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ASSOCIATION OF SKELETAL MUSCLE AND PSYCHOLOGICAL RESPONSES TO IMMOBILITY AFTER MAJOR INJURY

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ASSOCIATION OF SKELETAL MUSCLE AND PSYCHOLOGICAL RESPONSES TO IMMOBILITY AFTER MAJOR INJURY

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Nursing
at the University of Kentucky

By
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2019

ABSTRACT OF DISSERTATION

ASSOCIATION OF SKELETAL MUSCLE AND PSYCHOLOGICAL RESPONSES TO IMMOBILITY AFTER MAJOR INJURY

The purpose of this dissertation was to explore the physical and psychological responses to the combination of major trauma (Injury Severity Score [ISS] > 15) and variable periods of immobility. Specific aims were to: 1) develop a conceptual model that illustrates physiological and psychological alterations that occur after injury and subsequent immobility, and their association with skeletal muscle responses and recovery; 2) evaluate daily measures of skeletal muscle strength (bicep and quadricep) using dynamometry and skeletal muscle (rectus femoris and biceps brachii) muscle thickness measured with ultrasound in patients after major trauma; and 3) assess the predictive ability of anxiety and depressive symptoms after traumatic injury on delayed ambulation (>48 hours) following hospital admission.

Specific Aim 1 was addressed by development of a conceptual model to describe the association between injury responses, immobility and skeletal muscle after trauma based on a comprehensive review of the state of the science. This model guided the research reported in Aims 2 and 3. The second specific aim was addressed with the conduct of an observational study in which we evaluated daily skeletal muscle strength with dynamometry and muscle thickness with ultrasound to evaluate the impact of trauma and immobility on skeletal muscle in patients after major trauma (n = 19). Participants with delayed ambulation after trauma (more than 48 hours immobility) demonstrated significantly less muscle strength compared with those who had early ambulation (bicep: delayed ambulation 12.9 ± 3.8, early ambulation 17.7 ± 4.7, p = 0.004; quadriceps: delayed ambulation 9.9 ± 3.1, early ambulation 17.1 ± 4.6, p = 0.001). Muscle thickness was unchanged over time in those with delayed ambulation; however, in those who ambulated early, muscle thickness significantly increased by 0.17 cm (p = 0.008) from baseline to day 5. The third specific aim was addressed with data collected during the same observational study of patients after trauma (n = 19). Participants provided measures of anxiety and depressive symptoms at baseline. Anxiety was not a predictor of delayed ambulation; however, depressive symptoms increased the likelihood of delayed ambulation by 67% (Odds Ratio [OR]: 1.67, 95% CI: 1.02 – 2.72, p = 0.041).

Early ambulation was associated with significantly greater muscle strength and thickness as determined by dynamometry and muscle ultrasound, and depressive symptoms significantly increased the likelihood of delayed ambulation. Systematic evaluation of the association between trauma injury, immobility, skeletal muscle function and structure, and psychological state will provide an opportunity for the appropriate evaluation after injury and development of effective, tailored interventions to improve short- and long-term physiological and psychological recovery.

KEYWORDS: trauma, immobility, ambulation, skeletal muscle, anxiety, depressive symptoms

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April 17, 2019

Date

ASSOCIATION OF SKELETAL MUSCLE AND PSYCHOLOGICAL RESPONSES TO IMMOBILITY AFTER MAJOR INJURY

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This dissertation is dedicated to my parents, John and Susan: thank you for always believing in me and the power of education; and to Jody: this dissertation is as much yours as it is mine - thank you for standing by me during this journey.
I love you all.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER ONE

Introduction

Trauma and unintentional injury was the eighth leading cause of death worldwide in 2016, accounting for more than 5 million deaths and 9% of the worldwide mortality rate.[1,2] In the United States, trauma has remained the leading cause of death for persons aged 1 to 44 for the last decade, and accounted for nearly 3 million hospitalizations.[3] Although trauma has remained a leading cause of mortality in the United States, the rate of trauma-related deaths decreased from 2.72% in 2010 to 2.63% in 2015, despite the incidence of trauma increasing nearly 20%.[4,5] Increased survival after trauma contributes to approximately 12% of the worldwide disability; thus, many individuals who survive trauma experience short- and long-term consequences that influence their activities of daily living.

Up to 29% of patients hospitalized after trauma experienced a complication due to either the mechanism of injury or the management of the injuries.[6] Investigators who studied short-term consequences of trauma focused on complications such as hemorrhage, acute respiratory distress syndrome, acute kidney injury, organ failure, and death.[7-10] Long-term consequences of injury typically evaluated included physical and psychological functional disability, with evaluation of symptoms such as anxiety, depression, and post-traumatic stress disorder.[11-14] Immobility is an underreported consequence of injury and a contributor to overall disability, particularly as it relates to skeletal muscle dysfunction.

Immobility after trauma occurs because of injury or as a strategy to decrease metabolic demands following injury; however, prior investigators have demonstrated negative short- and long-term consequences of immobility.[15-17] For example, within 24 hours of immobility, there are detectable changes in skeletal muscle size and strength, and for each subsequent day of immobility, investigators found a loss 1.5 kg of skeletal muscle mass and 1-1.5% of muscle strength.[18] The inflammatory response to trauma also contributes to skeletal muscle changes; however, few investigators have focused on the synergistic results of trauma and immobility on skeltal muscle outcomes, with consideration of the psychological state after trauma. Paddon-Jones and colleagues determined that the combination of immobility and inflammation similar to that of severe injury produced a 3-fold greater loss of skeletal muscle mass and 28% greater reduction in muscle strength compared with matched controls who experienced immobility without inflammation.[19] Other investigators demonstrated that psychological symptom development following injury also significantly reduced functional outcomes.[13,14,20,21] For example, investigators found that 22% of patients after orthopedic trauma reported psychological symptoms at discharge, and symptoms were significantly associated with physical function limitations, such as impaired mobility.[20] Improved survival with increased prevalence of disability after trauma requires innovative research investigation to improve short- and long-term outcomes for this expanding population.

In Chapter Two, the manuscript presents a conceptual model that describes potential associations between injury response and immobility, with particular emphasis on physiological changes in skeletal muscle, and psychological symptoms after trauma, and how these might contribute to functional outcomes. Physiological changes in skeletal

muscle secondary to trauma response and immobility include decreased protein synthesis, catabolism, and muscle atrophy with subsequent decreased muscle mass, strength, and exercise capacity. Psychological symptoms, such as anxiety, depression, and PTSD, are proposed to significantly reduce motivation to engage in physical activity. Together, the physiologic and psychological responses decrease physical activity level. The long-term consequences are comorbid conditions, disability, and delayed return to previous activity. This conceptual model guided the development and conduct of an observational study reported in Chapters Three and Four.

Chapter Three is a report of a study to evaluate the association between skeletal muscle size, strength, and time to first full ambulation in patients (n = 19) after major trauma. We measured sociodemographic and clinical variables, and skeletal muscle size with ultrasound and muscle strength with dynamometry in patients after major trauma. Participants were subsequently categorized as early ambulation (n = 10; ambulated within 48 hours of admission) and late ambulation (n = 9; ambulated after 48 hours of admission) based on the mobilization protocol used by the trauma service. Time to first ambulation was 59 ± 50 hours (2.5 ± 2.1 days) after hospital admission. The early and late groups did not differ in any sociodemographic characteristics.

Participants who ambulated early displayed a 10% increase in bicep size on days 3 and 4 from baseline, and a 15% increase in bicep size on day 5 compared to baseline. There were no between or within group differences in rectus femoris size. Over the duration of the observations, participants who ambulated early displayed consistently more bicep strength (22-37%) than participants who ambulated later, and more quadriceps strength (26-46%) than the late group; however, both the late and early groups

showed improvement in quadriceps strength from baseline. The early group increased quadriceps strength by as much as 10% (day 4); while the late ambulation group displayed up to 22% (days 4 and 5) increase in quadriceps strength. There were detectable changes in skeletal muscle size and strength in patients admitted after major injury; ambulation within 48 hours of admission following major injury was associated with increased bicep size and more biceps and quadriceps strength.

Psychological symptoms after trauma include anxiety, depressive symptoms, and PTSD; these occur in approximately 30-40% of individuals after physical trauma.[22] In Chapter Four, we report an evaluation of the association between baseline anxiety and depressive symptoms and ambulation group (early: ambulated within 48 hours from admission, n = 10; late: ambulated after 48 hours from admission, n = 9) in patients after major trauma. The Hospital Anxiety and Depression Scale (HADS) was administered to evaluate the self-report of anxiety and depressive symptoms, and to evaluate how those were associated with mobility status (early versus later).[23] At baseline, six participants demonstrated symptoms of anxiety (HADS-Anxiety score ≥ 8) and four demonstrated depressive symptoms (HADS-Depression score ≥ 8). Those who were anxious at baseline had a significantly higher injury severity score (ISS) (anxiety ISS: 25; asymptomatic ISS: 19), took significantly longer to first ambulation (anxiety hours to ambulate: 78; asymptomatic hours to ambulate: 50), were younger (anxiety: 30 years; asymptomatic: 45 years), and all indicated their financial status as *makes less than ends meet* when compared to participants who were not anxious at baseline. Participants with baseline depressive symptoms all indicated their financial status as *makes less than ends meet,* and had a significantly shorter hospital length of stay (LOS) (depressive symptoms LOS: 3.3

days; asymptomatic LOS: 6.2 days) compared to participants without baseline depressive symptoms. Baseline anxiety was not predictive of ambulation group; however, depressive symptoms at baseline was predictive of delayed ambulation by nearly 2-fold (Odds Ratio [OR]: 1.67, 95% CI: 1.02 – 2.72, p = 0.041).

Chapter Five is a summary of each chapter and conclusions from these papers. Future directions for clinical research and potential implications for practice in this population are proposed.

CHAPTER TWO

Conceptualizing Injury and Immobility: An Organizing Framework to Guide Trauma Care

Synopsis

Traumatic injury is a leading cause of mortality in the United States and a major contributor to healthcare costs. Nearly one-third of patients develop a complication after a traumatic injury. However, disability and functional impairment after trauma as a consequence of treatment are not considered complications. Prescribed periods of immobilization and bed rest after trauma to decrease metabolic need, prevent further injury, and promote healing have serious negative effects that include acquired weakness and muscle wasting. Psychological responses after trauma may also negatively influence mobility during recovery. There is a need for better understanding of the interaction of trauma and subsequent immobility; thus, the purpose of this paper is to present a conceptual model of physiological and psychological alterations that occur after injury and immobility and affect short- and long-term recovery. A clearer understanding of the association among these alterations with recovery will support development of future research to decrease acquired disability due to immobility after trauma.

Introduction

Trauma has been among the four leading causes of death across all age groups for over a decade in the United States.[24] In 2015, there were over 860,000 cases of traumatic injury reported; 79% of these required hospitalization and 4.4% were fatal.[25] The cost of traumatic injuries totals over $585 billion annually, including direct medical care expenses and lost productivity as a result of injury.[26] Not surprisingly, hospital length of stay increased as severity of injury increased, with seven days the median hospital length of stay for the most severely injured.[25] Prior investigators found that nearly half (44%) of patients who survived their injuries did not return to their pre-injury functional status at 12 months following injury, which highlighted the long-term impact of trauma.[12]

Patients after trauma are at risk for a variety of complications due to the pathophysiology of trauma (Table 2.1). Interventions implemented to manage injuries such as prescribed immobilization can also lead to other consequences including muscle atrophy and weakness (Table 2.2).[15,17,27-30] Negative physiological effects of immobility begin as early as two hours after initiation and may result in lasting complications, such as myopathy and skeletal muscle deconditioning.[15,17,31-33]

Traumatic injury and associated prolonged immobility also affect psychological wellbeing.[34] More than half (56%) of individuals reported depression after injury, [14,35-39] and up to 32% developed posttraumatic stress disorder (PTSD).[40] The psychological care of acutely injured patients during hospitalization is often not prioritized,[12,41,42] and the immediate impact of psychological distress on acute recovery has not been systematically studied.[21,40,43]

Although management of traumatic injuries has improved survival, there remains a lack of understanding about the combined effect of trauma and immobility on skeletal muscle function after injury.[4,25] Thus, the purpose of this paper is to present a conceptual model of physiological and psychological alterations that occur after injury and immobility that may affect short- and long-term recovery, as they relate to skeletal muscle. A clearer understanding of the association of these alterations with recovery will support development of interventions intended to decrease acquired disability due to immobility after trauma. This model expands on prior conceptual models by incorporating current research findings related to trauma and subsequent immobility.

Prior Models Focused on the Effects of Immobility

Lujan and White used aerospace research findings to develop a physiologic model that described responses to prolonged supine position and simulated weightlessness during spaceflight.[44] Their model described how immobility produced deconditioned muscles and created a predominant tissue catabolic state resulting in muscle atrophy and bone demineralization, which reduced the subsequent weight-bearing ability of muscle tissue.[44,45] Heitkemper and colleagues developed a model to explain how individuals respond and adapt, both physically and psychologically, to adverse clinical situations.[46,47] Maloni merged concepts from these two prior models to develop a model that included both the physiological and psychological consequences of immobility.[45] Combined, these models provided the conceptualization of immobility during hospitalization as having both dynamic physiological and psychological consequences that must be considered concurrently.

Conceptual model

Building on the previous models, we developed a dual physiological and psychological pathway conceptual model of immobility that included the consequences of trauma and associated immobility to describe how trauma and its treatment led to decreased functional outcomes (Figure 2.1). The effects of trauma and subsequent immobility occur along two pathways, physiological and psychological. Along the physiological pathway, there are local and systemic responses that lead to loss of skeletal muscle. Locally, traumatic injury initiates an inflammatory response that results in neutrophil infiltration of the injured area, heightened lysosomal enzyme activity, and skeletal muscle degradation. Systemically, immobility due to injury and management of injury triggers proteolysis of skeletal muscle protein resulting in disuse atrophy. The consequence of these responses is reduction in skeletal muscle size, strength, and endurance. Along the psychological pathway, injury combined with immobility and its sequelae result in biobehavioral, cognitive, and sensory changes that contribute to the development of psychological symptoms that include anxiety, depression, and PTSD. These psychological symptoms can decreased motivation to engage in physical activity. The combined consequences on skeletal muscle ultimately delay return to previous activity or produce long-term disability.

Physiological Pathway

Decreased protein synthesis, catabolism, and muscle atrophy

Local consequences of injury on skeletal muscle

An inflammatory cascade initiated at the time of injury produces a multisystem, physiologic response to cellular injury, and when effective, ultimately restores

homeostasis.[48] Following skeletal myocyte injury or death, neutrophil infiltration of the injured area removes necrotic tissue through phagocytosis; this response peaks between 24 and 48 hours following injury.

The inflammatory response can cause additional damage due to the actions of proinflammatory cytokines such as interleukin-6 (IL-6) and tissue necrosis factor-alpha (TNF-α) at the site of injury and systemically.[49] These proinflammatory cytokines activate the ATP ubiquitin-proteasome pathway, which regulates the breakdown of extra- and intracellular skeletal muscle protein.[50] The ATP-ubiquitin pathway generates an enhanced proteolysis and decreases protein synthesis through alterations in myocyte differentiation and fusion into myotubes, thus impairing repair of muscle tissue after injury.[50-52] Proteolytic activation, coupled with the required energy expenditure for tissue repair after injury, delays anabolic processes and reduces muscle protein synthesis.[52,53] Gluconeogenesis is required to generate energy for cellular responses to injury; amino acids are diverted to the liver to be used as an intermediate energy source, which further depletes protein stores available for muscle repair.[48]

Systemic consequences of immobility on skeletal muscle

Prolonged periods of immobility stimulate similar inflammatory mediators with subsequent systemic skeletal muscle catabolism.[54] Immobility increases circulation of components of the ubiquitin-proteasome pathway and augments the production of proinflammatory cytokines, including IL-6 and TNF-α. These molecules stimulate proteolysis and muscle tissue loss, as seen in disuse atrophy.[54,55] Investigators have demonstrated that there is a 3-fold increase in proteolytic ubiquitin component expression in immobilized muscle after 10 days.[54,56] The ubiquitin-proteasome pathways triggered

after tissue injury are also active in the removal of sarcomere proteins in response to immobility. Multiple investigators have concluded proinflammatory responses to injury and immobility are synergistic, producing an exaggerated response in skeletal muscle compared to immobility alone.[19,31,53,57-60] In prior research, the combination of injury and immobility resulted in increased catabolism by up to 3-fold, decreased protein synthesis by up to 50%, and reduction of muscle mass by 6% or more with two weeks of bed rest.[19,52,53,57]

Decreased muscle mass, strength, and exercise capacity

Reduced protein synthesis, persistent catabolism, and atrophy following injury and immobility alter the functional ability of skeletal muscle.[19,58,59] Investigators have demonstrated that in the setting of immobility alone, there was significant loss of muscle mass, strength, and exercise capacity (Table 2.3); however, these changes are magnified in the concomitant setting of an inflammatory state, such as after injury or critical illness (Figure 2.2).[19,57-63] After injury and immobility, scientists demonstrated a 3-fold greater loss of muscle mass, a 28% reduction in leg extension strength, a 15% increase in fatigue index, and a 15% reduction in aerobic threshold compared to immobility alone (Figures 2.3 and 2.4).[19,61] These findings suggested that there are significant synergistic consequences for skeletal muscle existed in the setting of injury and immobility.

Psychological Pathway

Psychological responses to trauma and immobility

Scientific evidence supports an association of proinflammatory states with psychological disorders and symptoms that include mood changes, anhedonia, fatigue, decreased social interaction, and decreased physical activity.[64-67] Scientists have found

that concentrations of proinflammatory molecules like C-reactive protein (CRP) and IL-6 are significantly higher in individuals with clinical depression compared to socially integrated, non-depressed individuals.[68] The presence of elevated inflammatory mediators have also been found in other psychological states. Investigators determined that anxiety-provoking activities, such as public speaking, resulted in a 5% increase in circulating IL-6 and an associated 2-fold increase in CRP levels in individuals with PTSD.[64,69,70] The proinflammatory state that results from injury and immobility could be also associated with psychological symptoms that follow trauma.

Management strategies for patients after trauma may also influence the development of psychological symptoms. Ringdal and colleagues examined the relationship between delusional experiences during the ICU stay, anxiety, and depressive symptoms in patients hospitalized after trauma, and found that 26% reported delusional memories about their injuries and hospitalization. These individuals recalled hallucinations, nightmares, and paranoid delusions about others trying to hurt or kill them, and were nearly 3 times more likely to report anxiety and depressive symptoms compared to those without delusions.[43] Patients with delusional memories had more severe injury, were more often mechanically ventilated, and received nearly double the sedation compared to patients without delusions. Interventions required to manage patients who are more severely injured may result in altered cognitive and sensory perceptions and cognitive function.[43] Management strategies for traumatic injury, such as use of mechanical ventilation and sedation, were also associated with longer periods of immobility and nearly a three-fold longer timeframe for patients to return to baseline functional status.[71]

Immobility can also contribute to the development of psychological symptoms. Liu and colleagues found that immobilization resulted a significantly greater reduction in an individual's self-reported positive affect, including mood, energy level, and pleasurable engagement.[30,72] Other investigators determined that three hours of immobilization altered the ability of healthy volunteers to differentiate among positive, neutral, and negative-associated images when compared to individuals sitting in a chair for the same three hour period, suggesting that there may be an association between positioning, such as recumbent, and increased negative thoughts.[73] Thus, prior investigators linked immobility with blunted emotional responses and poorer psychological health.[30,73]

As many as 30-40% of patients experienced anxiety, depression, and PTSD following trauma.[22,37,40,43,74] Schnyder and colleagues concluded demographic risk factors and greater life stress increased the likelihood of psychological symptoms after trauma by 1.5 times.[74] The majority of psychological evaluations of patients after trauma occurred post-hospitalization;[12-14,21,37,75-77] however, investigators have suggested that inpatient screening and intervention were warranted during the acute injury phase.[36,37] Previous investigators found that 20% of hospitalized patients had high levels of PTSD symptoms, 20% met criteria for acute stress disorder, and 36% had high levels of depressive symptoms after trauma.[36] Patients after trauma with concurrent depression, anxiety, and PTSD demonstrated a 1.6 times increased risk of re-hospitalization and 1.5 times increased risk of all-cause mortality at 5 years following injury compared to those without these psychological disorders.[78] These findings support the association of

psychological symptoms and disorders after traumatic injury with negative short and long-term outcomes.

Decreased motivation

Investigators have repeatedly demonstrated that physical activity and exercise were an effective management strategy for mental health disorders including depression, anxiety, and PTSD.[79-82] However, individuals with psychological disorders might be disengaged to participate in physical activity for a number of reasons. These include lack of motivation and avoidance of symptoms associated with their disorder, such as hyperarousal symptoms associated with PTSD. Investigators found that 73% of patients with PTSD or other psychological symptoms identified lack of motivation as the largest barrier to engaging in physical activity.[79,80,82,83] Additionally, Rutter and colleagues determined that hyperarousal symptoms predicted decreased engagement in exercise.[82] Symptoms associated with psychological disorders after trauma might incite decreased motivation to engage in activity like ambulation or physical exercise.

PTSD and depressive symptoms have also been associated with decreased physical and social functioning, role limitations, and vitality.[82] Investigators also determined that exercise avoidance was a negative mediator of both PTSD and depressive symptoms with poorer health status (i.e., obesity and sleep disturbances). The loss of interest or enjoyment in usual activities characteristic of these disorders may contribute to decreased motivation to engage in activity.[82] This evidence supports the relationship between psychological symptoms, reduced motivation, and a decreased engagement in activity.

Investigators have also established an association between psychological symptoms and decreased activity after injury. Individuals after injury subsequently diagnosed with depression were nearly 3 times more likely to spend the day in bed, and 3 times more likely to have reductions in their usual activity at 3 months post-injury.[13] Thus, injury and immobilization, with subsequent psychological symptoms, may interact to reduce activity level.

Decreased Activity

The decrease in activity level following trauma compounds the physical and psychological consequences of traumatic injury, indicating that early mobilization after trauma may be beneficial.[16,17] Prior investigators demonstrated engagement in physical activity reversed the muscle deconditioning from periods of immobilization.[84-87] Suetta and colleagues found that the loss of muscle size and strength that resulted from immobilization could be restored through prescribed retraining exercises (young men: +8%; older men: +4%) and strength (young men: +19%; older men: +30%).[86] Other investigators found engagement in short periods of out of bed activity mitigated the catabolic effects associated immobilization.[88] Mulder and colleagues found that during bed rest in healthy, young, male volunteers, muscle cross-sectional area was maintained and strength was increased 12% by 25 minutes of upright, out-of-bed exercise for 5 days.[88]

Activity to mitigate deconditioning of skeletal muscle in the clinical setting could be achieved through early mobilization protocols. A number of investigators have described both the challenges and benefits of these protocols.[89-94] Some barriers that have been identified which impede the implementation of early mobilization protocols include

inadequate staffing and time constraints, lack of education for both healthcare staff and patients about the consequences of deconditioning, patient perceptions of the need to rest, fear of patient safety compromise, and lack of interdisciplinary collaboration.[18,89] Other investigators found that the benefits of early mobilization protocols such as reduced ICU and hospital length of stay, increased discharge home versus rehabilitation facility, and increased functional independence outweighed the barriers and challenges.[92,95,96]

Health care providers may be able to increase motivation to engage in activity by first addressing the psychological symptoms experienced by patients after trauma.[97-99] Investigators found that a positive affect towards rehabilitation was predictive of higher engagement in therapeutic activities, and that denial of severity of health state was predictive of being less engaged.[98] Health care professionals, particularly nurses, are positioned to enhance and foster development of positive affect by employing interventions such as coaching, reflection of positive aspects of life, and focusing on hope to envision the best possible outcome.[98,100,101] Investigators have also suggested that useful ways to increase hope and increase positive outcomes related to therapy and rehabilitation is to address outcome expectations.[99] Strategies such as providing a convincing rationale for therapy, expressing faith in the patient's ability, increasing the credibility of the health care provider, providing outcome education, and comparing progress with expectations are all useful strategies to engage and motivate patients to participate in activity after injury and subsequent immobility.[97-101]

Consequences

Data about the acute consequences of skeletal muscle responses in patients after trauma who experience subsequent immobilization are lacking; however, there is

sufficient evidence of the long-term consequences of physiological and psychological alterations following injury and immobility.[12,13,35,75,76,102] These are likely initiated during the acute phase of recovery. Davydow and colleagues found that less than half (44%) of patients after trauma had returned to their prior major activities after 12 months.[12] Other investigators concluded that the consequences for patients after injury included impaired mobility (37%), impaired ability to engage in self-care (21%), difficulty in engaging in usual activities such as household chores, work, and leisure activities (47%), pain and discomfort (50%), and anxiety and depression (41%).[102] At one year after injury, patients after trauma were nearly 2.5 times less likely to return to work, and on average, used 9 more full days of sick leave per month when compared to age, gender, and municipality-matched healthy individuals.[13,103] These findings demonstrated the consequences of trauma extended beyond the individual, and had societal impacts as well. These long-term consequences of injury and immobilization are derivatives of the acute complications related to skeletal muscle changes and accompanying psychological distress. To adequately address these long-term consequences, investigators should direct their efforts at the acute phase of recovery after injury.

Discussion

Following a traumatic injury, individuals experience physiological alterations that may directly and indirectly alter skeletal muscle structure and function, and be associated with psychological symptoms like anxiety, depressive symptoms, and PTSD that may decrease the motivation to ambulate. The primary injury, secondary effects of inflammation and heightened catabolic state, which subsequently alter skeletal muscle structure and function, reduce skeletal muscle activity and contribute to decreases in

muscle function. Simultaneously, psychological symptoms alter motivation to engage in activity which increases the detriment to muscle function. These effects influence short and long-term functional outcomes after traumatic injury.

The model can be used clinically to develop and test interventions such as comprehensive rehabilitation programs that address both physical and psychological recuperation for patients after trauma. For example, early mobility protocols have been found to be effective, cost-effective interventions that reduce physiological alterations such as acquired weakness and disability during hospitalization and contribute to better patient outcomes. These include shorter length of stay and higher levels of functional health. However, these investigations have not simultaneously evaluated the physiological and psychological components of hospitalization after trauma.[89-93,96,104,105] Additionally, there is a lack of evidence about the impact psychological symptoms following injury have on physical recovery and rehabilitation in the acute setting, which highlights the need for future comprehensive research.[37]

Our conceptual model is based on strong theoretical and empirical evidence. This model provides a comprehensive understanding of the complex interactions among injury, inflammation, immobility, and the psychological responses to both injury and immobility that produce short and long-term patient effects on physical function. The model can be used to support the development and evaluation of interventions to increase mobility during hospitalization and improve short and long-term outcomes in this population. Results of rigorous scientific studies will provide evidence for the development of clinical guidelines to optimize patient care and education of clinicians to support maximum functional recovery after injury.

Conclusion

Trauma can result in reduction in quality of life, disability, and death, particularly when skeletal muscle function is altered by injury, inflammation, and immobility. Additionally, psychological responses to trauma and immobility further compromise skeletal muscle by decreasing the motivation to engage in activity. The relationship between the physiologic and psychological responses to trauma as they relate to skeletal muscle structure and function have not been simultaneously investigated; consequently, this model was developed to conceptualize this phenomenon. Rigorous scientific testing of and subsequent use of this conceptual model may support a comprehensive understanding of the complex physiological and psychological responses and interactions with skeletal muscle structure and function after traumatic injury. Subsequent preservation of skeletal muscle structure and function by the use of early and effective interventions would optimize patient outcomes, reduce disability and promote restoration of functional ability to patients after trauma.

Table 2.1. Complications associated with traumatic injury.

Complication	Time to Onset	Prevalence
Coagulopathy [106,107]	Hypercoagulopathic state coincides with secondary rise in platelets and coagulation proteins 96 hours after injury; VTE formation occurs around 7-10 days	Up to 11%
Hemorrhage [7,108]	Loss of 100% of blood volume within 24 hours *OR* 50% within 4 hours *OR* 150 mL per minute	Accounts for up to 40% of mortality after trauma
Acute respiratory distress syndrome [10]	24-48 hours following injury	Up to 25%
Urinary tract infection [109,110]	24 to 120 hours following trauma	Up to 4.5%

Table 2.1. continued

Renal failure [8]	Serum creatinine ≥26.5 µmol/L within 48 hours *OR* Serum creatinine ≥1.5 times baseline within 7 days	Up to 20%
Liver failure [111]	3-16 days following trauma	5-10%
Metabolic disturbances/insulin resistance [112,113]	Within hours of and up to 24-48 hours after injury there is a decreased metabolic rate; 2 to 7 days after injury ensues a catabolic phase; weeks to months after injury begins the anabolic or restorative phase	Triglycerides provide 50–80% of the energy consumed after trauma. Proteolysis and protein turnover accounts for 1.5% daily loss in body lean mass. Gluconeogenesis increases endogenous glucose availability by 150% but stores are used up within 12-24 hours; 50-75% of patients experience insulin resistance.

Table 2.1. continued

Muscle loss [113,114]	Muscle degeneration and inflammation occur within minutes of injury and last up to two weeks; regeneration begins within 7 days post-injury and lasts around 2 weeks; fibrosis is the last phase following injury and can last for up to 4 weeks post-injury	Proteolysis and protein turnover accounts for 1.5% daily loss in body lean mass
Integumentary changes [107,115]	Within 72 hours, depending on devices, braces, and orthopedic fixation techniques	From 4.5-20%
Psychological symptoms [22,116]	From the time of hospitalization to 6 months after	Anxiety up to 40% Depression up to 30% Post-traumatic stress disorder up to 30%
Number(s) in parenthesis designate citation(s).		

Table 2.2. Complications associated with immobility

Complication	Time to Onset	Prevalence
Coagulopathy [117,118]	Thrombus formation has been detected as early as 4 days of immobilization	Incidence increases to 80% in patients who are on bed rest more than 7 days
Cardiovascular [15,17]	*Orthostatic intolerance*: within 24 hours *Heart rate variability*: 7-14 days	*Orthostatic intolerance*: reduction in circulating volume by 600 mL leading to hypotension *Heart rate variability*: resting heart rate increases ≥10 beats per minute

Table 2.2. continued

Respiratory failure [119,120]	Lower lobe atelectasis identified within 48 hours of recumbent position by chest radiographs	Up to 46% of patients who have critical illness neuromuscular abnormalities with prolonged bed rest have respiratory failure requiring mechanical ventilation
Urinary tract infection [121]	6 to 24 hours depending on severity and location of obstruction or volume of residual	From 15-36% with large post-void residual volumes, ineffective flow, obstruction, and stagnant urine, associated with decreased mobility and bed rest
Integumentary changes [17]	Within 2 hours at a pressure of at least 70 mmHg	Up to 38%

Table 2.2. continued

Metabolic disturbances/insulin resistance [17,122]	Within 5 days of bed rest	Up to 67% increase in insulin resistance after 5 days of bed rest
Muscle loss [17,18,58]	Muscle atrophy is measurable within 3 to 5 days of bed rest; reduction in strength and aeorbic capacity detectable within 10 days	1.5 kg of skeletal muscle mass and 1-1.5% of strength lost per day of immobilization
Psychological symptoms [14,73]	Emotional dulling is present as early as 3 hours of bed rest	3-times increase in likelihood of spending the day in bed if individual is depressed
Number(s) in parenthesis designates citation(s).		

Table 2.3. Comparisons of changes in muscle size and strength between traumatic injury and immobility.

	Injury	Immobility
Decreased muscle mass [19,53,57,60,63,123]	Leg lean muscle mass reduced by 1.4 kg Leg lean muscle mass reduced by 0.5 kg	Leg lean muscle mass reduced by 0.4 kg Leg lean muscle mass reduced by 0.6 kg Quadriceps volume (cm^3) reduced by 21% Triceps volume (cm^3) reduced by 29% Total muscle volume reduced by 6 ± 2%
Decreased muscle strength [19,58-60,123]	Leg extension strength reduced by 28%	Leg extension strength reduced by 23% Lower extremity strength reduced 13 ± 4% Knee flexor strength reduced by 14 ± 15% Plantar flexor strength reduced by 22 ± 7% Squat strength reduced by 34% Calf press strength reduced by 32%

Table 2.3. continued

Decreased exercise capacity [59,61,63]	Fatigue index (%) increased by 15% in injured patients VO_2 max (ml/kg/min) was 8% lower in injured patients Aerobic threshold (ml/kg/min) was 15% lower in injured patients	Fatigue index increased by 12.1 ± 12.7% VO_2 max (ml/kg/min) was reduced by 11 ± 4% Fast-twitch 2b muscle fiber presence increased by 22.2 ± 19.3%
VO_2 max = peak aerobic capacity; Fatigue index = (peak power−minimum power)/peak power ×100 (%). Number(s) in parenthesis designate citation(s).		

Figure 2.1. Conceptual model of the skeletal muscle response and recovery trajectory from the combined effects of immobility and trauma along with psychological adaptation after injury.

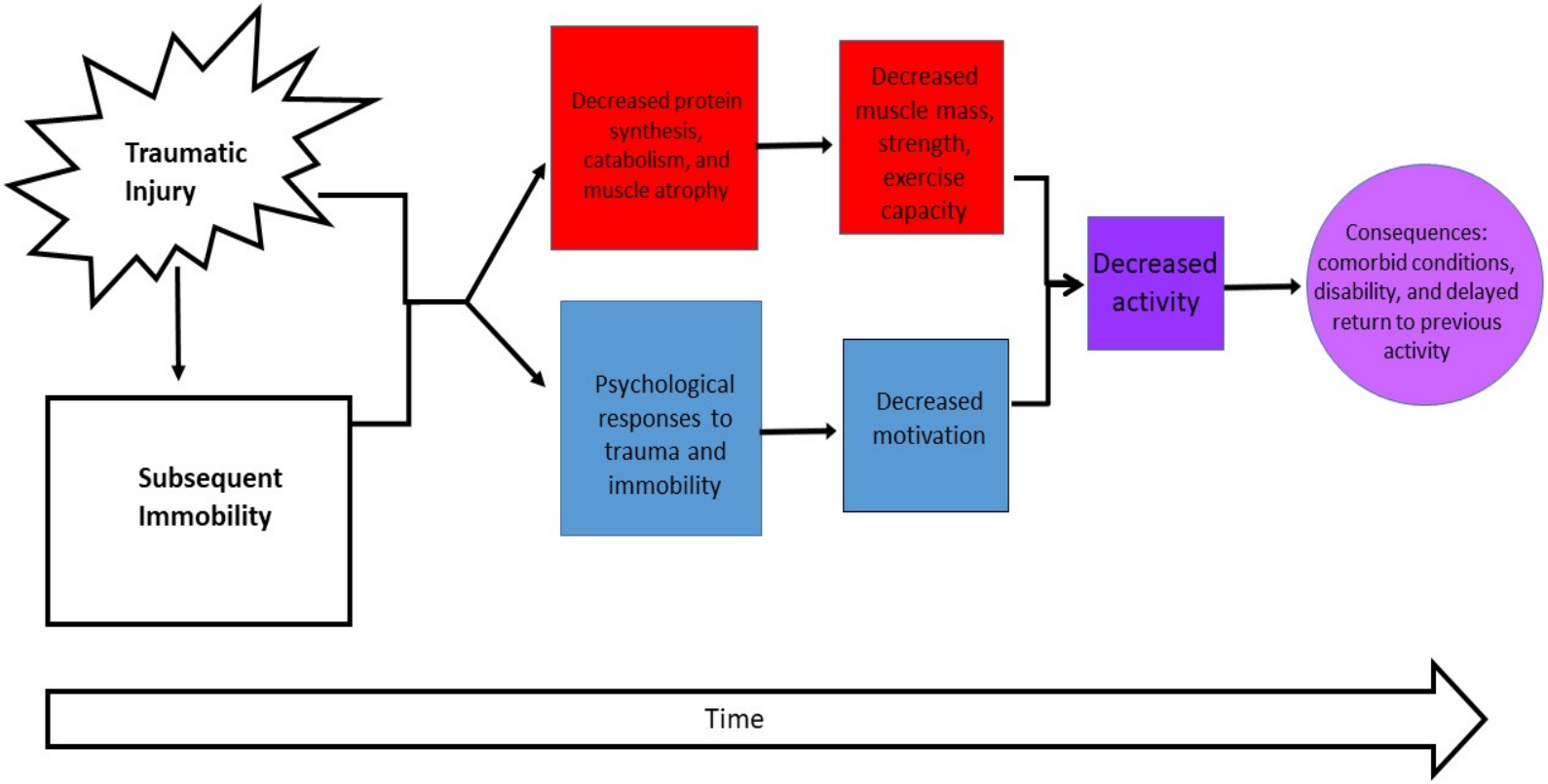
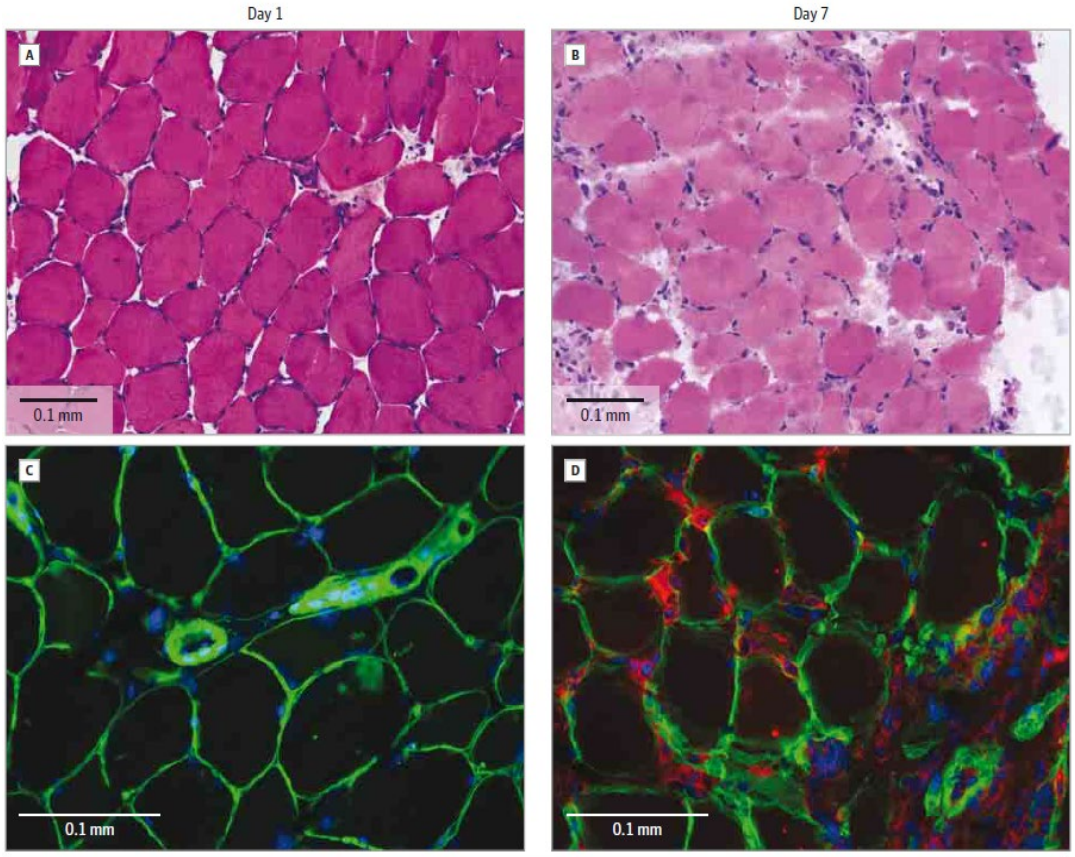


Figure 2.2. Comparison of histological slides of skeletal muscle biopsies taken from patients at day 1 of intensive care compared to day 7 of intensive care illustrating necrosis and macrophagic activity via immunostaining. Reprinted with permission.[124]



Healthy muscle is seen on day 1 (A, C) with necrosis and a cellular infiltrate on day 7 (B, D). This infiltrate was CD68 positive on immunostaining, indicating macrophage origin (red). A, B are hematoxylin and eosin stain, and C, D was immunostaining, with CD68 for red, laminin (myofiber outline) for green, and 4',6-diamidion-2-pheylidole (a nuclear marker) for blue.

Figure 2.3. Difference in lean leg muscle mass lost after 28 days of bed rest (-0.4 kg, $p < 0.05$) and bed rest with simulated hypercortisolemia (-1.4 kg, $p < 0.05$) in healthy volunteers. Figure adapted from data presented by Paddon-Jones et al. (2004) and Paddon-Jones et al. (2006), with permission.[19,123]

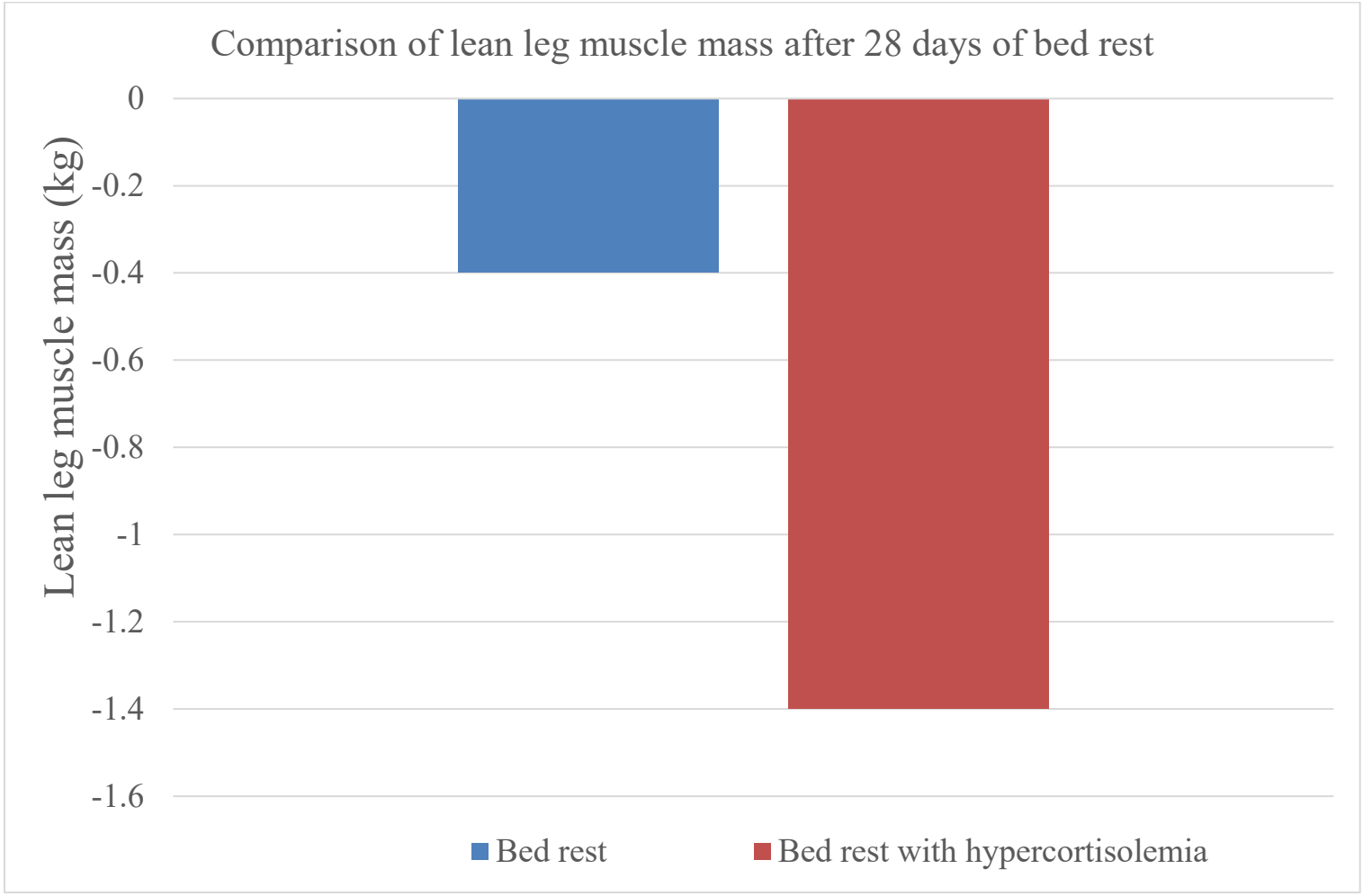
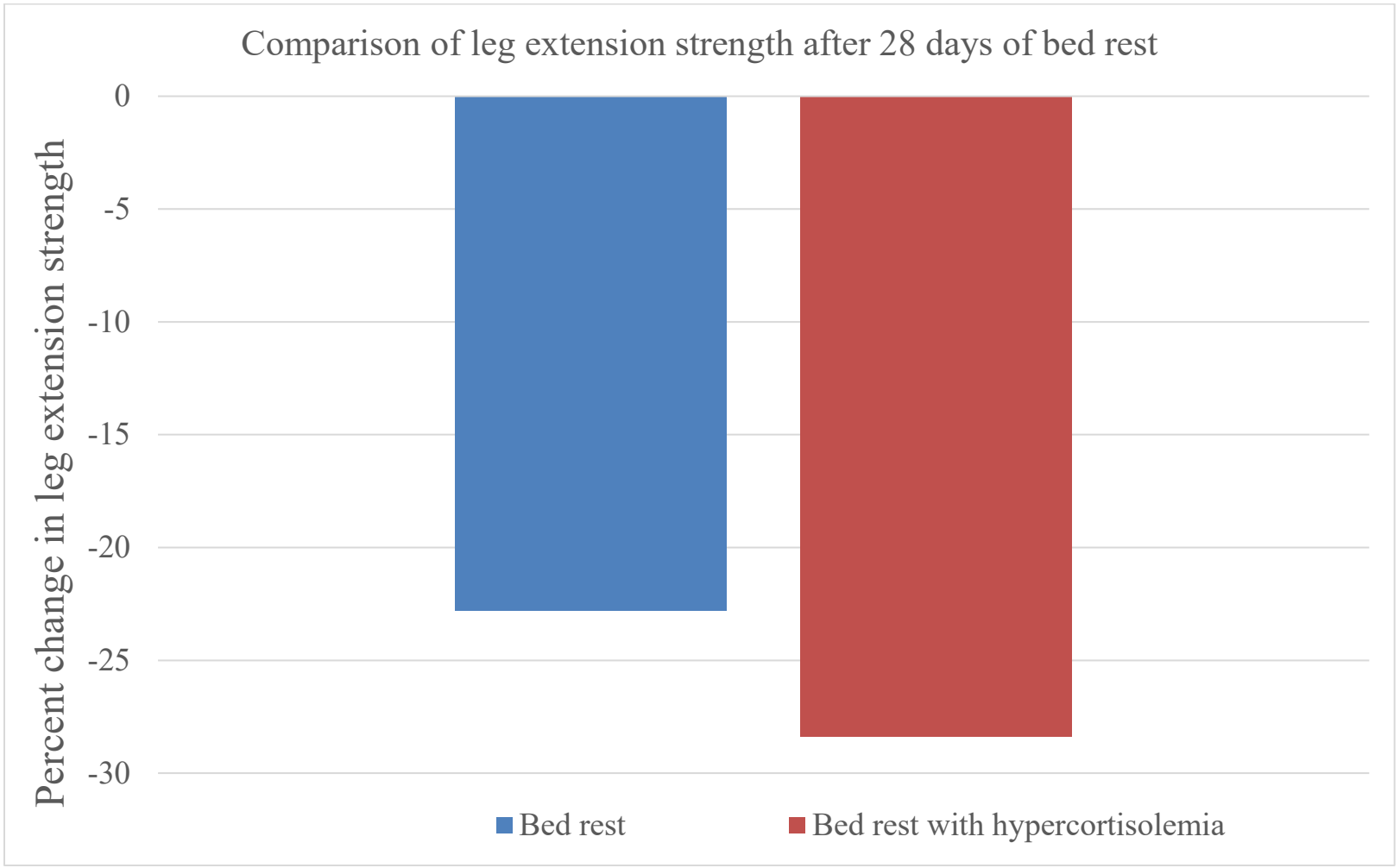


Figure 2.4. Difference in leg extension strength percent change after 28 days of bed rest (-22.8%, $p < 0.05$) and bed rest with simulated hypercortisolemia (-28.4%, $p < 0.05$) in healthy volunteers. Figure adapted from data presented by Paddon-Jones et al. (2004) and Paddon-Jones et al. (2006), with permission.[19,123]



CHAPTER THREE

The Association of Time to First Ambulation with Upper and Lower Extremity Skeletal Muscle Size and Strength in Adults after Major Traumatic Injury

Synopsis

Trauma and management of injuries often results in reduction in, or loss of mobility, which can lead to skeletal muscle deconditioning, degradation, and sustained disability. Prior investigators examined changes in skeletal muscle due to injury and immobility separately; however, the skeletal muscle consequences of combined immobility and trauma have not been systematically investigated. The purpose of this study was to determine the association of time to first ambulation (Early - within 48 hours of admission *or* Delayed - after 48 hours of admission) with upper and lower extremity skeletal muscle size and strength in patients after major trauma. Early ambulation was associated with increased bicep size from baseline. The Early ambulation group was significantly stronger in both upper and lower extremity muscles compared with the Delayed ambulation group at baseline (Early group baseline bicep 17.7 ± 4.74 lbs. of force, Delayed group baseline bicep 12.89 ± 3.82 lbs. of force, $p = 0.004$; Early group baseline quadriceps 17.08 ± 4.56 lbs. of force, Delayed group baseline quadriceps 9.87 ± 3.08 lbs. of force, $p < 0.001$). The Early ambulation group had more bicep (22-37%) and quadriceps strength (26-46%) throughout the study. Participants in the Delayed ambulation group demonstrated a 22% increase in quadriceps strength on days 4 and 5 from baseline. Early ambulation, within 48-hours after admission for trauma, was associated with increased bicep size, and greater bicep and quadriceps strength compared with those who ambulated later.

Background

In the United States, trauma and unintentional injury is the leading cause of death for individuals aged 1 to 44 years; trauma accounted for 5.4% of all deaths in 2015.[3] The mortality rate for injured persons was reduced from 2.72% in 2010 to 2.63% in 2015[4,5]; however, the prevalence of trauma and unintentional injury increased by nearly 20% during the same period.[4,5] The annual financial impact of trauma in the United States is estimated to be almost $700 billion, and nearly half (44%) of patients who survived their injuries did not return to their pre-injury functional status at 12 months after injury.[12,125] Thus, this population uses significant direct and indirect health care resources, exhibits long-term functional consequences, and would benefit from systematic study to improve outcomes during and following hospitalization.

Traumatic injuries and their management often induce reduction in, or loss of mobility, which can lead to skeletal muscle deconditioning and degradation, and sustained disability.[76] Historically, periods of immobility were prescribed to preserve energy and promote healing in critically ill and injured individuals.[16,28] The proposed benefits of prescribed immobilization included decreased metabolic demand.[17,28] However, this benefit was far outweighed by negative consequences in multiple organ systems.[17,18,95] Immobility was subsequently shown to reduce muscle strength by as much as 1.5% per day of bed rest,[16] and to decrease muscle cross-sectional areas by 2% over 7 days of strict immobility.[126] Thus, immobility alone, even for a short period, resulted in debilitating changes in skeletal muscle.

There are also skeletal muscle changes specifically associated with trauma.[16,127-129] Previously, scientists projected that the combination of immobility and traumatic

injury produced a loss of up to 28% in skeletal muscle strength,[19] and an estimated three time greater loss of muscle mass when compared to the effects of immobility alone.[19,57] Thus, the combination of trauma and immobility is significant, and may negatively affect outcomes including degree of disability and delayed return to previous functional level.[12,13,21]

Although research evidence supports early mobilization of patients after trauma to reduce the negative consequences of prolonged immobilization, such as pneumonia and venothromboembolism,[18,91-93,96,130] patients after trauma may have difficulty with ambulation because of the location and severity of injuries, or complications from injury.[131-133] Prior investigators focused on changes in skeletal muscle due to prolonged immobility and traumatic injury in separate investigations; however, a systematic investigation of the skeletal muscle consequences of the combination of immobility and trauma is required for a comprehensive understanding of skeletal muscle responses after trauma.

Purpose

The purpose of this study was to explore the association of time to first ambulation with upper and lower extremity skeletal muscle size and strength in patients after major trauma.

The specific aim of this study was to compare 5 daily measures of skeletal muscle size using ultrasound of the rectus femoris and biceps muscles, and strength using dynamometry of the biceps and quadriceps muscle after admission while controlling for age and sex in two groups of adult patients hospitalized for major trauma (Injury Severity

Score [ISS] > 15): early (first ambulation achieved within 48 hours from admission) and delayed (first ambulation achieved after 48 hours).

Methods

Design

This was a single-center, prospective, observational study conducted at a large, academic, Level 1 trauma center in the southeastern United States. We collected sociodemographic and baseline clinical data from interview and medical record review upon enrollment. Each participant had measures of upper and lower extremity skeletal muscle size (ultrasound) and strength (dynamometry) made each day between 0800 and 1000; vital signs and laboratory values were obtained from the electronic medical record each day. For variables measured more than once each 24-hour period, the highest and lowest values for the period were abstracted. Upon discharge, time to first ambulation, ICU and hospital length of stay, discharge disposition, and discharge destination were determined from the medical record. Participants were categorized as early ambulation (within 48 hours of admission) or late ambulation (greater than 48 hours after admission) based on the trauma unit ambulation protocol (Table 3.1.).

Sample

All patients admitted to the trauma service between April 2018 and August 2018 were screened for eligibility. Patients were approached for participation if they: 1) had a primary diagnosis of trauma with an ISS ≥ 15 indicating severe injury; 2) were 18 years of age or older; and 3) were able to read and write in English. Patients were excluded if they: 1) had a diagnosis of unstable pelvic or spine fractures, or spinal cord injury

resulting in quadriplegia or paraplegia, or traumatic brain injury with inability to follow commands or communicate; 2) were determined to have terminal status; 3) had written prescription for continued mobility restriction; 4) had a burn injury; 5) were diagnosed with pre-existing conditions that at baseline impaired mobility (i.e. neuromuscular diseases); 6) demonstrated persistent hyperglycemia as defined as the inability to achieve glycemic control (blood glucose < 200 mg/dL.) within 48 hours of admission despite use of institutional insulin protocols; 7) received neuromuscular blockade for more than 24 hours after admission; and 8) were determined to have a modified sequential organ failure assessment (mSOFA) score >11, which indicated higher probability of mortality. Exclusion criteria reduced potential confounding effects on mobility status and skeletal muscle structure and function, and ensured a more homogeneous group of participants.[16,17,134-142]

We recruited a non-probability sample of 19 patients admitted after major traumatic injury. With approximately 10 participants per group (Early and Delayed ambulation) and an a priori alpha level of .05, the power of the mixed model F test to detect a significant main effect of time or time by group interaction would be at least 95%, assuming a large effect size.(38) Under these same conditions, and also assuming a large effect size, the power of the ANOVA F test to detect a significant main effect of group should be at least 75%. The assumption of a large effect size was based on a prior study of knee flexion in similar patients;[58] over a 10-day period, the degree of change in outcome exceeded a large effect size, as defined by Cohen.(38) Power estimates were made using nQuery Advisor (Elashoff, 1995-2005, Saugus, MA).

Setting

This study was conducted with patients admitted to the trauma/surgical services at a large, academic, Level 1 trauma center in the southeastern United States, which included a total of 24 ICU beds, 12 progressive care/step-down beds, and 28 ward/acute care unit beds. In fiscal year 2016, patients who experienced trauma accounted for 44% of patients on this service. Nurse to patient ratio varied depending on the level of care, with a typical ratio of 1:2 in the ICU, 1:3 in the progressive care units, and 1:5 in the acute care units. In fiscal year 2016, the average hospital LOS for patients after trauma was 8.2 days.

Measures

Sociodemographic and clinical variables

Sociodemographic variables were obtained from the electronic medical record and patient interview, and included age, sex, race, marital status, insurance status, payment/insurance type, employment status, and perceived economic status (makes: less than ends meet, ends meet or more).

Data related to clinical variables were also extracted from the electronic medical record and included admission diagnosis; type of trauma (blunt, penetrating); toxicology screening for substances of abuse; preinjury comorbid diagnoses; vital signs that included daily minimum and maximum values for heart rate, blood pressure, oxygen saturation by pulse oximetry, respiration rate, and body temperature; laboratory values when available that included daily minimum and maximum values for serum glucose, white blood cell count, serum potassium, serum creatinine, serum calcium, serum chloride, serum sodium,

and blood urea nitrogen; daily mSOFA score [137]; length of ICU and hospital stay, and discharge disposition. To determine eligibility, we used the ISS calculated from raw abbreviated injury scale sub-scores, which was derived from reporting by the hospital-attending physicians.[143] ISS has been demonstrated to be a reliable (intraclass correlation coefficient [ICC]: 0.975, 95% CI: 0.961-0.985) and valid instrument (area under the curve = 0.885) for scoring and predicting trauma severity and mortality.[5,144,145]

Mobility

Mobility was previously defined as any type of movement of an individual, such as stretching, sitting, rolling, standing, or walking.[146] For our study, mobility was considered to be full ambulation determined by documentation of a maximum score of 5 on the medical record mobility scorecard (Table 3.1.).[147] The time to first full mobility, the time from admission to documentation of a maximum mobility score of 5, was recorded in hours.

Muscle Size

Muscle size was defined as the muscle thickness in centimeters of the rectus femoris and biceps brachii muscles; this was the distance from the adipose–muscle interface to the muscle-muscle interface (rectus femoris) and muscle–bone interface (biceps brachii) in a single transverse ultrasound image (Figure 3.1a; 3.1b.).[148-150] The thickness of each muscle was measured daily by taking three separate ultrasound images (Philips Lumify L12-4, Amsterdam, Holland); the average of these was used as the daily measure. The dominant-sided muscle was used for all measures when available.

Ultrasonography has been widely used to measure muscle size, and is a valid and highly reliable measurement.[149,151-156] In comparison to magnetic resonance imaging, which is considered the gold standard for assessment of muscle size, measures of quadriceps muscle size demonstrated excellent correlation, low coefficient of variation, and good visual agreement on Bland and Altman plots (ICC: 0.84-0.99; coefficient of variation [CV]: 0.5-1.9%).[156-160] The PI participated in an intensive, 10-hour training program provided by a qualified emergency medicine physician with fellowship training in ultrasonography. This training consisted of theoretical and practical application of ultrasound for muscle measures. Prior scientists demonstrated that novice ultrasound examiners achieved accurate and precise recordings and assessment of images following training from an expert in ultrasonography.[161,162] Compared with experts in ultrasonography, novice examiners provided reliable ultrasound measures of muscle size with as few as 6.5 hours of training (ICC: 0.58-0.95; CV 2.93-12.08).[161] The reliability of image acquisition and measurement was improved when hours of training increased to 20 (ICC: 0.86-0.94).[163] The expert trainer for this study served as a second-rater for 10% of collected images to assess inter-rater reliability; this was determined to be acceptable (ICC: 0.856).

Muscle Strength

Muscle strength was defined as the peak amount of isometric force a muscle exerted against resistance in pounds.[164,165] We measured strength of the biceps and quadriceps daily until discharge by making three separate dynamometry measures five minutes apart and averaging those values (Commander Muscle Tester, JTECH Medical, Utah, USA). The dominant-sided muscle was used for all measures when available.

Investigators previously demonstrated adequate reliability and validity of dynamometers to measure muscle strength in the clinical setting.[165-167] Dynamometry had good intra-rater (ICC ≥ 0.75) and inter-rater reliability (ICC ≥ 0.75) when determining peak force generation.[167] Concurrent validity analysis supported good relationships (ICCs ≥ 0.70) between handheld dynamometry and the gold standard for strength measurement, fixed dynamometry, when analyzing peak force generation among muscle groups tested.[167] The PI participated in an intensive 5-hour training program from a doctorally prepared physical therapist in the use of hand held dynamometry with this population. This training included education about the theoretical foundation of strength measures, the function and use of both fixed and hand-held dynamometers and their comparisons, training about instrument care, positioning for optimal measurement and patient safety, evaluation of technique with healthy volunteers (i.e. staff nurses), and the maintenance of universal precautions.

Procedure

Screening, Consent, and Enrollment

We received Institutional Review Board approval for this study following full review. Each day, all patients admitted to the trauma service with a trauma diagnosis were evaluated for study inclusion. Those who met inclusion criteria were approached for study participation. Ability to provide consent was determined with the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) instrument.[168] The UBACC is a 10-item scale that assessed the understanding of individuals for clinical trial protocols and research participation. The instrument was developed and tested among individuals with schizophrenia and healthy individuals. Each item was scored on a

scale from 0 to 2, with 0 demonstrating non-comprehension of the question, and 2 reflecting full comprehension. A total score of 12 indicated appropriate ability to provide consent. Participants must have scored a 2 on items 4 (*Do you have to be in this study if you do not want to participate?*) and 6 (*If you participate in this study, what are some of the things you will be asked to do?*), and scored at least a 1 on all other items to be considered appropriate for consent. Investigators determined that the UBACC had desirable internal consistency for both patients with schizophrenia (Cronbach's $\alpha = 0.77$) and healthy controls (Cronbach's $\alpha = 0.76$), interrater reliability (ICC = 0.84-0.98), and desirable construct validity when correlated against the gold standard for consent capacity, the MacArthur Competency Assessment Tool for Clinical Research (correlation coefficients, 0.23-0.55, $p < 0.05$).[168] Informed consent was obtained from participants deemed capable of providing informed consent.

Baseline data

Data for baseline clinical variables were collected from the electronic medical record and sociodemographic variables were obtained from participant interview and medical record review. Baseline muscle size then strength measures were made as follows:

Muscle Size

Muscle size measures were made with a portable, color Doppler, 34 mm. aperture, M-mode, high resolution, broadband linear array transducer (*Philips Lumify L12-4, Amsterdam, Holland*). The site of muscle size measurement was identified using specific landmarks, and marked with an indelible pen and covered with a waterproof, transparent dressing to ensure daily consistency of measures.[156] Measurement locations were

identified after the participant spent 20 minutes lying supine in bed in a relaxed state to ensure measures were not affected by fluid shifts associated with position change.[156] The biceps brachii muscle was identified along the medial aspect of the upper arm, two-thirds the distance from the medial acromion of the scapula to the fossa cubit, with the arm abducted and the forearm extended at the elbow and supported on the adjustable bedside table.[153] The rectus femoris muscle was identified along the anterior surface of the thigh, two-thirds distance from the anterior superior iliac spine to the superior patella border.[149,169]

A small amount (nickel-sized portion) of a water-soluble transmission gel was applied to the ultrasound transducer head to produce an acoustic connection between the skin and the transducer head, reduce friction, and improve transmission of sound waves to the tissue below the transducer.[170] Special care was taken to be consistent in applying minimal pressure during scanning to avoid compression of the muscle.[156] Musculoskeletal mode was used throughout the study, and depth and gain were adjusted until the landmark of the respective bone was clearly visible below the muscle body. The images were screen-captured, and the muscle thickness was calculated in centimeters directly from the tablet screen using calipers built into the ultrasound software, and subsequently recorded on the data collection form *(Galaxy S2 tablet, Samsung, San Jose, CA; Philips Lumify L12-4, Amsterdam, Holland)*. Two additional images of each muscle were acquired, and the mean value of the three recordings was calculated and used as the daily measurement. For each participant, the biceps were measured followed by the rectus femoris. The dominant-sided muscle was used for all measures when available.

Muscle Strength

After completion of muscle size measures, participants were seated on the edge of the bed with their feet dangling.[165] If the participant could not tolerate sitting on the edge of the bed, they were placed in a high Fowlers position for biceps strength testing and a dorsal recumbent position for quadriceps strength testing.[171] The site for placement of the dynamometer head to make the muscle strength measurement was identified using specific landmarks, and marked with an indelible pen and a waterproof, transparent dressing to ensure daily reliability of measures. For biceps strength measurement, the dynamometer head was placed at the radial-ulnar joint approximately 1 cm proximal to the wrist with the elbow flexed at a ninety-degree angle, and the forearm in supine position.[165] For the quadriceps strength measurement, the dynamometer head was placed distal to the anterior tibia, and immediately proximal to the talocrural joint.[165] The dynamometer was placed at the marked position, and the PI applied gentle pressure against the skin. The participant was instructed to exert force against the resistance of the PI, as if attempting to extend the leg into a straight line, or to touch the unilateral shoulder in a linear fashion, with as much effort as possible, without causing pain. Each measure was made over 5 seconds with a 5-minute equilibration period between subsequent measures to allow for recovery. The peak isometric contraction in pounds of force achieved was recorded. Two additional measures were made, and the mean value of the three recordings was calculated and recorded. For each participant, the biceps strength was measured first and the strength of the quadriceps was measured subsequently. The dominant-sided muscle was used for all measures when available.

Daily data

Data on daily clinical variables were extracted from the electronic medical record. Measurements of muscle size and muscle strength were made as previously described. At completion of all study procedures, the time to first ambulation was calculated in hours from admission, and the ICU and hospital LOS, complications during the hospitalization, and the discharge disposition were obtained from the medical record.

Data Management

All data collection forms were coded with an assigned participant number to maintain confidentiality; data were transferred from data collection forms to an electronic data spreadsheet and analyzed using IBM SPSS Statistics for Mac, Version 24.0 (IBM, Armonk, NY) and SAS for Windows, Version 9.3 (SAS Institute, Inc., Cary, NC). Data were double entered and compared for entry error; all identified errors were corrected.

Data Analysis

Descriptive statistics including means (standard deviations) and frequencies (percent) were used to characterize the sample. Patients were categorized as Early (within 48 hours after admission) or Delayed (after 48 hours after admission) ambulation based on the time of first ambulation after admission. We compared sociodemographic and clinical variables for these two groups using independent t tests and Chi square or Fisher's exact statistics based on the level of measurement of each variable.

To respond to our specific aim, we used a two-way repeated measures analysis of variance (RM-ANOVA). Fixed effects included ambulation group (Early or Delayed) and time (study day), as well as interaction effects. Fisher's least significant difference procedure for pairwise comparisons post-hoc analysis identified the location of

significant differences. Because the mean length of stay across the sample was 5.6 ± 3.2 days, analyses were conducted using five days of measurement (Baseline/Day 1, Day 2, Day 3, Day 4, and Day 5). This analysis strategy was appropriate for this repeated measures design, and allowed for retention of all patient data in the model.[172] As a correction for multiple comparisons, a conservative alpha level of .01 was used throughout.

Results

Characteristics of the participants

Participants (n = 19) were primarily male (63%), Caucasians (68%) who were 40 ± 17 years old (Table 3.2.). Over half of the participants were single (53%), and nearly two thirds reported a household income that was inadequate to make ends meet (63%). Most (79%) of the participants were unemployed; however, 84% of participants had some type of health care insurance. Most participants experienced blunt trauma (84%) and scored an average ISS of 21 ± 4. More than half (53%) had a positive toxicology screen on admission. The most prevalent comorbidities were hypertension (32%), chronic pain (16%), and alcohol abuse (16%). All patients survived their injuries, and the average ICU length of stay was 1.4 ± 2.1 days; hospital length of stay was 5.6 ± 3.2 days, and the average time to first ambulation was 59 ± 50 hours (2.5 days). Nearly two-thirds (74%) of participants were discharged home; one fourth were discharged to an inpatient rehabilitation facility (26%).

Comparison of patients based on time to first ambulation

Participants were categorized into Early (within 48 hours of admission) and Delayed (after 48 hours of admission) ambulation groups based on the time from admission to first ambulation. Ten participants (53%) were categorized into the Early ambulation group and 9 into the Delayed ambulation group. There were no differences in sociodemographic variables between these two groups (Table 3.2). At baseline, those in the Early ambulation group demonstrated significantly more baseline biceps and quadriceps strength compared with those in the Delayed ambulation group (Early group bicep 17.7 ± 4.7 lbs. of force, Delayed group bicep 12.9 ± 3.8 lbs. of force, $p = 0.004$; Early group quadriceps 17.1 ± 4.6 lbs. of force, Delayed group quadriceps 9.9 ± 3.1, $p = 0.001$). There were no other differences in any of the clinical variables (Table 3.2).

Muscle size associated with first ambulation

Size of the biceps brachii and rectus femoris were compared with RM-ANOVA (Table 3.3). The assumptions were met, in that the models exhibited linear relationships, with no evidence of a higher order term necessary when reviewing residuals; the variances were homogeneous between groups (given relatively little evidence of any influence points in the influence analysis), and the studentized residuals were approximately normally distributed. The fixed effects of the mixed model included group (Early or Delayed) and day (Study Days 1-5) and their interactions. Covariates included age and gender. For biceps size, the interaction term of group by day was significant ($F(4, 47), 3.68, p = 0.011$). There were no differences in bicep size between groups; however, post-hoc analysis determined that in the Early ambulation group there was an increase in bicep size from day 1 and days 3, 4, and 5, by 0.25, 0.25, and 0.38 cm,

respectively (Figure 3.2.). There were no differences between or within groups over five days of measurement for the rectus femoris muscle (Figure 3.3.).

Muscle strength associated with first ambulation

Strength of the biceps and quadriceps were compared with RM-ANOVA (Table 3.3.). The assumptions of the mixed model procedure were met and the covariance structure type specified was variance components. The fixed effects of the mixed model included group (Early or late) and day (Study Days 1-5) and their interactions. Covariates included age and gender. Participants who ambulated Early demonstrated significantly more strength in both biceps and quadriceps at baseline and throughout the study (Table 3). The interaction term of group by day for biceps strength was significant ($F(4, 47)$, 3.66, $p = 0.011$). Participants in the Early group exhibited increased biceps strength on days 3 and 5 compared to measures made on days 1 and 2 (Figure 3.4). In the Delayed ambulation group, participants demonstrated increased strength on days 4 and 5 compared to day 2 measures.

The main effects of group ($F(1, 13)$, 19.55, $p = 0.0007$) and day ($F(4, 47)$, 5.68, $p = 0.0008$) were significant for quadriceps strength; however, the interaction of group by day was not ($p = 0.69$). On average, the participants in the Early ambulation group were 6.2 pounds of force stronger compared with the late group across all days (Figure 4). On days 3 and 4, Early group participants were nearly 2 pounds of force stronger compared to day 1 measures, and more than 2 pounds of force stronger compared to day 2. The Early group displayed a loss of strength on day 5 compared with days 2, 3, and 4. In the Delayed ambulation group, participants displayed increased strength on days 3, 4, and 5 compared to days 1 and 2 (Figure 3.5.).

Discussion

We evaluated the association between time to first ambulation and skeletal muscle size and strength in patients after major injury. Participants were grouped based on time to first ambulation from admission and were determined to be either Early (within 48 hours) or Delayed (after 48 hours) first ambulation. At baseline, there were no differences in sociodemographic variables between these groups. Muscle size for the biceps and rectus femoris did not differ between the Early and Delayed groups; however, participants who ambulated early increased bicep size on days 3, 4, and 5 compared with baseline. Muscle strength in both upper and lower extremities did differ between the groups; participants who ambulated early demonstrated more biceps and quadriceps strength at baseline and throughout the study compared to the late ambulation group. However, patients in both the Early and Delayed groups increased strength in both the biceps and quadriceps across study days; however, on day 5 the Early group exhibited a significant decrease in quadriceps strength.

Our participants maintained muscle size over five days of observation with variable durations of immobilization during hospitalization following major trauma; however, prior investigators reported that five days of bed rest in healthy volunteers resulted in up to a 3% reduction in muscle cross-sectional area.[88] Other investigators found a 9% reduction in cross-sectional area of the rectus femoris in critically ill patients who required mechanical ventilation and sedation; muscle size reduction was evident as early as 72 hours after ICU admission, and after 10 days of ICU care, cross-sectional area loss had increased by more than 3-fold.[124,170] Gruther and colleagues also found that ICU length of stay was associated with a larger degree of loss of quadriceps muscle thickness;

this loss was greatest at 2-3 weeks of stay in the ICU.[173] Compared with these investigations, our patients were on average 16 years younger, had a lower severity of illness indicated by a significantly shorter mean length of ICU stay (10 days), and most participants in other studies had not experienced traumatic injury.[170] Thus, our participants were not comparable with those of other investigators. Additionally, our participants were not on strict bed rest and ambulation was performed per unit protocol. Sequential muscle size measures have not been previously reported in patients after trauma; thus, the association of trauma and length of immobility is currently unclear. . Our rigorous exclusion criteria likely influenced the ability of our participants to maintain some degree of activity while on bed rest, which may have preserved skeletal muscle size. However, we did not examine or control for potential confounding variables, such as activity level before full ambulation and nutrition status, which could have influenced muscle size in our patients. .

We used ultrasound-captured images of muscle thickness to measure muscle size. Other investigators used different measures of muscle size that included cross-sectional area (CSA) determined by ultrasonography. Consequently, our measure of muscle size were not comparable with those made in similar studies of critically ill adults.[124,170] Parry and colleagues suggested that CSA, rather than thickness, was a more accurate measure of muscle size because it provided a more precise measure of size, and was more sensitive to detection of change over time when compared with measures of thickness. Previous investigators demonstrated that muscle thickness measures underestimated size by as much as 8%.[170,174] We were unable to use CSA for our study, as this measure requires either extended field of view ultrasonography technology or digitizing software,

and these were unavailable for this investigation.[156,175]. Thus, our measure of skeletal muscle size may not have been adequately sensitive to detect significant changes. Despite this limitation, it has been suggested that percent change in thickness correlates closely to percent change in cross-sectional area ($r = 0.69$, $p < 0.01$), thus validating use of thickness to assess the change in muscle size over time.[176]

We found that bicep size increased from baseline in the Early ambulation group on days 3, 4, and 5. In contrast, Mulder and colleagues found that 5-days of strict bedrest with a daily 25 minute out of bed exercise routine that included heel raises, squats, and hopping in place, only maintained muscle size.[88] Other investigators who implemented prescribed, short, out-of-bed exercise regimens during bed rest found that engagement in activity reduced the loss of muscle compared to bed rest alone.[59,60] The increase in bicep size of our participants might be attributed to in-bed activity prior to first ambulation. However, the level and frequency of activity, both in and out of bed, was not measured in our study or in other prior investigations.[59,60,88] Subsequent studies should include measures of in-bed activities, such as wearable, spatial activity trackers that monitor patient activity both in and out of bed, to determine their influence on skeletal muscle maintenance during immobility after injury.[177]

Prior investigators reported changes in muscle strength associated with immobility.[88,178] Mulder and colleagues found a decrease in knee extensor strength by 8% over a five-day period in healthy, male volunteers who were on strict bed rest.[88] However, our patients not only maintained muscle strength over five days, but also increased strength over time. Samosawala and colleagues found that over five-days of ICU stay bicep strength was reduced by over 12% (-2.1 pounds of force) and quadriceps

strength was reduced by over 13% (-2.7 pounds of force) in critically ill adults.[178] However, compared with our participants, patients were on average 9 years older, had a mean ICU stay 8 days longer with 22% requiring mechanical ventilation, and were all admitted for non-trauma diagnoses. The significant differences in patient populations in prior studies of muscle strength precluded comparison of findings, but suggested that lack of activity, regardless of when it occurs, is detrimental to muscle-related outcomes. Subsequent investigations should include measures of all potentially confounding variables, particularly in-bed activities, for a comprehensive understanding of skeletal muscle responses.

We found those who ambulated earlier were significantly stronger at baseline and demonstrated greater strength during the five days of the study compared with those who ambulated later. Previous investigators determined there was a predictive relationship between baseline handgrip strength and return to ambulation in elderly, hospitalized patients.[179,180] Beseler and colleagues determined that baseline strength was associated with increased walking ability in elderly, hospitalized patients admitted for non-trauma reasons. Savino and colleagues also found that those elderly patients who experienced hip fracture who were also in the highest tertile of grip strength at baseline had a nearly 3-fold increase in likelihood of walking after surgery.[179,180] Thus, our finding that those individuals with greater strength prior to admission were able to ambulate earlier than those with less baseline strength was consistent with prior research findings. This finding suggests that pre-injury strength or condition prior to injury is an important factor in muscle responses after injury that requires investigation.

We observed differences in strength over the five days of measurement in both groups. Patients in the Early group demonstrated peak strength on days 3 and 4, and those in the late group peaked on day 4 and 5. However, those in the Early group had a statistically significant reduction in quadriceps strength on day 5. This could be due to the volitional nature of the measure or the discharge of stronger patients prior to day 5 measures. Mulder and colleagues also found a 12% increase in strength from baseline during 5 days of bed rest with daily-prescribed exercise.[88] Those who ambulated early likely did so because they were stronger compared with those who ambulated after 48 hours. Those in the Early group also may have experienced a ceiling effect, as their strength was already maximized for their condition. In contrast, it is possible that because those in the late group were weaker at baseline they had greater room for improvement in strength.

The ability of skeletal muscle to sustain damage, such as injury or disuse atrophy, but preserve strength, may be explained by its modular structure.[181] Skeletal muscle fibers are long, multinucleated cells with the contractile units organized into myofibrils further arranged into units called sarcomeres; a single muscle fiber can contain millions of sarcomeres. This structure allows normal contractile units to compensate for nearby damaged units.[181] The theory of the myonuclear domain also proposes the myonucleus directs an area of nearby cytoplasm and regulates the protein turnover to support the domain. Thus, when myonuclei are damaged they are removed, primarily by apoptosis, resulting in muscle atrophy.[32] However, Zhong and colleagues found that during disuse, the removal of myonuclei was not a prerequisite for atrophy, but resulted in fiber type change; thus, the unit retained size and contractile ability.[182] This theory may in part

explain the lack of significant reduction in muscle size, and the preservation of strength in our investigation. Future investigation is required to provide a more comprehensive understanding of the complex interactions that accompany traumatic injury and subsequent immobilization as they relate to skeletal muscle size and strength. Improvement in the understanding of these interactions will be useful to better tailor treatments and interventions related to physical rehabilitation for patients after trauma.

Limitations

This study was conducted in a single center with a small, homogeneous sample. Our participants may not represent the trauma population as a whole, and our statistical analyses lacked power in spite of an a priori power analysis. We used a large effect size based on a prior investigation for our power analysis, and we did not control for numerous confounding variables such as nutritional status, comorbidities, and activities during bedrest, or pain level that may have influenced our outcome variables. Another limitation to consider in our investigation was the variation in sample size across the period of observation. Patient length of stay was 5.6 ± 3.2 days; thus, sample size varied for the daily measures. We used a mixed model approach to retain and use all cases regardless of length of stay.[172] Recent investigators also suggested that cross-sectional area, rather than thickness, was a better indicator of muscle size with ultrasonography. However, this measure required the use of specialized computer software and conversion algorithms that were not available for this investigation. Lastly, dynamometry is a volitional measure that requires exertion of maximal effort by the participant. Although three measures were made and the mean value was used for analysis, we could not

control degree of patient effort. Pain or motivation might also have influenced these measures.

Conclusions

Early ambulation within 48 hours of admission for major trauma was associated with increased bicep size and greater muscle strength in the biceps and quadriceps muscles over time. Participants who ambulated earlier in their hospital stay after injury also exhibited greater muscle strength at all time points compared with those who ambulated later. Preservation of skeletal muscle size and strength during hospitalization after injury is vital to reduce short- and long-term disability. Additional systematic study will provide further evidence about the relationships among traumatic injury, time to ambulation, and muscle size and strength to guide the development and evaluation of interventions to reduce acquired disability observed after trauma.

Table 3.1. Early mobility protocol used by trauma service at study institution that is standard of care for all patients admitted to the trauma service with the study institution's mobility scorecard used for all adult inpatients.

- Assessment and documentation of mobility score within 24 hours of admission
- Mobilization activities beginning immediately upon stabilization of hemodynamic and respiratory parameters, ideally within 24-48 hours of admission
- Nursing initiated patient mobilization should occur a minimum of twice daily to the maximum patient capability (i.e. in addition to treatment from physical or occupational therapy)
- Nurses and patient care assistants collaborate with multidisciplinary team members (physicians, occupational and physical therapists, respiratory therapy, Clinical Nurse Specialists, etc.) as needed to achieve daily mobility goals
- Documentation of the highest achieved mobility score, with assistance required and distance ambulated when appropriate, at least once per 12-hour shift

Table 3.1. continued

Score	*Activity*	*Considerations*	*Duration/Instructions*	*Frequency*
1	• Patient ordered/condition dictated bedrest and HOB less than 30 degrees, completely immobilized or prone positioning	• Unless orders prohibit, all patients should be verticalized via reverse Trendelenburg in order to maintain vascular tone • Maintain HOB elevation/Reverse Trendelenburg as high as orders/condition permit • Hemodynamically unstable patients should be turned slowly/gradually and given approximately 5 minutes to equilibrate	Every 1-2 hours	Every 1-2 hours

Table 3.1. continued

1 cont.		• Turn a minimum of every two hours if physiologically permitted		
2	• HOB elevated 30-45 degrees • Turn a minimum of every two hours • Note: use this score for patients who are mechanically lifted to the chair	• Pay special attention to offload coccyx. • Reposition in the chair every 30 minutes to 1 hour	Every 1-2 hours Note: 2 hour maximum time limit in chair	Every 1-2 hours Note: up to chair for meals, if possible
3	• Patient positioned at edge of bed, legs dangling with assistance present for balance and safety with core engaged	• Multiple personnel recommended	Increase incrementally as patient tolerates and document time dangled	2-3 times per day

Table 3.1. continued

4	• Stand at the bedside • Stand and pivot to chair as tolerated	• Multiple personnel recommended • Reposition in char every 30 minutes to 1 hour	Increase incrementally as patient tolerates and document time standing Note: 2 hour maximum time limit in chair	2-3 times per day
5	• Ambulation in room or hallway with assist or device as needed	• Multiple personnel recommended • Consult physical and/or occupational therapy for assistive device, if needed	Increase incrementally as patient tolerates and document distance ambulated	2-3 times per day

Table 3.2. Characteristics of participants (n = 19) and comparison of sociodemographic and baseline clinical variables between Early and Delayed groups.

	Total Sample (N = 19)	Early Ambulation (within 48 hours) (n = 10)	Delayed Ambulation (after 48 hours) (n = 9)	P-value
Age in years	40 ± 17	41 ± 18	39 ± 17	0.84
Gender				0.43
Male	12 (63%)	7 (70%)	5 (56%)	
Race				0.63
Caucasian	13 (68%)	7 (70%)	6 (67%)	
African-American	6 (32%)	3 (30%)	3 (33%)	
BMI (kg/m^2)	26.4 ± 4.8	25.2 ± 3.7	27.8 ± 5.7	0.26
Marital status				0.13
Married	9 (47%)	3 (30%)	6 (67%)	
Single	10 (53%)	7 (70%)	3 (33%)	

Table 3.2. continued

Health -insurance	16 (84%)	9 (90%)	7 (78%)	0.46
Type of payment/insurance				0.59
Public	9 (47%)	5 (50%)	4 (44%)	
Private or self-pay	10 (53%)	5 (50%)	5 (56%)	
Employment status				0.67
Employed	4 (21%)	2 (20%)	2 (22%)	
Unemployed	15 (79%)	8 (80%)	7 (78%)	
Economic status				0.57
Makes less than ends meet	12 (63%)	6 (60%)	6 (67%)	
Makes ends meet or more	7 (37%)	4 (40%)	3 (33%)	
History of hypertension	6 (32%)	3 (30%)	3 (33%)	0.63
History of chronic pain	3 (16%)	1 (10%)	2 (22%)	0.46
History of diabetes	2 (11%)	2 (20%)	0 (0)	--

Table 3.2. continued

History of alcohol abuse	3 (16%)	1 (10%)	2 (22%)	0.46
Positive toxicology screen	10 (53%)	6 (60%)	4 (44%)	0.41
Blunt trauma	16 (84%)	8 (80%)	8 (89%)	0.54
ISS	21 ± 4	21 ± 4	20 ± 5	0.83
Hours to ambulate	59 ± 50	29 ± 12	92 ± 56	**0.003**
Hospital length of stay in days	5.6 ± 3.2	4.7 ± 2.7	6.6 ± 3.6	0.22
ICU length of stay in days	1.4 ± 2.1	1.6 ± 2.3	1.2 ± 2.0	0.71
Discharge disposition				0.12
Home	14 (74%)	9 (90%)	5 (56%)	
Other inpatient facility	5 (26%)	1 (10%)	4 (44%)	
Baseline mSOFA	1.7 ± 1.2	1.7 ± 1.3	1.7 ± 1.1	0.95
Baseline pain rating (0-10 scale)				
24-hour mean	6 ± 2	6 ± 2	6 ± 3	0.92

Table 3.2. continued

Baseline glucose level (mg/dL)				
24-hour mean	134 ± 52	140 ± 66	125 ± 26	0.58
Baseline WBC count (k/uL)				
24-hour mean	12.9 ± 5.5	15.4 ± 4.7	9.4 ± 4.6	0.019
Baseline serum calcium level (mg/dL)	8.6 ± 0.6	8.5 ± 0.7	8.6 ± 0.5	0.88
Baseline muscle size (cm)				
Biceps Brachii	2.56 ± 1.18	2.46 ± 1.30	2.67 ± 1.10	0.72
Rectus Femoris	3.17 ± 1.29	3.21 ± 1.53	3.13 ± 1.04	0.90

Table 3.2. continued

Baseline muscle strength (lbs of force)				
Biceps	15.4 ± 4.9	17.7 ± 4.7	12.9 ± 3.8	**0.004**
Quadriceps	13.7 ± 5.3	17.1 ± 4.6	9.9 ± 3.1	**0.001**

Values are mean ± SD or f (%)

Comparisons were performed with independent t tests or Chi square/Fisher's exact test based on level of measurement and distribution of data.

Abbreviations: BMI, Body Mass Index; ISS, Injury Severity Score; ICU, Intensive Care Unit; mSOFA = modified sequential organ failure assessment; mg/dL. = milligrams per deciliter; k/uL = thousand cells per microliter; cm = centimeter; lbs. = pounds

Table 3.3. Comparison of mean values for bicep and rectus femoris size using ultrasound and bicep and quadriceps strength using dynamometry in patients after trauma who ambulated early (≤ 48 hours of admission) or delayed (> 48 hours of admission).

	Day 1	Day 2	Day 3	Day 4	Day 5
Bicep size (cm)					
Early	2.46 ± 1.30 (n =10)	2.58 ± 1.24 (n =10)	2.71 ± 1.32[b] (n = 9)	2.71 ± 1.58[b] (n = 6)	2.84 ± 0.44[b] (n = 5)
Delayed	2.67 ± 1.10 (n = 9)	2.64 ± 1.01 (n = 9)	2.72 ± 1.00 (n = 8)	2.78 ± 1.08 (n = 7)	2.81 ± 0.80 (n = 6)
Rectus Femoris size (cm)					
Early	3.21 ± 1.53 (n =10)	3.19 ± 1.58 (n =10)	3.21 ± 1.55 (n = 9)	3.14 ± 1.84 (n = 6)	3.16 ± 0.40 (n = 5)
Delayed	3.13 ± 1.04 (n = 9)	3.09 ± 0.99 (n = 9)	3.19 ± 1.02 (n = 8)	3.17 ± 1.11 (n = 7)	3.08 ± 0.97 (n = 6)

Table 3.3. continued

Bicep strength (lbs. of force)					
Early	17.70 ± 4.74[a] (n =10)	17.84 ± 5.24 [a] (n =10)	19.66 ± 3.16 [a,b,c] (n = 9)	18.03 ± 4.90 [a] (n = 6)	18.79 ± 1.55 [a,b,c] (n = 5)
Delayed	12.89 ± 3.82 (n = 9)	11.11 ± 3.48 (n = 9)	12.50 ± 4.61 (n = 8)	13.14 ± 5.63[c] (n = 7)	14.60 ± 7.34[c] (n = 6)
Quadriceps strength (lbs. of force)					
Early [f]	17.09 ± 4.56 (n =10)	16.60 ± 5.48 (n =10)	18.67 ± 4.03 [b,c] (n = 9)	18.84 ± 3.19 [b,c] (n = 6)	16.35 ± 2.07 [b,d,e] (n = 5)
Delayed	9.87 ± 3.08 (n =9)	10.00 ± 3.51 (n = 9)	11.61 ± 4.20[b,c] (n = 8)	12.00 ± 5.42[b,c] (n =7)	12.00 ± 7.02[b,c] (n = 6)

Table 3.3. continued

Data are mean ± SD

cm: centimeters; lbs.: pounds;

a: different from Delayed group on same day; **b:** different from Day 1/baseline within same group; **c:** different from Day 2 within same group; **d:** different from Day 3 within same group; **e:** different from Day 4 within same group; **f:** difference between group. All significant differences are at $p \leq 0.01$.

Figure 3.1a. The dotted line between each + indicates the measurement for the thickness of a bicep measure, 2.31 cm.

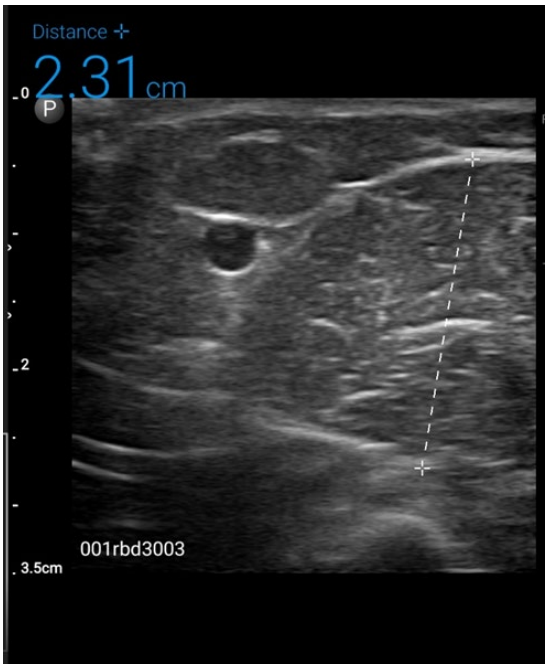


Figure 3.1b. The dotted line between each + indicates the measurement for the thickness of a rectus femoris measure, 2.5 cm.

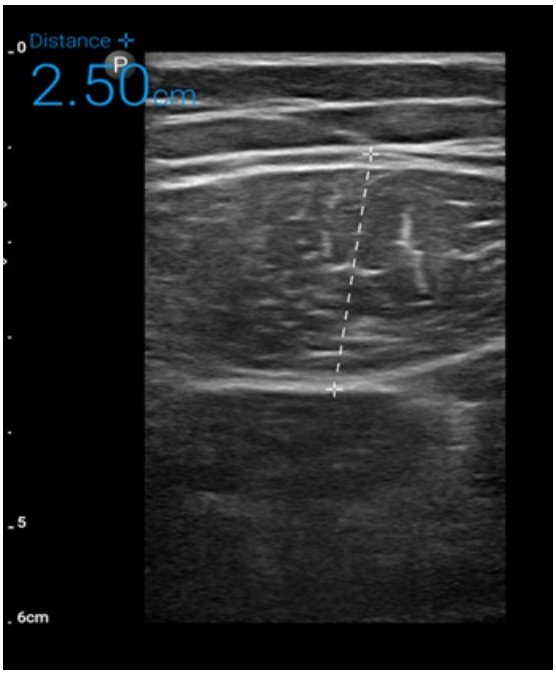
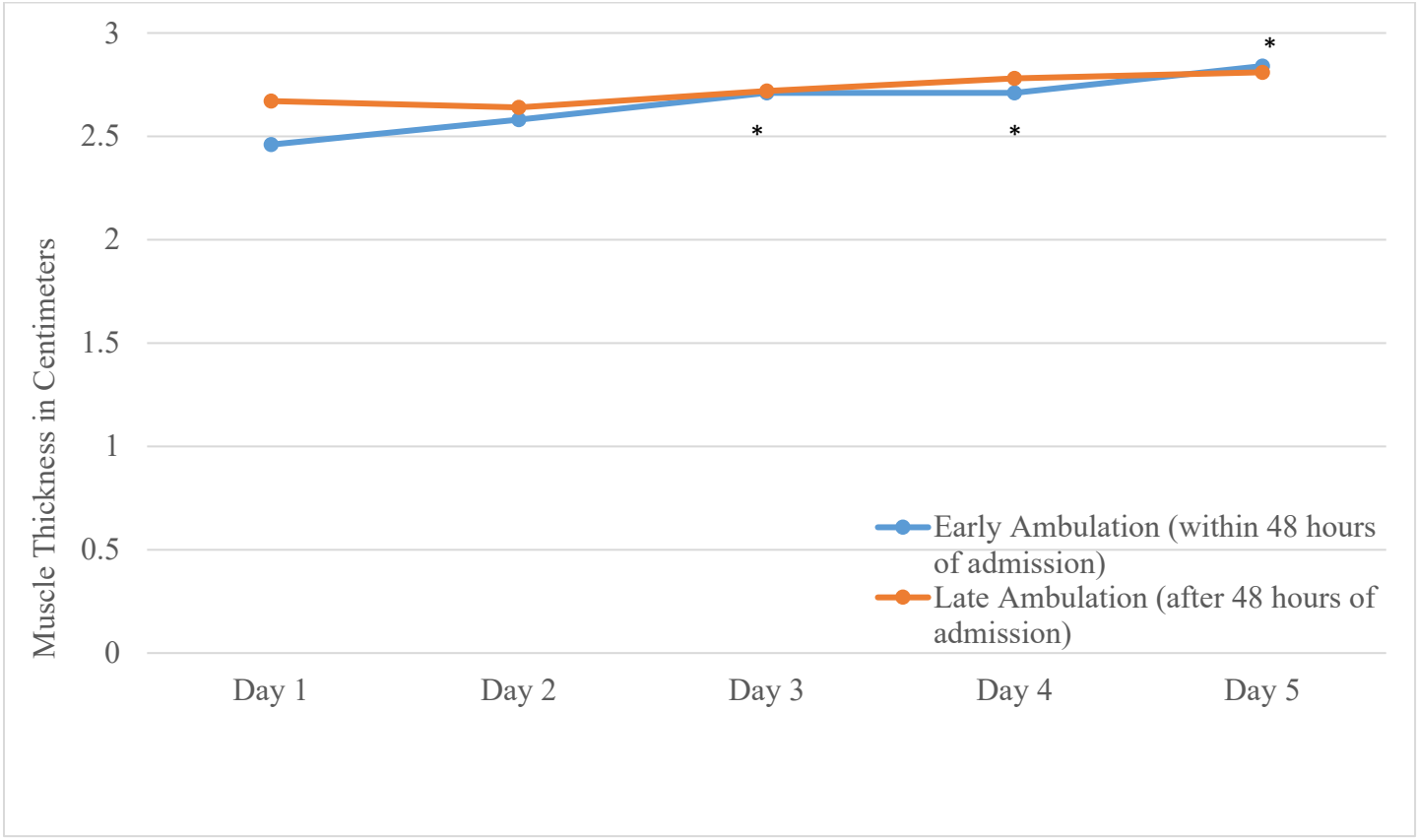
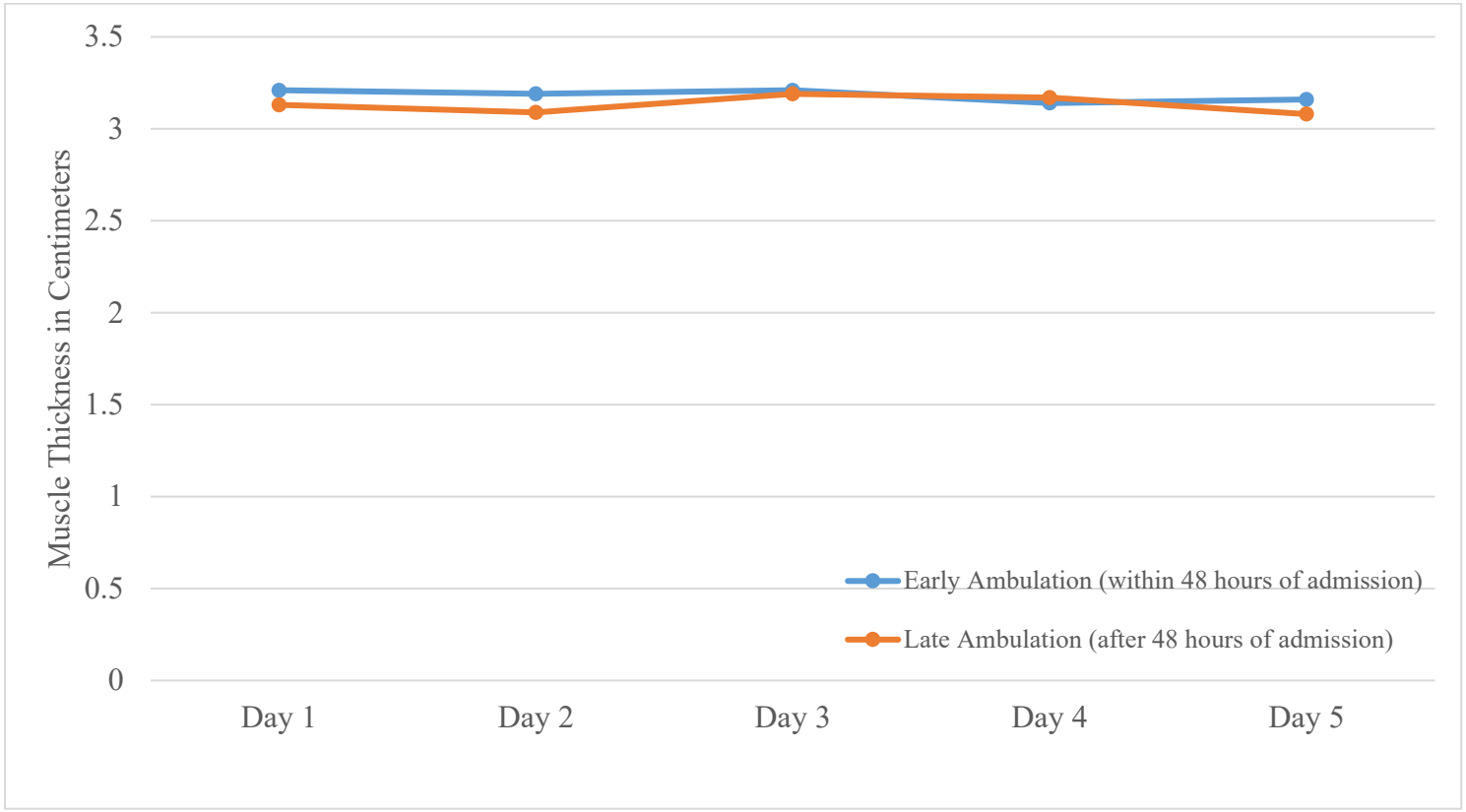


Figure 3.2. Trajectory of bicep size (centimeters) determined by ultrasound imaging in patients after major trauma with early (within 48 hours) and late (after 48 hours) ambulation.* indicates difference compared to baseline within group in the early group ($p \leq 0.01$)



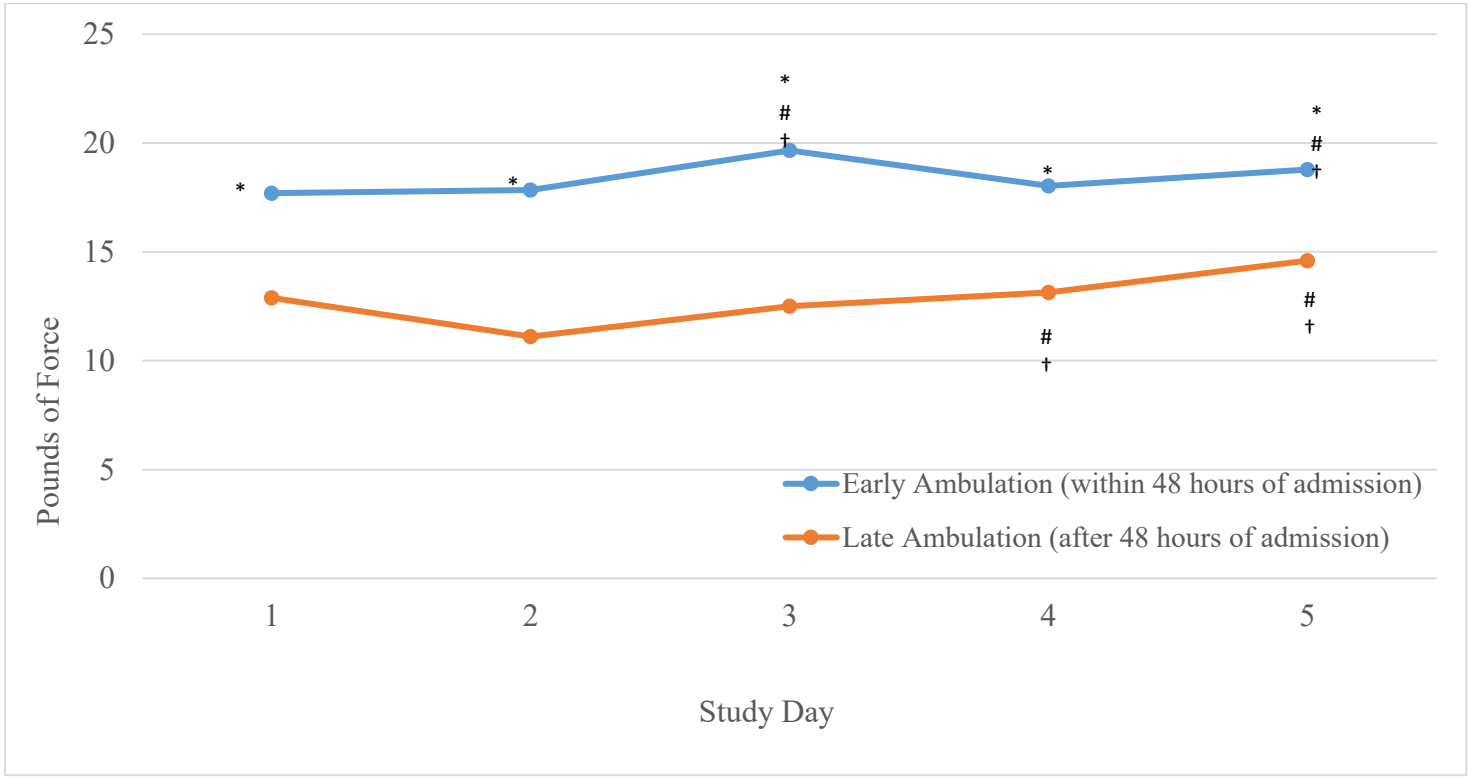
Early (n)	10	10	9	6	5
Delayed (n)	9	9	8	7	6

Figure 3.3. Trajectory of rectus femoris size (centimeters) determined by ultrasound imaging in patients after major trauma with early (within 48 hours) and late (after 48 hours) ambulation.



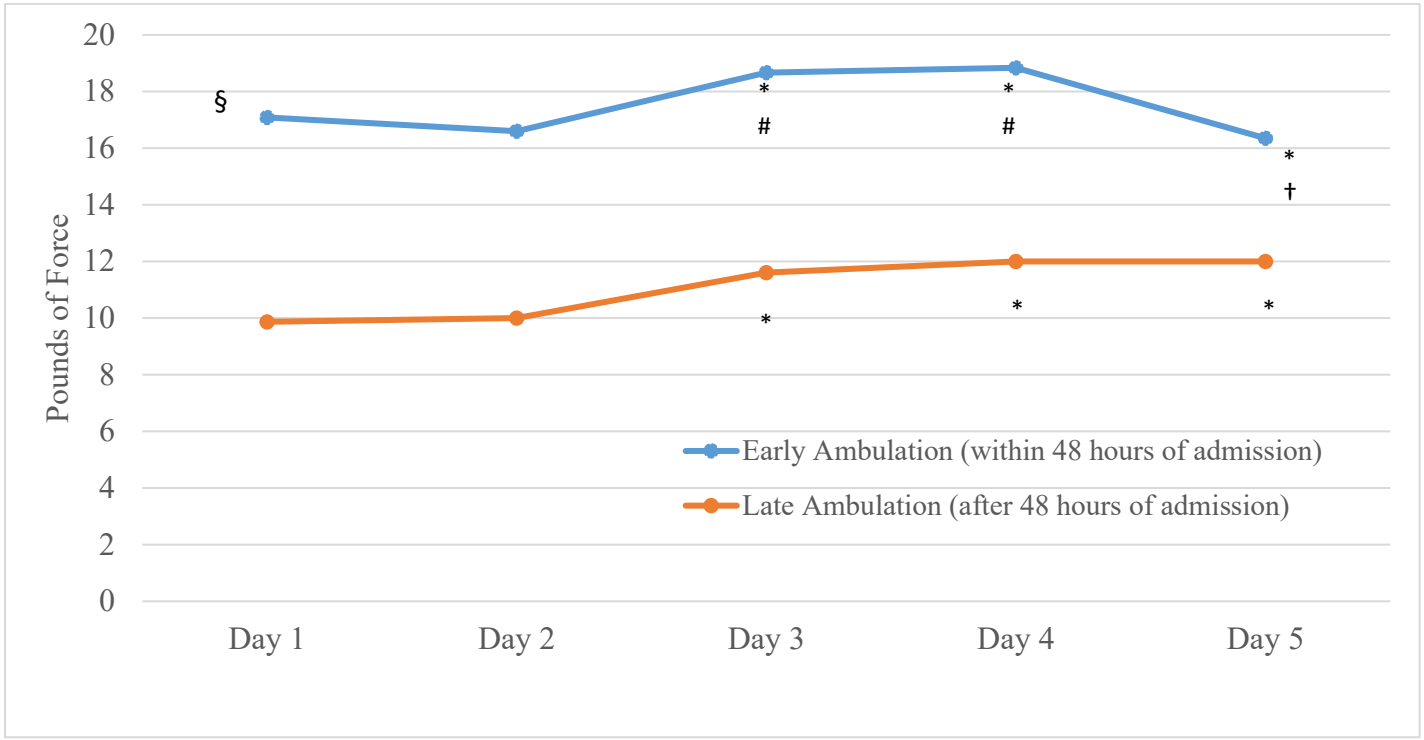
Early (n)	10	10	9	6	5
Delayed (n)	9	9	8	7	6

Figure 3.4. Trajectory of biceps strength (pounds of force) determined by dynamometry in patients after major trauma with early (within 48 hours) and late (after 48 hours) ambulation. * indicates difference between groups at same day (p ≤ 0.01); # indicates difference compared to baseline within group (p ≤ 0.01); † indicates difference compared to day 2 within group (p ≤ 0.01).



Early (n)	10	10	9	6	5
Delayed (n)	9	9	8	7	6

Figure 3.5. Trajectory of quadriceps strength (pounds of force) determined by dynamometry in patients after major trauma with early (within 48 hours) and late (after 48 hours) ambulation. § indicates difference between groups ($p \leq 0.01$); * indicates difference from baseline within group ($p \leq 0.01$); # indicates difference compared to day 2 within group ($p < 0.01$); † indicates difference compared to day 3 within group ($p \leq 0.01$); ‡ indicates difference compared to day 4 within group ($p \leq 0.01$).



Early (n)	10	10	9	6	5
Delayed (n)	9	9	8	7	6

CHAPTER FOUR

Depressive symptoms, but not anxiety, predict delayed ambulation in patients after major traumatic injury

Synopsis

Psychological symptoms, such as anxiety and depression, occur in up to 40% of patients after traumatic injury and may influence readiness to ambulate after severe injury. The purpose of this study was to compare sociodemographic and clinical variables of those who reported baseline anxiety and depressive symptoms with those who were symptom free, and to determine the predictive power of anxiety and depressive symptoms at baseline for time to first ambulation in patients after major trauma. At baseline, anxiety was present in 32% of patients; 21% reported depressive symptoms. Baseline anxiety did not predict ambulation group. However, for each one point increase in baseline depressive symptom score, the likelihood patients would be in the late ambulation group increased by 67% (Odds Ratio [OR]: 1.67, 95% CI: 1.02 – 2.72, $p = 0.041$). Psychological state was associated with time to first ambulation after major injury. Depressive symptoms were more likely in the patients who ambulated later (> 48 hours of admission).

Introduction

More than 200,000 deaths occur in the U.S. from injury annually. This is equivalent to one death every three minutes.[3] Advances in management reduced trauma-related mortality by 3.3% from 2010 to 2015; however, the incidence of trauma continued to grow, with 2.8 million people requiring hospitalization for injuries in 2015.[3,4,25] Disability is also a consequence of trauma.[11] In 2014, the World Health Organization estimated that 100 million people were living with disabilities worldwide, and traumatic injury was responsible for as much as 12% of that disability. Thus, traumatic injuries were associated with short-and long-term consequences for individuals, their families, and society.[11,125,183]

In addition to disability, investigators identified other long-term consequences of traumatic injury including development and persistence of psychological symptoms such as anxiety, depressive symptoms, and post-traumatic stress disorder (PTSD).[14,22,36,37,40,43] These psychological states may persist for weeks to years after injury, and have been reported by up to 30-40% of patients after traumatic injury.[14,22,36,37,40,43] Investigators determined that the presence of psychological symptoms after injury was also associated with impaired functional health, with 44% of patients after trauma reporting difficulty returning to normal activity.[21,43] Richmond and colleagues found that after traumatic injury patients with depression reported significantly worse quality of life at 3, 6, and 12-months following injury compared to patients without depression.[21] Although there is evidence that psychological symptoms after trauma exist and are associated with long-term functional consequences, there is limited evaluation of how psychological symptoms in the acute injury period alter early physical activity and rehabilitation.[22,37,184]

Early physical activity after hospitalization for critical illness has been associated with improved patient outcomes that included up to a 3 day decreased length of stay in the intensive care unit (ICU), a 3-day reduction in hospital length of stay, a 7% decreased prevalence of ventilator-associated pneumonia, and a 30% increase in functional status at discharge.[92,96,131,185] Despite these benefits, investigators have also identified a number of barriers for engagement in physical activity while hospitalized. These included physical constraints, which included difficulty with adaptation to functional limitations, pain and other symptoms like fatigue associated with disease, and psychological barriers, such as fear, anxiety, depressive and PTSD symptoms, and lack of motivation.[186-191] A systematic exploration of the complex interaction of anxiety and depressive symptoms with physical activity in patients after trauma could provide insight for development of interventions to reduce associated disability and optimization of outcomes. Thus, the purpose of this study was to compare sociodemographic and clinical variables of those who reported baseline anxiety and depressive symptoms with those who were symptom free, and to evaluate the association of baseline anxiety and depressive symptoms with time to first ambulation during hospitalization in patients after major trauma (Injury Severity Score [ISS] > 15). We hypothesized that those with more psychological distress (anxiety or depressive symptoms) at baseline would have a greater likelihood of late ambulation (after > 48 hours of admission).

Methods

Design

This was a prospective, observational study conducted at a large, academic, Level 1 trauma center in the southeastern United States. Upon enrollment, sociodemographic

and baseline data were collected by interview and medical record review, and anxiety and depressive symptoms were measured. Time of first full ambulation was determined by medical record review after hospital discharge. Participants were grouped as either early (within 48 hours of admission) or late (after 48 hours of admission) ambulation, based on the trauma unit ambulation protocol.

Sample and Setting

We screened all patients with an admitting diagnosis of traumatic injury between April and August 2018. Patients were eligible for participation and approached for consent if they had: 1) a primary diagnosis of traumatic injury with an ISS > 15 indicating major injury; 2) were 18 years of age or older; and 3) were able to read and write in English. Patients were excluded if they had: 1) injuries that impaired mobility , i.e. unstable pelvic or spine fractures, spinal cord injury resulting in quadriplegia or paraplegia, or traumatic brain injury with inability to follow commands or communicate; 2) were determined to have terminal status; 3) had written prescription for mobility restriction; 4) had a pre-existing disease at baseline that impaired mobility (i.e. neuromuscular diseases); and 5) had a pre-existing diagnosis of anxiety, depression, schizoaffective disorder, or bipolar disorder. These exclusions controlled for potentially confounding variables that could influence time to mobility or psychological symptoms.

Following screening and recruitment, we enrolled 19 patients hospitalized for major trauma. Sample size for this study was estimated with a power analysis conducted for an evaluation of the association between time to ambulation and skeletal muscle size and strength measures during hospitalization.[192] Following all data collection, participants were grouped based on the time in hours to first documented ambulation

(early - within 48 hours of admission or late - after 48 hours of admission). A cutoff point of 48 hours was used because this represented the latest time to target first ambulation per the trauma unit early mobility protocol. The trauma units at the study institution included 64 total beds: 24 intensive care (ICU), 12 progressive care/step-down beds, and 28 ward/acute care unit beds. The average length of stay (LOS) for patients after trauma was 8.2 days in fiscal year 2016.

Measures

Sociodemographic and clinical variables

Sociodemographic variables obtained from the electronic medical record and patient interview included age, sex, race, marital status, insurance status and type, employment status, and self-reported economic status (choices - makes less than ends meet, ends meet, more than ends meet). Clinical variables included admission diagnosis and mechanism of injury; type of trauma (blunt, penetrating); admission toxicology results for substances of abuse and/or alcohol; ICU and hospital length of stay, and discharge disposition; these variables were collected from the electronic medical record.

ISS

The ISS is a measure of severity of injury that is significantly associated with morbidity and mortality.[143] This measure: 1) allows the degree of traumatic injury to be categorized into one of six categories ranging from minor to untreatable; 2) was based on the Abbreviated Injury Scale;[143] and 3) has demonstrated reliability in determining accurate injury severity grading (intraclass correlation coefficient [ICC]: 0.975, 95% CI:

0.961-0.985).[143,144] The ISS was calculated from raw abbreviated injury scale sub-scores determined by the attending physician.

Anxiety and depressive symptoms

Anxiety is a state of mental uneasiness that induces physical and emotional discomfort. Anxiety may be a trait, a personality characteristic that is long-lasting and consistent, or a state, which is temporary in response to a situation.[193,194] Depression is a condition characterized by symptoms such as sadness, difficulty concentrating, anhedonia, sleep pattern disturbances, excessive guilt, and in some cases thoughts of suicide.[193] Symptoms of anxiety and depressive symptoms were measured using the Hospital Anxiety and Depression Scale (HADS).[23] The HADS is a 14-item, self-report measure with two sub-scales; seven items evaluate self-reported anxiety, and seven items measure self-reported depression. Each item is rated on a four-point scale from 0 to 3, with 0 indicating no symptom and 3 indicating greater symptom frequency over the past week. The subscales are used as independent measures of anxiety and depressive symptoms. Total score for each subscale ranges from 0 to 21 with higher scores indicating greater frequency of the reported symptom. The total score of the HADS ranges from 0 to 42, with higher scores indicating a greater degree of reported psychological disturbance.[23] Established cut-points for each sub-scale are available and include normal (0–7), mild (8–10), moderate (11–14) or severe (15–21).[23,195]. The HADS instrument has demonstrated reliability in patients after trauma, (total Cronbach's $\alpha = .94$, anxiety subscale Cronbach's $\alpha = .92$, and depression subscale Cronbach's $\alpha = .88$) and accuracy (anxiety subscale: sensitivity = .75, specificity = 0.69, Receiver Operating Characteristic [ROC] curve = .83; depression subscale: sensitivity = .62, specificity = .92,

ROC curve = .82) when compared to the DSM-IV criteria for the clinical diagnoses of anxiety and depression.[195]

Time to First Ambulation

Time to first full ambulation was defined as the number of hours from admission to the first ambulation indicated by documentation in the medical record. Participants were grouped as early (within 48 hours of admission) or late (> 48 hours of admission) ambulation. This cut-point was based on the mobility protocol used by the trauma service.

Procedure

After Institutional Review Board approval, the primary investigator evaluated all daily admissions to the trauma service. Eligible and willing patients completed the University of California, San Diego Brief Assessment of Capacity to Consent instrument to evaluate their capacity to consent.[168] After consent, sociodemographic and baseline clinical data were obtained from the medical record and participant interview, and participants completed the HADS instrument. The PI administered the HADS to each participant by reading the questions and marking the participant selection. Responses were repeated back to the participant and recorded on a paper copy of the survey. Time to first ambulation was determined by medical record review upon patient discharge. Data were transferred from paper data forms to a data spreadsheet; data were double entered and compared for entry error with correction of identified errors or identification of missing data.

Data analysis

Descriptive statistics including means (standard deviations) and frequencies (percent) were used to characterize the sample. Patients were also categorized based on subscale scores for anxiety and depression; those who scored over the cut point for each symptom were grouped as symptomatic. Those participants with baseline anxiety and depressive symptoms were compared to those without. We used logistic regression to determine whether baseline anxiety and depressive symptom scores predicted the late ambulation group. Both variables were entered into the same block. Although the HADS-anxiety and HADS-depression subscale scores did not violate the assumption of multicollinearity (tolerance: 0.387, variance inflation factor [VIF]: 2.6), the small sample size and high correlation between the subscales (Pearson r = 0.8) was of concern; thus, separate regression models for baseline anxiety and baseline depressive symptoms subscale scores were performed. All data analyses were performed with IBM SPSS Statistics for Mac version 24.0 (Armonk, NY) and SAS for Windows version 9.3 (Cary, NC) with an a priori alpha level of 0.05 to indicate significance.

Results

Characteristics of the participants

Participants were primarily Caucasian (68%) males (63%) aged 40 ± 17 years (Table 4.1.). The majority of participants were unmarried (53%), reported a household income less than adequate to make ends meet (63%), and were unemployed (79%). Most participants were covered by health insurance with over half (56%) received government-based health care support, either Medicaid or Medicare. Hypertension (32%), chronic pain (16%), and alcohol abuse (16%) were the most prevalent comorbidities.

Participants' injuries were primarily a result of blunt trauma and the average ISS was 21 ± 4. More than half of participants (53%) had a positive toxicology (drugs, alcohol, or a combination of both) screen at admission. Hospital length of stay was 5.6 ± 3.2 days and the time to first ambulation was 59 ± 50 hours. At baseline, three participants (16%) self-reported anxiety, one (5%) reported depressive symptoms, three (16%) reported both anxiety and depressive symptoms, and 12 (63%) reported neither symptom. All participants survived their hospitalization, and nearly two-thirds (74%) of participants were discharged home.

Comparison of anxious and non-anxious groups

One-third of participants met the HADS cut-point for anxiety (HADS-anxiety subscale score ≥ 8) at baseline (Figure 4.1.). Based on scores and established cut points, 67% of participants with anxiety reported mild anxiety and 33% severe anxiety (Figure 4.2.). Those who reported baseline anxiety were 15 years younger (symptomatic 30 ± 14 years, asymptomatic 45 ± 17 years, $p = 0.03$), had household income less than enough to meet ends (symptomatic (100%), asymptomatic (46%), $p = 0.04$), were more severely injured (symptomatic ISS 25 ± 4, asymptomatic ISS 19 ± 3, $p = 0.002$), and took 28 hours longer to ambulate (symptomatic 78 ± 64 hours, asymptomatic 50 ± 42 hours, $p = 0.03$) (Table 4.1.). There were no other differences between these groups.

Comparison of those with and without depressive symptoms

Depressive symptoms were reported by 21% ($n = 4$) of our participants at baseline (i.e. HADS-depression ≥ 8) (Figure 4.3.). Of the participants with baseline depressive symptoms, 75% reported mild and 25% moderate symptoms; none of the participants

reported severe depressive symptoms (Figure 4.4.). Significantly more symptomatic patients (HADS-depression score > 8) perceived their household income was less than enough to meet ends (symptomatic 100%, asymptomatic 53%, p = 0.05) when compared with those without depressive symptoms. In addition, participants who reported baseline depressive symptoms had a shorter hospital length of stay compared to those without depressive symptoms (symptomatic LOS 3.3 ± 1.0 days, asymptomatic LOS 6.2 ± 3.3 days, p = 0.008). The HADS-anxiety score was also significantly higher in those with baseline depressive symptoms (symptomatic 12 ± 5, asymptomatic 5 ± 3, p = 0.002) (Table 1.). The mean anxiety score in those with depressive symptoms indicated a moderate degree of anxiety. There were no other significant differences between these groups.

Anxiety and depression scores as predictors of ambulation group

The fit for the anxiety subscale model was acceptable, as determined by the Omnibus Test of Model Coefficients (HADS-anxiety score p = 0.01) and the Hosmer-Lemeshow test (HADS-anxiety score p = 0.270). Baseline anxiety subscale scores were not predictive of ambulation group (p = 0.055). Thus, our proposed hypothesis that anxiety would predict later ambulation was not supported in our analysis.

The model fit for the depressive symptoms regression model was also acceptable as determined by the Omnibus Test of Model Coefficients (HADS-depression score p = 0.03) and Hosmer-Lemeshow test (HADS-depression score p = 0.322). For each one-unit increase in baseline HADS-depression subscale score, patients were 67% more likely to be in the late ambulation group (Odds Ratio [OR]: 1.67, 95% CI: 1.02 – 2.72, p = 0.041).

Thus, our hypothesis that depressive symptoms would predict later ambulation was supported (Table 4.2.).

Discussion

We evaluated anxiety and depressive symptoms in adult patients hospitalized for major trauma. At baseline that 32% of our participants reported anxiety, 21% described depressive symptoms, and 16% reported both anxiety and depression. Baseline anxiety score was not predictive of late ambulation. However, as hypothesized, depressive symptoms at baseline increased the likelihood of late ambulation.

Previous investigators reported anxiety and depressive symptoms in as many as 40% of patients after trauma, but those symptoms were most often measured months after the injury and hospitalization.[14,22,40,43] Investigators who measured anxiety and depressive symptoms during hospitalization for injury found that 17 - 45% of patients reported anxiety, while 36 - 42% of patients reported depressive symptoms.[11,36,37,196] In a large, 3-year epidemiologic evaluation of patients after trauma, Holbrook and colleagues found that 60% of patients had depressive symptoms at hospital discharge, and at 6-month follow up 31% continued to report depressive symptoms. These investigators suggested that psychological symptoms were present in the acute phase following injury, and these persisted over time.[11,36,37,39,196] The prevalence of psychological symptoms in our participants was consistent with other investigators; however, we did not evaluate the longevity or severity of these symptoms after hospitalization.

The prevalence of self-reported psychological symptoms in our participants was lower than that found by previous investigators possibly due to differences in

instrumentation and time chosen for measurement. The HADS, which measures symptom presence and severity for the prior week, was completed soon after hospital admission by our participants. Prior investigators who used the HADS in patients after trauma primarily measured psychological symptoms at discharge.[11,197] Other investigators who measured psychological symptoms during hospitalization after injury used the Depression Anxiety Stress Scale short-form (DASS-21) and the Center for Epidemiological Studies Depression Scale (CES-D).[36,37,39,198] In future investigations, using an instrument that is intended to capture acute symptoms, rather than the HADS which reflected symptoms for the previous 7 days, or the use of measurement timing for the HADS to be appropriate should be considered to optimize the measurement of these symptoms.

We found that participants who had baseline anxiety were 15 years younger, reported an inadequate household income, were more severely injured, and took longer to achieve first ambulation. Ringdal and colleagues found that at ICU discharge patients with anxiety after trauma were 6 years younger than those without anxiety, and concluded anxiety might have been related to a fear of acquired disability.[43] Anxiety related to socioeconomic status might have been more prevalent in our participants and contributed to the anxiety level, as many of these participants were unemployed and less established in the workforce. Previous investigators found that persons with severe financial strain were nearly four-times more likely to have depressive and/or anxiety disorders compared with individuals who had adequate financial resources.[199] We found that a more severe degree injury was also associated with anxiety, which was similar to previous investigators. Ringdal and colleagues found that a higher severity of injury was

significantly associated with anxiety at hospital discharge; other investigators found that serious injury doubled the predictive power for psychological distress compared with minor injury.[43,200]

Participants who were anxious at baseline achieved their first ambulation 28 hours later than those who were not anxious. The fear-avoidance model suggests that fear results in a dichotomized response: confrontation or avoidance of the event.[201] Rutter and colleagues found that "feeling jumpy or easily startled" was strongly correlated with lower engagement in exercise and decreased functional health (i.e. physical and social functioning, role limitations because of emotional and physical problems, bodily pain, general mental health, vitality, and general health perceptions) in younger patients after trauma.[82] Other investigators found that a 1-point increase in HADS-Anxiety score was associated with a 22% increased fear of falling by in patients after hip fracture.[202] Thus, baseline anxiety following major injury may have been associated with the perceived fear, such as a pain, falling, or syncope, related to the first ambulation after traumatic injury, which might have contributed to avoidance and delayed ambulation.

Those who reported depressive symptoms at baseline also perceived inadequate financial resources. Dijkstra-Kersten and colleagues found that severe financial strain was associated with a four-fold increase in the likelihood of depressive symptoms.[199] In addition, McGonagle and colleagues reported that financial difficulties were associated with more acute stress rather than chronic; thus, it is plausible that the acute nature of the trauma combined with inadequate financial resources could have been responsible for the depressive symptoms of our participants.[199,203] Our participants with baseline depressive symptoms were also discharged nearly three days earlier compared with those who did

not report depressive symptoms. In contrast, Haupt found that length of stay after injury for those with depressive symptoms was 32% longer compared to those without depressive symptoms, and Sullivan and colleagues found that presence of depressive symptoms was associated with a two-day longer hospital stay.[204,205] However, Zatzick and colleagues found no difference in length of stay between patients who had depressive symptoms and those who did not after trauma.[206] The potential reasons for the shorter length of stay in our small sample are unclear, but require additional study. Potential areas for focus include degree of social support, job and financial strain, and use of and dependence on alcohol and/or other substances of abuse, as more than half of our participants tested positive for these on hospital admission. Our participants could have requested early discharge because of concern about additional family and financial strain, or loss of access to their substance of choice.

Anxiety was the most prevalent psychological symptom reported in our participants; however, baseline anxiety score did not predict late ambulation group as we hypothesized. Hayashi and colleagues also found that baseline HADS-anxiety scores were not associated with ambulation time in patients after total hip and total knee arthroplasty.[207] Conversely, Oude Voshaar and colleagues found that baseline fear of falling delayed mobility by 11% in patients after hip fracture, which suggested that baseline anxiety did influence activity.[208,209] In these prior investigations, the participants examined were older (mean age 68-80 years) adults admitted for isolated orthopedic injuries and procedures, which reduced comparability with our participants.[207,208] It is likely that inadequate power limited the ability to determine predictive power in our study. In future investigations, a larger sample size would allow for more comprehensive

evaluation of the association of psychological health with ambulation in patients after trauma, and allow for control of confounding variables such as pain, substance abuse, and comorbid conditions, which could also influence this outcome.

Depressive symptom score predicted the late ambulation group, which supported our hypothesis. Prior investigators found that depressive symptoms were associated with decreased levels of physical activity after injury.[190,210,211] Rosenbaum and colleagues found that symptoms of depression were associated with less time spent walking during hospitalization after trauma.[190] Atay and colleagues also found that persons with depressive symptoms were 40% less active at 6 weeks, and 36% less active at 6 months following hip replacement surgery.[210] Kempen and associates reported that persistent depressive symptoms post-injury continued to reduce activity at 8-weeks, 5-months, and 1-year[211] As Atay and Kempen examined older adults (mean age 70 – 79 years) with isolated hip fractures, these investigations were not directly comparable to our population in age or severity of injury.[210,211] In these prior investigations, participant self-report of activity level was used, rather than an objective measure like that in our investigation, which could have limited the validity of the relationships reported.[190,210,211] Reduction in activity is a hallmark symptom of depression.[212-214] However, researchers have postulated there is an acute phenomenon induced by inflammation in the presence of infection or injury termed sickness behavior.[214] DePalma and colleagues used the Sickness Impact Profile to quantify these symptoms in patients after severe trauma (mean ISS 34 ± 11), and found that mobility was reduced by 25% and ambulation decreased by 27%.[213] The phenomenon we captured and described as depressive symptoms may have been confounded by sickness behavior, considering the acute nature of the injuries and

hospitalization. Further investigation of hospitalized, acutely injured patients is warranted to clarify these relationships between psychological symptoms, injury, and activity during the acute phase of recovery from injury to provide evidence for clinicians to appropriately recognize psychological symptoms, and to suitably intervene to reduce the potential for lasting disability after trauma.

Limitations

The study was conducted at a single institution with a small, homogeneous sample thus, our findings are likely not generalizable to all patients after trauma. Additionally, because of the small sample size, we were unable to control for potential confounding variables, such as pain and comorbid conditions, which might impact both time to ambulation and psychological symptoms.[215] The HADS is a self-report instrument that measures two psychological symptoms. As symptoms are subjective, self-report is the only appropriate method for measurement. Our baseline measurement might have been more reflective of the psychological state prior to the injury and hospitalization because HADS symptoms are rated for the previous week. Further investigation should focus on change in these symptoms over time and their association with outcomes. [23] This instrument has been previously used in a number of other investigations of patients after trauma.[22,195,200,211] The method of instrument administration for our study may have introduced social desirability and response bias because the individual provided oral responses to the PI in the hospital setting; different responses might have been obtained if the participant completed the instrument in a private setting alone. Lastly, we only captured state anxiety, which is influenced by trait characteristics.[193,194] Although we excluded participants with pre-existing diagnoses of anxiety, depression, schizoaffective

disorder, or bipolar disorder, participants could have had an undiagnosed psychiatric condition. Additionally, more than half of our participants were positive for alcohol and/or substances of abuse on admission toxicology analysis, which may have indicated a substance abuse disorder and underlying psychological disorders that could influence mood, behavior, and overall psychological state.

Conclusions

Anxiety and depressive symptoms were prevalent in this population, were often co-occurring, and were associated with later ambulation. Depressive symptoms, but not anxiety predicted later ambulation. It is important to investigate the association between these symptoms and ambulation after injury in a larger sample to understand the complex interactions that occur between injury and associated psychological symptoms, to clarify how such interactions influence inpatient rehabilitation and ambulation, and to support the development of targeted interventions to provide systematic and evidence-based care for patients after trauma.

Table 4.1. Characteristics of participants and comparison of those with and without self-reported anxiety and depressive symptoms.

		Baseline Anxiety			*Baseline Depressive symptoms*		
	Total Sample (N = 19)	Asymptomatic (n = 13)	Symptomatic (n = 6)	P-value	Asymptomatic (n = 15)	Symptomatic (n = 4)	P-value
Age in years	40 ± 17	45 ± 17	30 ± 14	**0.03**	42 ± 17	34 ± 17	0.42
Male gender	12 (63%)	10 (77%)	2 (33%)	0.13	10 (67%)	2 (50%)	0.60
Race				0.61			0.56
Caucasian	13 (68%)	8 (62%)	5 (83%)		11 (73%)	2 (50%)	
African American	6 (32%)	5 (38%)	1 (17%)		4 (27%)	2 (50%)	

Table 4.1 continued

Married	9 (47%)	7 (54%)	2 (33%)	0.63	7 (47%)	2 (50%)	0.91
Insured	16 (84%)	12 (92%)	4 (67%)	0.22	13 (87%)	3 (75%)	0.53
Unemployed	15 (79%)	10 (77%)	5 (83%)	0.75	11 (73%)	4 (100%)	0.70
Economic Status				**0.04**			**0.05**
Makes less than ends meet	12 (63%)	6 (46%)	6 (100%)		8 (53%)	4 (100%)	
Makes ends meet or more	7 (37%)	7 (54%)	0 (0%)		4 (47%)	0 (0%)	
Positive toxicology screen	10 (53%)	6 (46%)	4 (67%)	0.63	7 (47%)	3 (75%)	0.58

Table 4.1 continued

Blunt trauma	16 (84%)	11 (85%)	5 (83%)	1.0	12 (80%)	4 (100%)	0.33
ISS	21 ± 4	19 ± 3	25 ± 4	**0.02**	20 ± 4	24 ± 6	0.09
Hours to ambulate	59 ± 50	50 ± 42	78 ± 64	**0.03**	59 ± 56	67 ± 21	0.45
Hospital LOS (days)	5.6 ± 3.2	5.2 ± 3.0	6.5 ± 3.8	0.41	6.2 ± 3.3	3.3 ± 1.0	**0.008**
ICU LOS (days)	1.4 ± 2.1	1.2 ± 1.8	1.8 ± 2.9	0.65	1.5 ± 2.1	1.3 ± 2.5	0.86
Baseline HADS-Anxiety Score	6 ± 5	4 ± 3	11 ± 4	**<0.001**	5 ± 3	12 ± 5	**0.002**

Table 4.1 continued

Baseline HADS-Depression Score	4 ± 3	3 ± 3	7 ± 3	**0.01**	3 ± 2	9 ± 2	**<0.001**
Discharge disposition				0.64			0.95
Home	14 (74%)	10 (77%)	4 (67%)		11 (73%)	3 (75%)	
Other inpatient facility	5 (26%)	3 (23%)	2 (33%)		4 (27%)	1 (25%)	

Values are mean ± SD or f (%)

Comparisons were performed with independent t-tests, Chi square or Fisher's exact test based on level of measurement and distribution of data.

Abbreviations: HADS: Hospital Anxiety and Depression Scale; BMI: Body Mass Index; ISS: Injury Severity Score; LOS: length of stay; ICU: Intensive Care Unit

Table 4.2. Logistic regression analyses for prediction of delayed ambulation group (> 48 hours from admission).

Variable	**B**	**Exp β**	**95% CI**	**P-value**
ISS score	-0.44	0.65	0.38 – 1.09	0.10
HADS-anxiety subscale score	0.61	1.84	0.99 – 3.42	0.055
ISS = Injury Severity Score; HADS = Hospital Anxiety and Depression Scale *Omnibus Test of Model Coefficients: p = 0.01; Hosmer-Lemeshow test: p = 0.270*				
Variable	**B**	**Exp β**	**95% CI**	**P-value**
ISS score	-0.20	0.82	0.61 – 1.11	0.19
HADS-depression subscale score	0.51	1.67	1.02 – 2.72	0.041
ISS = Injury Severity Score; HADS = Hospital Anxiety and Depression Scale *Omnibus Test of Model Coefficients: p = 0.03; Hosmer-Lemeshow test: p = 0.322*				

Figure 4.1. Number of participants s who were asymptomatic (HADS-Anxiety subscale score ≤ 7) and symptomatic (HADS-Anxiety subscale score ≥ 8) from anxiety at baseline.

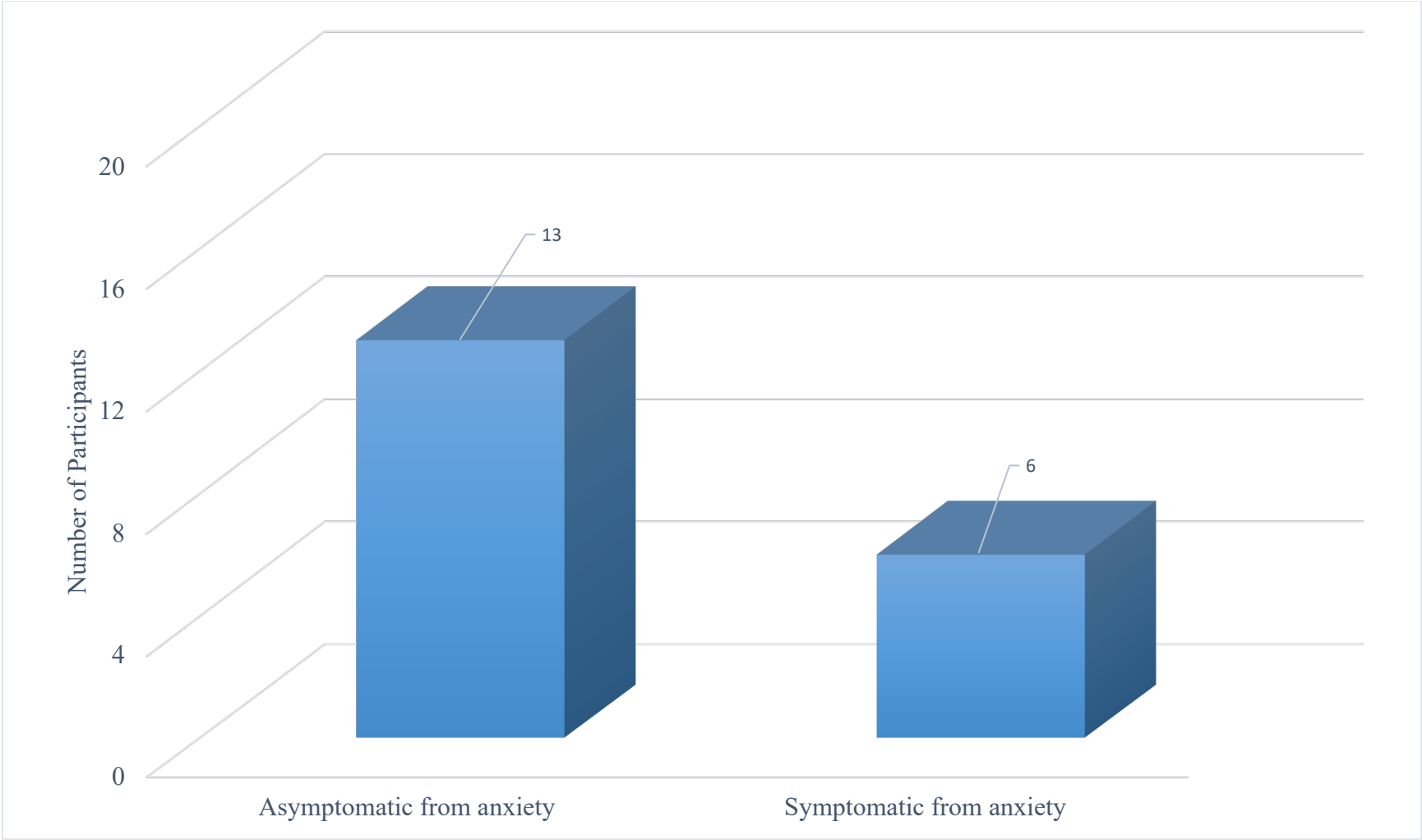


Figure 4.2. Distribution of the severity of baseline anxiety symptoms based on established HADS cut points.

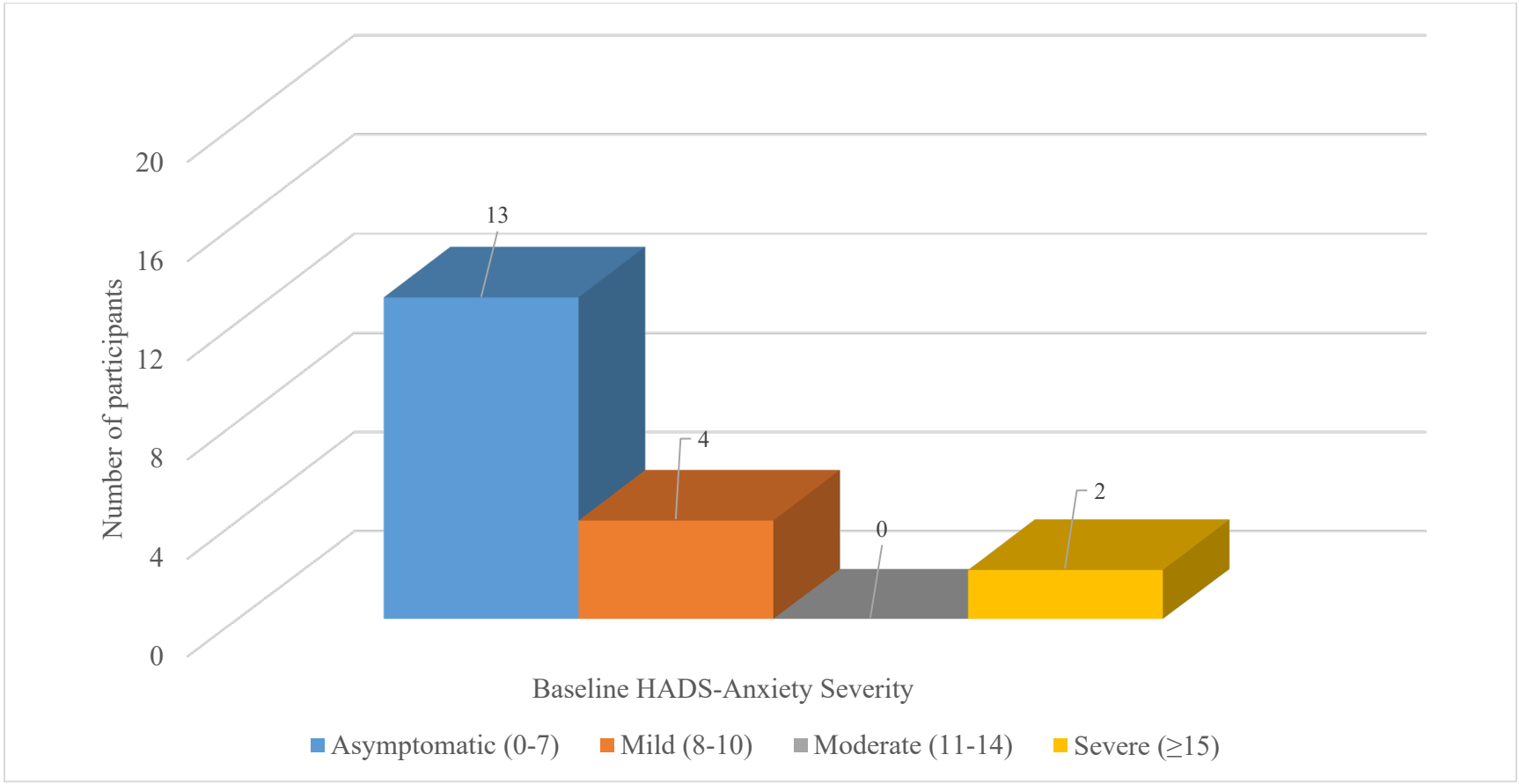


Figure 4.3. Number of participants of participants who were asymptomatic (HADS-Depression subscale score ≤ 7) and symptomatic (HADS-Depression subscale score ≥ 8) from depression at baseline.

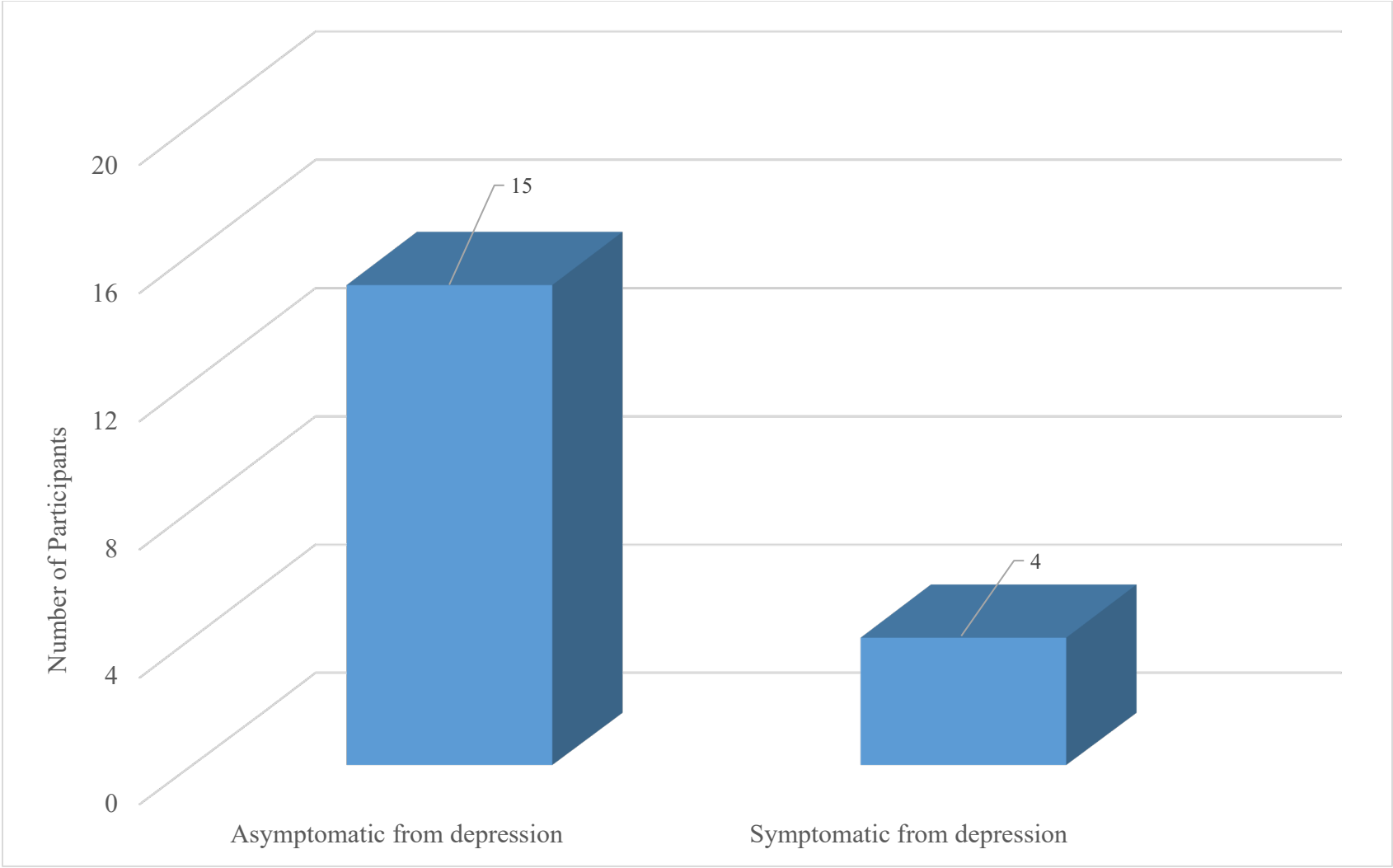
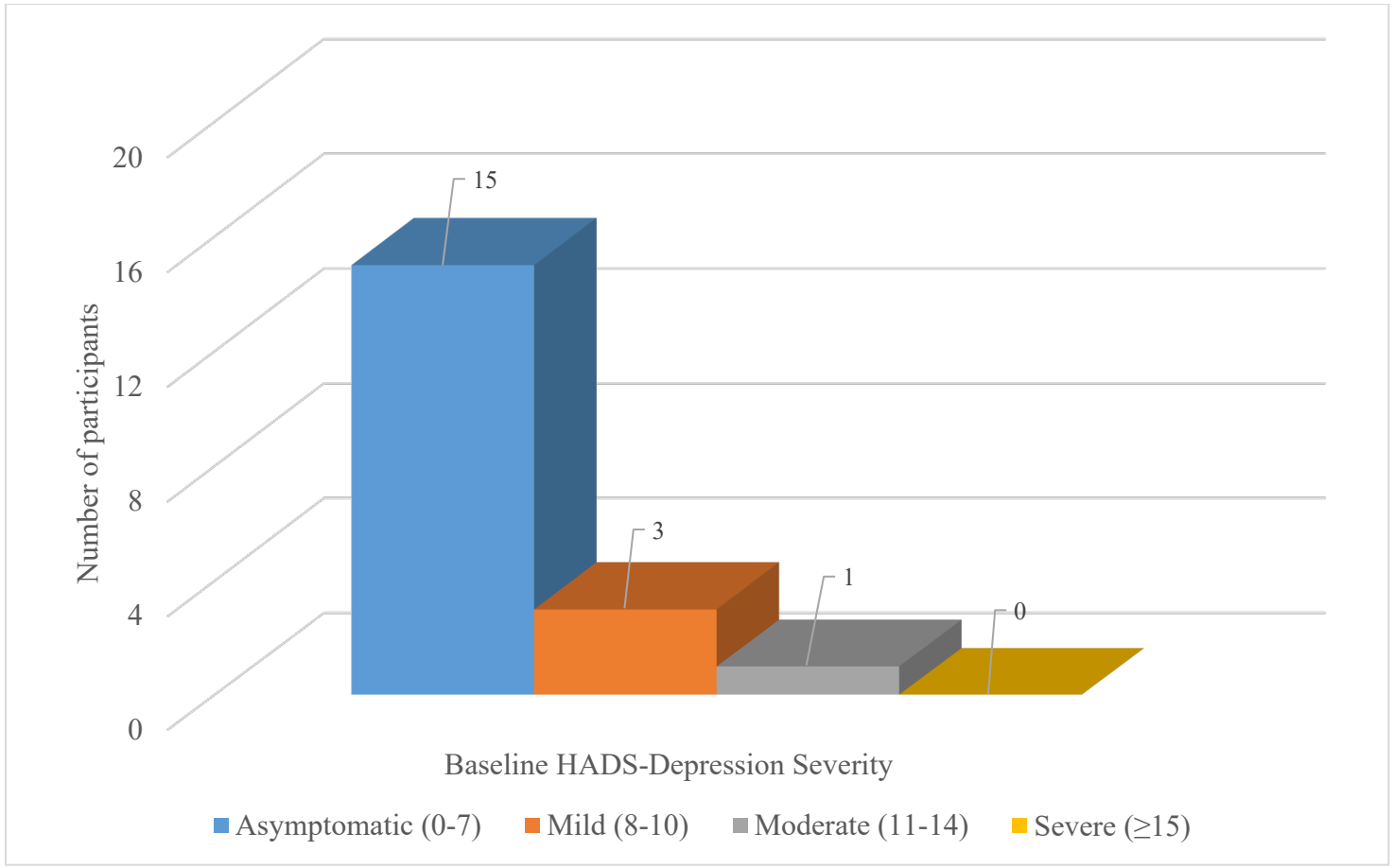


Figure 4.4. Distribution of the severity of baseline depressive symptoms based on established HADS cut points.



CHAPTER FIVE

Conclusions

Summary of Findings and Future Directions

The purpose of this dissertation was to explore the physical and psychological responses associated with major trauma (Injury Severity Score [ISS] > 15) and immobility. Although the trauma mortality rate declined nearly 3.5% from 2010 to 2015, despite an increase in 20% of hospitalizations, trauma has remained a leading cause of mortality in the United States for over a decade.[4,5] While advances in trauma care have reduced mortality, up to 44% of patients after injury do not return their pre-injury functional level by 12-month follow-up.[12] Patients after trauma who subsequently were diagnosed with depression in the year following injury were nearly 8.5 times less likely to return to pre-injury levels of activities of daily living [odds ratio (OR) 8.37, 95% CI 3.78-18.53].[13] These reductions in functional status produced considerable loss of quality of life. Reduced functional ability also imposed a substantial direct and indirect financial cost for the individual, their family and society. Thus, it is imperative that research efforts focus on understanding the contribution of physiological and psychological effects of immobility after traumatic injury to delayed return of functional ability and development of long-term disability.

The first manuscript in this dissertation was a conceptual model adapted from prior research in aerospace science and studies with a variety of acute and chronic populations prescribed bedrest. The model describes our current state of knowledge about the skeletal muscle physiological and individual psychological responses to trauma and

immobility. Additionally, the model depicted the combination of physiological and psychological effects, and how their synergistic relationship may delay or prevent the return of optimal functional status after injury. Suggestions for future research are intended to test and further develop this model and include: 1) evaluation of the degree of inflammation experienced after injury and subsequent immobility; 2) identification of risk factors for skeletal muscle compromise and psychological symptom development; 3) determination of appropriate measurement strategies for both physiological and psychological consequences of trauma and subsequent immobility; 4) identification of other variables that might influence recovery such as nutrition, prior functional status and activity level, prior psychological state, social support and available resources; and 5) how these variables influence functional recovery following injury. This model provided guidance for the conduct of studies reported in the second and third manuscripts.

In the second manuscript, we reported daily measures of skeletal muscle size using ultrasonography, and muscle strength using dynamometry in patients after major trauma. Our patients were categorized as those who ambulated early (within 48 hours of admission) and those whose ambulation was late (after 48 hours of admission) based on the trauma unit ambulation protocol; the group measures were compared and change over time evaluated. Muscle size was not different between the two groups; bicep size increased significantly by 15% from baseline measures in the early ambulation group only. At baseline and throughout observation, participants in the early ambulation group exhibited significantly greater muscle strength compared to those in the late ambulation group; this may have been an important factor in their earlier ambulation. Muscle strength increased over the first 5 days from baseline in all patients. In addition to muscle

size and strength, future research should incorporate robust measures of activity that include frequency of activity and objective measurement of activities that occur during bed rest. Future investigations should also include: 1) measurement and evaluation of the association of confounding variables such as pain, medications that interact with skeletal muscle size and function such as steroids, neuromuscular blocking agents and statins; 2) interventions required during hospitalization that include the number and length of surgical procedures, and use of immobilization management strategies such as traction or external fixation; 3) requirement for and mode and length of mechanical ventilation; and 4) nutritional status, daily intake and/or supplementation, with muscle and activity related outcomes.

In the third manuscript, we reported the association of anxiety and depressive symptoms with ambulation group, early or delayed, in the same sample of patients after trauma. At baseline, 32% of participants self-reported mild or severe anxiety, while 21% described mild to moderate depressive symptoms. Anxiety score was significantly higher in those who ambulated late, but anxiety was not predictive of delayed ambulation group in regression analyses. This was likely due to inadequate statistical power. For each one-unit increase in depressive symptom score, self-reported depressive symptoms increased the likelihood of delayed ambulation by 67%. Thus, self-reported anxiety and depressive symptoms were associated with the delayed ambulation; this supported our a priori hypothesis. This investigation provided a beginning understanding of the association of psychological state following traumatic injury during hospitalization with ambulation and its potential importance. Future investigations should focus on: 1) determination of the most appropriate instruments to measure psychological symptoms in this population; 2)

evaluation of the trajectory of psychological symptoms over time during hospitalization and after discharge; and 3) evaluation of anxiety and depressive symptoms as a mediator or moderator for time to first ambulation after injury.

There are several limitations of this dissertation. First, the data collection for this dissertation was conducted at a single trauma center. Hospital culture, adherence to national guidelines, and individual nursing and medical practices could influence patient outcomes. Second, we studied a small sample of homogeneous patients. Although we performed an a priori power analysis, we lacked statistical power. We had few prior studies upon which to base our effect size. Due to the exploratory nature of this study, we could not control for variables that might also affect outcomes, which include pain, comorbidities, and nutritional status. Third, we measured muscle thickness as the indicator of muscle size. Other scientists have suggested that cross-sectional area provides better measure of muscle size when using ultrasonography; however, we did not have access to the necessary technology for this measure. Fourth, we used dynamometry to measure muscle strength; this is a volitional measure that requires maximal effort by the participant. We could not determine or control the degree of patient effort, which could have been influenced by confounding variables like pain. In an attempt to mitigate this confounding potential, efforts were made to make measures near the same time each day to allow for anticipation of the procedures and preemptive treatments like pain medication that were necessary to promote participation. Lastly, we measured anxiety and depressive symptoms with the HADS, a self-report instrument that measures symptoms over the prior week. Self-report is the only appropriate method to measure subjective symptoms; however, individuals may be reluctant to report psychological

symptoms because of cultural bias and social stigma associated with these symptoms. In addition, the PI assisted the patients to complete this instrument, which introduced potential for social desirability and response bias.

Consequences of traumatic injury include reduced quality of life and disability when skeletal muscle function is altered by injury, inflammation, immobility, and psychological responses. Further investigation is required to more clearly understand the complex interactions among these variables. Once a better understanding has been established, development and investigation of early and effective interventions to preserve skeletal muscle structure and function, and to identify and intervene for symptoms of psychological distress could be warranted. The goal of early intervention would be restoration of individual functional ability and optimization of patient outcomes after trauma, with a reduction of the burden of acquired disability.

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VITA

Jacob T. Higgins

EDUCATION

Institution	*Degree*	*Date degree conferred*	*Field of study*
University of Kentucky	BSN	December 2012	Nursing

PROFESSIONAL POSITIONS HELD

Dates	*Institution and Location*	*Position*
August 2018 – present	University of Kentucky, College of Nursing	Adjunct Faculty, Traditional Undergraduate Nursing Program
November 2017 – present	UK HealthCare, Department of Nursing Professional Development, Lexington, KY	Nursing Research Fellow
August 2016 – August 2018	UK HealthCare, Department of General Surgery, Lexington, KY	Clinical Research Nurse Coordinator
June 2014 – August 2016	UK HealthCare, Department of General Surgery, Lexington, KY	On-call Research Nurse
January 2013 – August 2016	UK HealthCare, Lexington, KY	Staff Nurse, Charge Nurse Trauma ICU

HONORS

November 2017	UK HealthCare Nursing Research Fellowship
August 2017	Betsy M. Holliday and Eunice S. Milton Scholarship Recipient
August 2015	Robert Wood Johnson Foundation, Future of Nursing Scholar
December 2012	Central Baptist Senior Student Leadership Award

PROFESSIONAL PUBLICATIONS

Higgins, J., Bugajski, A.B., Church, D., Oyler, D., Parli, S., Halcomb, P., Fryman, L., & Bernard, A.C. A Psychometric Analysis of the Clinical Institute Withdrawal Assessment- Alcohol, revised tool in Acutely Ill and Injured Hospitalized Patients. *Journal of Trauma Nursing*. Jan/Feb 2019;26(1):41-49.

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Frazier, S.K., **Higgins, J**., Bugajski, A., Jones, A.R., & Brown, M.R. Adverse reactions to transfusion of blood products and guideline-based prevention and management. *Critical Care Nursing Clinics of North America*. 2017 Sep;29(3):271-290.

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