Impact of Traumatic Lower Extremity Injuries Beyond Acute Care: Movement-Based Considerations for Resultant Longer Term Secondary Health Conditions

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Significance: Advances in field-based trauma care, surgical techniques, and protective equipment have collectively facilitated the survival of a historically large number of service members (SMs) following combat trauma, although many sustained significant composite tissue injuries to the extremities, including limb loss (LL) and limb salvage (LS). Beyond the acute surgical and rehabilitative efforts that focus primarily on wound care and restoring mobility, traumatic LL and LS are associated with several debilitating longer term secondary health conditions (*e.g.*, low back pain [LBP], osteoarthritis [OA], and cardiovascular disease [CVD]) that can adversely impact physical function and quality of life.

Recent Advances: Despite recent advancements in prosthetic and orthotic devices, altered movement and mechanical loading patterns have been identified among persons with LL and salvage, which are purported risk factors for the development of longer term secondary musculoskeletal conditions and may limit functional outcomes and/or concomitantly impact cardiovascular health.

Critical Issues: The increased prevalence of and risk for LBP, OA, and CVD among the relatively young cohort of SMs with LL and LS significantly impact physiological and psychological well-being, particularly over the next several decades of their lives.

Future Directions: Longitudinal studies are needed to characterize the onset, progression, and recurrence of health conditions secondary to LL and salvage. While not a focus of the current review, detailed characterization of physiological biomarkers throughout the rehabilitation process may provide additional insight into the current understanding of disease processes of the musculoskeletal and cardiovascular systems.

Keywords: amputation, biomechanics, cardiovascular disease, limb salvage, low back pain, osteoarthritis

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SCOPE AND SIGNIFICANCE

Extremity trauma, including limb loss (LL) and limb salvage (LS), is commonly associated with an elevated risk for secondary health conditions (*e.g.*, low back pain [LBP], osteoarthritis [OA], cardiovascular disease [CVD]) that can significantly limit physical function, reduce quality of life (QoL), and life expectancy. This review

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provides an extensive commentary regarding resultant secondary health effects of extremity trauma in service members (SMs), with a particular focus on functional outcomes and quality of movement.

TRANSLATIONAL RELEVANCE

Physiologic biomarkers provide an opportunity to enhance translation in future work to examine the pathophysiology of the secondary health conditions associated with traumatic LL from a basic science perspective. While this approach is yet to be fully explored and thus was not a primary focus of this review, such biomarkers may augment traditional analyses and support more comprehensive risk characterization, thereby allowing clinicians and researchers to better mitigate disease onset or progression.

CLINICAL RELEVANCE

The increased prevalence of secondary health effects following traumatic extremity injuries places a significant physical and psychosocial burden on SMs with LL and LS. Altered movement patterns often result in mechanical loading of the spine and lower extremities, potentially increasing the risk of LBP and OA. Adopting a biopsychosocial model of treatment/care may allow clinicians to utilize a multifaceted approach to treat chronic pain and dysfunction associated with resultant health effects of LL.

BACKGROUND

Musculoskeletal disorders are the most prevalent source of disability in the United States.[1,2] As a result, the annual direct costs associated with treatment total a substantial $900 billion.[3] Among these, extremity amputation, or LL, is projected to affect an estimated 3.6 million people by the year 2050.[4] Approximately 185,000 individuals undergo either an upper or lower extremity amputation annually, primarily due to trauma, dysvascular disease, and/or osteosarcoma.[5–7] While the incidence of LL due to dysvascular etiologies has steadily risen among the civilian sector, trauma remains a leading source of LL within the Military Health System. However, prior estimates of the current/future impact of LL do not include SMs injured during combat nor do they consider individuals with LS; an alternative to amputation in which heroic measures are undertaken by the military surgical teams at all echelons of care to preserve as much form and function of the traumatically injured limb as possible. Despite these surgical efforts and advances in orthotic technology, many with LS are unable to achieve preinjury functional outcomes, much like those with LL.

The combat theaters of Operations: Enduring Freedom (OEF), Iraqi Freedom (OIF), New Dawn, Inherent Resolve, and Freedom's Sentinel were characterized by high-energy munitions and explosives. With advances in personal protective equipment, field-based trauma care, and surgical techniques, injuries sustained as a result of these often-improvised devices are now survivable at higher rates than conflicts past. However, traumatic extremity injuries, including LL and LS, remain a hallmark casualty of recent conflicts. Across all services, 52,351 military personnel have been wounded in action since 2001[8]; more than half of evacuated SMs have sustained extremity injuries and nearly a quarter of these are open fractures.[9] In addition, 1,703 SMs sustained injuries requiring major (or multiple) limb amputation (As of October 1, 2016; Data source: EACE-R). The decision to amputate a limb may be made in as few as 24 h post-trauma, during the first hospitalization as a secondary surgical intervention, or potentially years after LS (*i.e.*, delayed amputation).[10–13] Factors contributing to the decision include the extent and severity of injuries and resources available during the rehabilitation process.[14] Recent evidence suggests that SMs who undergo LS will typically experience more expansive complications than individuals who undergo amputation.[15–17] LS has been associated with significantly higher rates of rehospitalization, greater numbers of surgical procedures, and higher rates of surgical complications.[18,19]

Initial wound care and rehabilitation after LL and/or LS are critical to the recovery process. Such efforts are generally categorized by nine distinct phases, each with specific goals and objectives.[20] The complexity and interdependence between each phase elucidate the need for an efficient interdisciplinary approach within the overall rehabilitation paradigm. Despite these comprehensive and substantive efforts, persons with LL and LS are at an increased risk for acute secondary health conditions such as phantom limb pain, wounds/sores, vascular and nerve damage, infection, decreased physical function, and psychosocial issues. Furthermore, beyond these acute conditions, persons with LL and LS are also at an elevated risk for longer term complications including LBP, OA, and CVD, among others. Importantly, once the disease progression initiates, these longer term resultant conditions will plague these individuals for life, as SMs with extremity trauma are typically younger than 30 years at the time of injury and thus will continue living with their injuries for several decades.[17]

The long-term economic burden of trauma-related LL and LS is significant. Edwards *et al.* predicted the long-term (40 year) cost of trauma repair, rehabilitation, and lifelong prosthetic support of British soldiers wounded in Afghanistan to be approximately $444 million.[21] In the United States, the estimated average lifetime cost of treatment for unilateral lower LL is $342,716 and $1.4 million for Vietnam and OIF/OEF veterans, respectively.[22] However, such estimates are likely conservative, not fully accounting for costs associated with novel technology/repairs or, perhaps exponentially more economically burdensome over the longer term, for the wide range of healthcare costs associated with the treatment of secondary health conditions. The ability to evaluate, predict, and ultimately treat these resultant health conditions would not only help reduce these costs but also, and most importantly, preserve and/or improve function and QoL for those with LL and LS.

The risk for secondary health conditions is often related to physiological adaptations to trauma or pervasive surgical complications, poor biomechanics, and/or the prosthetic (orthotic) device itself. For SMs, in particular, the young age at which these injuries occur likely presents a unique challenge over the longer term and further highlights the importance for understanding resultant health conditions secondary to extremity trauma. Notably, the cumulative effects of many years of functional adaptations during gait and movement with extended prosthetic/orthotic device use in otherwise young and active SMs remain unclear.[23,24] This is an important distinction from civilian populations as a majority of civilians with LL are over the age of 50, incurred LL as a result of vascular damage/complications, are likely less active, and may present with different resultant health conditions/outcomes for less time.[25] Thus, as a preliminary step toward addressing this knowledge gap, the purpose of this review is to provide a commentary regarding resultant health conditions associated with high-energy extremity trauma, with a primary focus on biomechanical features of movement and associated functional limitations. In particular, we highlight considerations for longitudinal care aimed at maximizing QoL, for those with both LL and LS.

DISCUSSION

Low back pain

The World Health Organization describes LBP as any pain or discomfort for a variable duration in the lumbar spine region.[26] The onset of pain may occur suddenly, coincident to a singular traumatic event, or develop over time with age or as the result of repeated microtrauma from a given (or set of) activity(ies). Often, LBP is considered idiopathic, as pain may be present without pathoanatomical evidence of disease or structural abnormality. LBP costs nearly $100 billion annually in the United States, with a majority of this cost associated with lost wages and decreased productivity.[27] While cross-sectional figures indicate that chronic LBP affects up to 33% of adults in the general population, the incidence in persons with LL who report LBP secondary to trauma is nearly double (52–76%).[28–31] Along with this significantly higher prevalence, nearly 50% of persons with LL have reported LBP as "more bothersome" than either residual or phantom limb pain and as having a significant reduction in overall QoL metrics.[28,30,32] While the exact etiology of LBP within this population is unclear, there is a growing body of evidence suggesting that altered lumbopelvic mechanics during the (repetitive) gait cycle likely influences such risk.

Persons with lower LL frequently develop altered movement patterns to maintain balance and achieve forward progression in walking. Movement patterns can be influenced by the following, either individually or in combination: socket fit/prosthetic alignment, general deconditioning, leg length discrepancies, complications within the residual limb, and muscular imbalances.[33,34] More specifically, altered movement patterns during gait affect trunk and pelvis mechanics and contribute, at least in part, to the increased incidence of LBP in persons with lower LL and may be dependent on the extent of injury or ultimate level of amputation.[35–38] These alterations and asymmetries may increase loads on the lumbar spine during gait which, when considering the repetitive gait cycle, over time may thus contribute to the occurrence or recurrence of LBP. For example, persons with transfemoral LL tend to exhibit 10° of anterior pelvic tilt, which is considered to be a compensatory mechanism to assist in the ability to achieve hip extension during gait. Increased anterior pelvic tilt is associated with increased lumbar lordosis, which is linked to an increased incidence of LBP in persons with LL.[28,39] Previous work has demonstrated that increased loads on the lumbar spine are a direct source of LBP in the general population.[40,41] Mechanical loading of the passive and active structures of the spine is affected by both internal and external loads, such as forces produced by muscular activation, ligamentous tension, gravity, and inertia.[42]

These loads can be significant, as potentially small alterations in trunk (which accounts for nearly 2/3 of the body's mass) movement may increase joint reaction loading due to increased muscular contractions of the surrounding musculature.[43] The increased demand on the active structures (muscles) may lead to increased forces and joint loading on the passive structures (discs and vertebrae). The accumulation of these altered loads over time has the potential to augment degenerative joint changes in the spine.[40]

Similar to uninjured individuals with LBP, persons with transfemoral LL exhibit irregular trunk–pelvis coordination and movement variability.[44] Specifically, persons with LL tend to walk with a large lateral trunk lean toward the affected side; a possible neuromuscular strategy/compensation to assist in forward progression during gait.[42] This frontal plane motion has been reported to increase peak joint reaction forces and moments asymmetrically in the lumbar spine (L5-S1 integration specifically) in this population. A recent report suggested this observed frontal plane motion as a possible mechanistic pathway through which recurring exposure to altered trunk motion and cumulative spinal loading may contribute to LBP in persons with lower LL.[42] Persons with transfemoral LL (with current LBP) exhibit larger axial trunk rotations when compared to those without LBP, which may subsequently affect vertebral disc degeneration and potentially contribute to LBP recurrence.[45,46] Previous evidence demonstrated degenerative changes in the lumbar spine via radiographic imaging in 76% of persons with LL, potentially supporting the role of increased trunk motion leading to degenerative changes in this population.[47]

While LBP is commonly cited as a secondary health effect of LL, persons with LS may also experience LBP as a result of altered movement patterns during gait and functional activities.[48] Persons with LS typically experience reduced ankle function, which is associated with altered gait mechanics and increased metabolic cost.[34,49,50] However, the influence of distal LS on proximal (trunk/pelvis) biomechanics remains unstudied to date. Currently, a paucity of evidence exists relative to the prevalence of LBP in the LS population. Therefore, further work is needed to elucidate the relationship between LS and the development of LBP.

In summary, LBP has been reported as the most important health-related physical condition contributing to a reduced QoL among veterans who had sustained a traumatic lower extremity amputation over 20 years prior.[32] Thus, identifying factors contributing to the development and recurrence of LBP, such as a widely prevalent and "bothersome" secondary health concern, is critical for improving long-term health. Abnormal mechanical loading of lumbar spine, altered trunk and pelvis coordination, and psychosocial factors may influence the prevalence of LBP in this population. Therapeutic interventions that address the underlying impairment(s) in trunk neuromuscular responses and/or motor control strategy may also contribute to reducing the prevalence and incidence of LBP among SMs with lower extremity trauma, thereby improving longer term functional outcomes by mitigating a significant secondary impairment with a substantial adverse impact on daily activities. Further evidence is needed to understand the relationship between these risk factors and the incidence of LBP in persons with LL. In particular, no studies to date have evaluated the influence of different prostheses or orthoses on the incidence of LBP in the traumatic LL and LS populations.

Osteoarthritis

The National Institute of Arthritis and Musculoskeletal and Skin Diseases describes OA as a joint disease affecting the cartilage, often characterized by pain and stiffness within a joint and limitations in physical function.[51] The primary pathology is articular cartilage deterioration, although evidence suggests that possible morphological changes of bone are reflective of disease onset. Within the joint, articular cartilage functions to dissipate forces sustained by the bony structures throughout motion. During activities such as walking or running, when the loading velocity and intensity of the structures are increased, the cartilage's ability to dissipate forces is reduced.[52] In the general population, mechanical loading of the knee joint during walking has been associated with the presence, severity, and progression of knee OA.[53–56] Persons with unilateral lower LL are 17 times more likely to suffer from knee OA in the intact limb when compared to able-bodied individuals.[57]

As previously noted, persons with LL frequently develop altered movement patterns during gait. Of particular importance here, those with unilateral LL preferentially utilize their intact limb, leading to increased and prolonged loading of the intact joints. Mechanical alterations in static and dynamic alignment of the knee joint may affect joint loading as increased forces are incurred through medial or lateral aspects of the joint. The external knee adduction moment (EKAM) is a vastly reported risk factor for knee OA based on its relationship with internal loading of the medial joint surface.[58] The size of the EKAM and its respective angular impulse are associated with knee OA severity and progression.[53,55,59,60] During gait, individuals with lower LL asymmetrically load their intact limb to a greater extent than their involved limb, suggesting that mechanical factors play a role in the increased incidence of knee OA in this population.[36,61] For example, Lloyd *et al.* identified larger peak knee adduction moments in the intact relative to involved limb.[62] This increased mechanical loading may be explained by decreased push-off power and ground reaction forces demonstrated with conventional prosthetic feet.[61,63] Push-off power generated by the prosthetic foot instance may affect the ground reaction forces at heel strike in the intact limb as the velocity of an individual's center of mass changes from an anterior and inferior direction to an anterior and superior direction during gait.[64] The redirection of the center of mass is caused by the ground reaction impulse through the gait cycle, crudely relative to double-limb support.[64] If the prosthetic stance foot lacks adequate push-off power to propel the center of mass anteriorly, the intact limb must compensate by performing more work to move the center of mass anterior and superior, resulting in increased ground reaction forces and loading of the intact limb.[61] Morgenroth *et al.* suggested that by utilizing a prosthetic foot with increased push-off power, the peak EKAM of the intact limb may be reduced and therefore potentially decreasing the OA risk.[61] This was supported as a powered ankle–foot prosthetic was able to decrease the EKAM and vertical ground reaction force in persons with lower LL, however, the prosthetic used was unable to alter the knee joint loads of the intact limb.[65] Similar to LBP, the progression and severity of OA may be further amplified by psychosocial determinants; anxiety, depression, coping strategies, and stress have also been associated with increased pain in patients with OA.[66–68]

OA is not exclusive to the LL population as individuals with LS present with similar (sometimes larger) gait and movement deviations. As high as 95% of OA diagnoses among combat-wounded SMs are post-traumatic in origin.[69] Chronic pain, nerve damage, and volumetric muscle loss are common barriers to LS rehabilitation and may serve as confounding factors in the development of OA treatment plans.[70,71] Ankle–foot orthoses (AFOs) are commonly used to assist ankle function or offload painful structures.[72] Optional therapies that include sports medicine-based interventions utilizing a dynamic AFO (*e.g.*, the Intrepid Dynamic Exoskeletal Orthosis) are available to LS patients. Such devices are designed to improve functional performance on tasks such as walking, changing directions, sit-to-stand, and ascending stairs.[48] While dynamic AFOs are suggested to improve functional capabilities, evidence is inconclusive in its ability to positively alter gait parameters related to OA as well as the effects of long-term use.[34,73,74]

Treatment modalities focused on reducing symptoms and OA disease progression in persons with LL and LS are vital to improving QoL. The Osteoarthritis Research Society International recommends biomechanical interventions, intra-articular corticosteroids, exercise (land and water based), self-management and education, strength training, and weight management.[75] Autologous platelet-rich plasma (PRP) therapy is a therapeutic intervention that delivers high concentrations of growth factors to an area to stimulate healing.[76] Recent evidence suggests that PRP may provide relief of knee OA symptoms in younger patients within the early stages of cartilage degeneration.[77–79] Strength training (weight and body-weight training) and exercises such as t'ai chi have demonstrated the ability to improve overall function in decreasing pain in OA patients and may also serve to assist in weight management.[80,81] Weight reduction is considered a pragmatic therapy for knee OA as overweight individuals demonstrate a high prevalence of knee OA and the risk of severity progression increases 35% for every 5 kg of weight gain.[82] Strength training and weight management are considered integral aspects of the rehabilitation paradigm for persons with LL as deficits in strength and increases in weight influence gait, joint loading, movement efficiency, and cardiovascular health. Canes, knee braces, and foot orthotics are other potential treatment options to decrease movements at the knee, reduce pain, and improve function.[83–85]

In summary, biomechanical factors likely play a substantial role in the risk for OA secondary to extremity trauma, whether LL or LS. While the prevalence of OA in LL and LS populations may decrease as technological improvements in prostheses and orthoses are realized, further evidence is needed to determine the specific relationship between different classes or features of these devices and OA risk factors. Unfortunately, recent technological advancements in prosthetic devices have outpaced orthotic devices, the benefits of which are evident in the biomechanical characteristics of persons with LL versus LS. Nevertheless, LS typically presents with more complex neurovascular injuries and other unique challenges, which can negatively affect functional outcomes.

Cardiovascular disease

CVD is defined by a vast array of diseases affecting the heart and blood vessels.[86] CVD may present as coronary artery disease, stroke, arrhythmias, cardiomyopathy, heart disease, peripheral artery disease, aneurysms, venous thrombosis, and/or carditis.[86,87] While CVD is largely preventable, it remains the leading cause of death worldwide, particularly in lower socioeconomic demographics.[86] The American Heart Association reports there are ~85 million individuals with CVD in the United States, causing a staggering 2,200 deaths each and every day.[88] This is accompanied by direct and indirect costs of nearly $315 billion.[89] Risk factors for CVD include, but are not limited to, family history and genetics, high cholesterol and lipids, high blood pressure, diabetes, metabolic syndrome, obesity, and kidney disease.[89] In addition, significant combat trauma may be a risk factor for the development of CVD.[90–92] For example, Hrubec and Ryder conducted a 30-year follow-up of World War II veterans with lower LL and demonstrated that the relative risk of CVD mortality was increased 2.4–4 times that of persons with LS.[90] Similarly, Modan *et al.* reported significantly higher mortality rates of persons with traumatic lower LL when compared to able-bodied controls, suggesting that CVD was the primary cause (21.9% vs. 12.1%, $p < 0.001$).[91]

The pathophysiology of increased mortality rates may be a result of systemic and/or regional hemodynamic effects of trauma.[91,93–97] Obesity and hypertension secondary to decreased overall activity levels may lead to insulin regulation complications in persons with LL.[97] When compared to uninjured controls with no difference in body mass index, blood pressure, or lipid levels, persons with LL exhibited significantly higher increased fasting plasma insulin levels as well as insulin resistance.[96] Increased plasma insulin levels and insulin resistance are risk factors for atherosclerosis and metabolic syndrome, considered precursors to CVD. The role of psychological stressors in the development of CVD is not well understood; however, psychosocial factors have demonstrated involvement in the pathogenesis of CVD.[98,99] Depression and post-traumatic stress disorder have been associated with increased incidence of CVD, while veterans with high levels of cynical distrust and anger demonstrate an accelerated progression of atherosclerosis, a risk factor for CVD.[100–102] Limited evidence precludes a definitive relationship between psychosocial factors and CVD risk in persons with LL, and therefore, future work should prospectively examine the relationship between psychosocial factors/stressors and the development of CVD.

Hemodynamically, proximal amputation increases the risk of CVD development based on alterations in proximal arterial flow. Pathogenic mechanisms may include early reflection pulse waves. Early return reflection pulse waves are produced at arterial occlusion sites and have been linked to a myriad of medical complications.[103] An early returned reflection pulse wave creates a second systolic peak, which results in an increase in aortic pressure. The increased aortic pressure generates an increased left ventricular load resulting in left ventricular hypertrophy, atherothrombosis, and ultimately cardiac death.[104] Vollmar *et al.* suggested that persons with traumatic LL above the knee were five times more likely to suffer from abdominal aortic aneurysms when compared to healthy controls.[94] A possible explanation may be that after amputation, blood flow is decreased by ~25% in the terminal aorta due to altered flow paths in the visceral and renal arteries, resulting in a disrupted flow pattern at the aortic bifurcation.[95] Altered flow patterns, paired with increased shear stress along the convex aspect of the aorta and decreased shear stress along the concave aspect, are theorized to damage aorto-iliac blood vessels by increasing hydraulic forces within the aorta.[95] Persons with transfemoral LL should have regular consultations with appropriate medical personnel to assess the risk of abdominal aortic aneurysm.[95]

While the hemodynamic effects of trauma appear to influence CVD risk, addressing modifiable risk factors may be an effective strategy to help decrease CVD risk. It is widely accepted that habitual exercise with activities such as running, walking, bicycling, rowing, and swimming increases aerobic capacity and decreases the risk of CVD. When joined with dietary modifications, regular exercise can effectively reduce excess body weight, another risk factor for CVD. Moreover, the increased risk of CVD in persons with LL highlights the importance of managing modifiable risk factors, engaging in preventative treatment strategies, and adopting an active lifestyle.

SUMMARY

Maintaining an active lifestyle is critically important for physiological health, psychological well-being, and overall QoL. Such guidance is no different for individuals with LL and LS. However, given the limited (but growing) body of evidence relating movement abnormalities to altered musculoskeletal demands that may lead to the development of longer term secondary conditions in this population, additional consideration for the quality of movement during recreational and daily activities is warranted. While the overwhelming focus of recent efforts has been on persons with LL, the aforementioned secondary health conditions are likely also major concerns for those with LS. As such, we posit that an underlying focus of clinical care and future research, in both cohorts, should be toward mitigating concomitant risk for the development or recurrence of chronic pain.

While advances in trauma care and prosthetic/orthotic technologies may eventually mollify acute and subacute secondary health effects of extremity trauma, longitudinal tracking is urgently needed to better understand the mechanisms by which secondary health effects develop and progress in this population. Such efforts should encompass a transdisciplinary team, in which a comprehensive suite of evaluation metrics are employed; for example, traditional clinical evaluation and movement analysis supplemented with local and systemic physiological biomarker analyses and next-generation imaging modalities. In doing so, a better understanding of the specific pathways for the development of these secondary health effects can be realized, thus enabling clinicians to develop and prescribe appropriate treatment interventions. Ultimately, diminishing risk factors relative to the degeneration of joint and cardiovascular function will reduce the overall prevalence of secondary health conditions and improve QoL for our nation's injured SMs and veterans over the longer term.

TAKE-HOME MESSAGES

- Living with LL and LS over time leads to increased morbidity and mortality from secondary medical and musculoskeletal problems. Awareness of the long-term health risks associated with LL and LS, as well as the physiologic and biomechanical origin of these risks, is critical to improving outcomes
- Understanding the pathogenesis of the secondary health conditions of traumatic LL and LS and salvage may help guide optimal management in acute, subacute, and chronic phases of care for these individuals
- Reducing modifiable risk factors through patient education, identifying appropriate support systems, encouraging proper gait mechanics, and utilizing the prescription of evolving technologies may help mitigate long-term health conditions

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Abbreviations and Acronyms

AFO = ankle–foot orthoses
CVD = cardiovascular disease
EACE = Extremity Trauma and Amputation Center of Excellence
EKAM = external knee adduction moment
LBP = low back pain
LL = limb loss
LS = limb salvage
OA = osteoarthritis
OEF = Operation Enduring Freedom
OIF = Operation Iraqi Freedom
PRP = platelet-rich plasma
QoL = quality of life
SM = service member
USUHS = Uniformed Services University of the Health Sciences
WRNMMC = Walter Reed National Military Medical Center