages of this mode of testing is the safety it provides for those with pre-existing muscular and/or ligamentous injuries (Baltzopoulos & Brodie, 1989) making it useful in a rehabilitative setting. As such, isokinetic dynamometers have been used in multiple research projects in paediatric and adult burn injured patients (Al-Mousawi et al., 2010; Alloju et al., 2008; Ebid et al., 2014; Ebid et al., 2012; Grisbrook et al., 2013; Grisbrook et al., 2012; Pena et al., 2016; Suman & Herndon, 2007; Suman, Spies, Celis, Mlcak, & Herndon, 2001; Suman, Thomas, Wilkins, Mlcak, & Herndon, 2003). In a review of literature by Nedelec et al. (2016) it was surmised that whilst a useful tool, isokinetic dynamometry was not always a clinically feasible tool. Primarily, the size and cost of the required equipment make it prohibitive to obtain and the expertise required to operate the equipment would limit its clinical applicability to only a small percentage of burn centres worldwide.

Repetition maximum testing is a process undertaken to quantify the maximal strength of the muscle or muscle group in question. The test involves performing a particular resistance exercise, with progressively increasing loads, until a load can only be lifted a predetermined number of repetitions. For example, a one-repetition maximum would be the heaviest load lifted for one full repetition. As documented in the American College of Sports Medicine guidelines, a percentage of a tested one-repetition maximum can be used to prescribe the intensity of RT according to the specified goals of that RT programme (Garber et al., 2011). A three repetition-maximum (3RM) assessment has been used in previous burns research to prescribe initial training loads for exercise groups (Al-Mousawi et al., 2010; Cucuzzo, Ferrando, & Herndon, 2001; Hardee et al., 2014; Przkora et al., 2007; Suman & Herndon, 2007; Suman et al., 2001; Suman et al., 2003). It has also been utilised as an outcome measurement tool to assess change in strength after an intervention period (Cucuzzo et al., 2001; Paratz et al., 2012). The repetition-maximum assessment process requires less expensive and specialist equipment than isokinetic dynamometry. However, due to the nature of the test requiring maximal dynamic muscular fatigue, the time taken to perform it safely and the need for multiple familiarisation sessions to achieve consistent results (Ploutz-

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Snyder & Giamis, 2001), this process may not be conducive to the assessment of many muscle groups in one session, or to regular re-assessment. As such, this may reduce its applicability in an acute clinical setting such as in burn injury, particularly if regular re-assessment is forecast.

What is currently lacking in clinical practice for rehabilitation of a burn injured patient is an objective, low cost, time efficient and easy-to-apply muscle strength assessment. Such a measurement tool would allow for regular monitoring of the patient, assess the effectiveness of rehabilitation and provide objective data for the adjustment of exercise prescription in association with the patient's changing clinical status. Therefore, exploring the reliability and validity of new methods of muscle strength assessment is a warranted pursuit. Hand held dynamometry (HHD) is a method of testing isometric muscle strength with inherent advantages. It is known to be a reliable assessment of muscle strength (Mentiplay et al., 2015; Stark, Walker, Phillips, Fejer, & Beck, 2011) and recently has been shown to have value in predicting one-repetition maximum in biceps and quadriceps muscles which may be useful for RT prescription (Tan, Grisbrook, Minaee, & Williams, 2018). The advantages of HHD include lower cost, greater time efficiency, portability and ease of use when compared with isokinetic dynamometry (Stark et al., 2011). A disadvantage of HHD is that reliability of the test is reliant on the strength of the assessor (Stone, Nolan, Lawlor, & Kenny, 2011; Thorborg, Bandholm, Schick, Jensen, & Holmich, 2013; Wikholm & Bohannon, 1991). Grip strength dynamometry is another form of hand held dynamometry which can be used as a sentinel measurement of muscle strength, but may also inform other health related outcomes (Bohannon, 2015). It has previously been used in interventional burns research (Paratz et al., 2012), however it has only been assessed as having acceptable within-session reliability, construct and criterion validity in patients with a healed burn wound (Clifford, Hamer, Phillips, Wood, & Edgar, 2013). Hand held dynamometry of the appendicular musculature has not been assessed for its clinical applicability in burns. With the advantages of HHD in mind, HHD presents as a promising mode of assessment for patients with a burn injury which would assist clinicians in prescribing appropriate strength training rehabilitation and monitoring muscle strength outcomes. It may prove useful across the spectrum of burn injury recovery from acute phase exercise to long term rehabilitation. Prior to widespread use of HHD, further investigation of its clinical applicability in the burn injured population

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is required. Of particular interest is its performance as an assessment tool in the acute care setting and across a range of burn injury severity.

1.3 Resistance Training – A Brief Overview

Resistance training (RT) is a mode of exercise which involves the muscles working against an external load, or resistance. Appropriately prescribed resistance training programmes, with appropriately targeted loading, have been widely advocated in review articles as the most effective method for achieving improvements in muscular strength and lean body mass (Garber et al., 2011; Hass, Feigenbaum, & Franklin, 2001; Kraemer & Ratamess, 2004). The American College of Sports Medicine Position Stand (Garber et al., 2011) also highlight the many health benefits that RT is known to provide such as improved; cardiovascular risk factors, body composition, insulin sensitivity and bone mass, as well as benefits to mental health and energy. Given the wide range of benefits it provides, RT now forms part of the exercise recommendations made by national organisations such as the Australian Government Department of Health (Brown, Bauman, Bull, & Burton, 2013), the American College of Sports Medicine (American College of Sports, 2009; Garber et al., 2011) and Canadian Society for Exercise Physiology (Behm, Faigenbaum, Falk, & Klentrou, 2008).

1.3.1 Resistance Training in Clinical Groups

The application of effectively structured RT provides benefits in many clinical settings. During periods of inactivity and bed rest, RT has been shown in small group research to mitigate the negative effects on muscle protein turnover, muscle size and muscle strength (Akima et al., 2000; Ferrando, Tipton, Bamman, & Wolfe, 1997; Trappe et al., 2004). In populations with cancer, exercise programmes which incorporate RT have been determined to be safe and beneficial. Systematic reviews and meta-analyses support the benefit to oncology patients in quality of life (Mishra et al., 2012) muscle strength and body composition (Keilani et al., 2017) as well as fatigue (Dennett, Peiris, Shields, Prendergast, & Taylor, 2016). Many other groups of patients also benefit from RT. Older adults with sarcopenia have demonstrated enhancements in muscle mass and strength using RT as a treatment option and prevention strategy (Law, Clark, & Clark, 2016). Other literature review results have

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recommended exercise and RT for improvement in blood results in diabetes (Umpierre et al., 2011), greater muscle strength, endurance and improved disease risk factors in heart disease (Pollock et al., 2000) and greater muscle strength in kidney disease (Smart et al., 2013). The evidence for exercise in clinical groups continues to grow. This highlights the widespread benefits for RT, not only for improving strength but also the positive impact on general health and quality of life. However, the effectiveness of RT after burn injury has not been comprehensively demonstrated.

1.3.2 Resistance Training in Burn Injury

There are several plausible reasons as to why RT might be a useful intervention in the burn injured population. These include rebuilding muscle mass lost to wasting, development of muscle strength, increasing physical work capacity and improving general health profiles.

Non-systematic reviews of the literature have acknowledged that general exercise programmes of six to 12 weeks duration are beneficial after discharge from the acute hospital setting (Nedelec et al., 2016; Porter, Hardee, Herndon, & Suman, 2015). Benefits to the patient have included improvements in muscle strength, lean mass, aerobic capacity, function and quality of life. However, systematic review or quantitative synthesis of data has not been used to evaluate the strength or quality of these outcomes. In previous studies, RT has been undertaken alongside structured cardiovascular exercise, potentially obscuring evidence of the unique contribution of RT in these benefits. Therefore, there is a need for a systematic and in-depth review of the current literature to evaluate the effect of RT after burn injury.

Research into the implementation of exercise training in burn injury is limited and our knowledge of exercise prescription parameters across the spectrum of burn injury is not complete. The prescription of exercise after burn injury, in both adult and paediatric populations has traditionally been implemented after hospital discharge and up to two years after the occurrence of the burn injury. There is a lack of literature which investigates the prompt incorporation of individually prescribed RT at the time of the burn injury, leaving clinicians without a well-established, evidence based

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approach to rehabilitation, particularly in the acute setting. Nedelec et al. (2016) in their non-systematic review of literature summarise that studies to date have focussed on rehabilitation of severe burn injury only, suggesting that understanding the effect of exercise training on non-severe burn injuries would be important for the completeness of understanding rehabilitation effects. All surviving burn injuries will require rehabilitation and it is vital that therapists providing this are equipped with evidence which is comprehensive and applicable to the entire rehabilitation journey of every patient.

1.4 Summary of Knowledge Gaps Addressed

Resistance training has been the topic of limited previous research in burns rehabilitation and although positive results have been published, most studies are of low quality, are similar in their prescription principles and interpretation is limited by their small sample size. Chapter Two of this thesis, "*Resistance Training for Rehabilitation after Burn Injury: A Systematic Literature Review & Meta-Analysis"* presents a systematic and critical appraisal of the current literature plus quantitative data pooling regarding the use and impact of RT after burn injury.

Assessment of a patient with a burn injury needs to be multi-faceted. Whilst there is a range of quality of life assessments to choose from, there is a comparative lack of specific, functional assessment tools which are applicable in the burn population. There is no patient reported outcome measurement tool specific to lower limb burns. The LLFI-10 is a tool with promising clinimetric properties which needs further assessment of its clinical applicability to patients with lower limb burn injuries. Chapter three of this thesis "*The Lower Limb Functional Index – A reliable and valid functional outcome assessment in burns"* presents a study which assesses the LLFI-10 for clinical applicability as an assessment of lower limb function in patients with a lower limb burn injury.

For the assessment of muscle strength, hand held muscle strength dynamometry could be a clinically useful tool in burn injured patients. There are many advantages to using hand held dynamometry, however no work has been completed to assess the reliability,

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validity and clinical applicability of this equipment, nor has a standardised methodology been developed for use in patients with a burn injury. Consideration needs to be given to how to address the main limitation of HHD, which is the impact of operator strength on achieving valid and consistent recordings. Chapter Four "*Grip and Muscle Strength Dynamometry are Reliable and Valid in Patients with Acute Minor Burn Wounds"* and Chapter Five "*Grip and Muscle Strength Dynamometry in Acute Burns: Evaluation of an Updated Assessment Protocol"* are two studies which investigate the use of HHD as an efficient and clinically applicable method of assessing muscle strength after burn injury and provide a methodology for use.

There is no accepted gold standard prescription for exercise therapy for reducing physical dysfunction after a burn injury. In the studies where RT has been investigated, intervention has not begun until the chronic phase of the injury. As such, there remains a lack of understanding of the use and effects of RT on QoL, physical function, muscle strength and muscle mass when implemented during the acute phase of burn injury treatment and rehabilitation. Chapter Six of this thesis "*The efficacy of resistance training in addition to usual care for adults with acute burn injury: A randomised controlled trial"* is a report of a trial undertaken to assess the effect of an individually prescribed, progressive RT program commenced during the acute phase of burn injury recovery.

1.5 Aims of the Research Programme

The aims of this Doctor of Philosophy thesis are to:

- Systematically evaluate the current state of the evidence regarding the use of resistance exercise training as therapy in burns rehabilitation.
- Assess the reliability and validity of the LLFI-10 for use in a population with lower limb burn injury.
- Examine the clinical applicability of hand held muscle strength dynamometry as a mode of muscle strength assessment in the acute burn injured population.
- Develop and rigorously test an evidence informed resistance training programme for use in acute burn injury.

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Chapter 2 Resistance Training for Rehabilitation after Burn Injury: a Systematic Literature Review and Meta-Analysis

Preface

There is no previous systematic review of evidence, or quantitative pooling of data relating to the unique effect of resistance training in rehabilitation from burn injury. Presented is a systematic review and meta-analysis assessing the quality of evidence and magnitude of the effect of resistance training after burn injury. This chapter is published as:

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Resistance Training for Rehabilitation after Burn Injury: A Systematic Literature Review & Meta-Analysis

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2.1 Abstract

BACKGROUND: Resistance training is beneficial for rehabilitation in many clinical conditions, though this has not been systematically reviewed in burns. The objective was to determine the effectiveness of resistance training on muscle strength, lean mass, function, quality of life and pain, in children and adults after burn injury.

METHODS: Medline & EMBASE, PubMed, CINAHL and CENTRAL were searched from inception to October 2016. Studies were identified that implemented resistance training in rehabilitation. Data were combined and included in meta-analyses for muscle strength and lean mass. Otherwise, narrative analysis was completed. The quality of evidence for each outcome was summarised and rated using the GRADE framework.

RESULTS: Eleven studies matched our inclusion criteria. Primary analysis did not demonstrate significant improvements for increasing muscle strength (SMD 0.74, 95% CI -0.02 to 1.50, p=0.06). Sensitivity analysis to correct an apparent anomaly in published data suggested a positive effect (SMD 0.37, 95% CI 0.08 to 0.65, p=0.01). Psychological quality of life demonstrated benefit from training (MD=25.3, 95% CI 3.94 to 49.7). All studies were rated as having high risk of bias. The quality of the evidence was rated as low or very low.

CONCLUSION: Further research with robust methodology is recommended to assess the potential benefit suggested in this review.

Keywords
Burns; Resistance Training; Rehabilitation; Exercise Therapy; Review; Meta-analysis

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2.2 Introduction

People recovering from a burn injury will experience a range of challenges throughout their recovery. It has been reported that physical dysfunction and quality of life continue to be adversely affected up to three years after the initial burn injury (Klein et al., 2011; Renneberg et al., 2013; Wasiak et al., 2014). Survivors are also challenged by long term reductions of muscle mass and strength (Ebid, Omar, & Abd El Baky, 2012; Hart, Wolf, Chinkes, et al., 2000; Hart, Wolf, Mlcak, et al., 2000; Porter, Hurren, Herndon, & Borsheim, 2013; St-Pierre, Choiniere, Forget, & Garrel, 1998), which can limit their ability to perform activities of daily living and participate in physical activity. Whilst a traumatic injury such as a burn will instigate this catabolic processes, bed rest and inactivity have been shown to amplify catabolism of skeletal muscle (Ferrando, Stuart, Sheffield-Moore, & Wolfe, 1999). In these circumstances, it would appear that early and intensive rehabilitation likely matters to an individual's physiological profile and functional recovery.

The aim of rehabilitation is ultimately the return of a person's physical capability and independence. In burns, modes of rehabilitation vary widely between facilities, as no evidence based consensus on best practice rehabilitation has been established. The American College of Sports Medicine recommend resistance training (RT) as a mode of exercise to promote several health benefits, including improvements in the muscle mass and strength of healthy adults (Garber et al., 2011). Similar recommendations have also been made for children and adolescents (Lloyd et al., 2014). Resistance training, where muscles are required to contract against an opposing load, has been shown to be a beneficial form of rehabilitation in clinical populations prone to muscle wasting, providing stimuli to increase protein synthesis and muscle mass. This has been demonstrated in conditions such as HIV, cancer, rheumatoid arthritis, chronic renal impairment and bed rest (Ferrando, Tipton, Bamman, & Wolfe, 1997; Little & Phillips, 2009; Zinna & Yarasheski, 2003). In trauma populations, RT guidelines have been developed in spinal cord injury with modifications specific to the nature of that injury and recommendations for exercise have been published in burn injury (Nedelec et al., 2016).

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Evidence relating to the efficacy of RT as a mode of exercise after burn injury to improve a patient's outcomes has not been systematically reviewed. Neither has it been established as a routine practice for recovery and rehabilitation after a burn injury. This review aimed to evaluate the effectiveness of RT in children and adults rehabilitating from burn injury. Specifically, we were interested in the effect of RT on muscle strength, lean body mass, physical function, quality of life and pain. The safety profile of RT in this population was also examined.

2.3 Methods

The protocol for this review was registered in the PROSPERO International prospective register of systematic reviews (registration number CRD42015024527).

Inclusion criteria

Types of studies

Randomised and non-randomized controlled trials were included to ensure a thorough evaluation of the effects of the intervention. We included studies where RT was compared to usual rehabilitation care or any rehabilitation activity that did not include RT. Studies where there was no comparison to a burned patient group were excluded. We included only studies available in English that had been published in full.

Types of participants

Studies of children and adults who experience a burn injury were included in this review. No limits have been placed on the extent or agent of the burn injury, the setting in which the RT occurred or the time post injury in which training commenced. Participants in studies investigating the effect of a pharmacological agent in conjunction with RT were excluded, unless the study design enabled us to estimate the unique effect of RT.

Types of interventions

Only studies which performed RT to recognised principles of the American College of Sports Medicine were included (Garber et al., 2011). The parameters of RT for inclusion were: a minimum of two RT sessions per week, training at an intensity of at least 40% of a one-repetition maximum for at least two sets of eight repetitions per

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individual exercise. A minimum of two weeks of RT were required for inclusion as improvements in muscle mass have been noted to occur with two weeks of RT (Abe, DeHoyos, Pollock, & Garzarella, 2000). Studies that include RT as a standalone treatment as well as those that use RT as part of a multimodal treatment regimen were considered. We included trials that compared RT with no treatment or another active treatment other than RT.

Outcome measures of interest

The outcomes of interest were: muscle strength, lean body mass, physical function, quality of life and pain. The occurrence of any adverse events from the intervention was also assessed.

Search strategy

A sensitive search strategy was developed to identify publications relevant to this review. To identify relevant articles the following databases were searched from inception to October 2016: Medline, EMBASE, PubMed, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL). In addition to the electronic searches, reference lists of all included studies and review articles relevant to the topic were checked. The references of potential papers retrieved were examined to identify any additional papers not captured through the initial search strategy. Abstracts from burns conferences (International Society for Burn Injury, American Burn Association and Australian and New Zealand Burn Association) were also checked to identify papers which may not have been identified through the initial search strategy. We attempted to communicate with study authors when additional information or where clarification of study procedure or data were required.

Selection of studies

Two authors (PG & TG) independently reviewed the titles generated by the literature search. Relevant abstracts were independently assessed by the same two authors. Full text reports were obtained for further assessment against our inclusion criteria. In the event of disagreement, discussion between the two authors occurred to achieve consensus. Where consensus was not reached, a third reviewer (DE) was used to independently assess the study to determine inclusion.

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Data extraction and management

One author (PG) extracted all data from the included studies using a standardised extraction form. These data were checked and confirmed by two other authors independently of each other (BW & DE). Where differences in extraction existed, a plan was made to review the study and discuss to achieve consensus. The following data were extracted:

- Participant demographic details: number of participants recruited, withdrawals, loss to follow up, age and total burn surface area (TBSA).
- Intervention characteristics: time from injury to commencement of training, location of training, mode of training, volume of training, intensity of training and control group treatments.
- Outcome assessments: muscle strength, lean body mass, function, quality of life, pain and adverse events.
- Information pertaining to the assessment of risk of bias.

Where multiple longitudinal assessments were performed in a study, data provided at the end of the intervention period were used for quantitative analysis. A narrative description was undertaken of data from other time points.

Two studies investigated the use of RT in combination with a pharmacological agent: Oxandralone and growth hormone (Przkora, Herndon, & Suman, 2007; Suman, Thomas, Wilkins, Mlcak, & Herndon, 2003). Only data from groups who did not receive a pharmacological agent as a co-intervention to RT were used in this review.

Assessment of risk of bias

Included studies were assessed using a risk of bias tool adapted from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011). The selection of items and operational criteria appropriate to this clinical area for each item were agreed upon by the study team *a priori*. Non-randomised comparison studies were assessed on the same criteria as RCT's. The tool assessed the following categories as being at high, low or unclear risk of bias: sequence generation, allocation concealment, blinding (participants, therapists and outcome assessor), incomplete outcome data, selective outcome reporting and other biases.

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For individual items, where insufficient information was provided by study authors, risk of bias was determined to be "unclear". Where one or more items were deemed as high risk, the study was given an overall rating of "high risk". These assessments were undertaken by the authors as per the data extraction processes. To assess publication bias, visual inspection of funnel plots was planned but due to insufficient data, was not undertaken.

Where studies utilised self-report assessment, the participant was deemed to be the assessor. In this circumstance, low risk of bias can only be given for blinding of outcome assessment where the participant is adequately blinded to their group allocation. This was relevant to outcomes assessed by patient reported surveys for quality of life and function.

Data synthesis

Results from clinically homogeneous trials were combined using a random effects meta-analysis with Review Manager (RevMan) v5.3 where adequate data existed to support this. Estimates of effect were calculated and are presented for each outcome as mean differences (MD) and 95% CIs where measurement tools were identical, or, standardised mean differences (SMD) and 95% CIs where tools were different. Where only standard error was provided, this was converted to standard deviation (SD) using an in-built calculator within RevMan. Data were summarized in forest plots. Where inadequate data was available for meta-analysis, results were presented as a narrative synthesis with mean difference and 95% confidence intervals calculated from the study data using RevMan.

The overall quality of evidence for each outcome measure was summarised and rated using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) framework and approach (Guyatt, Oxman, Schunemann, Tugwell, & Knottnerus, 2011). Strength of the evidence for each outcome was considered against the following factors: design limitations (downgrade if > 25% of the participants were from studies with a high risk of bias), inconsistency (downgrade once if heterogeneity was statistically significant and $I^2 \geq 50\%$ or when reported treatment effects were in opposite directions), imprecision (downgrade once if, for continuous data, the number

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of participants was below 400), indirectness (downgrade once for direct evidence if >50% of participants were outside of the target group) and publication bias (downgrade once for direct evidence of publication bias). Single studies with fewer than 400 participants were considered both inconsistent and imprecise. These ratings were completed by one author (PG), then independently checked and confirmed by a second co-author (BW).

Assessment of heterogeneity

Statistical significance of heterogeneity was assessed using the Chi^2 test and deemed significant where the p-value <0.05. The amount of heterogeneity was estimated using the I^2 test. Where heterogeneity was deemed to exist ($I^2 \geq 50\%$), we explored pre-planned, age based sub group analyses for each of the outcome measures. Due to lack of variation in study's populations, we were unable to perform other planned sub group analyses. These included burn injury factors (TBSA ≥15% or <15% and burn agent), intervention characteristics (intensity of prescription ≥70% of 1 repetition max or <70%) and duration of intervention (≥6 weeks or <6 weeks).

Sensitivity analysis

A *post-hoc* sensitivity analysis was carried out for the muscle strength outcome. An imputed SD was used for two studies Ebid et al. (Ebid, El-Shamy, & Draz, 2014; Ebid, Omar, et al., 2012) as we believed the SDs provided in the studies were miscalculated. Contact with the primary author was attempted to request further clarification, but a reply was not forthcoming.

2.4 Results

Characteristics of included studies

The flow of studies through this review can be viewed in Figure 2.1. We identified 11 studies (n=325) that complied with the selection criteria and were included in this review (Al-Mousawi et al., 2010; Cucuzzo, Ferrando, & Herndon, 2001; Ebid et al., 2014; Ebid, Omar, et al., 2012; Hardee et al., 2014; Mowafy, El-Sayed, El-Monaem, & Osman, 2016; Paratz, Stockton, Plaza, Muller, & Boots, 2012; Przkora et al., 2007; Suman & Herndon, 2007; Suman, Spies, Celis, Mlcak, & Herndon, 2001; Suman et al., 2003) (Table 2.1).

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Nine studies (Al-Mousawi et al., 2010; Cucuzzo et al., 2001; Ebid et al., 2014; Hardee et al., 2014; Mowafy et al., 2016; Przkora et al., 2007; Suman & Herndon, 2007; Suman et al., 2001; Suman et al., 2003) included only paediatric burn patients, whilst two studies (Ebid, Omar, et al., 2012; Paratz et al., 2012) were from adult populations. All studies chose to include only patients with major burn injuries. The range of mean TBSA values across all included studies was 29.9% - 62% TBSA. Resistance training was commenced at various time points ranging from final skin grafting and healing, to 6 months after the initial burn injury (see Table 2.2).

Resistance training was undertaken using free weights and cable weights for all studies except two studies by (Ebid et al., 2014; Ebid, Omar, et al., 2012) where training was undertaken with an isokinetic dynamometer. The intensity of training progressed from 60% of repetition maximum (RM) up to 85% RM in training protocols using free and cable weights. In studies using the isokinetic dynamometer, the initial intensity was set at 50% - 60% of average torque. Training occurred three times per week for the duration of 6 weeks in (Paratz et al., 2012) and 12 weeks in all other studies (see Table 2.2).

We excluded 24 other studies for not meeting our inclusion criteria. Reasons for exclusion were: comparisons made to non-burned participants (Ahmed, Abdel-aziem, & Ebid, 2011; Grisbrook et al., 2013; Grisbrook, Reid, et al., 2012); investigated outcomes not appropriate to this review (Celis, Suman, Huang, Yen, & Herndon, 2003; Chao, Suman, Herndon, Sidossis, & Porter, 2014; Grisbrook, Wallman, et al., 2012; Suman, Mlcak, & Herndon, 2002); review articles (Disseldorp, Nieuwenhuis, Van Baar, & Mouton, 2011; Nedelec et al., 2016; Porter, Hardee, Herndon, & Suman, 2015; Serghiou, Cowan, & Whitehead, 2009); not assessing RT as an intervention (Benjamin, Andersen, Herndon, & Suman, 2015; Ebid, Ahmed, Mahmoud Eid, & Mohamed, 2012; Neugebauer, Serghiou, Herndon, & Suman, 2008; Saraiya, 2003); inadequate amount of RT performed (Parrott, Ryan, Parks, & Wainwright, 1988); control group participating in RT (Cronan, Hammond, & Ward, 1990; Kim et al., 2016; Pena et al., 2015; Porro et al., 2013; Rosenberg et al., 2013); no English translation available (Martin Martinez, Diez Sanz, Corona Fernandez, Garcia Aragon, & Gonzalez Fraile, 2014); unable to acquire study manuscript (Casa, Caleffi, Bocchi,

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Ferraro, & Del Piano, 1990); and results which had been previously reported in other individual trials (Wurzer et al., 2016).

Risk of bias in included studies

The results of our risk of bias assessment are displayed in detail in Table 2.3 and Figure 2.2.

Allocation (selection bias)

Only two studies (Ebid et al., 2014; Ebid, Omar, et al., 2012) described their process for allocation and concealment adequately to be assessed as low risk of bias, whilst one study (Paratz et al., 2012) was rated as having a high risk. Concealment of allocation was also rated low risk for two studies (Ebid et al., 2014; Ebid, Omar, et al., 2012) and high risk for one (Paratz et al., 2012).

Blinding (performance bias and detection bias)

No studies were assessed to have adequately blinded participants or assessors throughout the research process. Blinding of outcome assessment was rated low risk for one study (Ebid et al., 2014) and high risk for one (Paratz et al., 2012). The high risk rating given to the study by Paratz et al. (2012) was due to their utilisation of self-report surveys for primary outcome measures. Their high risk of bias for participant blinding meant that blinding of outcome assessment must also be high risk.

Incomplete outcome data (attrition bias)

One study was deemed at high risk of bias for participant attrition where of the 100 subjects initially enrolled and randomised, 69 remained after death, exclusion or withdrawal. However, of these final 69, data from only 44 patients were included in analysis due to lack of compliance with the intervention (Suman et al., 2003). One study was rated as unclear in their participant attrition as patient compliance was not reported (Mowafy et al., 2016).

Selective reporting (reporting bias)

One study (Mowafy et al., 2016) was judged to be at high risk of bias for selective outcome reporting for not providing any between group results. All other studies were deemed low risk.

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Participants analysed in group to which allocated

Suman et al. (2003) was rated as being at high risk of bias for this category. It was evident that intention to treat analysis was not undertaken where data was only analysed for 44 of the 69 participants who were not excluded or withdrawn from the study. All other studies were deemed to be low risk.

Other potential sources of bias

Seven studies were rated high risk for some other bias. In one study, a small number of patients received pharmacological agents as part of another trial (Suman & Herndon, 2007). One study did not provide any patient data at baseline (Mowafy et al., 2016), whilst one other did not provide muscle strength data at initial assessment. There was a group of studies which did not provide baseline comparison of groups at the time of recruitment into the study as randomisation and initial patient assessment occurred months apart (Al-Mousawi et al., 2010; Przkora et al., 2007; Suman & Herndon, 2007; Suman et al., 2001; Suman et al., 2003). The lack of variability in sample size for outcomes precluded conclusions for publication bias.

Effects of interventions

Muscle strength

Results of knee extension strength were combined and assessed in a meta-analysis as this was the muscle group most consistently assessed and treated (n=295). Modes of strength assessment were isokinetic dynamometry or 3-repetition maximum. No statistically significant effect was seen (SMD 0.74, 95% CI -0.02 to 1.50, p=0.06) and significant heterogeneity existed (I^2 =88%, p <0.001). Subsequently, sub group analysis was undertaken in which adult and paediatric populations were analysed separately.

In children (n=229), there was no statistically significant effect of RT on knee extension strength (SMD 0.57, 95% CI -0.32 to 1.46, p=0.21) and significant heterogeneity remained (I^2 =88%, p <0.001). Two studies (n=66) were performed with adult burns patients (Ebid, Omar, et al., 2012; Paratz et al., 2012). A significant effect on muscle strength was demonstrated in favour of RT in this subgroup (SMD 1.42,

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95% CI 0.87 to 1.97, p<0.001) with no evident heterogeneity (I^2 =0%, p =0.84) (Figure 2.3).

Post-hoc sensitivity analysis was undertaken with SDs imputed for the studies by (Ebid et al., 2014; Ebid, Omar, et al., 2012). The imputed SD was the median of all other SD values in the analysis. The effect of RT on muscle strength for the whole group was significant in favour of RT (SMD 0.37, 95% CI 0.08 to 0.65, p=0.01) and heterogeneity was assessed as non-significant (I^2 =32%, p=0.15). For children, the effect was statistically significant (SMD=0.27, 95% CI 0.01 to 0.53, p=0.04), yet not significant in adults (SMD=0.89, 95% CI -0.19 to 1.97, p=0.11) (Figure 2.4 & Figure 2.5).

Other measures of muscle strength

Knee flexion strength was assessed by two studies (Cucuzzo et al., 2001; Ebid, Omar, et al., 2012). When combined, a small effect was seen in favour of the training groups (SMD 0.65, 95% CI 0.14 to 1.17) (Figure 2.6).

The results of individual muscle groups which were unable to be combined are displayed in Table 2.4. Significant between group differences were shown in latissimus dorsi pull-down strength both immediately after the training period and at 6 weeks after training cessation, no significant differences were seen for any of the other muscle groups tested.

Lean mass

Seven studies (n=205) assessed the effect of resistance training on whole body lean mass (Al-Mousawi et al., 2010; Hardee et al., 2014; Przkora et al., 2007; Suman & Herndon, 2007; Suman et al., 2001; Suman et al., 2003). Six studies used a dual-energy X-ray absorptiometry (DXA) scan, whilst one (Mowafy et al., 2016) calculated lean mass using a formula of "subtracting body fat weight from body weight". All assessments of lean mass were completed in paediatric populations. The results for studies performing a DXA scan to assess lean mass were combined. The overall effect was non-significant (MD 1.87kg, 95% CI -2.55 to 6.30, p=0.41) with no observable heterogeneity (I^2=0%, p=1.00) (Figure 2.7). Mowafy et al. (2016) reported a significant effect of training using their calculation of lean mass (MD 0.86 kg 95% CI 0.11 to 1.61).

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Physical function

Patient function was assessed using a combination of self-reported surveys and physical assessment procedures. Data were not sufficient to perform meta-analysis for either mode. Table 2.5 shows calculated mean difference and 95% CI for function assessments. In the study by Paratz et al. (2012), patient reported surveys were used to assess lower and upper limb function. The Lower Extremity Functional Scale (LEFS) (Binkley, Stratford, Lott, & Riddle, 1999), where a high score equates to improved function was used to assess the lower limb. The Quick-Disability of Arm, Shoulder and Hand (Quick-DASH) survey (Beaton, Wright, Katz, & Group, 2005), where a lower score means improved function was used to assess the upper limb. Physical assessments of function included shuttle walk distance (Paratz et al., 2012) and the six minute walk test (Cucuzzo et al., 2001) for adults and gait speed was assessed in children (Ebid, Omar, et al., 2012). Despite the reports of significant group differences in upper limb function, shuttle walk distance and six-minute walk test, the only significant between-group difference calculated by our group was for gait speed (MD=10.9 m/min, 95% CI 7.97, 13.8).

Quality of life

Quality of life was assessed by Paratz et al. (2012) using the Burn Specific Health Scale-Abbreviated (BSHS-A). Results were taken from each of the four quality of life domains as well as the overall score. Mean difference and 95% CI's are displayed in Table 2.6. A significant effect was noted for the psychological domain in favour of the training group, 6 weeks after cessation of training (MD=25.3, 95% CI 3.94 to 49.7).

Pain

No studies included in this review investigated pain as an outcome variable.

Adverse events

No studies directly investigated whether RT produced adverse events in patient groups. However, it was noted in one study (Al-Mousawi et al., 2010) that one RT participant demonstrated a decrease in lean mass after the intervention period.

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Quality of the evidence

Judgements of the quality of evidence using GRADE can be found in Table 2.7. All outcomes were rated as having “low” to “very low” quality evidence. The quality of evidence was downgraded on the basis of design limitations, inconsistency and imprecision.

2.5 Discussion

Summary of main results

This review was undertaken to investigate the effects of resistance training when performed in patients with a burn injury. We assessed both changes in muscle physiology as well as changes in quality of life in participants undertaking resistance training.

Initial meta-analysis of knee extensor strength data demonstrated no effect of strength training on knee extensor strength. Sub-group analysis demonstrated a significant effect of training on knee extensor strength in adult burns patients. No evidence on an effect on knee extensor strength was noted in the paediatric population. Half of the studies in adults with burn injury commenced rehabilitation prior to six months post injury, whilst in paediatric studies, rehabilitation was consistently commenced at six months after the burn injury. One hypothesis may be that in the six months between injury and commencement of formal rehabilitation, children recover a portion of their muscle strength through daily activity and play, mitigating some of the effectiveness of late rehabilitation. However, physical activity levels post burns were not quantified and time to commencing rehabilitation after injury may be a factor to consider in future research.

Results for the muscle strength meta-analysis may be confounded by the inclusion of data which may not be credible (Ebid et al., 2014; Ebid, Omar, et al., 2012). When imputed SDs were used, a significant effect on muscle strength for the whole group of studies was demonstrated, in favour of training after burn injury, though the statistical significance of effects for the subgroups of adults and children were changed. That the results of the overall analysis and the subgroup analyses are not robust to changes in

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the SDs of 2 studies from one research group indicates that they should be treated with caution.

We used back transformation to provide an estimate of the clinical change of knee extensor muscle strength for all studies. Using original data, the estimated change was 22.4 Nm (95% CI -14.7, 28.7) in intervention conditions and 19.9 Nm (95% CI -13.1, 25.5) in control conditions. It is not clear how this value translates into functional change, however, unit conversion (ConvertUnits.com, 2017) suggests that this estimate of effect would be equivalent to only 2.29 (-1.49 to 2.93) kilogram-metres and 2.04 (-1.33 to 2.60) kilogram-metres of force respectively. Determining the minimal clinically important difference of such measurements would assist clinicians in deciding on the clinical value of interventions explored in research.

Hamstring strength was assessed in one adult and one paediatric study where, when combined, the overall effect was in favour of training after a burn injury. One paper assessed Latissimus dorsi muscle strength in adults and our calculations of a mean difference demonstrated significant improvement in participants undertaking training. Several individual muscle groups that were assessed but unable to be included in meta-analysis showed no additional benefit of RT.

We also found no evidence of a significant benefit from RT on lean mass in paediatric burns patients. No adult studies assessed lean mass, therefore we are unable to comment on the effect and further research should be considered in adults.

The results of studies investigating the effect of RT on physical function were synthesized narratively. Self-report of functional ability demonstrated no difference in lower limb function between training and control groups, whilst upper limb function was reported to be significantly improved in the training group (Paratz et al., 2012). However, this was not supported when mean difference and 95% CI's were calculated by our group using the available data. In children, gait speed was determined to be significantly greater in the RT group (Ebid, Omar, et al., 2012). However, with our concerns about the credibility of the SD reported in this study, interpretation of this finding should be undertaken with caution. Walking distance in adults and children were reported as being significantly greater after intervention for the training groups

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(Cucuzzo et al., 2001), however, our calculations of between group differences do not support this view.

One study assessed quality of life as an outcome measure (Paratz et al., 2012). In this study, the exercise group was seen to have greater quality of life scores for the psychological domain of the BSHS-A six weeks after the training intervention had ceased. The authors also described the same result for the General domain of the BSHS-A, however, our calculated MD and 95% CI does not support this difference in the General domain of quality of life.

Pain and safety were not utilised as outcome measures in any of the included studies. The failure to report adverse events represents an important omission from the literature and future research should address this as a priority.

Quality of the evidence

Using the GRADE approach, the overall quality of evidence for all outcomes assessed in this review was "low" to "very low". This was due, in part, to limitations in the size and design of included studies and all studies were rated as high risk of bias overall.

Bias was regularly introduced due to allocation procedures. In some studies, consent and randomisation occurred on the day of admission to acute care, often six months prior to starting the training intervention. This made the judgement of baseline compatibility difficult as the primary outcome measures could not be recorded at the time of randomisation. In addition, participants randomised to control and experimental conditions likely interacted with the research team for a significant period prior to commencement of treatment and it is possible that this may introduce substantial bias to the estimate of the treatment effect.

The current literature has poor quality reporting of allocation and concealment procedures. Just two out of eleven studies attained a low risk of bias rating. Unclear ratings were given to the remaining nine studies, as the study procedures were not described in sufficient detail. Lack of reporting clarity is an issue which has been highlighted and reported to occur in therapeutic intervention studies previously (Moher et al., 2010; Yamato, Maher, Saragiotto, Hoffmann, & Moseley, 2016) and

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these factors are known to be associated with exaggerated effect sizes (Savovic et al., 2012; Wood et al., 2008).

The reporting practices in the majority of included studies made estimation of the size of any treatment effect difficult. Bland and Altman (2011) have discussed how the use of within group analysis can be misleading when used to infer differences between groups. We found this to be a significant issue for this review, as many study outcomes were reported using only within group analyses and between group differences inferred from disparate within group effects. This often occurred when treatment groups did not appear to be comparable at baseline assessment. Unfortunately, the studies in question did not perform group comparisons at baseline, or attempt to adjust baseline values to allow appropriate comparison of between group results. This may have led to over interpretation of treatment effects when summarising an individual study's results and goes some way to explaining why a collection of generally positively reported trials yield largely negative results when entered into meta-analyses. Additionally, we assume that all interventions were delivered effectively in all studies. However, this is not consistently clear in the reports. The use of checklists such as the TIDieR framework (T. Yamato et al., 2016) or CONSORT (Moher et al., 2010) would be recommended in order to improve the clarity and depth of reporting in future trials.

Small sample sizes were a consistent feature of all studies in this review. Subsequently, most comparisons have only small numbers contributing to the estimate of the treatment effect contributing to the imprecision of evidence in this review. It is known that, though often underpowered to detect effects, published small studies often report more favourable effects of an intervention, though with less precision than larger studies (Dechartres, Trinquart, Boutron, & Ravaud, 2013). In this case, some of the positive effects reported in this review might be influenced by small study bias and the associated issue of publication bias. Though we found no formal evidence of publication bias, the relatively small number of studies and lack of larger studies means that this assessment lacks sensitivity.

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Strengths & limitations

We included only studies which were published or available in English which may introduce bias into this review. However, after our thorough search of the literature, we identified only one study which was excluded for this reason as no translation was available.

The use of a multi-modal exercise programme in the included studies has made it difficult to elicit whether RT is the sole cause of benefit in rehabilitation. To determine the mode of exercise most advantageous for burn patient recovery, future work may consider choosing just one mode of exercise training to assess.

Agreements and disagreements with other studies or reviews

Our conclusions from this review for muscle strength and lean body mass differ with the conclusions from previous qualitative reviews from this body of literature. Nedelec et al. (2016) selected studies pertaining to burns rehabilitation from the literature and extracted individual study data. After a narrative review of results, they concluded that significant improvements in muscle strength and lean body mass are achieved after exercise training (including RT). However, risk of bias assessments and meta-analysis of results were not undertaken in this review. Additionally, their conclusion was based largely on the within group changes reported by each study. Despite the shortage of supportive data analysis, practice guidelines were recommended by the authors that exercise training should begin after discharge from acute care and last 6 to 12 weeks in duration. Whilst their interpretation of results may differ to our meta-analysis, the authors acknowledge that it would be beneficial to further investigate the prescription parameters of exercise training in burn rehabilitation. The authors recommend manipulating training variables in patients with a burn injury, including the time to commencement, duration and location of undertaking an exercise training programme. In support of this recommendation, Disseldorp et al. (2011) have concluded in their own review that due to the similarities of training protocols in published studies, our knowledge of the effectiveness of different training variables in burns exercise rehabilitation is not complete. They too suggest that future research should investigate a variety of training variables in rehabilitating burn injury.

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Progressive RT was recommended for outpatient burn rehabilitation by Porter et al. (2015). Their non-systematic review of the literature concluded that RT improved the physiological function of burns patients, including muscle strength and was a useful strategy to improve lean body mass. This review also did not perform risk of bias assessments or meta-analysis of results. Therefore, their conclusions are likely to also be based largely upon within group analyses performed in the individual studies. The authors have suggested that more effort should be made to identify the specific regimens of RT that would be most effective in optimising patient outcome.

Future research recommendations

It is necessary that rehabilitation specialists understand the unique effect of exercise in individuals with burn injury. The outcomes of this review would suggest that the literature is lacking variation in the prescription of exercise training in this patient cohort. In order to more completely understand the effects of training in burn injury, future research should focus on currently unknown prescription variables, such as testing exercise training during the acute and sub-acute injury phase, as well as in minor and moderate sized burns. The length of a training intervention should be investigated to gain an understanding of what the minimum effective training period could be to improve outcomes in individuals with a burn injury.

In addition to ongoing assessment of the effect of exercise on physiological outcomes of muscle strength and body composition, research in adults and children should look to include patient centered outcomes such as quality of life and physical function, including return to recreation and work. The safety of patients undertaking exercise should also be systematically investigated.

It is necessary to move toward studies which are adequately powered, where allocation is transparently randomised and concealed, and where blinded assessment can be truly undertaken to improve the quality of research outcomes. This review has identified the need for attention to reporting standards in order to improve the quality and clarity of research. Future trials should adhere to CONSORT guidance, including that related to the reporting of the development and evaluation of complex interventions (Hoffmann et al., 2014). This will help to eliminate ambiguity of methodology and results, ensuring clear interpretation of important outcomes.

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Conclusions

This review has determined that low quality evidence suggests some positive effects of RT on muscle strength and psychological quality of life in adults with burns. Post-hoc sensitivity analysis suggests a positive effect of RT on muscle strength in all patients recovering from burn injury. Analyses did not suggest an effect for RT on lean body mass in children. However, consideration needs to be taken of the low quality of evidence currently available for these outcomes in the burn injury rehabilitation literature.

The quality of evidence available for this review suggests that that additional well designed and robust longitudinal research is required to understand the effect of RT after burn injury in order to implement it successfully in rehabilitation. We noted a general lack of studies measuring outcomes which may be more meaningful to the patient group, such as pain, quality of life and return to work, sport and hobbies. Future research would benefit from this type of assessment in addition to those which investigate muscular physiology.

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Contributions of authors

PG: Lead researcher, study selection, data entry, data analysis, lead writing of review.
TG: Appraisal of review, study selection, methodological advice.
BW: Appraisal of review, independent assessor, expert methodological advice.
DE: Appraisal of review, independent assessor, expert subject advice.
FW: Appraisal of review, expert subject advice
NEO: Appraisal of review, expert methodological advice, statistical advice.

Differences between protocol and review

The review was compliant with the protocol registration published on PROSPERO. No differences were noted between the two.

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2.7 Figures

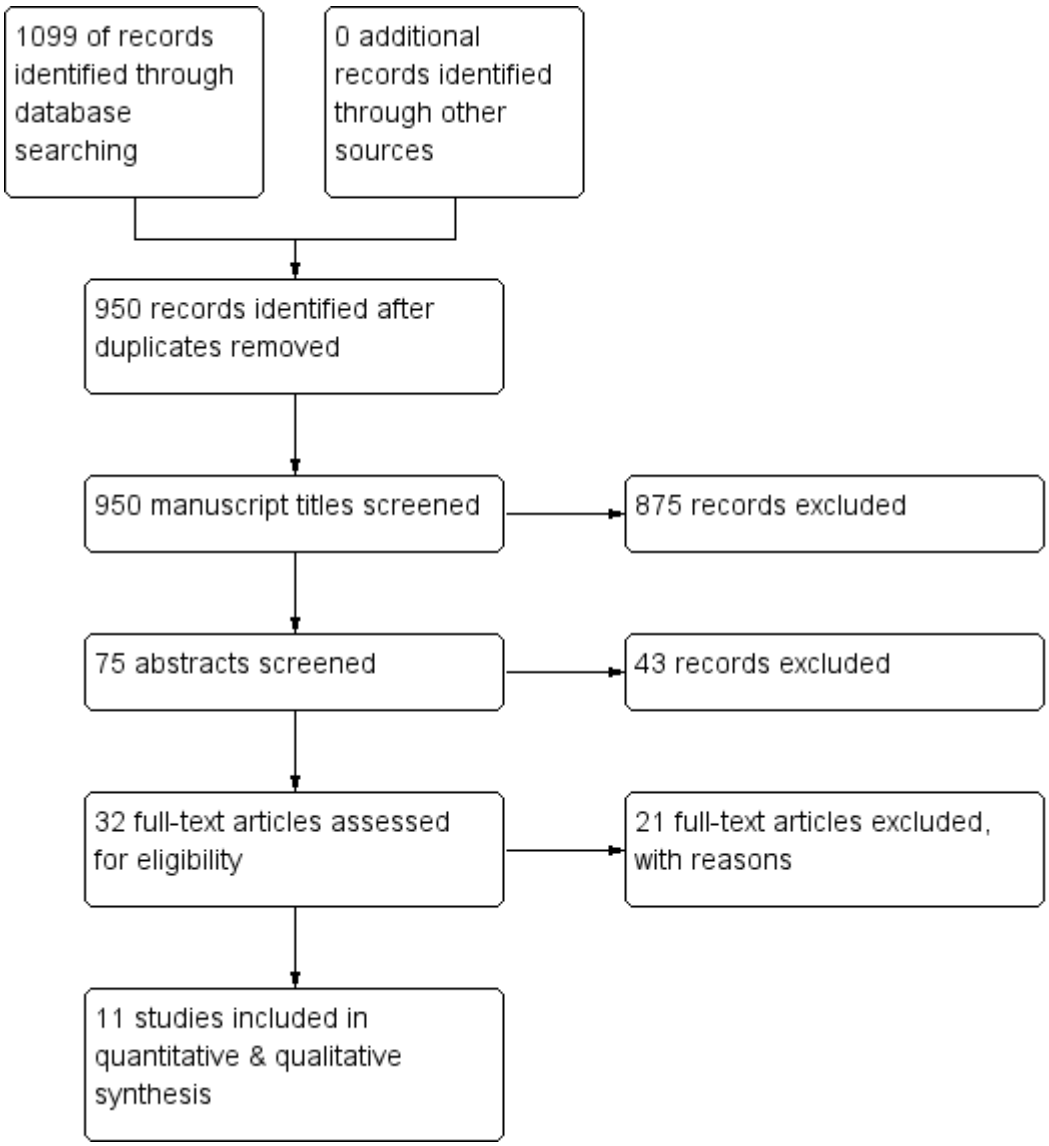

Figure 2.1 Flow of studies through review process

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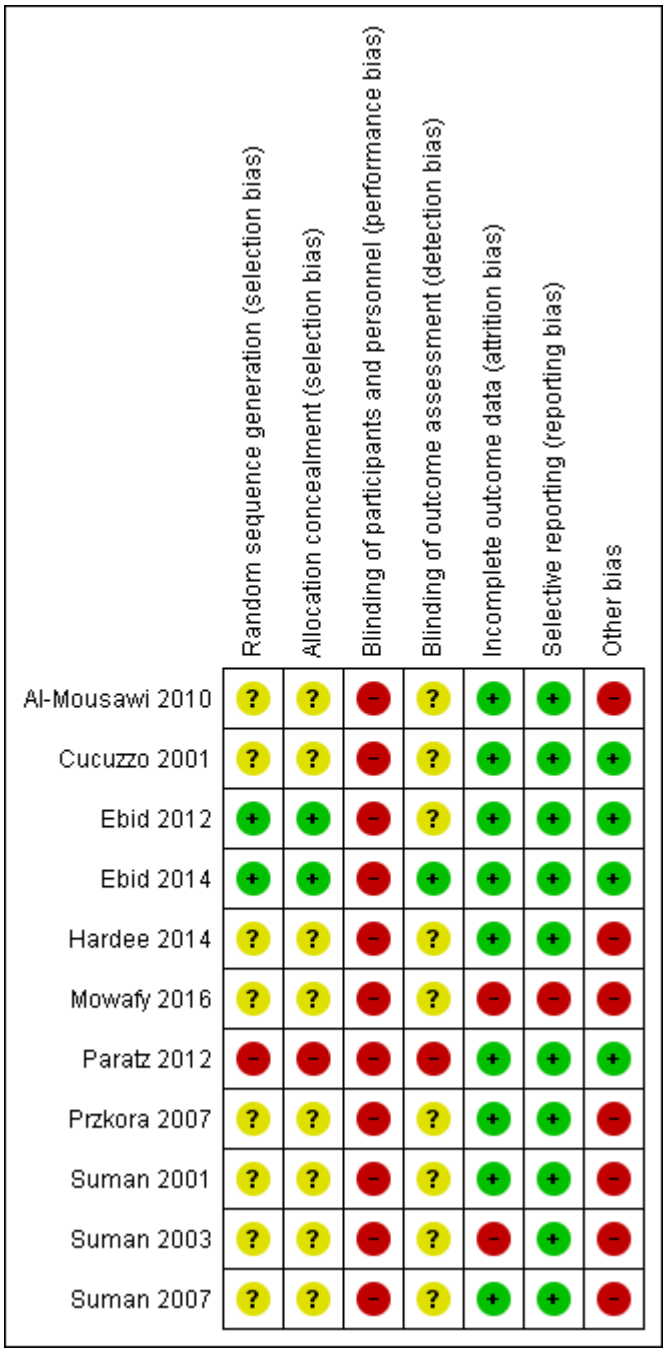

Figure 2.2 Risk of Bias Summary: authors judgement for each risk of bias domain

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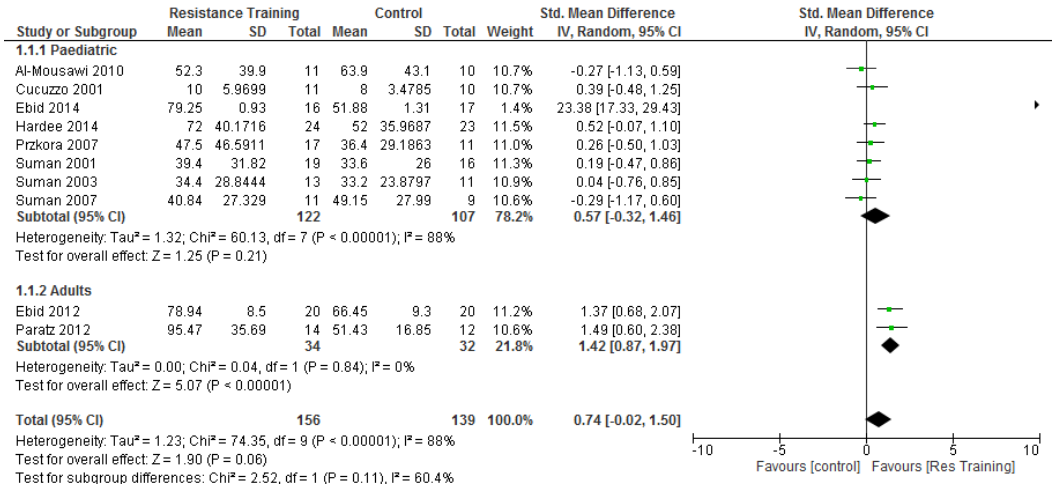

Figure 2.3 Forest plot of results for knee extensor strength

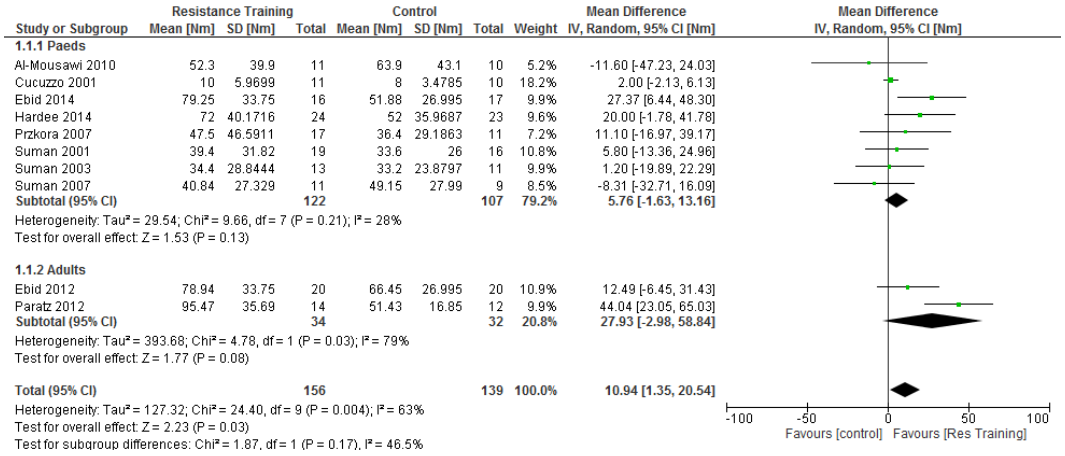

Figure 2.4 Forest Plot of results for knee extensor strength, with imputed SD values for Ebid et al. (2012 & 2014)

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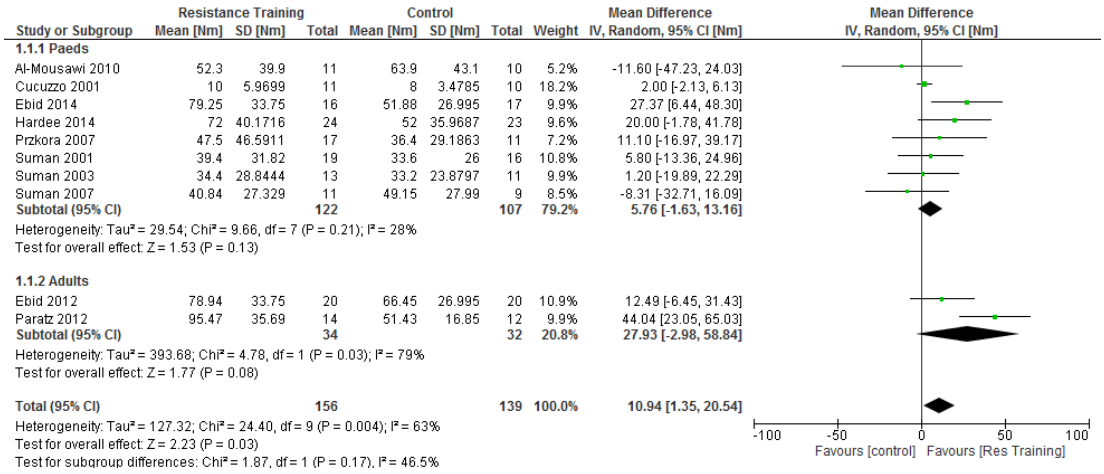

Figure 2.5 Forest Plot of results for knee extensor strength, with imputed SD values for Ebid et al. (2012 & 2014)

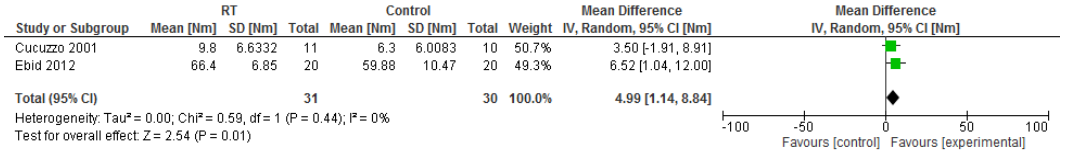

Figure 2.6 Forest plot of results for hamstring muscle strength

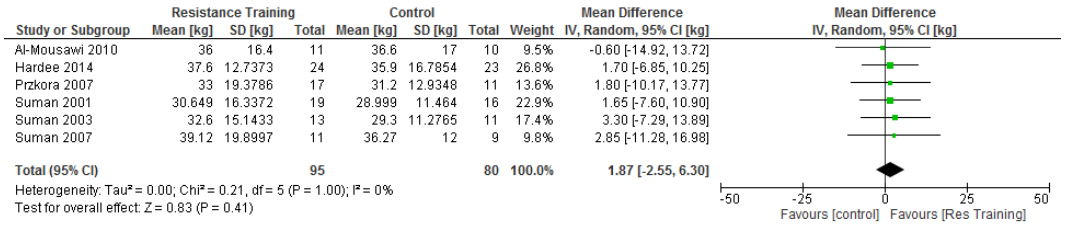

Figure 2.7 Forest plot of results for lean mass

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2.8 Tables

Table 2.1 Characteristics of included studies

Author	Country	Study Design	Sample Size	Age (mean ± SD) years	TBSA (mean ± SD) %
Al-Mousawi, Williams et al. (2010)	USA	RCT 12 weeks supervised training vs. no supervised training	Exercise=11 Control=10	Exercise=12.2 ± 3.2 Control=13.7 ± 3.6	Exercise=61 ± 13 Control=56 ± 15
Cucuzzo, Ferrando et al. (2001)	USA	RCT 12 weeks supervised training vs. no supervised training	Exercise=11 Control=10	Exercise=11.9 ± 1.2 Control=9.2 ± 1.4	Exercise=62 ± 15.2 Control=57.1 ± 13.3
Ebid, Omar et al. (2012)	Egypt	RCT 12 weeks supervised training vs. no supervised training	Exercise=20 Control=20	Exercise=24.6 ± 5.3 Control=27.3 ± 8.6	Exercise=46.5 ± 3.1 Control=44.5 ± 6.5
Ebid, El-Shamy et al. (2014)	Egypt	RCT 12 weeks supervised training vs. no supervised training	Exercise=18 Control=19 Withdrawals=4 (2 from both groups)	Exercise=13.4 ± 1.2 Control=13.6 ± 1.1	Exercise=42.1 ± 3.1 Control=42.4 ± 3.1
Hardee, Porter et al. (2014)	USA	RCT 12 weeks supervised training vs. no supervised training	Exercise=24 Control=23	Exercise=13 ± 4.9 Control=13 ± 4.8	Exercise=59 ± 9.8 Control=60 ± 14.4
Mowafy, El-Sayed et al. (2016)	Egypt	Comparison trial 12 weeks supervised training vs. no supervised training	Exercise=15 Control=15	Unknown	Unknown
Paratz, Stockton et al. (2012)	Australia	Non-randomised trial 6 weeks supervised training	Exercise=16 Control=14	Exercise=30.4 ± 10.1 Control=42.4 ± 14.6	Exercise=47 ± 13.6

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		vs. no supervised training	Withdrawals=4 (2 from both groups)		Control=29.9 ± 8.9
Przkora, Herndon et al. (2007)	USA	RCT 12 weeks supervised training vs. no supervised training. Testing Oxandralone or Placebo ± Exercise	Exercise (OXEX)=14 Exercise (PLEX)=17 Control (OX)=9 Control (PL)=11	OXEX=12.1 ± 2.9 PLEX=10.9 ± 3.7 OX=11.8 ± 3.3 PL=11.8 ± 3.3	OXEX=52.1 ± 12.7 PLEX=55.6 ± 14.8 OX=54.7 ± 11.7 PL=53.4 ± 10.3
Suman, Spies et al. (2001)	USA	RCT 12 weeks supervised training vs. no supervised training	Exercise=19 Control=16	Exercise=10.5 ± 4.0 Control=11 ± 4.8	Exercise=59.4 ± 14.4 Control=58 ± 17.7
Suman, Thomas et al. (2003)	USA	RCT 12 weeks supervised training vs. no supervised training. Testing use of Growth Hormone or Saline placebo ± Exercise.	Exercise (GHEX)=10 Exercise (SALEX)=13 Control (GH)=10 Control (SAL)=11 Withdrawls=25	GHEX=11 ± 2.5 SALEX=10.5 ± 2.5 GH=11.5 ± 5.1 SAL=10.8 ± 2.3	GHEX=60.3 ± 6 SALEX=58.5 ± 10.1 GH=53.4 ± 10.3 SAL=59.4 ± 14.4
Suman and Herndon (2007)	USA	RCT 12 weeks supervised training vs. no supervised training	Exercise=11 Control=9	Exercise=11.8 ± 4.9 Control=13.4 ± 5.4	Exercise=61 ± 6.6 Control=56 ± 6

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Table 2.2 Exercise prescription characteristics of included studies

Al-Mousawi, Williams et al. (2010)	
Interventions	Hospital Based Exercise Group: Time to begin intervention: 6 months post burn. Location: Hospital/ Rehab Centre Mode: Isotonic Intensity: Week 1: 50-60% 3RM, Week 2-6: 70-75% 3RM, Week 7-12: 80-85% 3RM Volume: Week 1: familiarisation, Week 2-6: 4-10 repetitions, Week 7-12: 8-12 repetitions Rest: Not documented Frequency: 3x per week Duration: 12 weeks Additional: Aerobic training 30 minutes 3x per week. Standard of Care Group: Home based programme as instructed by the Physiotherapy and Occupational Therapy staff intended to be performed for 1 hour, twice daily. No supervised exercise therapy was undertaken
Outcomes	Muscle strength: Isokinetic peak torque (Nm) at 150 deg/sec for concentric knee extension. Lean mass: DXA scanning of whole body (kg).
Notes	Two participants in each group were unable to undergo strength testing. One participant in intervention group had 5% loss in lean body mass post intervention.
Cucuzzo, Ferrando et al. (2001)	
Interventions	In-House Exercise Programme Study Group: Time to begin intervention: 6 months post burn. Location: Hospital Wellness Centre Mode: Isotonic, isometric & isokinetic Intensity: Phase 1: 50% 3RM, Phase 2: 70-85% 3RM Volume: Phase 1: 4-10 repetitions, Phase 2: 8-15 repetitions. Volume increased 10% - 20% each week Rest: Not documented Frequency: 3x per week Duration: 12 weeks Additional: Aerobic exercise 20 minutes 3x per week Home Group: No prescribed or supervised exercise training.

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	Patients were referred to local outpatient facility for ongoing therapy. The number of appointments attended was not standardised across centres. Did not train with weights but were permitted to continue daily activities.
Outcomes	Muscle strength: 3 repetition maximum for knee extension, knee flexion, elbow flexion, elbow extension, and forearm (anatomical movement not clarified) strength. Function: 6 minute walk test to assess distance walked.
Notes	Strength training was stated to focus on overloading primarily "key" muscle groups "namely knee extensor and elbow flexors".
Ebid, Omar et al. (2012)	
Interventions	Isokinetic Group: Time to begin intervention: 6 months post burn. Location: Clinic Mode: Isokinetic @ 150 deg/sec Intensity: 60% average peak torque Session 1-5: 1-5 sets, Sessions 6-24: 6 sets, Sessions 25-36: 10 sets Volume: 10 repetitions Rest: Not documented Frequency: 3x per week Duration: 12 weeks Additional: Aerobic training and stretches No Exercise Group: Performed a prescribed home exercise programme including: range of motion exercises, stretching, splinting, massage, functional activities, ambulation and activities of daily living. No supervised isokinetic exercise was performed.
Outcomes	Muscle strength: Isokinetic muscle peak torque at 150 deg/sec for knee extensors and knee flexors Function: Gait speed assessment in metres per minute
Ebid, El-Shamy et al. (2014)	
Interventions	Isokinetic Group: Time to begin intervention: at hospital discharge. Location: Clinic Mode: Isokinetic @ 150 deg/sec Intensity: 50% average peak torque Session 1-5: 1-5 sets, Sessions 6-24: 6 sets, Sessions 25-36: 10 sets Volume: 10 repetitions Rest: Not documented

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	Frequency: 3x per week Duration: 12 weeks Additional exercise: Stretching & walking Control Group: Home based stretching and range of motion programme. Also completed an unquantified walking programme 3 times per week.
Outcomes	Muscle strength: Isokinetic muscle peak torque at 150 deg/sec for knee extensor muscle group. Lean Mass: Circumferential measures of quadriceps size
Hardee, Porter et al. (2014)	
Interventions	RET (intervention) Group: Time to begin intervention: discharge form acute hospital. Location: In hospital rehabilitation. Mode: Isotonic Intensity: Week 1: 50-60% 3RM, Week 2-6: 70-75% 3RM, Week 7-12: 80-85% 3RM Volume: 4-10 reps, weeks 7-12: 8-12 repetitions Rest: - Frequency: 3x per week Duration: 12 weeks Additional: Aerobic training 20-40 mins @ 70-85% VO2 peak. SOC (control) Group: Prescribed a home based programme of stretching & mobility. No supervised exercise training.
Outcomes	Strength: Isokinetic peak torque 150 deg/sec for knee extensors. Lean body mass (kg): DXA scanning for the whole body, trunk, legs and arms.
Notes	Muscle strength was only assessed after the intervention “because of medical limitations such as impaired mobility and incomplete wound closure at the time of discharge”.
Mowafy, El-Sayed et al. (2016)	
Interventions	Intervention Group: Unknown time from burn to commence intervention Location: Facility Mode: Isotonic Intensity: Week 1: 50-60% 3RM, Week 2-6: 70-75% 3RM, Week 7-12: 80-85% 3RM Volume: weeks 2-6: 4-10 reps, weeks 7-12: 8-12 repetitions Rest: Unknown

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	Frequency: 3x per week Duration: 12 weeks Additional: Aerobic training 30 mins @ 70-75% VO2 peak. Control Group: Prescribed a home based programme of splinting, stretching, ROM exercises, strength (non-progressive) exercises, scar management. No supervised exercise training.
Outcomes	Lean body mass (kg/M^2): calculation of fat mass subtracted from total body mass
Paratz, Stockton et al. (2012)	
Interventions	Exercise Group: Time to begin intervention: after final grafting procedure. Mode: Isotonic. Intensity: Week 1: 60% 3RM Volume: Increased 5-10% weekly Rest: Not documented Frequency: 3x per week Duration: 6 weeks supervised. After completion patients were encouraged to continue exercise but unsupervised. Additional: Stretching programme. Aerobic exercise @ 80% HRpeak 3x per week. Strength exercises included hand strengthening using mechanical device, foam or putty. Self-Management Group: Prescribed a home based stretching programme. No supervised exercise training undertaken.
Outcomes	Muscle strength: 3 repetition maximum & grip strength dynamometry. Function: Quick-DASH & LEFS surveys (patient reported). Quality of life: Burn Specific Health Scale – Abbreviated (patient reported).
Notes	Patients were reviewed monthly in outpatient clinics and reported exercise participation to therapists.
Przkora, Herndon et al. (2007)	
Interventions	Intervention Group (PLEX Group): Time to begin intervention: 6 months post burn Mode: Isotonic Intensity: Week 1: 50-60% 3RM, Week 2-6: 70-75% 3RM, Week 7-12: 80-85% 3RM

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	Volume: Week 1: 3x 4-10 reps, week 2-6: 3x 4-10 reps, week 7-12: 3x 8-12 reps Rest: ~ 1 min Frequency: 3x per week Duration: 12 weeks Additional: Aerobic training 5x per week 20-40 mins @ 70-85% VO2 peak. 1 hour Physiotherapy daily – ROM and stretches Control Group (PL Group): Home based exercise programme including stretches, positioning and ROM. No formal exercise training.
Outcomes	Muscle strength: Isokinetic knee extension strength (Nm) at 150 deg/ sec Lean mass: DXA scanning of whole body and trunk (kg). Fitness: VO_2
Notes	Only data from non-pharmacologically treated participants were included in this review.
Suman, Spies et al. (2001)	
Interventions	Supervised Exercise Group (REx): Time to begin intervention: 6 months post burn Mode: Isotonic Intensity: Week 1: 50-60% 3RM, Week 2-6: 70-75% 3RM, Week 7-12: 80-85% 3RM Volume: Weeks 2-6: 4-10 reps, weeks 7-12: 8-12 repetitions Rest: Not documented Frequency: 3x per week Duration: 12 weeks Additional: Aerobic training 20-40 mins @ 70-85% VO2 peak. Non-exercising Group (R): Home based Physiotherapy and Occupational therapy programme was provided.
Outcomes	Muscle strength: Isometric knee extension. Muscle strength: Isokinetic knee extension 90 deg/ sec, average power & total work Lean mass: DXA scanning of whole body, trunk, leg and arm Fitness: VO_2
Suman, Thomas et al. (2003)	
Interventions	Intervention group (SALEx group): Time to begin intervention: 6 months post burn

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	Mode: Isotonic Intensity: Week 1: 50-60% 3RM, Week 2-6: 70-75% 3RM, Week 7-12: 80-85% 3RM Volume: Weeks 2-6: 4-10 reps, weeks 7-12: 8-12 repetitions Rest: 1 min Frequency: 3x per week Duration: 12 weeks Additional: Aerobic training 20-40 mins @ 70-85% VO2 peak. Control Group (SAL group): Home based Physiotherapy and Occupational therapy programme was provided for non-exercise groups.
Outcomes	Muscle strength: Isokinetic knee extension strength at 150 deg/ sec Lean mass: DXA scanning for whole body, trunk, leg and arm. Fitness: VO_2
Notes	Only data from non-pharmacologically treated participants were included in this review.
Suman and Herndon (2007)	
Interventions	Exercise Group: Time to begin intervention: 6 months post burn Mode: Isotonic Intensity: Week 1: 50-60% 3RM, Week 2-6: 70-75% 3RM, Week 7-12: 80-85% 3RM Volume: Weeks 2-6: 4-10 reps, weeks 7-12: 8-12 repetitions Rest: Not documented Frequency: 3x per week Duration: 12 weeks Additional: Aerobic training 20-40 mins @ 70-85% VO2 peak. No Exercise Group: Nil formal training. 2 hours of therapy PT & OT daily.
Outcomes	Muscle strength: Isokinetic knee extension at 150 deg/ sec. Detraining assessed at 12 weeks post training period. Lean mass: DXA scanning of whole body (kg)
Notes	Growth hormone given to 3 Control group children as part of another study

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Table 2.3 Risk of bias of included studies

Al-Mousawi, Williams et al. (2010)		
Bias	Rating	Support for Judgement
Random sequence generation (selection bias)	Unclear	No comment of sequence generation details
Allocation concealment (selection bias)	Unclear	No detail provided of concealment.
Blinding of participants and personnel (performance bias)	High	Exercise supervised and supported only for intervention group. No blinding of therapist to allocation & treatment.
Blinding of outcome assessment (detection bias)	Unclear	No detail provided by authors.
Incomplete outcome data (attrition bias)	Low	No drop out.
Selective reporting (reporting bias)	Low	Nil.
Other bias	High	No baseline comparison for primary outcome. Randomisation occurs months prior to commencement of intervention.
		No between-group comparison of baseline for primary outcome was provided.
Cucuzzo, Ferrando et al. (2001)		
Bias	Rating	Support for Judgement
Random sequence generation (selection bias)	Unclear	No comment on sequence generation process.
Allocation concealment (selection bias)	Unclear	No detail of concealment.
Blinding of participants and personnel (performance bias)	High	Exercise supervised and supported only for intervention group. No blinding of therapist to allocation & treatment.
Blinding of outcome assessment (detection bias)	Unclear	No detail provided by authors.
Incomplete outcome data (attrition bias)	Low	No drop out
Selective reporting (reporting bias)	Low	Within and between group outcomes discussed.
Other bias	Low	
Ebid, Omar et al. (2012)		

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Bias	Rating	Support for Judgement
Random sequence generation (selection bias)	Low	Random sequence generator in Excel computer program.
Allocation concealment (selection bias)	Low	Password protected allocation.
Blinding of participants and personnel (performance bias)	High	Exercise supervised and supported only for intervention group. No blinding of therapist to allocation & treatment.
Blinding of outcome assessment (detection bias)	Unclear	Likely that same therapist performed all assessments & treatments.
Incomplete outcome data (attrition bias)	Low	No drop out reported.
Selective reporting (reporting bias)	Low	Nil.
Other bias	Low	Nil.
Ebid, El-Shamy et al. (2014)		
Bias	Rating	Support for Judgement
Random sequence generation (selection bias)	Low	Allocation randomised through use of opaque envelopes prepared individually.
Allocation concealment (selection bias)	Low	Registration clerk performed allocation procedures.
Blinding of participants and personnel (performance bias)	High	Exercise supervised and supported only for intervention group. No blinding of therapist to allocation & treatment.
Blinding of outcome assessment (detection bias)	Low	Stated that assessors were blinded to treatment allocation.
Incomplete outcome data (attrition bias)	Low	4/37 participants drop out (~11%)
Selective reporting (reporting bias)	Low	Nil.
Other bias	Low	Nil.
Hardee, Porter et al. (2014)		
Bias	Rating	Support for Judgement
Random sequence generation (selection bias)	Unclear	No detail of sequence generation.
Allocation concealment (selection bias)	Unclear	No detail of concealment.
Blinding of participants and personnel (performance bias)	High	Exercise supervised and supported only for intervention group.

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		No blinding of therapist to allocation & treatment.
Blinding of outcome assessment (detection bias)	Unclear	No detail on blinding of allocation provided.
Incomplete outcome data (attrition bias)	Low	No drop out recorded.
Selective reporting (reporting bias)	Low	
Other bias	High	No between group comparison of baseline muscle strength for primary outcome was provided.
Mowafy, El-Sayed et al. (2016)		
Bias	Rating	Support for Judgement
Random sequence generation (selection bias)	Unclear	No detail of sequence generation.
Allocation concealment (selection bias)	Unclear	No detail of concealment.
Blinding of participants and personnel (performance bias)	High	Exercise supervised and supported only for intervention group. No blinding of therapist to allocation & treatment.
Blinding of outcome assessment (detection bias)	Unclear	No detail on blinding of allocation provided.
Incomplete outcome data (attrition bias)	High	No information provided of drop-out rate.
Selective reporting (reporting bias)	High	No between group analyses.
Other bias	High	No baseline assessment or comparison provided for burns severity or patient demographics. No between group comparison of baseline for primary outcome was provided.
Paratz, Stockton et al. (2012)		
Bias	Rating	Support for Judgement
Random sequence generation (selection bias)	High	Allocation not randomised.
Allocation concealment (selection bias)	High	City dwelling patients allocated to intervention group and rural patient to control group.
Blinding of participants and personnel (performance bias)	High	Exercise supervised and supported only for intervention group.

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		No blinding of therapist to allocation & treatment.
Blinding of outcome assessment (detection bias)	High	Participants not blind to allocation, therefore where self-assessment is required (Quick-DASH, LEFS, BSHS-A), blinding not possible.
Incomplete outcome data (attrition bias)	Low	4/30 (~13%) removed or withdrawn.
Selective reporting (reporting bias)	Low	Nil.
Other bias	Low	
Przkora, Herndon et al. (2007)		
Bias	Rating	Support for Judgement
Random sequence generation (selection bias)	Unclear	No detail provided about randomisation.
Allocation concealment (selection bias)	Unclear	No information provided.
Blinding of participants and personnel (performance bias)	High	Exercise supervised and supported only for intervention group. No blinding of therapist to treatment or allocation described.
Blinding of outcome assessment (detection bias)	Unclear	No information provided.
Incomplete outcome data (attrition bias)	Low	No dropout reported
Selective reporting (reporting bias)	Low	
Other bias	High	Randomisation occurs months prior to commencement of intervention. No between-group comparison of baseline for primary outcome was provided.
Suman, Spies et al. (2001)		
Bias	Rating	Support for Judgement
Random sequence generation (selection bias)	Unclear	No detail provided on methods for allocation.
Allocation concealment (selection bias)	Unclear	No detail provided.
Blinding of participants and personnel (performance bias)	High	Exercise supervised and supported only for intervention group. No blinding of therapist to treatment or allocation described.

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Blinding of outcome assessment (detection bias)	Unclear	No detail provided.
Incomplete outcome data (attrition bias)	Low	Nil drop out.
Selective reporting (reporting bias)	Low	
Other bias	High	Randomisation occurs months prior to commencement of intervention. No between group comparison of baseline for primary outcome was provided.

Suman, Thomas et al. (2003)		
Bias	Rating	Support for Judgement
Random sequence generation (selection bias)	Unclear	No detail provided on methods for allocation.
Allocation concealment (selection bias)	Unclear	No detail provided.
Blinding of participants and personnel (performance bias)	High	Exercise supervised and supported only for intervention group. No blinding of therapist to treatment or allocation described.

Blinding of outcome assessment (detection bias)	Unclear	No detail provided.
Incomplete outcome data (attrition bias)	High	25/69 = 36% drop out. No intention to treat analysis performed.
Selective reporting (reporting bias)	Low	No estimate provided on variability of between group differences.
Other bias	High	Randomisation occurs months prior to commencement of intervention. No between-group comparison of baseline for primary outcome was provided.

Suman and Herndon (2007)		
Bias	Rating	Support for Judgement
Random sequence generation (selection bias)	Unclear	No detail provided on allocation process.
Allocation concealment (selection bias)	Unclear	No detail provided by authors.
Blinding of participants and personnel (performance bias)	High	Exercise supervised and supported only for intervention group. No blinding of therapist to treatment or allocation described.

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Blinding of outcome assessment (detection bias)	Unclear	No detail provided by authors.
Incomplete outcome data (attrition bias)	Low	Nil drop out.
Selective reporting (reporting bias)	Low	
Other bias	High	Growth hormone given to some children as part of another study. Randomisation occurs 6 months prior to commencement of intervention. No between group comparison of baseline for primary outcome was provided.

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Table 2.4 Calculated mean difference & 95% CI of strength assessment results not included in meta-analysis

Author	Muscle Group	Mean Difference	95% CI
Cucuzzo, Ferrando et al. (2001)	Biceps	1.10	-2.37 to 4.57
	Triceps	1.50	-1.60 to 4.60
	Forearm	1.50	-2.24 to 5.24
Paratz, Stockton et al. (2012)	Latissimus Dorsi	20.94	11.8 to 30.08*
	Latissimus Dorsi 6 weeks [a]	26.7	15.18 to 38.22*
	Grip (L)	-2.63	-11.37 to 6.11
	Grip (L) 6 weeks [a]	0.03	-10.32 to 10.38
	Grip (R)	-3.26	-12.52 to 6.00
	Grip (R) 6 weeks [a]	-0.97	-11.32 to 9.38

[a] assessment at 6 weeks after cessation of the training period.
* significant mean difference between intervention and control groups.
3 RM: three repetition maximum test
GSD: grip strength dynamometry, best of three attempts

Table 2.5 Calculated mean difference & 95% CI for function assessment – self report & physical assessment.

Self-Report Assessment of Function

Author	Measure	MD	95% CI
Paratz, Stockton et al. (2012)	LEFS	6.09	-6.73 to 18.9
	LEFS 6 week [a]	9.20	-6.00 to 24.4
	Quick-DASH	-7.12[b]	-23.0 to 8.76
	Quick-DASH 6 week [a]	-8.45[b]	-23.2 to 6.35

Physical Assessment of Function

Author	Measure	MD	95% CI
Paratz, Stockton et al. (2012)	Shuttle Walk Test (m)	233.3	-21.9 to 488.6
	Shuttle Walk Test 6 week [a]	242.5	-4.88 to 489.9
(Ebid, Omar et al. 2012)	Gait Speed (m/min)	10.9	7.97 to 13.8*
Cucuzzo, Ferrando et al. (2001)	6-Minute Walk Test (m)	68.0	-87.4 to 223.4

* Significant between group difference ($p<0.05$).
[a] assessment at 6 weeks after cessation of the training period.
[b] Negative value signifies less disability ie. improved function

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Table 2.6 Calculated mean difference & 95% CI for quality of life assessment

Author	BSHS-A Domain	MD	95% CI
Paratz, Stockton et al. (2012)	Total	17.8	-20.2 to 55.8
	Total 6 week [a]	33.6	-12.6 to 80.2
	Physical	4.94	-3.76 to 13.6
	Physical 6 week [a]	8.68	-0.36 to 17.7
	Psychological	11.2	-5.83 to 28.2
	Psychological 6 week [a]	25.3	3.94 to 46.7*
	General	3.01	-3.53 to 9.55
	General 6 week [a]	5.03	-4.18 to 14.24
	Social	5.47	-3.95 to 14.9
	Social 6 week [a]	9.65	-0.13 to 19.4

* Significant between group difference ($p<0.05$).
[a] assessment at 6 weeks after cessation of the training period.

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Table 2.7 GRADE judgements for comparisons

Comparison	Result	Design Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE Judgement
Muscle Strength							
Knee Extension	SMD 0.74 Nm, 95% CI -0.02 to 1.50	Down one (>25% high risk bias)	Down one (I^2 =88%, p <0.001)	None	Down one (n=295)	None	Very Low
Knee Flexion	SMD 0.65, 95% CI 0.14 to 1.17	Down one (>25% high risk bias)	None	None	Down one (n=61)	None	Low
Latissimus Dorsi	MD 20.94, 95% CI 11.8 to 30.08	Down two (>25% high risk of bias. Contributing study not randomised)	Down one (single study)	None	Down one (n=26)	None	Very Low
Biceps	MD=1.10 kg, 95% CI -2.37 to 4.57	Down one (>25% high risk bias)	Down one (single study)	None	Down one (n=21)	None	Very Low
Triceps	MD=1.5 kg, 95% CI -1.60 to 4.60	Down one (>25% high risk bias)	Down one (single study)	None	Down one (n=21)	None	Very Low
Forearm	MD=1.5 kg, 95% CI -2.24 to 5.24	Down one	Down one (single study)	None	Down one (n=21)	None	Very Low

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		(>25% high risk bias)					
Grip Left	MD= -2.63 kg, 95% CI -11.37 to 6.11	Down two (>25% high risk bias. Contributing study not randomised)	Down one (single study)	None	Down one (n=26)	None	Very Low
Grip Right	MD= -3.26 kg, 95% CI -12.52 to 6.00	Down two (>25% high risk bias. Contributing study not randomised)	Down one (single study)	None	Down one (n=26)	None	Very Low
Lean Mass							
Whole Body (DXA Scan)	MD=1.87kg, 95% CI -2.55 to 6.30	Down one (>25% high risk of bias)	None	None	Down one (n=175)	None	Low
Whole Body Formula	MD=0.86 kg 95% CI 0.11 to 1.61	Down one (>25% high risk of bias)	Down one (single study)	None	Down one (n=30)	None	Very Low
Physical Function							
LEFS	MD=6.09, 95% CI -6.73 to 18.9	Down two	Down one (single study)	None	Down one (n=26)	None	Very Low

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		(>25% high risk bias. Contributing study not randomised)					
Quick-DASH	MD= -7.12, 95% CI -23.0 to 8.76	Down two (>25% high risk bias. Contributing study not randomised)	Down one (single study)	None	Down one (n=26)	None	Very Low
Shuttle Walk	MD=233.3, 95% CI -21.9 to 488.6	Down two (>25% high risk bias. Contributing study not randomised)	Down one (single study)	None	Down one (n=26)	None	Very Low
Gait Speed	MD=10.9, 95% CI 7.97 to 13.8	Down one (>25% high risk of bias)	Down one (single study)	None	Down one (n=40)	None	Very Low
6-Minute Walk Test	MD=68.0, 95% CI -87.4 to 223.4	Down one (>25% high risk of bias)	Down one (single study)	None	Down one (n=21)	None	Very Low
Quality of Life							

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BSHS-A Total	MD=17.8, 95% CI -20.2 to 55.8	Down two (>25% high risk bias. Contributing study not randomised)	Down one (single study)	None	Down one (n=26)	None	Very Low
BSHS-A Physical	MD=4.94, 95% CI -3.76 to 13.6	Down two (>25% high risk bias. Contributing study not randomised)	Down one (single study)	None	Down one (n=26)	None	Very Low
BSHS-A Psychological	MD=11.2, 95% CI -5.83 to 28.2	Down two (>25% high risk bias. Contributing study not randomised)	Down one (single study)	None	Down one (n=26)	None	Very Low
BSHS-A General	MD=3.01, 95% CI -3.53 to 9.55	Down two (>25% high risk bias. Contributing study not randomised)	Down one (single study)	None	Down one (n=26)	None	Very Low
BSHS-A Social	MD=5.47, 95% CI -3.95 to 14.9	Down two (>25% high risk bias. Contributing	Down one (single study)	None	Down one (n=26)	None	Very Low

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	study not randomised)

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

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2.9 Corrigendum

A correction was made to the original manuscript. This did not affect the overall results of the analyses, or conclusions of the originally published paper.

A corrigendum was published in the journal *Burns* as:

Gittings, P. M., Grisbrook, T. L., Edgar, D. W., Wood, F. M., Wand, B. M., & O'Connell, N. E. (2020). Corrigendum to 'Resistance Training for Rehabilitation After Burn Injury: A Systematic Literature Review & Meta-Analysis'[Burns 44 (2018) 731-751]. *Burns: journal of the International Society for Burn Injuries*, *46*(5), 1240-1241.

The author's final version is presented with changes to suit the style and format of this thesis.

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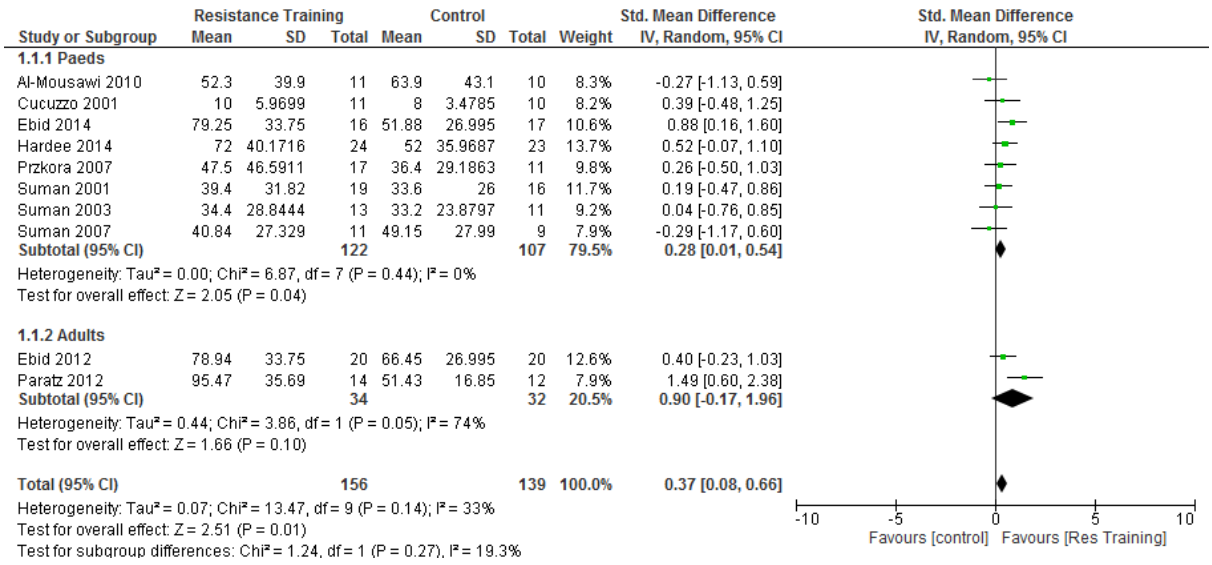
The text on page 39 of this thesis should now read:

"Post-hoc sensitivity analysis was undertaken with SDs imputed for the studies by [7,21]. The imputed SD was the median of all other SD values in the analysis. The effect of RT on muscle strength for the whole group was significant in favour of RT (SMD 0.37, 95% CI 0.08–0.66, p=0.01) and heterogeneity was assessed as non-significant (I^2=32%, p=0.15). For children, the effect was statistically significant (SMD=0.28, 95% CI 0.01–0.54, p=0.04), yet not significant in adults (SMD=0.90, 95% CI 0.17–1.96, p=0.10) (Fig. 4)"

The correct Figure 2.5 is below and the same caption as the currently published text should be used:



Forest plot of results for knee extensor strength, with imputed SD values for Ebid et al. (2012 & 2014)

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Chapter 3 The Lower Limb Functional Index – A reliable and valid functional outcome assessment in burns.

Preface

There are no patient reported, functional outcome measurement tools which have been assessed for use in patients recovering from burn injury. This study examines the clinical applicability of the Lower limb Functional Index-10 as an assessment of lower limb function after a burn injury. This chapter is published as:

Gittings, P. M., Heberlien, N., Devenish, N., Parker, M., Phillips, M., Wood, F. M., & Edgar, D. W. (2016). The Lower Limb Functional Index - A reliable and valid functional outcome assessment in burns. *Burns, 42*(6), 1233-1240. doi: 10.1016/j.burns.2016.03.028

The author's final version of the manuscript is presented with modifications to suit the style and format of this thesis.

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3.1 Abstract

Lower limb injuries account for up to 40% of all burns in Western Australia and affect physical function. Lower limb specific functional assessments are available to monitor recovery, yet no scale has been assessed for use in burns. The Lower Limb Functional Index (LLFI) which is validated in musculoskeletal patients was investigated for applicability in burn injury.

Reliability was assessed using Cronbach's alpha, principal components analysis and Rasch analysis. Validity was assessed using Spearman's correlation coefficient with quality of life assessments (BSHS-B & SF-36) and physical assessments (TUG & ankle ROM). Regression analysis was performed with burn severity measures, time of recovery and location of the burn.

The LLFI-10 was applied 1368 times on 739 patients at regular time points. It was internally consistent ($\alpha>0.8$) and unidimensional. Associations were demonstrated with the BSHS-B and SF-36 (rho= -0.56 – -0.72, $p<0.001$), TUG (rho=0.41, $p<0.001$) and ankle ROM (rho=-0.31 – -0.35, $p<0.001$). The LLFI-10 also showed associations ($p<0.001$) with time since injury (rho= -0.29), age (rho=0.12) and TBSA (rho=0.12).

The LLFI-10 is a reliable and valid tool to assess function in lower limb burn injuries. This study supports the use of the LLFI-10 as part of a battery of assessment for lower limb burn recovery.

Abbreviations
LLFI: Lower Limb Functional Index
LLFI-10: Lower Limb Functional Index-10
ROM: Range of motion
TUG: Timed up and go

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3.2 Introduction

Burns to the lower limb account for up to 40% of injuries admitted in Western Australia (Duke, Rea, Semmens, & Wood, 2012). Patients suffering lower limb burn injuries experience impairments in joint range of motion, muscle strength, and balance (Fauerbach et al., 2001; St-Pierre, Choiniere, Forget, & Garrel, 1998). These will contribute to long lasting physical disability, an impaired capacity to work or return to work and poor quality of life (Brych et al., 2001; Edgar, Dawson, Hankey, Phillips, & Wood, 2010; van Baar et al., 2006; Wasiak et al., 2014).

Despite the high incidence and associated physical disability of lower limb burns, there is a lack of self-reported survey tools to accurately measure recovery of function. Such tools may be best utilized where physical assessment of the patient is challenging or not possible. For example, Western Australia has a total area of 2,529,875km^2 with one burns service to provide treatment for the entire state. Regular physical follow up of patients at scheduled time points is challenging and is a significant cost burden on the patient and health system.

Currently, assessment of functional recovery is undertaken using a battery of validated physical tests (Finlay, Phillips, Wood, & Edgar, 2010) and quality of life assessments including the Burns Specific Health Scale Brief (BSHS-B) and the Medical Outcomes 36-item Short Form Health Survey (SF-36). Both quality of life survey tools provide an accurate evaluation of a burn patient's general health status (Edgar et al., 2010; Finlay et al., 2010). However, these generic tools lack in-depth specificity to the anatomical areas of burn injury.

Specific lower limb functional scales have been recommended for use in the unique burns population (Falder et al., 2009). The Lower Limb Functional Index (LLFI) is a reliable and valid functional assessment tool. It has demonstrated superior psychometric properties and readability when compared to other lower limb scales (C. P. Gabel, Melloh, Burkett, & Michener, 2012). However, the LLFI is yet to be tested as an outcome measure in the burns population.

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The aim of this study was to determine the reliability and validity of the LLFI in the lower limb burns population by testing the hypotheses;

1. The LLFI would be a reliable assessment of lower limb function after burn injury if Cronbach's alpha is >0.8.
2. Criterion validity would be demonstrated if lower limb function, as measured by the LLFI, improved significantly when the BSHS-B and SF-36 indicate an improved quality of life outcome.
3. Construct validity would be demonstrated if lower limb function as measured by the LLFI increases for younger age, less severe burn injury (smaller TBSA and no surgical intervention) and improving physical functional ability (decreased timed up and go and increased ankle range of motion).

3.3 Methods

Design

A retrospective cohort of patients initially admitted to the Burns Service for management of their injury from 2008 – 2014 was recruited for analysis. Patients were included if they had a lower limb burn, irrespective of burns to other areas.

Procedures

The Lower Limb Functional Index-10 (LLFI-10) is a 10-item, abbreviated version of the LLFI which was used for this study (appendix 1). On admission to hospital, participants were asked to complete the LLFI-10 in retrospect to the injury. This enabled determination of their pre-burn lower limb functional status. At one, three, six and 12 months post burn, patients were asked to complete the LLFI-10, recording their current ability. At these times, patients were also encouraged to complete the BSHS-B and SF-36. A trained assessor also undertook the Timed Up and Go test (TUG) and ankle range of motion (ROM) assessments. When a patient was unable to comprehend written English, an accredited translator or family member was used to assist completion of surveys as only English versions where available. Patients who were unable to attend outpatient clinic were mailed the surveys for completion.

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Outcome Measures

Lower Limb Functional Index

The LLFI is a self-reported questionnaire which was developed to improve assessment of the functional status of patients with a lower limb condition. It has been validated for use in populations with lower limb musculoskeletal conditions (Cuesta-Vargas, Gabel, & Bennett, 2014; Duruturk, Tonga, Gabel, Acar, & Tekindal, 2015; C. P. Gabel et al., 2012). Additionally, the tool has recently been used in assessing lower limb function in a population with HIV-related distal sensory polyneuropathy (Galantino et al., 2014).

The LLFI-10 is a shorter, four-part version of the LLFI, developed to improve efficiency of assessment (C. Gabel, 2007). This version is composed of four component parts. Part 1 asks the patient if their injured leg affects their ability to perform 10 pre-determined functional tasks. The patient must agree (1 point), partly agree (1/2 point) or not agree (0 points) with each statement. A total score out of 10 is obtained. Part 2 asks the patient to choose five activities that are important to them and rate their ability to perform each activity from no problem performing (0) to unable to perform normally (10). A total score is obtained. In Part 3, a single question asks the patient to rate their ability to perform pre-injury duties from 0-100%. In Part 4, the patient is asked to rate overall status on a scale from "no problem" (0) to "worst possible" (10). For parts 1, 2 and 4; a smaller score represents superior function.

Burn Specific Health Scale Brief (BSHS-B)

The BSHS-B is a reliable and valid self-rated assessment of quality of life after burn injury (Finlay et al., 2014; Willebrand & Kildal, 2008). It contains 40 questions across nine subscales with excellent internal consistency (Willebrand & Kildal, 2008). In the WA context, the nine BSHS-B subscales were treated as four clinically separate domains; work, affect & relations, function and skin involvement. This research compared the function and total BSHS-B scores to LLFI domain scores.

Short Form 36

The SF-36 is a self-rated quality of life questionnaire scoring across eight domains. These domains are; Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health. Physical and mental

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health component summaries are also derived from the survey (Ware, 2000). The SF-36 has been validated for use in the burns population (Edgar et al., 2010). This study compared the physical function domain score and the physical component summary of the SF-36 to LLFI domain scores.

Physical Function Assessments

The timed up and go (TUG) and ankle dorsi-flexion range of motion (ROM) were used as physical assessments of lower limb function. The TUG assessment is a test recording the amount of time taken to stand from a chair, walk 3m and return to the chair. It has been previously validated in burns (Finlay et al., 2010) and goniometry of joint ROM is known to be a reliable assessment in burns populations (Edgar, Finlay, Wu, & Wood, 2009).

Data Analysis

All statistical analyses were performed using STATA/SE (V.13.1, StataCorp, College Station, Texas). Statistical significance was set for p-value <0.05.

Descriptive statistics of the population were obtained and the distribution of the data was tested. Results were presented as mean and SD or median and IQR based on the normality test.

Preliminary Analysis

Analysis of reliability using Cronbach's alpha, factor analysis and univariate validity using Spearman's correlations was undertaken with a preliminary subset of data. The aim was to investigate the inter-relationship of the survey's four parts prior to completing our in-depth final analyses. Prior to initiating final analyses, additional LLFI-10 data had been collected and was added to create our final dataset.

Reliability

Reliability of the LLFI-10 was assessed by internal consistency and was calculated using Cronbach's alpha. Factor structure was explored using a polychoric correlation matrix and calculating eigenvalues for Parts 1 and 2 of the LLFI-10.

Rasch Analysis

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Rasch analysis was used in conjunction with more classical testing to assess the underlying trait of the LLFI-10, lower limb function. Item responses "sometimes" and "always" from part 1 of the LLFI-10 were combined to create a dichotomous outcome indicating the presence of disability or no limitation. This was done to allow for a simplified and traditional Rasch analysis and interpretation. One Rasch model assumption is a unidimensional construct of the underlying trait (Hardouin, 2007). Therefore, demonstrating good fit with the Rasch model would confirm that items of the LLFI-10 do map to the underlying trait and item scores can be summated to provide an overall score of lower limb function. A good fit with the Rasch model is seen where the Andersen LR and R1c goodness of tests have a p-value >0.05 (Hardigan, 2010). Where goodness of fit tests indicated misfit, the Rasch analysis was repeated after manually removing the most outlying LLFI-10 item until a good fit was achieved. This enabled us to identify any items that may decrease the precision of the estimate of lower limb function.

Criterion Validity

The LLFI-10 surveys completed on admission were not used in longitudinal analyses of validity as they lacked a BSHS-B, SF-36 or physical assessment for comparison.

The BSHS-B (function domain and total score) and SF-36 (physical function and physical component score) were used to assess criterion validity. Spearman's correlation coefficient was used to determine the univariate associations with the LLFI-10.

Construct Validity

Spearman correlation coefficient was used to investigate univariate associations of the LLFI-10 with age, indicators of burn severity (TBSA, surgery), time post burn, the Timed Up and Go (TUG) and ankle dorsiflexion ROM. Longitudinal random-effects regression analyses with spline transformations were performed to understand the longitudinal associations of the LLFI-10 with age, TBSA and surgery in this sample population. A stepwise process was undertaken to deliver the final multivariable model. The spline regression model exhibited knots for each continuous independent variable. These indicated the value at which a change in magnitude (slope) of association with the LLFI-10.

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To confirm validity assumptions, negative associations were hypothesized for time post burn, quality of life and ROM measurements as scoring systems for these assessments opposed that of the LLFI-10.

Correlations were deemed to be small (rho <0.2), moderate (rho=0.2 – 0.5), good (rho=0.5 – 0.75) or excellent (rho >0.75) (Portney & Watkins, 2000). However, comparative measures were deemed as redundant if correlation coefficient is calculated at rho ≥0.8 (Moyé, 2003).

Ethics

Ethics approval was granted for this study by Royal Perth Hospital HREC 13-116. Data were collected under a waiver of consent provision (RPH EC 2009/065).

3.4 Results

Preliminary Analyses

Analyses were undertaken on a preliminary cohort of patients who completed a total of 562 LLFI-10 surveys, prior to the final analysis described below.

Cronbach's alpha was calculated for Part 1 (α=0.86) and Part 2 (α=0.85) of the LLFI-10. We were able to demonstrate excellent internal consistency of the instrument. As data were categorical, polychoric correlation matrices and exploratory factor analyses were performed to determine the factor structure of the LLFI-10. Only one eigenvalue was shown to be >1.0 for Part 1 and Part 2, confirming a uni-dimensional structure.

Spearman's correlation coefficient found statistically significant associations between all parts of the LLFI-10. Part 3 had a strong correlation with Part 1 (rho=0.65), whilst Parts 2 and 4 displayed excellent associations (rho=0.83 & 0.79 respectively).

The unidimensional structure of Part 1 and strong correlations between parts of the LLFI-10 informed our decision that it was necessary only to use Part 1 to perform the final analyses for the purposes of this study.

Final Analyses

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Data from 739 patients with lower limb burns were utilised. A total of 1368 LLFI-10 surveys were completed by the participants, 747 of these were completed at follow up time points. The median age of the sample was 35 years (range 15-91yrs). Males accounted for 72% of the sample group. Median TBSA was 3% (range 0.1 – 70%). The distribution of TBSA across the sample can be viewed in Figure 3.1. Eighty-two percent (82%) of the sample required surgical intervention. Assessment for normality confirmed data exhibited a skewed distribution.

Reliability

Polychoric rho was >0.48 for LLFI-10 items pre burn and post burn injury. A sole eigenvalue was estimated to be >1.0 in principal component analysis, confirming that the LLFI-10 has a single component structure. One component accounted for 74% & 67% of the LLFI-10 outcome variance in pre burn and post burn assessments respectively.

Rasch Analysis

In pre-burn assessment, the Andersen LR test (p=0.495) & R1c statistic (p=0.606) were non-significant. This indicated that the items of Part 1 measured a single trait and justified the summation of item scores to provide an estimate of lower limb function. Post burn Rasch analysis demonstrated misfit (Andersen LR p<0.001, R1c p<0.001). After removing the survey item pertaining to sleep disturbance and repeating the analysis, a good fit to the Rasch model was achieved (Andersen LR p=0.124, R1c p=0.219).

Criterion Validity

The LLFI-10 post-burn displayed moderate to strong significant associations with the BSHS-B, SF-36, TUG and ankle dorsiflexion ROM (Table 3.1).

Construct Validity

Spearman correlation coefficients demonstrated significant associations between the LLFI-10 and time after burn injury. Age and TBSA demonstrated significant, yet small correlations with the LLFI-10. Requirement for surgery was not associated with the LLFI-10 (Table 3.1). The final multivariable regression model confirmed that changes in the LLFI-10 score were associated with time since burn, age and TBSA (Table 3.2).

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These associations indicate a recovery of function after the burn injury and are represented in Figures 3.2 and 3.3.

Comparative performance of LLFI-10 with other functional measures

A series of longitudinal random-effects regression analyses were conducted which examined the association between each functional measure and TBSA, time since injury and the interaction between time and TBSA. Table 3.3 shows the results of the analysis. LLFI-10 is significantly associated with both TBSA (p=0.037) and time of recovery (p=0.004) and it is significantly associated with their interaction (p<0.001). Timed Up and Go is only associated with TBSA (p=0.012) and ROM is associated with time of recovery (R: p=0.005; L: p=0.004).

3.5 Discussion

This retrospective study has demonstrated we can accept our hypotheses that the LLFI-10 is a reliable and valid functional assessment tool after lower limb burns. However, our hypothesis surrounding surgery was an unexpected exception.

There are a number of factors which would be responsible for the lack of association of surgical intervention with lower limb functional outcome. Firstly, the sensitivity of the LLFI-10 in the burns population remains unknown. Secondly, it is possible that over time a floor effect occurs, reducing the overall association of surgical intervention with the LLFI-10. However, this will require further investigation. Rehabilitation and compliance with the best practice recommendations for early mobilization of lower limb skin grafts (Edgar, 2012), in addition to the small average TBSA of our sample make for key contributors to the similarity of functional outcome that surgically managed patients achieve when compared to those who were conservatively managed.

In assessing recovery after a burn injury, our analyses indicate that the items of Part 1 of the LLFI-10 can be summated to provide an appropriate estimate of lower limb function. Rasch analysis has suggested that item 4 “I sleep less well” may in fact decrease the precision of this estimate when assessed after the burn injury. Given that this item does not directly refer to a physical task, whilst the other items of the LLFI-

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10 relate to the ability to perform physical activities, this inference may be accurate and warrants future investigation.

The LLFI-10 is shown to be sensitive to both TBSA and time of recovery, as well as the interaction of the two variables. Thus, there is a different rate of change in the LLFI-10 depending upon the size of burn, with a negative coefficient indicating that the rate of change is slower for larger burns. Therefore, the LLFI-10 is an appropriate tool for burn injuries and applicable at any time in the recovery spectrum to measure lower limb function.

Self-reported lower limb function was associated with quality of life after the burn injury. The LLFI-10 also exhibited moderately strong correlations with physical functional assessments, the TUG (rho=0.41) and ankle ROM (rho=-0.31 – -0.34). The data suggest that the LLFI-10 is capable of providing unique information regarding functional outcome. This may be because the LLFI-10 is a task specific tool, whereas physical measures of function assess at a more generic impairment level. Additionally, none of the other functional outcome measures tested show the same degree of sensitivity, particularly to TBSA and time of recovery.

Falder et al. (2009) previously identified a lack of self-report lower limb functional scales in burns. The LLFI-10 is a scale, now tested in burns, which can be used to assess lower limb function across time and be utilized as part of an assessment battery for burns patients.

In clinical practice, Part 1 of the LLFI-10 is able to provide an appropriate assessment of lower limb function in burns patients. However, the “sleep” item may decrease the precision of this assessment post burn injury. Analysis of survey results could include a sensitivity analysis to measure the overall effect of removing this item from assessment. Part 2 of the LLFI-10 had an excellent correlation with Part 1 (rho=0.82). Whilst a useful tool to develop individualized rehabilitation goals for the patient, the information provided from Part 2 can be viewed as redundant as an additional measure of longitudinal recovery. Further, with respect to the logistics of use, activity selection was not standardized and did not consistently cover the entire spectrum of low energy to high energy physical activities. This made the longitudinal use of that part of the

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scale more difficult. In addition, the lack of an order for recording activities in Part 2 contributed to challenging interpretation of the results for the sample. Part 3 provides an assessment of current function which displayed a good association with Part 1 (rho=0.65). This part of the tool was noted to be simple to complete by the patient and to interpret by the clinician. Part 4 had an excellent correlation with Part 1 which approached redundancy (rho=0.79). In addition, patients reported this question to be difficult to interpret. Therefore, Part 4 may be of less clinical use than Parts 1 and 3 when utilizing this tool to measure recovery of function after lower limb burn injury. The results of this study therefore suggest that Part 1 (pre-determined functional tasks) and Part 3 (% premorbid function) are most worthwhile for use and little additional information is delivered over time when using the other parts of the scale.

Limitations of Study

Each patient completed on average less than two LLFI-10's indicating that some patients did not return for scheduled follow up after their injury. The statistical methods were chosen, however, for their robustness to missing data, particularly as the sample was relatively large and spanned a broad range of severity (TBSA). We did not have information available for the location of burn injury, which may have been a useful variable to further evaluate the validity of the LLFI-10, particularly in context of surgery.

Future Research

This study suggests that further investigation into sensitivity of the LLFI-10 is warranted. This would also highlight the most appropriate time points to utilize the LLFI-10 after burn surgery. Thus, future research to investigate the performance of the LLFI-10 may include test-retest reliability in lower limb burn population in order to quantify its sensitivity in clinical practice. The ability of the LLFI-10 score to gauge and predict long term recovery of lower limb burns would also be of benefit to clinicians and patients alike.

Conclusion

The LLFI-10 can provide additional information specific to lower limb burn recovery. It should be used in conjunction with other validated tools as part of a comprehensive lower limb burn outcome assessment battery.

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Conflict of Interest

There is no conflict of interest to declare.

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3.7 Tables

Table 3.1 Correlations between LLFI-10 and Measures of Burn Severity, Quality of Life and Physical Function.

	rho	p-value
Time Post Burn	-0.29	**<0.001**
Age	0.12	**0.001**
TBSA	0.12	**0.003**
Surgery	0.01	0.804
BSHS Function	-0.56	**<0.001**
BSHS Total	-0.67	**<0.001**
SF-36 PF	-0.71	**<0.001**
SF-36 PCS	-0.72	**<0.001**
TUG	0.41	**<0.001**
ROM DF Left	-0.35	**<0.001**
ROM DF Right	-0.31	**<0.001**
Bold values are statistically significant results		

Table 3.2 Final Multivariable Longitudinal Regression Model for LLFI-10 using Maximum Likelihood Estimation

Variable (knot position)	Coefficient	*p*-value	95% CI
Time post burn (33 days)	-0.60	0.000	-0.77, -0.43
Time post burn (88 days)	-0.35	0.000	-0.52, -0.18
Time post burn (181 days)	0.22	0.009	0.05, 0.38
Time post burn	-0.31	0.000	-0.48, -0.14
Age	0.03	0.000	0.02, 0.04
TBSA (1 %)	0.82	0.000	0.58, 1.06
TBSA (10%)	-0.15	0.208	-0.38, 0.08
TBSA	0.30	0.014	0.06, 0.53
Bold values are statistically significant results			

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Table 3.3 Association between functional measures and TBSA, time since injury and their interaction

Functional indicator	Variable	Coefficient	*p*
LLFI-10	TBSA	-0.0013	**0.037**
	Time	-0.00013	**0.004**
	TBSAxTime	-0.000014	**<0.001**
	_cons	0.143	**<0.001**
Time up & go	TBSA	0.08523	**0.012**
	Time	-0.00387	0.156
	TBSAxTime	-0.00007	0.583
	_cons	7.04	**<0.001**
Ankle dorsal flexion ROM (right)	TBSA	-0.03046	0.413
	Time	0.00891	**0.005**
	TBSAxTime	-0.00017	0.204
	_cons	12.31	**<0.001**
Ankle dorsal flexion ROM (left)	TBSA	-0.04853	0.188
	Time	0.00896	**0.004**
	TBSAxTime	-0.00025	0.060
	_cons	12.74	**<0.001**

Bold values are statistically significant results

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3.8 Figures

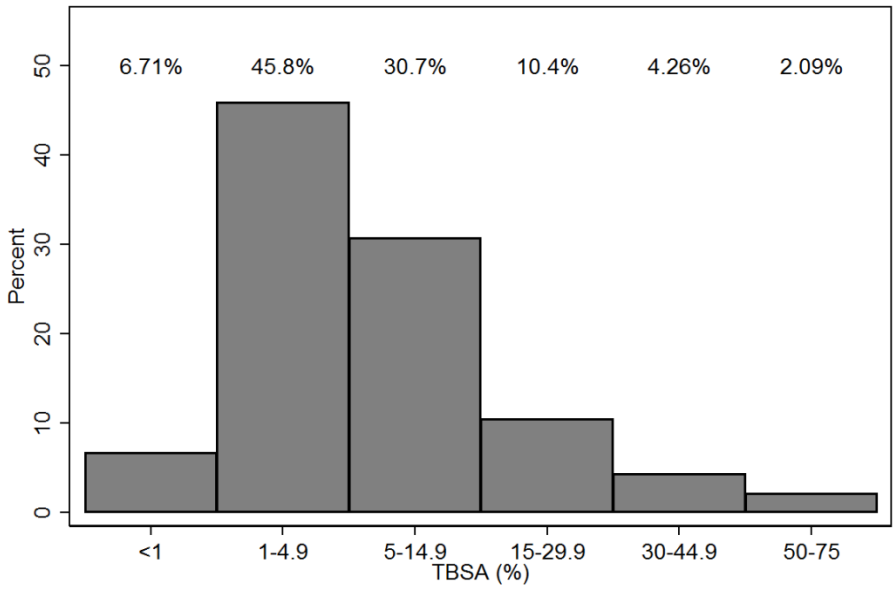

Figure 3.1 Distribution of TBSA across this sample.

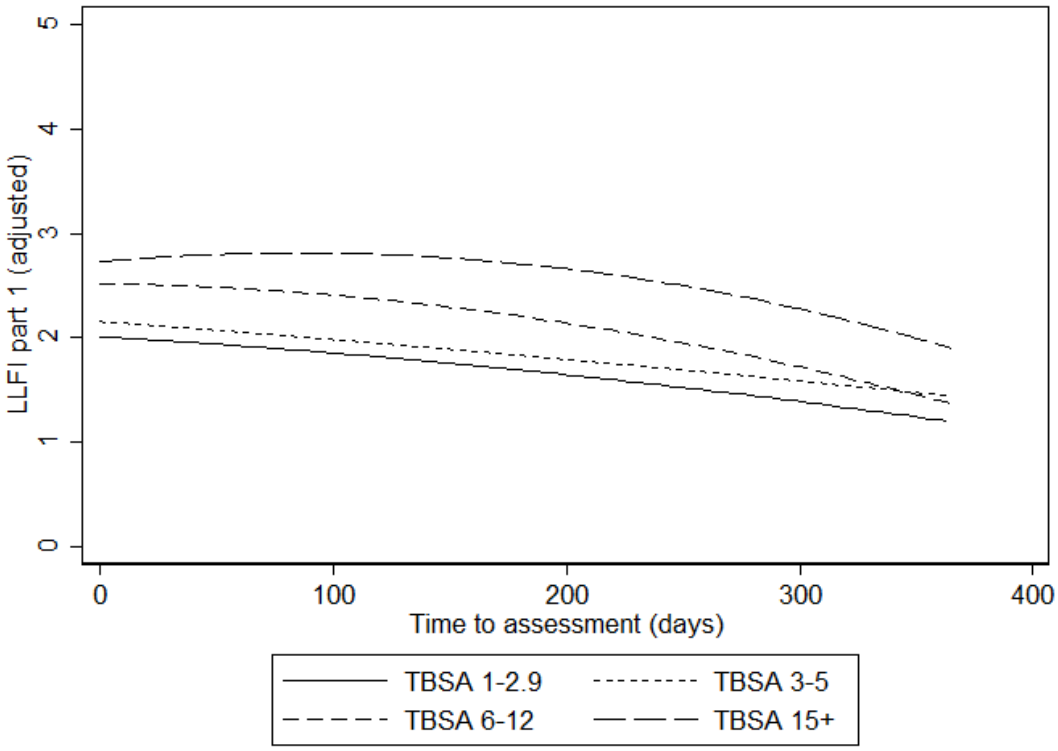

Figure 3.2 LLFI-10 Part 1 total score over time, adjusted for age and categorized by TBSA.

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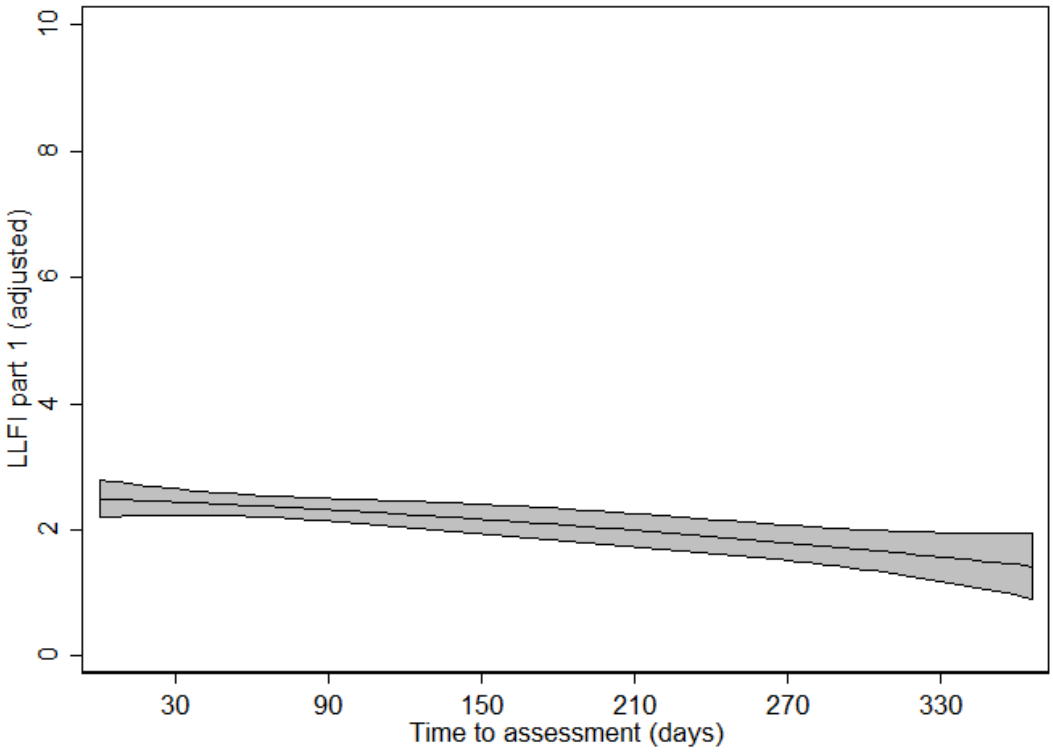

Figure 3.3 LLFI-10 Part 1 total score over time, adjusted for age & TBSA

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Chapter 4 Grip and Muscle Strength Dynamometry are Reliable and Valid in Patients with Acute Minor Burn Wounds

Preface

The assessment of muscle strength in patients with acute and healing burn wounds has not been examined. This is a reliability and validity study assessing the clinical applicability of using hand held dynamometry to measure muscle strength in patients with acute, minor burn injury. This chapter is published as:

Gittings, P., Salet, M., Burrows, S., Ruettermann, M., Wood, F. M., & Edgar, D. (2016). Grip and Muscle Strength Dynamometry Are Reliable and Valid in Patients With Unhealed Minor Burn Wounds. *J Burn Care Res, 37*(6), 388-396. doi: 10.1097/BCR.0000000000000414

The author's final version of the manuscript is presented with modifications to suit the style and format of this thesis.

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4.1 Abstract

Objective: Small burns are common and can cause disproportionate levels of disability. The ability to measure muscle impairment and consequent functional disability is a necessity during rehabilitation of patients. This study aimed to determine the reliability and validity of grip and muscle strength dynamometry in patients with unhealed, minor burn wounds.

Methods: Grip and muscle strength were assessed three times on each side. Assessment occurred at presentation for the initial injury and again every other day (or every five days beyond 10 days post injury) until discharge from the service. Reliability was assessed using intra-class correlation. Minimum detectable differences (MDD) were calculated for each muscle group. Validity was assessed using regression analysis incorporating appropriate burn severity measures and patient demographics.

Results: Thirty patients with total burn surface area ≤15% were assessed. Both grip and muscle strength demonstrated very good reliability (ICC 0.85 – 0.96). Minimum detectable differences ranged from 3.8 – 8.0kg. Validity of both forms of dynamometry was confirmed through associations with gender for all muscle groups ($p<0.001$). In addition, grip strength was associated with the dominant hand ($p=0.002$) and time to assessment ($p<0.001$). Strength was seen to improve over time in all muscle groups.

Conclusions: Grip and muscle strength dynamometry are reliable and valid assessments of strength and are applicable for clinical use in patients who have unhealed, minor burn wounds.

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4.2 Introduction

Burn injuries are associated with a high burden of disease (Mock, Peck, Krug, & Haberal, 2009; Peck, 2011). In Western Australia, more than 25,000 patients have been admitted to hospital for burn related injury since 1983 (Duke et al., 2011). Similar to other developed nations, in a recent study of Western Australian patients, 90% of the burns population were classified as having a minor burn. At the Western Australia Burns Service, a minor burn is defined as TBSA <15% (Finlay et al., 2014) as medical treatment for major burns is started at this level of injury. It has been reported that patients with minor burns can experience considerable disability and absenteeism from work as a result of their injury (Shakespeare, 1998). Further, hand burn injuries cause disproportionately prolonged alterations in functional and participation outcomes (Holavanahalli, Helm, Gorman, & Kowalske, 2007; Moore, Dewey, & Richard, 2009; van Baar et al., 2006).

Treatment and rehabilitation of burns is aimed at returning patients to their pre-injury level of function. To support clinicians in assessing the effects of prescribed interventions, reliable and valid outcome measures are necessary (Brown, Mills, & Muller, 2003). Patients with burn injuries are a unique population who can present challenges to accurate measurement of progress. Therefore, it is important to possess measurement tools that have been tested for use in this specific population. Further, as the majority of burn injuries requiring management are classified as minor burns, tools specifically validated for use with a minor burn will have a much broader and accurate application in burn care.

Many clinically applicable outcome measures have previously been validated for measurement of functional recovery in the burns population (Dale Edgar, McMahon, & Plaza, 2014). These include measures of quality of life: the Burn Specific Health Scale-Brief (Willebrand & Kildal, 2008), the Short Form-36 (D. Edgar, Dawson, Hankey, Phillips, & Wood, 2010), the Quick Disability of Arm Shoulder and Hand upper limb functional survey (Wu, Edgar, & Wood, 2007); active range of movement measurements (D. Edgar, Finlay, Wu, & Wood, 2009); balance and coordination tests (Finlay, Phillips, Wood, & Edgar, 2010). More recently, grip strength dynamometry (GSD) was confirmed to be valid beyond one month post injury in patients with healed

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burn wounds (Clifford, Hamer, Phillips, Wood, & Edgar, 2013). Despite the number of tools available, clinicians still lack a simple and reliable method of measuring clinically significant and real time changes of muscle strength in patients with unhealed, minor burn wounds.

Isometric muscle strength testing has been reliably applied using hand held muscle strength dynamometry (MSD) in healthy (Mentiplay et al., 2015) and various clinical (Bohannon, 1986; Dowman et al., 2015; Visser et al., 2003) populations. The hand held dynamometer is a cheap and effective method for quantifying the isometric muscle strength of an individual. In clinical populations, isometric muscle strength, as assessed by dynamometry, has been shown to correlate with functional performance (Lima et al., 2015) and exercise capacity (Kamiya et al., 2014), whilst also being able to detect disease related impairments in strength (Dorsch, Ada, & Canning, 2015). This simple method of muscle strength assessment has potential clinical applicability that has yet to be tested in a burns population.

This study aimed to investigate the reliability, minimal detectable difference and validity of isometric muscle and grip strength testing in patients with unhealed, minor burn wounds. This study aimed to test the following hypotheses and assumptions of validity (b-f):

a) Intra-class correlation coefficients for GSD and MSD will exceed 0.75, establishing test-retest reliability.
b) Strength as assessed by GSD and MSD will be reduced when total burn surface area (TBSA) is more extensive.
c) Lower limb MSD values will be reduced in the presence of a lower limb burn.
d) Upper limb MSD & GSD values will be reduced in the presence of an upper limb burn.
e) Muscle strength as assessed by GSD & MSD will improve as pain decreases.
f) Muscle strength as assessed by GSD & MSD will improve over time after burn injury.

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4.3 Methods

Participants

Subjects were recruited from Royal Perth Hospital between January and July 2012. Inclusion criteria were as follows:

- Over 16 years of age,
- Consent obtained within 96 hours of burn injury, and
- Total burn surface area (TBSA) ≤ 15%.

No limitation was placed on burn agent or depth. Inpatients and outpatients were both considered. The study criteria were designed to enhance generalizability to the broader minor burn population by not placing restriction on location of burn. Participants' exclusion criteria were as follows:

- Patients who were medically unstable,
- Electrical burn injuries,
- Musculoskeletal injury or disease which would contraindicate muscle strength testing,
- Neurological conditions less than three months old, and
- Patients who were unable to comprehend instructions.

Procedure

All subjects provided consent to participate and ethics approval was granted by the Clinical Quality and Safety Register BCORP CSQU 080429-1. As this project was particularly concerned with minor burn wounds, both admitted and ambulatory patients were recruited. Testing of patients began on their initial presentation to the burns service. After a standardised warm up of active shoulder, elbow and lower limb range of motion exercises (see Appendix 1), patients underwent testing of muscle groups; biceps, triceps, deltoids, hamstring and quadriceps using a muscle strength dynamometer. Grip strength was measured with grip strength dynamometry. These muscle groups were chosen for assessment as they were considered key to completing many daily functional activities and were amenable to being repeatedly assessed in a standardised manner.

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Testing was completed every second day until 10 days post injury, or until discharge. Where burns care extended beyond 10 days, assessment continued every fifth day until discharge from the acute burn service. Left and right sides were assessed three times on each day of testing. After each testing session, using a visual analogue scale, pain score was recorded for the level of pain experienced during the testing process. Testing was ceased for 48 hours after surgical intervention.

Outcome Measurement

Grip Strength Dynamometry

Hand grip strength was assessed with the Jamar hand held dynamometer (Surgical Synergies, WA, Australia). The Jamar dynamometer measures peak grip strength on a scale from 0 – 90kg of force and has been regarded as the gold standard for grip strength assessment (Shechtman, Davenport, Malcolm, & Nabavi, 2003). Assessment was undertaken in 90^{o} of elbow flexion. Each participant performed three tests, alternating left and right hands. The standardised testing positions and instructions were applied for each participant (Table 4.1, Figure 4.1).

Muscle Strength Dynamometry

Peak isometric muscle strength was assessed using the Layfayette Muscle Meter no 01163 (SI Instruments, SA, Australia). This is a hand held dynamometer that records muscle strength in kilograms, pounds or Newtons of force. In this study, kilograms was utilised. The Lafayette muscle meter was chosen for ease of application in an acute burns population. The low cost compared to other strength assessment equipment potentially makes it a widely available tool for clinicians. Three make tests were carried out on each muscle. The testing was carried out by one assessor. Standardised positions and instructions were utilised for each participant in accordance with the American Society of Hand Therapists as outlined in Mathiowetz, Weber, Volland, and Kashman (1984) (Table 4.2, Figures 4.2 a-e).

Data Analysis

Analysis was performed using Stata V.12 (Stata Corp, Chicago). Significance was set at α=0.05. The distribution of each muscle strength variable was checked to determine the most appropriate analytical methods.

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Descriptive Analysis

Patient characteristics were summarised using medians, ranges and proportions as appropriate.

Reliability

Intra-class correlation coefficients (ICC) were calculated using variance components from hierarchical linear mixed models (HLMM) with no covariates. This was undertaken between all three tests of the dominant side for each muscle group during a single testing session for the same person. For this reliability study, data from the first testing session was chosen. This ensured that analysis of data from the acute phase of wound healing was undertaken, to truly understand the performance of the tools in patients with wounds and pain. Intra-class correlation coefficients were calculated again excluding the first test in the case where a learning effect was identified. Fatigue or learning effects were investigated by examining the differences in the estimated groupwise mean strength between tests using a HLMM.

These analyses were repeated adjusting for the potential effect of pain during assessment on the reliability of the muscle strength testing. An ICC >0.75 was accepted as having adequate reliability and an ICC >0.90 was defined as excellent reliability (Portney & Watkins, 2000).

Minimum Detectable Difference

Minimum detectable difference (MDD) was calculated for each muscle group, based on the second and third tests from the first day assessments, using the following formula:

$MDD\ (95\%) = t \times SD_{baseline} \times \sqrt{(2(1-rho\_testretest))}$

where the t-distribution value corresponding to the sample size was substituted for t and the standard deviation of the second test sample was used for $SD_{baseline}$. This value allows an understanding of the real change measurable by the tool (Finlay et al., 2010).

Validity

Hierarchical linear mixed models regression analyses were also used to evaluate associations between clinical variables and strength measurements from the first day of assessment of each muscle group. Clinical variables used to examine validity

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included time to assessment post burn, gender, age, side dominance, TBSA, pain, requirement for surgery and location of burn. Surgery was included as a quasi-measure of burn depth and therefore severity. Univariate analysis was performed, followed by multivariable analyses. Due to the expected large influence of gender, all clinical measures were initially included in the multivariable analyses to ensure that potential effects emerging after adjusting for gender were not missed. Non-significant variables were then removed in a manual backward stepwise process until the final model was determined. The level of significance accepted was $\alpha < 0.05$.

Temporal Recovery

Longitudinal analysis using HLMM was performed on sentinel measures of strength for upper and lower limbs, using all three assessment measures for each person. Sentinel measures of biceps and quadriceps strength were selected to be the key limb muscle groups; in addition to grip strength. The influence of gender, age, dominance, TBSA, pain and surgery on muscle strength was analysed for each muscle group, with time post burn accounted for in all cases. Interactions between time and clinical measures were investigated for variables that may have affected the pattern of muscle strength change over time. Variables that displayed a significant association with muscle strength and time were included in multivariable analyses and non-significant associations were subsequently removed in a step-wise manner to determine the final model.

Assumptions of linearity were assessed using plots with locally weighted scatterplot smoothing (LOWESS), multivariable regression splines and fractional polynomials. When non-linearity was identified, piecewise regression was performed based on knots determined by the regression spline calculations to facilitate a simpler interpretation of regression coefficients.

All HLMM employed maximum likelihood estimation (MLE) that ensures patients with some missing observations on the outcome are not excluded, thereby reducing the introduction of bias. MLE maximises together, the likelihood based on complete data and the likelihood based on partial data to produce more robust parameter estimates as long as missing data is missing at random.

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4.4 Results

Descriptive

A sample of 30 patients was recruited for this study. Descriptive statistics are detailed in Table 4.3.

Reliability

Quadriceps and hamstrings assessments demonstrated a significant learning effect between Tests 1 and 2, which was not evident between Tests 2 and 3. Grip strength measures demonstrated a fatigue effect between Tests 1 and 2, again not evident between Tests 2 and 3. Intra-class correlations based on Tests 2 and 3 exceeded 0.9 for all muscle groups other than quadriceps (ICC=0.85) (Table 4.4). Pain did not influence the ICC scores.

Minimum Detectable Difference

The MDD's for muscle strength assessments ranged from 3.8kg – 8.0kg for all muscle groups and grip strength (Table 4.4). Grip exhibited the greatest MDD (8.0kg) and deltoids the lowest (3.8kg) for muscle strength testing.

Validity

Males demonstrated significantly stronger muscle strength in all univariate models. Time post burn was associated with increased hamstring ($p=0.007$) and grip strength ($p=0.007$), while dominance was associated only with grip strength ($p=0.002$). Burn injury factors such as surgery, pain and TBSA were not associated with muscle and grip strength results (Table 4.5). However, multivariate analysis did demonstrate changes in the associations of these variables.

In multivariate models, male gender continued to be associated with increased muscle strength in all groups. Grip strength was positively associated with dominance ($p<0.001$) and time since burn ($p<0.001$). However, increasing age and right sided hand burns were associated with decreased grip strength ($p<0.001$). Hamstring strength was positively associated with time post burn injury and pain scores ($p<0.001$), yet negatively associated with TBSA ($p<0.001$). Quadriceps strength decreased with advancing age ($p=0.003$) (Table 4.6).

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Temporal Recovery

Gender and dominance were associated with muscle strength for each of the sentinel muscle groups (biceps, quadriceps and grip). Male gender and the dominant side were associated with greater muscle strength for biceps, quadriceps and grip strength (Table 4.7).

Biceps and quadriceps strength increased in a linear trajectory. Small changes in strength were seen each day post burn, biceps increased 0.1 kg per day (95%CI: 0.02, 0.18, p=0.012) and quadriceps 0.18 kg per day (95%CI: 0.04, 0.33, p=0.011). Grip followed a non-linear pattern (Table 4.5). Between days 1 and 3 grip strength was found to decrease by 1.76kg per day (95%CI: -2.9, -0.62, p=0.002) while between days 4 and 6 grip strength was found to increase by 1.13kg per day (95%CI: 0.41, 1.85, p=0.002). No significant changes in grip strength were detected for the period following day 6 (p=0.29).

4.5 Discussion

This project confirmed hand held MSD and GSD to be reliable assessments of strength in patients with unhealed minor burn wounds. All muscle groups had excellent reliability, except for quadriceps where the ICC was lower (ICC=0.85), though reliability remains acceptable for clinical use. Due to the learning and fatigue effects noted between Tests 1 and 2, in the clinical setting a practice test is advised prior to formal testing.

The MDD for GSD in this study was greater than in our previous work with burns patients who were tested at least one month after their injury (Clifford et al., 2013). We deduce that the decrease in sensitivity of grip strength reflects the variability of hand grip performance due to the presence of an unhealed wound and the associated inflammatory response, which may affect muscle activation and strength. For MSD, this study is the first instance, to our knowledge, of reporting the MDD in a burns population. Clinician application of these values makes for a more constructive tool in measuring the effect of chosen interventions. The MDD is important in the

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interpretation of clinical testing as it will indicate the change in muscle strength measured before clinicians can assume a real change has occurred.

Muscle strength was significantly greater for males in all muscle groups. Our finding aligns with what has been demonstrated in the general population (Andrews, Thomas, & Bohannon, 1996; Danneskiold-Samsøe et al., 2009; Luna-Heredia, Martin-Pena, & Ruiz-Galiana, 2005). Muscle strength is known to decrease with age (Danneskiold-Samsøe et al., 2009; Luna-Heredia et al., 2005), similarly, in our group of acute burns patients, age was significantly associated with decreasing grip and quadriceps strength. Grip strength was significantly greater in the dominant hand, again mirroring the general population (Luna-Heredia et al., 2005). Based on these findings, validity can be confirmed for these measurement tools.

The temporal recovery of muscle strength has assisted to confirm validity of dynamometry in patients with unhealed, minor burn wounds. Sentinel assessments of upper and lower limb strength showed improvement over the first 20 days of recovery post burn. Grip strength initially decreased over the first three days post burn, and then improved over the next three days, whereas biceps and quadriceps demonstrated recovery in a linear manner. This confirms our hypothesis of a measureable change in muscle strength over time. As might be expected, dominance and gender were associated with the magnitude of muscle strength, while the pattern of recovery was not affected by these variables.

However, not all results were as predicted. The location of the burn wound in our study did not influence muscle strength measurements. However, the presence of a right sided hand burn was associated with reduced grip strength when compared to no hand burn. This effect was not evident for a left sided hand burn. We surmise this is most likely to be due to artefact secondary to the small subgroup size for hand burns in this study (see Table 1). Additionally, our assumption of associations of muscle strength with burn severity and pain were not confirmed in this study. The hamstrings were the only muscle group to demonstrate a statistical association; however, the magnitude of this was below the MDD and thus, we would suggest did not reach clinical significance. No other associations with surgery, TBSA or pain were demonstrated. Whilst sensitive, we acknowledge that this methodology may not be sensitive enough

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to detect all differences due to variables that could be considered influential to strength changes in patients with minor burn wounds.

In a minor burn sample such as this, the effect of burn injury factors on muscle strength may not be as pronounced as in more severe burns. Further, the model of care provided for burns patients in this setting is one of rehabilitation starting from the time of injury. Undertaking early rehabilitation, not limited to therapeutic exercise, may assist to hasten the return of strength and functional ability after a burn injury. In practice, we have a strong focus on providing adequate pain relief to facilitate engagement in rehabilitation and normal function throughout the entire day. Additionally, we observe that skeletal muscle contractions performed during muscle testing and exercise have a positive influence on perceived pain, helping to optimise function, movement and muscle strength after burn injury. From our presented results, we would hypothesise that in burn patients with unhealed, minor wounds, the severity and location of the injury should not confound the use of muscle and grip strength dynamometry, which are useful tools for measuring patient progress and outcome.

Conclusion

Muscle and grip strength dynamometry are reliable and valid clinical tools that are appropriate to use in assessment of the change of muscle strength in patients with unhealed, minor burn wounds.

Limitations

Although reliability and validity are demonstrated, we appreciate that the limited sample size of this study may contribute to the inconsistent associations of muscle strength assessment with burn injury factors. Additionally, our data had limited precision in the categorisation of depth of injury, therefore surgery was utilised as a quasi-measure of burn depth and thus, injury severity.

It has been considered that difficulty stabilising the dynamometer by hand during muscle testing may have contributed to the reduced ICC for the quadriceps muscle group. This has previously been documented as a factor in testing on other populations (Wikholm & Bohannon, 1991).

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Future Studies

While these results are applicable to the majority of burn patients, further investigation into larger burn injuries would improve generalizability of our results. Testing the reliability of the MSD to assess multi-joint movements and the effect of an external stabiliser in burns patients on MSD reliability would also be beneficial. Another area for future work could investigate an association of early strength dynamometry measurements with functional and quality of life outcomes in the burns patient.

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4.6 References

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4.7 Tables

Table 4.1 Jamar Grip Strength Dynamometry Protocol

Equipment:
• Chair • Jamar grip strength dynamometer (GSD)
Preparation:
• Patient seated in a chair
Procedure:

• The patient completes a standardised warm up and stretches prior to testing consisting of:
  ○ 20 repetitions of flexion and extension of both elbows
  ○ 20 repetitions of abduction and adduction of both shoulders
  ○ 10 squats
• The first time a patient was tested they were allowed one practice trial
• Posture: seated with their shoulder adducted and neutrally rotated, elbow at 90 degrees flexion, forearm in neutral position and wrist between 0 and 30 degrees flexion and between 0 and 15 degrees ulnar deviation. Patient holds GSD
• GSD in second setting (grip span 4.8cm)
• Three alternating left and right, 2 second sustained contractions of maximal efforts performed.
• The peak force generation recorded after every trial

Standardised Instructions:
<u>Start:</u> • 'This device measures the strength of your hands. Please squeeze it as hard as you can with one hand, alternating between left and right. • 'If at any stage you feel dizzy, nauseous or high levels of pain, stop' <u>Verbal encouragement during each trial:</u> • 'Squeeze as hard as you can. Harder! Harder! Relax. <u>Post-Trial:</u> • A pain score was recorded prior to and after testing, determined by the question: "Could you give your pain a score? With "0" being no pain and "10" the worst pain imaginable."

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Table 4.2 Hand Held Muscle Strength Dynamometry Protocol

Equipment:

- High chair
- (Lafayette /Nicolas) Hand Held Muscle Strength Dynamometer

Preparation:

- A pain score should be recorded prior to the testing determined by the question: Could you give your pain a score with 0 being no pain and 10 the worst pain imaginable.
- The patient completes a standardised warm up and stretches prior to testing consisting of:
  - 20 repetitions of flexion and extension of both elbows
  - 20 repetitions of abduction and adduction of both shoulders
  - 10 squats
- Patient is seated in height adjustable chair, set to height so that feet won't touch the ground during testing.
- Instructions are given prior to testing

Patient Posture & HHD Positions:

- *For each position where the location of the burn or donor site prohibits the correct position, the test can only be performed if an acceptable placement can be found with minor adjustments (no more then 2cm from assigned location). In case this is not possible this measurement must be omitted.*
- *Patient is not allowed to use hands to grip the chair when measuring lower limbs, therefore hands should be laid in lap when testing lower limbs.*

Biceps

- **Posture:** Patient sitting, elbow flexed to 90 degrees, forearm in supination.
- **Position:** Distal radial-ulnar joint palmar side (~1 cm proximal to wrist).

Triceps

- **Posture:** Patient sitting, elbow flexed to 90 degrees, forearm in supination.
- **Position:** Distal radial-ulnar joint dorsal side (~1 cm proximal to wrist).

Deltoids

- **Posture:** Patient sitting, elbow flexed to 90 degrees.
- **Position:** Immediately proximal to lateral epicondyle of elbow.

Quadriceps

- **Posture:** Patient sitting on anti-slip mat and towel, knee in 90 degrees flexion.
- **Position:** Distal anterior tibia immediately proximal to talo-crural joint.

Hamstrings

- **Posture:** Patient sitting on anti-slip mat and towel, knee in 90 degrees flexion.
- **Position:** Calcaneus.

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Procedure:
• One example trial on each muscle on the first test occasion is allowed. • The HHD is placed in position and a 'make-test' is performed (ie. Maximal isometric muscle contraction) • Each individual muscle trial lasts 5 seconds • The peak isometric contraction will be recorded after every trial. • The muscles are tested in the following order; biceps; triceps; deltoid; quadriceps; hamstrings; on the left and then repeated on the right side of the patient. • The whole procedure is repeated three times.
• **Standardised Instructions:**
• **Start:** ➢ 'This is a test of you maximal muscle strength. You will be given one practice for each of the muscle groups tested, followed by three recorded trials' ➢ 'If at any stage you feel dizzy, nauseous or high levels of pain, stop' • **Verbal encouragement during each trial:** ➢ "match my resistance" ➢ "as hard as you can"

Table 4.3 Descriptive Statistics n=30

	n (%) or Median(IQR)[#]	
Male Gender	25	(83.3)
Age	28.5	(20)[#]
TBSA	5.0	(2.8)[#]
Surgery	13	(43)
Right Hand Dominant	27	(90)
Upper Limb Burn	17	(56.7)
Hand Burn	14	(46.7)
Lower Limb Burn	10	(33.3)
Foot Burn	5	(16.7)

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Table 4.4 Intra-class correlation coefficients and minimum detectable differences (kg) for all muscle groups

	n	Tests 1, 2 & 3 ICC (95%CI)		Test 2 & 3 ICC (95%CI)		MDD[#]
Biceps	29	0.91	(0.86, 0.95)	0.94	(0.90, 0.96)	5.55
Triceps	29	0.85	(0.76, 0.91)	0.91	(0.85, 0.94)	4.19
Deltoid	29	0.89	(0.83, 0.93)	0.92	(0.88, 0.95)	3.87
Hamstring	28	0.89	(0.82, 0.93)	0.90	(0.84, 0.94)	5.88
Quadriceps	28	0.80	(0.70, 0.87)	0.85	(0.76, 0.91)	7.83
Grip	30	0.95	(0.92, 0.97)	0.96	(0.93, 0.98)	8.02

[#] Based on tests 2 and 3

95% CI = 95% confidence interval

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Table 4.5 Univariate Hierarchical Linear Mixed Models of first assessment for Muscle Groups

Key: Coefficient (95% CI) p-value	Biceps	Triceps	Deltoids	Hamstring	Quadriceps	Grip
Time since burn	1.37 (-0.31, 3.05) p= 0.11	0.78 (-0.57, 2.13) p= 0.26	0.77 (-0.43, 1.96) p= 0.21	**2.36** **(0.67, 4.07)** **p= 0.007**	1.27 (-0.64, 3.19) p= 0.19	**4.62** **(1.28, 7.95)** **p= 0.007**
Gender Male	**12.1** **(7.89, 16.3)** **p< 0.001**	**9.54** **(6.35, 12.7)** **p< 0.001**	**9.06** **(6.33, 11.8)** **p< 0.001**	**11.1** **(6.89, 15.4)** **p< 0.001**	**10.4** **(4.93, 15.8)** **p< 0.001**	**26.6** **(18.1, 35.1)** **p< 0.001**
Age	0.02 (-0.11, 0.14) p= 0.78	0.06 (-0.04, 0.15) p=0.25	0.67 (-0.02, 0.15) p= 0.11	-0.01 (-0.14, 0.11) p=0.83	-0.09 (-0.22, 0.04) p= 0.18	-0.18 (-0.44, 0.07) p= 0.15
Dominant Side	0.87 (-0.85, 2.59) p= 0.32	0.03 (-0.89, 0.95) p= 0.94	-0.02 (-0.87, 0.83) p= 0.96	0.69 (-0.36, 1.74) p= 0.19	0.64 (-1.0, 2.27) p= 0.45	**4.98** **(1.75, 8.20)** **p= 0.002**
TBSA	0.43 (-0.44, 1.30) p= 0.33	0.17 (-0.52, 0.85) p= 0.64	0.11 (-0.50, 0.72) p= 0.71	-0.07 (-0.92, 0.78) p= 0.87	-0.07 (-1.04, 0.88) p= 0.87	0.16 (-1.70, 2.01) p= 0.87

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Pain	0.42 (-0.81, 1.65) p= 0.51	-0.09 (-1.06, 0.89) p= 0.86	0.25 (-0.62, 1.11) p= 0.57	1.04 (-0.13, 2.21) p= 0.08	1.12 (-0.19, 2.43) p= 0.09	1.12 (-1.48, 3.73) p=0.39
Surgery	1.17 (-3.33, 5.66) p= 0.61	-0.85 (-4.44, 2.75) p= 0.64	-0.92 (-4.06, 2.22) p= 0.57	0.69 (-3.89, 5.27) p= 0.77	2.72 (-2.42, 7.85) p= 0.30	1.34 (-8.24, 10.9) p=0.78
Burn Location^						
Left	-3.69 (-9.87, 2.48) p= 0.24	-1.23 (-6.17, 3.72) p= 0.63	-0.76 (-5.01, 3.48) p= 0.72	0.65 (-6.65, 7.96) p= 0.86	-2.28 (-10.5, 5.93) p= 0.59	-7.13 (-20.5, 6.20) p= 0.29
Right	-0.22 (-7.80, 7.36) p= 0.95	-1.30 (-7.32, 4.72) p= 0.67	3.92 (-1.27, 9.11) p= 0.13	-3.49 (-12.3, 5.34) p= 0.43	-1.39 (-11.4, 8.65) p= 0.79	2.11 (-14.1, 18.3) p= 0.79
Bilateral	1.97 (-3.12, 7.06) p= 0.44	1.55 (-2.64, 5.75) p=0.46	2.36 (-1.12, 5.84) p= 0.18	1.57 (-5.01, 8.15) p= 0.64	-0.36 (-9.02, 8.30) p= 0.93	1.33 (-9.65, 12.3) p= 0.81

^ Arm burn for upper limb muscle groups, leg burn for lower limb muscle groups

Significant results in bold ($p < 0.05$)

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Table 4.6 Final multivariate hierarchical linear mixed models of first assessment

Muscle Group	Variable	Coefficient (95% CI)		p-value
Biceps	Gender Male	12.8	(8.70, 16.8)	**<0.001**
	Constant	14.2	(10.1, 18.3)	**<0.001**
Triceps	Gender Male	10.4	(9.58, 11.2)	**<0.001**
	Constant	11.8	(8.73, 14.8)	**<0.001**
Deltoids	Gender Male	8.77	(5.99, 11.5)	**<0.001**
	Constant	11.9	(9.02, 14.4)	**<0.001**
Hamstrings	Days Post Burn	1.24	(0.91, 1.57)	**0.03**
	Gender Male	11.4	(10.3, 12.4)	**<0.001**
	TBSA	-0.50	(-0.63, -0.38)	**0.044**
	Pain	0.88	(0.69, 1.06)	**0.015**
	Constant	14.6	(13.3, 15.9)	**<0.001**
Quadriceps	Gender Male	12.2	(7.33, 17.1)	**<0.001**
	Age	-0.15	(-0.25, -0.05)	**0.003**
	Constant	32.9	(27.9, 38.0)	**<0.001**
Grip	Days Post Burn	2.27	(2.11, 3.34)	**<0.001**
	Gender Male	27.9	(25.9, 29.8)	**<0.001**
	Age	-0.31	(-0.36, -0.26)	**<0.001**
	Dominant	4.98	(3.72, 6.24)	**0.002**
	Burn Location [a]	-1.85	(-7.54, 3.84)	0.52
	Burn Location [b]	-7.23	(-8.89, -5.57)	**0.002**
	Burn Location [c]	-2.49	(-6.35, 1.38)	0.21
	Constant	27.4	(20.8, 33.9)	**<0.001**

[a] Left side hand burn only. Reference group no burn on hand.

[b] Right side hand burn only.

[c] Bilateral hand burn.

Significant results in bold ($p < 0.05$)

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Table 4.7 Multivariable regression models assessing muscle strength over time

Muscle Group	Variable	Coefficient (95% CI)		p-value
Biceps	Days Post Burn	0.10	(0.02, 0.18)	**0.012**
	Gender Male	12.3	(8.28, 16.2)	**<0.001**
	Dominant	0.49	(0.06, 0.91)	**0.024**
Quadriceps	Days Post Burn	0.18	(0.04, 0.33)	**0.011**
	Gender Male	10.3	(5.41, 15.2)	**<0.001**
	Dominant	1.12	(0.40, 1.84)	**0.002**
Grip	Day 1-3	-1.76	(-2.90, -0.62)	**0.002**
	Day 4-6	1.13	(0.41, 1.85)	**0.002**
	Day 7-20	0.11	(-0.09, 0.31)	0.286
	Gender Male	26.1	(17.1, 35.0)	**<0.001**
	Dominant	3.70	(2.89, 4.51)	**<0.001**

Significant results in bold ($p < 0.05$)

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4.8 Figures

Figure 4.1 GSD testing position

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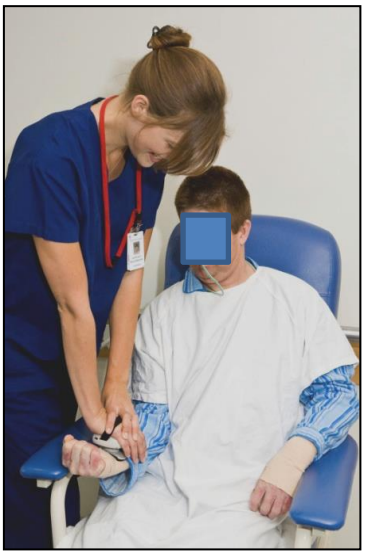
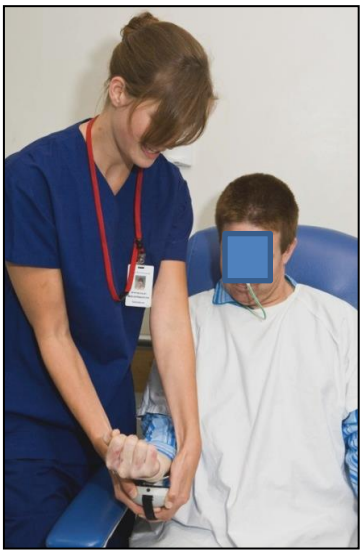


A



B

C

D

E

Figure 4.2 MSD testing positions – (a) Biceps, (b) triceps, (c) deltoids, (d) hamstrings, (e) quadriceps

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Chapter 5 Grip and Muscle Strength Dynamometry in Acute Burn Injury: Evaluation of an Updated Assessment Protocol.

Preface

Chapter Four determined that muscle and grip strength dynamometry were reliable and valid assessments of muscle strength in patients who have a minor burn injury. This study aimed to assess the applicability of these same muscle strength assessments in burn injured patients with moderate and major burn injuries. It also tests the assessment method in new muscle groups and with the use of a system of external stabilisation. This Chapter is published as:

Gittings, P. M., Hince, D. A., Wand, B. M., Wood, F. M., & Edgar, D. W. (2018). Grip and Muscle Strength Dynamometry in Acute Burn Injury: Evaluation of an Updated Assessment Protocol. *J Burn Care Res*. doi: 10.1093/jbcr/iry010

The author's final version of the manuscript is presented with modifications to suit the style and format of this thesis.

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5.1 Abstract

External stabilization is reported to improve reliability of hand held dynamometry, yet this has not been tested in burns. We aimed to assess the reliability of dynamometry using an external system of stabilization in people with moderate burn injury and explore construct validity of strength assessment using dynamometry.

Participants were assessed on muscle and grip strength three times on each side. Assessment occurred three times per week for up to four weeks. Within session reliability was assessed using intraclass correlations calculated for within session data grouped prior to surgery, immediately after surgery and in the sub-acute phase of injury. Minimum detectable differences were also calculated. In the same timeframe categories, construct validity was explored using regression analysis incorporating burn severity and demographic characteristics.

Thirty-eight participants with total burn surface area 5 – 40% were recruited. Reliability was determined to be clinically applicable for the assessment method (intraclass correlation coefficient >0.75) at all phases after injury. Muscle strength was associated with sex and burn location during injury and wound healing. Burn size in the immediate period after surgery and age in the sub-acute phase of injury were also associated with muscle strength assessment results.

Hand held dynamometry is a reliable assessment tool for evaluating within session muscle strength in the acute and sub-acute phase of injury in burns up to 40% total burn surface area. External stabilization may assist to eliminate reliability issues related to patient and assessor strength.

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5.2 Introduction

Decreased muscle strength is a significant impairment which burn injured patients are faced with after their injury (St-Pierre, Choiniere, Forget, & Garrel, 1998). For this reason muscle strength is regularly targeted in rehabilitation programs. The prescription of therapeutic exercise requires an accurate and consistent mode of assessment to monitor both the necessity and effectiveness of a chosen treatment. Hand held dynamometry (HHD) has been shown to assess muscle strength reliably when compared to isokinetic dynamometry (Mentiplay et al., 2015), the reference standard in muscle strength testing. The advantages of HHD include lower cost, increased time efficiency, greater portability and ease of use compared to isokinetic dynamometry (Stark, Walker, Phillips, Fejer, & Beck, 2011). Our group has previously demonstrated HHD, including muscle strength and grip strength dynamometry, to be reliable and valid in the assessment of muscle strength in patients with acute, minor burn wounds (Gittings et al., 2016) and patients with a recently healed upper limb burn injury (Clifford, Hamer, Phillips, Wood, & Edgar, 2013), though there is currently no data available for people with more severe burn injuries.

Although deemed appropriate to use in a burn injured population, we have identified aspects of the assessment process which warrant further development. Other authors have demonstrated the strength of the clinician performing the assessment can affect the reliability of results, particularly when compared between different assessors (Stone, Nolan, Lawlor, & Kenny, 2011; Thorborg, Bandholm, Schick, Jensen, & Holmich, 2013; Wikholm & Bohannon, 1991). A solution proposed utilizes external stabilization to enhance reliability of testing procedures. By implementing an external system of stabilization, it is possible to reduce variability that exists in relation to the physical strength of the assessor. Minimizing the strength differential between tester and assessor in this way has been shown to improve reliability in other populations (Bohannon, Bubela, Wang, Magasi, & Gershon, 2011; Tourville et al., 2013).

In burns, the use of HHD has not been tested in patients with moderate or major burn injury. Nor has the use of external stabilization been evaluated. To be able to demonstrate reliability and validity in this population would allow for wider application of the tool in a burns clinical environment. This study aimed to assess the

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reliability of HHD using an external system of stabilization in people with moderate burn injury. We also aimed to explore construct validity of strength assessment using HHD with external stabilization by exploring the effects of age, sex, total burn surface area (TBSA), location of burn, type of surgery, time post burn and pain intensity on strength assessment.

5.3 Methodology

Participants

Subjects were recruited from the State Adult Burns Unit at Royal Perth Hospital & Fiona Stanley Hospital between August 2014 and April 2017. Inclusion criteria were as follows:

- TBSA 5% to 40%,
- Consent obtained and able to begin assessment within 72 hours of the burn injury, and
- Aged 18 years or older.

Exclusion criteria were:

- Length of admission <72 hours,
- Electrical injury,
- Palmar hand burns,
- Concomitant trauma preventing participation in an exercise program,
- Musculoskeletal or neurological conditions or injuries preventing participation in an exercise program, and
- Patients unable to comprehend English language.

Procedure

Only patients who were admitted as inpatients to the burns unit for treatment of their injury were approached for recruitment. Consent to participate was provided by all subjects. Ethical approval was granted by the Royal Perth Hospital HREC 14-008 & The University of Notre Dame Australia HREC 014138F.

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Testing of muscle strength commenced within 72 hours of the burn injury. Testing was undertaken up to three times per week for a period of up to four weeks. After surgery, testing was ceased for 48 to 72 hours as per our standard surgical and rehabilitation practices. At the commencement of each session, a short, active warm up consisting of upper limb and/or lower limb ergometry and stretches was completed by patients. At the commencement of the testing procedures, a score out of 10 representing a baseline level of pain intensity was collected from each patient (0=no pain, 10=worst pain imaginable). The muscle strength testing procedure described by Gittings et al. (2016) was adjusted and utilized. The specific changes made to the original protocol included exclusion of the assessment of hamstrings, whilst adding assessment of shoulder press and leg press combined muscle strength, as these movements were more applicable to our standard, clinical exercise regimen. External traction belt stabilization was introduced for all muscle groups in the updated testing procedures. The testing order was standardized with three alternate trials of left and right sides of elbow flexion, elbow extension, shoulder abduction, shoulder press, grip strength, isolated knee extension and leg press.

Outcome Measurement

Muscle Strength Dynamometry

Peak muscle strength in kilograms of force was recorded for each trial using a hand held Lafayette Muscle Meter no. 01165 (SI Instruments, SA, Australia). This device is a portable, hand held dynamometer capable of quantifying muscle strength up to a recommended limit of 136 kg. Each participant received a demonstration of the testing procedure and standard instructions to push against the dynamometer as hard as possible for the duration of the test. Encouragement to do so was provided during the active testing process. Three isometric muscle tests of five seconds each were performed on left and right sides for each muscle group. A traction belt (Pelican Manufacturing P/L, Australia), equivalent to an automobile seat belt strap with adjustable buckles was set up over the dynamometer, to a fixed anchor point. The belt length was adjusted to provide resistance in a position suitable to facilitate an isometric contraction from the participant as seen in Figure 5.1a-e. In the case of elbow extension stabilization was provided against the arm rest of the chair and for leg press, stabilization was provided against an immoveable footplate. The positioning of each test is described in Table 5.1 and pictured in Figure 5.1. Where the location of the burn

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wound was not tolerated by the patient and prevented the planned placement of the dynamometer, a gel pad was used to improve comfort or the dynamometer was moved to a comparable position within 5cm of the standard placement. Separate analyses were undertaken for left and right side for each muscle group.

Grip Strength Dynamometry

Grip strength was assessed in kilograms using a Jamar handheld dynamometer (Surgical Synergies, SI Instruments, SA, Australia). Instruction and demonstration of the test was provided at the initial testing session. Each test lasted for ~three seconds and encouragement to squeeze the dynamometer as hard as possible was provided during the test. Subjects performed three tests alternating between left and right hands. Positioning for this test is outlined in Table 5.1 & Figure 5.1. No additional stabilization was required for GSD as there is no interaction between the physical capacities of tester and participant. The assessor did provide support of the dynamometer to facilitate consistent elbow positioning of patients.

Data Analysis

Descriptive statistics were used to describe demographic and clinical characteristics of participants. The distribution of the muscle strength variables was assessed to determine appropriate analytical methods. Results are presented as appropriate based on distribution of data. All analyses were completed using STATA v14.0 (StataCorp, Chicago, IL).

Reliability

Within session reliability was assessed by calculation of ICCs for each muscle group, on each side, using multilevel mixed-effects linear regression, initially with no covariates. A learning effect was identified on comparison of estimated mean strength between the first and subsequent assessment trials for lower limb muscle groups. Therefore, the decision was made to calculate ICCs for all muscle groups, excluding the first trial, from each assessment session. ICC's were also calculated following adjustment for the effect of pain intensity as reported by the subject at the commencement of muscle strength assessment. Clinically applicable reliability was accepted where ICCs >0.75. Excellent reliability was indicated by an ICC >0.9 (Portney & Watkins, 2000). We chose to assess within session reliability

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longitudinally defined in the time frame categories of: prior to surgery (initial); immediately after surgery; and, at three weeks after the burn injury (sub-acute), to assess the use of muscle strength assessment across the timeline of acute wound healing after a burn injury. The assessment immediately after surgery included only the sub-set of participants who required surgical intervention. In the sub-acute phase, data for all participants were included in analyses.

Minimal Detectable Difference

Based on trials two and three on the first assessment day, minimal detectable difference (MDD) was calculated for each muscle group for the initial testing session using the following distribution based formula (Haley & Fragala-Pinkham, 2006):

$$MDD\ (95\%) = t \times SD_{baseline} \times \sqrt{(2(1-rho\_testretest))}$$

Where the t was the t-distribution value for the sample size and $SD_{baseline}$ was represented by the standard deviation for the second muscle test trial. Minimum detectable differences were also calculated, based on trials two and three, for the immediately post-operative and sub-acute phases of injury using the same formula.

V*alidity*

Linear mixed-effects regression was utilized to assess the associations of clinical variables and muscle strength assessments for each muscle group. This was undertaken using trials two and three at initial, post-surgery and sub-acute time points. Random effects components for participants were accounted for in the analyses. The clinical variables assessed were TBSA, pain, assessment session number, type of surgery required, age, sex and burn location. Type of surgery was categorized as no surgery, ReCell® only and split skin grafting (SSG). These categories were used as a quasi-measure of burn depth in analysis due to ambiguities in recordings of burn depth. In practice in Western Australia, a SSG is used to acutely reconstruct burns of greater depth when compared to the use of ReCell® only. Age, TBSA, surgery type and burn location were included in regression analysis as categorical variables. Age and TBSA were categorized to aggregate the small effect size per unit of measure, presenting a more clinically meaningful result compared to when continuous variables were modelled. Age was dichotomized into ≤30 years or >30 years, whilst TBSA was categorized as 5-10%, 11-20%, 21-30% and 31-40% TBSA. Burn location for arm,

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hand and legs were categorized as left, right, bilateral or none. As one subject was reported to have received conservative management, the "no surgery" reference group category was not appropriate to include in the multivariable analyses.. All variables were initially assessed using univariate analysis. Variables which displayed associations with muscle strength, accepted as $\alpha=0.1$, were entered into multivariable analysis. Variables were removed in a manual, backward step-wise manner to determine the final model. For explanatory variables in the final model, the level of statistical significance was accepted at $\alpha=0.05$.

5.4 Results

Thirty-eight patients, with a TBSA range of 6-40%, were recruited in the allocated timeframe to participate in this study. Patients took part in 318 strength assessment sessions made up of 953 individual muscle group assessments. Patients attended assessment sessions until the end of four weeks. Their demographic and descriptive details are outlined in Table 5.2. Missing assessment data can be attributed to participants who ceased attending assessment sessions because of complete wound healing or disengagement with the burns service. Analysis was completed to compare these sub-groups of participants at the sub-acute time point, there was no difference between those who ceased attending session and those who continued assessment. Surgical limitations meant that, on occasion, some muscle groups could not be assessed safely in the assessment session immediately after surgery. The original patients recruited to this project did not have access to leg press in the sub-acute phase due to a lack of specific equipment at the time and explains the available leg press data in the sub-acute analyses.

Unadjusted ICCs are presented, as adjustment for pain intensity did not affect the overall outcomes. Clinically applicable within session reliability was observed for all muscle groups across each time point after burn injury. In the sub-acute phase data, we assessed the effect of excluding patients who required a second surgery during that period of recovery. In doing so, we determined that only five patients required a second surgery. Exclusion of these participants resulted in nil or minimal changes to the ICCs, whilst maintaining clinically applicable to excellent within session

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reliability. Minimal detectable differences are also reported in Table 5.3 for initial, post-operative and sub-acute phase testing.

Validity

In multivariate models, sex, burn location, surgery type and TBSA were associated with muscle strength across all assessed time points. Males demonstrated greater muscle strength. Age was negatively associated with strength in the sub-acute period of recovery only. Arm burns were associated with reduced strength around the elbow joint. The presence of a hand burn was associated with significantly lower shoulder press and grip strength. Leg burns were associated with a reduction of strength in knee extension only after surgery. Burn size as assessed by TBSA was only associated with a decrease in muscle strength after surgery. Results of multivariate analysis are presented in Table 5.4.

5.5 Discussion

This study was undertaken to update a muscle strength testing protocol our group has previously published (Gittings et al., 2016). Updates to the protocol included new muscle group assessment for shoulder press and leg press, as well as utilizing external stabilization during testing. The patient group was extended to include patients with moderate to major burn injury (ie. 5 – 40% TBSA). Thus, we have demonstrated that our updated HHD testing protocol improves on the previous standard method [4] and extends the applicable TBSA range from 0 – 40% TBSA, providing a reliable tool for evaluating within session muscle strength in this patient group. Clinically acceptable reliability was demonstrated for all assessed periods of injury acuity. Intraclass correlations prior to and immediately after surgery exceeded 0.75. In the sub-acute phase of injury, reliability was improved and ICC's for all muscle groups exceeded 0.85. Hand held dynamometry has historically demonstrated issues with reliability related to assessor sex and strength (Stone et al., 2011; Thorborg, Bandholm, Schick, et al., 2013). The use of external stabilization has been shown to ameliorate biases related to this problem and improve testing reliability (Jackson, Cheng, Smith, & Kolber, 2017; Kolber, Beekhuizen, Cheng, & Fiebert, 2007; Thorborg, Bandholm, & Holmich, 2013; Tourville et al., 2013; Valentin & Maribo, 2014). In this study and in practice we confirmed the use of external stabilization to be useful in reducing the

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assessor-patient strength disparity throughout our clinical testing procedures. We would continue to recommend a rehearsal test in clinical practice, as a learning effect after the first of three trials was noted to occur.

The sensitivity of MSD can be interpreted from the calculated MDD's for this group. The MDD's in this group are greater during the initial testing period when compared to our previous work which assessed MDD's on the first testing session (Gittings et al., 2016). Larger MDD's indicate greater variability and suggest that comparison between muscle strength measures, particularly at different time points of the healing continuum, should be made carefully as changes in the assessed muscle strength may be attributed to changes in a number of performance factors other than an appreciable change in strength. We believe the variability present in this group could be related to the greater range of burn severity included in the current study, but may also be attributed to effects of other physical and psychological effects of a burn injury which were not assessed such as anxiety, fatigue and malaise. In the sub-acute phases of injury of recovery, the MDDs are noted to be less, indicating a reduction in variability of host response during the assessment process. Therefore, an observed change during the sub-acute phase of burn injury is more likely to demonstrate a true change in muscle strength. These values allow us, as clinicians, to be able to estimate clinically important changes in muscle strength throughout the rehabilitation journey of patients. The sensitivity of this measurement process however did not appear to be sufficient to determine an effect of surgery and age on muscle strength. In agreement with our results, in an uninjured population with a similar age range to our sample, Lopes et al. (2017) determined there was no effect of age on hand grip strength. Conversely, other literature assessing appendicular muscle strength have determined increasing age to be a factor considered influential in decreasing muscle strength in the general population (Andrews, Thomas, & Bohannon, 1996; Danneskiold-Samsoe et al., 2009; Stoll, Huber, Seifert, Michel, & Stucki, 2000). For lower limb muscles test results in the sub-acute time period, our assessment method identified or confirmed an association with age when dichotomized as greater than, or less than 30 years. The age range of our sample was 18 – 50 years and while no association was evident when assessed as a continuous variable, validity was indicated when broader age categories were compared.

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Construct validity can be confirmed for muscle strength assessment using HHD as the tool is able to detect the effect of sex and burn location over time, as well as an effect of TBSA, surgery type and age in the post-operative and sub-acute phases. Other aspects of validity such as criterion related, discriminatory and predictive validity of HHD in burns remain unknown. On initial assessment, MSD was able to distinguish a difference in muscle strength between males and females, whilst leg press on the right side approached a statistically significant sex difference in strength. Location of burn was associated with a change in muscle strength for left biceps, triceps and shoulder press, as well as grip strength bilaterally. Immediately after surgery, injury factors, specifically TBSA and surgery type showed associations with the assessment of muscle strength using HHD, whilst sex and burn location continued to be associated. We would postulate that the effect of leg burn location on knee extension muscle strength immediately after surgery may be attributable to the addition of a donor site on the thigh. In the sub-acute phase of recovery, surgery type, age ≤ 30 and sex remain associated with muscle strength in this group. In all cases of a sex difference, males were seen to have greater muscle strength than females, consistent with the general population (Danneskiold-Samsoe et al., 2009; Gunther, Burger, Rickert, Crispin, & Schulz, 2008; Schlussel, dos Anjos, de Vasconcellos, & Kac, 2008; Stoll et al., 2000). Whilst location of burn was not influential on the reliability of the testing method, it is a unique challenge to muscle strength testing in this population. We have shown that the burn location can influence the magnitude of muscle strength and this may reflect a limitation of the testing technique, particularly if wound location is in the immediate vicinity of a testing site. Therefore, caution should be taken when making repeated, comparison measures in this situation.

The assessment procedure was able to show that requiring SSG, or greater burn depth, was associated with reduced muscle strength for elbow flexion, shoulder press, knee extension and leg press when compared to ReCell® only in both the immediate post-operative and sub-acute periods. The absence of association in the pre-operative period may suggest that the depth of a burn injury is not influential on muscle strength initially, but becomes a factor to consider in patient management and the provision of rehabilitation, based on the assessment of muscle strength using this method, after surgery has occurred. Using type of surgery as a quasi-measure of burn depth, or volume of tissue damage, was implemented due to ambiguities in the recording of burn

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depth. This may be interpreted as surgery type being the influential factor on muscle strength, however the two variables are not mutually exclusive. We would conclude that the analyses suggest that the HHD and the strength assessment procedures described herein are able to determine differences between the severities of burn injuries, as the HHD was also able to do so between different sizes of burn injury.

An effect of TBSA on muscle strength was only seen immediately after surgery where muscle strength decreased in more severe burns. Generally, more severe burn injuries will require longer and more invasive surgical procedures. The addition of a large donor site wound and the relative increase of TBSA from this, may contribute to the effect on muscle strength that we have seen immediately after surgery. So too may patient fatigue and anxiety of movement in the first assessment and exercise session after surgery. No effect of TBSA was seen during the initial or sub-acute assessments. At initial assessment, the large MDD and apparent lack of sensitivity may contribute to the lack of evidence of an effect of TBSA on muscle strength. In the sub-acute period, the low MDD's would suggest that burn injured patients are more stable and their physical assessments less influenced by the factors observed prior to and after surgical intervention. Thus, a change in muscle strength, as measured by our method, is more likely to be an accurate reflection of the underlying and true change in the sub-acute period. Analysis using TBSA may be limited by using a single value for TBSA which is recorded at the time of injury and maintained as an unchanged data point throughout the wound healing process. It may be more accurate to, in future, consider ongoing re-evaluation of unhealed TBSA and anatomical location to enhance the understanding of unhealed wounds on muscle strength and functional outcomes.

Location of the burn injury was associated with poorer muscle strength in a number of muscle groups. For interpretation of these results, it must be noted that the majority of participants presented with bilateral arm and/or leg injuries. For example, only one out of thirty patients with leg burns presented with a left sided injury, whilst 27 had a bilateral leg burn injuries and of 31 patients with arm burns, 20 were bilateral injuries. The association of burn location with muscle strength we observed and purport to primarily be influenced by the positioning for testing. The dynamometer may require to be positioned on the skin in close proximity to, or over, a wound particularly during elbow and knee testing, which could influence performance of the test. Hand burns

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were associated with decreased shoulder press and grip strength, which is not surprising as both require the dynamometer to interface with the hand. A burn in this location can lead to physical positioning difficulties and discomfort, affecting the testing process. Over time, as wound healing occurs, the location of burn should have less of an effect on testing and force generation. This is evident in the loss of association with muscle strength in the sub-acute recovery period.

Pain intensity at rest prior to testing did not affect the reliability of results at any of the time points analyzed. Nor was it associated with the magnitude of muscle strength. We did not ask the patient about their pain during the testing process and the results from that from of assessment might return different results to the ones seen here. Self-reported pain intensity is best conceptualized as the individual's assessment of threat to bodily tissue (Moseley, 2007). This is likely to include factors such the person's appraisal of the state of peripheral tissue health and beliefs about the current robustness and capacity of the body. Pain however, should not be considered an exclusion for participation in strength assessment and exercise programs. Our facility's clinical practice is to provide a prescription of adequate pain relief regularly throughout the day as a priority to allow full participation in rehabilitation which begins from the day of hospital admission. We believe that having a quick and simple measure of a person's perceived maximal capacity at any particular time point is imperative for the safe prescription and monitoring of strength training across the whole rehabilitative journey and the results reported here support the reliability of this form of testing in both the acute and sub-acute phases of rehabilitation.

Conclusion

Muscle and grip strength dynamometry are reliable clinical assessment tools for evaluating within session muscle strength in burns. This tool can be used in burns up to 40% TBSA, during the first 4 weeks of recovery from a burn injury. Provision of a practice test for patients prior to official recording should occur in clinical application. Additionally, we encourage a system of external stabilization to be implemented during testing to eliminate reliability issues related to patient and assessor strength.

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5.7 Tables

Table 5.1 Updated positioning for hand held dynamometry assessment.

Elbow Flexion

- **Posture:** Patient sitting, elbow flexed to 90 degrees, forearm in supination.
- **Position of dynamometer:** Distal radial-ulnar joint palmar side (~1 cm proximal to wrist).

Elbow Extension

- **Posture:** Patient sitting, elbow flexed to 90 degrees, forearm in pronation.
- **Position of dynamometer:** Distal radial-ulnar joint palmar side (~1 cm proximal to wrist).

Shoulder Abduction

- **Posture:** Patient sitting, shoulder abducted to 90 degrees, elbow flexed to 90 degrees.
- **Position of dynamometer:** Immediately proximal to lateral epicondyle of elbow.

Shoulder Press

- **Posture:** Patient sitting, shoulder abduction 90 degrees and full shoulder external rotation. Elbow flexion 90 degrees. Full Wrist extension.
- **Position of dynamometer:** Over thenar/ hypothenar eminence.

Knee Extension

- **Posture:** Patient sitting, knee in 90 degrees flexion.
- **Position of dynamometer:** Distal anterior tibia immediately proximal to talo-crural joint.

Leg Press

- **Posture:** Patient sitting, hip & knee flexion to achieve knee 90deg flexion.
- **Position of dynamometer:** Between sole of foot and foot plate.

Grip Strength

- **Posture:** Patient sitting. Shoulder in adduction, elbow flexion to 90 degrees, forearm & wrist in neutral position.
- **Position of dynamometer:** Patient holding grip strength dynamometer.

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Table 5.2 Descriptive Statistics of Sample n=38

	N (%) or Median (IQR)
Sex male	33 (74%)
Age	30 (23 – 39) *
TBSA	14 (9 – 20) *
- 5-10% TBSA	13 (34%)
- 11-20% TBSA	17 (45%)
- 21-30% TBSA	5 (13%)
- 31-40% TBSA	3 (8%)
Surgery	37 (97%)
- No Surgery	1 (3%)
- ReCell ® Only	10 (26%)
- Split Skin Graft	27 (71%)
Arm Burn	28 (74%)
Hand Burn	25 (66%)
Leg Burn	30 (79%)
Foot Burn	8 (21%)

* data presented as Median (IQR)

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Table 5.3 Intraclass Correlations (ICC) plus Minimal Detectable Difference (MDD) for all muscle groups at initial, after surgery & sub-acute time points. No adjustment for any covariates.

	Left				Right			
	N	**ICC**	**95% CI**	**MDD (kg)**	**N**	**ICC**	**95%CI**	**MDD (kg)**
Initial								
Elbow Flexion	36	0.912	(0.839, 0.954)	7.65	37	0.834	(0.711, 0.911)	9.82
Elbow Extension	37	0.918	(0.851, 0.956)	5.16	37	0.850	(0.737, 0.920)	6.32
Shoulder Abduction	37	0.926	(0.864, 0.961)	5.15	37	0.858	(0.749, 0.924)	6.59
Shoulder Press	37	0.878	(0.780, 0.935)	7.43	37	0.778	(0.623, 0.880)	8.22
Knee Extension	35	0.870	(0.767, 0.932)	11.0	34	0.837	(0.711, 0.915)	12.3
Leg Press	37	0.919	(0.852, 0.957)	19.6	36	0.853	(0.735, 0.924)	25.6
Grip	36	0.962	(0.928, 0.980)	8.37	36	0.963	(0.931, 0.980)	8.15
After Surgery								
Elbow Flexion	36	0.968	(0.939, 0.983)	5.33	37	0.928	(0.868, 0.962)	6.57
Elbow Extension	33	0.893	(0.802, 0.945)	5.51	33	0.905	(0.824, 0.952)	4.66
Shoulder Abduction	37	0.915	(0.845, 0.955)	4.62	37	0.871	(0.772, 0.931)	6.33
Shoulder Press	36	0.957	(0.920, 0.978)	4.53	36	0.856	(0.742, 0.924)	6.79
Knee Extension	33	0.885	(0.788, 0.941)	11.2	34	0.829	(0.694, 0.912)	14.9
Leg Press	32	0.912	(0.833, 0.955)	21.5	32	0.842	(0.714, 0.919)	23.7
Grip	35	0.966	(0.935, 0.982)	8.88	35	0.956	(0.916, 0.977)	10.3
Sub-Acute								
Elbow Flexion	30	0.930	(0.864, 0.966)	6.96	30	0.957	(0.915, 0.979)	5.08
Elbow Extension	30	0.884	(0.781, 0.942)	4.85	30	0.898	(0.806, 0.949)	4.81
Shoulder Abduction	30	0.906	(0.819, 0.953)	4.18	30	0.869	(0.754, 0.935)	4.57
Shoulder Press	30	0.910	(0.827, 0.955)	5.99	30	0.873	(0.762, 0.937)	6.37
Knee Extension	30	0.892	(0.795, 0.947)	11.5	30	0.884	(0.778, 0.943)	11.8
Leg Press	26	0.925	(0.847, 0.965)	15.8	26	0.928	(0.854, 0.966)	16.9
Grip	29	0.912	(0.828, 0.957)	7.98	29	0.970	(0.939, 0.985)	5.97

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Table 5.4 Final multivariable linear mixed model of muscle strength assessment

INITIAL	**LEFT**		**RIGHT**	
	Variable	**Coeff. (95% CI) p-value**	**Variable**	**Coeff. (95% CI) p-value**
Elbow Flexion	Sex female	-10.5 (-18.0, -3.00) 0.006	Sex female	-7.30 (-14.2, -0.375) 0.039
	Arm Burn Left [a]	-13.1 (-21.8, -4.45) 0.003	Constant	26.5 (24.0, 29.1) <0.001
	Arm Burn Right [a]	1.43 (-6.19, 9.05) 0.712		
	Arm Burn Bilateral [a]	-6.92 (-13.8, -0.026) 0.049		
	Constant	31.1 (24.9, 37.1) <0.001		
Elbow Extension	Sex female	-8.86 (-13.8, -3.87) <0.001	Sex female	-7.49 (-12.1, -2.92) 0.001
	Arm Burn Left [a]	-8.58 (-14.3, -2.81) 0.004	Constant	18.6 (16.9, 20.2) <0.001
	Arm Burn Right [a]	0.827 (-4.23, 5.89) 0.749		
	Arm Burn Bilateral [a]	-2.85 (-7.40, 1.70) 0.219		
	Constant	20.2 (16.2, 24.3) <0.001		
Shoulder Abduction	Sex female	-9.12 (-14.3, -3.96) 0.001	Sex female	-8.03 (-12.7, -3.38) 0.001
	Constant	18.6 (16.7, 20.5) <0.001	Constant	19.0 (17.3, 20.7) <0.001
Shoulder Press	Sex female	-11.5 (-16.9, -6.12) <0.001	Sex female	-5.31 (-10.3, -0.303) 0.038
	Hand Burn Left [b]	-10.2 (-15.1, -5.31) <0.001	Constant	19.5 (17.6, 21.3) <0.001
	Hand Burn Right [b]	-7.28 (-12.1, -2.49) 0.003		
	Hand Burn Bilateral [b]	-8.05 (-12.8, -3.25) 0.001		
	Constant	24.9 (21.5, 28.3) <0.001		
Knee Extension	Sex female	-16.1 (-24.7, -7.40) <0.001	Sex female	-15.8 (-25.8, -5.86) 0.002
	Constant	32.0 (29.0, 34.9) <0.001	Constant	32.5 (29.1, 35.9) <0.001

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Leg Press	Sex female	-22.0 (-42.0, -1.96) 0.031	No association	
	Constant	83.2 (75.8, 90.6) <0.001		
Grip	Sex female	-27.3 (-39.0, -15.5) <0.001	Sex female	-23.3 (-35.0, -11.6) <0.001
	Hand Burn Left [b]	-29.1 (-39.5, -18.8) <0.001	Hand Burn Left [b]	-16.6 (-26.9, -6.34) 0.002
	Hand Burn Right [b]	-17.0 (-26.3, -7.74) <0.001	Hand Burn Right [b]	-27.7 (-37.0, -18.5) <0.001
	Hand Burn Bilateral [b]	-22.9 (-32.2, -13.6) <0.001	Hand Burn Bilateral [b]	-20.1 (-29.4, -10.8) <0.001
	Constant	52.4 (45.6, 59.1) <0.001	Constant	53.8 (47.1, 60.6) <0.001
POST-OPERATIVE	**LEFT**		**RIGHT**	
Elbow Flexion	Arm Burn Left [a]	-13.4 (-23.9, -2.90) 0.012	Surgery SSG[f]	-8.91 (-14.7, -3.14) 0.002
	Arm Burn Right [a]	5.80 (-3.24, 14.8) 0.208	Constant	26.1 (21.1, 31.1) <0.001
	Arm Burn Bilateral [a]	-5.32 (-13.0, 2.34) 0.17323.0 (16.4,		
	Constant	29.6) <0.001		
Elbow Extension	Sex female	-6.18 (-11.8, -0.610) 0.030	Sex female	-7.23 (-11.6, -2.89) 0.001
	Constant	16.1 (14.1, 18.1) <0.001	TBSA 11-20 [d]	-0.749 (-2.41, 3.91) 0.642
			TBSA 21-30 [d]	1.98 (-3.25, 7.23) 0.458
			TBSA 31-40 [d]	-6.86 (-12.1, -1.62) 0.010
			Constant	17.6 (15.1, 20.1) <0.001
Shoulder Abduction	Sex female	-5.76 (-11.0, -0.470) 0.033	Sex female	-7.21 (-12.0, -2.34) 0.003
	Constant	15.8 (13.8, 17.8) <0.001	TBSA 11-20 [d]	-4.13 (-7.92, -0.348) 0.032
			TBSA 21-30 [d]	-5.53 (-10.9, -0.183) 0.043
			TBSA 31-40 [d]	-11.3 (-17.8, -4.90) 0.001
			Constant	21.1 (18.0, 24.2) <0.001
Shoulder Press	Sex female	-6.80 (-13.4, -0.164) 0.045	Sex female	-6.13 (-10.8, -1.43) 0.011

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	Constant	16.8 (14.3, 19.3) <0.001	Surgery SSG[f]	-4.62 (-8.39, -0.853) 0.016
			Constant	21.5 (18.2, 24.9) <0.001
Knee Extension	Sex female	-10.2 (-19.7, -0.738) 0.035	Leg Burn Left [c]	-13.7 (-32.7, 5.28) 0.157
	Leg Burn Left [c]	-19.6 (-37.8, -1.46) 0.034	Leg Burn Right [c]	-7.87 (-22.1, 6.34) 0.277
	Leg Burn Right [c]	-2.22 (-15.8, 11.3) 0.748	Leg Burn Bilateral [c]	-12.3 (-19.7, -4.94) 0.001
	Leg Burn Bilateral [c]	-12.0 (-19.2, -4.69) 0.001	Surgery SSG[f]	-7.83 (-15.2, -0.469) 0.037
	Constant	35.7 (29.7, 41.8) <0.001	Constant	39.4 (31.1, 47.8) <0.001
Leg Press	No associations		Sex female	-24.7 (-44.3, -5.06) 0.014
			TBSA 11-20 [d]	-1.65 (-16.6, 13.3) 0.828
			TBSA 21-30 [d]	-14.5 (-36.9, 7.92) 0.205
			TBSA 31-40 [d]	-55.5 (-93.9, -17.1) 0.005
			Surgery SSG[f]	-20.6 (-37.0, -4.30) 0.013
			Constant	96.1 (81.0, 111.2) <0.001
Grip	Hand Burn Left [b]	-26.0 (-38.6, -13.5) <0.001	Hand Burn Left [b]	-11.5 (-22.8, -0.330) 0.044
	Hand Burn Right [b]	-4.49 (-15.5, 6.56) 0.426	Hand Burn Right [b]	-25.5 (-35.7, -15.2) <0.001
	Hand Burn Bilateral [b]	-18.9 (-30.8, -6.94) 0.002	Hand Burn Bilateral [b]	-21.0 (-31.7, -10.4) <0.001
	Constant	41.2 (34.0, 48.4) <0.001	Constant	44.5 (38.1, 51.0) <0.001
SUB-ACUTE	**LEFT**		**RIGHT**	
Elbow Flexion	Sex female	-12.7 (-19.6, -5.82) <0.001	Sex female	-11.3 (-17.6, -4.85) 0.001
	Surgery SSG[f]	-9.64 (-14.9, -4.30) <0.001	Surgery SSG[f]	-10.4 (-15.3, -5.48) <0.001
	Constant	33.1 (28.3, 37.9) <0.001	Constant	33.7 (29.3, 38.1) <0.001
Elbow Extension	Sex female	-8.40 (-12.4, -4.39) <0.001	Sex female	-8.14 (-12.4, -3.88) <0.001
	Constant	20.3 (18.6, 21.8) <0.001	Constant	20.0 (18.5, 21.6) <0.001

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Shoulder Abduction	Sex female	-8.52 (-12.5, -4.51) <0.001	Sex female	-7.80 (-11.4, -4.16) <0.001
	Constant	18.5 (17.1, 20.0) <0.001	Constant	18.8 (17.5, 20.1) <0.001
Shoulder Press	Sex female	-10.0 (-16.1, -3.93) 0.001	Sex female	-7.82 (-12.8, -2.86) 0.002
	Surgery SSG[f]	-6.77 (-11.4, -2.15) 0.004	Age ≤ 30 [e]	-3.63 (-7.01, -0.253) 0.035
	Constant	25.3 (21.2, 29.5) <0.001	Constant	23.6 (21.1, 26.0) <0.001
Knee Extension	Surgery SSG[f]	-11.3 (-19.0, -3.59) 0.004	Age ≤ 30 [e]	-10.1 (-17.8, -2.33) 0.011
	Constant	38.4 (31.9, 45.0) <0.001	Constant	37.2 (31.6, 42.9) <0.001
Leg Press	Age ≤ 30 [e]	-16.9 (-30.3, -3.24) 0.015	Sex female	-35.4 (-57.0, -13.8) 0.001
	Constant	81.1 (71.4, 90.9) <0.001	Surgery SSG[f]	-29.8 (-44.9, -14.8) <0.001
			Constant	100.7 (87.6, 113.8) <0.001
Grip	Sex female	-15.5 (-24.5, -6.54) 0.001	No associations	
	Constant	40.2 (37.3, 43.1) <0.001		

[a] Reference group = no arm burn

[b] Reference group = no hand burn

[c] Reference group = no leg burn

[d] Reference group = TBSA 5-10%

[e] Reference group = age >30 years

[f] Reference group = ReCell Only surgical intervention

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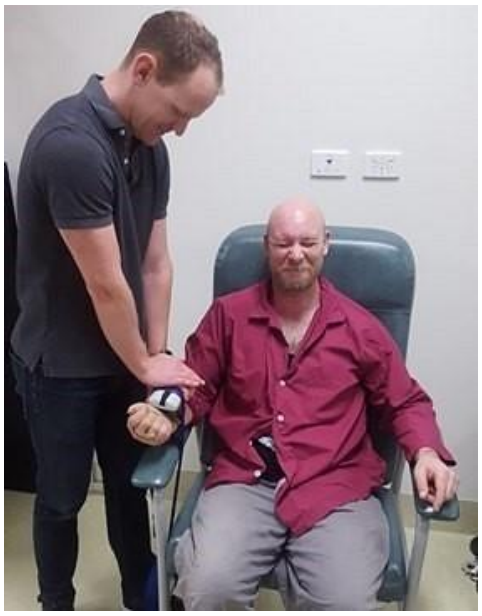
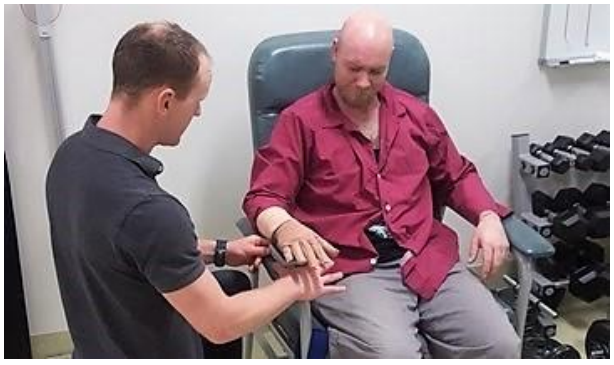
5.8 Figures

Figures 5.1 Positioning for Hand Held Dynamometry, including description of external stabilisation for elbow flexion (a), elbow extension (b), shoulder abduction (c), shoulder press (d), knee extension (e), leg press (f) and grip (g)



a) Traction belt over top of dynamometer, attached to anchor point below chair.



b) Stabilisation provided by arm rest of chair

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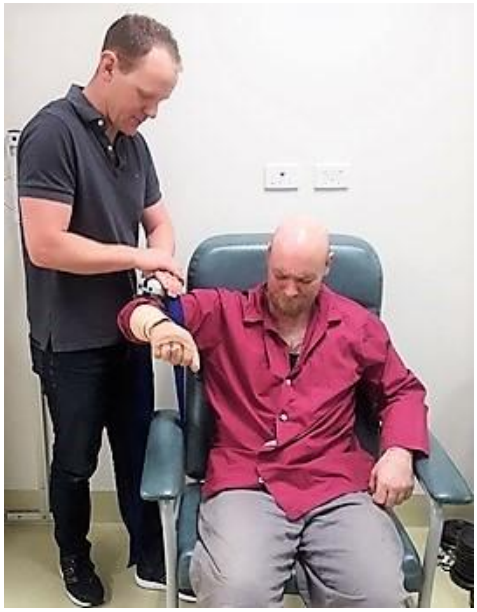
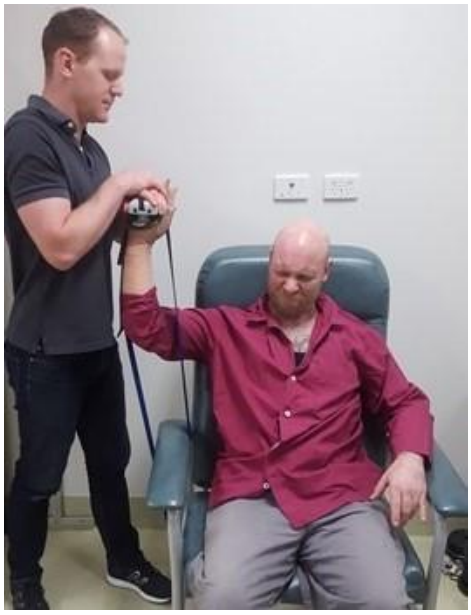


c) Traction belt over top of dynamometer, attached to anchor point below chair.



d) Traction belt over top of dynamometer, attached to anchor point below chair.

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e) Traction belt over top of dynamometer, attached to anchor point on chair.

f) Stabilisation from foot plate of leg press machine.

g) Assessor supporting dynamometer to ensure consistent elbow position.

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Chapter 6 The efficacy of resistance training in addition to usual care for adults with acute burn injury: A randomised controlled trial.

Preface

As highlighted in Chapter 2, commencing exercise, in particular resistance training during the acute phase of a burn injury has not previously been investigated. This is a randomised, controlled trial in which we examine the impact of undertaking resistance training within 72 hours of a burn injury. The effects of resistance training on quality of life, physical disability, muscle strength, body composition and inflammation are presented. We utilise assessment procedures validated in Chapters Three, Four and Five of this thesis. This paper also comments on the feasibility and safety of this exercise regimen, in this group of patients.

The presented chapter is a manuscript which has been developed and formatted for submission and has been accepted for publication in the journal *Burns* as:

Gittings, P.M., Wand, B.M., Hince, D.A., Grisbrook, T.L., Wood, F.M., & Edgar, D.W. The efficacy of resistance training in addition to usual care for adults with acute burn injury: A randomised controlled trial.

The author's version of the manuscript is presented with modifications to suit the style and format of this thesis.

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The efficacy of resistance training in addition to usual care for adults with acute burn injury: A randomised controlled trial

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6.1 Abstract

Resistance training immediately after a burn injury has not been investigated previously. This randomised, controlled trial assessed the impact of resistance training on quality of life plus a number of physical, functional and safety outcomes in adults with a burn injury.

Patients were randomly assigned to receive, in addition to standard physiotherapy, four weeks of high intensity resistance training (RTG) or sham resistance training (CG) three days per week, commenced within 72 hours of the burn injury. Outcome data was collected at six weeks, three and six months after burn injury. Quality of life at 6 months was the primary endpoint. Data analysis was an available cases analysis with no data imputed. Regression analyses were used for all longitudinal outcome data and between-group comparisons were used for descriptive analyses.

Forty-eight patients were randomised resistance training (RTG) (n=23) or control group (CG) (n=25). The RTG demonstrated improved outcomes for the functional domain of the Burn Specific Health Scale-Brief ($p=0.017$) and the Quick Disability of Arm Shoulder and Hand ($p<0.001$). Between group differences were seen for C-reactive protein and retinol binding protein ($p=0.001$). Total quality of life scores, lower limb disability, muscle strength and volume were not seen to be different between groups ($p>0.05$).

Resistance training in addition to usual rehabilitation therapy showed evidence of improving functional outcomes, particularly in upper limb burn injuries. Additionally, resistance training commenced acutely after a burn injury was not seen to be harmful to patients.

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6.2 Introduction

Despite the ongoing improvements in burn care, physical impairment and diminished quality of life (QoL) continue to be significant burdens after burn injury. A known and expected outcome for patients after a burn injury is a protracted deficit of skeletal muscle strength which has been demonstrated in both adults (Bjornhagen, Schuldt Ekholm, Larsen, & Ekholm, 2018; Ebid, Omar, & Abd El Baky, 2012; Omar, Abd El Baky, & Ebid, 2017; St-Pierre, Choiniere, Forget, & Garrel, 1998) and children (Alloju, Herndon, McEntire, & Suman, 2008; Cambiaso-Daniel et al., 2018; Ebid, El-Shamy, & Draz, 2014). St-Pierre et al. (1998) found muscle strength to be significantly reduced in adult patients on average three years after injury when compared to matched, unburned control participants. Similarly, paediatric studies have reported long term skeletal muscle impairment in burn injured children up to four years after injury when compared to non-burned individuals (Alloju et al., 2008; Cambiaso-Daniel et al., 2018; Ebid et al., 2014). It is considered that muscle mass reduction related to the catabolic response to a major burn injury (Hart et al., 2000; Jeschke et al., 2011) is a primary cause of reduced force generating capacity of muscle after an injury. Reduction of muscle mass and strength is exacerbated by the deleterious effects of bed rest or unloading (Gao, Arfat, Wang, & Goswami, 2018) imposed upon patients after a burn injury, highlighting the importance of movement and physical rehabilitation.

Skeletal muscle is necessary for movement and locomotion and an association between muscle strength and functional ability has been documented in populations including healthy older adults (Bouchard, Heroux, & Janssen, 2011; Samuel, Rowe, Hood, & Nicol, 2012), and in clinical groups with osteoarthritis (Hall et al., 2017; Judd, Thomas, Dayton, & Stevens-Lapsley, 2014). Additionally, it is possible that an ongoing reduction in strength and movement in burns patients may play a role in scar contracture formation over time. With these outcomes in mind, loss of skeletal muscle strength after a burn injury will contribute to post-burn disability. Previously, self-reported physical function has been demonstrated to be below baseline levels for up to three years after burn injury (Jarrett, McMahon, & Stiller, 2008; Kildal, Andersson, & Gerdin, 2002; Klein et al., 2011; Wasiak, Paul, et al., 2014) and further, was noted to be a key factor in the ability of people to return to work after a

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burn injury (Esselman et al., 2007). Grisbrook et al. (2012 & 2013) concluded that self-reported function was significantly impaired in a burn injured group when compared to matched controls on average six years after their burn injury. In addition, QoL has been shown to be reduced in both the short-term and long-term after a burn injury (Grisbrook et al., 2012; Koljonen, Laitila, Sintonen, & Roine, 2013; Moi, Haugsmyr, & Heisterkamp, 2016; Spronk et al., 2018; Spronk et al., 2019). Functional deficits after a burn has been a concept usually reserved for major burn injuries. However, minor severity burn injuries have been demonstrated to have a sustained negative impact on physical function (Shakespeare, 1998) and QoL (Finlay et al., 2014; Spronk et al., 2019; Wasiak, Lee, et al., 2014), suggesting that all severities of burn injury may necessitate rehabilitation in an attempt to ameliorate ongoing impairments and disability.

When prescribed with an appropriate training load, it has been established that resistance training (RT) is an effective method of increasing skeletal muscle mass and muscle strength (Garber et al., 2011). As such, it forms part of the recommended exercise guidelines of national bodies and health groups to improve general health, prevent disease and optimise health in clinical populations (Garber et al., 2011; Hordern et al., 2012; Pollock et al., 2000; Smart et al., 2013). Regarding the utilisation of RT after a burn injury, our recent systematic review and meta-analysis suggested that RT may have some positive effect on muscle strength, yet there is a lack of available data for patient reported outcome measures assessing function and QoL (Gittings et al., 2017). It was also established that the current evidence base for RT after burn injury is of low to very low quality and that future longitudinal research should employ robust methodologies to improve the overall quality of data available on this matter (Flores, Tyack, Stockton, Ware, & Paratz, 2018; Gittings et al., 2017). Previous research has not investigated RT in the acute care setting and has only evaluated exercise programmes of at least six weeks in duration which may not be a practicable length of time within an acute care setting. Furthermore, research has been limited to major burn injuries only, meaning that the unique effect of RT across the whole spectrum of burn injury severity remains unknown (Disseldorp, Nieuwenhuis, Van Baar, & Mouton, 2011; Nedelec et al., 2015).

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Thus, there is a need to conduct high quality randomised trials which investigate the optimal prescription and mode of exercise training, as well as the effect of implementing training within the acute care setting (Gittings et al., 2017; Nedelec et al., 2015; Porter, Hardee, Herndon, & Suman, 2015). There are unique challenges for a burn injured patient which make the acute period a difficult time in which to calculate training load and complete exercise. In addition, there is a potential for competing physiological demands such as the breakdown of skeletal muscle as an additional energy source and the desired hypertrophic response of that muscle to exercise and RT. As such, no study to date has assessed the effect of RT prescription during the acute injury phase, and none have included physiological measures of body composition at this critical time.

To address the uncertainties in the literature, we designed a randomised controlled trial to test a unique RT programme for use in acute burn injury rehabilitation. The primary aim of this study were to examine whether participation in early RT improves QoL. Secondary aims examined self-report physical disability, muscle strength and body composition after burn injury. Patient length of stay, as well as the safety and feasibility of a progressive, high load RT program in patients with acute burn injury was also examined.

6.3 Methods

Trial Design

This study is a parallel, randomised, controlled intervention trial. Ethics approval was granted from University of Notre Dame Australia HREC (014138F) and Royal Perth Hospital HREC (2014-008). It was registered on the Australian and New Zealand Clinical Trial Registry (ACTRN12614001156673). The registered trial describes a study that planned to randomise 60 participants. This sample size was derived from a sample size calculation utilising the primary outcome of quality of life. This study has been closed prior to completion of the recruitment target due to a slower than anticipated recruitment rate and exhaustion of funding. This report represents an analysis of the data available at the time of trial closure.

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Participants

Participants who met inclusion criteria were recruited by the primary investigator upon admission to the adult burns unit between August 2014 and December 2017. Participants were deemed eligible if they were over 18 years of age, had a burn injury of 5% – 40% TBSA, were able to provide consent and able to commence exercise training within 72 hours of the burn injury. If patients were initially admitted to the intensive care unit, they were allowed to participate in the study if they were transferred to the burns unit and could commence training within one week of injury. Patients were excluded if they were admitted later than 72 hours after their injury, had surgery prior to recruitment, sustained an electrical burn injury, palmar hand burn injury, associated injuries or emergency surgery affecting participation in exercise training, including fracture, amputation, acquired brain injury or peripheral neural injury or any pre-existing medical condition which may affect exercise participation.

After providing consent to participate within 72 hours of injury, subjects were assigned into the control group (CG), or the RT group (RTG). Allocation to treatment group was via a concealed randomisation process. Randomisation tokens stating allocation to the CG or RTG were placed into sealed, opaque envelopes with an equal allocation ratio. After entry into the study an independent staff member drew an envelope to allocate participants to a treatment group. Upon allocation, assessment and exercise training for the study commenced immediately in a supervised rehabilitation gym on the burns unit. Those allocated to the CG undertook usual physiotherapy rehabilitation plus sham RT whereas those in the RTG group undertook usual physiotherapy rehabilitation plus progressive RT. Participation in the study exercise programme was for four weeks after enrolment for both groups. Outcome assessment was planned to occur at multidisciplinary review clinics at six weeks, three months and six months after the burn injury.

Control Intervention

Standard physiotherapy for all participants in this study consisted of respiratory care, extensive mobilisation from the day of injury and all exercise other than RT including stretching, active range of movement, balance and postural exercises, as well as the use of the treadmill, stationary bike and upper limb cycle ergometer.

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Assessment of maximum voluntary isometric contraction (MVIC), as described in the outcome measurement section, was completed for elbow flexion, elbow extension, shoulder abduction, shoulder press, knee extension, leg press and grip strength for three trials on both left and right sides using a hand held Lafayette Muscle Meter no. 01165 (SI Instruments, SA, Australia). The assessment methodology has been described in detail in a prior publication (Gittings, Hince, Wand, Wood, & Edgar, 2018). After testing, sham RT was implemented for the CG, in place of standard physiotherapy, three days per week for four weeks from enrolment. These sessions included bilateral bicep curls, lateral deltoid fly, overhead shoulder press, knee extensions and leg press. Three sets of 10 repetitions of each exercise were completed using 1kg dumb-bells or with minimum resistance set on a cable weighted multi-gym (BodyCraft Xpress Pro, BodyCraft, Ohio). Sham RT sessions were completed under supervision of a physiotherapist or exercise physiologist and in isolation from other burns patients in order to maintain blinding. A verbal pain score using a scale of 0 (no pain) to 10 (most extreme pain) was asked prior to commencing each session to determine baseline pain intensity and 10 minutes after the completion of each session to determine highest pain intensity experienced during training. Patients were asked to inform the supervising therapist if pain exceeded 7/10 during the exercise session and if they wished to cease the session.

Experimental Intervention

Participants in the RTG group also received standard physiotherapy. In addition, a RT programme was undertaken three times per week, utilising continual reassessment of muscle strength to prescribe intensity. The RT sessions were completed in place of standard physiotherapy for that day's treatment. This was continued for a four-week period after enrolment. All intervention sessions related to this study were completed in the burn unit gymnasium in isolation from other rehabilitating patients to maintain participant blinding to group allocation. Exercise sessions were completed with the supervision of a qualified Physiotherapist or Exercise Physiologist. At each session, MVIC was measured in kilograms of force for muscles previously described for the control group. This was followed by a RT session of bilateral bicep curls, lateral deltoid fly, overhead shoulder press, knee extensions and leg press using both free weights and a cable weighted multi-gym.

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The intensity of RT exercise was prescribed at 70% of MVIC for that day, thereby titrating the training load to reflect current capacity. The prescription of RT utilised in this study was informed by strength training recommendations from the American College of Sports Medicine Position Stand (Garber et al., 2011) . This study adapted the definition of high intensity RT for novice exercisers as 70% of one-repetition maximum and volume was prescribed at three sets of 8-12 repetitions for each exercise. A verbal pain intensity score was collected and utilised as described in the *control intervention* section above. Gym-based exercise was stopped for two days for all patients after surgical intervention to repair the burn wounds, as per our burn service protocols.

Outcome Measurement

Comprehensive assessments of QoL, self-report physical disability, muscle strength, body composition and adverse events were completed at clinic reviews planned for six weeks, three months and six months after the occurrence of the burn injury.

Primary Outcome

The primary outcome for this study was patient reported QoL, as assessed by the Burn Specific Health Scale-Brief (BSHS-B) at six months after burn injury. The BSHS-B is a 40-item burn specific assessment of QoL validated for use in both minor and severe burn injuries (Finlay et al., 2014; Kildal, Andersson, Fugl-Meyer, Lannerstam, & Gerdin, 2001; Willebrand & Kildal, 2008). The BSHS-B assesses QoL across nine separate domains as well as providing a total score (Kildal et al., 2001). Subsequent work has shown that the nine BSHS-B domains can be further simplified into three main domains; "*Function", "Affect and Relations"* and *"Skin Involvement",* plus the subscale of *"Work"* (Willebrand & Kildal, 2008). In all cases, a higher score indicates greater QoL. The total score and function domain scores were used for longitudinal analysis in this study. Outcome assessor blinding was achieved for the primary outcome measure as participants were blinded to their group allocation throughout the six-month enrolment period and act as their own assessor in self-report surveys.

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Secondary Outcomes

Self-reported disability

Physical disability was assessed using patient-reported surveys. The Quick Disability of Arm, Shoulder and Hand (Quick-DASH) was utilised for participants with burns to the upper limbs and the Lower Limb Functional Index-10 (LLFI-10) for those with burns on the lower limb. These surveys have previously been found to be reliable and valid for use with patients recovering from a burn injury (Gittings et al., 2016; Wu, Edgar, & Wood, 2007). For both surveys, a low score indicates less disability. Outcome assessor blinding was achieved as participants were blinded to their group allocation and acted as their own assessor when completing these surveys.

Muscle Strength

Muscle strength was measured as an MVIC in kilograms of force by belt stabilised, hand held dynamometry using a previously validated assessment protocol (Gittings et al., 2016; Gittings et al., 2018). Pre-selected key muscle groups for upper and lower limbs were biceps, quadriceps and grip strength. These were used for ongoing outcome assessment of muscle strength after the intervention period. To minimise confounding from learning effects, the first effort was discarded and only data from the second and third attempt combined for analysis (Gittings et al., 2018). Using data from the second and third assessments of MVIC, a mean strength value was generated for combined left and right sided elbow flexion, knee extension and grip strength. These were also combined to create a total single strength measure for each assessment time point. This outcome was assessed by a researcher who was not blinded to group allocation.

Body Composition

A series of estimates of body composition using bioimpedance spectrospcopy (BIS) were also evaluated. Patients were asked to lie supine and electrodes were place on one upper limb and the ipsilateral lower limb as per manufacturer's instructions for a tetra-polar arrangement of electrodes. Whole body BIS measures were taken using the SFB7 (Impedimed ®, Queensland, Australia) in triplicate with one second intervals between measurements. Assessment of BIS was undertaken by non-blinded research personnel. Bioimpedance spectroscopy measures the impedance to an

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electric current through the body at various frequencies to calculate the fat mass, fat free mass, intracellular water and extracellular water components of body composition. Resistance (R) is the impedance to flow of the electrical current from the intra- and extracellular water (Kyle et al., 2004). At zero frequency, BIS measures only the extracellular water component (Ro). At high frequency, BIS measures both intra- and extracellular water components (Rinf) (Kyle et al., 2004). These values are used to determine the intracellular resistance (Ri) using the equation:

$$(Ri = Rinf - Ro)$$

Intracellular water volume is represented by Ri and is used in this study as an estimate of muscle cell volume. Low Ri values are representative of higher intracellular volume and for this study is an estimate of greater muscle cell volume. Bioimpedance spectroscopy has been demonstrated to be reliable and valid for measuring compartment volumes in acute burn injury. (Kenworthy et al., 2017; Kenworthy et al., 2018)

Length of Stay

All participants entered into the study were inpatients. The impact of RT on length of stay was calculated by a blinded assessor as the number of days each patient was resident in the burns unit for inpatient management.

Feasibility

Resistance training in this study population has many inherent challenges due to the acuity of the burn injury. The feasibility of undertaking RT in an acutely burn injured population was assessed through an examination of the number of complete and incomplete exercise sessions and for each group.

Adverse Events & Blood Markers of Inflammation and Protein Turnover

Patient reported pain intensity in excess of pre-defined limits for ceasing exercise (a rating of greater than 7/10) and the requirement for more than one surgical procedure were considered adverse events for this study.

C-reactive protein (CRP) was included as a marker of systemic inflammation. A high concentration of CRP is indicative of inflammation (Clyne & Olshaker, 1999).

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Retinol binding protein (RBP) was included in this study as an indication of nutritional status and protein turnover. It is a high turnover visceral protein which has been noted to be at low concentration during a state of protein depletion and higher concentrations after nutritional correction (Carpentier, Barthel, & Bruyns, 1982). The concentration of RBP is expected to decline immediately after trauma reaching a maximal decrease in up to nine days after injury. It is then expected to increase in concentration with recovery (Cynober et al., 1985; Zabetian-Targhi, Mahmoudi, Rezaei, & Mahmoudi, 2015). In this study, these markers were included to monitor for adverse events related to progression of the inflammatory response, muscle protein catabolism or nutritional impairment which may be related to the intervention. Blood samples were collected from a subset of 31 participants by venepuncture at admission, weekly during the training period, as well as six weeks, three months and six months after enrolment. The number of participants providing blood samples was limited by funding to undertake the analyses of samples. After centrifugation of the sample, CRP was analysed immediately and serum aliquots were stored at -80^{o}C for batch analysis of RBP by ELISA immunoassay (R&D Systems Inc., Minneapolis, USA).

Sample Size

A sample size calculation was undertaken using the BSHS-B total score. To achieve 90% power to detect a difference of 10.0 with a standard deviation of 16.0 (based on a past WA burn cohort, unpublished data) in the BSHS-B total score with a significance level of 0.05, 30 participants in each group were required with 3 repeat measurements.

Data Analysis

Data analysis was completed using STATA v 14.0 (StataCorp, Chicago, IL). Descriptive statistics were used to describe the demographic and clinical characteristics of the sample, as well as elements of safety and feasibility of the exercise program. Baseline comparison of variables was completed using Wilcoxon Rank Sum and Chi Square tests. An assessment of missing data for both groups at six weeks, three months and six months was completed using descriptive statistics. The number of complete and incomplete RT sessions for each group was used as an assessment of the feasibility of RT in this group. Data analysis was an available cases

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analysis, all participants' data were analysed based on their group allocation but no missing data were imputed.

The regression analyses used to analyse QoL, disability, muscle strength and body composition were all conducted including the fixed effects for group, time from burn injury (in weeks) and the interaction of these two variables. The interaction term acted as the test of hypothesis for these analyses. Time from burn injury in weeks was included as a continuous variable to account for the variability in timing of follow up assessments between groups. Covariables which displayed $\alpha \leq 0.1$ were included in multivariable regression analysis and the final model was determined using manual backward removal of variables based on magnitude of coefficients and p-values where a significance level of $\alpha \leq 0.05$ was used.

Quality of Life

Due to left skew of BSHS-B data, a dichotomous variable was generated for both the total BSHS-B score and the functional domain score. These dichotomous variables signify whether or not participants had reached a level of recovery equivalent to the upper 95% confidence level of mean scores for Western Australia population data by gender and age (Kvannli, Finlay, Edgar, Wu, & Wood, 2011). Due to the injury specific nature of the survey, population data was not available to create a dichotomous variable for analysis of the other domains of the BSHS-B. To assess the effect of the intervention on QoL, a logistic regression model with a robust estimator clustered by subject was used. Total burn surface area, age and gender were included as covariables in these regression models.

Secondary Outcome Analysis

All other outcomes assessed in this study were secondary outcomes and should be viewed as exploratory analyses.

Self-reported disability

To assess the effect of treatment on self-reported disability, separate analyses were undertaken for those with upper limb (Quick-DASH) and lower limb burns (LLFI-10). These analyses included all collected questionnaires. Where a participant had both upper and lower limb burns, both surveys were completed and data from these

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individuals were included in both analyses. Negative binomial mixed effects regression was chosen due to the over-representation of true zero scores, indicating 0% disability, in both surveys. This model treats the scores for the surveys as counts. As such, any scores that fell between two integers were rounded to the nearest whole number to allow for this model to be used. Clinically relevant covariables of age, gender, TBSA and muscle strength were assessed in this regression model. For LLFI-10 only quadriceps muscle strength was included whilst for Quick-DASH the combined biceps and grip strength was used.

Muscle Strength

Strength data was summarised using mean ± SD for both groups. The effect of treatment on muscle strength was assessed using mixed effects linear regression with maximum likelihood estimation for the combined muscle strength value. Muscle strength at time of enrolment (baseline) was included as a covariable to adjust for differences in initial muscle strength values between the two groups. To assess the impact of clinically relevant covariables on the outcome variable, adjustment for gender, age, TBSA and RT history prior to enrolment was undertaken. Similar analysis was undertaken for individual muscle groups; biceps, quadriceps and grip strength with left and right sided values combined.

Body Composition

Triplicate measures of BIS from each assessment were averaged to produce an average Ri value for analysis. Clinically relevant covariables of age, gender and TBSA were assessed using linear regression. Baseline Ri was assessed as a covariable to adjust the model for differences in baseline readings between the groups. Random effects for participants were included in all models.

Length of Stay

Length of stay was compared between groups using ranksum assessment.

Adverse Events & Blood Markers of Inflammation and Protein Turnover

Repeat surgery and the number of sessions in which pain scores exceeded 7/10 were reported by group to investigate safety of the RT intervention. Exploratory analyses of CRP and RBP on a subset of study participants were undertaken. C-reactive

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protein results were rounded to the nearest whole number to perform a mixed effects negative binomial regression analysis. Retinol binding protein was analysed using a random intercept linear regression model. Clinical and patient factors were included in both analyses as covariables and were removed in a stepwise manner as determined by coefficients and p-values which were considered significant at $\alpha \leq 0.05$ to determine the final model of each. For CPR analysis a (0, 0, 0.5) fractional polynomial transformation of days since burn injury was identified as best describing this mixed data. For RBP analyses, an inverse square root transformation was completed for time since burn injury in weeks due to the non-linear relationship with RBP.

6.4 Results

The flow of participants through the study is outlined in Figure 6.1. During the study recruitment period, 224 patients were screened and 66 patients were approached for recruitment. Fifty participants consented to participate and were allocated to a treatment group. One participant from each group requested to be withdrawn from the study after randomisation at their request to cease participating. Forty-eight participants were therefore included in the final sample for data analysis. All data for the two participants who requested withdrawal from the study was removed and not included in any analysis. Three participants of the original 48 were lost to all three of these follow up assessments and were not able to be contacted. Data were available for analysis for the primary outcome from 38 participants (79%) at 6 weeks, 35 participants (73%) at 12 weeks and 34 participants (71%) at 26 weeks. For secondary outcomes, the number of participants with available data for analysis differed from the numbers described for the primary outcomes. This was principally related to the inability to collect physical follow up data from patients who chose not attend in person for review and/or chose not to return surveys via post. Demographic and clinical characteristics of both groups are outlined in Table 6.1. There were no significant baseline differences between groups for any of the measured demographic or clinical variables (Table 6.1). A descriptive assessment of missing data throughout the study was completed from which there was no indication of significant bias introduced to the study (Supplementary Table 6.1).

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Thirty-eight participants (79%) completed at least seven training sessions (CG n=19, RTG n=19), the equivalent of at least two days of RT per week. Thirty-eight sessions (9.5 % of all sessions) were not completed in their entirety during the study. Ten participants from the CG and nine participants from the RTG group recorded 15 and 23 incomplete sessions respectively for reasons including pain, fatigue, nausea during a session, or, limitations to testing related to dressings and surgical limitations.

Primary Outcome

The observed proportions of participants meeting the pre-defined level of recovery as described in the data analysis section for the BSHS-B are summarised in Table 6.2. There was no difference in the odds of recovery across time between the RTG and CG group based on the total BSHS-B total score (OR=0.991, p=0.802). In contrast, for every increase of one week, the *Function* domain of the BSHS-B demonstrates a further 20% increase in the odds of recovery in the RTG group, compared with the CG (OR =1.21, p=0.017) (Table 6.3). Figures 6.2a & 6.2b show the predicted probability of recovery for both groups across time.

Secondary Outcomes

Self-reported disability

A summary of functional outcome survey results are shown in Table 6.4. The rate of change of the LLFI-10 score across weeks was not different between groups (IRR 0.978; 95% CI 0.944 to 1.01; p=0.223) (Table 6.5). Figure 6.3a represents these data graphically. For the Quick-DASH, the RTG demonstrated a significantly greater rate of recovery compared to the CG (IRR 0.770; 95% CI 0.670 to 0.886; p<0.001) (Table 6.5). Upper limb function was dependent on severity of injury in this model, where as expected, higher TBSA was related to greater reported disability (IRR 1.08; 95% CI 1.02 to 1.14; p=0.014). Figure 6.3b presents data for the Quick-DASH graphically.

Muscle Strength

Average values for muscle strength of the two groups across the study period are shown in Table 6.6. The rate of change in muscle strength was not significantly different between groups as indicated by the interaction term after adjustment for

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baseline muscle strength, TBSA and gender (co-eff 0.637; 95% CI -0.111 to 1.38; p=0.095). Muscle strength improved significantly over time for the CG (co-eff 1.25; 95% CI 0.716 to 1.78; p<0.001) and no significant difference in muscle strength between the treatment groups was seen (Table 6.7). Figure 6.4 presents these data graphically. A similar effect was seen for individual muscle groups. Biceps, quadriceps and grip strength improved over time, but there was no significant difference between groups. These results can be found in Supplementary Table 6.2.

Body Composition

There was no difference in the interaction term for the change of Ri over time between the CG and RTG after adjustment for baseline Ri, TBSA and gender (co-eff 3.11; 95% CI -1.83 to 8.07; p=0.217).However, overall Ri did decrease with weeks since the burn injury (co eff -4.18; 95% CI -8.14 to -0.225; p=0.038). (Table 6.8). Figure 6.5 represents this graphically.

Length of Stay

Median length of inpatient hospital stay was 13 days (IQR 9-16) for the CG and 12 days (IQR 9-16) for the RTG. The difference in length of stay between groups was not statistically significant (z=0.300, p = 0.764).

Adverse Events & Blood Markers of Inflammation and Protein Turnover

A total of 6 participants (12 %) required repeat surgery to their burn wounds, these were distributed equally between the CG and RTG. Two participants in each group required a total of two surgeries and one participant from each group required three surgeries. Participants rated their highest pain as >7/10 in 57 exercise sessions (15.1% of total sessions: CG=30 sessions, 15 subjects, TBSA 6-27% & RTG=27 sessions, 13 subjects, TBSA 6-40%). Nine of these sessions were ceased at request of the participants due to excessive pain (CG=6 session, RTG=3 sessions).

C-reactive protein increased initially after injury then reduced over time for the study population. After adjustment for TBSA and age, there was a significant interaction for treatment group and days since injury and the RTG tended to have a lower peak and faster reduction in CRP concentration. Figure 6.6 demonstrates this graphically. The RBP concentration increased for the first two weeks after injury then plateaued

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for the study population. After adjustment for weeks after burn injury, gender, age and RT history, RBP concentrations were on average higher in the RTG (8.16 µg/mL; 95% CI 3.26, 13.06; P=0.001) (Table 6.9).

6.5 Discussion

This study offers support for the potential benefits associated with the use of early RT as an adjunct to our usual, proactive physiotherapy treatment of acute burn injury. While we found no evidence of a difference between RTG and CG for the total BSHS-B QoL score, there was evidence of a significant difference in the function domain in favour of the RTG. Among the secondary outcomes explored in this study, RT was found to have contributed to improving the rate of recovery of upper limb disability after a burn injury. Exploratory analysis indicated a faster improvement in CRP and RBP concentration for the RTG after adjustment for clinical variables. For other secondary outcomes, we found no evidence that RT offered benefits above those obtained with standard physiotherapy care for lower limb function, a composite measure of muscle strength or body composition. Length of inpatient hospital stay was also the same for both groups. Results from trial monitoring and blood analysis indicate that a RT intervention at this acute phase of injury is both a safe and feasible option for this clinical group.

There is plausibility in our findings for QoL in this study as the BSHS-B survey assesses items which are unrelated to physical function and contribute to the total BSHS-B score. These are unlikely to be impacted by RT. Conversely, the survey items related to functional status could conceivably be influenced by RT. Paratz, Stockton, Plaza, Muller, and Boots (2012) have previously reported improvements in all 4 main domains of the Burn Specific Health Score-Abbreviated (BSHS-A) for their exercise group in comparison to self-management. The BSHS-A is a predecessor version of the Burn Specific Health Scale survey, from which the BSHS-B has been developed in order to improve the clinical use of the Scale to measure QoL after a burn injury. The differences between this study and our results reported here could conceivably stem from differences in the control treatments of the two studies, non-randomised group assignment in the Paratz et al. (Paratz et al., 2012)

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study, the duration of intervention applied, the difference in acuity of the patient groups and the different QoL assessment tool used.

In the present study, the RTG demonstrated significantly greater recovery of upper limb function compared to the CG. This result is in keeping with Quick-DASH results from a previous non-randomised clinical trial (Paratz et al., 2012) and provides further evidence that RT could form an important aspect of optimal upper limb rehabilitation after a burn injury. However, our study found no evidence of an additional benefit of early RT for lower limb physical function. This result is in contrast to previous work (Paratz et al., 2012) where lower limb function was assessed with a different outcome tool, the Lower Extremity Functional Scale (LEFS) (Paratz et al., 2012), and, as previously mentioned there are numerous clinical and methodological differences between this study and ours. A lack of apparent statistical association between functional ability and muscle strength in this study may relate to the variation of muscle strength in comparison to the very small variation of scores for the LLFI-10 and QuickDASH. Another consideration for this finding is whether lower limb RT exercises offered a training stimulus greater than what was received through standard care alone. Our facility practices a philosophy of early ambulation for all patients as a standard of care. This includes extensive mobilisation commenced from the day of hospital admission and again within 48 hours after surgery, as well as the use of stairs, stationary bikes and body weight lower limb exercises. It is possible that early RT in the acute injury phase does not provide a substantially greater training load for the lower limbs beyond that gained from this approach.

Our data did not find evidence that the addition of four weeks of RT to standard care leads to an increase in muscle strength or cellular volume greater than that seen in usual care alone. Training in the sub-acute and long term rehabilitation phases of injury have previously shown a benefit for muscle strength in adults where training duration was six weeks or more (Ebid et al., 2012; Paratz et al., 2012). Again, the clinical and methodological differences between these studies and ours should be considered when comparing results. A longer duration of RT may be required throughout and beyond the acute injury phase for an ongoing difference in muscle strength and volume to be realised. However, in an adult population, it must be

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considered that a longer rehabilitation period may be unfeasible due to the demands of returning to work and other social or financial responsibilities which may take priority upon discharge from hospital.

Resistance exercise in this clinical group might have wider implications for patient health as participation in RT was linked to a reduced peak and faster improvement in an inflammation biomarker (CRP). This suggests an anti-inflammatory action from RT after burn injury, though this finding would benefit from further investigation. Exercise and physical activity are established as having an anti-inflammatory effect, particularly when undertaken on a regular basis (Allen, Sun, & Woods, 2015). A previous systematic literature review and meta-analysis has documented improvements in CRP following exercise training in clinical and non-clinical groups (Fedewa, Hathaway, & Ward-Ritacco, 2017). This review concluded that exercise resulted in small but significant reductions in CRP (Fedewa et al., 2017), offering support for the reduction of CRP concentration seen in the RT group in this study.

The RT programme assessed in our study was informed by guidelines for healthy adults as there are no prior guidelines for RT in burn injured adults. In uninjured populations, significant increases in muscle strength (Abe, DeHoyos, Pollock, & Garzarella, 2000; Brook et al., 2015; Coetsee & Terblanche, 2015; Jenkins et al., 2016; Nuzzo, Barry, Jones, Gandevia, & Taylor, 2017) have been demonstrated to occur within four weeks of the commencement of a RT program. There is also some evidence to support increases of muscle thickness in that same period of time (Brook et al., 2015; Seynnes, de Boer, & Narici, 2007). These studies supported our choice of implementing a four week exercise training protocol in burn injured patients. Further, the duration of RT was deemed to be feasible in the WA context as patients are likely to be still receiving care from the burns service during this time. The shorter training duration assessed in this study would improve the generalisability of RT prescription, as access to ongoing long-term treatment may not be feasible in many services.

Implications in Practice

This study has presented evidence supporting a number of benefits from participation in a novel four week RT program commenced immediately after a burn injury. It is

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the first study to assess the effect of a RT program in acute burn injury and the four week training duration is shorter than programs previously delivered in burn injured populations, which range from 6 to 12 weeks (Ahmed, Abdel-aziem, & Ebid, 2011; Al-Mousawi et al., 2010; Clayton et al., 2017; Cucuzzo, Ferrando, & Herndon, 2001; Ebid et al., 2014; Ebid et al., 2012; Hardee et al., 2014; Mowafy, El-Sayed, El-Monaem, & Osman, 2016; Paratz et al., 2012; Pena et al., 2016; Porro et al., 2013; Rosenberg et al., 2013; Suman & Herndon, 2007; Suman, Spies, Celis, Mlcak, & Herndon, 2001; Suman, Thomas, Wilkins, Mlcak, & Herndon, 2003). The beneficial results, safety and feasibility described in this study highlight that early RT is a suitable rehabilitation practice for patients with an acute burn injury.

Assurances about the safety of RT in such an acute population are important. The addition of a high intensity RT programme to our standard of care, early mobilisation approach was not of detriment to our study group. In fact, there is evidence of improvement in outcomes from participation in prescribed, early RT. We detected no negative effects on QoL, disability, muscle strength or muscle volume related to participation in early RT. Additionally, RT was not seen to impair protein turnover or nutrition status as assessed by RBP concentrations. It is also unlikely that RT was the primary cause of requiring more than one operative procedure given the equal distribution of these cases across both groups. Our data suggests that the majority of patients voluntarily continued to exercise beyond a recommended stopping point of greater than 7/10 pain intensity. Eighty percent of the sample completed at least seven exercise sessions, or, the equivalent of two training days per week, a frequency which is supported by the literature to provide benefit from RT (Garber et al., 2011; Hass, Feigenbaum, & Franklin, 2001). Additionally, there was a similar number of discontinued or incomplete RT sessions recorded across both groups in this study indicating that RT is a practical rehabilitation mode in acute burn injury.

The use of hand held muscle dynamometry (HHD) to assist in the prescription of training load was another novel concept used in this study. We have validated the use of HHD as a method to assess muscle strength outcome in burn injuries (P. Gittings et al., 2016; Gittings et al., 2018) and it has been shown to be able to accurately predict the reference standard assessment of one-repetition maximum of chosen muscle groups (Tan, Grisbrook, Minaee, & Williams, 2018). This study demonstrates

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the first standardised method for HHD being used in the prescription of RT load in burn injured patients. It was found to be a time-efficient method of assessment and prescription. Given the relatively low cost of the equipment used, particularly in comparison to tools such as isokinetic dynamometry, it is also likely a cost–effective assessment tool. Having a time and cost effective method of assessing muscle strength enabled us to optimise training load on a daily basis, an important consideration in the acute care setting where large fluctuations in capacity are common.

Limitations

The findings presented here need to be interpreted with the study limitations in mind. This study was closed earlier than anticipated, as a result the number of subjects enrolled did not meet the pre-planned recruitment target. However, in its current form this study is the largest exercise trial conducted with an adult burn injured population. Larger studies, ideally from multiple centres would be required to improve the precision of the inferences drawn from the trends shown in the current study. Other limitations of this study relate to the introduction of performance, detection and attrition bias.

Therapists were not blinded to group allocation, so the results presented here may be subject to some performance bias. The secondary outcomes of muscle strength and body composition were collected by a non-blinded assessor so may be confounded by detection bias, though as we found no between group difference in muscle strength or body composition, this is unlikely to change the interpretation of the results. There is some evidence of attrition bias in the current study. For the primary outcome, data was available from approximately 80% of participants at the 6 week review and approximately 70% of participants by the 6 month review. Missing data was accounted for by the use of repeated measures and statistical analyses which were robust to missingness, including the use of regression models utilising maximum likelihood estimation. However, this study does contain a number of methodological strengths. Allocation was random and concealed and the baseline equivalence suggests randomisation was successful in controlling for selection bias. Participants were blinded to group allocation and all assessments and treatment occurred in isolation to help maintain blinding for the duration of the study. Also,

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assessors were blinded for the primary outcome measure and available cases were analysed in the group they were originally assigned.

It is acknowledged that grip strength was used as part of the muscle strength outcome measurement, yet exercises which directly trained grip strength were not included in the training protocol. Grip strength can be used as a surrogate measure of global muscle strength in healthy people and hospitalised patients (Özyürek et al., 2017; Porto et al., 2019; Wind, Takken, Helders, & Engelbert, 2010) and was included in this study as such. Future studies may consider including grip specific exercises into their protocol. In the present study, we assessed and trained muscle groups as described in the methods section, however long term outcome was based on select, sentinel muscle groups for the upper limb and lower limb. This was done as a way of obtaining quality long term muscle strength data, whilst also reducing the assessment burden on participants who were required to undergo multidisciplinary reviews during these follow up visits to the service. It may be that a different mode of muscle strength assessment would return different results to those reported here.

We were not able to limit fluid intake during exercise or assess the hydration status of participants prior to measurement of body composition using BIS. We appreciate that this is a factor which may influence the calculated values provided by the BIS device. To manage this, we utilised and analysed only the raw BIS values which will improve the interpretability of the data and the validity for comparisons within an individual.

Future Research

Multi-centre research projects are essential to increase the precision of estimates of treatment effects and generalisability of findings in this group of patients. To ascertain the precision of MVIC to be able to prescribe dynamic RT, further patient group specific investigation may be warranted. Investigation of exercise rehabilitation during the acute injury period should continue to explore different dosages of exercise training as rehabilitation during this important time period has previously been untested. Short duration training programs would be recommended to improve the practicality of research, particularly in adult populations who have social and financial responsibilities to attend to as soon as possible after a burn injury. However, further data is required to fully assess the efficacy of short duration

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training programs. Understanding the physical and psychological outcomes of exercise training across the continuum of burn injury recovery will enable treating teams to be able to provide best practice rehabilitation and provide the best opportunities for optimal recovery. All future rehabilitation research must be undertaken with robust methodology, adequate sample size and accurate reporting which are vital to continue to improve the quality of rehabilitation data available in this patient group.

CONCLUSION

Progressive RT in addition to usual physical rehabilitation appears both safe and feasible in the acute phase post burn injury. There is evidence that progressive RT leads to improvements in QoL and disability in this population, though this is primarily apparent in patients with upper limb burns. There is no evidence of harm to patients participating in an early RT programme after a burn injury.

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CONFLISTS OF INTEREST

No conflicts of interest to declare.

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6.7 Tables

Table 6.1 Sample descriptive statistics

	CG[1]	RTG[2]	Test Statistic	p-value
Number of Participants	25	23		
Age (years) [median (IQR)]	33 (24 – 43)	30 (25 – 33)	z = 0.981	0.327
Gender [n (%)]			Chi^2= 0.012	0.913
• **Male**	22 (88%)	20 (87%)		
• **Female**	3 (12%)	3 (13%)		
RT[3] History [n (%)]			Chi^2 =0.763	0.382
• **No**	18 (72%)	19 (83%)		
• **Yes**	7 (18%)	4 (17%)		
Total Burn Surface Area [Median (IQR)]	14 (9 – 20) %	12 (10 – 20) %	z = 0.289	0.772
Number of Surgeries [n (%)]			Chi^2 = 1.14	0.768
• **0**	0 (0%)	1 (4%)		
• **1**	22 (88%)	19 (83%)		
• **2**	2 (8%)	2 (9%)		
• **3**	1 (4%)	1 (4%)		
Surgery Type [n (%)]			Chi^2 = 5.23	0.156
• **Nil**	0 (0%)	1 (4%)		
• **ReCell Only**	10 (40%)	3 (13%)		
• **SSG[4] & ReCell**	13 (52%)	17 (74%)		
• **SSG Only**	2 (8%)	2 (9%)		
Location of Burn [n (% of group)]				
• **Arm Burn**	19 (76%)	17 (74%)	Chi^2 = 0.028	0.868
• **Leg Burn**	20 (80%)	19 (82%)	Chi^2 = 0.054	0.817
• **Hand Burn**	15 (60%)	15 (65%)	Chi^2 = 0.139	0.709

[1] Control group
[2] Resistance training group
[3] Resistance Training
[4] Split Skin Graft

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Table 6.2 Observed proportions of participants categorized as below or above the upper 95%CI for population normal scores on the Burns Specific Health Scale-Brief (BSHS-B) total scores and function domain scores at each follow up assessment [n (%)]. Range of weeks of assessment after burn injury included

	BSHS Function CG[1]	BSHS Function RTG[2]	BSHS Total CG	BSHS Total RTG
6 week review				
Below	10 (53%)	14 (74%)	16 (84%)	17 (89%)
Above	9 (47%)	5 (26%)	3 (16%)	2 (11%)
n	19	19	19	19
Week of review (min, max)	5.57, 11.7	4.86, 9.57	5.57, 11.7	4.86, 9.57
12 week review				
Below	7 (41%)	6 (33%)	14 (82%)	12 (67%)
Above	10 (59%)	12 (67%)	3 (18%)	6 (33%)
n	17	18	17	18
Week of review (min, max)	11.4, 19.5	10.4, 19.7	11.4, 19.5	10.4, 19.7
26 week review				
Below	5 (31%)	1 (5%)	9 (56%)	11 (61%)
Above	11 (69%)	17 (95%)	7 (44%)	7 (39%)
N	16	18	16	18
Week of review (min, max)	23.4, 38.7	22.3, 40.7	23.4, 38.7	22.3, 40.7

[1] Control Group
[2] Resistance Training Group

Table 6.3 Final logistic regression model for the Burn Specific Health Scale-Brief (BSHS-B) total score and function domain. No adjustment for total score. Adjustment for TBSA for the function domain (n=43, obs=107).

BSHS-B	Variable	Odds Ratio	95% CI	p-value
Total Score	Group#Weeks	0.991	0.926, 1.06	0.802
	Group (RTG[1])	1.28	0.228, 7.21	0.778
	Weeks	1.05	0.989, 1.11	0.106
Function Domain	**Group#Weeks**	**1.21**	**1.03, 1.41**	**0.017***
	Group (RTG)	**0.107**	**0.017, 0.656**	**0.016***
	Weeks	**1.05**	**1.01, 1.11**	**0.038***
	TBSA[2]	**0.893**	**0.815, 0.978**	**0.015***

*p <0.025
[1] Resistance training group
[2] Total Burn Surface Area

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Table 6.4 Summary of group scores for functional assessments Lower Limb Functional Index-10 (LLFI) & Quick Disability of Arm Shoulder and Hand (QDASH) [median (IQR)]

	Control Group		RT Group	
	n	**Median (IQR)**	**n**	**Median (IQR)**
LLFI Domain 1 – Baseline	18	0.0 (0.0 – 0.0)	15	0.0 (0.0 – 0.0)
LLFI Domain 1 – 6 week	17	1.5 (0.0 – 3.0)	12	2.5 (1.5 – 4.5)
LLFI Domain 1 – 12 week	15	0.5 (0.0 – 2.5)	14	0.75 (0.5 – 3.0)
LLFI Domain 1 – 26 week	14	1.0 (0.0 – 2.0)	13	0.5 (0.0 – 2.0)
QDASH General – Baseline	18	0.0 (0.0 – 2.27)	14	0.0 (0.0 – 0.0)
QDASH General – 6 week	17	18.18 (9.09 – 25.0)	13	18.18 (9.09 – 22.73)
QDASH General – 12 week	15	6.82 (0.0 – 20.45)	10	2.27 (0.0 – 2.27)
QDASH General – 26 week	14	0.0 (0.0 – 9.09)	10	0.0 (0.0 – 0.0)

Table 6.5 Final negative binomial regression models for Lower Limb Functional Index-10 scores (n=33, obs=86) & Quick Disabilities of Arm Shoulder and Hand scores with adjustment for TBSA (n=80 observations, 32 groups).

	Variable	***IRR[1]***	***95% CI***	***p-value***
LLFI-10	Group # Weeks (RTG[2])	0.978	0.944, 1.01	0.223
	Group (RTG)	1.76	0.782, 3.95	0.172
	Weeks	0.979	0.956, 1.00	0.093
Quick-DASH	**Group # Weeks (RTG)**	**0.770**	**0.670, 0.886**	**<0.001***
	Group (RTG)	**7.91**	**1.65, 37.9**	**0.010***
	Weeks	**0.931**	**0.899, 0.964**	**<0.001***
	TBSA[2]	**1.08**	**1.01, 1.14**	**0.014***

* p<0.05
[1] Incident Rate Ratio
[2] Resistance training group
[3] Total Burn Surface Area

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Table 6.6 Observed total combined muscle strength for average scores of left and right sided elbow flexion, knee extension and grip strength in kilograms, by group allocation [mean (SD)]. Range of actual week of assessment after burn injury included.

	Control Group	n	Weeks	Resistance Training Group	n	Weeks
Baseline	185.6 (51.9)	25	0.142, 0.571	172.6 (54.5)	23	0.142, 0.857
6 Week Assessment	194.1 (46.3)	23	5.57, 8.71	195.9 (48.4)	16	4.86, 9.57
12 Week Assessment	195.1 (45.3)	16	11.4, 15.8	211.8 (41.2)	15	10.4, 17.4
26 Week Assessment	204.5 (39.0)	17	23.4, 40.3	219.3 (53.1)	16	22.3, 40.7

Table 6.7 Final multivariable mixed effects linear regression model for combined muscle strength adjusted for gender, TBSA & baseline muscle strength (n=48, obs=447).

Variable	*β Co-eff*	*95% CI*	*p-value*
Group # Weeks (RTG[1])	0.637	-0.111, 1.384	0.095
Group (RTG)	-13.4	-27.7, 0.834	0.065
Weeks	**1.25**	**0.716, 1.786**	**<0.001***
Baseline muscle strength	**0.320**	**0.140, 0.499**	**<0.001***
Gender (Female)	**-47.1**	**-76.0, -18.2**	**0.001***
TBSA[2]	**-1.90**	**-2.88, -0.927**	**<0.001***

* p <0.05
[1] Resistance training group
[2] Total Burn Surface Area

Table 6.8 Final multivariable mixed effects linear regression model for average Ri (avri) adjusted for gender, TBSA & baseline avri (n=29, obs=58)

Variable	*β Co-eff*	*95% CI*	*p-value*
Group # Weeks (RTG)	3.12	-1.83, 8.07	0.217
Group (RTG)	-0.548	-117.8, 116.7	0.993
Weeks	**-4.18**	**-8.14, -0.225**	**0.038***
Baseline avri	**0.407**	**0.256, 0.558**	**<0.001***
Gender (Female)	**176.4**	**33.5, 319.4**	**0.016***
TBSA[2]	**22.4**	**14.8, 30.0**	**<0.001***

* p <0.05
[1] Resistance training group
[2] Total Burn Surface Area

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Table 6.9 Final mixed effects linear regression model for Retinol Binding Protein. Adjusted for age, RT History, sex and time from burn injury (inverse square transformation).

	Abs diff mean RBP[1]	95% CI	p-value
Group (CG[2])	**8.16**	**3.26, 13.06**	**0.001***
Age	**0.42**	**0.15, 0.69**	**0.003***
RT[3] history	**12.85**	**5.96, 19.75**	**<0.001***
Sex (male)	**-9.01**	**-17.33, -0.69**	**0.034***
Weeks since injury[4]	**-126.12**	**-149.66, -102.57**	**<0.001***

[1] Absolute mean difference for Retinol Binding Protein
[2] Control group
[3] Resistance training
[4] Inverse square transformation of weeks since burn injury
* $p<0.05$

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Supplementary Table 6.1 Comparison of key baseline variables between those that were and weren't available at each time point, by group.

	6 Week				12 Week				26 Week			
	CG[1]		RTG[2]		CG		RTG		CG		RTG	
	Avail*	Miss[#]	Avail	Miss	Avail	Miss	Avail	Miss	Avail	Miss	Avail	Miss
Baseline Mean Combined Strength	171.4 (n=22)	238.6 (n=3)	169.9 (n=19)	185.0 (n=4)	176.4 (n=18)	187.4 (n=7)	171.3 (n=18)	177.2 (n=5)	171.3 (n=17)	196.9 (n=8)	173.5 (n=19)	168.4 (n=4)
TBSA[1] (median)	13.5 (n=22)	20.0 (n=3)	12.0 (n=19)	14.8 (n=4)	13.5 (n=18)	20.0 (n=7)	12.0 (n=18)	16.0 (n=5)	14.0 (n=17)	14.0 (n=8)	12.0 (n=19)	15.5 (n=4)
Age (median)	34.0 (n=22)	24.0 (n=3)	30.0 (n=19)	27.0 (n=4)	37.5 (n=18)	23.0 (n=7)	29.0 (n=18)	32.0 (n=5)	36.0 (n=17)	25.5 (n=8)	28.0 (n=19)	35.0 (n=4)
LOS[2] (median)	12.5 (n=22)	15.0 (n=3)	11.0 (n=19)	14.0 (n=4)	12.5 (n=18)	15.0 (n=7)	11.5 (n=18)	12.0 (n=5)	13.0 (n=17)	13.0 (n=8)	11.0 (n=19)	13.0 (n=4)
Number RT Sessions (median)	9 (n=22)	8 (n=3)	10 (n=19)	5.5 (n=4)	9.0 (n=18)	6.0 (n=7)	10.0 (n=18)	6.0 (n=5)	9.0 (n=17)	6.0 (n=8)	10.0 (n=19)	6.5 (n=4)
Gender Male	86.4% (n=19)	100% (n=3)	89.5% (n=17)	75.0% (n=3)	83.3% (n=15)	100% (n=7)	88.9% (n=16)	80.0% (n=4)	82.4% (n=14)	100% (n=8)	89.5% (n=17)	75.0% (n=3)
No prior RT History	68.2% (n=15)	100% (n=3)	84.2% (n=16)	75% (n=3)	72.2% (n=13)	71.4 (n=5)	77.8% (n=14)	100% (n=5)	70.5% (n=12)	75.0% (n=6)	79.0% (n=15)	100% (n=4)

* Available cases at follow up time point
[#] Missing cases at follow up time point
[1] Control group
[2] Resistance training group
[3] Total burn surface area
[4] Length of inpatient hospital stay

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Supplementary Table 6.2 Final multivariable mixed effects linear regression model for biceps, quadriceps, grip muscle strengths adjusted for gender, TBSA & baseline muscle strength.

Muscle Strength	*Variable*	*β Co-eff*	*95% CI*	*p-value*
Biceps (n=48)	Group # Weeks (RTG[1])	0.078	-0.116, 0.272	0.431
	Group (RTG)	-3.19	-7.44, 7.05	0.140
	Weeks	**0.512**	**0.371, 0.654**	**<0.001***
	Baseline muscle strength	**0.647**	**0.495, 0.799**	**<0.001***
	TBSA[2]	**-0.600**	**-0.899, -0.302**	**<0.001***
Quadriceps (n=46)	Group # Weeks (RTG[1])	0.202	-0.149, 0.554	0.259
	Group (RTG)	-6.99	-14.6, 0.609	0.071
	Weeks	**0.496**	**0.237, 0.756**	**<0.001***
	Baseline muscle strength	**0.399**	**0.194, 0.604**	**<0.001***
	TBSA[2]	**-0.605**	**-1.12, -0.085**	**0.022***
Grip (n=47)	Group # Weeks (RTG[1])	-0.078	-0.373, 0.217	0.605
	Group (RTG)	2.02	-3.10, 7.14	0.440
	Weeks	**0.576**	**0.365, 0.786**	**<0.001***
	Baseline muscle strength	**0.664**	**0.559, 0.769**	**<0.001***

* p <0.05
[1] Resistance training group
[2] Total Burn Surface Area

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6.8 Figures

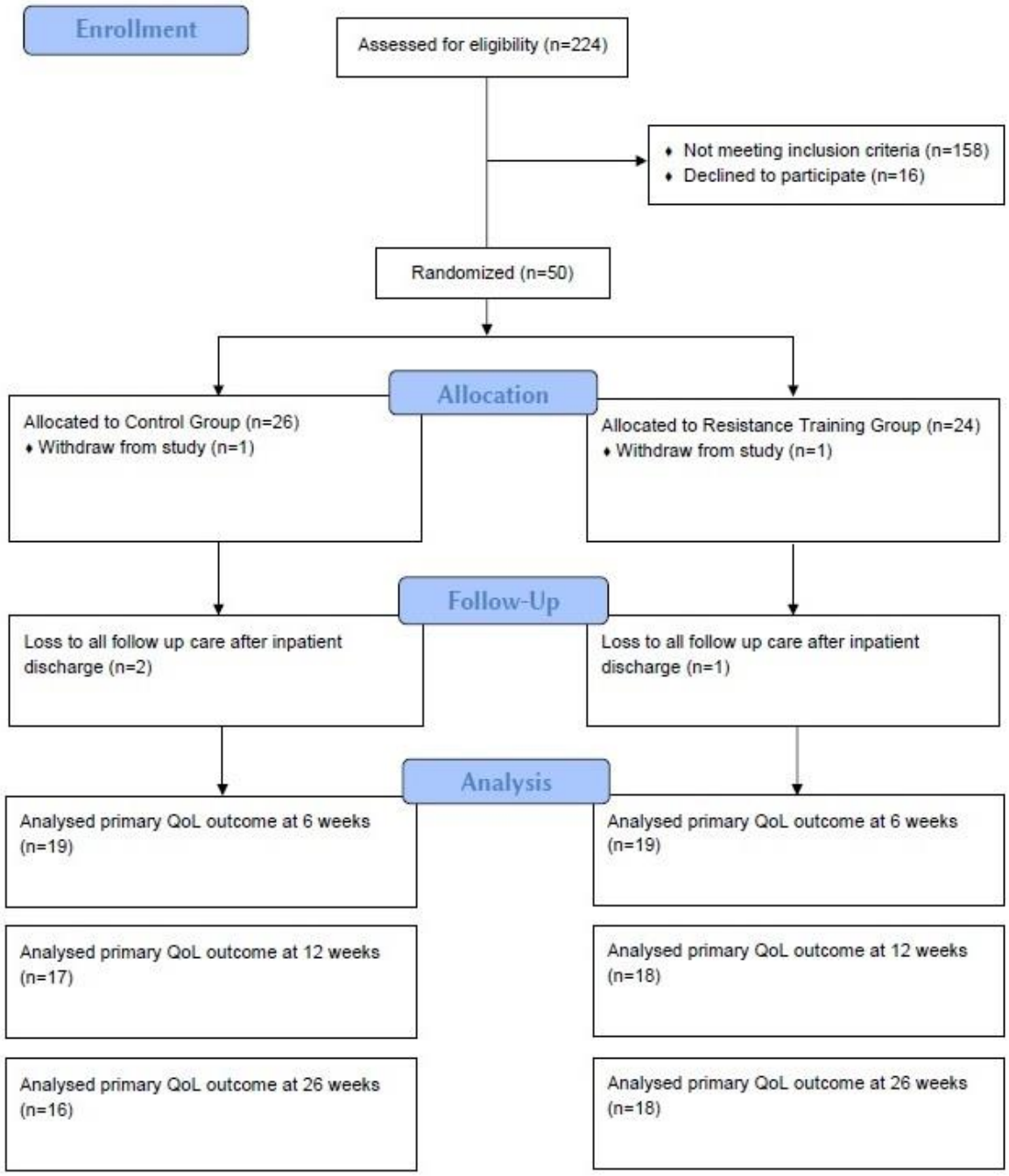

Figure 6.1 Flow of participants through the study

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Figure 6.2a

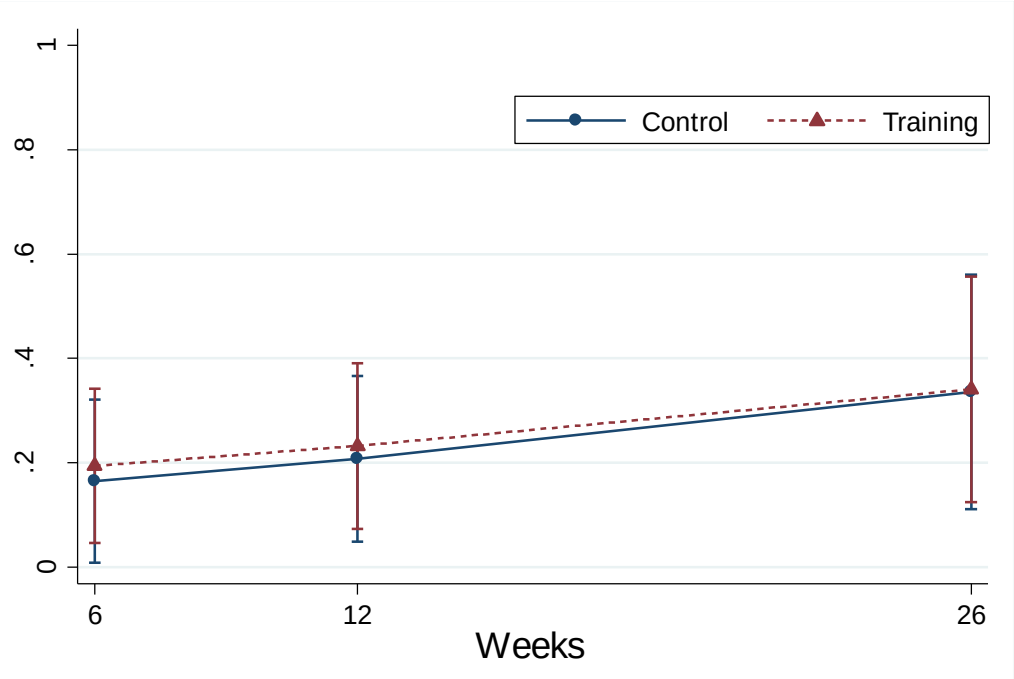
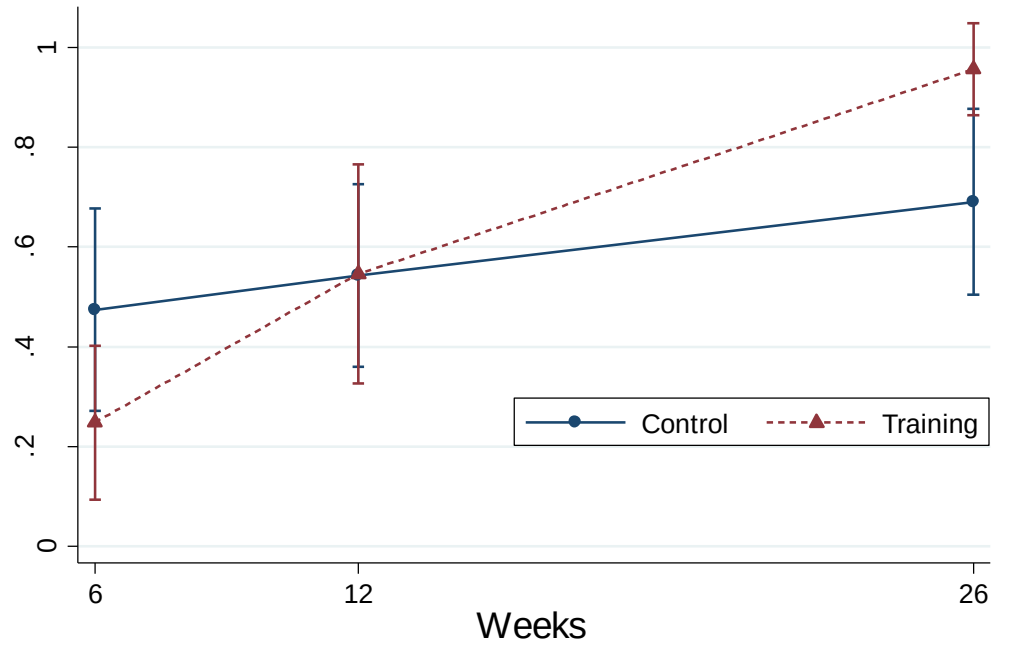


Figure 6.2b



Figures 6.2 Predicted probabilities of achieving recovery at 6 weeks, 12 weeks & 26 weeks after burn injury on the total score of the Burn Specific Health Scale with no covariable adjustment (Figure 6.2a), and the function domain score of the Burn Specific Health Scale Brief with adjustment for TBSA (Figure 6.2b).

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Figure 6.3a

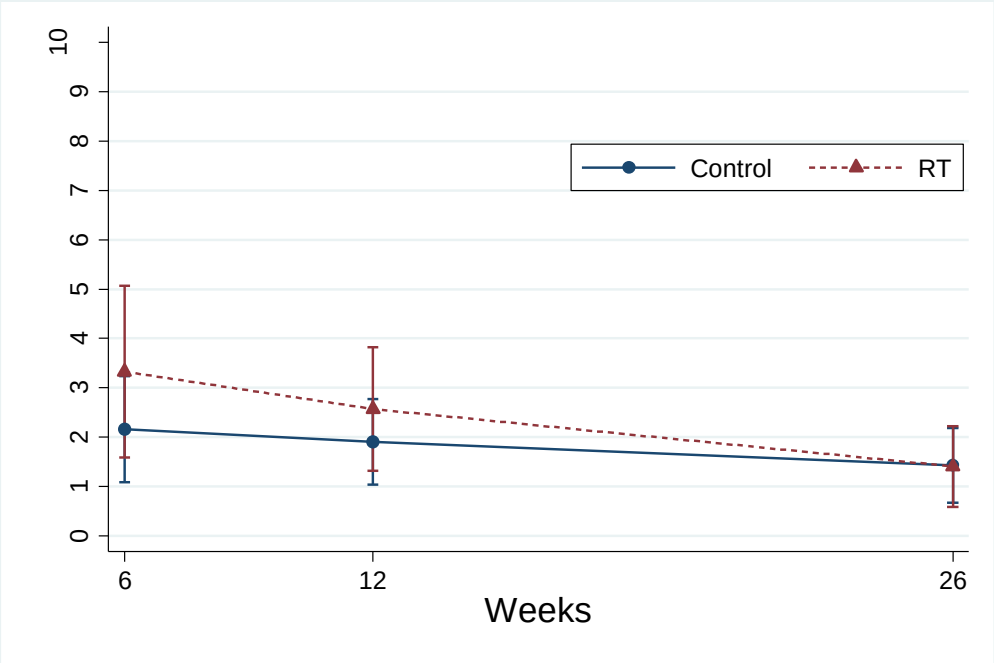
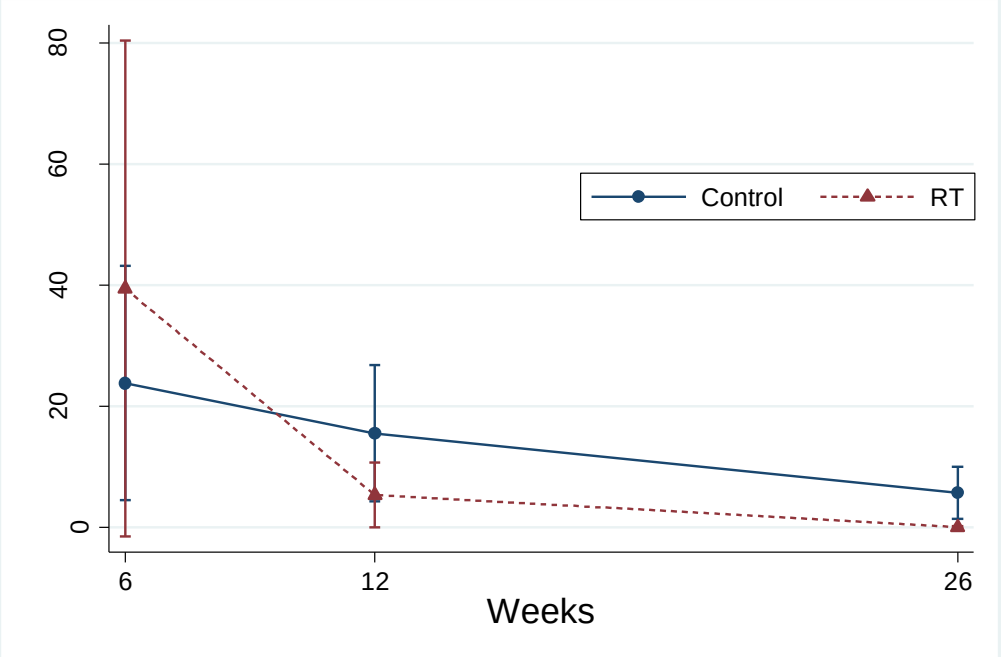


Figure 6.3b



Figures 6.3 Predicted Lower Limb Functional Index-10 (LLFI-10) scores at 6 weeks, 12 weeks & 26 weeks after burn injury, no covariate adjustment (Figure 6.3a). Predicted Quick Disability of Arm, Shoulder and Hand survey (Quick-DASH) scores at 6 weeks, 12 weeks & 26 weeks after burn injury, adjusted for TBSA (Figure 6.3b).

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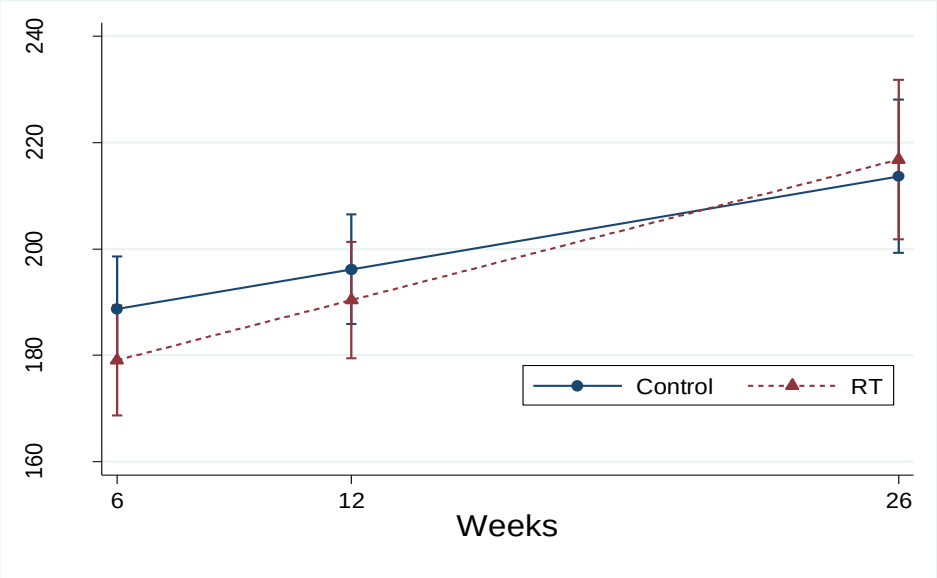

Figure 6.4 Average combined mean muscle strength at 6 week, 12 week & 26 weeks after burn injury adjusted for gender, TBSA & baseline muscle strength.

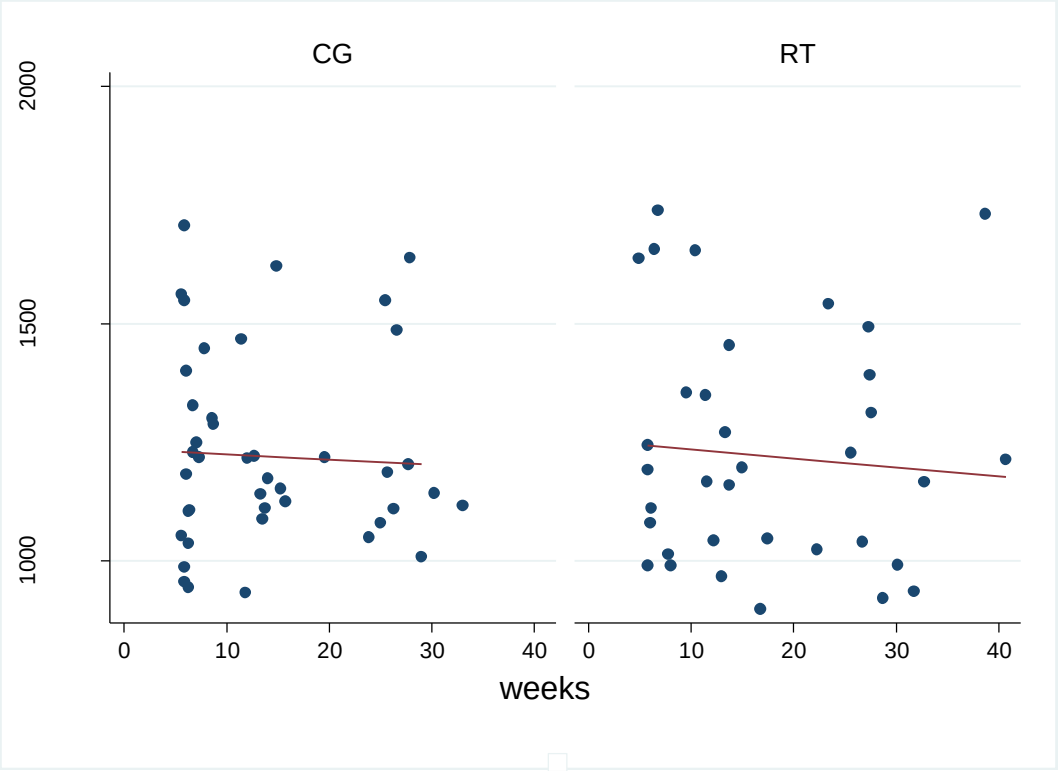

Figure 6.5 Bioimpedance spectroscopy scatter plot for CG & RT groups with fitted predicted mean line.

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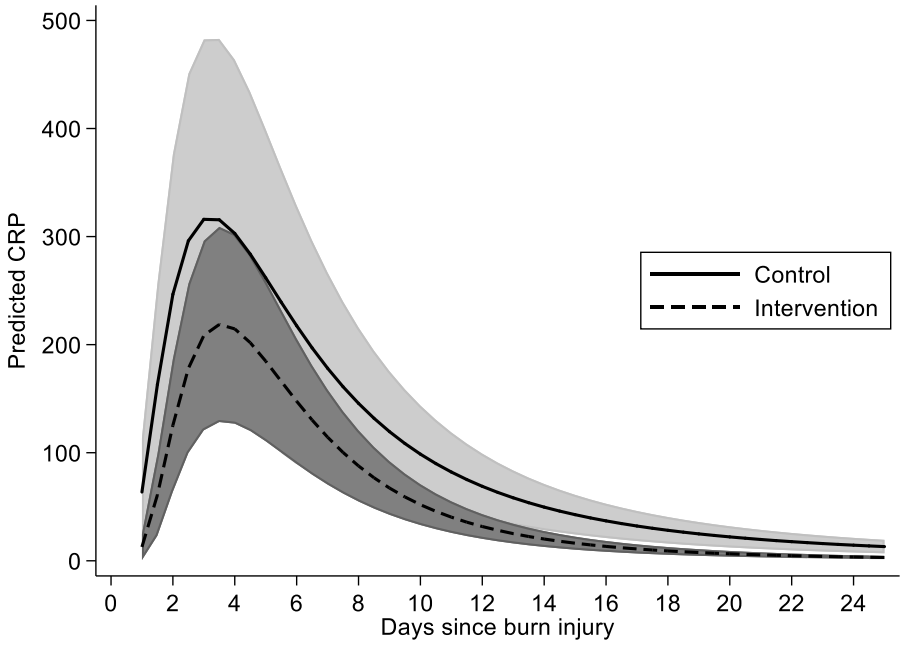

Figure 6.6 Predicted mean C-Reactive Protein over time. Shaded areas represent 95% CI's for the treatment groups predicted curve.

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Chapter 7 Discussion

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This chapter will review the main findings of this thesis, summarise the implications of the research findings as well as outline recommended avenues of future research.

7.1 Main Findings of this Thesis

7.1.1 Status of the Pre-existing Published Research

Chapter Two of this thesis was the first review to systematically evaluate the current evidence assessing the unique effect of resistance training (RT) after a burn injury. Meta-analyses were undertaken to assess the effect of RT on muscle strength and lean mass when compared to not undertaking RT. After a sensitivity analysis, knee extensor strength demonstrated a significant effect favouring RT. Subgroup analysis was performed to elucidate the effects for adults and children separately and an effect favouring RT was only apparent in paediatric studies. Knee flexor muscle strength demonstrated an effect favouring RT after burn injury, though only two studies provided data for this meta-analysis (one adult, one paediatric). Insufficient data were found to enable a meta-analysis of upper limb muscle strength in burns patients to be undertaken. Lean mass was assessable only in paediatric studies and meta-analysis did not show a significant effect associated with RT. Insufficient data were available to assess the effect of RT on quality of life and physical function using meta-analysis. Only one study utilised a quality of life outcome assessment, whilst physical function was assessed in three studies using five different outcome measurements, introducing heterogeneity which did not allow for quantitative synthesis.

The low quality of the available evidence was an important finding of Chapter Two. The body of literature was assessed as having high risk of bias across multiple domains. Sequence generation and allocation concealment were often not described to a standard that allowed definitive assessment, whilst blinding of participants and outcome assessors was regularly not undertaken or not reported sufficiently to enable a judgement to be made. Other possible bias was introduced into studies where a six month gap existed between participant randomisation and commencement of the intervention without clear reporting of group characteristics at the commencement of treatment. These biases introduced uncertainty to the robustness of the documented results which were used in the meta-analyses. The quality of the evidence for each

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outcome in this literature review was rated as very low due to design limitations, inconsistency and imprecision. Additionally, inadequate data presentation was common and within group analyses were frequently used to suggest treatment effectiveness despite unclear between group differences.

7.1.2 Methodological Enhancements for Research and Clinical Applications

An observed lack of patient reported functional outcome measurements for lower limb burn injuries prompted an assessment of the reliability and validity of the Lower Limb Functional Index-10 (LLFI-10) in Chapter Three. It was concluded that this tool should be part of an assessment of lower limb functional status after a burn injury. This study demonstrated that Part 1 of this tool was the primary section of assessment and could be used in conjunction with Part 3, providing a shortened format to reduce clinician and patient burden of assessment. Part 2 of the LLFI-10 was deemed to be redundant to part 1, whilst part 4 was less useful clinically. The LLFI-10 was assessed to have a single factor structure and summation of scores from part 1 was an appropriate approach to scoring lower limb function after a burn injury. Construct validity was confirmed as the LLFI-10 score was associated with changes in age, time from burn injury and TBSA. Criterion validity of the LLFI-10 was also confirmed by significant and clinically relevant associations with the physical domain of the Burn Specific Health Scale-Brief quality of life survey (BSHS-B), as well as the Timed Up and Go and active ankle range of motion. The LLFI-10 has had test-retest reliability and minimum clinically important difference established in previous work (Ryland, Grisbrook, Wood, Phillips, & Edgar, 2016), furthering our understanding of the clinical utility of this outcome measurement tool.

Chapters Four and Five of this thesis examined the applicability of using hand held dynamometry (HHD) as an assessment of muscle and grip strength in acute burn injury. An initial measurement protocol was developed and tested in acute minor burns and data confirming excellent test-retest reliability of HHD as presented in Chapter Four. Minimal detectable differences ranging between 4kg – 8kg were calculated for all assessed muscle groups. Construct and criterion validity were confirmed through associations with gender and time from burn injury, confirming HHD as an appropriate

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assessment in populations with minor burn injury. Having demonstrated the clinical applicability of HHD, Chapter Five expanded on the previously validated assessment protocol. In this analysis, dynamometry was undertaken on patients with acute burn injuries, including patients with injuries of greater severity than in the preceding study. In addition, two new muscle actions were assessed and a system of external stabilisation was utilised in an effort to optimise the reliability of testing. Hand held dynamometry was again confirmed to demonstrate excellent reliability, plus construct and criterion validity. The new protocol assessed in this study was determined to be clinically applicable to use throughout the acute, immediately post-operative and sub-acute periods of recovery for patients with burn injuries up to 40% TBSA. In conjunction with the results from Clifford, Hamer, Phillips, Wood, and Edgar (2013) who established grip strength dynamometry as reliable and valid in healed burn injuries, isometric HHD should be viewed as an appropriate assessment of muscle strength to be used across the time course of burn injury recovery. Importantly, the tested methodology in this thesis was safe and well tolerated by patients with an acute burn injury, emphasising that it could be used repeatedly as part of the assessment of patient capacity.

7.1.3 Effects of Early Rehabilitation

Chapter Six was a randomised controlled trial devised to address the gaps in the burn injury rehabilitation literature highlighted in Chapter Two. Participants undertook a planned four-week resistance training (RT) programme commencing within 72 hours of the burn injury. Intensity of the RT programme was prescribed using the muscle strength assessment protocols tested in Chapter Five. This was the first project to implement and study a RT programme during the acute phase of a burn injury. To address previously highlighted methodological issues in the pre-existing literature, randomisation was stringently implemented and rigorous blinding of participants was maintained throughout the study period.

There was evidence to support that the addition of early RT in rehabilitation was associated with improvements in functional aspects of health related QoL and upper limb disability after a burn injury. Inflammatory profile was also seen to be positively influenced by participation in early RT after a burn injury. There was no evidence that

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early RT resulted in improvements for overall health related quality of life (QoL), lower limb disability, muscle strength or muscle volume compared to sham RT. In this study, participation in an early RT programme was concluded to be a feasible pursuit for clinicians and patients. Importantly, RT was not shown to be harmful or detrimental to the outcomes of the participants in this study.

7.2 Implications of the Research Findings

7.2.1 Implications for Research Reporting

The systematic literature review in Chapter Two concluded that the reporting standards of the methods and outcomes in the current body of literature pertaining to rehabilitation in burn injury were of low quality. It is important that future interventional research in burn injury rehabilitation attains a high quality standard of reporting of methodology and outcomes. This is to guarantee that findings of research are clear, transparent and interpretable to the consumer. Recommendations to use checklists to guide report writing, such as TIDieR or CONSORT (Moher et al., 2010; Yamato et al., 2016) were made in Chapter Two. In order to further improve the quality of rehabilitation trials, the methodology of studies should be planned to be robust and minimising risk of bias should be a priority. The use of within group analysis is seen to be ultimately misleading for the consumer of research literature (Bland & Altman, 2011). Therefore, clear reporting of outcomes and the use of appropriate statistical analysis is required to optimise the quality and interpretability of future research.

7.2.2 Implications in Clinical Practice & Clinical Research

Outcome measurement is important for monitoring the capability and recovery of patients. Having access to outcome measurement tools that have been proven to be reliable and valid in a certain patient group gives clinicians confidence that their assessments are accurate and providing the relevant data they require. Chapters Three, Four and Five of this thesis have contributed to the pool of outcome measurement tools which can be confidently used after burn injury to monitor the effect of

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interventions and assess patient outcome. There was a noted lack of patient-centred lower limb outcome measurement tools tested in burn injury (Falder et al., 2009) and Chapter Three of this thesis has been able to address that deficit. It confirms the LLFI-10 as a reliable and valid tool which should be used as part of an assessment of lower limb function for patients after a lower limb burn injury. Further to this, clinical research will benefit from having a reliable and valid lower limb specific, patient-reported survey tool which can provide accurate and interpretable data on lower limb function.

The HHD protocols tested in Chapters Four and Five have proven to be suitable for use in a burn injured patient group. The implementation of external stabilisation in Chapter Five was effective in overcoming known bias related to assessor-patient strength discrepancies which has been shown in other studies (Jackson, Cheng, Smith, & Kolber, 2017; Kolber, Beekhuizen, Cheng, & Fiebert, 2007; Thorborg, Bandholm, & Holmich, 2013; Tourville et al., 2013; Valentin & Maribo, 2014). Hand held dynamometry is a time efficient and effective option for muscle strength assessment when compared with other modes of strength testing (Stark, Walker, Phillips, Fejer, & Beck, 2011; Tan, Grisbrook, Minaee, & Williams, 2018), an important feature in a clinical group of patients prone to daily fluctuations in physical capacity. Whilst an isometric assessment of strength may not traditionally be thought to be directly comparable to a dynamic assessment of strength, recent research has demonstrated its ability to predict a one-repetition maximum strength test (Tan et al., 2018) which supports its potential as an exercise prescription tool. Chapter Six of this thesis demonstrated that the data obtained from HHD could be used to aid in the prescription of a training load for resistance training (RT) exercise on a daily basis.

The results presented in Chapter Six of this thesis are the first of their kind, as previous studies have not been undertaken in the acute phase of a burn injury. This is the first study of exercise in burns that provides an estimate of treatment effect relatively free of allocation, performance and detection bias. An early RT programme after burn injury was shown to be safe and feasible. This demonstrates that a change in practice toward early physical activity and prescribed exercise after a burn injury and/ or skin graft surgery is practical for burn services to achieve. Further to this, participation in early RT is beneficial to patient outcome and this mode of exercise should form part

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of an early rehabilitative approach to burn injured patients. Our results demonstrate the positive impact of early RT in adults, which can sit in conjunction with other literature suggesting positive patient outcomes from exercise during the long term rehabilitation phase (Ebid, Omar, & Abd El Baky, 2012; Paratz, Stockton, Plaza, Muller, & Boots, 2012).

7.3 Future Research

Research designed to improve rehabilitation practices after a burn injury has been dominated by studies in paediatric populations and there has been no study that we are aware of regarding the effectiveness of early rehabilitation. As such, there is limited understanding of the optimal rehabilitation parameters for the adult burn injured cohort. This thesis presents the first and only results pertaining to RT in acutely injured burns patients. An important lesson for future research in this field is the matter of sample size. Data collection for this project was undertaken for three and a half years at one burn centre which provides care for a population of 2.6 million people in Western Australia. The sample size attained for this study after that period of time was 48 participants. This reflects the difficulty of undertaking a rehabilitation study at a single burn centre and highlights the need for future research teams to consider how to achieve an adequate sample size for their study. Multi-centre collaboration, locally and internationally, on future rehabilitation projects is the most obvious answer and will be necessary to improve the precision of estimates of treatment effects in future research. The rehabilitation study in Chapter Six of this thesis documents a number of possible methodological enhancements and intriguing findings which may benefit from future investigation.

The RT programme utilised in Chapter Six should be further evaluated to increase overall sample size and improve the precision of the estimates reported. We evaluated the capacity of patients on a daily basis by measuring maximum voluntary isometric contraction (MVIC) using HHD. A set volume and frequency of RT was then prescribed at an intensity of 70% of the MVIC on that day, which was based on a RT prescription for optimising muscle strength. However, there may be value in investigating other prescriptions and modes of exercise which are likely to have a unique impact on patient rehabilitation. There are alternate RT prescriptions and

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dosages used in society for training load aimed at optimising improvements in muscular endurance and power (American College of Sports, 2009). Testing these alternate RT programmes would require a change in the intensity and volume of RT than was assessed in Chapter Six. It would provide a unique perspective on the effectiveness and practicality of training in acutely injured patients and an opportunity to establish the parameters of an optimal training dose for this patient cohort. In addition to RT, understanding the unique effect of appropriately dosed aerobic exercise in acute and long-term recovery from burn injury would be beneficial. However, it must be acknowledged that many small sample studies assessing many different exercise training prescriptions will not improve the quality of the data for our understanding of best practice exercise rehabilitation after a burn injury.

Appropriately dosed exercise can have positive effects on many body systems. There is an understanding that burn injury triggers a larger inflammatory response in comparison to other trauma (Mace et al., 2012) and inflammatory markers have been demonstrated to be chronically elevated after a burn injury (Jeschke et al., 2011). Inflammation after a burn has been associated with other systemic consequences, including immune dysfunction which could be associated with the earlier onset of numerous health problems (Barrett, Fear, Waithman, Wood, & Fear, 2019). Exercise is known to mediate systemic inflammation and regular exercise is known to reduce chronic inflammation (Allen, Sun, & Woods, 2015). As such, the results pertaining to C- reactive protein concentrations presented in Chapter Six are of interest for future investigation. Examination of the trajectory of concentration of specific inflammatory markers and cytokines during and after an acute exercise intervention would provide greater understanding of the effect of acute exercise on inflammation after a burn. If high resistance exercise can be demonstrated to be effective at reducing inflammation in burn injured populations, this should further encourage the utilisation of early exercise prescription after burn injury for reducing the risk of complications related to chronic inflammation.

An important physiological response to monitor during rehabilitation of a burn injury is muscle mass. It has been well established that muscle catabolism is a consequence of the upshift in metabolic response after a burn (Hart et al., 2000; Porter, Hurren, Herndon, & Borsheim, 2013). Conversely, one primary goal of participation in RT is

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to increase the muscle mass of the participant. Given the conflicting actions on muscle mass of the hyper-metabolic response and RT, accurate and non-invasive real time muscle mass assessment would assist with monitoring the effectiveness of exercise and nutritional interventions for patients with a burn injury. Chapter Six demonstrated bioimpedance spectroscopy as a promising tool for this purpose and no detrimental effects on cellular volume with RT after burn injury were seen. Future validation of bioimpedance spectroscopy for this purpose is recommended for the individual clinical populations utilising this method of physical assessment.

The inclusion of patient centred and patient reported outcomes measuring constructs such as physical function and quality of life will be beneficial to continue in future research of rehabilitation. Patient centred outcome measurement tools provide therapists with an insight into the patients' perception of effectiveness of a chosen intervention. There are an abundance of outcome measurement tools available for the assessment of burn injured patients which have been outlined in the literature (Falder et al., 2009; Griffiths et al., 2017; Spronk et al., 2018). However, in planning new research, it will be important to be mindful that using a variety of outcome assessments to measure a single construct of recovery will result in heterogeneity of the data available on rehabilitation, thereby making it difficult to establish recommendations or practice standards based on data pooling from multiple studies. It is recommended to utilise tools previously deemed reliable and valid in the burn injured population. Core outcome measurement tools have been previously proposed in order to guide a unified approach to outcome assessment in burns (Edgar, McMahon, & Plaza, 2014; Falder et al., 2009). Yet, it is noted that there is no one battery of assessment tools which is consistent across the burn care world (ISBI Practice Guidelines Committee, 2018). Burn care centres need to consider minimizing measurement variation via adopting a consistent approach to outcome measurement, otherwise risk an inability to compare outcomes reliably across the burn care world in the future. In addition, pain and adverse events are patient centred outcomes that should continue to be included in future research to guide the choice of safe treatment regimens to be provided to patients.

The lessons learned during and due to this series of stuies demonstrate that methodological rigor is possible, though remains an area of required future

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improvement for rehabilitation studies. Appropriately powered studies have been challenging to obtain in rehabilitation trials, therefore the pursuit of multi-centre trials, or prolonging recruitment time to achieve the desired sample size is needed. This will improve the generalizability of research findings in this important area of ongoing study. It is important that future research is designed to maintain the rigorous standards expected of high quality interventional trials and the quality of reporting results must be considered. Exercise during the acute burn injury period is safe to undertake and early RT exercise has been shown to have beneficial effects for this patient group.

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7.4 References

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Appendices

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Appendix A Statement of Contribution by Co-Authors

1. Gittings, P. M., Grisbrook, T. L., Edgar, D. W., Wood, F. M., Wand, B. M., & O'Connell, N. E. (2017). Resistance training for rehabilitation after burn injury: A systematic literature review & meta-analysis. *Burns*. doi:10.1016/j.burns.2017.08.009

Study conception and design was undertaken by PG, BW and DE. PG was responsible for the search strategy and study selection was completed by PG and TG. Data extraction was completed by PG with arbitration by BW and DE. Data analysis and interpretation was conducted primarily by PG with expert methodological, statistical and interpretaion advice from NOC. PG was responsible for drafting the manuscript, with review and editing from BW, DE, TG, FW and NOC. All authors reviewed and approved the final published version of this manuscript.

2. Gittings, P. M., Heberlien, N., Devenish, N., Parker, M., Phillips, M., Wood, F. M., & Edgar, D. W. (2016). The Lower Limb Functional Index - A reliable and valid functional outcome assessment in burns. *Burns*, *42*(6), 1233-1240. doi:10.1016/j.burns.2016.03.028

The conception and design of this study was carried out by PG & DE. Data collectionwas performed by NH, MB and ND. Data analysis and interpretation was carried out by PG, DE & MP. Drafting of the manuscript was performed by PG with review and advice from DE, MP and FW. All authors reviewed and approved the final published version of this manuscript.

3. Gittings, P., Salet, M., Burrows, S., Ruettermann, M., Wood, F. M., & Edgar, D. (2016). Grip and Muscle Strength Dynamometry Are Reliable and Valid in Patients With Unhealed Minor Burn Wounds. *J Burn Care Res*, *37*(6), 388-396. doi:10.1097/BCR.0000000000000414

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Study conception and design was by DE and MS. Data collection was undertaken by MS. Data analysis and interpretation was undertaken by PG, SB and DE. The responsibility of drafting the manuscript was by PG with support and ongoing review from SB, DE and FW. Review of the submitted manuscript was undertaken by all authors.

4. Gittings, P. M., Hince, D. A., Wand, B. M., Wood, F. M., & Edgar, D. W. (2018). Grip and Muscle Strength Dynamometry in Acute Burn Injury: Evaluation of an Updated Assessment Protocol. *J Burn Care Res*. doi:10.1093/jbcr/iry010

Study conception and design was completed by PG, DE and BW. Data collection for this paper was completed by PG. Data analysis and interpretation was undertaken by PG, DH, BW and DE. Manuscript drafting was completed by PG with reviews completed by DH, BW, FW and DE until the final published manuscript was achieved. All authors reviewed and approved the final published version of this manuscript.

5. Gittings, P.M., Wand, B.M., Hince, D.A., Grisbrook, T.L., Wood, F.M., & Edgar, D.W. The efficacy of resistance training in addition to usual care for adults with acute burn injury: A randomised controlled trial.

Study conception and design was completed by PG, DE and BW. Data collection for this paper was completed by PG. Data analysis and interpretation was undertaken by PG, DH, BW and DE. Manuscript drafting was completed by PG with reviews completed by DH, BW, FW and DE until the final published manuscript was achieved. All authors reviewed and approved the final version of this manuscript which has been submitted for publication.

All co-authors provided consent to the inclusion of articles submitted and accepted the declaration of authorship made by the candidate.

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Appendix B Lower Limb Functional Index-10

Global Assessment Body And Limbs ™: PRO Tools - Lower Limb Functional Index– LLFI -10 © CP Gabel 2002-07

(Print on BLUE Paper) **LOWER LIMB FUNCTIONAL INDEX- 10** DATE:_____

NAME:_____ INJURY_____ ☐ LEFT LEG ☐ RIGHT LEG

PLEASE COMPLETE ALL 4 PARTS:

Your lower limb (leg) may make it difficult to do some things you normally do. This list contains sentences people use to describe themselves when they have such problems. Think of yourself now or over the last few days.
If an item describes you mark the box. If not leave the box blank. If an item partly describes you Use a Half (½) mark.

DUE TO MY LEG:

PART 1.

☐ 1.	I avoid heavy jobs eg. cleaning, lifting more than 5kg or 10lbs, gardening etc.
☐ 2.	I have pain almost all the time.
☐ 3.	I have difficulty with normal home or family duties and chores.
☐ 4.	I sleep less well.
☐ 5.	I need assistance with personal care eg. washing and hygiene.
☐ 6.	My regular daily activities (work, social contact) are affected.
☐ 7.	I am unable to move as fast as I would wish.
☐ 8.	I have difficulty with prolonged or extended standing.
☐ 9.	I have difficulty bending, squatting and / or reaching down.
☐ 10.	I have problems with my balance on uneven surfaces and/or with unaccustomed footwear.

MDC (90% Confidence): 6.67% or 1.67 LLFI points. Change less than this may be due to error

PART 2.

Patient Specific Index (PSI): Think of 5 activities that are important to you and affected by your leg problem. If you cannot think of 5, choose from those you have marked above.
Score each activity on a scale range as follows, you may use Half (½) marks if you wish:
0=BEST: Never affected / Can do activity normally. **10=WORST:** Always affected / Can't do activity at all

	ACTIVITY	*Score*
1.		
2.		
3.		
4.		
5.		

PART 3.
In all your activities or work, where 100% is what you did before the injury: **What is your current % of Pre-injury Duties?**
(eg. Workers not working, sports people not participating = 0%)

_____ %

PART 4.

In the last few days, as a whole person, due to your LEG, rank your Overall Status compared to your normal level before the injury?

(Circle a number) **0 1 2 3 4 5 6 7 8 9 10**

Normal / No Problem — Half Way — Worst Possible

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Appendix C Quick-DASH

THE QuickDASH OUTCOME MEASURE

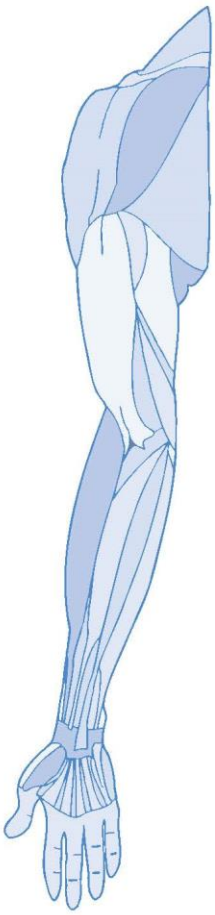
INSTRUCTIONS

This questionnaire asks about your symptoms as well as your ability to perform certain activities.

Please answer *every question*, based on your condition in the last week, by circling the appropriate number.

If you did not have the opportunity to perform an activity in the past week, please make your *best estimate* of which response would be the most accurate.

It doesn't matter which hand or arm you use to perform the activity; please answer based on your ability regardless of how you perform the task.



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*Quick*DASH

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. Open a tight or new jar.	1	2	3	4	5
2. Do heavy household chores (e.g., wash walls, floors).	1	2	3	4	5
3. Carry a shopping bag or briefcase.	1	2	3	4	5
4. Wash your back.	1	2	3	4	5
5. Use a knife to cut food.	1	2	3	4	5
6. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	1	2	3	4	5

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
7. During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups?	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
8. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem?	1	2	3	4	5

Please rate the severity of the following symptoms in the last week. *(circle number)*	NONE	MILD	MODERATE	SEVERE	EXTREME
9. Arm, shoulder or hand pain.	1	2	3	4	5
10. Tingling (pins and needles) in your arm, shoulder or hand.	1	2	3	4	5

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
11. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5

*Quick*DASH DISABILITY/SYMPTOM SCORE = $\left(\left[\frac{\text{(sum of n responses)}}{n}\right] - 1\right) \times 25$, where n is equal to the number of completed responses.

A *Quick*DASH score may <u>not</u> be calculated if there is greater than 1 missing item.

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WORK MODULE (OPTIONAL)

The following questions ask about the impact of your arm, shoulder or hand problem on your ability to work (including homemaking if that is your main work role).

Please indicate what your job/work is:_____

❒ I do not work. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week.

Did you have any difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for your work?	1	2	3	4	5
2. doing your usual work because of arm, shoulder or hand pain?	1	2	3	4	5
3. doing your work as well as you would like?	1	2	3	4	5
4. spending your usual amount of time doing your work?	1	2	3	4	5

SPORTS/PERFORMING ARTS MODULE (OPTIONAL)

The following questions relate to the impact of your arm, shoulder or hand problem on playing *your musical instrument or sport or both*. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you.

Please indicate the sport or instrument which is most important to you:_____

❒ I do not play a sport or an instrument. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week.

Did you have any difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for playing your instrument or sport?	1	2	3	4	5
2. playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
3. playing your musical instrument or sport as well as you would like?	1	2	3	4	5
4. spending your usual amount of time practising or playing your instrument or sport?	1	2	3	4	5

SCORING THE OPTIONAL MODULES: Add up assigned values for each response; divide by 4 (number of items); subtract 1; multiply by 25.
An optional module score may <u>not</u> be calculated if there are any missing items.

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Appendix D Burn Specific Health Scale-Brief

Current Date: __ __ / __ __ / __ __ __ __

INSTRUCTIONS

This form contains questions which in one way or another are related to problems or feelings that people may experience sometimes. A number of questions concern your previous burn in one way or another.

There are five possible answers for each question. The alternatives are given at the top of each page.

Read every question carefully. Your task is to identify which answer (only one!) that best describes you or how you feel in general, in other words not just now. Put one "cross" in the square which corresponds to your answer. Don't skip any items. If you believe that any question is unclear, or this is unclear, contact the person who mailed you this inquiry.

The questions are written in the form of statements. We will start with an example (which is not found in the actual inquiry):

	Extremely	Quite a bit	Moderately	A little bit	Not at all
My burn itches a lot.	X	O	O	O	O

Thank you for completing this questionnaire

Your answers will help us in our effort to understand the difficulties which patients afflicted by burns might encounter as well as possible aids given by health care.

Work quickly and do not consider each question too long!

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How much difficulty do you have?

		Extreme	Quite a bit	Moderate	A little bit	None/not at all
1.	bathing independently ?	O	O	O	O	O
2.	dressing yourself?	O	O	O	O	O
3.	getting in and out of a chair?	O	O	O	O	O
4.	signing your name?	O	O	O	O	O
5.	eating with utensils?	O	O	O	O	O
6.	tying shoelaces, bows, etc?.	O	O	O	O	O
7.	picking up coins from a flat surface?	O	O	O	O	O
8.	unlocking a door?	O	O	O	O	O
9.	working in your old job performing your old duties?	O	O	O	O	O

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To what extent does each of the following statements describe you?

		Extremely	Quite a bit	Moderate	A little bit	Not at all
10.	I am troubled by feelings of loneliness.	O	O	O	O	O
11.	I often feel sad or blue.	O	O	O	O	O
12.	At times, I think I have had an emotional problem.	O	O	O	O	O
13.	I am not interested in doing things with my friends.	O	O	O	O	O
14.	I don't enjoy visiting people.	O	O	O	O	O
15.	I have no one to talk to about my problems.	O	O	O	O	O
16.	I have feelings of being trapped or caught.	O	O	O	O	O
17.	My injury has put me further away from my family.	O	O	O	O	O
18.	I would rather be alone than with my family.	O	O	O	O	O
19.	I don't like the way my family acts around me.	O	O	O	O	O

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20.	My family would be better off without me.	O	O	O	O	O
21.	I feel frustrated because I cannot be sexually aroused as well as I used to.	O	O	O	O	O
		Extremely	Quite a bit	Moderate	A little bit	Not at all
22.	I am simply not interested in sex any more.	O	O	O	O	O
23.	I no longer hug, hold or kiss.	O	O	O	O	O
24.	Sometimes, I would like to forget that my appearance has changed.	O	O	O	O	O
25.	I feel that my burn is unattractive to others.	O	O	O	O	O
26.	My general appearance really bothers me.	O	O	O	O	O

Below you will find a number of questions about your damage.

To what extent does each of the following statements describe you?

	Extremely	Quite a bit	Moderate	A little bit	Not at all

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27.	The appearance of my scars bothers me.	O	O	O	O	O
28.	Being out in the sun bothers me.	O	O	O	O	O
29.	Hot weather bothers me.	O	O	O	O	O
30.	I can't get out and do things in hot weather.	O Extremely	O Quite a bit	O Moderate	O A little bit	O Not at all
31.	It bothers me that I can't get out in the sun.	O	O	O	O	O
32.	My skin is more sensitive than before.	O	O	O	O	O
33.	Taking care of my skin is a bother.	O	O	O	O	O
34.	There are things that I've been told to do for my burn that I dislike doing.	O	O	O	O	O
35.	I wish that I didn't have to do so many things to take care of my burn	O	O	O	O	O
36.	I have a hard time doing all the things I've been told to take care of my burn.	O	O	O	O	O

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37.	Taking care of my burn makes it hard to do other things that are important to me.	O	O	O	O	O
38.	My burn interferes with my work.	O	O	O	O	O
39.	Being burned has affected my ability to work.	O	O	O	O	O
40.	My burn has caused problems with my working.	O	O	O	O	O

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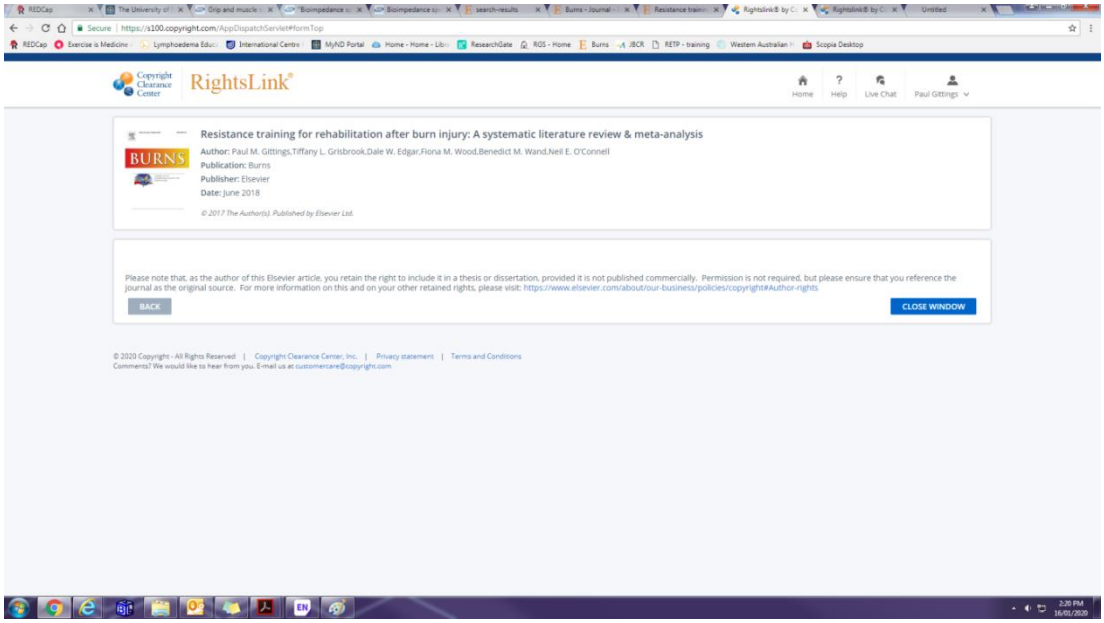

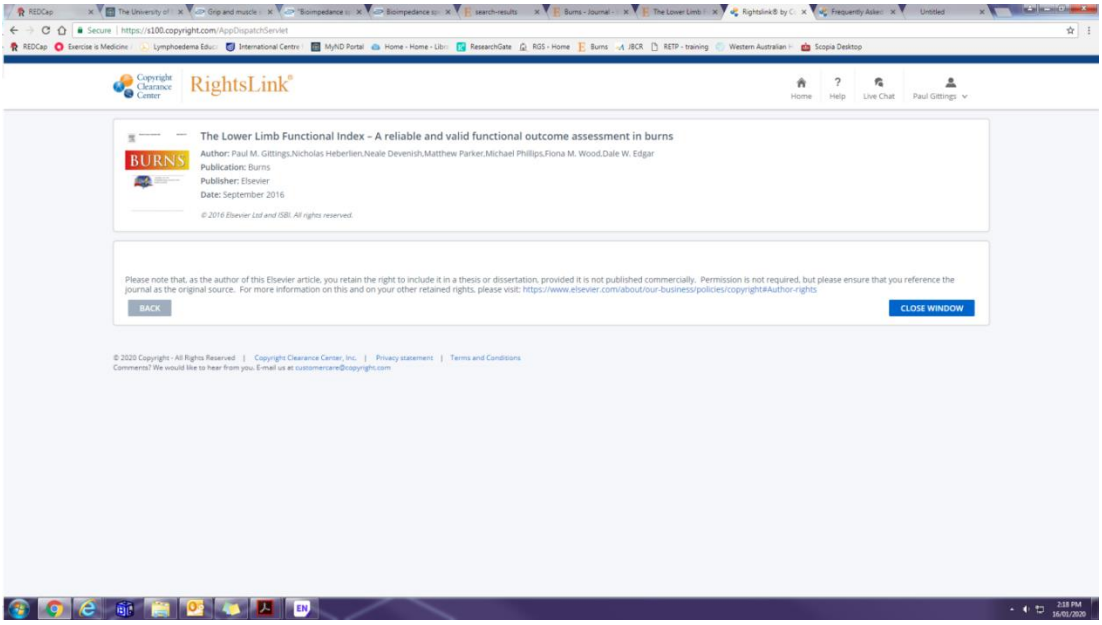

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Appendix F Research ethics approvals

Government of Western Australia
Department of Health
South Metropolitan Health Service

Royal Perth Hospital

8th May 2014

Mr Paul Gittings
Burns Unit
Royal Perth Hospital

Dear Paul

Project Title: **Does exercise training improve muscle strength and function after burn injury?**
Protocol No: **N/A**
HREC Reference: **REG 14-008**

The ethics application for the project referenced above has been **approved** by the Royal Perth Hospital Human Research Ethics Committee (EC00270).

The following documents have been approved for use in this project:

- Study Protocol **(No version)**
- Patient Information and Consent Form. **(Version 1.0, 04/03/2014)**
- Burn Specific Health Scale **(No version)**
- Short Form (SF-36) **(Version 2)**

The approval is **valid to 08/05/2017** and on the basis of compliance with the 'Conditions of HREC Approval for a Research Project' (attached).

The nominated participating site in this project is:

Royal Perth Hospital

- If additional sites are recruited prior to the commencement of, or during the research project, the Coordinating Principal Investigator is required to notify the RPH HREC. Notification of withdrawn sites should also be provided to the HREC in a timely fashion.

- A copy of this ethical approval letter must be submitted by all site Principal Investigators to the Research Governance Office or equivalent body or individual at each participating institution in a timely manner to enable the institution to authorise the commencement of the project at its site/s.

This letter constitutes ethical approval only. This project cannot proceed at any site until separate site authorisation has been obtained from the Chief Executive, or delegate, of the site under whose auspices the research will be conducted.

The RPH Ethics Committee is registered with the Australian Health Ethics Committee and operates according to the NHMRC National Statement on Ethical Conduct in Human Research and International Conference on Harmonisation – Good Clinical Practice.

Should you have any queries about the HREC's consideration of your project, please contact (08) 9224 2292. The HREC's Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Ethics Office, (08) 9224 2292 or rph.hrec@health.wa.gov.au.

Yours sincerely

PROF FRANK VAN BOCKXMEER
Chairman, RPH Human Research Ethics Committee

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28 April 2016

Dr Dale Edgar & Mr Paul Gittings
School of Physiotherapy
The University of Notre Dame Australia
Fremantle Campus

Dear Dale and Paul,

Reference Number: 014138F

Project Title: "Does exercise training improve muscle strength and function after burn injury?"

Your application for an amendment to your approved research project has been reviewed by the university's Human Research Ethics Committee in accordance with the *National Statement on Ethical Conduct in Human Research* (2007). I am pleased to advise that ethical clearance has been granted for this proposed study.

All research projects are approved subject to standard conditions of approval. Please read the attached document for details of these conditions.

On behalf of the Human Research Ethics Committee, I wish you well with your study.

Yours sincerely,

Dr Natalie Giles
Research Ethics Officer
Research Office

cc: A/Prof Joanne Connaughton, Acting Dean, School of Physiotherapy;
Prof Ben Wand, SRC Chair, School of Physiotherapy

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