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STUDY PROTOCOL

Revealing the Progression of Pain Pathways and Identifying Chronification of Pain Predictors After an Isolated Lateral Ankle Sprain: Project RECOIL

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Abstract: Persistent pain is a common complaint among civilians and military personnel after a lateral ankle sprain (LAS). Most individuals who experience pain after an LAS self-report a moderate pain intensity level that interferes with activity. This pain experience is mostly described through study designs and outcomes that limit the understanding of the acute to chronic pain transition after an LAS. The purpose of this prospective study is to quantify the prevalence rate of chronic ankle pain at 6-months post-injury and identify susceptibility and resiliency factors that contribute to pain chronification after an LAS. The objective of this study will be accomplished through a two-site prospective cohort study design with data collected at four timepoints (<7 days post-LAS, 3-, 6-, and 12-months post-LAS). A target sample size of 200 men or women (100 per site) between 18 and 45 years of age who sustain an acute LAS within the previous 7-days will be enrolled. Participants will complete a series of standardized electronic surveys at each timepoint to self-report the presence of chronic ankle pain, healthcare utilization patterns, subsequent musculoskeletal injury, and new co-morbid conditions. Additionally, participants will complete validated patient-reported outcomes (PROs) electronically to characterize the pain burden and undergo quantitative sensory testing to assess mechanical pain sensitivity via pressure pain thresholds, pain facilitation via temporal summation, and pain inhibition via a conditioned pain modulation response at all timepoints. Lastly, clinician-based outcomes will be completed at 3-, 6-, and 12-months post-LAS to examine dynamic postural control, functional performance, and walking mechanics. We hypothesize that 30% of participants will self-report chronic ankle pain at 6-months post-injury. In addition, chronic pain at 6-months will be predicted by a combination of healthcare utilization patterns, prolonged levels of peripheral sensitization and pain facilitation, and worse functional performance and PROs.

Keywords: comorbidity, epidemiology, dynamic balance, healthcare utilization, patient-reported outcomes, prospective, observational, quantitative sensory techniques, walking

Introduction

More than 2 million people in the United States are treated annually for a lateral ankle sprain (LAS).[1,2] An LAS commonly occurs because of excessive inversion and internal rotation of the rearfoot on the tibia, which may or may not occur with an increased plantarflexion angle.[3–5] This biomechanical mechanism typically results in the anterior talofibular ligament and calcaneofibular ligament to be injured.[5] As a result, individuals with an acute LAS experience immediate pain, swelling, and loss of function that can cause substantial time loss from work (~7 days) and physical activity (~14 days).[6,7] An LAS is also the number one reason for lost duty days within the United States Military, with the average lost number of duty days ranging from 45 to 55 days.[8] Therefore, an LAS is a common joint injury that interferes with a person's ability to perform activities of daily living, participate in physical activity, and complete required training or occupational duties among Service members and civilians.

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Unfortunately, many individuals who sustain an LAS continue to experience symptoms long after returning to work, physical activity, or duty. Prolonged ankle pain is one of the primary symptoms that most individuals report.[9,10] Up to 40% of active-duty Service members report ankle pain 6-months post-LAS.[11] Similar prevalence rates (50–79%) have been documented among civilian populations, with the longest follow-up occurring 6-years post-LAS.[12] Individuals who develop persistent ankle pain report moderate intensity levels that interfere with walking, running, and vigorous activities.[12] Those with persistent pain display worse fear of injury, physical health, and emotional well-being than those without pain.[13] Persistent pain is also the chief complaint that individuals report when seeking long-term follow-up care.[14,15] Lastly, prior authors have suggested persistent pain associated with a history of multiple ankle sprains is a contributing symptom of early separation from military service.[16] These data collectively demonstrate that persistent pain post-LAS is a debilitating symptom for both civilians and active-duty Service members that warrants further attention.

Authors investigating persistent pain post-LAS have used various definitions for long-term pain (ie, chronic),[12] varying endpoints to assess for the presence of pain or outcomes,[12] and only evaluated the effect pain has on physical function or quality of life.[13,17–20] This limited scope of research is also based on secondary analyses or cross-sectional and retrospective study designs that limit the understanding of the complex transition from acute to chronic pain.[12,13,17–20] As a result, significant gaps in knowledge exist for the basic epidemiology of chronic ankle pain, the natural evolution of pain-generating pathways, or how changes in clinician and patient outcomes interact with co-morbidities and contribute to the chronification of ankle pain. Prospectively evaluating such outcomes can provide valuable insight for identifying risk or protective factors in patients susceptible to pain chronification – a vital component to developing personalized therapies at critical windows of opportunity.

To generate a substantial step towards this goal, the current study will implement a prospective study design that will follow the Heuristic Model of Pain to assess the longitudinal course of pain mechanisms and pain burden.[21] For example, Quantitative Sensory Testing (QST) techniques can provide an avenue to evaluate prolonged peripheral sensitization after an LAS through pressure algometry.[21–23] At the same time, other QST techniques can be used to evaluate central sensitization by assessing the balance between levels of pain facilitation (ie, temporal summation) and inhibition (ie, condition pain modulation).[21,24] Secondly, the Heuristic Model of Pain outlines the importance of characterizing the sensory and affective qualities of pain through patient-reported outcomes (PROs) because chronic pain is a deeply personal experience.[21] A direct benefit of this comprehensive model for pain assessment is that other biopsychosocial outcomes can be incorporated to identify risk or protective factors for individuals susceptible to chronification. Therefore, this study will accomplish the following specific aims:

- Specific Aim 1: Quantify the prevalence rate of chronic ankle pain and its relationship to healthcare utilization patterns, episodes of ankle joint "giving way", and the new musculoskeletal injuries or co-morbid conditions throughout the first 12-months post-LAS.
- Specific Aim 2: Compare mechanical pain sensitivity levels, pain facilitation and inhibition levels between participants who do and do not develop chronic pain 6- and 12-months post-LAS.
- Specific Aim 3: Identify co-morbid conditions, clinician-based outcomes, and patient-reported outcomes that are predictive of chronic ankle pain at 6-months and 12-months post-LAS.

Material and Methods

Study Design

A multi-site prospective cohort study design will be used to enroll civilians and active-duty Service members from the University of Kentucky (UK) and Womack Army Medical Center (WAMC) at Fort Bragg (Figure 1).

Ethical Approval

The Revised Common Rule's Cooperative Research Provision (45 CFR 46.114) established in the United States for institutions engaged in multi-site research was followed to obtain ethical approval. Ethical approval was first obtained by the UK Institutional Review Board (IRB# 87032, IRB of Record) in accordance with the Declaration of Helsinki, with a reliance agreement and ethical approval granted by the WAMC Human Research Protection Program Office.

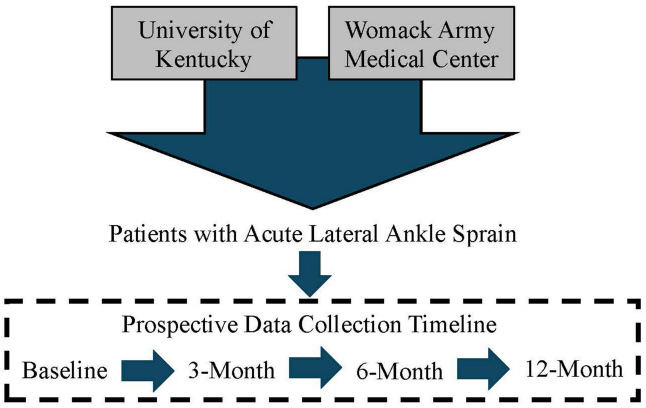

Figure 1 Study sites, target population, study design, and data collection timepoints.

Additionally, the protocol was reviewed and approved by the United States Army Medical Research and Development Command (USAMRDC) Office of Human Research Oversight.

Participants

A target sample size of 200 hundred men and women will be enrolled between UK (n = 100) and WAMC (n = 100). Participants will be recruited from the campus surrounding community associated with UK. Meanwhile, active-duty Service members and dependents will be recruited through WAMC physical therapy and orthopedic clinics that provide care to diverse populations at Fort Bragg.

Individuals between 18 and 45 years of age who sustain an acute LAS within the previous 7-days will be included. An LAS will be defined as an incident in which the rearfoot was inverted and resulted in a combination of swelling, pain, and time lost from activity for at least 1 day.[25]

Individuals will be excluded if they: 1) are diagnosed with a concomitant injury (eg, fracture), 2) sustain an LAS more than 8-days prior to enrollment, 3) report a history of any lower extremity injury within 6-months prior to enrollment, 4) report a history of lower extremity surgery, 5) diagnosed with chronic low back pain, neck pain, or other joint pain besides at the ankle, 6) report any neurological disease, vestibular or visual disturbance, or any other condition that would affect balance and gait, 7) are pregnant, or 8) do not speak English.

Enrollment and Informed Consent Procedures

All individuals interested in participating will be pre-screened over the phone by a member of the study team using an inclusion/exclusion criteria checklist. Individuals who are eligible to participate based on the pre-screen will be sent a copy of the informed consent document to review and scheduled to meet in-person with a member of the study team who is trained to obtain informed consent. During the in-person meeting, the trained study team member will further discuss the details of the study, confirm inclusion/exclusion criteria, and provide ample opportunity for potential participants to ask questions. All study team members discussing consent will be in civilian clothing and identify themselves by their professional title and not their military rank (if relevant) to minimize coercion or undue influences. Written informed consent will be obtained from all participants prior to formal engagement in any research activities.

Study Procedures

Participants who are deemed eligible and provided written informed consent will complete a standardized baseline assessment at the time of enrollment (Figure 1). Participants will then be scheduled for an in-person standardized assessment at 3-, 6- and 12-months post-LAS (Figure 1).

An overview of the outcomes to be collected at each timepoint is provided in Table 1. The overall order in which outcomes are collected will be the same at both sites and consistent across all timepoints. Specifically, participants will first undergo the QST described below. In between these assessments, participants will be asked to complete all self-

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Table 1 Outcome Measures to Be Collected at Each Timepoint

Outcome Measure	Timepoint			
	Baseline	3-Months	6-Months	12-Months
Chronic Ankle Pain		X	X	X
Healthcare Utilization Patterns	X	X	X	X
Episodes of ankle "giving way"		X	X	X
New Musculoskeletal Injury		X	X	X
New Physician Diagnosed Co-morbidity		X	X	X
Quantitative Sensory Testing	X	X	X	X
Patient-Reported Outcomes	X	X	X	X
Star Excursion Balance Test		X	X	X
Hop-to-Stabilization		X	X	X
Walking Mechanics		X	X	X

reported questionnaires electronically through REDCap (Research Electronic Data Capture). Participants will then finish the testing session by completing the Star Excursion Balance Test, Hop-to-Stabilization, and walking mechanics assessment. A more complete description of how each outcome measure will be performed is described below. To reduce attrition, participants will complete the self-reported questionnaires electronically if they are unable to attend a follow-up assessment in-person.

Primary Outcome Measure

Chronic Ankle Pain

The presence of chronic ankle pain will be documented 6- and 12-months post-LAS through a self-reported questionnaire. Chronic pain will be defined as "pain that occurs on at least half of the days for 6-months or more".[26] This is aligned with the Fiscal Year 19 Chronic Pain Management Research Program congressional appropriation definition of chronic pain caused by combat- and training related physical trauma including musculoskeletal joint injuries. Therefore, participants will be asked to answer the question (yes or no) "Have you experienced ankle pain on at least half of the days for the past 6 months?".

Secondary Outcome Measures

Healthcare Utilization Patterns

Healthcare utilization patterns 3-, 6-, and 12-months post-LAS will be collected through a self-reported questionnaire. Specific healthcare utilization patterns captured will include the use of opioid or non-opioid prescriptions related to the index injury and outcomes associated with physical rehabilitation.

Opioid and Non-Opioid Prescriptions

Participants will be asked to self-report any opioid or non-opioid medications prescribed by their treating physician at the time of injury. Additionally, participants will be asked to self-report any opioid or non-opioid prescription refills for their injury at 3-, 6-, and 12-months post-LAS. The prescription dosage (ie, strength, number of pills) will be documented for each opioid or non-opioid medication prescribed at all timepoints.

Physical Rehabilitation

Participants will be asked to self-report if they were referred to physical rehabilitation at the time of injury (ie, baseline). At the subsequent follow-up timepoints, participants will be asked: 1) the date of their first rehabilitation visit, and 2) the overall number of physical rehabilitation visits attended.

Episodes of Ankle Joint "Giving Way"

Participants will be asked to self-report if they have experienced an episode of ankle joint "giving way" at 3-, 6- and 12-months post-LAS. An episode of "giving way" will be defined as "a temporary uncontrollable sensation of instability or

rolling over one's ankle".[25,27] Data collected will include the number of "giving way" episodes for each limb and time since most recent episode.

New Musculoskeletal Injury

Participants will be asked to self-report any new musculoskeletal injury occurring in the upper extremity, back, or lower extremity at 3-, 6-, and 12-months post-LAS. A musculoskeletal injury will be defined as 1) an injury that required the participant to seek medical attention from a healthcare provider or 2) an injury that required the participant to not participate in normal physical activity for one or more consecutive days. Data collected for each musculoskeletal injury will include: 1) body site, 2) time since injury, 3) if the injury is recurrent, 4) pain intensity at its worst following the injury, and 5) if medical treatment was provided. Specific emphasis will be placed on quantifying the number of lower extremity musculoskeletal injuries at 6- and 12-months post-LAS.

New Physician Diagnosed Co-Morbidities

Participants will be asked to complete a self-reported questionnaire to identify if they were diagnosed by a physician with a new co-morbidity since their LAS. Co-morbid conditions of interest will include cardiometabolic syndromes, sleep disorders, mental health conditions, chronic pain, concussion/traumatic brain injury, alcohol substance abuse, numbness, phobia, or psychosocial and behavioral disorders.[14]

Quantitative Sensory Techniques

Mechanical Pain Sensitivity

Peripheral mechanical pain sensitivity will be assessed via pressure pain thresholds (PPTs). A digital, handheld, clinical-grade pressure algometer (Model FPX 50, Wagner Instruments, Greenwich, CT) equipped with a $1cm^2$ rubber disc attachment will be used to introduce mechanical pain and quantify PPTs.

All test sites were selected based on published data evaluating PPTs after an acute LAS.[22] Specifically, PPTs will be assessed across the second metacarpal on the ipsilateral side of the injured limb and bilaterally over the 1) anterior talofibular ligament (ATFL); 2) deltoid ligament; 3) lateral malleolus; and 4) tibialis anterior muscle belly. Table 2 provides a description detailing how each test site will be identified and participant positioning. The limb tested first will alternate with every consecutive participant enrolled at each site, with half the participants being tested on the injured limb first and the other half tested on the un-injured limb first.

The test sites will be marked using the anatomical landmark descriptions listed in Table 2 and each participant will be instructed on how the PPT test is performed. All PPTs will be performed by placing the rubber disc attachment over the skin and applying a constant rate of 40 KPa/sec pressure perpendicular to the anatomical landmark. Participants will verbally acknowledge the moment they perceive the mechanical pressure to become painful. The algometer will then be immediately removed, and the PPT will be recorded in Newtons.

Table 2 Body Site Description and Participant Position for Each Anatomical Site Tested for All Pressure Pain Thresholds

Anatomical Site	Body Site Description	Participant Positioning
Anterior Talofibular Ligament	A quarter of the distance between the most anterior aspect of the fibula and talar neck.	Seated on a standard plinth with the knees flexed to 90° and feet flat on the plinth.
Deltoid Ligament	Between the distal aspect of the medial malleolus and navicular tuberosity	Seated on a standard plinth with the knees flexed to 90° and feet flat on the plinth.
Tibialis Anterior Muscle Belly	One-third of the line between the tip of the fibula and the tip of the medial malleolus.	Seated on a standard plinth with the knees flexed to 90° and feet flat on the plinth.
Lateral Malleolus	Most prominent projection of the lateral malleolus.	Side lying with the involved limb extended and non-test limb flexed to 90°.
Second Metacarpal	Just proximal to the 2nd metacarpophalangeal joint on the dorsal side of the hand.	Closed fist with the palmar side of hand resting against a standard plinth.

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Two practice trials will be performed over the participant shoulder at a non-painful site. Two test trials will be performed at each body site with a 30-second rest between trials. The average PPT at each body site will be used for statistical analysis.

Temporal Summation

Pain facilitation is commonly assessed through temporal summation of second pain. Temporal summation of second pain is the increased perception of pain response to repetitive noxious stimuli and is viewed as an indirect method for evaluating the hyperexcitability of the central nervous system.[28–30] Previously published methodology for performing a temporal summation assessment through mechanical stimuli will be followed.[31,32] Mechanical stimuli will be applied using a von Frey filament (Touch-Test Sensory Evaluator; North Coast Medical, Gilroy, CA) calibrated to bend at 180g of force.

Temporal summation will be tested at: 1) the ATFL of the injured ankle and 2) between the 2nd and 3rd metacarpal (not over a vein or bone) and approximately half the distance from the metacarpophalangeal joint and wrist.

Participants will first be positioned in a chair with their feet flat on the ground. Both test sites will be marked, and each participant will be instructed on how the temporal summation test is performed. First, a single mechanical stimulus will be applied with the filament at the tested body site. Participants will then be asked to rate their level of perceived pain intensity using a "0" (*no pain at all*) to "10" (*worst pain imaginable*) Numerical Rating Scale (NRS). Next, a series of 10 mechanical stimuli will be applied with the filament to the tested body site at a rate of 1 tap per second. Participants will then be asked to immediately rate the greatest level of pain intensity during the 10 stimuli using the same "0" to "10" NRS.

One trial at each body site will be performed. Temporal summation will be calculated as the difference between the single stimulus pain rating and the pain rating after the 10 stimuli. Scores at each tested body site will then be used for statistical analysis.

Condition Pain Modulation

A conditioned pain modulation (CPM) protocol is commonly used to evaluate centrally derived pain inhibition pathways. This is accomplished by quantifying the reduction of pain experienced at one body site in response to the introduction of a second noxious conditioning stimuli applied to a remote region of the body (eg, "pain inhibits pain"). Therefore, recommendations for experimentally performing a CPM protocol will be followed.[33]

The most commonly applied conditioning stimulus utilized in pain studies is cold water immersion.[34] Therefore, the conditioning stimulus will be introduced by requiring participants to submerge the contralateral hand of the injured ankle (eg, right ankle, left hand) into a cold-water bath cooled to 2–5° Celsius. Participants will be instructed to submerge their hand until the water covers the wrist and refrain from closing their hand. While their hand is submerged, participants will be asked to verbally report their cold-water pain intensity every 30 seconds using a "0" (*no pain at all*) to "10" (*worst pain imaginable*) NRS. Participants will be allowed to voluntarily remove their hand from the cold-water bath at any time or verbally instructed to remove their hand once they report a 7/10 pain using the NRS or after 3-minutes of immersion. The time mark that participants remove their hand from the cold-water bath will be recorded.

Two mechanical test stimuli will be applied across the injured ATFL and ipsilateral tibialis anterior muscle belly immediately after the conditioning stimulus (Table 2). Each mechanical test stimuli will be administered consistent with the methods described above for obtaining a PPT.

A CPM index score will be calculated for the ATFL and the ipsilateral tibialis anterior muscle belly. This index score will be calculated using the average PPT values obtained during the battery of mechanical pain sensitivity testing and those captured immediately after the cold-water immersion. Therefore, the following equation will be used:

$$[(post\ PPT\ score - pre\ PPT\ score) \div pre\ PPT\ score] \times 100 = Conditioned\ Pain\ Modulation\ Index\ Score$$

A positive percent change score would represent an increase in PPT after the conditioning stimulus and suggest the presence of pain inhibition.

Patient-Reported Outcomes

Table 3 provides a complete description of the measurement scale, number of items, scoring, and interpretation of each PRO to be collected. Therefore, a brief description of the PROs is listed below.

Pain Catastrophizing Scale (PCS)

The PCS is a dimension-specific PRO that assesses catastrophic thinking related to pain.[35] In addition to calculating the total score, items can be divided to assess feelings of rumination, magnification, and helplessness. The PCS has demonstrated good test–retest reliability (Spearman $\rho = 0.88$) and high internal consistency (Cronbach's $\alpha = 0.92$).[36]

Defense & Veterans Pain Rating Scale (DVPRS)

The DVPRS was developed by the Army Pain Management Task Force over concerns associated with the inconsistent implementation of a standard NRS across military settings and its clinical value.[37] The DVPRS has demonstrated acceptable psychometric properties.[37,38]

Table 3 Description of the Design, Scoring and Interpretation for Each Patient-Reported Outcome to Be Collected

Patient-Reported Outcome	Measurement Scale	Number of Items	Scoring	Interpretation
Dimension-Specific Patient-Reported Outcome				
Pain Catastrophizing Scale	5-point Likert Scale	13-items	All items summed together.	Higher scores represent increased catastrophizing
Defense & Veterans Pain Rating Scale	11-point NRS	5-items	Each item scored independently.	Higher scores represent increased pain intensity / interference
Adult PROMIS Scale v2.0 - Pain Intensity 3a	5-point Likert Scale	3-items	T-score and standard error calculated via REDCap using item-level calibrations.	Higher T-score represents worse pain intensity
Adult PROMIS Short Form v1.1 – Pain Interference 4a	5-point Likert Scale	4-items	T-score and standard error calculated via REDCap using item-level calibrations.	Higher T-score represents more problems with pain hindering activities
Fear-Avoidance Beliefs Questionnaire	7-point Likert Scale	16-items	All items summed together.	Higher scores represent increased fear-avoidance beliefs
Short-Form McGill Pain Questionnaire-2	11-point Numerical Rating Scale	22-items broken into four subscales: 1. Continuous Pain: 6-items 2. Intermittent Pain: 6-items 3. Neuropathic: 6-items 4. Affective Descriptors: 4-items	Subscale scores are calculated as the mean of the items.	Higher subscale scores represent more intense symptoms
Pain Self-Efficacy Questionnaire	7-point Likert Scale	10-items	All items summed together.	Higher scores represent more self-efficacy towards overcoming the experience of pain to perform activities
Perceived Stress Scale-10	5-point Likert Scale	10-items	All items summed together.	Higher scores represent increased perceived stress levels
Generic Patient-Reported Outcome				
Modified Disablement in the Physical Active Scale	5-point Likert Scale	16-items total items broken into two subscales: 1. Physical: 12-items 2. Mental: 4-items	All items for each subscale are added together	Higher scores indicate greater physical limitations or lower emotional well-being
Region-Specific Patient-Reported Outcome				
Foot & Ankle Disability Index	5-point Likert Scale	34-items broken into two subscales: 1. ADL: 26-items 2. Sport: 8-items	All items for each subscale are added together and converted to a percentage	A lower percentage represents greater functional limitations

Abbreviations: NRS, Numerical Rating Scale; PROMIS, Patient-Reported Outcomes Measurement Information System; ADL, Activities of Daily Living; REDCap, Research Electronic Data Capture.

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Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity Scale & Interference Short-Form

Surveys from the PROMIS were selected because of the methodology around the validation process for multiple clinical pathologies, and psychometric properties of health domains, including pain intensity and pain-interference.[39]

Fear-Avoidance Beliefs Questionnaire (FABQ)

The FABQ is a dimension-specific PRO designed to assess fear of pain and avoidance beliefs.[40] The FABQ has demonstrated high test–retest reliability (intraclass correlation coefficient [ICC] = 0.90)[41] and acceptable internal consistency (Cronbach's α = 0.662 to 0.704).[42]

Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2)

The SF-MPQ-2 is an updated PRO that assesses the sensory and affective symptoms commonly associated with neuropathic and non-neuropathic pain.[43] The SF-MPQ-2 is suggested to be a useful instrument for studies examining the epidemiology, natural progression, mechanisms, and treatment responses for neuropathic or non-neuropathic pain.[43] The SF-MPQ-2 has demonstrated high internal consistency (Cronbach's α = 0.91 to 0.95).[43]

Pain Self-Efficacy Questionnaire (PSEQ)

The PSEQ is a dimension-specific PRO that examines a persons' confidence performing activities despite their pain.[44] The PSEQ has demonstrated acceptable test–retest reliability (r = 0.73) and high internal consistency (Cronbach's α = 0.92).[44]

Perceived Stress Scale (PSS-10)

The PSS-10 is a dimension-specific PRO that measures the personal stress an individual is currently experiencing.[45] The PSS has demonstrated good test–retest reliability (r = 0.85) and internal consistency (Cronbach's α = 0.84).[45]

Modified Disablement in the Physically Active Scale (mDPA)

The mDPA is a 16-item generic PRO designed to evaluate activity limitations, participation restrictions, and emotional well-being.[46] The mDPA has demonstrated high test–retest reliability (ICC = 0.943)[46] with the summary components demonstrating adequate internal consistency (Cronbach's α = 0.941 to 0.878).[47]

Foot and Ankle Disability Index (FADI)

The FADI is a 34-item region-specific PRO created to assess functional limitations during activities of daily living and physical activity related to foot and ankle conditions.[48] The FADI has demonstrated good test–retest reliability (ICC = 0.84 to 0.89) and is sensitive to detecting change.[48]

Clinician-Based Outcomes

Star Excursion Balance Test (SEBT)

The modified SEBT is a clinical measure of dynamic balance that includes only the anterior, posteromedial, and posterolateral reach directions. The SEBT requires participants to balance on a single-limb (ie, involved limb) and performs a maximal reach with the non-stance limb (ie, un-involved limb).[49]

Participants will perform each direction of the SEBT barefoot for the involved limb. Participants will be positioned facing a tape measure secured to the floor and toes at zero for the anterior reach direction.[49] In contrast, participants will be positioned with their heel at zero and the tape measure at a 135° angle for the posteromedial and posterolateral reach directions.[49]

Participants will first be instructed to place their hands on their hips and then transition from a double-limb to a single-limb stance on the involved limb. Once stable, participants will perform a maximal reach with their non-injured limb for each direction and gently touch the tape measure with the most distal part of the foot while maintaining a single-limb stance. Participants will then return to a double-limb stance without losing balance, and the distance reached is recorded. Participants will be provided with four practice trials, followed by three test trials in each reach direction.[50] A trial will be discarded and repeated if 1) the participant loses balance, 2) hands are removed from the hips, 3) weight is transferred to the non-stance limb; or 4) the heel of the stance limb raises off the floor.

The average reach distance for all three directions will be calculated, normalized to the length of each participants stance leg, and represented as a percentage of leg length. Leg length will be measured as the linear distance between the anterior superior iliac spine and the medial malleolus. Greater normalized reach distances represent better dynamic balance.

Hop-to-Stabilization

Functional performance will be assessed using the forward hop-to-stabilization task. To accomplish this task, participants will begin standing at a distance equal to 40% of their height from a landing zone outlined on the floor (40 × 60 cm box). Participants will initiate this task by performing a double-limb forward jump over a 30 cm hurdle placed halfway between the starting line and landing zone. Participants will then land on their involved limb within the landing zone, obtain their balance, place their hands on the hips, and remain as still as possible for five seconds. Trials will be discarded and repeated if they do not land completely in the target area, touch down with the other foot, or twist or hop on the stance-leg after landing.

Prior to beginning the task, an inertial measurement unit (IMU) will be secured to the low back (L4/L5). Tri-axial data from the IMU will be sampled at 120Hz. Data synchronization, sensor settings, and trial identifications will be controlled using the IMU research Application (for iOS developed by Xsens Technologies) on a tablet. Acceleration and gyroscopic data for each test trial will be processed using a custom MATLAB code (the MathWorks, Natick, MA, USA). The stabilization phase will be assessed using the dynamic postural stability index (DPSI) values calculated from the root-mean-square of accelerometer and rotational velocity magnitudes.

Participants will be provided with three practice trials and 10 attempts to successfully complete 5 test trials to minimize fatigue. The DPSI from five successful trials will be averaged and used for statistical analysis. Greater DPSI values will indicate greater postural disturbance and worse task performance.

Overground Walking Mechanics

All participants will be fitted with wireless force insoles (Loadsol, Novel Electronics, St. Paul, MN, USA) that are placed in their normal footwear. The insoles are designed to cover the entire foot and are comprised of 3-sensors dividing the foot into posterior, medial, and lateral region. Forces in each region will be sampled at 100 hz and recorded via Bluetooth through the Loadapp iOS application (Novel Electronics, St. Paul, MN, USA).

The insoles will be calibrated prior to data collection using recommended procedures described in thorough detail elsewhere.[51] Briefly, participants will be weighed prior to data collection and their is weight calculated in Newtons (N). Calibration of each insole will be confirmed and accepted if the insole is within 5% of the participants bodyweight when fully loaded during a single-limb stance. If the calibration is not acceptable, the manufacturer's guidelines will be followed to re-calibrate the insole.

Participants will walk across a 9.11m walkway at a self-selected pace to assess walking mechanics. Participants will start and stop each trial 1.52m on either side of the walkway to prevent any acceleration or deceleration effect (total walkway 12.15m).[52,53] Participants' self-selected walking speed will first be determined by having participants complete five practice trials and calculating the average walking speed using time gates at each end of the walkway. Five test trials within 5% of each participants average walking speed will then be performed and used for statistical analysis.

Raw force data for each test trial will be exported from the Loadapp application to a.csv file for processing. The middle 5 steps from each trial (n = 25 steps total) will be identified and averaged for statistical analysis. A publicly available MATLAB code will be used to calculate the average loading rate (Δ Force (N)/Δ Time (seconds)) for each limb.[51,54]

Power Analysis

The primary outcome is the development of chronic ankle pain at 6-months. We anticipate that 30% of participants will develop chronic ankle pain at 6-months based on a prospective study.[11] Thus, 167 participants will allow for estimating the proportion of patients who develop chronic ankle pain with a 7% margin of error and 95% confidence intervals. Additionally, a sample size of 167 participants will allow for 80% power to detect moderate effect sizes for the

quantitative sensory testing techniques between those who do and do not develop chronic ankle pain. Furthermore, a sample size of 167 participants will allow for identifying predictors of chronification using up to 5 covariates (co-morbidity, clinical outcomes, PROs) assuming p-values less than 0.05 are statistically significant. Lastly, to account for 15% attrition during the study, a target of 200 participants will be enrolled (ie, 100 participants per site).

Statistical Plan and Data Analysis

All statistical analysis will be completed with Statistical Analysis System (SAS) v9.4 (SAS Institute, Cary, NC, USA). Summary statistics will be calculated for demographic variables, prevalence rate of chronic ankle pain at 6- and 12-months, healthcare utilization measures, subsequent musculoskeletal injury, and new co-morbidities. Normality and constant various assumptions will be assessed. Continuous data will be assessed by two-sample t-tests and categorical variables will be assessed with chi-square tests to look for differences between the participants who do and do not develop chronic ankle pain. Binary logistic regressions will be used to examine the relationship between chronic pain at 6- and 12-months with healthcare utilization measures, subsequent musculoskeletal injury, and new co-morbidities. Separate analysis of covariance models controlling for unbalanced demographic data (age, sex, race/ethnicity) and injury severity will be performed if needed. The asymptotic level of significance will be set at $p \leq 0.05$ for all analyses.

Pain assessments will be measured at baseline, 3-months, and 6-months post-LAS. Normality and constant various assumptions will be assessed. A linear mixed model will be fit to assess differences over time between groups (chronic pain vs no pain) for each dependent variable. Non-parametric analyses, transformations, or separate analyses of covariance models controlling for unbalance demographic data (age, sex, race/ethnicity) and injury severity will be performed if needed. In addition, various correlation structures will be considered to estimate the within-subject correlation. The patterns of missing endpoint data will be assessed and, if necessary, techniques to handle missing data will be considered including, but not limited to, multiple imputation and last value carried forward and their sensitivity evaluated. P-values obtained for the multiple comparisons will be adjusted using appropriate methods.

The dichotomous outcome (chronic pain vs no pain) will be fit with a generalized linear mixed model to identify previously diagnosed co-morbid conditions, clinical outcomes, and PROs that predict chronic pain at 6- and 12-months post-LAS. These statistical models will allow for comparisons and examination of complex relationships among outcomes and co-morbid conditions and outcomes. Models which include demographic variables and injury severity will also be considered. Models with statistical interaction effects will be used to check for any combinations of variables under study that are related to each quantitative outcome. The asymptotic level of significance will be set at $p \leq 0.05$ for all analyses. Planned exploratory analysis for all aims will be performed to examine differences in military and civilian populations.

Discussion

The best available data indicate that between 50% and 79% of civilians and 40% of active-duty Service members report persistent pain within 6-months post-LAS.[11,12] Individuals who experience persistent ankle pain have worse functional outcomes and display diminished physical and mental health-related quality of life.[13,17,18] Despite this empirical evidence, there is a significant gap in the current knowledge regarding the basic prevalence rate of chronic pain after an LAS and factors that contribute to the progression from acute to chronic pain. To our knowledge, this will be the first prospective study to quantify the prevalence of chronic ankle pain post-LAS and examine its relationship with healthcare utilization patterns, subsequent musculoskeletal injury, and the development of new co-comorbidities. Additionally, this study will be the first to identify the susceptibility and resiliency factors underlying the transition from acute to chronic pain by prospectively assessing pain-generating pathways, clinician-based outcomes, and PROs post-LAS. We hypothesize that individuals who report chronic pain at 6-months post-LAS will receive delayed/fewer healthcare services, prolonged levels of peripheral sensitization and pain facilitation, and worse functional performance and PROs will be predictive of chronic pain.

Several clinical practice guidelines recommend that an LAS be managed conservatively with timely physical rehabilitation, non-steroidal anti-inflammatory drugs or non-opioid analgesics, and rest, ice, compression, and elevation.[55–58] Additionally, systematic reviews have supported the use of a prophylactic ankle brace or other devices to reduce the risk of injury during activity after an LAS.[59,60] Unfortunately, research has shown that many patients (~30%) are prescribed opioids to minimize their pain, and very few (~20%) are referred for physical rehabilitation.[14,61–64] Published data also indicate that

the odds of a recurrent LAS, proximal joint injury, and functional limitations can increase if a patient fails to receive timely physical rehabilitation.[14,15,65] These data provide support to our hypothesis that healthcare utilization patterns post-LAS contribute to the development of chronic pain. Furthermore, once chronic pain develops, prior studies have documented that the pain intensity and severity of functional deficits are amplified by an increase in ongoing co-morbidities.[66,67] We believe that identifying the relationship between time to specialized care, co-morbidities, and the development of chronic ankle pain may elucidate strategies to minimize the downstream effects currently documented post-LAS in both civilians and military populations.

Traumatic joint injuries activate peripheral nociceptors that relay signals to the central nervous system (CNS) that are processed with the cortex as acute pain.[68,69] Ramiro-González et al[22] demonstrated reduced sensitivity to mechanical pain over the ligamentous stabilizers within the first 2-days of being diagnosed with an acute LAS. Reduced sensitivity to mechanical pain provides evidence that an acute LAS is associated with the presence of localized peripheral sensitization.[22] Although these findings were cross-sectional, prolonged activation of peripheral nociceptors can extend the time pain is experienced and amplify its intensity. This is supported by prior studies that have shown reduced levels of mechanosensitivity over various lower extremity neuromuscular structures among individuals with chronic ankle instability, regardless of whether they experience persistent pain or not.[70] Therefore, these published data provide evidence to support our hypothesis that peripheral nociceptors around the ankle may continue to be activated long after an acute LAS and may contribute to the progression of chronic ankle pain.

Noxious stimuli relayed to the CNS from peripheral nociceptors are under constant modulation by cortical pathways. This constant modulation of noxious stimuli can disrupt pain processing pathways within cortical structures, causing more widespread pain. Changes in central pain processing are referred to as nociplastic pain and can occur independently of nociceptive pain or in combination.[71] While empirical data indicating that the presence of nociplastic pain occurs post-LAS is sparse, there is indirect evidence that suggests this pain pattern may develop. Wang et al[72] found evidence of neuroplastic alterations within the functional connectivity of pain processing (ie, insula) and motor control areas (ie, cingulate motor areas) among patients with ankle pain. Individuals with chronic ankle instability exhibit central sensorimotor alterations such as lower levels of corticomotor excitability,[73–75] increased cortical inhibition,[76] and less microstructural integrity of cortical tracts responsible for governing movement.[77] As a result, we cannot rule out the possibility that our prospective study may also find that individuals who develop chronic ankle pain present with an imbalanced pain modulation profile.[24] In other words, individuals who develop chronic pain may experience increased pain facilitation and diminished pain inhibition levels throughout the first 12-months post-LAS.

Regardless of the exact pain pattern found in this prospective study, there will be direct benefits of examining both peripheral and central pain mechanisms post-LAS. For instance, the QST data collected will allow for investigation into how different pain generating pathways evolve naturally and contribute to the chronification of pain or change in response to rehabilitation or recurrent injury. Secondly, characterizing the pattern of pain will help inform future clinical trials on selecting novel mechanism-based therapies to target either peripheral or central pathways. Lastly, the QST data collected during this prospective study can serve as normative data for future authors or clinicians to reference. Therefore, we believe that the QST data collected will have multiple short-term and long-term benefits.

While the descriptive healthcare utilization patterns and comparison of pain pathways will advance our current knowledge of the chronification of pain, the Federal Pain Research Strategy lists identifying susceptibility and resilience factors that underline the transition from acute to chronic pain as a top priority.[78] In response to that objective, our prospective study aims to examine a variety of biopsychosocial outcomes post-LAS that are supported by the existing literature. For example, a recent systematic review found individuals with chronic ankle instability who experience pain report moderate intensity levels that interfere with walking, running, and vigorous activities.[12] This pain-related interference is supported by empirical data demonstrating individuals with painful chronic ankle instability have worse dynamic postural control and more episodes of giving way.[17] Pain is also identified as a known barrier to human performance and job-related duties among military personnel.[79] However, pain does not only impact physical function as evidence suggests that psychosocial outcomes account for as much or more of the variation in symptoms than accounted by an LAS itself. Notably, lower self-efficacy levels within the first 3-weeks after injury were found to be better predictors of pain intensity than injury severity.[80] Similar relationships between levels of pain catastrophizing, injury-related fear, pain, and physical function have been documented among

individuals with chronic ankle instability.[81] A secondary analysis of published data has also shown that individuals with painful chronic ankle instability report worse fear of injury, physical health, and emotional well-being than those without pain.[13] Therefore, we believe the outcomes selected for this objective will allow our research team to engage with patients by capturing their positive experiences with recovery post-LAS (ie, resilience factors) and ineffective coping strategies (ie, susceptibility factors). Prospectively capturing these data will allow for future research to examine the effectiveness of multimodal therapies that target both physical and psychosocial side effects of an LAS.

The nature of our study design will have an impact on both short- and long-term patient care post-LAS. For example, prospectively evaluating the course of pain from an acute episode to chronic is likely to reveal vital information for developing new therapeutic targets to prevent chronic pain or reverse its course including the underlying mechanisms to address, key timepoints to intervene, endpoints and outcomes to assess treatment effectiveness. The translation of this information into clinical practice will be driven by knowledge products in the form of peer-reviewed journal submissions, clinician training for pain assessments, and patient education materials that will be available for open access.

Ethics Approval and Consent to Participate

The study protocol was approved by the University of Kentucky Institutional Review Board (IRB) in compliance with all applicable Federal regulations governing the protection of human subjects (IRB # 87032) and the Declaration of Helsinki. A reliance agreement and ethical approval have also been granted by Womack Army Medical Center's Human Research Protection Program in compliance with the single IRB protocol. This protocol has also been reviewed and approved by the United States Army Medical Research and Development Command (USAMRDC) Office of Human Research Oversight. All methods will be carried out in accordance with relevant guidelines and regulations set forth by the approved IRB protocol. Informed consent will be obtained from all participants before volunteering.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The views expressed in this manuscript are of those of the authors and do not necessarily reflect the views, opinions, or policies of the Uniformed Services University of the Health Sciences, the US Departments of Army/Navy/Air Force, Department of Defense, nor the US Government. The authors report no conflicts of interest in this work.

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